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Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Patients with Cytologically Proven Node-positive Breast Cancer at Diagnosis

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ABSTRACT

Background. The performance of sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NCT) was investigated in patients with locally advanced breast cancer (LABC).

Methods. After NCT of 178 patients with cytology-proven axillary/supraclavicular nodes metastasis at the time of diagnosis, SLNB using radioisotope was performed including completion node dissection between 2008 and 2011. The detection rate, sensitivity, false negative rate (FNR), negative predictive value (NPV) and accuracy of SLNB were analyzed.

Results. SLNB was successfully performed in 169 (94.9 %) patients. Tumor nonresponse and extensive residual nodal disease were found to be significantly associated with detection failure of sentinel nodes. Sensitivity, FNR, NPV, and accuracy of SLNB were 78.0, 22.0, 75.8, and 87.0 %, respectively, and a greater number of retrieved SLNs increased all four of these performance measures. Conversion to node-negative disease was achieved in 69 (40.8 %) patients: 24 % of patients with the luminal A subtype, 51.6 % of patients with the luminal B, 51.7 % of patients with the HER2-enriched, and 58.5 % of patients with the triple-negative breast cancer (TNBC) subtype. Luminal B, HER2-enriched, and TNBC subtypes showed comparable responses to NCT; however, the TNBC subtype had a significantly better FNR and accuracy.

Conclusions. SLNB was found to be technically feasible, but its routine use was not recommended for LABCs after NCT. However, acceptable performance was noted for locally advanced TNBCs, and thus SLNB might be safely considered in these selected patients.

Neoadjuvant chemotherapy (NCT) has been established as a standard therapeutic modality for patients with locally advanced or early stage breast cancer.[1–3] The presence of axillary lymph node (ALN) metastasis is important for decision making regarding the use of chemotherapy and NCT is considered an effective and safe treatment option for node-positive breast cancers at presentation. Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in patients with clinically node-negative disease and is now considered a standard procedure.[4] A meta-analysis of clinical trials demonstrated no statistical difference in survival or nodal recurrence between SLNB and ALND groups, but it did find a significant reduction in postoperative morbidity and an improvement of quality of life in the SLNB group.[5]

In patients with biopsy-proven ALN metastasis at diagnosis, the current standard surgical procedure for axilla is completion ALND at definitive surgery after NCT.[6] However, 20–70 % of node-positive patients experience pathologic complete remission (pCR) of ALNs after NCT depending on the chemotherapeutic implemented.[7,8] Thus, it is questionable whether ALND is optimal for all patients receiving NCT for management of locally advanced breast cancer (LABC).

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The identification rate of sentinel lymph node (SLN) has been reported to be 88.0–98.0 % with a false negative rate (FNR) of SLNB from 5.1 to 29.6 %.[9–12] Despite the inconsistent success rate, most studies have concluded that SLNB after NCT is technically feasible; nevertheless, it is not routinely recommended in node-positive patients at diagnosis.[13–15] FNRs of SLNB in early stage breast cancer have been reported in clinical trials to vary from 7.3 to 9.8 %, and the recommended acceptable range is $\leq$5 % according to current clinical guidelines.[16–19] However, it is not clear whether these FNRs of SLNB are acceptable in initially node-positive LABC patients after NCT.

If SLNB was highly reproducible and accurate, the procedure could be carried out in a less morbid axilla-conserving manner for selected patients after NCT, even in some patients with initially involved ALNs. Therefore, we investigated the diagnostic performance of SLNB after NCT in LABC patients with cytology-proven node metastasis at diagnosis, by examining detection rate, sensitivity, FNR, negative predictive value (NPV), and accuracy of SLNB.

PATIENTS AND METHODS

Patient Selection

Three hundred seventy-four cT1–cT3 patients who received NCT between January 2008 and December 2011 were retrospectively selected from the Severance Hospital breast cancer registry. A total of 196 patients who did not undergo SLNB after NCT ($n = 189$) or who did not have cytologically confirmed node metastasis at diagnosis ($n = 7$) were excluded. This study was approved by the institutional review board of Severance Hospital, Yonsei University Health System (4-2012-0273).

