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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role of Axillary Lymph Node Dissection versus Sentinel Lymph Node Dissection in Breast Cancer Patients with Clinical N2b–N3c Disease Who Receive Adjuvant Radiotherapy

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ABSTRACT

Background. For breast cancer with advanced regional lymph node involvement, axillary lymph node dissection (ALND) remains the standard of care for staging and treating the axilla despite the presence of undissected lymph nodes. The benefit of ALND in this setting is unknown.

Objectives. We sought to describe national patterns of care of axillary surgery and its association with overall survival (OS) among women with cN2b–N3c breast cancer who receive adjuvant radiotherapy.

Patients and Methods. We identified female patients with cN2b–N3c breast cancer from 2012 to 2017 from the National Cancer Database. Clinical and demographic information were analyzed using Wilcoxon rank sum and χ^2 tests. Predictors of receipt of ALND and predictors of death were identified with multivariable logistic regression modeling. Inverse probability of treatment weighting was implemented to adjust for differences in treatment cohorts. The Kaplan–Meier method was used to evaluate OS.

Results. We identified 7167 patients. Of these, 922 (13%) received SLNB and 6254 (87%) received ALND; 7% were cN2b, 19% cN3a, 24% cN3b, 19% cN3c, and 31% cN3, not otherwise specified. Predictors of receipt of ALND were age 50–69 years [odds ratio (OR) 1.3, $p < 0.01$], cN3a (OR 7.6, $p < 0.01$), cN3b (OR 2.8, $p < 0.01$), and cN3c (OR 4.2, $p < 0.01$). Predictors of death included cN3c (OR 1.9, $p < 0.01$), age 70–90 years (OR 1.5, $p = 0.01$), and positive surgical margins (OR 1.5, $p < 0.01$). After cohort balancing, ALND was not associated with improved OS when compared with SLNB (HR 0.99, $p = 0.91$).

Conclusions. ALND in patients with advanced nodal disease was not associated with improved survival compared with SLNB for women who receive adjuvant radiotherapy.

Keywords Breast cancer · Lymph node dissection · Sentinel node biopsy · Adjuvant radiation · Radiation oncology

BACKGROUND

The extent of regional lymph node involvement remains one of the most important prognostic indicators in the management of invasive breast cancer and serves as a guide for adjuvant and neoadjuvant therapy decisions.[1,2] Management of clinically node-negative (cN0) breast cancer patients has evolved over the past three decades, with sentinel lymph node biopsy (SLNB) largely replacing routine axillary lymph node dissection (ALND) to stage the axilla in cN0 patients, reserving ALND for select patients with a positive SLNB.[3,4] In patients with known regional nodal metastases (cN+), ALND was historically the standard of care to reliably identify nodal metastases, stage the axilla, and maintain locoregional control.[5–7]

Compared with SLNB, ALND is associated with significant morbidity, including lymphedema, sensory loss, and worse patient-reported quality of life and arm function scores.[8]

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Given the morbidity of ALND, modern studies have aimed to reduce the need for axillary surgery, primarily in patients with cN0 breast cancer found to have pathologic positive nodes (pN+) on SLNB. Results from the ACOSOG Z0011 trial in 2010 found that completion ALND did not improve overall survival, disease-free survival, or locoregional recurrence rates among eligible women with cT1–T2 cN0 invasive breast cancer who underwent breast-conserving therapy (BCT) and were found to have one to two positive nodes on SLNB.[9,10] This trial supported the use of SLNB alone among eligible women, and 10-year results confirm the stability of these findings.[11] These findings have been replicated in subsequent trials, which showed that ALND can be avoided in a majority of Z0011-eligible patients with excellent regional control.[12] Similarly, the EORTC 10981/22023 AMAROS trial compared ALND with axillary radiotherapy in cT1–2 cN0 breast cancer after a positive SLNB and found no difference in 5-year axillary recurrence rate, though lymphedema was more frequent in the ALND arm (28% versus 14%).[13] The 10-year analysis confirms a low axillary recurrence rate after both axillary radiation and ALND with no difference in overall survival (OS), disease-free survival (DFS), and locoregional control.[14]

Currently, axillary lymph node dissection remains a requirement for most patients with cN+ and more advanced nodal disease (cN2–N3).[15,16] In the presence of clinically positive nodal metastases, ALND omission is only recommended if use of neoadjuvant therapy results in a pathologic complete response on subsequent SLNB, or in the case where all of the following criteria are met: only one to two lymph nodes are positive, cT1–T2, no preoperative chemotherapy, and radiotherapy is planned.[15,17] For patients with a greater burden of nodal metastatic disease (cN2–N3), uncertainties of the role and utility of ALND remain. Specifically, there is a paucity of data for the role of ALND in patients with nodal disease that is not dissected by conventional nodal surgery. Standard ALND includes axillary levels I and II, reserving level III (or infraclavicular) dissection only for cases with gross disease in level II and/or level III.[17] Surgical nodal evaluation excludes IM and supraclavicular nodes owing to substantial morbidity, and in light of similar concerns regarding morbidity, the dissection of level III is often omitted thus leaving gross disease in the axillary level III, IM, or supraclavicular basins (cN2b and cN3a–c disease). The goal of the current study is to assess outcomes of patients with advanced clinical nodal disease treated with ALND or SLNB followed by adjuvant radiotherapy.

