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Factors Associated With Additional Axillary Disease in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy for Breast Cancer

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Abstract

Background: In previous studies, breast cancer patients with positive sentinel lymph node(s) (SLN) after neoadjuvant chemotherapy (NAC) frequently had additional nonSLN involvement. Per guidelines, residual SLN disease warrants completion axillary lymph node dissection (cALND), which has increased morbidity. Given recent improvements in NAC, we hypothesized that nonSLN positivity may be lower than previously reported for certain subgroups.

Methods: We retrospectively reviewed breast cancer patients who received NAC and had positive lymph nodes on SLN biopsy or targeted axillary dissection and underwent cALND at one institution in 1/2018-8/2023. Associations between nonSLN positivity and clinicopathologic factors were assessed with Fisher's exact test and multivariable logistic regression.

Results: There were 122 female patients. Median age was 48 years. Initially, 15 patients (12.3%) were cN0 and 107 patients (87.7%) were cN1. Largest SLN deposit was macrometastasis in 96 patients (78.7%), micrometastasis in 23 patients (18.9%), and isolated tumor cells in 3 patients (2.5%). Overall, 53 patients (43.4%) had nonSLN involvement. NonSLN positivity was higher in patients with cN1, ER+ HER2-, ypT2-3, SLN macrometastasis, and multiple positive SLN. On multivariable analysis, cN1 and ER+ HER2- remained associated with nonSLN positivity.

Discussion: Among patients with positive SLN after NAC, clinically node positive and ER+ HER2- patients were more likely to have nonSLN involvement. Our findings support guidelines to consider omitting cALND in clinically node negative patients. With improving NAC, optimal axillary sampling, and radiation, omitting cALND may be safe in some clinically node positive triple negative or HER2+ patients with low volume residual disease, but further research is needed.

Keywords

breast cancer, neoadjuvant chemotherapy, axillary lymph node dissection, lymph node metastasis

Key Takeaways

- Among patients with positive sentinel lymph nodes after neoadjuvant chemotherapy, 43% had additional nonsentinel lymph node involvement and rates were higher in patients with clinically positive nodes, ER+ HER2- subtype, large residual tumor in the breast (ypT2-3), sentinel lymph node macrometastasis, and multiple positive sentinel lymph nodes.
- On multivariable analysis, clinically positive nodes and ER+ HER2- subtype remained significantly associated with nonsentinel lymph node positivity.
- With recent improvements in neoadjuvant chemotherapy, the proportion of patients with positive nonsentinel lymph nodes was lower than previously reported for some subgroups, particularly

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clinically node positive triple negative or HER2+ patients with minimal residual disease in the breast and sentinel lymph nodes.

Introduction

Over the last 2 decades, the use of neoadjuvant chemotherapy (NAC) for operable breast cancer has increased and there have been improvements in its efficacy. The advantages of NAC include in vivo assessment of response, which has prognostic significance and therapeutic implications, and tumor downstaging may enable less extensive surgery in the breast and axilla.[1-4] Patients who convert from clinically node positive to clinically node negative after NAC can undergo targeted axillary dissection. However, if there is residual disease in sentinel lymph node(s) (SLN) after NAC, guidelines recommend completion axillary lymph node dissection (ALND), which is associated with significant risks and morbidity including lymphedema, restricted arm movement, nerve deficits, and pain.[1-3] The recommendation for completion ALND is based on concerns that residual tumor is chemotherapy resistant and initial nodal burden may be underestimated after partial response. Also, previous small retrospective studies have found that the proportion of patients with positive SLN who have additional nonSLN involvement is much higher after NAC than in the upfront surgery setting.[2-8] However, there is limited and inconsistent data on clinicopathologic factors, including volume of SLN disease, that may impact the probability of positive nonSLN after NAC since those patients underwent immediate ALND until recently.[2-8] If nonSLN positivity could be predicted, then some patients could be safely spared from completion ALND.

