



Patterns of Axillary Management in Stages 2 and 3 Hormone Receptor-Positive Breast Cancer by Initial Treatment Approach

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ABSTRACT

Background. Data regarding axillary management after neoadjuvant endocrine therapy (NET) are lacking. This study examined axillary management of hormone receptor-positive (HR+) patients based on initial treatment with NET, neoadjuvant chemotherapy (NAC), or upfront surgery.

Methods. Patients with stage 2 or 3 HR+/HER2– breast cancer treated between 2012 and 2015 were identified in the National Cancer Database. The study examined axillary surgery [sentinel lymph node biopsy (SLNB), SLNB followed by axillary lymph node dissection (ALND), or upfront ALND] by initial treatment stratified by cN0/N1 using pairwise comparisons and multivariable logistic regression.

Results. Of 92,204 eligible patients, 2138 (2.3%) received NET, 11,014 (12%) received NAC, and 79,052 (85.7%) received surgery. Among 60,998 cN0 patients, attempted SLNB was more likely for surgery patients (86.2%, 47,159/54,684) and NET patients (85.8%, 1342/1564) than for NAC patients (79.9%, 3793/4750) (both $p < 0.001$).

Among 31,206 cN1 patients, attempted SLNB was more likely for the surgery patients (46.0%, 11,201/24,368) than for the NET patients (41.8%, 240/574; $p = 0.05$) or the NAC patients (39.8%, 2491/6264; $p < 0.0001$). The differences between surgery and NET did not persist in the adjusted analyses. Among both the cN0 patients ($n = 13,856$) and the cN1 patients ($n = 8688$) with pN1 disease shown by SLNB, the NET patients were treated with ALND less frequently than those receiving NAC or surgery ($p < 0.0001$ for all comparisons). In the multivariate analysis, for the patients with pN1 disease shown by SLNB, NET use was associated with increased odds of undergoing SLNB alone [cN0 patients: odds ratio (OR), 1.31, 95% confidence interval (CI), 1.04–1.64; cN1 patients: OR 1.45; 95% CI 1.00–2.10].

Conclusions. For stages 2 and 3 HR+/HER2– patients, SLNB use after NET was similar to that for upfront surgery. Among those with pN1 disease, the NET patients were less likely to undergo ALND. Additional outcomes data are needed to guide axillary management after NET.

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Axillary management has evolved rapidly during the past 10 years, with increasing use of sentinel lymph node biopsy (SLNB) and decreasing use of axillary lymph node dissection (ALND). Several studies have examined the omission of ALND, in favor of either observation or axillary radiation, among clinically node-negative patients treated with upfront surgery and found to have limited-volume pathologic nodal disease.^{1–5} In these trials, local regional recurrence (LRR) outcomes were not affected by omission of ALND, overall event rates were low, and the oncologic safety of these practices has proved to be durable.^{6–9} Although data for the upfront surgery population

support minimizing axillary surgery, controversy exists regarding the role of regional nodal irradiation (RNI) when ALND is omitted in this setting, which is the subject of the currently enrolling TailorRT trial.¹⁰

Among clinically node-positive patients, three trials—American College of Surgeons Oncology Group (ACOSOG) Z1071,¹¹ SENTinel NeoAdjuvant (SENTINA),¹² and Sentinel Node Following NeoAdjuvant Chemotherapy (SN FNAC)¹³—demonstrated that SLNB may be a reasonable axillary staging procedure after neoadjuvant chemotherapy (NAC) for those with clinical evidence of nodal response. Although the two larger trials, ACOSOG Z1071 and SENTINA, were criticized for overall high false-negative rates, unplanned subset analyses showed technical factors that resulted in acceptable false-negative rates, and many providers currently offer SLNB after NAC in this setting.^{14–16}

Collectively, these efforts have resulted in avoidance of ALND for many patients, yet they have been agnostic to tumor subtype. In the modern era, optimal initial treatment selection often is predicated on tumor subtype, and as such, implementation of axillary de-escalation strategies also should be considered in this context. Optimal management of the axilla in hormone receptor-positive (HR+) patients and strategies to avoid ALND after neoadjuvant endocrine therapy (NET) have not been studied. Using the National Cancer Database (NCDB), we examined axillary management among stages 2 and 3 HR+ breast cancer patients by initial treatment strategy (NET, NAC, or upfront surgery) and report factors associated with receipt of attempted SLNB, completion ALND (cALND), and RNI.

