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ORIGINAL ARTICLE – BREAST ONCOLOGY

Impact of Residual Nodal Disease Burden on Technical Outcomes of Sentinel Lymph Node Biopsy for Node-Positive (cN1) Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

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ABSTRACT

Background. Recent trials have demonstrated the feasibility of sentinel lymph node biopsy (SLNB) for cN1 breast cancer patients after neoadjuvant chemotherapy (NAC). This study evaluated the technical outcomes of SLNB by residual nodal disease volume.

Methods. From a prospective database, cT1-3 cN1 patients receiving NAC and surgery from 2016 to 2017 were identified. Performance measures of post-NAC physical exam and imaging-based axillary assessment were compared. For the patients who converted to cN0 and underwent SLNB, adequate mapping (defined as $\geq$ 3 SLN) and the false-negative rate (FNR) of intraoperative SLN evaluation were assessed by residual nodal disease volume (ypN1-3 vs ypN0[i+]/ypN1mi vs ypN0).

Results. Of 156 cT1-3 cN1 patients, 96 converted to cN0 and underwent SLNB. Adequate mapping was achieved for 64 patients (66.7%) and was not associated with nodal volume ($p = 0.12$). The FNR of the intraoperative SLN evaluation was 37.8%, and smaller nodal volume was associated with FNR ($p < 0.01$). Of 36 patients (37.5%) who achieved an axillary pathologic complete response, 24 (66.7%) had three or more negative SLNs and were safely spared axillary lymph node dissection (ALND). The positive predictive values of physical exam versus imaging-based post-NAC nodal assessment were respectively 88% and 69.8%.

Conclusions. This study showed SLNB to be an effective tool for minimizing axillary surgery in cN1 patients treated with NAC. However, important technical limitations exist, such as inability to identify three SLNs in more than two-thirds of patients and high-false negative rates for intraoperative SLN evaluation, particularly for patients with small residual nodal volumes. Preoperative counseling should include realistic assessment of the potential need for ALND in this population.

Modern neoadjuvant chemotherapy (NAC) regimens achieve axillary pathologic complete response (pCR) for a substantial proportion of node-positive breast cancer patients.[1–4] The rates of axillary pCR vary by receptor status, with best results achieved for human epidermal growth factor receptor 2-positive (HER2+) (70–97%) and triple-negative disease (47%), followed by estrogen receptor-positive (ER+)HER2− disease (21%).[1,4,5]

Sentinel lymph node biopsy (SLNB) has emerged as an attractive strategy for identifying patients with axillary pCR after NAC who may safely avoid the morbidity of

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axillary lymph node dissection (ALND). However, given the important prognostic implications of post-NAC nodal status,[6,7] the technical characteristics of SLNB must be optimized to ensure accurate axillary staging. Importantly, the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) trial found high rates of non-SLN disease for all patients with positive SLN regardless of disease volume,[8] suggesting the importance of identifying even low-volume disease including isolated tumor cells (ITCs; < 0.2 mm) and micrometastases (> 0.2–2 mm) in the NAC population.

Recent clinical trials have demonstrated acceptable false-negative rates (FNR) for SLNB in cN1 patients after NAC when certain technical requirements are met, specifically use of dual-tracer technique, retrieval of three or more SLNs, and use of immunohistochemistry (IHC).[3,8,9] Although effort has focused on minimizing the FNR of SLNB, limited data exist addressing oncologic outcomes for patients treated with this approach.[10–12] Differing methods of clinical axillary assessment after NAC, including physical examination alone or with axillary imaging, and limited data concerning the impact of post-NAC axillary disease burden on technical outcomes of SLNB also have led to controversy concerning patient selection for this approach.

Given the ongoing uncertainties, we adopted a standard framework for using SLNB for node-positive breast cancer patients treated with NAC at our institution and are committed to prospective monitoring of quality metrics and outcomes. This report describes the technical outcomes of SLNB by volume of residual nodal disease, including SLN-mapping rates and accuracy of intraoperative evaluation. It also describes patterns of axillary management and compares performance between post-NAC axillary physical examination and imaging to predict final nodal status.

