Scientific Article

Use of regional nodal irradiation and its association with survival for women with high-risk, early stage breast cancer: A National Cancer Database analysis

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Abstract

Purpose: The role of regional nodal irradiation (RNI) for patients with breast cancer remains controversial, particularly on the basis of nodal involvement. Using the National Cancer Database, we aimed to validate published data on whether expanding treatment fields from whole-breast irradiation (WBI) to encompass the regional nodes (WBI+RNI) affected overall survival (OS) for patients with node-positive (pN1-3) or high-risk node-negative (pN0) breast cancer treated with breast-conserving surgery and adjuvant chemotherapy.

Methods and materials: Women diagnosed with invasive breast cancer between 2004 and 2012 who met the selection criteria for the National Cancer Institute of Canada MA.20 trial were identified and stratified by receipt of RNI. Propensity score matching was used to compare 1:1 matched pairs of patients. Five-year OS was estimated using the Kaplan-Meier method. We used multivariate logistic regression to predict receipt of WBI+RNI and a multivariable Cox model to examine associations between patients’ demographic, tumor, and treatment characteristics and OS using double robust estimation.

Results: Of 23,567 patients, 6,920 (29%) received WBI+RNI and 16,647 (71%) WBI. Median follow-up was 56 months. Use of WBI+RNI increased from 25.2% in 2004 to 32.2% in 2012.
(P < .001). Patients receiving WBI+RNI more often had negative hormone-receptor status, ≥5 cm tumors and >1 involved node, and were not privately insured. For all patients, the 5-year OS rates were 90.8% with WBI+RNI versus 92.6% with WBI (P < .001). In the matched cohort (n = 10,922), the corresponding 5-year OS rates were 92% and 91.9% (P = .45), respectively. On multivariate analysis, WBI+RNI did not affect OS in the matched cohort (hazard ratio, 1.02; 95% confidence interval, 0.89-1.17, P = .76), regardless of pathologic nodal status.

**Conclusions:** In this large retrospective analysis, use of WBI+RNI did not affect 5-year OS rates for women with high-risk, early stage breast cancer undergoing breast-conserving surgery and adjuvant chemotherapy, regardless of nodal status, which confirms the findings of the MA.20 trial.

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**Introduction**

Breast cancer remains the most common cancer in women, with over 246,000 new cases estimated annually in the United States.1 Given this high incidence, clinicians are constantly challenging standards of care in the hopes of improving quality of life and survival. The traditional treatment for most breast cancers is multimodality therapy that consists of definitive surgery (ie, mastectomy or breast-conserving surgery [BCS]), systemic therapy, and radiation therapy.

For patients who undergo BCS, the benefit of whole-breast irradiation (WBI) is uncontested, with an associated 50% reduction in disease recurrence and a reduction in the breast cancer death rate of approximately one sixth.2 Similar long-term survival benefits have been reported for patients with significant or even low nodal disease burden, defined as 1 to 3 positive regional lymph nodes, who undergo postmastectomy radiation therapy.3 Although regional, undissected, draining lymphatics are typically included in radiation target volumes after mastectomy, whether regional nodal irradiation (RNI) had any additional value for patients with early stage breast cancer undergoing BCS remained largely unanswered and thus prompted several large, randomized clinical trials.4-6

Of these trials, the National Cancer Institute of Canada (NCIC) MA.20 trial randomized 1,832 women diagnosed with early stage, node-positive (pN1-3) or high-risk node-negative (pN0) breast cancer who had received BCS and adjuvant chemotherapy into 2 radiation treatment groups: WBI versus WBI with comprehensive RNI (WBI+RNI). At 10 years, WBI+RNI was found to confer a significant improvement in disease-free survival (DFS) from 77% to 82% (P = .01) but no improvement in overall survival (OS; 81.8% vs 82.8%; P = .38).6 These results are comparable to those of the European Organization for Research and Treatment of Cancer (EORTC) 22922 clinical trial, which randomized the use of RNI for women with either a central/medial primary tumor or an externally located tumor with axillary involvement treated with BCS or mastectomy.7 Directly after the demonstration of a DFS benefit from these studies, the National Comprehensive Cancer Network changed its recommendations for patients with 1 to 3 positive axillary lymph nodes; it removed the category 2b designation that was associated with WBI+RNI and no longer left to physician discretion the inclusion of internal mammary lymph nodes as a target.7

One noteworthy limitation of the NCIC MA.20 trial was that its conclusions were largely driven by node-positive patients (n = 1655) and therefore led to underpowered subgroup analyses for those with node-negative disease (n = 177). In this retrospective study, we hypothesized that a survival benefit may be evident in a more modern and larger study population; thus, we analyzed the National Cancer Database (NCDB) to investigate the patterns of use and effect of WBI+RNI on the survival of patients with breast cancer who met the MA.20 selection criteria. We also hypothesized that a difference in OS outcomes by radiation treatment technique (WBI vs WBI+RNI) might be evident from a subset analysis of larger cohorts of patients with node-positive and high-risk node-negative breast cancer.