METHODS

Study Setting and Population

The NCDB was queried between the years 2012 and 2015 to identify breast cancer patients with detailed axillary surgery information. Female patients with HR+, human epidermal growth factor receptor 2-negative (HER2-), clinical stage 2 or 3 (T categories 1–4 and/or N categories 0 and 1) breast cancer were included, with staging per NCDB-assigned classification by the American Joint Committee on Cancer (AJCC) 7th edition. Patients with any prior malignancy, inflammatory breast cancer, unknown stage or clinical nodal status, unknown receptor status, or unknown breast or axillary surgery were excluded (Table S1).

Definition of Variables

The study outcomes included receipt of SLNB as the initial axillary surgical staging procedure, cALND for

those with pathologic N1 disease (pN1) identified by SLNB, and receipt of RNI for pN1 patients who underwent SLNB alone, all by initial treatment approach (NET, NAC, or upfront surgery). In this study, pN1 disease included micrometastatic disease but not isolated tumor cells.

Axillary surgery was defined by the scope of the regional lymph node surgery variable, which included three options: SLNB, SLNB followed by cALND including patients who did not map to a sentinel node, and upfront ALND. Patients who had SLNB alone or SLNB followed by cALND were considered to have received an attempted SLNB.

Neoadjuvant treatments were identified by the systemic surgery sequence variable. Patients had neoadjuvant systemic therapy if the start date of systemic therapy was at least 30 days before their surgery date. If the start date for systemic therapy was identical to that for endocrine therapy, the patients were grouped as NET, and if the date was identical to the start date for chemotherapy, they were grouped as NAC. If the patient received both treatments, they were grouped as NAC. Pathologic negative nodes after neoadjuvant therapy were used as a surrogate for axillary pathologic complete response (pCR) for clinically node-positive patients.

Statistical Analysis

Rates of NET use, NAC use, and upfront surgery were examined by year for all the patients. Descriptive analyses compared patient characteristics according to treatment group. The patients then were stratified by clinical nodal status (cN0, cN1). Pairwise comparisons were performed for attempted SLNB rates by treatment strategy (NET, NAC, upfront surgery), and multivariable logistic regression was first performed for the attempted SLNB. The multivariable factors included initial treatment approach, age, clinical tumor category, facility, breast surgery, race, insurance status, income, comorbidity score, histology, grade, year of diagnosis, and region of treatment.

Descriptive analyses compared the patients by treatment approach who had an attempted SLNB and were found to have pN1 disease. Chi square and pairwise analyses (with Bonferroni correction) were used as appropriate. An adjusted analysis was performed to examine factors associated with the performance of SLNB alone for patients found to have pN1 disease, again with stratification by clinical nodal status. An interaction test was performed between age and initial management approach to determine whether patient age modifies the independent effect that NET or NAC has on axillary management. Finally, an adjusted analysis was performed to determine factors associated with RNI among patients who had pN1 disease and SLNB alone (in both cN0 and cN1 populations).

This study received a waiver from the Brigham and Women's Hospital Institutional Review Board review committee.

RESULTS

Initial Treatment Approach and Trends Over Time

The eligibility criteria were met by 92,204 patients. For their initial treatment, 2.3% of the patients ($n = 2138$) received NET, 12% ($n = 11,014$) received NAC, and 85.7% ($n = 79,052$) received upfront surgery. The rates of NET (1.9% in 2012 to 3% in 2015) and NAC (11.6–12.2%) increased slightly over time, whereas the rates for upfront surgery decreased (86.5–84.8%; $p < 0.001$). Among those receiving preoperative systemic therapy, NET use increased over time (14.1% in 2012 to 19.5% in 2015; $p < 0.001$) (Fig. 1). The median duration of NET was 152 days [interquartile range (IQR), 97–205 days], and the median duration of NAC was 148 days (IQR, 125–174 days). Among the older patients and those with a greater comorbidity burden (as measured by the Charlson–Deyo comorbidity score¹⁷), higher proportions of patients received NET and upfront surgery, and lower proportions received NAC. Higher proportions of patients with T3–T4 disease received NET or NAC, and a higher proportion of patients with cN1 disease received NAC (Table 1).

Attempted SLNB Rates

Overall, 71.8% (66,226/92,204) of the patients had an attempted SLNB. Of the 60,998 cN0 patients, 52,294 (86.9%) had an attempted SLNB. A pairwise comparison

showed that attempted SLNB was similarly likely for the cN0 patients treated with NET (85.8%, 1342/1564) and those treated with upfront surgery (86.2%, 47,159/54,684) ($p = 0.62$), whereas the NAC patients were less likely than either group to have an attempted SLNB (79.9%, 3793/4750) ($p < 0.001$ for both comparisons).

