Ann Surg Oncol (2019) 26:3517–3525
https://doi.org/10.1245/s10434-019-07583-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Surgical Management of the Axilla in Clinically Node-Positive Patients Receiving Neoadjuvant Chemotherapy: A National Cancer Database Analysis

Stephanie M. Wong, MD[1,2], Anna Weiss, MD[1,2], Elizabeth A. Mittendorf, MD[1,2], Tari A. King, MD[1,2], and Mehra Golshan, MD, MBA[1,2]

[1]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; [2]Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA

ABSTRACT

Background. The feasibility of sentinel lymph node biopsy (SLNB) in patients with clinically node-positive (cN+) disease who convert to clinically node-negative (cN0) disease following neoadjuvant chemotherapy (NAC) has been evaluated in several large clinical trials, but it remains unclear whether the approach has been broadly adopted in the United States.

Methods. The National Cancer Database was used to identify women diagnosed with cN+ breast cancer who received NAC followed by surgery between 2012 and 2015. Trends in axillary surgery were evaluated and multivariable logistic regression analyses performed to determine factors associated with receipt of SLNB.

Results. Of 12,965 women cN+ at baseline, the use of SLNB increased from 31.8% in 2012 to 49% in 2015 ($p < 0.001$). Using axillary pCR as a surrogate for patients who convert to cN0 following NAC, among 5127 (39.5%) ypN0 patients, SLNB increased from 38.2 to 58.4% over the study period ($p < 0.001$), resulting in avoidance of axillary dissection in 42.2% of ypN0 patients by 2015. In adjusted analyses, factors significantly associated with SLNB attempt included cN1 disease, age < 45 years, treatment facility type, triple-negative and HER2-positive subtypes, and year of diagnosis. In women with residual isolated tumor cells (ITCs), micrometastases, and ypN1 disease, SLNB was the only axillary procedure performed in 36.9%, 23.6%, and 13.0% of cases.

Conclusions. The use of SLNB in cN+ patients receiving NAC increased significantly between 2012 and 2015. SLNB alone was performed in more than 10% of patients with ypN1 disease, 20% with micrometastases, and 35% with ITCs; the oncologic safety of omitting axillary dissection in these patients requires further evaluation.

The use of neoadjuvant chemotherapy (NAC) to limit the extent and morbidity of axillary surgery in patients presenting with clinically node-positive disease is an area of evolving interest. Historically, concerns regarding the potential for altered lymphatic drainage due to treatment-related fibrosis led to the assumption that sentinel lymph node biopsy (SLNB) may be inaccurate for axillary staging in patients with biopsy-proven nodal metastases.[1] While early reports suggested that SLNB may be technically feasible following NAC, its accuracy remained in question when single-institution series reported false-negative rates ranging from 9 to 21% in patients with clinically node-positive disease at presentation.[2–5]

Three large, multicentered, prospective trials published between 2013 and 2015 subsequently demonstrated the feasibility of SLNB in clinically node-positive patients who converted to clinically node negative following NAC. Together, the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, the European SENTinel NeoAdjuvant (SENTINA) trial, and the Canadian Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN

Prior Presentation: This study was presented as an oral presentation at the 2019 Annual Meeting of Society of Surgical Oncology, March 28, 2019, San Diego, CA.

First Received: 27 March 2019;
Published Online: 24 July 2019

M. Golshan, MD, MBA
e-mail: mgolshan@bwh.harvard.edu

FNAC) trial demonstrated false-negative rates between 5.2 and 10.8% when dual agent mapping was used to perform SLNB.[6–8] Removal of three or more sentinel lymph nodes, the use of immunohistochemistry to define node-positive disease, and confirmed excision of the previously biopsy-proven positive clipped node were shown to further decrease the false-negative rate of the SLNB procedure.[6,9,10]

Although these trials demonstrated feasibility of SLNB in clinically node-positive patients who respond to NAC, data on long-term oncologic safety associated with omission of axillary lymph node dissection (ALND) remain limited.[11,12] Despite the paucity of data regarding oncologic outcomes, recent studies suggest that this approach has been broadly adopted in clinical practices across the United States. A 2017 survey of American Society of Breast Surgeons members that assessed surgeons' attitudes reported a 40% increase in the use of SLNB in clinically node-positive patients following NAC, with 85% of respondents incorporating trial results into practice.[13] The objective of this study was to assess uptake at the population level by evaluating national trends in the surgical management of the axilla in patients with clinically node-positive disease treated with NAC between 2012 and 2015.