PATIENTS AND METHODS

Data

The National Cancer Database (NCDB) is a hospital-level patient registry, formed as a joint project between the American College of Surgeons and the American Cancer Society, which includes deidentified patient clinical and sociodemographic data and captures around 70% of cancer diagnoses in the USA, collected from about 1500 US medical centers. As such, institutional approval and informed consent were not required for the use of this database, as it does not contain identifiable patient information. The use of NCDB data for research purposes is compliant with the Health Insurance Portability and Accountability Act and does not pose any risk to patient confidentiality. The dataset used in this analysis includes patients diagnosed from 2004 to 2020.

Patient Selection

Adult female patients aged 18–90 years diagnosed with clinical N2b–N3c invasive breast cancer from 2004 to 2020 were identified from the National Cancer Database (NCDB). Cohort selection with inclusion and exclusion criteria is shown in Fig. 1. The NCDB began to record the surgical method of axillary staging for women with breast cancer in 2012, which allowed the differentiation between SLNB and ALND. Patients treated after 2017 were excluded to allow maturation of follow-up time, yielding a cohort of patients diagnosed between 2012 and 2017 to be included for analysis. Patients with metastatic disease at diagnosis (clinical M1), missing or unknown axillary surgery data, missing or unknown clinical nodal stage, and patients who did not receive radiotherapy were excluded from the analysis. Patients with cN2a disease were excluded as this represents fixed/matted metastases in ipsilateral level I and II axillary nodes, which would be accessible by ALND. Patients receiving neoadjuvant chemotherapy, adjuvant chemotherapy, and no chemotherapy were included. Patients with less than 6 months of follow-up time were excluded to allow for sufficient follow-up. Additional clinical and sociodemographic data include vital status, year of diagnosis, age, clinical T stage, primary site surgery, grade, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, receipt of anti-estrogen therapy, receipt of chemotherapy, race, ethnicity, insurance type, household income, Charlson comorbidity score, type of and distance to treatment facility, community type, and geographic region. Hormone receptor status was defined as positive if the tumor was estrogen receptor positive and/or progesterone receptor positive, whereas it was defined as negative if both receptors were negative.

Statistical Analysis

Standard Wilcoxon rank sum and χ^2 testing were used to characterize clinical and sociodemographic differences between chemotherapy and combined modality groups.