Of the 31,206 patients with clinically apparent nodal disease (cN1), 13,932 (45%) had an attempted SLNB. Attempted SLNB was less likely among the cN1 patients treated with NET (41.8%, 240/574; $p = 0.05$) or NAC (39.8%, 2491/6264; $p < 0.0001$) than among those treated with upfront surgery (46.0%, 11,201/24,368). The rates were similar between the NET and NAC patients ($p = 0.35$).

In adjusted analyses, the initial axillary staging strategy was similar for the patients treated with NET and those treated with upfront surgery [odds ratio (OR) for attempted SLNB: 1.01 (95% confidence interval (CI), 0.87–1.18) for the cN0 patients and 0.95 (95% CI, 0.80–1.13) for the cN1 patients; Table 2].

Surgical Management of Pathologic Nodal Disease

The overall pCR rate was significantly lower after NET (1.1%, 23/2138) than after NAC (8.4%, 930/11,014; $p < 0.001$) as was the nodal pCR rate [13.3% (76/571) after NET; 22.8% (1420/6233) after NAC; $p < 0.001$] (Table S2). Of all the patients, 36.9% (34,018/92,204) had pN1 disease and 14.5% (13,324/92,204) had pN2–3 disease. Most of the patients with pN2–3 disease (96.9%, 12,918/13,324) were treated with ALND.

The surgical management of the patients with pN1 disease was more variable. Of the women who had pN1

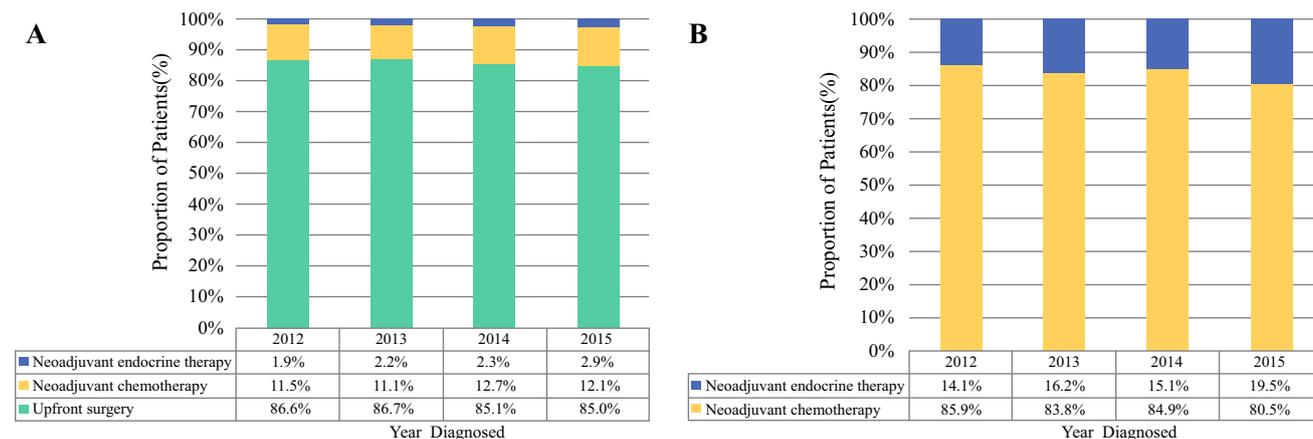


FIG. 1 National trends in neoadjuvant systemic therapy for American Joint Committee on Cancer (AJCC) 7th-edition clinical stages 2 and 3 hormone receptor-positive (HR+), epidermal growth factor receptor 2-negative (HER2-) breast cancer, 2012–2015. **a** Trends in neoadjuvant systemic therapy versus upfront surgery

for stages 2 and 3 HR+/HER2- breast cancer, National Cancer Database (NCDB) 2012–2015 ($n = 92,204$; $p < 0.001$). **b** Trends in neoadjuvant chemotherapy versus endocrine therapy for stages 2 and 3 HR+/HER2- breast cancer, NCDB 2012–2015 ($n = 13,152$; $p < 0.001$)

TABLE 1 Characteristics and axillary staging of stages 2 and 3 HR+/HER2– invasive breast cancer patients by initial treatment approach

