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ORIGINAL ARTICLE – BREAST ONCOLOGY

Trends in Regional Nodal Management of Breast Cancer Patients with Low Nodal Burden

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ABSTRACT

Background. American College of Surgeons Oncology Group Z0011 confirms the safety of omitting axillary lymph node dissection (ALND) and regional nodal irradiation (RNI) in breast cancer patients with one to two positive sentinel lymph nodes (SLNs), without compromising disease-free survival (DFS) and overall survival (OS). In contrast, the NCIC MA20 trial showed improved DFS in node-positive patients undergoing ALND and RNI. We sought to examine how these data have influenced the management of patients with limited nodal burden.

Methods. Using the National Cancer Database, patients diagnosed between 2010 and 2015 and who met the criteria for Z0011 were identified. Logistic regression was used to analyze factors associated with practice patterns. The Cox proportional hazards model was used to assess the association of ALND and RNI with OS.

Results. Omission of ALND in Z0011-eligible patients reached 89.2% in 2015. This Z0011-compliant group was more likely to undergo RNI compared with the non-compliant group (36.4% vs. 31.3%; $p < 0.05$), with RNI increasing to 43.8% by 2015. Factors associated with the use of RNI included later year of diagnosis [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.6–2.1], hormone receptor-negative tumor (OR 1.2, 95% CI 1.1–1.4), grade 3 tumor (OR 1.2, 95% CI 1.1–1.3), treatment at a non-academic site (OR 1.2, 95% CI 1.1–1.3) and two versus one positive SLN (OR 2.0, 95% CI 1.8–2.2). With 43 months median follow-up, RNI was not associated with improved OS.

Conclusion. Since the publication of Z0011, the omission of ALND has become widespread; however nearly half of these women now receive RNI. The optimal radiation therapy approach for this low nodal burden population warrants further study.

Management of the axilla continues to be a challenge for clinicians involved in the care of breast cancer patients. The morbidity of axillary lymph node dissection (ALND) is well known, and multiple studies over the past few decades have allowed us to safely eliminate this procedure for a significant number of patients. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial validated the use of sentinel lymph node biopsy (SLNBx) to avoid use of ALND for staging of pathologically node-negative patients.[1] The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial eliminated the need for ALND in women undergoing breast-conservation therapy who were found to have a low nodal tumor burden on SLNBx.[2] Management decisions have become more complex when considering adjuvant radiation therapy. Those who were spared ALND in the Z0011 trial proceeded to undergo adjuvant whole breast irradiation (WBI), with no plan for delivery of radiation to the axilla or other regional nodes, with excellent long-term local regional control and survival.[3] However, the recent publication of National Cancer Institute of Canada (NCIC) MA.20 and European Organisation for Research and Treatment of Cancer (EORTC) 22922 data has suggested that a decreased recurrence rate and improved disease-free

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survival (DFS) may be associated with regional nodal irradiation (RNI) for node-positive patients undergoing breast-conserving therapy.[2,4,5] However, it is important to note that in EORTC 22922, lymph node involvement was not subdivided by type of breast surgery, therefore it is impossible to infer information on how many EORTC 22922 patients would have been Z0011 eligible. In contrast, among the 1832 patients in the NCIC MA.20 trial, 1349 (73%) would have met Z0011 criteria, having one to two positive lymph nodes, no neoadjuvant systemic therapy, undergoing breast-conservation therapy, and planned adjuvant WBI.[4] This information poses the question of whether or not performing adjuvant RNI on patients with limited nodal burden is of benefit. Given the discordant conclusions reached by NICI MA.20/EORTC 22922 and ACOSOG Z0011, it is reasonable to suspect that national treatment patterns would be quite heterogeneous. The purpose of this study was twofold. First, to determine the national compliance to Z0011 criteria, and, second, to compare trends in the use of adjuvant RNI in patients with low nodal disease burden in order to determine how changes in surgical management may be influencing adjuvant radiation treatment decisions.