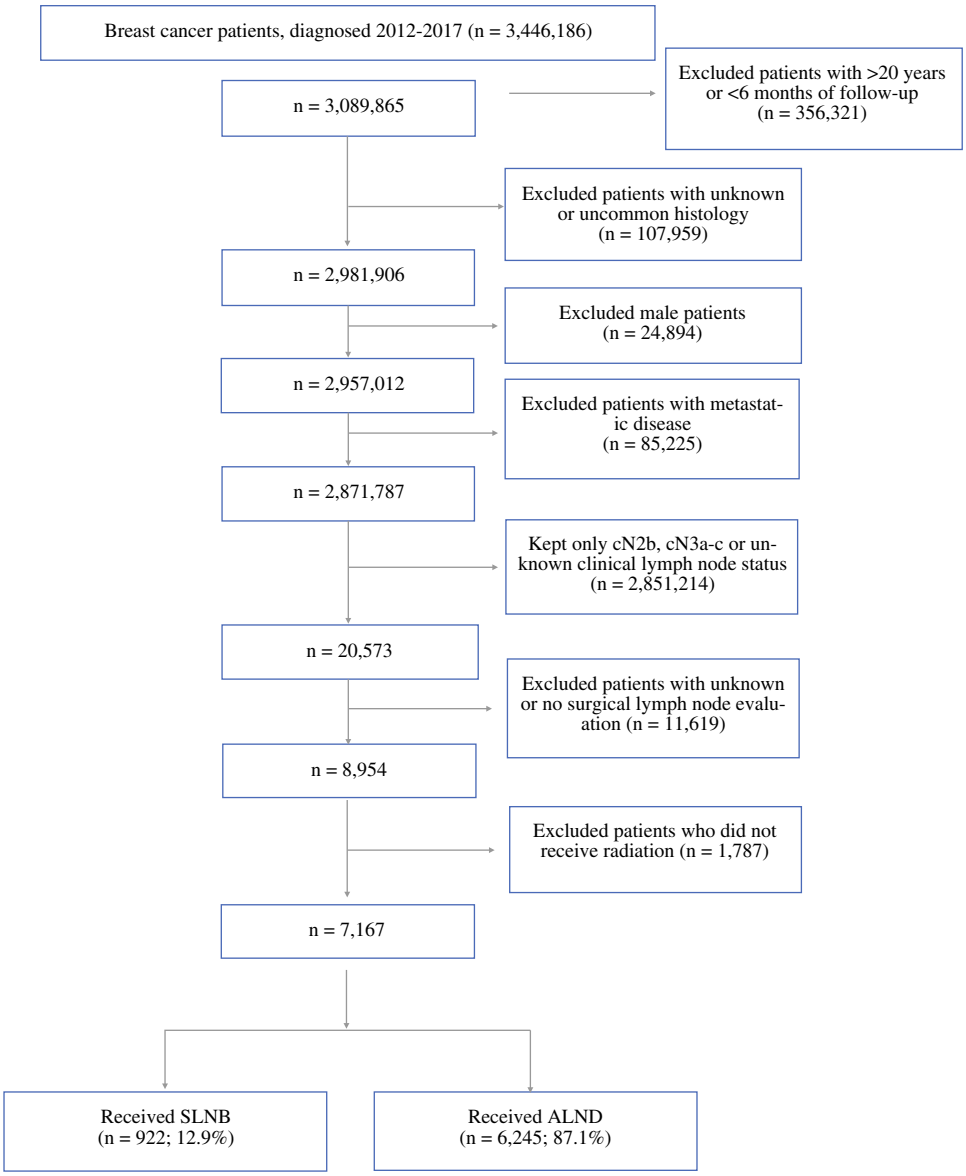

FIG. 1 Inclusion and exclusion criteria demonstrating the process of identifying our patient cohort using the National Cancer Database

Overall survival was defined as the time from diagnosis to death or censoring at last follow-up. Univariable and multivariable logistic regression models were used to identify predictors of receipt of ALND and factors associated with risk of death. Inverse probability of treatment weighting (IPTW) was implemented to adjust for underlying differences in clinical and sociodemographic factors, with IPTW selected over other balancing methods on the basis of diagnostic assessment of optimal balancing (Supplementary Fig. 1). Cox regression-based analyses were used to estimate the hazard ratio (HR) associated with type of axillary surgery after adjustment for known covariates, including age, race, Charlson comorbidity score, insurance type, facility type, education, receipt of chemotherapy, grade, primary site surgery, clinical T stage, surgical margin status, lymphovascular invasion (LVI), HER2 status, receipt of anti-estrogen therapy, and pathologic N stage. Kaplan–Meier estimators and log-rank tests were used to examine unadjusted and adjusted differences in survival between groups. The significance threshold of $p < 0.05$ was set for all analyses. STATA-IC-18 was used for all statistical analyses.[18]

RESULTS

Of the 3,089,865 breast cancer patients in the database, the final cohort consisted of 7167 patients with cN2b–N3c disease fitting our inclusion criteria, of which 922 (13%) received SLNB and 6245 (87%) received ALND (Table 1). The median age of the cohort was 54 years, and median follow-up was 4.4 years.

The proportion of patients with advanced nodal disease receiving ALND fell modestly during the study period,

starting with 93% of patients in 2012 and steadily declining to 81% of patients by 2017. There was a corresponding rise in the proportion of patients receiving SLNB, with 7% of patients in 2012 and increasing to 19% in 2017. The Kendall's tau correlation coefficient between proportion of patients receiving SLNB over time was found to be $\tau = 1.0$, the Kendall's score was 15, indicating a positive trend over time ($p < 0.01$). These results can be seen in Fig. 2.

The results of univariable and multivariable analysis for predictors of ALND as the surgical approach to the axilla are shown in Table 2. Factors predictive of receipt of ALND include cN3a [odds ratio (OR) 7.6, 95% confidence interval (95% CI) 5.4–11, $p < 0.01$], cN3b (OR 2.8, 95% CI 2.1–3.7, $p < 0.01$), cN3c (OR 4.2, 95% CI 3.1–5.7, $p < 0.01$), and cN3, not otherwise specified (NOS; OR 4.2, 95% CI 3.2–5.5, $p < 0.01$) compared with cN2b, receipt of adjuvant chemotherapy (OR 1.5, 95% CI 1.1–2.0, $p = 0.03$) compared with no chemotherapy, receipt of mastectomy (OR 3.3, 95% CI 2.8–4.0, $p < 0.01$) compared with lumpectomy, age 50–69 years (OR 1.3, 95% CI 1.1–1.6, $p < 0.01$) and age 70–90 years (OR 1.7, 95% CI 1.2–2.5, $p < 0.01$) compared with age < 50 years, and Charlson comorbidity score ≥ 1 (OR 1.4, 95% CI 1.1–1.8, $p = 0.02$) compared with Charlson comorbidity score of 0. Factors associated with receipt of SLNB include cT2 (OR 0.09, 95% CI 0.01–0.72, $p = 0.02$) and cT3 (OR 0.11, 0.01–0.87, $p = 0.04$) compared with clinical in situ disease (cTis) and hormone receptor negative tumors (OR 0.76, 95% CI 0.63–0.93, $p < 0.01$) compared with hormone receptor positive tumors.