There have been few small retrospective studies examining additional nonSLN involvement in patients with positive SLN after NAC, and most were conducted internationally. The median number of patients included in these studies was 171 (range 75-384) and some patients received treatment 15-20 years ago. By including patients who were treated so long ago, the results may not reflect outcomes with current NAC. There are variations between the studies with respect to initial clinical nodal stage(s), SLN mapping techniques, inclusion/classification of SLN isolated tumor cells (ITC), and use of immunohistochemistry. NonSLN positivity rates were 44-62%.[2-8] In the studies that compared patients who were initially clinically node negative vs positive, nonSLN positivity rates were 29-54% vs 47-71%, which was significantly lower in some but not all studies.[3-6] An association between positive nonSLN and SLN metastasis size was found in some studies[2,3,7] but not in other studies.[4,8] The number of positive SLN was a risk factor for positive nonSLN in most studies.[2-4,6,7] Other identified risk factors for positive nonSLN included: SLN extracapsular extension,[4] lymphovascular invasion,[2,5] pathologic tumor size or stage,[2,5] multifocal/multicentric tumor,[3,5] hormone receptor positivity,[6,7] and HER2 negativity.[3] The details of these previously published studies are shown in Table 1.

Given recent improvements in NAC, we hypothesized that nonSLN positivity may be lower than previously reported for certain subgroups of patients. The objective of this study was to determine if volume of residual SLN disease or other clinicopathologic factors are associated with additional nonSLN involvement after modern NAC.

Methods

The Institutional Review Board at City of Hope approved this study (protocol number 21247) and granted a waiver from informed consent. This study is a retrospective review at a single tertiary cancer center between January 2018 and August 2023. Patients with breast cancer who received NAC and had positive lymph nodes on SLN biopsy or targeted axillary dissection and underwent completion ALND were identified. Included patients received at least 4 cycles of NAC and those who were clinically node positive initially converted to clinically node negative after NAC. Clinical nodal status was assessed by physical exam for resolution of palpable lymphadenopathy in all patients. Post-treatment imaging was obtained at the discretion of the surgeon and medical oncologist (not standardized). SLN mapping was performed using dual tracers technetium-99 sulfur colloid and isosulfan blue and clipped lymph nodes were localized using seeds or wires for targeted axillary dissection. The decision to assess SLN using intraoperative frozen section was up to the surgeon's discretion and completion ALND could be performed immediately or at a subsequent operation. Lymph nodes were sliced into 2 mm thick sections and were stained with hematoxylin and eosin and immunohistochemistry for cytokeratin AE1-AE3. Lymph node metastasis size was classified according to the American Joint Committee on Cancer 8th Edition breast cancer staging guidelines: ≤.2 mm or 200 tumor cells were classified as ITC, .2-2.0 mm were classified as micrometastasis, and >2.0 mm were classified as macrometastasis.[1]

Demographic (age, race, ethnicity, and menopausal status), clinical, pathologic, treatment (NAC, surgery, adjuvant systemic therapy, and adjuvant radiation), and outcomes (recurrence and death) data were examined. Data were summarized as frequency for categorical variables and median with range or mean with standard deviation for continuous variables. Independent *t* test, Fisher's exact test, or Chi-squared test were used for between groups comparisons. A multivariable logistic regression was performed to assess associations between clinicopathologic factors and nonSLN positivity. Data

Table 1. Previously Published Retrospective Studies Examining Additional Nonsentinel Lymph Node Involvement in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy.

					Risk Factors for Positive nonSLN							
First Author	Location	Years	# of Patients	Positive nonSLN (%)	cN+	SLN met Size	# Of +SLN	LVI	pT Size or Stage	Multifocal	HR+	HER2-
Jeruss[5]	US	1997-2005	104	56	X			X	X	X		
Ryu[2]	Korea	2008-2014	140	49		X	X	X	X			
Liedtke[7]	Germany	2009-2012	75	55		X	X				X	
Leonardi[4]	Italy	2001-2017	265	62	X		X					
Chun[6]	Korea	2005-2016	384	44	X		X				X	
Moo[8]	US	2008-2017	171	61								
Sanders[3]	US	2006-2021	229	56		X	X			X		X

US, United States; SLN, sentinel lymph node(s); met, metastasis; LVI, lymphovascular invasion; HR, hormone receptor (estrogen or progesterone); HER2, human epidermal growth factor receptor 2.

were checked for multicollinearity with the Belsley-Kuh-Welsch technique. Heteroskedasticity and normality of residuals were assessed by the Breusch-Pagan test and the Shapiro-Wilk test, respectively. Odds ratios with 95% confidence intervals were reported. A P-value <.05 was considered statistically significant. Statistical analyses were conducted using SPSS® (IBM® SPSS® Statistics Version 25.0).