METHODS

Data for this study were sourced from the National Cancer Database (NCDB), a national oncologic data repository managed by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This study was exempt from the University of Texas MD Anderson Institutional Review Board given its retrospective nature and that no identifying information was collected from the NCDB file. From 1 January 2010 through 31 December 2015, data for women in the NCDB who met the inclusion criteria to be eligible for the study arm of the Z00011 trial were retrieved. This included a primary diagnosis of breast carcinoma, age $\geq$ 18 years, American Joint Committee on Cancer (AJCC) 7th edition clinical stage T1 or T2, clinical N0 and M0, treatment with lumpectomy and SLNBx, negative margins achieved after lumpectomy, and no more than two positive sentinel lymph nodes (SLNs). Exclusion criteria included patients with a history of prior cancer, neoadjuvant chemotherapy, a diagnosis of bilateral breast cancer or multicentric disease, treatment with mastectomy, pathologically node-negative patients, or patients with three or more positive SLNs (Fig. 1). Because axillary nodal procedure type is not reliable in the NCDB, and has been shown to underreport the frequency of SLNBx, we defined SLNBx and ALND according to the report of total nodes removed, in line with other studies.[6–8] If no more than five total nodes were removed, this was considered an SLNBx; if 10 or more total nodes were removed, this was considered an ALND. We excluded patients who had a total of six to nine lymph nodes removed.

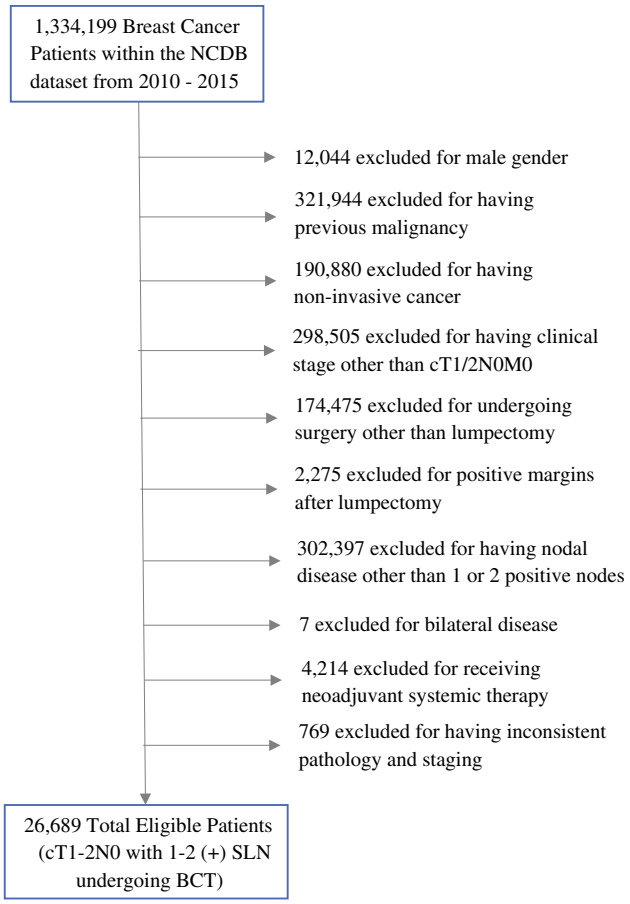

FIG. 1 Exclusion criteria. *NCDB* National Cancer Database, *SLNs* sentinel lymph nodes, *BCT* breast-conserving therapy

The cohort was then dichotomized based on whether they underwent completion ALND. A Z0011-compliant group was defined as patients who were found to have one or two positive SLNs but did not undergo any further axillary surgery, whereas a Z0011 non-compliant group was identified as patients who had one or two positive SLNs and then proceeded with a completion ALND. Radiation treatment patterns included adjuvant WBI alone, adjuvant WBI plus RNI, and no adjuvant radiation.

Statistical Analysis

The Chi square test was used to test associations between category variables, and the Wilcox rank-sum test or Kruskal–Wallis test was used to test differences for continuous variables between groups.[9] Logistic regression analysis was used to assess the multivariate relationship of

Z0011 compliance or radiation therapy pattern (WBI plus RNI vs. WBI only) with patient-, tumor-, and facility-level characteristics.[10] A logistic regression model was obtained by first including an initial set of candidate predictor variables with a p value < 0.05 in the univariate analysis. A stepwise elimination was then performed using 0.05 for the significance level of the Wald Chi square test for a variable to stay in the model. Once the list of variables to be used in the final model was selected, the functional form of each variable, and multicollinearity between the variables, was examined.