Factors significantly associated with increased risk for death are shown in Table 3. These included cN3c (OR 1.9, 95% CI 1.4–2.6, $p < 0.01$) and cN3, NOS (OR 1.6, 95% CI 1.1–2.0, $p = 0.02$) compared with cN2b, undergoing mastectomy (OR 1.3, 95% CI 1.1–1.5, $p = 0.01$) instead of lumpectomy, age 70–90 (OR 1.5, 95% CI 1.1–1.9, $p < 0.01$) compared with age < 50 years, Black race (OR 1.2, 95% CI 1.02–1.4, $p = 0.03$), grade 3 disease (OR 1.7, 95% CI 1.1–2.5, $p = 0.04$) compared with grade 1, positive surgical margins (OR 1.5, 95% CI 1.2–2.0, $p < 0.01$), not receiving anti-estrogen therapy (OR 1.8, 95% CI 1.4–2.4, $p < 0.01$), and Charlson comorbidity score ≥ 1 (OR 1.3, 95% CI 1.7–3.2, $p < 0.01$) compared with a score of 0. Factors significantly associated with a decreased risk of death include treatment at an academic/research program (OR 0.73, 95% CI 0.56–0.96, $p = 0.02$) compared with treatment at a community cancer program, and HER2-positive disease (OR 0.51, 95% CI 0.43–0.61, $p < 0.01$) compared with HER2-negative disease.

After adjustment for known covariates in the IPTW model, including pathologic nodal stage, surgery type for the primary breast tumor, receipt of anti-estrogen and chemotherapy, age, clinical T stage, margin status, and grade, ALND was not associated with an improved overall survival (OS) compared with SLNB alone, with a 5-year OS of 71.3% versus 69.6%%, respectively [hazard ratio (HR) 0.99, $p = 0.90$]. Survival curves are shown in Fig. 3.

When isolating patients who received neoadjuvant chemotherapy prior to surgery, there was no difference in the 5-year OS by nodal staging technique (ALND versus SLNB) for those with a nodal pathologic complete response (ypN0), those with residual nodal disease (ypN1-3), or in the overall cohort (ypN0-3). Results for the overall cohort and each subgroup are shown in Table 4.

DISCUSSION

In this study, we report the practice patterns and long-term outcomes of 7167 patients with breast cancer with advanced nodal disease treated with SLNB or ALND in the USA. We sought to evaluate whether the extent of axillary surgery was associated with OS in a specific subset of patients who are at a higher risk of local, regional, and distant recurrence. We did not observe a statistically significant change in OS with the receipt of ALND compared with SLNB among women with advanced clinical nodal stages who go on to receive adjuvant radiotherapy. Between 2012 and 2017, the proportion of patients in this cohort receiving ALND decreased, while the proportion of patients receiving SLNB increased, as seen in Fig. 2.

Modern trials addressing management of the axilla have primarily evaluated less extensive axillary surgery for clinically node-negative breast cancer. Both the EORTC 10981/22023 AMAROS and ACOSOG Z0011 trials demonstrated that around 30% of patients with one to two positive sentinel lymph nodes will have additional positive nodes. Despite the potential residual nodal burden, these cN0 patients did not appear to derive any benefit in locoregional control from completion ALND.[9,13] In comparison with these trials, the present study seeks to evaluate the benefit of ALND in a population of patients in whom residual nodal disease is guaranteed given the presence of involved lymph nodes that are not routinely addressed by axillary surgery. In our cohort of patients who were pN0, whether or not they received neoadjuvant chemotherapy, there was no difference in overall survival between nodal surgery techniques. This group of patients would not have been eligible for the above-mentioned trials.

Prospective data on the impact of axillary surgery extent on the outcomes of patients with more advanced nodal disease, including those with higher clinical nodal stages or more positive lymph nodes, are scarce. Data are primarily limited to the results of retrospective studies. One study by Bonneau et al. aimed to determine the effects of ALND versus SLNB on the survival of patients with three or more metastatic lymph nodes using the US Surveillance, Epidemiology, and End Results (SEER) database. In this study,

TABLE 1 Patient demographics and clinical characteristics. Patients were identified in the National Cancer Database. All patients had undissected, clinical N2b–N3c disease, were treated with adjuvant radiotherapy, and were diagnosed between 2012 and 2017

Patient demographics and clinical characteristics					
	SLNB ($n = 922$)		ALND ($n = 6,245$)		
	No	%	No	%	p*
Age (years)					< 0.001
< 50	424	46	2166	35	
50–69	427	46	3276	52	
70–90	71	8	803	13	
Clinical T stage					< 0.001
cT1	112	12	815	13	
cT2	473	51	2314	37	
cT3	217	24	1528	24	
cT4	109	12	1363	22	
Unknown	6	1	135	2	
Clinical N stage					< 0.001
cN2b	187	20	346	6	
cN3a	72	8	1255	20	
cN3b	282	31	1409	23	
cN3c	141	15	1232	20	
cN3, NOS	240	26	2003	32	
Pathologic T stage					< 0.001
pT0	381	43	1565	26	
pT1	298	34	1677	28	
pT2	145	16	1551	26	
pT3	50	6	854	14	
pT4	12	1	390	6	
Pathologic N stage					< 0.001
pN0	615	69	1671	28	
pN1	185	21	1277	21	
pN2	37	4	1049	17	
pN3	48	5	2054	34	
Primary site surgery					< 0.001
Lumpectomy	391	44	1222	20	
Mastectomy	499	56	4780	80	
Grade					< 0.001
1	21	2	209	3	
2	216	23	1768	28	
3	631	68	3706	59	
HR Status					< 0.001
HR positive	490	53	3930	63	
HR negative	427	47	2285	37	
Unknown	5	0.5	30	0.5	
HER2 receptor status					0.056
Positive	291	32	1748	28	
Negative	625	68	4435	71	
Unknown	6	0.6	62	1	
Hormone therapy					< 0.001
Did not receive	458	50	2499	40	
Received	457	50	3668	59	
Chemotherapy					< 0.001
None/unknown	153	17	961	15	