Demographics (<i>n</i> = 92,204)	Total	NET (<i>n</i> = 2138)	%	NAC (<i>n</i> = 11,014)	%	Upfront surgery (<i>n</i> = 79,052)	%
		<i>n</i>		<i>n</i>		<i>n</i>	
Age (years)							
< 45	13,864	73	0.5	2941	21.2	10,850	78.3
45–55	22,585	256	1.1	3346	14.8	18,983	84.1
55–65	24,117	605	2.5	2918	12.1	20,594	85.4
65–75	19,642	664	3.4	1548	7.9	17,430	88.7
75+	11,996	540	4.5	261	2.2	11,195	93.3
Race							
Caucasian	68,726	1658	2.4	7461	10.9	59,607	86.7
Black	10,631	223	2.1	1674	15.7	8734	82.2
Asian	2051	41	2.0	250	12.2	1760	85.8
Hispanic	6799	145	2.1	1011	14.9	5643	83.0
Other	3997	71	1.8	618	15.4	3308	82.8
Type of facility							
Community cancer center	8538	146	1.7	913	10.7	7479	87.6
Comprehensive community cancer center	40,365	840	2.1	4150	10.3	35,375	87.6
Academic/research center	27,126	782	2.9	3253	12.0	23,091	85.1
Integrated network cancer center	9853	348	3.5	1191	12.1	8314	84.4
Unknown	6322	22	0.4	1507	23.8	4793	75.8
Charlson–Deyo comorbidity score¹⁷							
0	76,502	1716	2.3	9653	12.6	65,133	85.1
1	12,619	325	2.6	1138	9	11,156	88.4
2+	3083	97	3.2	223	7.2	2763	89.6
Histology							
Invasive ductal carcinoma	65,416	1311	2.0	8687	13.3	55,418	84.7
Invasive lobular carcinoma	14,271	477	3.3	1234	8.7	12,551	88.0
Mixed ductal/lobular carcinoma	10,006	283	2.8	910	9.1	8813	88.1
Favorable/other histologies ^a	2511	67	2.7	174	6.9	2270	90.4
Grade							
1	13,880	572	4.1	1006	7.3	12,302	88.6
2	46,371	1131	2.4	4816	10.4	40,424	87.2
3	26,733	297	1.1	4284	16.0	22,152	82.9
Other/unknown	5220	138	2.6	908	17.4	4174	80.0
Clinical tumor category							
T1	9148	86	0.9	847	9.3	8215	89.8
T2	69,860	1429	2.0	6209	8.9	62,222	89.1
T3	10,572	407	3.9	2901	27.4	7264	68.7
T4	2624	216	8.2	1057	40.3	1351	51.5
Clinical nodal category							
N0	60,998	1564	2.6	4750	7.8	54,684	89.6
N1	31,206	574	1.8	6264	20.1	24,368	78.1
Breast surgical management							
Breast-conserving surgery	38,842	1076	2.8	3656	9.4	34,110	87.8
Mastectomy	53,349	1062	2.0	7357	13.8	44,930	84.2
Axillary staging procedure							
cN0							
SLNB attempt	52,294	1342	2.6	3793	7.2	47,159	90.2

TABLE 1 continued

Demographics (<i>n</i> = 92,204)	Total	NET (<i>n</i> = 2138) <i>n</i>	%	NAC (<i>n</i> = 11,014) <i>n</i>	%	Upfront surgery (<i>n</i> = 79,052) <i>n</i>	%
SLNB alone	36,420	1001	2.8	2668	7.3	32,751	89.9
SLNB + cALND	15,874	341	2.1	1125	7.1	14,408	90.8
Upfront ALND	8704	222	2.5	957	11.0	7525	86.5
cN1							
SLNB attempt	13,932	240	1.7	2491	17.9	11,201	80.4
SLNB alone	5319	118	2.2	1026	19.3	4175	78.5
SLNB + cALND	8613	122	1.4	1465	17.0	7026	81.6
Upfront ALND	17,274	334	1.9	3773	21.8	13,167	67.2

HR hormone receptor, *HER2* human epidermal growth factor receptor 2, *NET* neoadjuvant endocrine therapy, *NAC* neoadjuvant chemotherapy, *SLNB* sentinel lymph node biopsy, *cALND* completion axillary lymph node dissection, *ALND* axillary lymph node dissection

^aIncludes mucinous, metaplastic, tubular, papillary and medullary subtypes

disease, 70% (23,819/34,018) were treated with ALND (upfront or cALND). Among those treated with NET, NAC, or upfront surgery, the rates for ALND were respectively 57.4%, 79.1% and 69.1%.

Among 66,226 patients who had an attempted SLNB, 34% (22,544) were found to have pN1 disease (Table S3). Of these patients, 54.8% (12,345) underwent cALND, with a median of 11 lymph nodes (IQR, 7–16) removed, and 45.2% (10,199) underwent SLNB alone, with a median of 3 lymph nodes (IQR, 2–4) removed.