Results

There were 122 female patients. Demographic, clinical, and biopsy pathologic characteristics of all patients are shown in Table 2. The median age was 48 years (range 21-79 years) and 80/122 patients (65.6%) were premenopausal. Biologic subtype was ER+ HER2- in 81/122 patients (66.4%), HER2+ in 22/122 patients (18.0%), and triple negative in 19/122 patients (15.6%). The majority of patients (105/122, 86.1%) were clinical tumor stage 2 and 3. Prior to NAC, 15/122 patients (12.3%) were clinically node negative and 107/122 patients (87.7%) were clinically node positive (cN1). Among the patients with clinically positive nodes, 106/107 (99.1%) were histologically confirmed by core needle biopsy and 103/107 (96.3%) had clip placement allowing for subsequent localization for targeted axillary dissection. NAC regimens included doxorubicin/cyclophosphamide/paclitaxel (AC-T), docetaxel/cyclophosphamide (TC), docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP), and paclitaxel/carboplatin/doxorubicin/cyclophosphamide (TC-AC) with or without pembrolizumab. To assess treatment response among the patients who were initially clinically node positive, 33/107 (30.8%) had ultrasound and MRI, 27/107 (25.2%) had ultrasound, 27/107 (25.2%) had MRI, and 20/107 (18.7%) had no imaging. Of the patients who were initially clinically node negative, 3/15 (20.0%) had ultrasound and MRI, 4/15 (26.7%) had ultrasound, 2/15 (13.3%) had MRI, and 6/15 (40.0%) had no imaging.

Operative and surgical pathologic characteristics of all patients are shown in Table 3. Only 16/122 patients (13.1%) had pathologic complete response in the breast. Among patients with residual disease in the breast, the median pathologic tumor size was 1.6 cm (range .1-9.5 cm). The initial axillary operation was SLN biopsy in 19/122 patients (15.6%), including 15 patients who were clinically node negative and 4 patients who were clinically node positive but did not have their lymph node biopsied (n = 1) or clipped (n = 3) prior to NAC, and targeted axillary dissection in 103/122 patients (84.4%) who converted from clinically node positive to negative after NAC. The median number of SLN removed was 3 (range 1-16) and the median number of positive SLN was 1 (range 1-6). The median number of nonSLN removed was 9 (range 1-32). Intraoperative frozen section assessment of SLN was performed in 115/122 patients (94.3%) and was true positive in 97/115 patients (sensitivity 84.3%) and false negative in 18/115 patients (false negative rate 15.7%). Among the patients with false negative intraoperative frozen section, the largest SLN metastasis size was macrometastasis in 7/18 patients (38.9%), micrometastasis in 9/18 patients (50.0%), and ITC in 2/18 patients (11.1%). The proportion of patients with SLN ITC/micrometastasis was higher in those who had false negative intraoperative frozen section compared to those who had true positive intraoperative frozen section (11/18 61.1% vs 15/97 15.5%, $P < .001$).

Additional nonSLN involvement was present in the completion ALND specimens of 53/122 patients (43.4%). Additional nonSLN involvement was found in 1/3 patients (33.3%) with SLN ITC, 4/23 patients (17.4%) with SLN micrometastasis, and 48/96 patients (50.0%) with SLN macrometastasis ($P = .017$) (Figure 1). The mean number of positive nonSLN was greater in patients with SLN macrometastasis (1.4 ± 2.3) than in patients with SLN ITC/micrometastasis (.5 ± 1.1) ($P = .039$). On univariable analysis (Table 4), there were significantly higher rates of

Table 2. Demographic, Clinical, and Biopsy Pathologic Characteristics of All Patients With Breast Cancer Who Received Neoadjuvant Chemotherapy and Had Positive Sentinel/Targeted Lymph Nodes and Underwent Completion Axillary Lymph Node Dissection.

		n	% (Total = 122)
Age (years)	≤39	16	13%
	40-49	56	46%
	50-59	30	25%
	≥60	20	16%
Race/ethnicity	Non-Hispanic White	41	34%
	Hispanic/Latina	42	34%
	Asian/Pacific Islander	33	27%
	Black/African American	6	5%
Menopausal status	Premenopausal	80	66%
	Postmenopausal	42	34%
Clinical tumor stage	1	15	12%
	2	78	64%
	3	27	22%
	4	2	2%
Clinical nodal stage	0	15	12%
	1	107	88%
Histology	Invasive ductal carcinoma	108	89%
	Invasive lobular carcinoma	14	11%
Grade	1	4	3%
	2	68	56%
	3	50	41%
Biomarkers	ER+ HER2-	81	66%
	HER2+	22	18%
	Triple negative	19	16%
Ki-67	≤15%	39	32%
	16-39%	50	41%
	≥40%	33	27%
Lymphovascular invasion		26	21%