Table 1 (continued)

Patient demographics and clinical characteristics	SLNB ($n = 922$)		ALND ($n = 6,245$)		
	No	%	No	%	p*
Neoadjuvant	617	67	3583	57	
Adjuvant	152	16	1701	27	
Race					0.64
White	676	73	4597	74	
Black	172	19	1198	19	
Asian	49	5	274	4	
Other/unknown	25	3	176	3	
Ethnicity					0.76
Non-Hispanic white	602	65	4124	66	
Non-Hispanic Black	170	18	1186	19	
Hispanic	76	8	485	8	
Other	74	8	450	7	
Insurance status					< 0.001
Privately insured	619	67	3608	58	
No insurance	31	3	237	4	
Medicaid	102	11	753	12	
Medicare	165	18	1544	25	
Income					0.14
< US$40,227	141	18	962	18	
US$40,227–50,353	149	19	1177	22	
US$50,354–63,332	185	23	1281	24	
US$63,333 +	320	40	1981	37	
Residence					0.25
Metropolitan	786	85	5180	83	
Urban	101	11	815	13	
Rural	12	1	106	2	
Distance from treatment facility					0.053
< 50 miles	738	92	4931	90	
≥ 50 miles	61	8	535	10	
Facility Type					< 0.001
Community cancer program	39	4	385	6	
Comprehensive community cancer prog	296	32	2151	34	
Academic/research program	249	27	1840	29	
Integrated network cancer program	163	18	1057	17	
Geographical region					0.6
Northeast	121	16	967	18	
South	311	42	2173	40	
Midwest	172	23	1300	24	
West	143	19	993	18	
Charlson Comorbidity Score					< 0.001
0	835	91	5316	85	
1+	87	9	929	15	

SLNB sentinel lymph node biopsy, *ALND* axillary lymph node dissection

HR hormone receptor, *HER2* human epidermal growth factor receptor 2

*Based on χ^2-testing

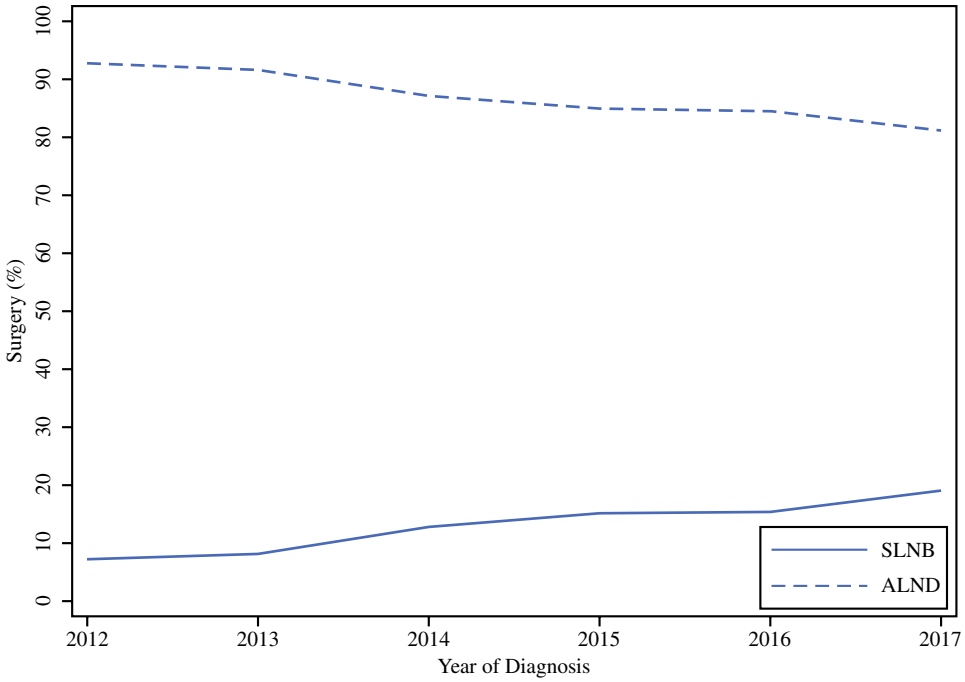

FIG. 2 Temporal patterns in the utilization SLNB versus ALND in breast cancer patients with undissected nodal disease. Patients were diagnosed between 2012 and 2017. Kendall's tau correlation coefficient indicates a positive trend of SLNB over time ($p < 0.01$). *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

the authors concluded that patients with cT1–T2 invasive breast cancer and at least three metastatic lymph nodes did not experience disease-specific or overall survival benefit from ALND after SLNB.[19] Unfortunately, there are no ongoing prospective studies addressing the role of ALND patients with very advanced clinical nodal burden with undissected disease. We did not find any survival difference between ALND and SLNB in our cohort with advanced nodal disease, even when isolating the highest risk groups. For patients with nodal disease that cannot be resected, our study suggests that there is no survival benefit to completion ALND when these patients go on to receive adjuvant radiotherapy.