At presentation, patients with clinically enlarged nodes or with radiologically nodal findings of loss of fatty hilum, cortical thickening >3 mm, a round shape, markedly hypoechoic cortex, or increased peripheral blood flow underwent ultrasound-guided fine needle aspiration cytology to confirm the presence of metastasis. A total of 178 patients with biopsy-proven ALN ($n = 170$) or supraclavicular lymph node (SCLN) metastasis ($n = 8$) at diagnosis who subsequently underwent NCT followed by curative surgery including SLNB and completion node dissection constituted the study cohort.

SLNB and Pathologic Assessment

At our institution, SLNs are detected using a radioisotope technique alone as previously described.[20,21] In brief, 0.5 mCi ^{99m}Tc Phytate (Korea Atomic Energy Research Institute, Daejeon, Korea) was diluted in 0.5 mL saline and injected into the subcutaneous layer of areolar tissue in the direction of the main primary tumor on the day of surgery. SLNs were defined as the hottest nodes identified by a handheld gamma probe (Neoprobe Gamma Detection System; Neoprobe Corporation, Dublin, OH) or as any nodes with a radioactive count of $\geq$10 % of the ex vivo count of the hottest node. After SLNB, all patients underwent concomitant completion level I/II ALND with or without SCLN dissection.

Regional nodes, including SLNs, were subjected to routine pathological examinations, which included hematoxylin and eosin staining with or without immunohistochemistry for cytokeratin. Lymph nodes were considered positive if metastatic foci were >0.2 mm and/or >200 tumor cells were detected by any methods described in the American Joint Committee on Cancer (AJCC) staging manual, 7th edition.[22] Nodes with isolated metastatic foci of $\leq$0.2 mm were considered negative.

Response to NCT and Clinicopathologic Factors

After 4–8 cycles of anthracycline with or without taxane-based NCT, the responses of tumors and nodes were comprehensively evaluated using clinical and radiological examinations, mainly on the basis of ultrasound. Primary tumor response to NCT was defined as complete or partial response according to the Response Evaluation Criteria in Solid Tumors, version 1.1.[23] Tumor nonresponse was considered progressive or stable disease. Regional nodal response was defined as the disappearance of metastatic nodes or no suspicious ultrasound finding in regional areas. Nodal nonresponse was defined as remaining findings suspicious for node metastasis after NCT.

Postoperative pathologic stage was based on the AJCC staging.[22] Histologic grade was assessed using the modified Bloom-Richardson classification.[24] Tumors with $\geq$1 % nuclear-stained cells were considered positive for estrogen receptor (ER) and progesterone receptor (PR) in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[25] Human epidermal growth factor receptor 2 (HER2) staining by HercepTest (Dako, Glostrup, Denmark) was interpreted as 0–3+ according to ASCO/CAP guidelines.[26] In HER2 2+ cases, fluorescence in situ hybridization (FISH) was performed using the PathVysion *HER2* DNA Probe Kit (Vysis, Downers Grove, IL) and *HER2* amplification was defined as a HER2 gene/chromosome 17 copy number ratio of >2.2 according to the ASCO/CAP guidelines.[26] HER2 was considered positive in cases with immunohistochemistry finding of 3+ or with gene amplification by FISH. On the basis of ER, PR, and HER2 findings, molecular subtypes were categorized into four

subgroups as follows: luminal A, ER positive and/or PR positive, and HER2 negative; luminal B, ER positive and/or PR positive, and HER2 positive; HER2-enriched, ER negative, PR negative, and HER2 positive; and triple-negative breast cancer (TNBC), ER negative, PR negative, and HER2 negative.

Statistical Analysis

Detection failure of SLNs was defined as an inability to identify hot nodes by lymphoscintigraphy or gamma probe. Sensitivity was calculated by dividing true positive (TP) findings by TP plus false negative (FN) findings. FNR was defined as the proportion of patients with negative SLNs who subsequently had ALNs metastasis among patients with $\geq$1 positive lymph node. NPV was calculated by dividing true negative (TN) findings by TN plus FN findings. Accuracy was defined as the proportion of patients with TP or TN among patients with successful SLNB.