The distribution of overall survival (OS) was estimated using the Kaplan–Meier method.[11] The log-rank test was performed to test the difference in survival between groups classified by Z0011 compliance or radiation therapy pattern.[12] Regression analyses of survival data based on the Cox proportional hazards model were conducted on OS. OS time was defined as the time from diagnosis to the time of death or the time of last contact.[13] OS was compared between the Z0011-complaint versus non-compliant population, and the WBI versus WBI plus RNI radiation pattern recipients.

SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and S-Plus version 8.04 (TIBCO Software, Inc., Palo Alto, CA, USA) were used to carry out the analyses.

RESULTS

Of the 1,334,199 breast cancer patients within the NCDB dataset from 1 January 2010 to 31 December 2015, a total of 26,689 patients met our study criteria (Fig. 1). Patient demographics, tumor characteristics, and treatment facility specifics are presented in Table 1.

Between 2010 and 2015, 76.7% (20,479) of patients with one to two positive SLNs did not receive completion ALND. The percentage of node-positive patients who underwent SLNBx alone dramatically increased each year (Fig. 2), from 41.8% (n = 1442) in 2010, when the Z0011 data were initially presented, to 89.2% (n = 4753) in 2015. Of note, the most substantive increase from 42 to 70%, was seen within 1 year of the reporting of Z0011 results. In the multivariate setting, Z0011 compliance was significantly associated with patient's age, race, education level, hormone receptor (HR) status, and facility type and location ($p < 0.05$) (Table 2). For example, compared with patients who were aged 70 years or older, younger patients were more likely to receive ALND [odds ratio (OR) 1.5, 95% confidence interval (CI) 1.4–1.7, for patients $<$ 50 years vs. patients $\geq$ 70 years]; African American patients were more likely to receive ALND than Caucasian patients (OR 1.2, 95% CI 1.1–1.3); patients with lower education were more likely to receive ALND than those with higher

TABLE 1 Description of the cohort

	N	%
Year of diagnosis		
2010	3450	12.9
2011	4168	15.6
2012	4317	16.2
2013	4473	16.8
2014	4957	18.6
2015	5324	20.0
Age (years)		
< 40	763	2.9
< 50	4224	15.8
< 60	7703	28.9
< 70	8180	30.7
≥ 70	5819	21.8
Race		
Missing	223	0.8
Black	2714	10.2
Other	1129	4.2
White	22,623	84.8
Insurance status		
Missing	262	1.0
Public insurance	11,148	41.8
Private insurance	14,860	55.7
Not insured	419	1.6
Treatment facility type		
Missing	763	2.9
Academic/research	7953	29.8
Community cancer	5556	20.8
Comprehensive cancer	12,417	46.5
Clinical T stage		
cT1	20,001	74.9
cT2	6688	25.1
Missing	6	0.02
Pathologic T stage		
pT0	11	0.04
pT1	17,790	66.57
pT2	8866	33.2
pT3	6	0.02
pT4B	1	0.00
pTx	9	0.03
Overall clinical stage		
1	19,863	74.5
2	6826	25.6
Overall pathologic stage		
0	10	0.04
1	5792	21.7
2	20,887	78.3
Number of positive axillary nodes		
1	21,687	81.3

TABLE 1 continued

	N	%
2	5002	18.7
Number of axillary nodes removed		
≤ 5	20,479	76.7
≥ 10	6210	23.3
Hormone receptor		
Missing	48	0.2
Negative	2341	8.8
Positive	24,300	91.1
Triple negative		
Missing	352	1.3
No	24,568	92.1
Yes	1769	6.6