METHODS

Data Source and Cohort Selection

The National Cancer Database (NCDB) was used to identify women with a histologically confirmed, first diagnosis of clinical T1-3 N1-2 invasive breast cancer (n = 175,012). Patients were excluded if they were treated with upfront surgery (n = 138,229), did not have estrogen, progesterone, or HER2 receptor status available (n = 6733), or if information on breast and axillary surgery and pathology was unknown (n = 5809). Our final analytic cohort included 12,965 women diagnosed with clinically node-positive breast cancer between 2012 and 2015 who received NAC followed by surgery. Because the study used de-identified data, the protocol was considered exempt from the Institutional Review Board of Brigham and Women's Hospital.

Variables and Outcomes of Interest

Our primary outcome of interest was axillary nodal surgery, derived from the *Scope of Regional Lymph Node Surgery* variable and categorized into three groups according to details abstracted from operative reports: SLNB, SLNB followed by axillary lymph node dissection (ALND), and upfront ALND. Patients who failed to map during SLNB and underwent ALND within the same operative procedure, and those who underwent SLNB followed by completion ALND as a separate surgical procedure were considered to have undergone SLNB followed by ALND. For adjusted analyses, women who had SLNB or SLNB followed by ALND were considered to have had a SLNB attempt.

Control variables included age, race, facility, Charlson-Deyo comorbidity score, histology, histologic grade, biologic subtype, clinical tumor size, clinical nodal status, primary surgery, and adjuvant radiation as categorized in Table 1. Additional variables of interest included year of diagnosis and pathologic nodal status following NAC. For pathologic nodal status, patients with isolated tumor cells and micrometastases were separated from ypN0 and ypN1 nodal groups to determine the independent effect of low volume residual nodal disease on receipt of additional axillary surgery.

Statistical Analysis

To determine whether there had been a significant uptake in SLNB over the study period, the annual rates of SLNB alone, SLNB followed by ALND, and upfront ALND between 2012 and 2015 were calculated then compared using the Mantel–Haenszel test for trend. Differences in demographic and clinicopathologic factors associated with SLNB attempt were assessed using Pearson's χ^2 test for categorical variables. Finally, to explore which preoperative factors independently predict SLNB attempt, a multivariable logistic regression model was constructed. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). All p values were two-sided, with a threshold of 0.05 used to indicate statistical significance.

RESULTS

Cohort Characteristics and Response to Therapy

Patient demographics and clinical characteristics of the final analytic cohort (n = 12,965) are shown in Table 1. The mean age of the cohort was 52.1 years, with 84.5% (n = 10,955) of the cohort presenting with clinical T2–T3 tumors and 85.7% (n = 11,111) with clinical N1 disease (Table 1). Axillary pathologic complete response (pCR), defined as ypN0 excluding patients with isolated tumor cells, was achieved in 39.5% (n = 5127). Axillary pCR and pathologic nodal status according to biologic subtypes are shown in Table 2, with axillary pCR rates ranging from 21.8% in estrogen receptor-positive/HER2-negative

TABLE 1 Cohort characteristics for patients with stage II–III invasive breast cancer who received neoadjuvant chemotherapy and were clinically node-positive, NCDB 2010–2015 (n = 12,965)

Characteristic	
Mean age—*n*, (%)	
< 45	3608 (27.8)
45–55	3943 (30.4)
55–65	3410 (26.3)
65–75	1636 (12.6)
75+	368 (2.8)
Race—*n*, (%)	
Caucasian	8153 (62.9)
Black	2584 (19.9)
Asian	266 (2.1)
Hispanic	1196 (9.2)
Unknown	766 (5.9)
Charlson-Deyo comorbidity score—*n*, (%)	
0	11,361 (87.6)
1	1359 (10.5)
2+	245 (1.9)
Histology—*n*, (%)	
Invasive ductal carcinoma	11,390 (87.9)
Invasive lobular carcinoma	694 (5.4)
Mixed ductal/lobular carcinoma	723 (5.6)
Favorable/other histologies[†]	158 (1.2)
Grade—*n*, (%)	
Grade I	530 (4.1)
Grade II	3921 (30.2)
Grade III	7481 (57.7)
Other/unknown	1033 (8.0)
Biologic subtype—*n*, (%)	
ER+/HER2−	6069 (46.8)
ER+/HER2+	1143 (8.8)
ER−HER2+	1968 (15.2)
ER−/HER2−	3785 (29.2)
Clinical tumor size—*n*, (%)	
cT1	2010 (15.5)
cT2	7139 (55.1)
cT3	3816 (29.4)
Clinical node status—*n*, (%)	
cN1	11,111 (85.7)
cN2	1854 (14.3)
Local management—*n*, (%)	
Breast conserving therapy	4370 (33.7)
Mastectomy	8595 (66.3)
Axillary management—*n*, (%)	
SLNB	2530 (19.5)
SLNB followed by ALND	2707 (20.9)
Upfront ALND	7728 (59.6)
Radiation—*n*, (%)	
No adjuvant radiation	2743 (21.2)
Adjuvant RT with regional nodal irradiation	6650 (51.3)
Adjuvant RT without regional nodal irradiation	3289 (25.4)
Adjuvant RT NOS/unknown	283 (2.2)