METHODS

Consensus Criteria for SLNB in Node-Positive Patients After NAC

Consensus criteria for the use of SLNB to evaluate node-positive breast cancer patients treated with NAC were adopted by the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) breast group in October 2015. Patients with clinical T0-3 (cT0-3) N1 disease who convert to clinically node-negative (cN0) status by physical exam after NAC are offered SLNB. Patients with T4 disease or bulky nodal disease (cN2-3) are not eligible for SLNB.

Biopsy of suspicious axillary nodes at presentation is performed to confirm N1 disease. Clips are not routinely placed in the biopsied node. Post-NAC axillary imaging is not routinely obtained but may be used at the discretion of the treating physicians. To perform SLNB, the dual-tracer technique is used.

During the time frame of this study, radiolabeled colloid was injected by the nuclear medicine department either the day before surgery (1.0-miC dose) or on the day of surgery (0.5-miC dose) in either an intra-dermal or intra-parenchymal fashion near the 12 o'clock position of the nipple-areolar complex. The type and volume of blue dye, the location of the blue dye injection, and the use of breast massage after injection are at the surgeon's discretion.

An SLN is defined as a node with radiotracer signal, blue dye, or both, and a palpable node may be considered an SLN at the surgeon's discretion. Intraoperative histologic evaluation (touch preparation cytology or frozen section) of all SLNs is performed. Completion ALND (cALND) is recommended if three or fewer SLN are identified and if any positive SLNs are identified intraoperatively or at final pathology unless in a clinical trial. Patients with three or more negative nodes shown at the final pathology may avoid cALND.

Patients and Data Sources

The DF/BWCC prospective breast oncology clinical operations quality database was queried to identify all non-metastatic, biopsy-proven, node-positive breast cancer patients who received NAC and surgery from January 2016 to October 2017. Patients with cT0-3 cN1 disease at presentation formed the SLNB-eligible population, and those who converted to cN0 after NAC and underwent SLNB with dual-tracer technique were included for analysis of technical outcomes.

The volume of residual nodal disease was collected for both sentinel and non-sentinel lymph nodes and categorized as axillary pCR (ypN0), ITCs (ypN0[i+]), micrometastases (ypN1mi), or macrometastases (ypN1-3). Patient demographics, clinical pre- and post-NAC characteristics, treatment details, and final pathology were abstracted from the prospective database. Medical chart review was performed for post-NAC axillary imaging data and volume of SLN disease.

Statistical Analysis

Failed SLN mapping was defined as no SLNs identified. Inadequate mapping was defined as fewer than three SLNs retrieved (i.e., patients with 0–2 SLNs identified). The FNR of the intraoperative evaluation was calculated as the proportion of all node-positive patients (ypN+) at the final pathology with negative intraoperative evaluations.

For the SLNB-eligible patients who converted to cN0 and underwent SLNB with dual-tracer technique, mapping

rates and FNR of intraoperative evaluation were compared by residual nodal disease volume using the *t* test. A univariate logistic regression model was used to identify factors associated with these outcomes. For all the SLNB-eligible patients, descriptive statistics were used to describe performance measures of post-NAC physical examination versus any axillary imaging for prediction of final nodal status.

Statistical significance was defined as a *p* value lower than 0.05. All analyses were performed using R version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria. (www.r-project.org).

RESULTS

We identified 208 non-metastatic, biopsy-proven, node-positive breast cancer patients who received NAC and surgery during the study period. Of these patients, 52 (25%) presented with cT4 or cN2-3 disease and were not eligible for SLNB. Among 156 SLNB-eligible patients, 48 (30.8%) proceeded directly to ALND after NAC due to persistent cN1 status by physical examination ($n = 24$), nodal imaging ($n = 13$), or non-documented decision ($n = 11$). The study excluded 12 (7.7%) patients with SLNB due to single-tracer technique. Therefore, 96 (61.5% of the SLNB-eligible) patients ultimately converted to cN0, underwent SLNB with dual tracer, and were included for analysis of technical outcomes and surgical patterns (Fig. 1). All 156 of the SLNB-eligible patients were included for analysis of clinical axillary assessment after NAC. The clinical and pathologic features of the study cohorts are detailed in Table 1.