ER, estrogen receptor, HER2, human epidermal growth factor receptor 2.

positive nonSLN among patients who had clinically positive nodes, ER+ HER2- subtype, large residual tumor in the breast (ypT2-3), SLN macrometastasis, and more than one positive SLN. On multivariable analysis (Table 5), clinically positive nodes and ER+ HER2- subtype remained significantly associated with nonSLN positivity. There was a trend toward higher nonSLN positivity in premenopausal patients, but it did not reach statistical significance. Additional nonSLN involvement was not associated with histology (invasive ductal carcinoma vs invasive lobular carcinoma), grade, Ki-67, multifocality/multicentricity, or lymphovascular invasion. NonSLN positivity rates stratified by clinical nodal stage, biologic subtype, and SLN metastasis size are depicted in Figure 2. No patients who were clinically node negative with triple negative or HER2 + tumors had positive nonSLN. No patients who were clinically node negative with SLN ITC/micrometastasis had positive nonSLN.

The vast majority of patients received adjuvant systemic therapy (116/122, 95.1%) and adjuvant radiation (120/122, 98.4%). Adjuvant systemic therapy regimens included endocrine therapy ± abemaciclib, trastuzumab ± pertuzumab ± endocrine therapy, ado-trastuzumab emtansine ± endocrine therapy, capecitabine, pembrolizumab, and olaparib. At median follow-up of 2.7 years (range .5-6.2 years), 17/122 patients (13.9%) had recurrence at one or more sites. 3/122 patients (2.5%) had ipsilateral breast or chest wall recurrence, 2/122 patients (1.6%) had axillary recurrence, and 16/122 patients (13.1%) had distant recurrence. Death occurred in 2/122 patients (1.6%); 1 patient died due to distant recurrence and 1 patient died of unknown causes.

Discussion

Overall, 43.4% of patients with residual SLN disease after NAC had additional nonSLN involvement at completion ALND. The rate of nonSLN positivity was significantly lower in patients with SLN ITC/micrometastasis compared to SLN macrometastasis (19.2% vs 50.0%). Those who were ER+ HER2- and clinically node positive were more likely to have positive nonSLN. Large residual tumor in the breast, SLN macrometastasis, and multiple positive SLN were also associated with nonSLN positivity on univariable analysis but did not remain significant on multivariable analysis.

The proportion of patients who had additional nonSLN involvement in our study was at the low end of the range reported in previous studies (44-62%).[2-8] This finding probably reflects recent improvements in the efficacy of NAC as our study was conducted during the most current time period. Recent advances in NAC have especially benefited HER2+ and triple negative patients so that may explain why ER+ HER2- patients had higher nonSLN positivity in our study but not in most previous studies. Our finding of lower nonSLN positivity in patients who were initially clinically node negative is consistent with several previous studies.[3-6] Large residual tumor in the breast, SLN metastasis size, and multiple positive SLN have been identified as risk factors for additional nonSLN involvement in some previous studies[2-7] and may not have remained significant on multivariable analysis in our study because of the small sample size.

NonSLN positivity among patients with SLN ITC/micrometastasis was lower than previously reported (up to 58%).[4,8] Previous studies that found high rates of nonSLN involvement even with low volume residual SLN disease have led to ongoing recommendations for completion ALND. In our study, the rate of positive nonSLN in patients with SLN ITC/micrometastasis after NAC was as low as during upfront surgery in previous studies (10-20%).[9-11] In the upfront surgery setting,

Table 3. Operative and Surgical Pathologic Characteristics of All Patients With Breast Cancer Who Received Neoadjuvant Chemotherapy and Had Positive Sentinel/Targeted Lymph Nodes and Underwent Completion Axillary Lymph Node Dissection.