ALND axillary lymph node dissection, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor, *NOS* not otherwise specified, *RT* radiotherapy, *SNLB* sentinel lymph node biopsy

patients to 66.4% in the estrogen receptor-negative/HER2-positive subgroup.

Trends in Axillary Surgery for Clinically Node-Positive Patients following Neoadjuvant Chemotherapy

Temporal trends revealed a significant increase in the use of SLNB for clinically node-positive patients post NAC, increasing from 31.8% in 2012 to 49.0% in 2015 ($p < 0.001$). By 2015, SLNB was the only axillary procedure performed in 25.7% of the entire cohort of clinically node-positive patients at baseline (Fig. 1a). In subset analysis using axillary pCR as a surrogate for patients who convert to clinically node negative following NAC, among 5127 ypN0 patients (39.5% of total cohort), the use of SLNB for initial axillary staging rose from 38.2% in 2012 to 58.4% in 2015 ($p < 0.001$). In this subgroup, the proportion of women who were spared an axillary dissection nearly doubled, from 22.8% in 2012 to 42.2% of ypN0 patients in 2015 ($p < 0.001$, Fig. 1b).

In those undergoing SLNB alone, the proportion of procedures with three or more sentinel lymph nodes removed also increased from 52.9% to 63.8% between 2012 and 2015 ($p = 0.01$), with a steady increase seen in patients who had three, four, and five or more nodes excised over the study period (Fig. 1c).

Factors Associated with Sentinel Lymph Node Biopsy following Neoadjuvant Chemotherapy

In adjusted analysis, age < 45 years at diagnosis, treatment facility, clinical N1 (vs. cN2) disease, HER2-positive and triple-negative subtype, and breast-conserving surgery (vs. mastectomy) were found to be independently associated with receipt of SLNB (Table 3). Of all variables included in the logistic regression model, year of diagnosis remained the strongest predictor for SLNB attempt such that, compared with 2012, patients diagnosed and receiving treatment in 2015 had a twofold increased odds of

TABLE 2 Axillary pathologic complete response rates according to biologic subtype, NCDB 2010–2015 (n = 12,965)

	Total	Axillary pCR[a] (%)	ypN0(i +)/ypN1mi (%)	ypN1 (%)	ypN2-3 (%)
Biologic subtype—*n,* (row %)					
ER+/HER2−	6069 (46.8)	21.8	5.3	41.6	31.3
TNBC	3785 (29.2)	51.0	7.0	29.7	14.2
ER+/HER2+	1143 (8.8)	49.1	5.6	19.1	8.8
ER−/HER2+	1986 (15.2)	66.4	5.3	27.1	16.6

ER estrogen receptor; *HER2* human epidermal growth factor receptor; *TNBC* triple-negative breast cancer; *pCR* pathologic complete response
[a]Defined as ypN0, excluding isolated tumor cells

undergoing a SLNB (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.84–2.27).

Definitive Axillary Management according to Pathologic Nodal Status

Among the 12,965 women who underwent NAC, 5127 (39.5%) achieved an axillary pCR (ypN0), 715 (5.5%) had low-volume residual nodal disease in the form of isolated tumor cells (ypN0i +) or micrometastases (ypN1mi), and 7123 (54.9%) had macrometastatic (ypN1-3) disease.

Axillary management according to pathologic nodal status are shown in Table 4, with decreasing rates of SLNB only seen with increasing residual nodal burden. Axillary dissection was omitted in 36.9% of patients with isolated tumor cells, 23.6% of patients with micrometastases, and 13% of patients with ypN1 macrometastatic disease (Table 4). Definitive axillary management in these nodal subgroups changed over time, with SLNB alone performed in 20.5% of patients with isolated tumor cells in 2012 increasing to 49.1% in 2015 ($p = 0.01$). Women with residual micrometastases also saw a significant increase in the use of SLNB alone, from 18.6 to 31.2% over the study period ($p = 0.03$). In women with ypN1 disease, the use of SLNB alone increased from 8.6% in 2012 to 15.6% in 2015 ($p < 0.001$).