Among 13,856 cN0 patients found via SLNB to have pN1 disease by pairwise analysis, the NET patients were treated with cALND less frequently (37.7%, 152/403) than the NAC patients (54.2%, 504/930; $p < 0.001$) or the upfront surgery patients (50.7%, 6344/12,523; $p < 0.001$). The cALND rates were similar between the NAC and upfront surgery patients ($p = 0.11$).

These findings persisted in the adjusted analysis. Use of NET was associated with increased odds for patients to undergo SLNB alone (OR, 1.31; 95% CI, 1.04–1.64; Table 3). Age did not modify the effect of approach (NET, NAC, or upfront surgery) on receipt of SLNB versus ALND for cN0 patients with pN1 disease ($p = 0.76$, test for interaction).

Among 8688 cN1 patients found via SLNB to have pN1 disease by pairwise analysis, the NET patients were treated with cALND less frequently (50.4%, 68/135) than the NAC patients (64.6%, 750/1161; $p < 0.001$) or the upfront surgery patients (54.2%, 4527/7392; $p = 0.001$). The cALND rates were highest in the NAC population ($p = 0.03$ vs. upfront surgery). In the adjusted analysis, the cN1 patients treated with NET trended toward treatment with SLNB alone if pN1 disease was discovered (OR, 1.45; 95% CI, 1.00–2.10; $p = 0.0496$; Table 3). Similar to the cN0 cohort,

age did not modify the effect of the approach (NET, NAC or upfront surgery) on receipt of SLNB versus ALND for the cN1 patients with pN1 disease ($p = 0.82$, test for interaction).

Receipt of RNI

In this study, RNI was delivered to 63.7% (8483/13,324) of the pN2–3 patients and 41.2% (14,017/34,018) of the pN1 patients. Among the patients with pN1 disease who received SLNB alone, 40.2% (4100/10,199) received RNI (Table S4). The rates for RNI were similar between the NET and upfront surgery patients for the cN0 ($p = 1.00$) and cN1 ($p = 0.59$) cohorts, but RNI was more likely for the NAC patients ($p < 0.01$ for all comparisons). The NET patients were equally as likely as the upfront surgery patients to receive RNI if they had SLNB alone for pN1 disease in both the cN0 (OR, 1.13; 95% CI, 0.86–1.49) and cN1 (OR, 0.75; 95% CI, 0.44–1.29) populations (Table 4). The factors associated with increased odds of receiving RNI among both the cN0 and the cN1 patients were treatment with NAC, grade 3 disease, T3 tumors, and increasing number of positive nodes in the pathologic evaluation. Decreased odds of receiving RNI were observed for the cN0 patients undergoing mastectomy.

DISCUSSION

Application of results from randomized trials examining axillary management of clinically node-negative and node-positive patients has resulted in substantial reductions in the performance of ALND.^{18–22} Differences in nodal

TABLE 2 Factors associated with attempted SLNB in stages 2 and 3 HR+/HER2- patients according to clinical nodal status

Characteristic	Adjusted odds ratio (OR) ^a of attempted SLNB	
	cN0 (n = 60,998) OR (95% CI) ^b	cN1 (n = 31,206) OR (95% CI) ^b
Initial treatment approach		
Upfront surgery	Reference	Reference
Neoadjuvant endocrine therapy	1.01 (0.87–1.18)	0.95 (0.80–1.13)
Neoadjuvant chemotherapy	0.74 (0.68–0.80)	0.87 (0.82–0.93)
Age (years)		
< 45	1.15 (1.05–1.27)	1.25 (1.14–1.36)
45–54	1.14 (1.07–1.22)	1.14 (1.07–1.22)
55–64	Reference	Reference
65–74	0.98 (0.90–1.07)	0.95 (0.87–1.04)
75+	0.76 (0.69–0.83)	0.85 (0.76–0.95)
Type of facility		
Community cancer center	Reference	Reference
Comprehensive community cancer center	1.61 (1.50–1.73)	0.96 (0.88–1.05)
Academic/research center	1.82 (1.68–1.98)	0.82 (0.75–0.90)
Integrated network cancer center	2.07 (1.87–2.29)	1.05 (0.95–1.17)
Unknown	1.69 (1.41–2.02)	0.88 (0.75–1.04)
Histology		
Invasive ductal carcinoma	Reference	Reference
Invasive lobular carcinoma	1.06 (0.99–1.13)	1.14 (1.06–1.23)
Mixed ductal/lobular carcinoma	1.11 (1.02–1.20)	1.02 (0.95–1.23)
Favorable/other histologies	1.03 (0.90–1.17)	1.02 (0.95–1.10)
Grade		
1	Reference	Reference
2	0.88 (0.82–0.94)	0.75 (0.70–0.81)
3	0.79 (0.73–0.85)	0.62 (0.57–0.68)
Other/unknown	0.78 (0.69–0.87)	0.68 (0.60–0.76)
Clinical tumor category		
T1	–	1.07 (1.02–1.13)
T2	Reference	Reference
T3	0.71 (0.66–0.76)	0.85 (0.79–0.91)
T4	0.40 (0.35–0.45)	0.56 (0.49–0.63)
Breast surgery		
Breast-conserving surgery	Reference	Reference
Mastectomy	0.49 (0.47–0.52)	0.57 (0.55–0.60)