**Patients and methods**

**Patient selection and variables**

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, which captures approximately 70% of all newly diagnosed cancer cases in the United States from more than 1,500 facilities that are accredited by the Commission. The database includes information on patient demographics, tumors, and disease staging as well as treatment details such as radiation therapy volumes and doses, which are not available in other databases. The current study sample was restricted to deidentified data from the NCDB for women aged 16 years or older who...
were diagnosed with invasive, non-metastatic breast cancer from 2004 through 2012.

Patient selection was strictly based on the entry criteria for the NCIC MA.20 clinical trial (ie, patients who have clinical T1-3 status, clinical N0-1 status, and pathologic node-positive [pN1-3] disease and undergo a complete axillary lymph-node dissection [ALND], defined as \( \geq 10 \) lymph nodes examined). Alternatively, patients could have pathologic node-negative (pN0) disease with high-risk features. High-risk features for pN0 disease included tumor \( \geq 5 \) cm in diameter or tumor 2 to 4.9 cm in diameter without a complete ALND and with either high-grade or hormone (estrogen and progesterone) receptor-negative status. Hormone receptor-positive status was defined as having either estrogen or progesterone positivity. Information with regard to lymphovascular invasion, a pathologic feature used in the NCIC MA.20 trial, was not available and therefore not included. Human epidermal growth factor receptor 2 status was available mainly for patients who were diagnosed during or after 2010 when its documentation became a requirement in the NCDB.

All patients underwent BCS followed by adjuvant chemotherapy and radiation therapy to the whole breast with or without RNI. Sequencing of multimodal therapy was verified by comparing the individual start dates of surgery, chemotherapy, and radiation therapy with the date of diagnosis. WBI+RNI was defined as radiation treatments consisting of photons, electrons, or both, given with the intent of including regional lymph nodes in the treatment field and delivered to a dose of 40 to 66 Gy.

The final cohort was meticulously screened to ensure that the variables used in the selection criteria matched other relatable clinicopathologic variables available in the NCDB (ie, the variable pertaining to pathologic nodal stage corresponded with the variable for the number of positive nodes). Patients were then stratified into 2 treatment groups depending on radiation treatment volume: WBI+RNI or WBI only.

**Statistical analysis**

Patient and tumor characteristics and delivered therapy were compared with \( \chi^2 \) tests. A multivariate logistic regression model was constructed with data from the entire patient group (ie, the unmatched cohort) to predict the likelihood of receipt of WBI+RNI. To reduce the influence of selection bias, we conducted a propensity score—matched analysis to identify pairs of patients who were matched 1:1 according to the following covariates, which were used in a multivariate logistic model to estimate propensity scores using a 5-to-1 digit greedy match algorithm: age at diagnosis, ALND, tumor size, hormone receptor status (positive or negative), number of positive lymph nodes (0, 1, 2, 3, or \( \geq 4 \)), Charlson Deyo comorbidity score, insurance status, income, education, and year of diagnosis.

The primary outcome of interest was OS, which was defined as the time from diagnosis to the time of death or last contact. OS for patients who were alive at the time of analysis was censored at the time of last contact, and the Kaplan-Meier method was used to estimate 5-year OS. With the propensity score—matched cohort, regression analyses of survival data on the basis of the Cox proportional hazards model were done using double robust estimation, and a stratified log-rank test was used to evaluate the difference in OS with the matched pairs as strata. Subset analyses were conducted with matched-cohort patients who had either pN1-3 or high-risk pN0 disease. All data analyses were done with SAS, Version 9.4 (SAS Institute, Cary, NC) and S-plus, Version 8.04 (TIBCO Software Inc., Palo Alto, CA) statistical software. Statistical significance was defined as a 2-sided \( P \) value < .05.

**Results**

**Patient and tumor characteristics**

Inclusion criteria are summarized in the CONSORT diagram in Figure 1. The entire group consisted of 23,567 patients, of whom 29% (\( n = 6,920 \)) received WBI+RNI and 71% (\( n = 16,647 \)) received WBI. The use of WBI+RNI increased from 25.2% to 32.2% during the study period (Fig 2; \( P < .001 \)). The median age was 55 years, and most patients were white, without comorbid conditions, privately insured, and resided in urban areas. On multivariate logistic regression, having hormone receptor-negative disease (odds ratio [OR], 1.17; 95% confidence interval [CI], 1.08-1.27; \( P < .001 \)), tumor \( \geq 5 \) cm versus \( < 2 \) cm in diameter (OR, 1.63; 95% CI, 1.31-2.02; \( P < .001 \)), and public versus private insurance (OR, 1.13; 95% CI, 1.05-1.22, \( P = .001 \)) were found to correlate with a higher probability of receiving WBI+RNI. Moreover, the likelihood of receiving WBI+RNI increased incrementally if the patient had \( > 1 \) positive regional node compared with having pN0 disease (OR for 2 positive nodes, 7.9 [95% CI, 7.9-7.9]; OR for 3 positive nodes, 14.2 [95% CI, 12.5-16.2]; OR for \( \geq 4 \) positive nodes, 36.2 [95% CI, 31.8-41.2]).