DISCUSSION

In this large, national study evaluating axillary management after NAC in women with clinically node-positive breast cancer, there was a significant increase in the use of SLNB for axillary staging. This trend was particularly pronounced amongst women who converted to pathologic node-negative disease, in whom the proportion of women who were spared an axillary dissection nearly doubled during the 4-year study period from 2012 to 2015. In adjusted analyses, SLNB was used more frequently in younger patients, those with HER2-positive or triple-negative disease, and in those able to undergo breast-conserving surgery, suggesting a selective de-escalation of local therapy for women with a high likelihood of clinical response.

Although axillary dissection was long regarded as standard therapy for patients presenting with clinically node-positive disease, these data suggest a shift in clinical practice following trial results, with SLNB being incrementally adopted to identify women who achieve an axillary pCR following NAC. This approach has been successfully implemented across several single-institution settings, with the goal of omitting ALND to avoid the morbidity of more extensive axillary surgery. The early experience from Memorial Sloan Kettering Cancer Center reported by Mamtani et al. in 2016 found that in 195 patients with biopsy-proven nodal metastases, 68% became eligible for SLNB following neoadjuvant therapy.[14] Furthermore, in 128 patients who underwent SLNB, 48% were able to undergo SLNB alone with three or more negative lymph nodes retrieved. Similar findings were reported from the Mayo Clinic, where Nguyen et al. found 48% of cN1 patients to be candidates for omission of ALND following neoadjuvant therapy.[12] This translated into decreasing rates of ALND for patients with node-positive breast cancer at presentation, which was performed in all patients in 2009 but in only 38% of patients by 2017. Lastly, review of our institutional experience showed that of 156 cN1 patients undergoing NAC, 96 (62%) converted to cN0 with NAC. Among these 96 patients, 64 (67%) underwent successful SLNB with dual tracer mapping and three or more lymph nodes removed. Overall, 25% of patients with a SLNB attempt were spared an ALND.[15] Studies of surgeons' attitudes towards SLNB reflect a similar transition abroad, with one nationwide survey conducted in the Netherlands in 2016 finding that 70% of participating surgeons were willing to omit ALND in node-positive patients with a favorable clinical and pathological response to NAC.[16]

Several technical factors have been demonstrated to lower the false-negative rate of SLNB in patients receiving NAC.[6,8,10,17,18] The use of dual agent mapping has been deemed necessary when adopting this approach, as both the