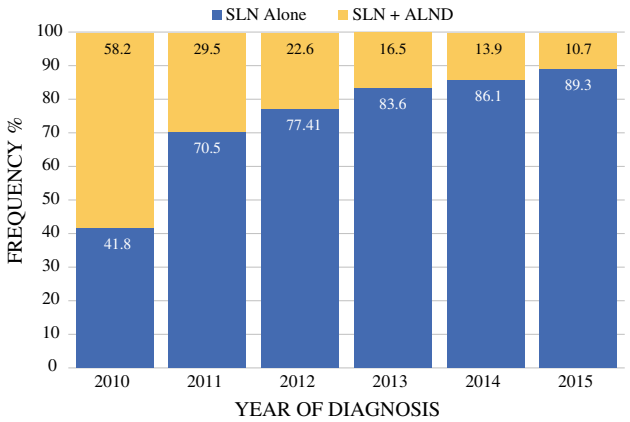

FIG. 2 Rates of completion ALND in women with one to two positive nodes. *ALND* axillary lymph node dissection, *SLN* sentinel lymph node

education (OR 1.2, 95% CI 1.1–1.3 for 29%+ vs. < 14%); and HR-negative patients, compared with HR-positive patients, were more likely to receive ALND (OR 1.6, 95% CI 1.4–1.8) (Table 2). Compared with patients who underwent surgery at an academic/research program, those who received their care at a community cancer program (OR 1.4, 95% CI 1.3–1.5) or comprehensive community cancer program (OR 1.2, 95% CI 1.1–1.3) were more likely to receive ALND, and compared with patients who received their surgery at cancer centers located in the Northeast area, those who underwent their surgery in the cancer centers located in the Midwest area (OR 1.3, 95% CI 1.2–1.5) were more likely to receive ALND (Table 2).

In regard to adjuvant radiation therapy, patients who had Z0011-compliant care were more likely to undergo WBI plus RNI (36.4% vs. 31.3%; $p < 0.05$), while 7.5% of the cohort did not undergo any adjuvant radiation therapy or their radiation status was unknown. In 2010, 29.6% of Z0011-compliant patients underwent adjuvant WBI plus RNI, gradually increasing to 43.8% in 2015 (Fig. 3). Within the Z0011-compliant population, we identified several factors that increased the likelihood of undergoing adjuvant WBI plus RNI (Table 3). Patients diagnosed in the later years of our study (OR 1.8, 95% CI 1.5–2.1, for 2015 vs. 2010), HR-negative patients (OR 1.2, 95% CI 1.1–1.4, compared with HR-positive patients), patients with higher grade tumors (OR 1.2, 95% CI 1.1–1.3, for grade 3 vs. grade 1), and those with two positive SLNs (OR 2.0, 95% CI 1.8–2.2, compared with only a single positive SLN) were more likely to receive extended radiation. Compared with patients who received their treatment at academic/research programs, those who received their care at community cancer programs or at comprehensive community cancer programs were more likely to receive WBI plus RNI (OR 1.2, 95% CI 1.1–1.3, and OR 1.2, 95% CI 1.1–1.3, respectively).

In the Z0011 non-compliant population, factors associated with receipt of RNI were similar to those seen in the Z0011-compliant group that underwent no ALND, with later year of diagnosis, higher tumor grade, and two versus one positive SLN all associated with a higher probability of RNI. Additionally, younger women were more likely to receive WBI plus RNI (OR 1.54, 95% CI 1.1–2.1, for age < 40 years compared with age > 70 years). However, unlike the Z0011-compliant cohort, in the group that underwent ALND, HR status and facility location were not associated with receipt of RNI (Table 3).

Five year OS in the Z0011-compliant population was found to be 93.5% (95% CI 92.9–94.2), and 93.7% in the Z0011 non-compliant population (95% CI 92.9–94.6%) (Fig. 4). With a median follow-up of 43.3 months, radiation therapy pattern was not significantly associated with OS (hazard ratio 1.1, 95% CI 1.0–1.3), after adjusting for patient's age, race, insurance, HR status, chemotherapy, hormone therapy, and Z0011 compliance status in the multivariate Cox PH model (Fig. 4).