To reduce bias, we identified 5,461 1:1 matched pairs in our propensity score—matched analysis for a matched cohort of 10,922 patients (Table 1). Demographic distributions were similar in this population by RNI status. Most patients (97.3%) had tumors that were \( < 5 \) cm. From a total of 834 patients, 7.6% had high-risk pN0 disease; of those with nodal involvement, 68.4% had pN1 disease.

**Survival analysis**

The median follow-up was 56 months. Survival curves are shown in Figure 3. For all patients, estimated 5-year
OS rates were 90.8% for patients who received WBI+RNI versus 92.6% for those who received WBI (Fig 3A; \( P < .001 \)). However, this difference in OS became insignificant in multivariate regression analysis after adjusting for other risk factors (hazard ratio [HR], 1.03; 95% CI, 0.92-1.16; \( P = .61 \)). Five-year OS rates for the matched cohort were similar at 92% for WBI+RNI and 91.9% for WBI (Fig 3B; \( P = .45 \)).

On multivariable analysis of the matched cohort (Table 2), WBI+RNI was not found to be an independent predictor of OS (HR, 1.02; 95% CI 0.89-1.17; \( P = .76 \)). Older age, higher comorbidity score, negative hormone receptor status, larger tumor size, increased number of positive regional lymph nodes, higher tumor grade, and having public insurance were found to negatively influence OS. Subset analyses on the basis of pathologic nodal status showed similar results, with no significant influence of WBI+RNI on OS in matched patients with either pN1-3 disease (HR, 0.98; 95% CI, 0.85-1.13; \( P = .75 \)) or high-risk pN0 disease (HR, 1.59; 95% CI, 0.96-2.67; \( P = .07 \)). Although the independent predictors of OS in the pN1-3 subgroup mirrored those of the overall matched cohort, only hormone receptor status remained a significant predictor of OS in the high-risk pN0 subgroup (Table 3).

**Discussion**

Although the long-term survival benefit of comprehensive radiation therapy, which encompasses undissected regional lymphatics within the radiation fields,
Table 1  Patient characteristics