Differences between groups were evaluated using the chi-square test or Fisher's exact test. A logistic regression model was used to explore parameters associated with residual regional node status after NCT. All statistical tests were two-sided, and $P < 0.05$ was considered significant. SPSS software, version 20.0 (SPSS Inc., Chicago, IL), was used for the analysis.

RESULTS

Patient Characteristics

Mean age at diagnosis was 48.4 $\pm$ 9.7 years (range 26–70 years). Mean size of primary tumor at presentation was 2.7 $\pm$ 1.3 cm (range 0.8–9.6 cm). A total of 108 (60.7 %) patients had cT2 and 63 (35.4 %) cT1 disease. NCT regimens were as follows: 8 (4.5 %) patients, anthracycline and cyclophosphamide (AC); 28 (15.7 %), concurrent anthracycline and taxane; 112 (62.9 %), AC followed by taxane; 17 (9.6 %), AC followed by taxane and TS-1; 5 (2.8 %) of TNBC subtype, carboplatin, docetaxel, and bevacizumab; and 8 (4.5 %) of HER2-enriched subtype, paclitaxel $\pm$ trastuzumab $\pm$ lapatinib (NeoALTTO study). Table 1 summarizes the patient characteristics.

Detection of SLNs

One or more SLNs were identified in 169 patients (detection rates, 94.9 %). Of 169 patients with successful SLNB and ALND, 10 (5.9 %) underwent simultaneous SCLN dissection due to radiologically suspicious or cytology-proven SCLN metastasis at diagnosis. Mean numbers of sentinel and regional nodes retrieved were 2.1 $\pm$ 1.6 (range 1–12) and 12.8 $\pm$ 6.3 (range 3–34), respectively. Table 1 shows clinicopathologic factors associated with successful SLNB. Tumor nonresponse and extensive residual nodal disease (ypN3) were significantly associated with SLNs detection failure. Of 9 patients with SLNs detection failure, only one luminal B subtype was node-negative after completion node dissection.

Diagnostic Performance of SLNB

In 169 patients with successful SLNB, a total of 352 SLNs were identified. A single SLN was detected in 73 (43.2 %) patients, two in 60 (35.5 %), and three or more in 36 (21.3 %). Conversion to node-negative disease was achieved in 69 (40.8 %) patients, and 36 (21.3 %) showed SLN metastasis alone (nonsentinel ALN-negative disease). Of 8 HER2-positive patients treated with targeted agents, 7 (87.5 %) were ypN0. Table 2 provides a comparison of SLNB results and final node statuses. Sensitivity, FNR, NPV, and accuracy of SLNB was 78.0, 22.0, 75.8, and 87.0 %, respectively. Because SLNB performance was associated with number of retrieved SLNs, diagnostic performance was investigated according to the number of SLNs examined. SLNB performance was the worst among patients with a single retrieved SLN and the best when $\geq$3 SLNs were evaluated (Table 3).

Characteristics and Performance by Molecular Subtype

Significantly better SLNB performance was demonstrated in 34 locally advanced TNBC subtypes, which was comparable to adjuvant setting. Table 4 shows clinicopathologic characteristics and performance by molecular subtype. The luminal A subtype demonstrated the lowest nodal pCR after NCT, therefore, higher TP and lower TN results. Luminal B, HER2-enriched and TNBC subtypes showed similar proportions of favorable tumor and node responses to NCT, but TNBC had a significantly lower FNR of 7.1 % and a better accuracy of 97.1 % than the other two subtypes.

Multivariate logistic analysis of 135 non-TNBC patients revealed that tumor and nodal response, the absence of LVI and HER2-positive tumor significantly predicted nodal pCR for non-TNBC subtypes (Table 5). Explorative analysis on FNR showed that SLNB performance had the lowest FNR (16.7 %) and the highest accuracy (95.8 %) for 24 non-TNBC subtypes with tumor and nodal response, the absence of LVI and HER2-positive tumor. This compared to a FNR of 25.0 % and an accuracy of 82.0 % for the 111 non-TNBC subtypes that did not fulfill all these parameters.