SLNB, sentinel lymph node biopsy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval

^aWith adjustment for race, insurance status, income, comorbidity score, year of diagnosis, and region of treatment

^bBold values are significant

disease burden and response to preoperative therapy, as predicated by tumor subtype,^{18,23} provide the opportunity to further define the optimal strategy for avoiding ALND.

High rates of breast and axillary pCR among HER2+ and triple-negative breast cancer patients have resulted in expanded use of NAC for these populations. In the HR+ clinically node-negative population, findings have

demonstrated that upfront surgery results in less ALND than NAC.²⁴ However, the impact of NET on the rates of SLNB versus ALND has not been examined in this population.^{18,24}

In this study, we assessed axillary management by initial treatment strategy (NET, NAC, or upfront surgery) among a large population of stages 2 and 3 HR+ breast cancer

TABLE 3 Factors associated with performance of SLNB alone as the definitive axillary surgery for stages 2 and 3 HR+/HER2– patients with pathologic node-positive (pN1) disease

Characteristic	Adjusted odds ratio (OR) ^a of SLNB alone	
	cN0 (n = 16,856) OR (95% CI) ^b	cN1 (n = 8688) OR (95% CI) ^b
Initial treatment approach		
Upfront surgery	Reference	Reference
Neoadjuvant endocrine therapy	1.31 (1.04–1.64)	1.45 (1.00–2.10)
Neoadjuvant chemotherapy	1.02 (0.88–1.19)	1.00 (0.86–1.16)
Age (years)		
< 45	0.96 (0.83–1.11)	1.20 (1.00–1.44)
45–54	0.99 (0.90–1.10)	1.10 (0.96–1.25)
55–64	Reference	Reference
65–74	1.08 (0.94–1.25)	1.25 (1.04–1.492)
75+	1.43 (1.21–1.69)	1.50 (1.21–1.86)
Type of facility		
Community cancer center	Reference	Reference
Comprehensive community cancer center	1.07 (0.93–1.23)	1.00 (0.85–1.18)
Academic/research center	1.08 (0.93–1.26)	0.95 (0.79–1.13)
Integrated network cancer center	1.02 (0.86–1.21)	0.89 (0.72–1.09)
Unknown	0.81 (0.61–1.08)	0.58 (0.41–0.81)
Histology		
Invasive ductal carcinoma	Reference	Reference
Invasive lobular carcinoma	1.21 (1.09–1.35)	1.20 (1.03–1.40)
Mixed ductal/lobular carcinoma	1.03 (0.92–1.16)	1.01 (0.86–1.19)
Favorable/other histologies	0.86 (0.61–1.20)	0.55 (0.34–0.87)
Grade		
1	Reference	Reference
2	0.87 (0.78–0.97)	0.73 (0.64–0.84)
3	0.80 (0.71–0.91)	0.61 (0.52–0.71)
Other/unknown	0.86 (0.71–1.05)	0.75 (0.59–0.95)
Clinical tumor category		
T1	–	1.00 (0.90–1.11)
T2	Reference	Reference
T3	1.13 (1.00–1.29)	1.05 (0.88–1.24)
T4	1.02 (0.77–1.35)	1.25 (0.90–1.73)
No. of LNs positive by pathologic evaluation		
1	Reference	Reference
2	0.38 (0.35–0.41)	0.46 (0.42–0.52)
3	0.20 (0.17–0.23)	0.30 (0.25–0.34)
Breast surgery		
Breast-conserving surgery	Reference	Reference
Mastectomy	0.27 (0.25–0.29)	0.38 (0.35–0.42)