|                        | All Patients No. (%) | % of All Patients Receiving RNI | P Value | No. of Matched Patients (%) | % of Matched Patients Receiving RNI | P Value |
|------------------------|----------------------|---------------------------------|---------|-----------------------------|------------------------------------|---------|
| Overall                | 23,567 (100)         | 29.4                            |         | 10,922 (100)                | 50                                 |         |
| Age at the time of diagnosis, y |                     |                                 |         |                             |                                    |         |
| <30                    | 124 (0.5)            | 29                              | <.001   | 49 (0.5)                    | 53.1                               | .22     |
| 31-40                  | 1920 (8.2)           | 28.4                            |         | 828 (7.6)                   | 52.4                               |         |
| 41-50                  | 6255 (26.5)          | 28.6                            |         | 2815 (25.8)                 | 51                                 |         |
| 51-60                  | 8157 (34.6)          | 28.3                            |         | 3761 (34.4)                 | 48.5                               |         |
| 61-70                  | 5510 (23.4)          | 31.1                            |         | 2704 (24.7)                 | 50.1                               |         |
| ≥70                    | 1601 (6.8)           | 32.7                            |         | 765 (7.0)                   | 50.5                               |         |
| Race                   |                      |                                 |         |                             |                                    |         |
| White                  | 18,825 (79.9)        | 29.5                            | .64     | 8830 (80.9)                 | 49.8                               | .32     |
| Black                  | 3604 (15.3)          | 29.2                            |         | 1631 (14.9)                 | 50.2                               |         |
| Other                  | 1138 (4.8)           | 28.2                            |         | 461 (4.2)                   | 53.4                               |         |
| Charlson Deyo comorbidity score |                  |                                 |         |                             |                                    |         |
| 0                      | 20,523 (87.1)        | 29.2                            | .22     | 9508 (87.1)                 | 49.9                               | .85     |
| 1                      | 2618 (11.1)          | 30.8                            |         | 1225 (11.2)                 | 50.7                               |         |
| 2                      | 426 (1.8)            | 30                              |         | 189 (1.7)                   | 50.8                               |         |
| Tumor size             |                      |                                 |         |                             |                                    |         |
| <20 mm                 | 7246 (30.8)          | 40.2                            | <.001   | 4695 (43)                   | 50.2                               | .92     |
| 20-49 mm               | 15,674 (66.5)        | 24.1                            |         | 5925 (54.3)                 | 49.8                               |         |
| ≥50 mm                 | 647 (2.7)            | 34.8                            |         | 302 (2.8)                   | 49.7                               |         |
| Tumor laterality       |                      |                                 |         |                             |                                    |         |
| Right                  | 11,607 (49.3)        | 29.8                            | .17     | 5442 (49.8)                 | 49.6                               | .38     |
| Left                   | 11,960 (50.8)        | 29                              |         | 5480 (50.2)                 | 50.4                               |         |
| Tumor grade            |                      |                                 |         |                             |                                    |         |
| Well differentiated    | 1964 (8.3)           | 37.7                            | <.001   | 1249 (11.4)                 | 48.8                               | .79     |
| Moderately differentiated | 6842 (29)          | 39.5                            |         | 4253 (38.9)                 | 49.6                               |         |
| Poorly differentiated   | 14,061 (59.7)        | 23                              |         | 5063 (46.4)                 | 50.3                               |         |
| Undifferentiated/anaplastic | 103 (0.4)      | 26.2                            |         | 43 (0.4)                    | 48.8                               |         |
| Unknown                | 597 (2.5)            | 36.7                            |         | 314 (2.9)                   | 55.7                               |         |
| Hormone receptor       |                      |                                 |         |                             |                                    |         |
| Negative               | 7875 (33.4)          | 20.7                            | <.001   | 2550 (23.4)                 | 49.8                               | .86     |
| Positive               | 15,692 (66.6)        | 33.7                            |         | 8372 (76.7)                 | 50                                 |         |
| Human epidermal growth factor receptor status | |                                 |         |                             |                                    |         |
| Negative               | 8279 (35.1)          | 32.9                            | <.001   | 3958 (36.2)                 | 50.9                               | .07     |
| Positive               | 1742 (7.4)           | 31.7                            |         | 767 (7.0)                   | 52.5                               |         |
| Unknown                | 13,546 (57.5)        | 26.9                            |         | 6197 (56.8)                 | 40.1                               |         |
| Pathologic node stage  |                      |                                 |         |                             |                                    |         |
| N0                     | 8394 (35.6)          | 5.1                             | <.001   | 834 (7.6)                   | 49.9                               | .92     |
| N1                     | 11,340 (48.1)        | 35.4                            |         | 7465 (68.4)                 | 50                                 |         |
| N2                     | 2800 (11.9)          | 64.3                            |         | 1920 (17.6)                 | 49.7                               |         |
| N3                     | 1033 (4.4)           | 65.1                            |         | 703 (6.4)                   | 51.2                               |         |
| No. positive nodes     |                      |                                 |         |                             |                                    |         |
| 0                      | 8394 (35.6)          | 5.1                             | <.001   | 834 (7.6)                   | 49.9                               | .97     |
| 1                      | 6005 (25.5)          | 27.2                            |         | 3134 (28.7)                 | 50.4                               |         |
| 2                      | 3459 (14.7)          | 40.7                            |         | 2683 (24.6)                 | 49.8                               |         |
| 3                      | 1880 (8.0)           | 51.9                            |         | 1650 (15.1)                 | 49.3                               |         |
| ≥4                     | 3829 (16.2)          | 64.5                            |         | 2621 (24)                   | 50.1                               |         |
| Year of diagnosis      |                      |                                 |         |                             |                                    |         |
| 2004                   | 1340 (5.7)           | 25.2                            | <.001   | 558 (5.1)                   | 51.8                               | .90     |
| 2005                   | 1405 (6.0)           | 25.1                            |         | 614 (5.6)                   | 48.7                               |         |
| 2006                   | 1630 (6.9)           | 24.5                            |         | 692 (6.3)                   | 49.9                               |         |
| 2007                   | 2051 (8.7)           | 26.8                            |         | 935 (8.6)                   | 48.8                               |         |
| 2008                   | 3410 (14.5)          | 28.4                            |         | 1617 (14.8)                 | 49.2                               |         |

(continued on next page)
has been validated through several high-quality studies of women with stage III breast cancer, the use of RNI for subgroups of women with stage I-II breast cancer remains controversial. Part of the dilemma stems from the substantial heterogeneity of this population, which makes it difficult to properly assess and balance their estimated recurrence risk after surgery and systemic therapy with the potential benefit and morbidity of RNI.