TABLE 1 Factors associated with detection failure of sentinel lymph node biopsy

Factor	Total ($n = 178$)	SLN detected ($n = 169$)	SLN not detected ($n = 9$)	P[a]
Age at diagnosis				
≤35 year	16 (9.0 %)	15 (8.9 %)	1 (11.1 %)	0.580
>35 year	162 (91.0 %)	154 (91.1 %)	8 (88.9 %)	
Menopausal status				
Before	103 (57.9 %)	99 (58.6 %)	4 (44.4 %)	0.496
After	75 (42.1 %)	70 (41.4 %)	5 (55.6 %)	
BMI				
<25 kg/m^2	129 (72.5 %)	122 (72.2 %)	7 (77.8 %)	>0.999
≥25 kg/m^2	49 (27.5 %)	47 (27.8 %)	2 (22.2 %)	
Tumor site				
Left	97 (54.5 %)	92 (54.4 %)	5 (55.6 %)	>0.999
Right	81 (45.5 %)	77 (45.6 %)	4 (44.4 %)	
Tumor location				
Upper outer quadrant	99 (55.6 %)	94 (55.6 %)	5 (55.6 %)	0.950
Upper inner quadrant	23 (12.9 %)	22 (13.0 %)	1 (11.1 %)	
Lower outer quadrant	40 (22.5 %)	37 (21.9 %)	3 (33.3 %)	
Lower inner quadrant	7 (3.9 %)	7 (4.1 %)	0 (0.0 %)	
Subareolar	9 (5.1 %)	9 (5.3 %)	0 (0.0 %)	
Regimens of NCT				
Anthracycline based	8 (4.5 %)	8 (4.7 %)	0 (0.0 %)	>0.999
Anthracycline plus taxane	157 (88.2 %)	148 (87.6 %)	9 (100 %)	
Targeted agents	13 (7.3 %)	13 (7.7 %)	0 (0.0 %)	
Tumor response to NCT				
Response	141 (79.2 %)	137 (81.1 %)	4 (44.4 %)	0.020
Nonresponse	37 (20.8 %)	32 (18.9 %)	5 (55.6 %)	
Node response to NCT				
Response	92 (51.7 %)	88 (52.1 %)	4 (44.4 %)	0.741
Nonresponse	86 (48.3 %)	81 (47.9 %)	5 (55.6 %)	
Histologic type				
Ductal	171 (96.1 %)	162 (95.9 %)	9 (100 %)	>0.999
Lobular and special[b]	7 (3.9 %)	7 (4.1 %)	0 (0.0 %)	
Pathologic tumor stage				
ypT0-is	66 (37.1 %)	65 (38.5 %)	1 (11.1 %)	0.315
ypT1–2	108 (60.7 %)	100 (59.2 %)	8 (88.9 %)	
ypT3	4 (2.2 %)	4 (2.4 %)	0 (0.0 %)	
Pathologic node stage				
ypN0	70 (39.3 %)	69 (40.8 %)	1 (11.1 %)	0.040
ypN1–2	98 (55.1 %)	92 (54.4 %)	6 (66.7 %)	
ypN3	10 (5.6 %)	8 (4.7 %)	2 (22.2 %)	
Pathologic TNM stage				
0	44 (24.7 %)	44 (26.0 %)	0 (0.0 %)	0.170
1–2	102 (57.3 %)	95 (56.2 %)	7 (77.8 %)	
3	32 (18.0 %)	30 (17.8 %)	2 (22.2 %)	
Histologic grade				
I/II	123 (69.1 %)	116 (68.6 %)	7 (77.8 %)	0.723
III	55 (30.9 %)	53 (31.4 %)	2 (22.2 %)	
Lymphovascular invasion				
Absent	157 (88.2 %)	150 (88.8 %)	7 (77.8 %)	0.287
Present	21 (11.8 %)	19 (11.2 %)	2 (22.2 %)	