DISCUSSION

Since the 2010 publication of Z0011, management of the axilla in patients with early-stage breast cancer has changed dramatically.[2] Historically, any evidence of metastasis to the axilla was an indication for ALND.[1] This aggressive treatment of the axilla placed patients at increased risk of complications, most commonly lymphedema.[14,15] In the Z0011 trial, patients with early disease, i.e. T1 or T2 invasive primary breast cancer, no palpable adenopathy, and one or two positive SLNs, were treated with lumpectomy, SLNBx alone, and adjuvant WBI.[2] Ten-year data from the Z0011 population published

TABLE 2 Association between patient- and facility-level factors and completion axillary lymph node dissection

Parameter		95% Wald confidence limits			*p*-value for comparison with the reference group	*p*-value for overall effect
		Odds ratio	Lower limit	Upper limit		
Age (years)	< 50	1.54	1.39	1.70	< 0.0001	< 0.0001
	< 60	1.29	1.18	1.42	< 0.0001	
	< 70	1.20	1.09	1.31	0.0001	
	≥ 70	Ref				
Year of diagnosis	2010	11.49	10.24	12.90	< 0.0001	< 0.0001
	2011	3.49	3.11	3.91	< 0.0001	
	2012	2.39	2.13	2.69	< 0.0001	
	2013	1.62	1.44	1.83	< 0.0001	
	2014	1.32	1.17	1.49	< 0.0001	
	2015	Ref				
Race	Black	1.21	1.09	1.34	0.0005	0.0006
	Other	1.17	1.00	1.38	0.054	
	White	Ref				
No high-school diploma, %	29+	1.19	1.07	1.32	0.0014	0.0008
	20–28.9	1.14	1.04	1.24	0.0036	
	14–19.9	1.13	1.04	1.22	0.0038	
	< 14	Ref				
Treatment facility type	Community cancer program	1.39	1.27	1.53	< 0.0001	< 0.0001
	Comprehensive community cancer program	1.23	1.14	1.33	< 0.0001	
	Academic/research program	Ref				
Facility location	Midwest	1.35	1.23	1.48	< 0.0001	< 0.0001
	South	1.06	0.97	1.16	0.22	
	West	1.01	0.90	1.12	0.89	
	Northwest	Ref				
Hormone receptor	Negative	1.60	1.44	1.77	< 0.0001	< 0.0001
	Positive	Ref				

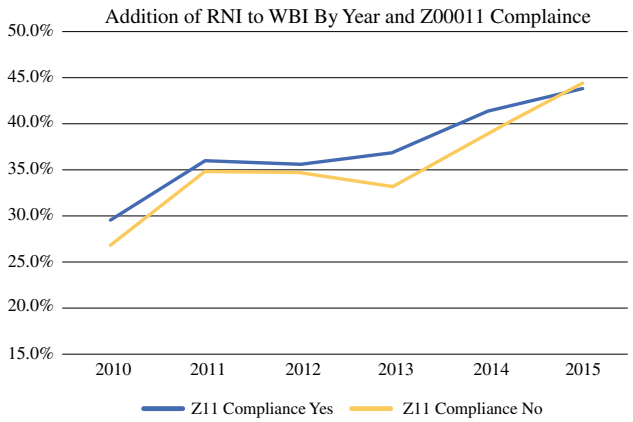

FIG. 3 Addition of RNI to WBI, by year and Z0011 compliance. *RNI* regional nodal irradiation, *WBI* whole breast irradiation

in 2017 demonstrated the OS for patients treated with SLNBx alone, despite having one or two positive SLNs, is non-inferior to patients treated with ALND.[16]

Surgeons are now able to safely omit ALND in select women. In order to investigate compliance among general surgeons treating breast cancer, Morrow et al. conducted a survey between 2013 and 2015.[17] That study found that of the 359 surgeons who responded to the survey, 49% would, inappropriately, perform an ALND on Z0011-appropriate patients if a single positive SLN was found. Further analysis of responding surgeons found that propensity to correctly omit ALND was directly related to higher breast cancer practice volume and participation in multidisciplinary tumor boards.[17] In contrast, our analysis demonstrated a rapid implementation of Z0011 recommendations into mainstream national practice, and, within 5 years of publication, approximately 90% of women who meet Z0011 eligibility did not receive completion ALND. Our findings are similar to and extend the findings of Ong