Table 1 (continued)

|                      | All Patients No. (%) | % of All Patients Receiving RNI | P Value | No. of Matched Patients (%) | % of Matched Patients Receiving RNI | P Value |
|----------------------|----------------------|-------------------------------|---------|----------------------------|------------------------------------|---------|
| 2009                 | 3850 (16.3)          | 28.8                          |         | 1826 (16.7)                | 49.9                               |         |
| 2010                 | 3803 (16.1)          | 31.6                          |         | 1888 (17.3)                | 50.6                               |         |
| 2011                 | 3245 (13.8)          | 33.6                          |         | 1507 (13.8)                | 51.3                               |         |
| 2012                 | 2833 (12.0)          | 32.2                          |         | 1285 (11.8)                | 49.6                               |         |
| Axillary lymph node dissection |                      |                               |         |                            |                                    |         |
| No                   | 8354 (35.4)          | 5.1                           | < .001  | 819 (8.0)                  | 49.9                               | 0.97    |
| Yes                  | 15,213 (64.6)        | 42.7                          |         | 10103 (93.0)               | 50                                 |         |
| Insurance type       |                      |                               |         |                            |                                    |         |
| Public               | 6520 (27.7)          | 32.3                          | < .001  | 3170 (29.0)                | 50.1                               | .94     |
| Private              | 16,228 (68.9)        | 28.1                          |         | 7469 (68.4)                | 49.9                               |         |
| Not insured          | 568 (2.4)            | 32.2                          |         | 283 (2.6)                  | 50.9                               |         |
| Unknown              | 251 (1.0)            | 28.3                          |         | —                          | —                                  | —       |
| Income level         |                      |                               |         |                            |                                    |         |
| <$30,000             | 2572 (10.9)          | 29.6                          | .13     | 1227 (11.2)                | 49.8                               | .45     |
| $30,000-$34,999      | 3581 (15.2)          | 29.7                          |         | 1744 (16.0)                | 48.3                               |         |
| $35,000-$45,999      | 6358 (27.0)          | 30.4                          |         | 3049 (27.9)                | 50.5                               |         |
| $46,000+             | 10,265 (43.5)        | 28.7                          |         | 4902 (44.9)                | 50.3                               |         |
| Unknown              | 791 (3.4)            | 28.1                          |         | —                          | —                                  | —       |
| Facility type        |                      |                               |         |                            |                                    |         |
| CCP                  | 4326 (18.3)          | 32.4                          | < .001  | 2094 (19.2)                | 53.5                               | < .001  |
| CCCP                 | 10,901 (46.3)        | 28.9                          |         | 5134 (47.0)                | 49                                 |         |
| Academic/research    | 6686 (28.4)          | 28.4                          |         | 2989 (27.4)                | 48.6                               |         |
| Other                | 1654 (7.0)           | 28.2                          |         | 705 (6.5)                  | 52.5                               |         |

RNI, regional nodal irradiation; CCP, community cancer program; CCCP, comprehensive community cancer program. Bold denotes statistical significance with P < 0.05.

The NCIC MA.20 clinical trial sought to address this and supports the use of RNI in patients with node-positive or high-risk, node-negative early stage breast cancer given the significant improvement in 10-year DFS and limited radiation-related toxicity. However, this optimization in locoregional control failed to translate into a significant OS benefit, although there was a trend toward improvement with RNI. Moreover, the MA.20 trial comprised 1,832 patients, of whom only 177 had pN0 disease. This

![Figure 3](https://via.placeholder.com/150)  

Figure 3  Kaplan-Meier 5-year overall survival estimates for (A) the entire group and (B) the propensity score—matched patients. WBI, whole-breast irradiation; WBI+RNI, whole-breast irradiation with regional nodal irradiation.
Improved locoregional and distant DFS are other meaningful endpoints that may translate into a systemic benefit from nodal irradiation. The MA.20 trial did show that WBI+RNI significantly improved the 10-year DFS rate, at 82% compared with 77% for WBI ($P = .01$). These findings were comparable to those of the EORTC 22922/10925 trial, which reported a 10-year DFS rate of 72% with WBI+RNI versus 69% without WBI+RNI ($P = .04$). Therefore, it is reasonable to conclude that reducing recurrence by using comprehensive nodal irradiation is a clinically relevant goal that should be discussed with every patient. Other pertinent patient and tumor characteristics that were found to be associated with poorer outcomes in the current study (e.g., increasing age, greater comorbidity, negative hormone receptor status, larger tumors, higher tumor grade, or nodal involvement) should also be considered in discussions of treatment options.

In fact, WBI+RNI is now recommended in various reviews and in national guidelines for reducing the risk of locoregional failure, specifically for all patients with node-positive disease.\textsuperscript{7,13,14} Traditionally, use of WBI+RNI has been widely accepted for patients with $>3$ positive lymph nodes.\textsuperscript{15,16} However, the results of the NCIC MA.20 and EORTC trials led to revisions in these recommendations to include some patients with relatively low nodal disease burden. In our matched cohort, more than 90% of patients had node-positive disease and underwent ALND. Approximately 24% of patients had $\geq 4$ positive nodes, which is a proportion that was substantially higher than the 5% reported in the NCIC MA.20 trial.