The median age of the 96 patients included in the analysis of SLNB technical outcomes was 45 years (range, 27–82 years), and the median presenting tumor size was 5 cm (range, 0–15 cm). Receptor status included 41 patients (42.7%) with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-negative (HER2−) disease, 31 patients (32.3%) with any HER2+ disease, and 24 patients (25%) with ER–HER2− disease. Overall, 96.8% of the HER2+ patients received dual anti-HER2-targeted therapy with trastuzumab/pertuzumab. Most of the HER2− patients ($n = 53$, 81.5%) received an adriamycin/cyclophosphamide/taxol (AC-T) regimen.

The final pathology showed that axillary pCR was achieved for 36 (37.5%) of the patients, whereas 5 (5.2%) of the patients had ITCs (ypN0[i+]), 11 (11.5%) had micrometastases (ypN1mi), and 44 (45.9%) had macrometastases (ypN1-3). The findings showed axillary pCR by receptor subtype as follows: ER+HER2− (7 of 41 patients, 17.1%), ER+HER2+ (6 of 16 patients, 37.5%), ER−HER2− (10 of 24 patients, 41.7%), and ER−HER2+ (13 of 15 patients, 86.7%).

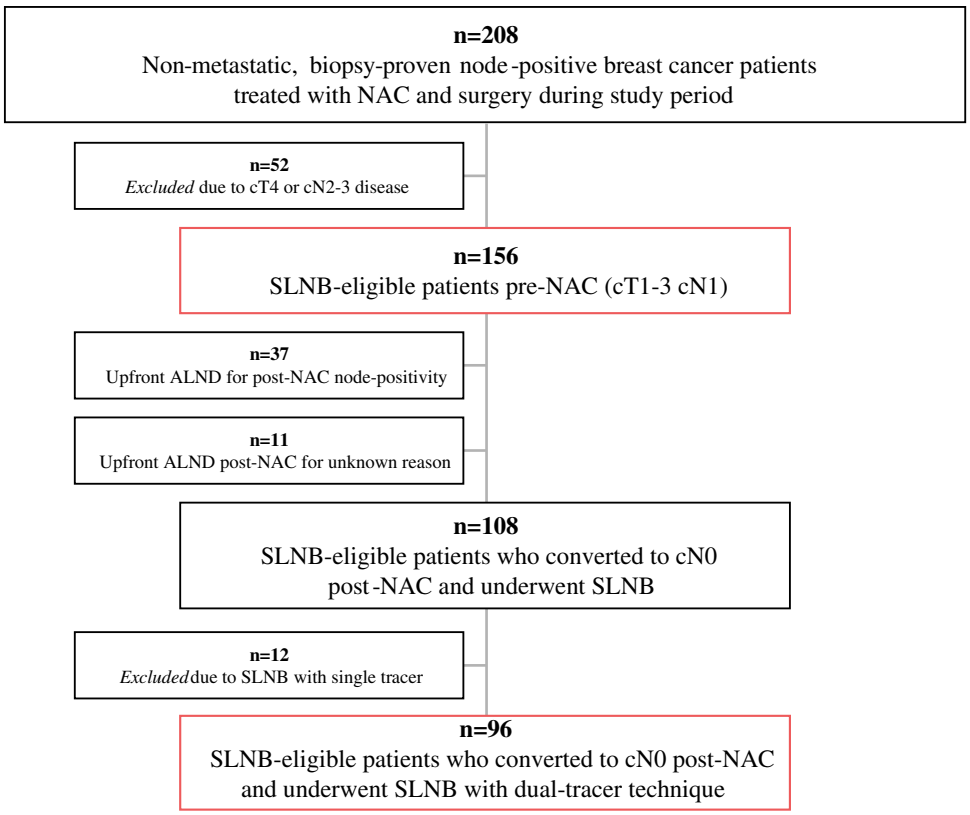

FIG. 1 Study cohort flow diagram. *NAC* neoadjuvant chemotherapy, *cT* clinical tumor stage, *cN* clinical nodal stage, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