TABLE 3 Multivariate logistic regression models of radiation therapy pattern as a function of patient factors within the Z0011-compliant or non-compliant cohorts

Parameter		Z0011-compliant cohort					Z0011 non-compliant cohort				
		Odds ratio	95% Wald confidence limits		*p* value for comparison with the reference group	*p* value for overall effect	Odds ratio	95% Wald confidence limits		*p* value for comparison with the reference group	*p* value for overall effect
			Lower limit	Upper limit				Lower limit	Upper limit		
Age (years)	< 40	NA					Ref				0.028
	< 50						1.54	1.13	2.10	0.0062	
	< 60						1.31	1.07	1.59	0.0074	
	< 70						1.17	0.98	1.40	0.082	
	≥ 70						1.17	0.98	1.41	0.078	
Year of	diagnosis	2010	Ref					Ref			
	2011	1.29	1.11	1.49	0.0008	< 0.0001	1.45	1.23	1.71	< 0.0001	< 0.0001
	2012	1.28	1.10	1.47	0.0010		1.44	1.21	1.73	< 0.0001	
	2013	1.35	1.17	1.55	< 0.0001		1.35	1.10	1.64	0.0033	
	2014	1.63	1.42	1.87	< 0.0001		1.75	1.44	2.13	< 0.0001	
2015	1.83	1.60	2.10	< 0.0001		2.15	1.74	2.65	< 0.0001		
Hormone receptor status	Negative	1.20	1.06	1.37	0.0040	0.0040	NA				
	Positive	Ref									
Grade	1	Ref					Ref				
	2	1.11	1.03	1.20	0.0055	0.0038	1.06	0.91	1.24	0.45	0.027
	3	1.19	1.08	1.31	0.0004		1.26	1.06	1.49	0.0078	
	4	1.08	0.31	3.76	0.90		0.99	0.19	5.26	0.99	
Number of positive axillary nodes	1	Ref				< 0.0001	Ref				< 0.0001
	2	1.99	1.82	2.16	< 0.0001		1.84	1.63	2.07	< 0.0001	
Treatment facility type	Community cancer program	1.22	1.12	1.33	< 0.0001	< 0.0001	NA				
	Comprehensive community cancer program	1.21	1.13	1.30	< 0.0001						
	Academic/ research program	Ref									

NA not applicable

et al., who also reported on the widespread adoption of Z0011 into clinical practice.[6] The rapid implementation of Z0011 recommendations stands in stark contrast to the typical 17 years expected for evidence-based findings to reach clinical practice.[18]

Although we report that Z0011 compliance is high, in the subset still receiving completion ALND we found that this operation was more likely to be performed in women of lower socioeconomic status, African American women, those with lower education level, and care at a community facility. Previous publications have noted that African Americans have disproportionally less access to surgeons practicing standard of care breast cancer management.[8] These data are in line with many other studies of clinical practice that show racial and socioeconomic treatment disparities.[19] Additionally, it appears that more aggressive tumor subtypes have a propensity to influence the decision to perform an ALND in Z0011-appropriate patients, with