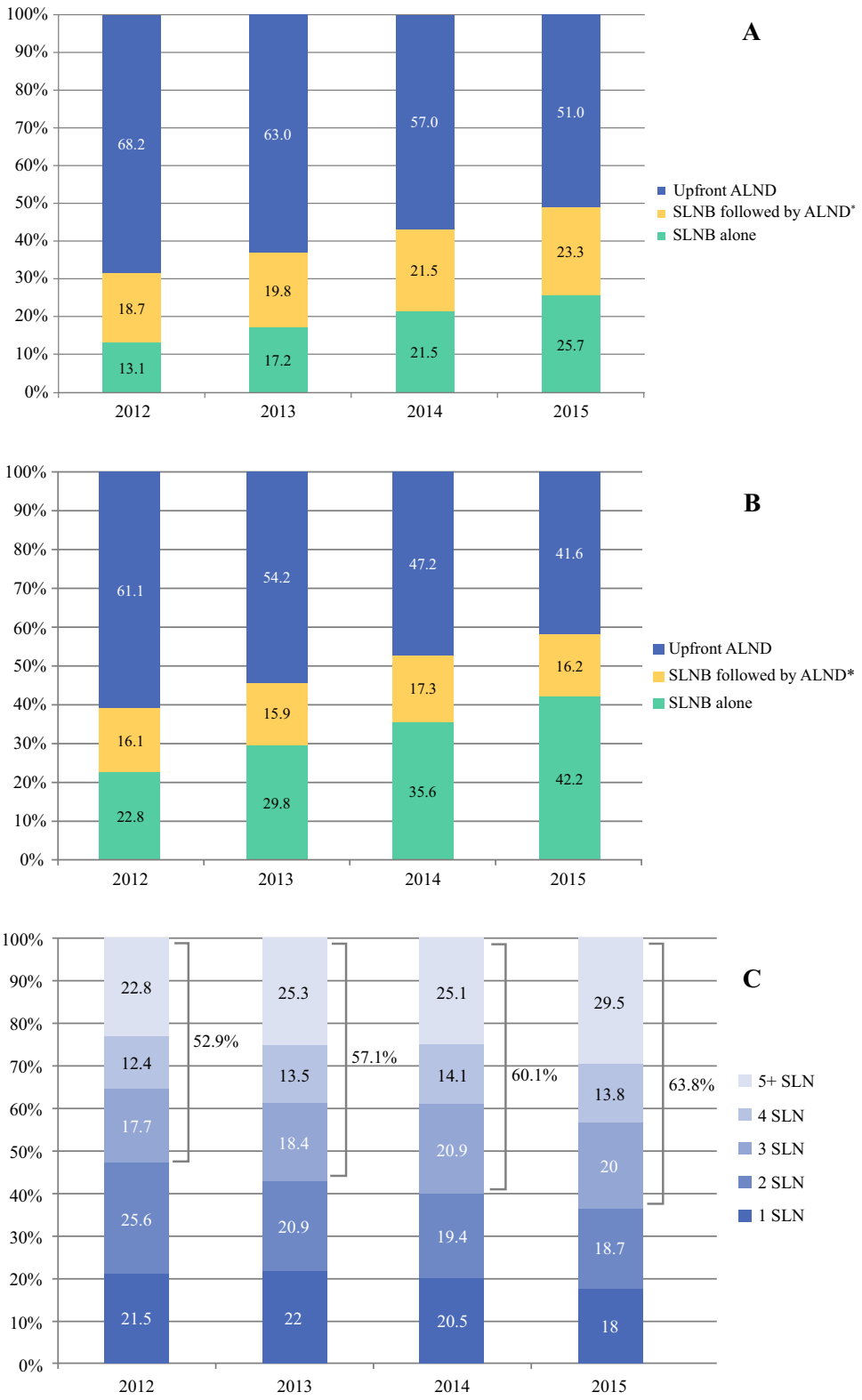

FIG. 1 **a** Annual trends in axillary management for women receiving neoadjuvant chemotherapy for clinically node positive disease, $p < 0.001$ ($n = 12{,}965$). **b** Annual trends in axillary management for clinically node-positive patients who convert to pathologically node-negative following neoadjuvant chemotherapy, $p < 0.001$ ($n = 5127$). **c** Annual increase in the number of sentinel lymph nodes removed in clinically node positive patients who underwent sentinel lymph node biopsy following neoadjuvant therapy from 2012 to 2015, $p = 0.01$ ($n = 2317$). *SLN* sentinel lymph node(s); *ALND* axillary lymph node dissection; *SLNB* sentinel lymph node biopsy

Z1071 and SENTINA trials failed to achieve their predetermined false-negative rate endpoints of < 10% when single agent mapping was used.[8,9] While the present analysis was unable to evaluate the use of dual agent mapping or the excision of preoperatively localized lymph nodes, questionnaire-based studies have found that, respectively, 86% and 82% of American surgeons who offer SLNB for this indication find these components

TABLE 3 Multivariable logistic regression analysis analyzing predictors of SLNB attempt in patients diagnosed with clinical T1-3 N1-2 disease and received neoadjuvant chemotherapy