Surprisingly, in our study WBI+RNI was not associated with an observed survival benefit in the subset analysis of patients with pN1-3 disease with either 1 to 3 positive nodes or $\geq 4$ positive nodes. Despite this finding, which was possibly influenced by uncontrolled clinico-pathologic factors such as lymphovascular space invasion and by limited follow-up time, the number of positive nodes remained a significant independent predictor of survival, as expected.\textsuperscript{17} Moreover, clinicians appear to be mindful of the potential benefit of WBI+RNI because the odds of receiving WBI+RNI were significantly increased for patients who had $>1$ positive node.

For patients with pN0 axillary breast cancer, the risk of internal mammary nodal involvement has previously been reported to be approximately 4% to 9%.\textsuperscript{18-21} However, this percentage, as well as the risk of locoregional failure, may be greater when combined with several adverse features, thereby arguing for a potential benefit of WBI+RNI. In our study, 834 patients (7.6%) had high-risk pN0 disease compared with 177 patients (9.7%) in the NCIC MA.20 trial. However, whereas the NCIC MA.20 trial results noted that WBI+RNI was associated with a trend toward improved outcomes (HR, 0.79; 95% CI, 0.61-1.02),\textsuperscript{5} our subset analysis showed the contrary

| Table 2 Multivariate analysis of the propensity score—matched cohort | Hazard Ratio (95% Confidence Interval) | $P$ value |
| --- | --- | --- |
| Radiation group |  |  |
| WBI only | 1 |  |
| RNI | 1.02 (0.89-1.17) | .76 |
| Age group, y |  |  |
| $\leq 70$ | 1 |  |
| $>70$ | 1.75 (1.40-2.20) | $< .001$ |
| Race |  |  |
| White | 1 |  |
| Black | 1.14 (0.95-1.36) | .16 |
| Other | 0.55 (0.34-0.89) | .02 |
| CD comorbidity score |  |  |
| 0 | 1 |  |
| 1 | 1.30 (1.06-1.59) | .01 |
| 2 | 2.32 (1.64-3.28) | $< .001$ |
| Hormone receptor status |  |  |
| Positive | 1 |  |
| Negative | 2.10 (1.80-2.46) | $< .001$ |
| HER status |  |  |
| Positive | 1 |  |
| Negative | 1.69 (1.13-2.51) | .01 |
| Unknown | 1.31 (0.89-1.93) | .16 |
| Tumor grade |  |  |
| Well differentiated | 1 |  |
| Moderately differentiated | 1.26 (0.91-1.73) | .17 |
| Poorly differentiated | 2.03 (1.47-2.78) | $< .001$ |
| Undifferentiated/anaplastic | 3.39 (1.65-6.97) | $< .001$ |
| Tumor size |  |  |
| $<20$ mm | 1 |  |
| $20-49$ mm | 2.1 (1.78-2.48) | $< .001$ |
| $\geq 50$ mm | 2.21 (1.53-3.18) | $< .001$ |
| No. positive nodes |  |  |
| 0 | 1 |  |
| 1 | 1.26 (0.94-1.69) | .12 |
| 2 | 1.76 (1.31-2.35) | $< .001$ |
| 3 | 1.77 (1.30-2.42) | $< .001$ |
| $\geq 4$ | 3.25 (2.48-4.26) | $< .001$ |
| Insurance |  |  |
| Private | 1 |  |
| Public | 1.27 (1.08-1.50) | .003 |
| Not insured | 1.28 (0.84-1.94) | .26 |

CD, Charlson Deyo; HER, human epidermal growth factor receptor status; RNI, regional nodal irradiation; WBI, whole-breast irradiation.

Bold denotes a statistical significance of $P < 0.05$. led to inadequately powered subgroup analyses and raised the question of whether a larger cohort was necessary to discern significant differences in OS by subset. Our retrospective analysis, based on a modern, matched cohort of more than 10,000 patients, externally validates the findings of the NCIC MA.20 randomized clinical trial in that no survival benefit was seen with the addition of RNI to WBI in this patient population.
This again may reflect limitations in our study population with regard to the effects of selection bias or the presence of high-risk clinical features that are not standardly reported or accessible via the NCDB. Conversely, it might indicate that some patients with early stage breast cancer may derive a marginal benefit from WBI + RNI.