			n % (Total = 122)
Breast operation	Partial mastectomy	31	25%
	Mastectomy	91	75%
Initial axillary operation	SLN biopsy	19	16%
	Targeted axillary dissection	103	84%
Pathologic tumor stage	0/is	16	13%
	1	64	52%
	2	36	30%
	3	6	5%
Pathologic multifocality		40	33%
Number of SLN	1	16	13%
	2	24	20%
	3	27	22%
	≥4	55	45%
SLN metastasis size	Isolated tumor cells	3	2%
	Micrometastasis	23	19%
	Macrometastasis	96	79%
Number of positive SLN	1	75	61%
	2	26	21%
	3	15	12%
	≥4	6	5%
NonSLN metastasis size	None	68	56%
	Isolated tumor cells	1	1%
	Micrometastasis	12	10%
	Macrometastasis	41	34%
Number of positive nonSLN	0	69	57%
	1	22	18%
	2	13	11%
	≥3	18	15%

SLN, sentinel lymph node(s).

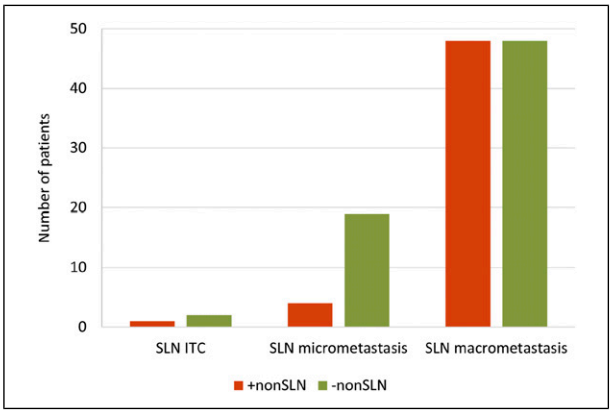


Figure 1. Additional nonsentinel lymph node (SLN) involvement was present in 1/3 patients (33.3%) with SLN isolated tumor cells (ITC), 4/23 patients (17.4%) with SLN micrometastasis, and 48/96 patients (50.0%) with SLN macrometastasis (P = .017).

randomized controlled trials have established that outcomes are equivalent after adjuvant radiation without ALND for patients with low volume SLN disease. However, it remains unknown whether a comparably low rate of positive nonSLN in patients with low volume SLN disease after NAC would translate to a similar lack of improvement in recurrence or survival with ALND compared to radiation that has been seen with upfront surgery.[11,12]

The sensitivity (84.3%) and false negative rate (15.7%) of intraoperative frozen section in our study were comparable to or better than previous studies.[8,13] The proportion of patients with SLN ITC/micrometastasis was higher in those who had false negative intraoperative frozen section compared to those who had true positive intraoperative frozen section. This is consistent with previous studies showing that low volume SLN disease is more likely to be missed on intraoperative frozen section.[8,13] Our findings suggest that for patients who are initially clinically node negative or have a low probability of positive nonSLN, it is not necessary to assess SLN with intraoperative frozen section or prepare for completion ALND and prophylactic lymphatic reconstruction; rather it may be advisable to wait for final pathology to assess the residual tumor burden.

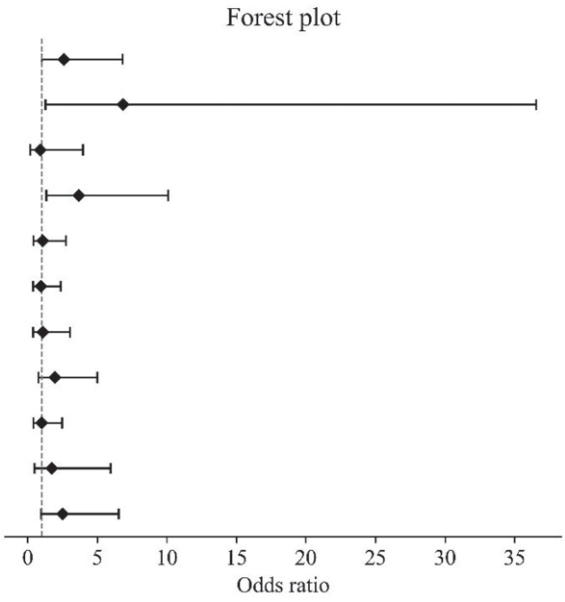
Table 4. Univariable Analysis of Associations Between Nonsentinel Lymph Node Positivity and Clinicopathologic Factors in Patients With Breast Cancer Who Received Neoadjuvant Chemotherapy and had Positive Sentinel/Targeted Lymph Nodes and Underwent Completion Axillary Lymph Node Dissection.