Neoadjuvant chemotherapy can have a significant impact on how the axilla is managed in the setting of a nodal pathologic complete response (pCR). While pCR details are not specifically captured by the NCDB, there were 2286 total patients who were pN0, 615 (69%) of the SLNB and 1671 (28%) of the ALND cohorts. To address the issue of potentially selecting a more favorable group to undergo SLNB and obscuring the benefit of ALND, we repeated the analysis for patients that were pN0 after neoadjuvant chemotherapy and compared it with those that were pN1–N3. In both cases the survival plots remained similar between techniques, confirming that ALND was not associated with an improved overall survival compared with SLNB alone in either scenario. Additionally, pathologic nodal stage was included as a covariate in the IPTW model, which can account for any confounding.

One strength of this study is limiting cases to those diagnosed starting in 2012, the time at which the type of axillary surgery (SLNB or ALND) started being reported in the NCDB. By restricting the year of diagnosis to 2012, we were able to identify the specific axillary surgery type, though this did limit the follow-up time. Prior studies relied on the number of lymph nodes removed as surrogates for the extent of axillary surgery, typically constraining SLNB to five or fewer lymph nodes and ALND to nine to ten or more, while excluding patients with lymph node counts that fall in between.[20,21] In comparison with a similar study by Park et al., the present study differs in several aspects. First, as mentioned, we reduce uncertainty of treatment received by identifying the specific axillary surgery type. This also allows us to include patients who had six to nine lymph nodes removed at surgery, as these patients were excluded from the above-mentioned analysis. Second, we excluded patients with cN2a disease, rather than including all cN2-3 patients, as these patients have disease that can be resected by means of ALND. Lastly, our methodology differs in employing IPTW for the adjustment of known covariates in our survival analysis. This study offers additional noteworthy strengths, including a considerable patient sample size, a diverse population of patients in a real-world setting, and the utilization of multiple distinct clinical variables.

There are limitations to this hospital-level database study that warrant addressing. As with all retrospective studies, the data is subject to certain biases, and retrospective evaluation of treatment can be confounded by indication as the selected patients are not randomized to treatment groups. Although cohorts were matched on the basis of available sociodemographic and clinical factors, we were unable to balance on the basis of all clinically relevant factors that

TABLE 2 Univariable and multivariable analysis of predictors of receipt of axillary lymph node dissection, with odds ratios > 1 predictive of receipt of an axillary lymph node dissection and < 1 predictive of receipt of a sentinel lymph node biopsy

Predictors of receipt of axillary lymph node dissection						
	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Clinical T stage						
cTis	–	–	–	–	–	–
cT1	0.26	0.10–0.80	0.03	0.15	0.02–1.2	0.07
cT2	0.18	0.10–0.60	< 0.01	0.09	0.01–0.72	0.02
cT3	0.25	0.10–0.80	0.02	0.11	0.01–0.87	0.04
cT4	0.45	0.10–1.5	0.18	0.18	0.02–1.4	0.10
cTx	0.80	0.20–3.3	0.77	0.26	0.03–2.5	0.24
Clinical nodal stage						
cN2b	–	–	–	–	–	–
cN3a	9.4	7.0–13	< 0.01	7.6	5.4–11	< 0.01
cN3b	2.7	2.2–3.4	< 0.01	2.8	2.1–3.7	< 0.01
cN3c	4.7	3.7–6.1	< 0.01	4.2	3.1–5.7	< 0.01
cN3, NOS	4.5	3.6–5.6	< 0.01	4.2	3.2–5.5	< 0.01
Surgery						
Lumpectomy	–	–	–	–	–	–
Mastectomy	3.1	2.6–3.5	< 0.01	3.3	2.8–4.0	< 0.01
Chemotherapy						
None or unknown	–	–	–	–	–	–
Neoadjuvant	0.92	0.76–1.1	0.42	0.87	0.65–1.2	0.37
Adjuvant	1.8	1.4–2.3	< 0.01	1.5	1.1–2.0	0.03
Age (years)						
< 50	–	–	–	–	–	–
50–69	1.5	1.3–1.7	< 0.01	1.3	1.1–1.6	< 0.01
70–90	2.2	1.7–2.9	< 0.01	1.7	1.2–2.5	< 0.01
Race						
White	–	–	–	–	–	–
Black	1.02	0.90–1.2	0.79	1.1	0.86–1.3	0.51
Asian	0.80	0.60–1.1	0.22	1.02	0.67–1.5	0.94
Other/unknown	1.04	0.70–1.6	0.16	1.2	0.69–2.2	0.47
Grade						
1	–	–	–	–	–	–
2	0.80	0.50–1.3	0.42	0.88	0.51–1.5	0.66
3	0.60	0.40–0.9	0.02	0.79	0.46–1.4	0.41
Insurance status						
Privately insured	–	–	–	–	–	–
Uninsured	1.3	0.90–1.9	0.17	1.6	0.96–2.8	0.07
Medicaid	1.3	1.01–1.6	0.04	1.2	0.92–1.6	0.17
Medicare	1.6	1.3–1.9	< 0.01	1.1	0.88–1.4	0.35
HER2 receptor status						
Negative	–	–	–	–	–	–
Positive	0.85	0.70–0.98	0.03	0.87	0.71–1.1	0.21
Hormone receptor status						
Positive	–	–	–	–	–	–
Negative	0.67	0.60–0.80	< 0.01	0.76	0.63–0.93	< 0.01
Facility type						
Community cancer program	–	–	–	–	–	–
Comprehensive community cancer program	0.74	0.50–1.05	0.09	0.89	0.60–1.3	0.55
Academic/research program	0.75	0.50–1.1	0.11	0.87	0.58–1.3	0.49