TABLE 1 Clinical and pathologic features of the overall study cohort

	All cT0-3 cN1 patients (SLNB-eligible) (n = 156) n (%)	SLNB-eligible patients who converted to cN0 after NAC and underwent SLNB with dual tracer (n = 96) n (%)
Median patient age: years (range)	46 (25–82)	45 (27–82)
Median tumor size at presentation: cm (range)	4.5 (0–15)	5.0 (0–15)
Clinical T-stage		
cT0	1 (0.6)	1 (1.0)
cT1	26 (16.7)	14 (14.6)
cT2	84 (53.8)	54 (56.3)
cT3	45 (28.8)	27 (28.1)
Palpable axillary nodes at presentation		
Yes	122 (78.2)	75 (78.1)
No	34 (21.8)	21 (21.9)
Histology		
Invasive ductal	139 (89.1)	82 (85.4)
Invasive lobular or mixed	17 (10.9)	14 (14.6)
Grade		
1	3 (1.9)	1 (1.0)
2	43 (27.6)	30 (31.3)
3	110 (70.5)	65 (67.7)
Lymphovascular invasion		
Yes	69 (44.2)	41 (42.7)
No	83 (53.2)	51 (53.1)
Unknown	4 (2.6)	4 (4.2)
Receptor status		
ER+ HER2−	70 (44.9)	41 (42.7)
ER+ HER2+	27 (17.3)	16 (16.7)
ER− HER2−	35 (22.4)	24 (25.0)
ER− HER2+	24 (15.4)	15 (15.6)
Neoadjuvant chemotherapy regimen		
AC-T	85 (54.5)	53 (55.2)
HER2-directed	52 (33.3)	30 (31.3)
Other taxane-based	10 (6.4)	8 (8.3)
Non-taxane-based	9 (5.8)	5 (5.2)
Palpable breast tumor after NAC		
Yes	66 (42.3)	38 (39.6)
No	90 (57.7)	58 (60.4)
Palpable axillary nodes after NAC		
Yes	25 (16.0)	0 (0.0)
No	131 (84.0)	96 (100.0)
Abnormal nodes on imaging after NAC		
Yes	43 (27.6)	14 (14.6)
No	29 (18.6)	25 (26.0)
Not performed	84 (53.8)	57 (59.4)
Final breast surgery		
BCS	65 (41.7)	37 (38.5)
Mastectomy	91 (58.3)	59 (61.5)

TABLE 1 continued

	All cT0-3 cN1 patients (SLNB-eligible) (n = 156) n (%)	SLNB-eligible patients who converted to cN0 after NAC and underwent SLNB with dual tracer (n = 96) n (%)
Final axillary surgery		
SLNB	52 (33.3)	45 (46.9)
cALND	104 (66.7)	51 (53.1)
Final ypT status		
ypTx	2 (1.3)	1 (1.1)
ypT0/is	37 (23.7)	25 (26.0)
ypT1	65 (41.7)	39 (40.6)
ypT2	40 (25.6)	23 (24.0)
ypT3	12 (7.7)	8 (8.3)
Final ypN status		
ypN0	56 (35.9)	36 (37.5)
ypN0(i+)	7 (4.5)	5 (5.2)
ypN1mi	14 (9.0)	11 (11.5)
ypN1	44 (28.2)	26 (27.1)
ypN2	25 (16.0)	14 (14.6)
ypN3	10 (6.4)	4 (4.2)

SLNB sentinel lymph node biopsy, *NAC* neoadjuvant chemotherapy, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *AC-T* adriamycin/cyclophosphamide/taxol, *BCS* breast-conserving surgery, *cALND* completion axillary lymph node dissection