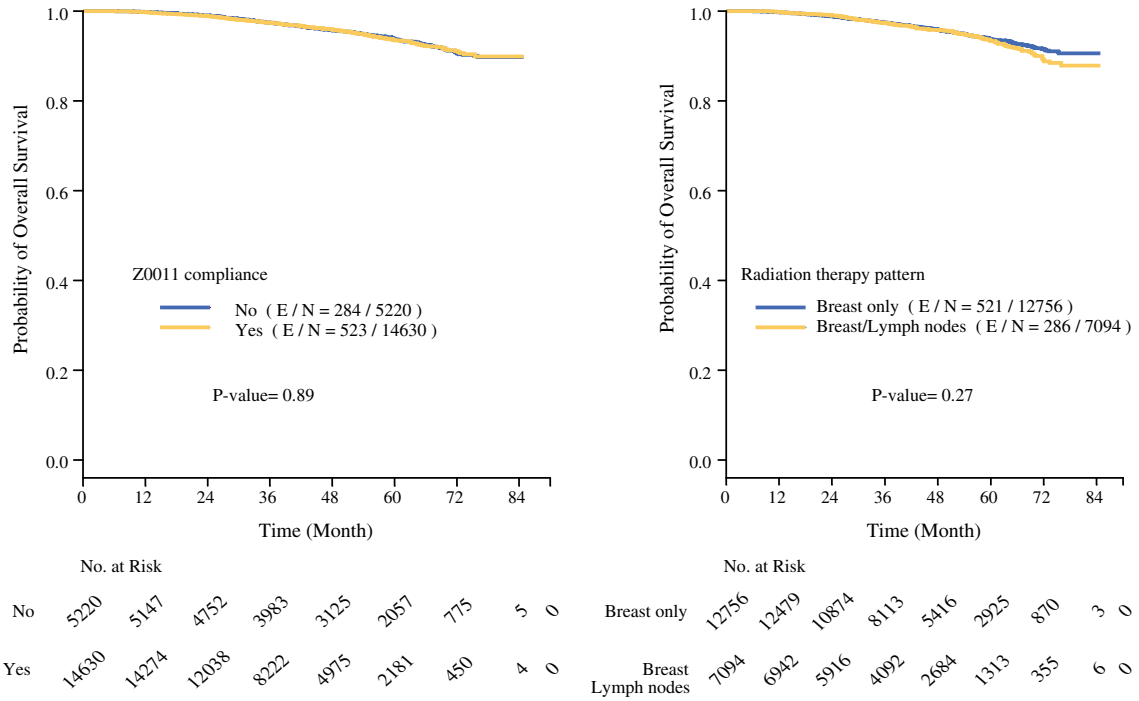

FIG. 4 Kaplan–Meier curve of survival, by Z0011 compliance or radiation therapy pattern. *E* events observed, *N* number at risk

younger age and HR negativity increasing the likelihood of completion ALND. These results are also similar to the findings of Ong et al., who similarly reported that age and tumor subtype appeared to influence the decision for completion ALND.[6] Although we cannot determine whether these disparities represent patient- or system-level barriers to compliance with Z0011, our findings highlight additional opportunity to improve on compliance with Z0011 practice guidelines.

A secondary goal of this study was to examine trends in regional nodal irradiation delivery to patients who did not undergo ALND. The original design of Z0011 required that the study population undergo adjuvant WBI without axillary tangents.[2] However, there has been speculation on the degree to which the non-blinded radiation oncologists delivered axillary tangents to the study population in the trial. A retrospective review of radiation fields delivered to Z0011 participants was performed and found that there was no significant difference in the therapy pattern between the two arms of the study.[20] However, it was found that almost half of the patients, equally in both arms, received radiation, including high tangents (cranial tangent border ≤ 2 cm from the humeral head), likely encompassing approximately 80% of the level I–II axilla.[21] An additional 19% of patients received RNI, including treatment to the level III axilla and supraclavicular fossa (but not necessarily the internal mammary chain), again evenly divided in both arms of the study. Since the extent of additional radiation fields appeared to have been balanced in the Z0011 trial, the impact of such treatment on local control and survival outcomes cannot be assessed.

Recent data from the prospective, randomized controlled trial NCIC MA.20 showed that the addition of RNI to WBI in women with node-positive and high-risk node-negative breast cancer is of benefit for regional recurrence and possible OS.[4] In the NCIC MA.20 trial, RNI included treatment of the internal mammary chain, level III axilla, and supraclavicular fossa. For patients with < 10 lymph nodes removed, or in whom > 3 lymph nodes were positive, an additional posterior field was used in the axilla in order to ensure adequate coverage of the level II–III axilla. At 10-year follow-up, the addition of RNI to WBI significantly increased locoregional DFS from 92.2 to 95.5%, as well as distant DFS from 82.4 to 86.3%. No difference was noted in OS between the two groups, however among the estrogen receptor (ER)-negative subgroup receiving WBI + RNI, there was a trend towards improved OS when compared with ER-negative patients undergoing WBI only (hazard ratio 0.69, 95% CI 0.47–1; $p = 0.05$). In the design of NCIC MA.20, any nodal positivity required completion ALND, therefore the results cannot be directly translated to the Z0011 population. However, of the 1832 patients in the NCIC MA.20 trial, 73% were found to only have one or two positive axillary lymph nodes, and were thus eligible for treatment under the Z0011 framework. Although there are certainly eligibility differences between the Z0011 and