Table 2 (continued)

Predictors of receipt of axillary lymph node dissection						
	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Integrated network cancer program	0.66	0.45–0.95	0.03	0.83	0.55–1.2	0.37
Geographical region						
Northeast	–	–	–	–	–	–
South	0.87	0.7–1.1	0.24	0.82	0.64–1.1	0.13
Midwest	0.95	0.7–1.2	0.66	0.94	0.71–1.2	0.62
West	0.87	0.7–1.1	0.29	1.02	0.76–1.4	0.90
Charlson comorbidity score						
0	–	–	–	–	–	–
1+	1.7	1.3–2.1	< 0.01	1.4	1.1–1.8	0.02

NOS Not otherwise specified, *HER2* Human epidermal growth factor receptor 2

may have guided risk categorization and treatment selection if they were not recorded within the database. Women who underwent ALND may have represented a healthier population, may have been perceived to have higher-risk disease, and may have received more aggressive therapy overall. The NCDB does not report on the reason for choosing one method of axillary clearance over another. Receipt of chemotherapy and its sequence (neoadjuvant or adjuvant) was included as a clinical variable, however, the NCDB does not capture information on the number of cycles given, the specific chemotherapy agents, doses, or whether patients completed their prescribed course. Additionally, the NCDB does not include data on local or distant relapses, second line therapy, acute or late treatment toxicities, disease-specific survival, or cause-specific mortality. The NCDB was chosen, as opposed to the Surveillance, Epidemiology, and End Results (SEER) database, to capture a larger and more diverse patient population, as SEER is limited to Medicare patients.

CONCLUSIONS

Management of the axilla in patients with breast cancer has undergone significant advancements over the past several decades. Randomized clinical trials have established that SLNB without completion ALND is sufficient for women with clinically node-negative disease. However, it is unclear whether ALND is necessary among patients who present with advanced nodal disease that will never be surgically addressed but do receive radiotherapy. Our findings suggest that the receipt of ALND is not associated with improved OS compared with receipt of a SLNB in women with cN2b–N3c breast cancer who receive adjuvant radiotherapy. In the absence of prospective randomized data, further multi-institutional analysis is warranted to establish the best surgical practices in the treatment of breast cancer with advanced clinical nodal disease.

TABLE 3 Univariable and multivariable analysis of predictors of likelihood of death, with odds ratios > 1 predictive of death

Predictors associated with risk of death after treatment						
	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Clinical T stage						
cTis	–	–	–	–	–	–
cT1	0.90	0.50–1.5	0.63	0.47	0.22–1.0	0.051
cT2	0.90	0.60–1.5	0.80	0.52	0.25–1.1	0.08
cT3	1.3	0.80–2.1	0.32	0.66	0.31–1.4	0.30
cT4	1.8	1.1–3.0	0.02	0.82	0.39–1.7	0.60
cTx	0.90	0.50–1.7	0.70	0.45	0.18–1.1	0.09
Clinical nodal stage						
cN2b	–	–	–	–	–	–
cN3a	1.9	1.5–2.4	< 0.01	1.4	0.98–1.9	0.06
cN3b	1.3	1.03–1.7	0.03	1.2	0.86–1.6	0.30
cN3c	2.0	1.6–2.5	< 0.01	1.9	1.4–2.6	< 0.01
cN3, NOS	1.7	1.3–2.1	< 0.01	1.5	1.1–2.0	0.02
Pathologic T stage						
pT0	–	–	–	–	–	–
pT1	1.8	1.6–2.1	< 0.01	1.4	1.1–1.7	< 0.01
pT2	2.4	2.0–2.8	< 0.01	1.4	1.1–1.8	< 0.01
pT3	3.5	3.0–4.2	< 0.01	1.6	1.2–2.1	< 0.01
pT4	5.8	4.6–7.3	< 0.01	1.9	1.4–2.8	< 0.01
Pathologic nodal stage						
pN0	–	–	–	–	–	–
pN1	1.9	1.6–2.3	< 0.01	1.7	1.4–2.2	< 0.01
pN2	3.1	2.6–3.6	< 0.01	2.5	2.0–3.2	< 0.01
pN3	3.3	2.9–3.8	< 0.01	2.7	2.2–3.5	< 0.01
Axillary surgery						
SLNB	–	–	–	–	–	–
ALND	2.1	1.7–2.5	< 0.01	1.2	0.94–1.5	0.14
Surgery						
Lumpectomy	–	–	–	–	–	–
Mastectomy	1.6	1.4–1.8	< 0.01	1.3	1.1–1.5	0.01
Age (years)						
<50	–	–	–	–	–	–
50–69	1.3	1.2–1.5	< 0.01	1.1	0.96–1.3	0.15
70–90	2.4	2.0–2.8	< 0.01	1.5	1.1–1.9	0.01
Race						
White	–	–	–	–	–	–
Black	1.4	1.2–1.5	< 0.01	1.2	1.02–1.4	0.03
Asian	0.80	0.60–1.03	0.08	0.96	0.7–1.3	0.80
Other/unknown	0.56	0.40–0.80	<0.01	0.53	0.33–0.85	0.01
Grade						
1	–	–	–	–	–	–
2	1.1	0.80–1.4	0.78	1.2	0.80–1.7	0.39
3	1.4	1.1–1.9	0.03	1.7	1.1–2.5	0.01
Insurance status						
Privately insured	–	–	–	–	–	–
Uninsured	1.3	0.90–1.7	0.09	1.1	0.77–1.6	0.57
Medicaid	1.2	1.04–1.4	0.01	1.2	0.93–1.4	0.20
Medicare	1.6	1.5–1.8	< 0.01	1.1	0.87–1.3	0.60