	NonSLN Positivity (%)	OR [95% CI]	*P*
Premenopausal vs postmenopausal	50% vs 31	2.2 [1.0-4.9]	.068
Clinical nodal stage 1 vs 0	48% vs 13	5.9 [1.3-27.5]	**.013**
Invasive lobular vs ductal carcinoma	50% vs 43	1.4 [.4-4.1]	.776
ER +HER2- vs HER2+/triple negative	54% vs 22	4.2 [1.8-10.0]	**.001**
Grade 1-2 vs 3	51% vs 32	2.3 [1.1-4.8]	.052
Ki-67 ≤ 20% vs > 20%	50% vs 39	1.6 [.8-3.3]	.283
Lymphovascular invasion present vs absent	50% vs 42	1.4 [.6-3.3]	.591
Pathologic tumor stage 2-3 vs 0-1	57% vs 36	2.3 [1.1-5.0]	**.043**
Multifocal vs unifocal	45% vs 43	1.1 [.5-2.4]	.962
SLN macrometastasis vs ITC/micrometastasis	50% vs 19	4.2 [1.5-12.1]	**.010**
≥2 vs 1 positive SLN	57% vs 35	2.5 [1.2-5.4]	**.022**

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; SLN, sentinel lymph node; ITC, isolated tumor cells.
Bolded p values are significant <.05.

Table 5. Multivariable Analysis of Associations Between Nonsentinel Lymph Node Positivity and Clinicopathologic Factors in Patients With Breast Cancer Who Received Neoadjuvant Chemotherapy and Had Positive Sentinel/Targeted Lymph Nodes and Underwent Completion Axillary Lymph Node Dissection.

	OR [95% CI]	p
Premenopausal	2.6 [1.0-6.8]	0.050
Clinical nodal stage 1	6.9 [1.3-36.5]	**0.024**
Invasive lobular carcinoma	0.9 [0.2-4.0]	0.878
ER+ HER2-	3.7 [1.3-10.1]	**0.012**
Grade 1-2	1.1 [0.4-2.8]	0.873
Ki-67 ≤ 20%	1.0 [0.4-2.4]	0.931
Lymphovascular invasion	1.1 [0.4-3.0]	0.881
Pathologic tumor stage 2-3	2.0 [0.8-5.0]	0.151
Multifocal/multicentric	1.0 [0.4-2.5]	0.979
SLN macrometastasis	1.7 [0.5-6.0]	0.383
≥ 2 positive SLN	2.5 [1.0-6.6]	0.057



ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; SLN, sentinel lymph node; ITC, isolated tumor cells.
Bolded p values are significant <.05.

Our study supports guidelines to consider axillary radiation without completion ALND in clinically node negative patients who have positive SLN after NAC.[1] Our findings especially support omission of completion ALND in clinically node negative patients with triple negative tumors, HER2+ tumors, or SLN ITC or micrometastases as none of these patients had positive nonSLN. With improving systemic therapy, optimal axillary sampling, and adjuvant radiation, omitting completion ALND may be safe in some patients with triple negative or HER2+ tumors who were clinically node positive and have minimal residual disease in the breast and SLN, but further research is needed to define that subgroup.

Disease free survival and overall survival are negatively impacted by even low volume residual nodal disease and are progressively worse with increasing nodal involvement, but that is not mitigated by ALND.[14,15] This finding likely reflects tumor biology in these patients who