SLNB Technical Outcomes

Adequate mapping ($\geq$ 3 SLNs) was achieved for 64 patients (66.7%). Of these patients, 16 (16.7%) failed to map (no SLNs identified), and 16 (16.7%) had only one or two SLNs retrieved (Table S1). Excluding the patients with failed mapping, the median number of SLNs retrieved was 4 (range, 1–10). No difference was observed in the rate of adequate mapping (p = 0.12) or the median number of SLNs retrieved (p = 0.27) by residual nodal disease volume (Table 2). However, the patients who failed to map had higher rates of nodal macrometastases (68.9% for 0 SLNs vs 43.8% for 1 or 2 SLNs vs 40.6% for $\geq$ 3 SLNs; p = 0.04; Table S1).

In the univariate analysis (Table 3), older age (p = 0.01) and lower histologic grade (p = 0.01) were associated with inadequate mapping, but not with residual nodal disease volume (p = 0.12). A trend for tumor larger than 5 cm also was observed (p = 0.06).

For 60 of the 64 patients with adequate mapping, intraoperative SLN evaluation was performed. The intraoperative and final evaluations found 23 patients to be ypN+ (true-positive) and 23 patients to be ypN0 (true-negative). The findings showed 14 patients to be ypN0 at the intraoperative evaluation but ypN+ at the final pathology (false-negative), yielding an FNR of 37.8% (14/37). The FNR at the intraoperative evaluation was significantly higher for SLN ITCs/micrometastases compared with macrometastases (66.7% vs 18.1%; p = 0.005, Table 2). In the univariate analysis (Table 3), smaller residual SLN disease volume (ITCs/micrometastases) was associated with false-negative intraoperative evaluation ($p < 0.01$), as was higher histologic grade ($p < 0.01$).

Axillary Assessment After NAC

Of 156 SLNB-eligible patients, 84 (53.8%) had physical examination of the axilla alone after NAC, and 72 (46.2%) had axillary imaging in addition to physical examination. The imaging methods were variable and included 35 ultrasound (US) procedures (48.6%), 27 magnetic resonance imaging (MRI) procedures (37.5%), 9 US and MRI procedures (12.5%), and 1 computed tomography (CT) procedure (1.4%).

Among 25 patients with persistent cN1 status by physical examination after NAC, 22 were node-positive at the final pathology. Among 43 patients with suspicious nodes on imaging after NAC, 30 were node-positive at the final pathology. Therefore, the positive predictive value (PPV) of physical examination for final ypN status was 88% (22/

TABLE 2 Sentinel lymph node (SLN) mapping and accuracy of intraoperative evaluation by volume of residual nodal disease on the final pathology for 96 patients who underwent SLN biopsy (SLNB) according to consensus criteria

	Axillary pCR (n = 36)	ITCs or micrometastases (n = 16)	Macrometastases (n = 44)	p value
Adequate SLN mapping: n (%)[a]	24 (66.7)	14 (87.5)	26 (59.1)	0.12
Median (range) number of SLN retrieved, excluding failed mapping	4 (1–8)	4 (1–7)	3 (1–10)	0.27
False-negative rate of intra-operative evaluation: n (%)[b]	–	10/15 (66.7)	4/22 (18.1)	0.005

pCR pathologic complete response, *ITC* isolated tumor cell

[a]Defined as ≥ 3 SLN retrieved

[b]In patients with adequate mapping

25), and the PPV of axillary imaging was 69.8% (30/43). The performance measures of axillary assessment methods are displayed in Table 4.