Table 3 (continued)

Predictors associated with risk of death after treatment						
	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Facility type						
Community cancer program	–	–	–	–	–	–
Comprehensive community cancer program	0.90	0.70–1.1	0.30	1.0	0.76–1.3	0.95
Academic/research program	0.64	0.50–0.8	< 0.01	0.73	0.56–0.96	0.02
Integrated network cancer program	0.79	0.60–1.01	0.06	0.83	0.62–1.1	0.21
Geographical region						
Northeast	–	–	–	–	–	–
South	1.2	0.90–1.4	0.08	1.0	0.86–1.3	0.64
Midwest	1.3	1.1–1.6	< 0.01	1.2	0.96–1.5	0.11
West	1.1	0.90–1.3	0.35	1.1	0.87–1.4	0.47
Distance to facility						
≤ 50 miles	–	–	–	–	–	–
> 50 miles	0.92	0.80–1.1	0.42	1.1	0.87–1.4	0.44
HER2 receptor status						
Negative	–	–	–	–	–	–
Positive	0.43	0.40–0.50	< 0.01	0.51	0.43–0.61	< 0.01
Margin Status						
Negative	–	–	–	–	–	–
Positive	2.1	1.7–2.5	< 0.01	1.5	1.2–2.0	< 0.01
Hormone receptor status						
Positive	–	–	–	–	–	–
Negative	1.6	1.5–1.8	< 0.01	1.3	1.01–1.7	0.045
Anti-estrogen therapy						
Received	–	–	–	–	–	–
Did not receive	1.7	1.5–1.8	< 0.01	1.8	1.4–2.4	< 0.01
Chemotherapy						
Received chemotherapy	–	–	–	–	–	–
Did not receive chemotherapy	3.1	2.4–4.0	< 0.01	2.3	1.7–3.2	< 0.01
Charlson comorbidity score						
0	–	–	–	–	–	–
1+	1.7	1.3–2.1	< 0.01	1.4	1.1–1.8	0.02

NOS Not otherwise specified, *SLNB* Sentinel lymph node biopsy, *ALND* Axillary lymph node dissection, *HER2* Human epidermal growth factor receptor 2

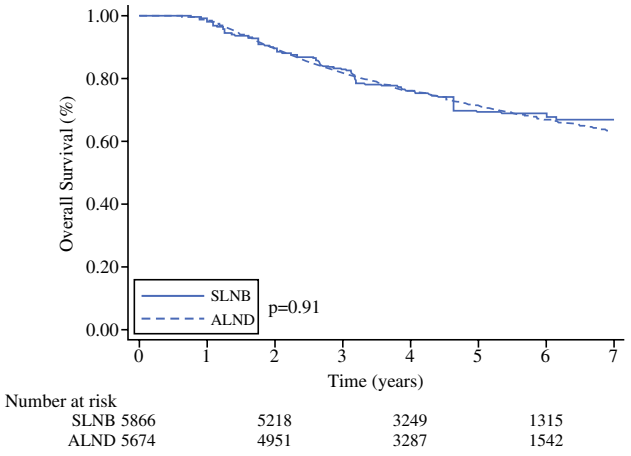

FIG. 3 Kaplan–Meier plot showing OS for cN2b–N3c undissected disease by sentinel lymph node biopsy (SLNB; solid) and axillary lymph node dissection (ALND; dashed) after inverse probability weighting (IPTW). *OS* overall survival

TABLE 4 The 5-year overall survival by pathologic nodal stage and receipt of neoadjuvant chemotherapy

	5-year Overall Survival (%)		
	SLNB	ALND	*p*-Value
Overall	69.6	71.3	0.91
pN0	86.3	82.2	0.09
pN1–N3	62.7	66.2	0.74
NAC	64.7	68.6	0.91
NAC, ypN0	85.2	80.4	0.07
NAC, ypN1–N3	53.8	61.1	0.92

SLNB Sentinel lymph node biopsy, *ALND* Axillary lymph node dissection, *pN0* Pathologic node negative, *pN1–3*, Pathology nodal stage 1–3, *NAC* Neoadjuvant chemotherapy

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