SLNB, sentinel lymph node biopsy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval; LN, lymph node

^aWith adjustment for race, insurance status, income, comorbidity score, year of diagnosis, and region of treatment

^bBold values are significant

TABLE 4 Factors associated with receipt of regional nodal irradiation (RNI) by patients with pN1 disease who underwent SLNB alone as their definitive axillary surgery

Characteristic	Adjusted odds ratio (OR) ^a of RNI receipt	
	cN0 (n = 2670) OR (95% CI) ^b	cN1 (n = 1430) OR (95% CI) ^b
Initial treatment approach		
Upfront surgery	Reference	Reference
Neoadjuvant endocrine therapy	1.13 (0.86–1.49)	0.75 (0.44–1.29)
Neoadjuvant chemotherapy	1.85 (1.50–2.29)	1.91 (1.51–2.42)
Age (years)		
< 45	1.23 (1.00–1.52)	1.30 (0.97–1.72)
45–54	1.08 (0.94–1.25)	1.25 (1.02–1.53)
55–64	Reference	Reference
65–74	1.02 (0.84–1.24)	1.10 (0.83–1.45)
75+	0.67 (0.54–0.85)	0.70 (0.50–0.97)
Type of facility		
Community cancer center	Reference	Reference
Comprehensive community cancer center	0.92 (0.76–1.12)	0.95 (0.74–1.23)
Academic/research center	0.89 (0.73–1.09)	0.98 (0.75–1.30)
Integrated network cancer center	1.04 (0.82–1.32)	1.6 (1.21–2.28)
Unknown	0.53 (0.36–0.79)	0.73 (0.44–1.22)
Histology		
Invasive ductal carcinoma	Reference	Reference
Invasive lobular carcinoma	1.16 (0.99–1.35)	1.02 (0.81–1.30)
Mixed ductal/lobular carcinoma	1.30 (1.10–1.52)	1.11 (0.86–1.42)
Favorable/other histologies	0.78 (0.48–1.26)	1.07 (0.74–1.53)
Grade		
1	Reference	Reference
2	1.17 (1.01–1.35)	1.20 (0.99–1.46)
3	1.27 (1.07–1.50)	1.47 (1.17–1.86)
Other/unknown	1.30 (0.98–1.71)	1.07 (0.74–1.53)
Pathologic tumor category		
T0	0.87 (0.33–2.60)	1.04 (0.58–1.87)
T1	0.91 (0.80–1.04)	0.99 (0.85–1.16)
T2	Reference	Reference
T3	2.20 (1.84–2.64)	1.64 (1.19–2.28)
T4	1.39 (0.79–2.46)	0.80 (0.37–1.73)
No. of LNs positive by pathologic evaluation		
1	Reference	Reference
2	1.86 (1.63–2.12)	1.54 (1.29–1.83)
3	2.32 (1.81–2.98)	1.71 (1.31–2.23)
Breast surgery		
Breast-conserving surgery	Reference	Reference
Mastectomy	0.69 (0.62–0.77)	0.93 (0.79–1.09)

SLNB, sentinel lymph node biopsy; CI, confidence interval; LN, lymph node

^aWith adjustment for race, insurance status, income, Charlson–Deyo comorbidity score, year of diagnosis, and region of treatment^bBold values indicate significance

patients and found that SLNB use after NET in both clinically node-negative and node-positive patients was similar to SLNB use with upfront surgery. However, among the patients with pN1 disease, those who received NET were less likely to undergo ALND. Use of RNI was similar among the pN1 patients who received NET or upfront surgery.

Although NET has proved to be effective in increasing breast conservation rates,^{25,26} axillary management after NET remains understudied. The ACOSOG Z1031 trial randomized post-menopausal patients to 16 weeks of pre-operative treatment with three aromatase inhibitors (AIs).²⁵ The patients with a poor response to NET, determined by a tumor Ki67 proliferation index higher than 10% after AI exposure, were switched to chemotherapy.²⁷ The trial did not pre-specify nodal management, but did report the definitive axillary surgery performed (SLNB or ALND). Despite similar rates of nodal positivity in the AI-alone cohort (44%) and the NAC cohort (43%), the patients who received AI alone were less likely to undergo ALND (33% vs. 69%). Although limited, these data are consistent with our findings that fewer NET-treated patients with positive nodes go on to receive cALND.

In this retrospective NCDB analysis, selection bias may have accounted for some of the lower odds of cALND among the NET patients. The patients who received NET were older, and it is well documented that axillary management in the older population can be more variable. We attempted to control for this potential bias with a multivariate analysis and an interaction analysis between age and initial treatment approach, which was not significant. Other explanations include coding inaccuracies or missing clinical information in the NCDB, such as no reliable measure of clinical response, which could help explain surgical and radiation decision making.