Axillary Management After SLNB

All 16 patients with failed SLN mapping underwent immediate cALND. The final pathology showed 5 of the patients to be ypN0 and 11 to be ypN+. Of the 16 patients with one or two SLNs retrieved, 11 underwent immediate cALND. Among these 11 patients, 5 had negative SLNs, of which 1 had non-SLN macrometastasis, 2 had SLN micrometastases (with neither showing additional non-SLN disease), and 4 had SLN macrometastases, all with additional non-SLN disease. Of the remaining five patients with one or two SLNs identified who did not undergo cALND, three had negative SLNs and received no further axillary treatment. One patient had a micrometastasis in one of two SLNs and received axillary radiation therapy (RT) after multidisciplinary review. The final patient had two positive SLNs and was randomized to axillary RT in the Alliance A011202 clinical trial.

Of 64 patients with adequate mapping, 24 had three negative SLNs at the final pathology and were spared ALND (25% of all SLNB attempts). One patient with three negative SLNs underwent cALND due to intraoperative suspicion of residual disease and had additional macrometastases identified. Among the remaining 39 patients who remained node-positive on SLNB, 23 underwent cALND and 16 received axillary RT alone, including 4 patients in the Alliance A011202 clinical trial. Among the 23 patients with positive SLNs who underwent cALND, 17 had SLN macrometastases. Of these 17 patients, 8 (47.1%) were found to have positive non-sentinel nodes, and 6 were found to have SLN micrometastases, 1 of whom (16.7%) had positive non-sentinel nodes. Axillary RT was undertaken as an alternative to cALND for all five patients with SLN ITCs, three patients with SLN micrometastases and four patients with SLN macrometastases who were not enrolled in a clinical trial.

DISCUSSION

This study was one among few prospective series to evaluate SLNB in node-positive breast cancer patients after NAC. It is the first study to investigate technical feasibility and outcomes stratified by volume of residual nodal disease. We confirmed that a significant proportion of SLNB-eligible patients achieve axillary pCR after NAC (36%), especially among HER2+ subtypes. The rates of conversion to cN0 by physical examination after NAC were high (84%), allowing the majority to meet the criteria for SLNB. When SLNB was performed using the dual-tracer technique, 67% of the patients with axillary pCR showed three or more negative SLNs and were spared ALND per consensus. However, we also demonstrated noteworthy technical limitations of SLNB in this population, such as the inability to identify three SLNs in more than two-thirds of the patients and a nearly 40% false-negative rate for intraoperative SLN evaluation. Preoperative counseling should therefore include a realistic assessment of the potential need for cALND, either in an immediate or delayed manner for patients with SLNB attempted.

The technical feasibility of SLNB after NAC for node-positive breast cancer patients has been established in three multicenter trials.[3,8,9] The ACOSOG Z1071 (Alliance) trial included 649 cT0-4 cN1-2 M0 patients,[3] and the SN FNAC study included 153 cT0-3 cN1-2 patients.[8] In both protocols, SLNB and ALND were performed for all the patients after NAC. The SENTINA trial was a multi-arm study including 592 cN1-2 patients who converted to cN0 by physical examination after NAC and underwent SLNB and ALND.[9] The detection rate (identification of at least 1 SLN) in these studies ranged from 80 to 93% and was improved with the use of dual tracers. The rates for identification of three or more SLNs were variable, ranging from only 34% in the SENTINA trial to 57% in the Alliance trial,[3] and as high as 86% in a recent cohort of 128 cT0-3 cN1 patients from Memorial Sloan Kettering Cancer Center (MSKCC) who converted to cN0 after NAC.[4]

TABLE 3 Univariate analysis of factors associated with inadequate sentinel lymph node (SLN) mapping (< 3 nodes identified) and false-negative intraoperative SLN histologic evaluation