As advancements in both surgical and nonsurgical therapies continue, the quest remains for treatments that have a low toxicity profile without compromising therapeutic benefit. Treatment of the axilla has been predominately surgical (ie, ALND), given its diagnostic and therapeutic properties. However, the significant morbidity of ALND, particularly lymphedema, has led to alternative methods of managing the axilla, such as sentinel lymph node dissection or axillary radiation therapy in select patients.22,23 Most of the women in our analysis fit what are considered to be acceptable criteria for sentinel lymph node dissection instead of ALND (T1-2 disease with 1-2 positive sentinel lymph nodes, not treated with neoadjuvant chemotherapy)7; thus, without a more nuanced characterization of the pathologic features of the patient population in our study, it is possible that they required neither ALND nor WBI + RNI. Indeed, a nuanced approach to electing for WBI + RNI is indicated for patients with 1 to 3 positive lymph nodes on the basis of published level I data.

Table 3  Multivariate subgroup analysis of the propensity score–matched cohort by pathologic nodal status

|                              | pN0 high risk |          | pN1-3 |          |
|------------------------------|--------------|----------|-------|----------|
|                              | HR (95% CI)  | P value  | HR (95% CI) | P value  |
| Radiation group              |              |          |       |          |
| WBI only                     | 1            |          | 0.98 (0.85-1.13) | .75       |
| RNI                          | 1.59 (0.96-2.67) | .07       | 1.7 (1.34-2.14) | < .001   |
| Age group, y                 |              |          |       |          |
| ≤70                          | 1            |          | 1.7 (1.34-2.14) | < .001   |
| >70                          | 1.95 (0.82-4.68) | .13       | < .001   |
| Race                         |              |          |       |          |
| White                        | 1            |          | 1.2 (0.99-1.44) | .06       |
| Black                        | 0.84 (0.45-1.58) | .59       | 1.7 (1.34-2.14) | < .001   |
| Other                        | 0.18 (0.01-2.96) | .23       | < .001   |
| CD comorbidity score         |              |          |       |          |
| 0                            | 1            |          | 1.33 (1.08-1.64) | .007      |
| 1                            | 0.85 (0.36-1.97) | .70       | 2.39 (1.68-3.4) | < .001   |
| 2                            | 1.42 (0.27-7.64) | .68       | < .001   |
| Hormone receptor status      |              |          |       |          |
| Positive                     | 1            |          | 1.68 (1.11-2.54) | .01       |
| Negative                     | 2.61 (1.39-4.90) | .003      | 2.03 (1.73-2.39) | < .001   |
| HER status                   |              |          |       |          |
| Positive                     | 1            |          | 1.68 (1.11-2.54) | .01       |
| Negative                     | 1.60 (0.42-6.12) | .49       | 1.35 (0.9-2.01) | .14       |
| Unknown                      | 0.88 (0.26-3.25) | .85       | < .001   |
| Tumor grade                  |              |          |       |          |
| Well differentiated           | NA           |          | 1.75 (1.48-2.07) | < .001   |
| Moderately differentiated    | 1            |          | 2.09 (1.77-2.46) | < .001   |
| Poorly differentiated         | 0.89 (0.42-1.89) | .76       | 2.21 (1.5-3.26) | < .001   |
| Undifferentiated/anaplastic  | NA           |          | 3.02 (1.41-6.44) | < .001   |
| Tumor size                   |              |          |       |          |
| <20 mm                       | NA           |          | 1.32 (1.12-1.57) | .001      |
| 20-49 mm                     | 1            |          | 1.23 (0.89-1.69) | .21       |
| ≥50 mm                       | 1.01 (0.44-2.75) | .84       | < .001   |
| Insurance                    |              |          |       |          |
| Private                      | 1            |          | 1.28 (0.83-1.99) | < .001   |
| Public                       | 0.83 (0.45-1.54) | .56       | < .001   |
| Not insured                  | 1.47 (0.40-5.42) | .56       | < .001   |
| Pathologic node              |              |          |       |          |
| N1                           | NA           |          | 1.75 (1.48-2.07) | < .001   |
| N2                           | NA           |          | 1.75 (1.48-2.07) | < .001   |
| N3                           | NA           |          | 2.99 (2.46-3.65) | < .001   |

CD, Charlson Deyo; CI, confidence interval; HER, human epidermal growth factor receptor status; HR, hazard ratio; NA, not applicable; RNI, regional node irradiation; WBI, whole-breast irradiation. Bold denotes a statistical significance of P < 0.05.

(HR, 1.59; 95% CI, 0.96-2.67; P = .07). This again may reflect limitations in our study population with regard to the effects of selection bias or the presence of high-risk clinical features that are not standardly reported or accessible via the NCDB. Conversely, it might indicate that some patients with early stage breast cancer may derive a marginal benefit from WBI + RNI.