Characteristic	Cohort	Proportion who underwent SLNB for axillary staging		Adjusted odds ratio for receipt of SLNB (95% CI)[†]
	No. (%)	%	*p* value*	
Age group (year)			< 0.0001	
< 45	3608 (27.8)	43.1		**1.37 (1.21–1.55)**
45–54	3943 (30.4)	41.6		**1.22 (1.11–1.34)**
55–64	3410 (26.3)	38.1		1.00
65–74	1636 (12.6)	37.9		0.97 (0.86–1.10)
75+	368 (2.8)	33.2		**0.76 (0.60–0.96)**
Race			0.26	
Caucasian	8153 (62.9)	40.8		1.00
Black	2584 (19.9)	40.4		0.94 (0.85–1.03)
Asian	266 (2.1)	42.1		1.02 (0.79–1.32)
Hispanic	1196 (9.2)	39.1		0.88 (0.78–1.00)
Other	766 (5.9)	37.1		0.79 (0.68–0.93)
Facility			< 0.001	
Community Cancer Center	989 (7.6)	36.7		1.00
Comprehensive Community Cancer Center	4762 (36.7)	41.2		**1.20 (1.03–1.38)**
Academic/Research Center	3872 (29.9)	38.2		1.05 (0.91–1.22)
Integrated Network Cancer Center	1371 (10.6)	42.8		**1.30 (1.09–1.55)**
Unknown	1971 (15.2)	43.0		**1.19 (1.00–1.44)**
Charlson-Deyo comorbidity score			0.03	
0	11,361 (87.6)	40.8		1.00
1	1359 (10.5)	37.7		0.93 (0.82–1.05)
2+	245 (1.9)	36.0		0.82 (0.62–1.07)
Histology			0.15	
Invasive ductal carcinoma	11,390 (87.9)	40.8		1.00
Invasive lobular carcinoma	694 (5.4)	38.6		**1.17 (0.98–1.38)**
Mixed ductal/lobular carcinoma	723 (5.6)	36.9		0.97 (0.83–1.14)
Favorable histologies	158 (1.2)	38.6		0.96 (0.69–1.34)
Histologic tumor grade			< 0.001	
Grade I	530 (4.1)	38.3		1.00
Grade II	3921 (30.2)	40.0		0.95 (0.78–1.15)
Grade III	7481 (57.7)	39.1		0.98 (0.81–1.19)
Unknown	1033 (8.0)	41.4		0.95 (0.76–1.18)
Clinical tumor size, cm			< 0.001	
cT1	2010 (15.5)	41.1		1.00
cT2	7139 (55.1)	42.7		**1.11 (1.01–1.24)**
cT3	3816 (29.4)	35.8		0.95 (0.85–1.07)
Clinical node status			< 0.001	
cN1	11,111 (85.7)	42.4		1.00
cN2	1854 (14.3)	28.7		**0.60 (0.54–0.67)**
Receptor status			0.001	
ER+/HER2−	6069 (46.8)	38.8		1.00
ER−/HER2+	1143 (8.8)	8.6		1.09 (0.95–1.25)
ER+/HER2+	1968 (15.2)	42.2		1.10 (0.98–1.22)
TNBC	3785 (29.2)	42.4		**1.13 (1.03–1.24)**

TABLE 3 continued

Characteristic	Cohort	Proportion who underwent SLNB for axillary staging		Adjusted odds ratio for receipt of SLNB (95% CI)[†]
	No. (%)	%	*p* value*	
Surgery			< 0.001	
Breast-conserving surgery	4370 (33.7)	50.0		**1.82 (1.68–1.97)**
Mastectomy	8595 (66.3)	35.5		1.00
Year of diagnosis			< 0.001	
2012	3180 (24.5)	31.8		1.00
2013	3080 (23.8)	37.0		**1.28 (1.53–1.91)**
2014	3345 (25.8)	43.1		**1.61 (1.46–1.79)**
2015	3360 (25.9)	49.0		**2.05 (1.84–2.27)**

CI confidence interval, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor, *SLNB* sentinel lymph node biopsy, *TNBC* triple-negative breast cancer

[†]Bold if statistically significant, $p < 0.05$

TABLE 4 Axillary management according to pathologic nodal status in patients who were clinically node positive and received neoadjuvant chemotherapy, NCDB 2010–2015 (n = 12,965)

	SLNB only	SLNB followed by ALND[†]	Upfront ALND	Total
ypN status—*n,* (row %)				
ypN0	1697 (33.1)	842 (31.1)	2588 (33.5)	5127 (39.5)
ypN0(i+)	79 (36.9)	43 (20.1)	92 (43.0)	214 (1.7)
ypN1mi	118 (23.6)	129 (25.8)	254 (50.7)	501 (3.9)
ypN1	553 (13.0)	1065 (25.0)	2644 (62.0)	4262 (32.9)
ypN2-3	83 (2.9)	628 (22.0)	2150 (75.2)	2861 (22.1)

ALND axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *ypN0* no regional lymph node metastases (excluding ITCs), *ypN0(i+)* isolated tumor cells, *ypN1mi* micrometastases (> 0.2 mm and ≤ 2.0 mm, approximately 200 cells), yp*N1* macrometastases in 1–3 axillary lymph nodes, yp*N2-3* macrometastases in four or more axillary lymph nodes

critical.[13] In addition, two-thirds of respondents cite the importance of removing three or more lymph nodes at the time of sentinel lymph node surgery, noting the well-established inverse relationship between false-negative rate and number of nodes removed.[19,20] Our data lend support to the notion that this is happening at the population level, with an observed increase in the mean number of lymph nodes removed in women undergoing SLNB alone following NAC. Interestingly, however, when biopsy-proven positive clipped nodes are targeted for removal following NAC, as has been described in the Targeted Axillary Dissection (TAD) or Marking the Axillary with Radioactive Iodine seeds (MARI) procedures, the false-negative rate from removing these nodes alone ranges from 4.2 to 7%.[17,18] Combining selective localization and removal of clipped nodes with dual-tracer SLNB, as described by Caudle et al. in TAD, has been shown to optimally minimize the false negative rate and is the subject of ongoing validation in the prospective Dutch RISAS trial.[21]