	Inadequate SLN mapping		False-negative Intraoperative evaluation	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	–	0.01	–	0.63
Palpable axillary nodes at presentation				
Yes	Reference	1	Reference	1
No	1.0 (0.3–3.3)		0.8 (0.1–3.6)	
No. of abnormal nodes on imaging at presentation				
1	Reference	0.76	Reference	0.4
2	0.7 (0.1–2.8)		0.8 (0.08–6.3)	
≥ 2	1.4 (0.4–4.7)		1.8 (0.22–17.0)	
Unknown	1.4 (0.5–4.0)		0.3 (0.05–1.6)	
cT stage at presentation				
cT0/cT1	Reference	0.06	Reference	0.9
cT2	1.5 (0.4–7.4)		1.2 (0.2–7.3)	
cT3	4.3 (1.1–22.2)		0.7 (0.09–5.3)	
Palpable breast tumor after NAC				
No	Reference	1	Reference	1
Yes	1.1 (0.4–2.5)		1.0 (0.5–2.5)	
Abnormal nodes on imaging after NAC				
Yes	Reference	0.38	–	0.44
No	0.4 (0.1–1.6)		Reference	
Not performed	0.8 (0.2–2.6)		2.3 (0.5–12.3)	
Breast surgery				
BCS	Reference	0.38	Reference	0.74
Mastectomy	1.6 (0.7–4.1)		1.4 (0.4–5.7)	
Histology				
Lobular/mixed	Reference	1	Reference	1
Ductal	0.9 (0.3–3.1)		1.3 (0.2–10.1)	
Grade				
1/2	Reference	0.01	Reference	< 0.01
3	0.3 (0.1–0.7)		22.6 (1.2–423.4)	
Lymphovascular invasion				
Yes	Reference	1	Reference	0.28
No	0.96 (0.4–2.3)		2.7 (0.7–1.1)	
Receptor status				
ER+ HER2−	1.1 (0.4–3.7)	0.2	0.3 (0.06–1.5)	0.12
ER+ HER2+	3.0 (0.8–12.1)		3.0 (0.3–73.1)	
ER− HER2−	Reference		Reference	
ER− HER2+	2.6 (0.7–10.8)		1.0 (0.03–30.4)	
Final ypT status				
ypT0/ypTis	Reference	0.16	Reference	0.19
ypT1	0.5 (0.2–1.4)		0.2 (0.007–1.2)	
ypT2	0.9 (0.3–2.7)		160.06 (0.002–0.7)	
ypT3	2.7 (0.5–15.4)		0.1 (0.003–2.6)	

TABLE 3 continued

	Inadequate SLN mapping		False-negative Intraoperative evaluation	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Largest overall nodal disease burden				
Macrometastases	Reference	0.12	–	–
ITC/micrometastases	0.2 (0.03–0.9)			
Axillary pCR	0.7 (0.3–18)			
Largest SLN disease burden				
Macrometastases	–	–	Reference	< 0.01
ITC/micrometastases			11.9 (2.7–66.2)	

OR odds ratio, *CI* confidence interval, *NAC* neoadjuvant chemotherapy, *BCS* breast-conserving surgery, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *ITC* isolated tumor cell, *pCR* pathologic complete response

Our SLN detection rate of 83.4% was within the range of the reported literature, and we found that three or more SLNs were identified in 66.7%. Adequate mapping and number of SLNs retrieved did not vary by extent of residual nodal disease. This effect has not been well-characterized previously, with few studies reporting details on factors associated with mapping outcomes or nodal disease volumes. In the SENTINA trial, only factors associated with detection rate were investigated, and tumor involvement of the SLNs showed no effect on the detection rate in the multivariate analysis (pN0; odds ratio [OR], 1.39; 95% confidence interval [CI], 0.694–2.78; $p = 0.353$).[9] In a single-institution series, Nguyen et al.[13] found that a greater mean number of SLNs were identified for negative versus positive SLNs in 193 cT0-4 cN1 patients after NAC (3.7 vs 3.0; $p = 0.001$). Given that the bulk of clinical trial data demonstrates that the FNR of SLNB becomes acceptable only when three or more SLNs are retrieved[3,9,14] and that the reported rates of achieving three or more SLNs vary significantly, further study is needed for better characterization of factors associated with this outcome. Our rate of 66.7% was similar to that in Alliance trial (57%)[3] but less than that observed in the MSKCC cohort (86%).[4] This likely is multi-factorial but may be related in part to more standardized SLNB methodology at MSKCC, including timing, dose, and location of injection of radiolabeled colloid, use of only one blue dye type (isosulfan blue), and routine inclusion of palpable nodes as SLNs.[4]