Finally, a seemingly large percentage (46%) of upfront surgery patients with cN1 disease received an attempted SLNB in this study, which may have skewed the cALND comparisons. This paradox also may be explained by coding inaccuracies. The type of axillary surgery was not recorded in the NCDB until 2012. Previously, the only axillary information available was the number of nodes examined and the number of positive nodes, so this relatively new data point may be inaccurate. An alternative explanation may be the NCDB definition of cN1 as positive nodes by palpation or fine-needle aspiration.

Since the initial publication of ACOSOG Z0011, several groups have reported that the use of ultrasound and even positive fine-needle aspiration does not accurately predict the need for ALND nor mandate its use.^{28,29} This level of nuanced decision making is not captured in the NCDB.

Thus, investigations into more granular institutional data and prospective clinical trials in the HR+ patient population are warranted.

A lack of consistency in axillary management evidenced by this study calls for a review of standard practices. Although only 86.2% of the cN0 upfront surgery patients underwent an attempted SLNB in this study, the recommendations for cN0 patients include axillary staging with SLNB. If one or two positive SLNs are identified further, axillary management is based on initial treatment strategy. In the upfront surgery population, omission of ALND is accepted for patients with micrometastases,¹ for those with macrometastases in one or two SLNs when breast conservation is performed,³ and for those with one or two positive SLNs when mastectomy is followed by post-mastectomy radiotherapy (PMRT).⁵ Patients with three or more positive nodes should receive both ALND and RNI.³⁰ If patients are treated with NAC and any size nodal metastasis is discovered in the pathologic evaluation, cALND is recommended because patients treated with NAC were not included in the Z0011, IBCSG 23-01, or AMAROS trials.

Among the cN1 population, axillary management also depends on the initial treatment strategy. ALND is recommended if a patient proceeds to upfront surgery. However, if a cN1 patient is treated with NAC and experiences a clinical nodal response, SLNB may be performed, and ALND may be potentially avoided if the patient experiences a pCR. Limited data exist to guide RNI decisions for patients who have a complete nodal response to NAC, but an ongoing clinical trial (NSABP-B51³¹) is examining the omission of RNI after SLNB for patients who achieve a pCR after neoadjuvant chemotherapy.

Contemporary studies have highlighted the significance of residual disease after NAC for LRR in both the breast-conserving therapy^{32,33} and mastectomy³⁴ cohorts by molecular subtype. It is well documented that patients with HR+ breast cancer are less likely to achieve a pCR after NAC than patients with other breast cancer subtypes.^{18,23} As such, studies addressing optimal management strategies for HR+ patients who remain node-positive after preoperative therapy are needed, such as the Alliance for Clinical Trials in Oncology A011202³⁵ trial evaluating whether axillary radiation is equivalent to ALND for patients who remain pathologically node-positive after NAC. This study will further inform management of HR+ clinically node-positive patients who receive NAC. However, patients treated with NET are excluded.

Unless enrolled on a clinical trial, the current recommendations for cN1 patients with residual nodal disease after NAC include ALND and RNI. In this study, the rates of cALND for NAC patients found to have pN1 disease seemed to be low (54% of cN0 and 65% of cN1 patients). It is impossible to determine within the scope of the NCDB

whether these variations in practice exist due to lack of knowledge or lack of agreement, but it is important to study these variations to highlight areas of insufficient best practice dissemination for surgeons.

As expected, the patients with cN0 or cN1 disease treated with NET were more likely to have residual nodal disease, yet they paradoxically were less likely to undergo cALND than the patients treated with NAC. It remains uncertain whether failure to achieve a pCR after NET in HR+ disease portends a poor prognosis and what impact residual nodal disease after NET may have on LRR. To further complicate selection of the proper initial treatment strategy and subsequent axillary management for HR+ breast cancer patients, no standard recommendations exist for patients treated with NET despite its increasing use.

In conclusion, in this analysis of NCDB data, the use of SLNB to stage the axilla for patients with stage 2 or 3 HR+ breast cancer was similar between the patients treated with NET and those treated with upfront surgery. Among the patients with pathologic nodal disease discovered by sentinel node biopsy, those who received NET were less likely to undergo cALND. None of the existing trials or guidelines for axillary management have included significant numbers of patients receiving NET, and outcomes data are needed to guide optimal axillary management for this patient population.

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