TABLE 1 continued

Factor	Total ($n = 178$)	SLN detected ($n = 169$)	SLN not detected ($n = 9$)	P^a
Estrogen receptor				
Negative	68 (38.2 %)	65 (38.5 %)	3 (33.3 %)	>0.999
Positive	110 (61.8 %)	104 (61.5 %)	6 (66.7 %)	
Progesterone receptor				
Negative	96 (53.9 %)	91 (53.8 %)	5 (55.6 %)	>0.999
Positive	82 (46.1 %)	78 (46.2 %)	4 (44.4 %)	
HER2				
Negative	114 (64.0 %)	109 (64.5 %)	5 (55.6 %)	0.724
Positive	64 (36.0 %)	60 (35.5 %)	4 (44.4 %)	
Molecular subtype				
Luminal A	78 (43.8 %)	75 (44.4 %)	3 (33.3 %)	0.681
Luminal B	34 (19.1 %)	31 (18.3 %)	3 (33.3 %)	
HER2-enriched	30 (16.9 %)	29 (17.2 %)	1 (11.1 %)	
TNBC	36 (20.2 %)	34 (20.1 %)	2 (22.2 %)	
Ki-67 before NCT ($n = 119$)				
<20 %	54 (45.4 %)	51 (45.1 %)	3 (50.0 %)	>0.999
≥20 %	65 (54.6 %)	62 (54.9 %)	3 (50.0 %)	
Type of surgery				
Breast-conservation surgery	82 (46.1 %)	80 (47.3 %)	2 (22.2 %)	0.181
Total mastectomy	96 (53.9 %)	89 (52.7 %)	7 (77.8 %)	

SLN sentinel lymph node, *BMI* body mass index, *NCT* neoadjuvant chemotherapy, *TNM* tumor node metastasis, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer

[a] Fisher's exact test

[b] Special histologic types included papillary carcinomas ($n = 2$) and mucinous carcinomas ($n = 2$)

DISCUSSION

The standard axilla management in node-positive patients is completion ALND.[2,6] However, previous studies have demonstrated that NCT clearly eradicates node metastasis in 19–23 % of patients on an anthracycline-based regimen, 29 % of patients on anthracycline and taxane regimens, and 74 % of patients with HER2-positive tumor treated with trastuzumab-containing regimens.[7,8,27,28] Thus, for patients achieving nodal pCR, ALND may constitute overtreatment. If SLNB works well in certain patient populations, axilla-conserving surgery would be possible.

Several studies have evaluated the feasibility and efficacy of SLNB for the prediction of final nodal status after NCT in clinically or cytologically node-positive patients. Although the timing of SLNB in patients scheduled for NCT is controversial, SLNs have been identified in ≥90 % in around half of the reports issued.[29] In addition to our successful SLNs detection in 94.9 %, SLNB after NCT was found to be technically feasible among LABC patients. However, SLNB after NCT is inevitably limited by the effects of NCT, that is, anatomical alterations or disruptions of lymphatic vessels by tumors, inflammation or fibrosis, blockage by necrotic and/or apoptotic cells or induction of nonuniform tumor regression among ALNs.[12,13,30] In the present study, patients with poor tumor or nodal response to NCT had higher SLN detection failure rates, which suggests that disruption or blockage of lymphatic pathways by residual tumors might affect the performance of radioisotope-based SLNB.

Since the eventual objective of SLNB is the accurate prediction of ALN status with less morbidity, FNR and accuracy are important. Although some studies have reported reliable FNRs after NCT as compared with FNRs in adjuvant settings, FNRs of up to 30 % have been reported in initially node-positive patients.[9,10,12] The FNR of present study was 22.0 %, which was significantly higher than that found in our earlier study in an adjuvant setting, and which suggests SLNB is unacceptable for routine use in LABCs.[20,21] However, the present study was limited by the lack of dual tracers (including blue dye) and by no removal of palpable cold nodes for SLN detection. Furthermore, the number of SLNs removed is known to be associated with the FNR of SLNB after NCT, and our present results consistently demonstrated a high FNR of 25.0 % in patients with a single SLN.[31] Pecha et al. reported no FN result in patients with ≥3 resected SLNs.[32] Although clinically node-positive patients before NCT constituted half of their study population, which was different from our population, at least ≥3 SLNs examined could lower FNRs of SLNB in combination with the present results. However, ≥3 SLNs were identified in 21.3 % (36 of 169) of our study population and 7.0 % (19 of 271) of study population by Pecha et al.[32] Further investigation is necessary to determine how many SLNs