False-negative rates of intraoperative SLN evaluation were high overall. Moreover, SLN ITCs and micrometastases were significantly more likely to yield false-negative results. The FNR of intraoperative SLN evaluation ranges from 32 to 42% in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 and other series of clinically node-negative patients treated with upfront SLNB, and is known to be higher for smaller-volume nodal disease.[15–19] We found that 16% of patients who underwent SLNB had only ITCs or micrometastases in the SLNs, similar to the findings in SN FNAC (16/145, 11%).[8] This represents a small but significant proportion of patients at high risk for false-negative intraoperative evaluations who need to return to the operating room for ALND.

Residual nodal disease at ALND for the patients with a positive SLN appeared to be less likely for SLN micrometastases in our cohort. However, these results should be interpreted with caution because the sample was small, and many patients with ITCs/micrometastases did not undergo ALND, introducing selection bias. In the SN FNAC study in which all the patients underwent ALND, the rates of positive non-sentinel nodes did not differ for the patients with SLN ITCs (57%), micrometastases (38%), or macrometastases (56%) ($p = 0.637$).[8] Particularly in the NAC population, any persistent axillary metastases may represent chemoresistant disease, and therefore may have an impact on long-term outcomes. The Alliance A011202 trial currently is investigating overall survival and locoregional recurrence after ALND versus axillary radiation in the setting of residual nodal disease found by SLNB after NAC.[20] However, patients with ITCs are not eligible for this trial, and patients with SLN micrometastases likely will be underrepresented. While awaiting these results, omitting ALND for patients with any residual axillary disease should be discouraged outside of a clinical trial.

Optimizing patient selection for SLNB after NAC may further improve rates for safe avoidance of ALND. For instance, among 13 SLNB-eligible patients who proceeded directly to ALND based on suspicious nodal imaging after NAC (but a negative physical examination), 7 (53.8%) were in fact found to be ypN0 at the final pathology. Ideally, a test with minimal false-positive axillary assessments (i.e., a high PPV) would avoid upfront ALNDs for patients with axillary pCR. Among our SLNB-eligible patients, physical examination had the highest PPV for final ypN status. The SN FNAC trial

TABLE 4 Performance measures of physical examination versus any axillary imaging for axillary assessment after neoadjuvant chemotherapy (NAC)

	PPV *n* (%)	NPV *n* (%)	Accuracy *n* (%)
Physical examination (*n* = 156)	22/25 (88.0)	53/131 (40.5)	75/156 (48.1)
Axillary imaging (*n* = 72)	30/43 (69.8)	13/29 (44.8)	43/72 (59.7)

PPV positive predictive value, *NPV* negative predictive value

demonstrated similar findings (PPV clinical examination 89% vs axillary ultrasound 81%).[8] Similarly, the PPV of post-NAC axillary ultrasound was 71.8% for 611 patients from the Alliance trial with available data,[21] lower than that of physical examination from the SN FNAC trial and our study. We therefore advocate for the use of physical examination alone over axillary imaging when patients are selected for SLNB after NAC.

CONCLUSIONS

For two-thirds of the node-positive breast cancer patients who converted to clinically node-negative status after NAC, SLNB successfully retrieved three or more sentinel nodes. Residual nodal disease volume did not have an impact on SLN mapping rates, but ITCs and micrometastases were more likely to yield false-negative intraoperative evaluations. Although 67% of the patients with axillary pCR were spared ALND, this corresponded to only 25% of all the SLNBs performed. Physical examination after NAC demonstrated a higher PPV than axillary imaging for final ypN status and should be considered an adequate method of axillary assessment before surgery to minimize unnecessary ALND. Although SLNB is an effective tool for minimizing axillary surgery in node-positive breast cancer patients, preoperative counseling should include a realistic assessment of the technical limitations and significant potential need for ALND in this population.

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