Many proponents of SLNB in the setting of clinically node-positive disease advocate that the procedure be offered selectively on the basis of patient age, tumor subtype, and extent of nodal disease prior to systemic therapy, because these factors have been shown to predict locoregional recurrence.[12,13,16,22] In our study, we found that among clinically node-positive patients, those who were older, presented with clinical N2 disease, or were of luminal A subtype were more likely to receive upfront ALND. In contrast, factors associated with clinical response to therapy—HER2-positive and triple-negative subtypes and breast conserving surgery—tended to predict SLNB receipt.

Although SLNB has been adopted to allow for de-escalation of local therapy following NAC, long-term oncologic outcomes for those achieving an axillary pCR by sentinel node evaluation only are limited, with ongoing clinical trials currently underway to assess the safety of omitting ALND in this population. Currently available evidence includes one single institution retrospective series

reported by Galimberti et al., where a subgroup of 70 clinically node-positive patients treated with NAC who converted to clinically node-negative following treatment and underwent a negative SLNB demonstrated no axillary recurrences at a median follow-up of 61 months.[11] The authors noted that chest-wall and/or regional nodal radiotherapy may be particularly important in clinically node-positive patients before neoadjuvant therapy, which is currently being evaluated in two, large, randomized trials. The NSABP B-51/RTOG 1304 trial will serve to confirm the oncologic safety of SLNB alone in women with clinically node-positive disease who have negative axillary staging and are randomized to regional nodal irradiation versus no further axillary therapy.[23] The Alliance A11202 trial will address the population of women with positive sentinel nodal disease, evaluating whether ALND can be omitted in favor of regional nodal irradiation in this population. Both trials will help to address important issues related to tailoring local treatment based on extent of nodal disease in women undergoing neoadjuvant treatment.

The oncologic safety of omission of ALND among patients with residual isolated tumor cells (< 0.2 mm) and micrometastases (0.2–2.0 mm) remains unclear. Prior literature has suggested that these patients represent a group with treatment-resistant disease who portend a poorer prognosis.[24,25] Several studies have noted that there is no relationship between the size of sentinel lymph node metastases and the likelihood of finding additional nodal disease.[6,26] Notably, the SN FNAC trial mandated the use of immunohistochemistry for sentinel node pathology on the basis of this finding, remarking that the rate of positive non-sentinel nodes is independent of the size of sentinel node metastases.[6] A retrospective study by Moo et al. confirmed this finding, with the authors demonstrating a 17% and 62% likelihood of additional non-sentinel node metastases in patients with residual isolated tumor cells and micrometastatic disease on SLNB, respectively.[26] Our study found that low-volume residual nodal disease was present in 5.5% of clinically node-positive women following neoadjuvant therapy and that up to 37% of these patients underwent SLNB alone despite the continued recommendation for ALND in this setting.[27] Accurate assessment and identification of residual nodal disease is particularly important in this setting given the opportunity for improved outcomes with the addition of adjuvant capecitabine in patients with triple-negative breast cancer or trastuzumab emtansine (T-DM1) in those with HER2-positive disease.[28,29]

This analysis has some limitations and, as with all population-based studies, must be interpreted within the context of the data. First, NCDB lacks information regarding clinical response to neoadjuvant therapy in patients undergoing surgery, necessitating the use of pathologic surrogates to define the cohort of patients most likely to have converted to clinically node-negative. Furthermore, granular data are not available on SLNB technique, including the use of dual tracer, immunohistochemistry to define node-negative disease, and excision of clipped nodes, all of which are important for determining practice patterns associated with the use of SLNB after NAC. Finally, detailed information regarding surgeons' attitudes, decision-making, or acceptance of more limited axillary surgery, which historically have been shown to vary widely, was not available.[30] Despite the stated limitations, to our knowledge this is the first study to assess national patterns in the adoption of SLNB for clinically node-positive patients undergoing NAC, with strengths that include the use of a modern, large cohort of patients treated in diverse practice settings across the United States.