NCIC MA.20 trials, there is significant overlap in the T1–2N0 ER-positive groups, which forces clinicians to have to choose which results to implement. These conflicting management strategies, as well as the ongoing challenges of reconciling data from these two local regional trials, are demonstrated in our findings, where we find a heterogeneity in the utilization of RNI in practice. Further clarity on the utility of RNI in women with limited nodal burden is expected from the NCIC MA.39/TAILOR RT trial. This ongoing phase III clinical trial is randomizing pT1/2, ER-positive, human epidermal growth factor receptor 2 (HER2)-negative patients with limited nodal burden and low Oncotype DX score to receive RNI or not. While the population accrued to TAILOR RT will not be identical to women enrolled in Z0011, the focus on the role of RNI specifically in women with limited nodal disease will be highly relevant to refine treatment for this sizeable population of women.

It is interesting to note that the increase in utilization of RNI preceded the full publication of the NCIC MA.20 trial results in 2015. We found two inflection points in the increase rates of extended field radiation. An initial increase is seen between 2010 and 2011, which corresponds to a year where a substantial jump was seen in compliance with the Z0011 findings, and prior to any data reporting from the NCIC MA.20 trial. This parallel suggests a reluctance to fully de-escalate the intensity of local regional management in node-positive patients. A second inflection point is noted starting in 2013, with a continuous increase in RNI rates through to the end of our study period. These years correspond to a relative plateau in compliance rates with Z0011, but follow the presentation of preliminary findings from NCIC MA.20 in 2011, and may represent the influence of reporting of these preliminary data. Given that the fully matured and vetted analysis of the NCIC MA.20 trial remained unavailable to the public until 2015, this pattern raises concern that, unlike prior decades, current ready access to information may be leading to premature adoption of clinical trial data into practice.

Finally, we found that OS was not impacted by type of radiation delivery or Z0011 compliance. In 2017, the 10-year follow-up survival data of the original Z0011 population demonstrated that after a median follow-up of 9.3 years, OS in the SLNBx-only population was non-inferior to the completion ALND population (86.3% vs. 83.6%).[16] Similarly, in the NCIC MA.20 trial, OS did not reach statistical significance.[4] While our cohort provides an opportunity to study the OS benefit from WBI + RNI, specifically in a Z0011-compliant population with limited nodal burden, median OS has not yet been reached in our cohort. In addition, interpretation of OS data from population databases is likely to be confounded by selection bias, and thus the impact on OS of adding RNI in a population that appears to otherwise be Z0011 compliant is best determined through prospective clinical trials.

This was a retrospective review of a large database, therefore there are limitations to the findings discussed. Most importantly, it is impossible to know for certain the exact reasoning behind clinicians' decisions to perform an ALND versus SLNBx alone, or what adjuvant radiation pattern to deliver. This could be due to tumor biology characteristics that are not captured in the NCDB, i.e. microscopic extracapsular extension of the involved SLNs, extranodal tumor emboli, or HER2 amplification. Additionally, within any retrospective database review, there is selection bias, which makes associations between RNI or Z0011 compliance on survival difficult to conclude. Despite this, our data provide information about the heterogeneity of 'real world' treatment patterns, likely reflecting the availability of multiple clinical studies with discordant recommendations, and suggests the need for further clinical trials that address this issue.

CONCLUSIONS

In our retrospective review of the NCDB from 2010 to 2015, we found that, nationally, practitioners quickly adopted the recommendations of Z0011 within just 1 year of its publication in 2010. The dramatic increase has plateaued to achieve a consistent rate of compliance of approximately 90%. However, as ALND rates are decreasing, RNI rates are increasing, and further study is required to clarify this relationship, as well as determine its benefit.

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