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One of the primary advantages of the NCDB is the ability to query data collected from nearly three-quarters of patients with cancer within the United States. As is true for all retrospective studies, however, this study had several limitations. First and foremost, treatment selection bias is difficult to control outside of the setting of a randomized, double-blinded control trial. We used a propensity score–matched analysis to reduce this bias, but in return, we sacrificed half of the original cohort in our matched pairs. Another major limitation was the lack of information with regard to which locoregional nodal basins were included in the radiation fields. The NCDB coding for WBI+RNI is dichotomous, which could lead to variations in the WBI+RNI volumes that were treated in our patients. Notably, during the time period examined, the NCI OncoLink guidelines recommended that RNI include the internal mammary chain lymph nodes only if these nodes were clinically or pathologically involved. Otherwise, treatment of this lymph node basin was left to physician discretion. Similarly, patients who were coded as receiving only WBI may have had radiation treatment of the low axilla, such as through the use of high tangents, which would not have been captured in the NCDB and could minimize even a marginal benefit of WBI+RNI in this study. Lastly, we were unable to further delineate the chemotherapy agents that were used (or the number of cycles) or explore meaningful events such as DFS, long-term cardiopulmonary effects, or rates of lymphedema, all of which are of particular concern given the implications of adding WBI+RNI to multimodality therapy.

In conclusion, several clinical trials and reviews have attempted to summarize the clinical implications of using WBI+RNI in the management of early stage breast cancer. Our findings replicate the results of the NCIC MA.20 randomized clinical trial in a larger cohort of patients who were treated throughout the United States and suggest that WBI+RNI as opposed to WBI conferred no additional OS benefit at 5 years for women with either node-positive or high-risk node-negative breast cancer who received BCS followed by adjuvant systemic therapy. Longer follow-up is required, and thoughtful patient selection that is based on all existing data with regard to RNI is recommended.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
2. Early Breast Cancer Trials’ Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378:1707-1716.
3. Early Breast Cancer Trials’ Collaborative Group, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383:2127-2135.
4. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015;373:317-327.
5. Hennquin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys. 2013;86:860-866.
6. Whelan TJ, Olivotto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015;373:1878-1879.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast cancer. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed August 10, 2016.
8. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at: Proceedings of the 26th Annual SAS Users Group International Conference, 2001, Cary, NC. Available at: http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed October 22, 2016.
9. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337:949-955.
10. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med. 1997;337:956-962.
11. Ragaz J, Olivotto IA, Spinelli JI, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97:116-126.
12. Liu J, Mao K, Jiang S, et al. The role of postmastectomy radiotherapy in clinically node-positive, stage II-III breast cancer patients with pathological negative nodes after neoadjuvant chemotherapy: An analysis from the NCDB. Oncotarget. 2016;7:24848-24859.
13. Speers C, Pierce LJ. Postoperative radiotherapy after breast-conserving surgery for early-stage breast cancer: A review. JAMA Oncol. 2016;2:1075-1082.
14. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused guideline update. Pract Radiat Oncol. 2016;6:e219-e234.
15. Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol. 2004;22:4247-4254.
16. Tseng YD, Uno H, Hughes ME, et al. Biological subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in a large national database. Int J Radiat Oncol Biol Phys. 2015;93:622-630.
17. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: Regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63:1508-1513.
18. Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomized trial. Eur J Cancer. 1999;35:1320-1325.
19. Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management — A systematic review. J Clin Oncol. 2008;26:4981-4989.
20. Estournet SH, Nieweg OE, Olmos RA, Rutgers EJ, Kroon BB. Lymphatic drainage patterns from the breast. Ann Surg. 2004;239:232-237.
21. Avissar E. A tailored approach to regional nodal irradiation. Breast Cancer Res Treat. 2016;155:1-2.
22. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol*. 2014;32:3600-3606.

23. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303-1310.

24. Shah C, Khan A, Arthur D, et al. Regional nodal irradiation: Examining the clinical implications of randomized trials. *Am J Clin Oncol*. 2016;39:90-91.

25. Haffty BG, Mahmoud O. The evolution of regional nodal irradiation in breast cancer. *Breast J*. 2015;21:32-41.

26. Verma V, Beriwal S. Internal mammary node radiation in light of the EORTC 22922 and MA.20 Trials—What have we really learned? *JAMA Oncol*. 2016;2:992-993.

27. Verma V, Vicini F, Tendulkar RD, et al. Role of internal mammary node radiation as a part of modern breast cancer radiation therapy: A systematic review. *Int J Radiat Oncol Biol Phys*. 2016;95:617-631.

28. Poortmans PM, Coles C, Bernier J. Treatment of regional lymph nodes in breast cancer—evidence in favor of radiation therapy. *JAMA Oncol*. 2016;2:989-990.

29. Thorsen LB, Offersen BV, Dano H, et al. DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol*. 2016;34:314-320.