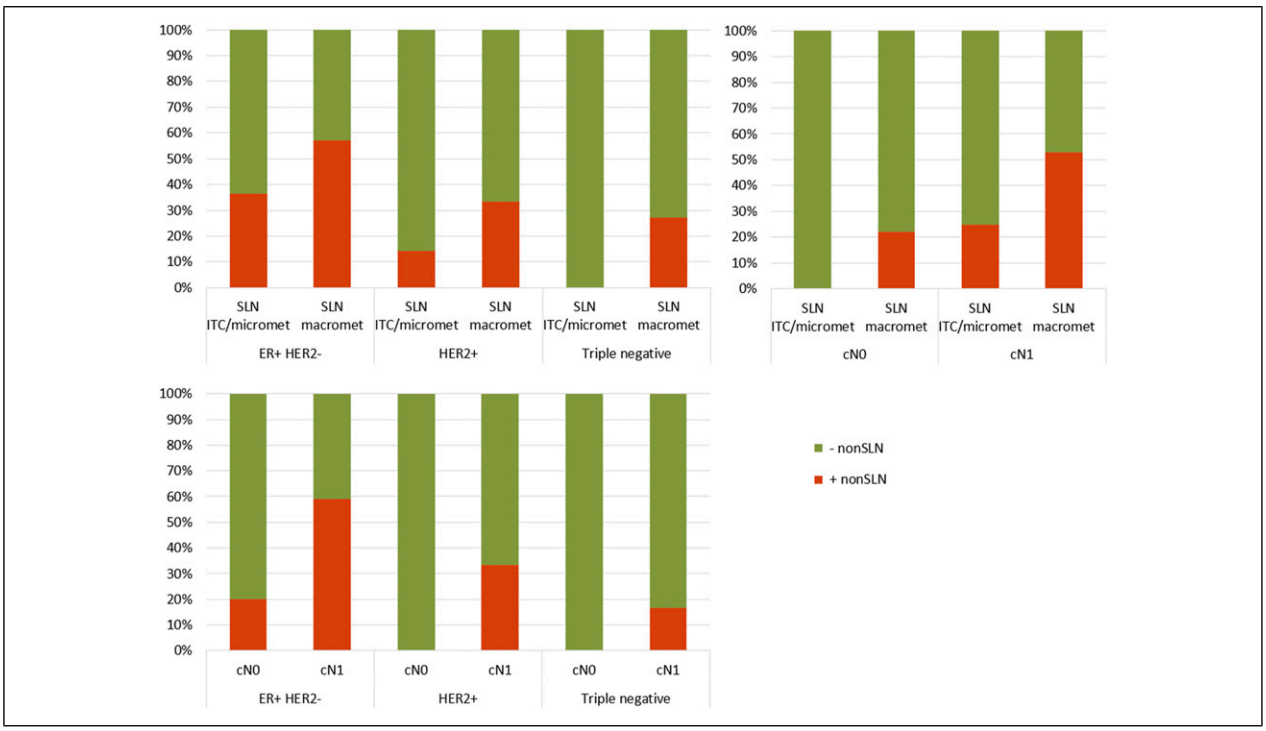


Figure 2. Nonsentinel lymph node positivity rates stratified by clinical nodal stage, biologic subtype, and sentinel lymph (SLN) metastasis size. No patients who were clinically node negative with triple negative or HER2+ tumors or SLN ITC/micrometastasis had positive nonSLN.

are more likely to be affected by distant metastasis than locoregional recurrence. Retrospective analysis of data from two national contemporary clinical trials on NAC (NSABP B40 and B41) found no increased recurrence without completion ALND in patients with residual SLN disease.[16] However, there is not yet level I evidence about recurrence after omission of ALND, so ALND remains the current standard of care for residual SLN disease after NAC.[1] The Alliance A011202 randomized controlled trial is currently comparing recurrence after axillary radiation vs completion ALND in patients with positive SLN after NAC.[17] While awaiting results of that trial, our study provides important information about the probability of additional nonSLN involvement that may help identify subgroups of patients with residual SLN disease after NAC who can be spared from completion ALND.

The significant limitations of this study include its single institution retrospective design and small sample size. There were very few patients who had SLN ITC so they were grouped with patients who had SLN micrometastasis for more powerful statistical analysis. There were too few patients who were initially clinically node negative to separately analyze risk factors for positive nonSLN in that subgroup. Also, our study only included patients who had completion ALND so there may be a selection bias for higher risk clinically node negative patients as lower risk patients may not have had completion ALND. Given the short follow-up, recurrence was not a primary outcome but has been included for completeness and should be interpreted with caution. The number of patients who had recurrence was insufficient to analyze factors associated with recurrence in this study.

Potential areas of future research include improving prediction of nonSLN positivity with additional information from imaging,[18] ctDNA testing,[19] and pathologic techniques such as one-step nucleic acid amplification to quantify tumor volume in SLN.[20] Also, data from several published studies could be compiled to develop a more comprehensive nomogram to predict additional nonSLN involvement in patients with residual SLN disease after NAC.

Declaration of Conflicting Interests

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