Our study highlights the growing use of SLNB following NAC in patients who are clinically node-positive at baseline, illustrating the adoption of clinical trial results into modern-day practice. However, SLNB with omission of ALND also is being employed in patients with low-volume residual disease after NAC, a population that may have significant residual disease left behind. As we await the results of further prospective trials evaluating optimal local therapy in patients with and without residual disease on SLNB, ALND should remain the standard for all patients with isolated tumor cells, micrometastases, and macrometastases identified on axillary pathology.

DISCLOSURES The authors have no relevant conflicts of interest to disclose. This study was supported by the Breast Cancer Research Foundation.

REFERENCES

1. King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat Rev Clin Oncol.* 2015;12:335–43.
2. Classe JM, Bordes V, Campion L, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. *J Clin Oncol.* 2009;27:726–32.
3. Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2005;23:2694–702.
4. Alvarado R, Yi M, Le-Petross H, et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. *Ann Surg Oncol.* 2012;19:3177–84.
5. Shen J, Gilcrease MZ, Babiera GV, et al. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. *Cancer.* 2007;109:1255–63.
6. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015;33:258–64.

7. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA.* 2013;310:1455–61.
8. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013;14:609–18.
9. Boughey JC, Suman VJ, Mittendorf EA, et al. Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). *Ann Surg.* 2015;261:547–52.
10. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). *Ann Surg.* 2016;263:802–7.
11. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. *Eur J Surg Oncol.* 2016;42:361–8.
12. Nguyen TT, Hoskin TL, Day CN, et al. Decreasing use of axillary dissection in node-positive breast cancer patients treated with neoadjuvant chemotherapy. *Ann Surg Oncol.* 2018;25:2596–602.
13. Caudle AS, Bedrosian I, Milton DR, et al. Use of sentinel lymph node dissection after neoadjuvant chemotherapy in patients with node-positive breast cancer at diagnosis: practice patterns of American Society of Breast Surgeons Members. *Ann Surg Oncol.* 2017;24:2925–34.
14. Mamtani A, Barrio AV, King TA, et al. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? Results of a prospective study. *Ann Surg Oncol.* 2016;23:3467–74.
15. Laws A, Hughes ME, Hu J, et al. Impact of residual nodal disease burden on sentinel node mapping and accuracy of intraoperative frozen section in node-positive (cN1) breast cancer patients treated with neoadjuvant chemotherapy (NAC). *J Clin Oncol.* 2018;36:584–4.
16. Vugts G, Maaskant-Braat AJ, de Roos WK, et al. Management of the axilla after neoadjuvant chemotherapy for clinically node positive breast cancer: a nationwide survey study in The Netherlands. *Eur J Surg Oncol.* 2016;42:956–64.
17. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol.* 2016;34:1072–8.
18. Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg.* 2015;261:378–82.
19. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol.* 2007;8:881–8.
20. McMasters KM, Tuttle TM, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. *J Clin Oncol.* 2000;18:2560–6.
21. van Nijnatten TJA, Simons JM, Smidt ML, et al. A novel less-invasive approach for axillary staging after neoadjuvant chemotherapy in patients with axillary node-positive breast cancer by combining radioactive iodine seed localization in the axilla with the sentinel node procedure (RISAS): A Dutch Prospective Multicenter Validation Study. *Clin Breast Cancer.* 2017;17:399–402.
22. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol.* 2012;30:3960–6.
23. Mamounas EP, White JR, Bandos H, et al. NSABP B-51/RTOG 1304: Randomized phase III clinical trial evaluating the role of postmastectomy chest wall and regional nodal XRT (CWRNRT) and post-lumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC. *J Clin Oncol.* 2014;32:TPS1141-1.
24. Fisher ER, Wang J, Bryant J, et al. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. *Cancer.* 2002;95:681–95.
25. Klauber-DeMore N, Ollila DW, Moore DT, et al. Size of residual lymph node metastasis after neoadjuvant chemotherapy in locally advanced breast cancer patients is prognostic. *Ann Surg Oncol.* 2006;13:685–91.
26. Moo TA, Edelweiss M, Hajiyeva S, et al. Is low-volume disease in the sentinel node after neoadjuvant chemotherapy an indication for axillary dissection? *Ann Surg Oncol.* 2018;25:1488–94.
27. NCCN Guidelines Version 3.2018 Breast Cancer. Published October 25, 2018. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 11 Nov 2018.
28. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med.* 2017;376:2147–59.
29. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380:617–28.
30. Morrow M, Jagsi R, McLeod MC, et al. Surgeon attitudes toward the omission of axillary dissection in early breast cancer. *JAMA Oncol.* 2018;4:1511–6.