TABLE 2 Comparison of SLNB result with regional node status after NCT

Characteristic	Regional node status after NCT			Total no. of patients
	Positive (%)		Negative (%)	
	Non-SLN (+)	Non-SLN (−)		
SLNB result				
Positive	42 (42.0 %)	36 (36.0 %)	–	78 (46.2)
Negative	22 (22.0 %)	–	69 (100 %)	91 (53.8)
Total no. of patients	100 (100 %)		69 (100 %)	169 (100 %)

SLNB sentinel lymph node biopsy, *NCT* neoadjuvant chemotherapy, *SLN* sentinel lymph node

TABLE 3 Diagnostic performance of SLNB according to the number of retrieved SLN

No. of retrieved SLNs	Sensitivity (%)	NPV (%)	FNR (%)	Accuracy (%)
1 ($n = 73$)	75.0	72.5	25.0	84.9
2 ($n = 60$)	78.9	73.3	21.1	86.7
≥3 ($n = 36$)	83.3	85.7	16.7	91.7

SLNB sentinel lymph node biopsy, *SLN* sentinel lymph node, *NPV* negative predictive value, *FNR* false negative rate

TABLE 4 Characteristics and performance of SLNB by molecular subtype

Factor	Luminal A ($n = 75$)	Luminal B ($n = 31$)	HER2-enriched ($n = 29$)	TNBC ($n = 34$)	Whole population ($n = 169$)	*P*
Pathologic tumor stage						
ypT0-is	20 (26.7 %)	13 (41.9 %)	15 (51.7 %)	17 (50.0 %)	65 (38.5 %)	0.035
ypT1–3	55 (73.3 %)	18 (58.1 %)	14 (48.3 %)	17 (50.0 %)	104 (61.5 %)	
Pathologic node stage						
ypN0	18 (24.0 %)	16 (51.6 %)	15 (51.7 %)	20 (58.8 %)	69 (40.8 %)	0.001
ypN1–3	57 (76.0 %)	15 (48.4 %)	14 (48.3 %)	14 (41.2 %)	100 (59.2 %)	
Histologic grade						
I/II	65 (86.7 %)	21 (67.7 %)	14 (48.3 %)	16 (47.1 %)	116 (68.6 %)	<0.001
III	10 (13.3 %)	10 (32.3 %)	15 (51.7 %)	18 (52.9 %)	53 (31.4 %)	
Ki-67 at diagnosis ($n = 113$)						
<20 %	31 (53.4 %)	8 (42.1 %)	9 (52.9 %)	3 (15.8 %)	51 (45.1 %)	0.033
≥20 %	27 (46.6 %)	11 (57.9 %)	8 (47.1 %)	16 (84.2 %)	62 (54.9 %)	
Status of SLNB						
Truly positive	46 (61.3 %)	9 (29.0 %)	10 (34.5 %)	13 (38.2 %)	69 (40.8 %)	0.002
Truly negative	18 (24.0 %)	16 (51.6 %)	15 (51.7 %)	20 (58.8 %)	78 (46.2 %)	
Falsely negative	11 (14.7 %)	6 (19.4 %)	4 (13.8 %)	1 (2.9 %)	22 (13.0 %)	
Performance of SLNB (%)						
Sensitivity	80.7	60.0	71.4	92.9	78.0	
FNR	19.3	40.0	28.6	7.1	22.0	
NPV	62.1	72.7	78.9	95.2	75.8	
Accuracy	85.3	80.6	86.2	97.1	87.0	

HER2 human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *is* in situ carcinoma, *SLNB* sentinel lymph node biopsy, *FNR* false negative rate, *NPV* negative predictive value

should be retrieved to evaluate nodal status accurately in this setting.

We suggested SLNB could be carried out in a selected group of LABCs that respond well to NCT, in which it is capable of acceptable FNRs and accuracies. As shown in Table 4, luminal A subtype had a nodal pCR of 24 % with an FNR of 19.3 %, which suggests the locally advanced luminal A subtype is unsuitable for SLNB after NCT.

TABLE 5 Logistic regression model for the prediction of residual node metastasis after NCT in 135 patients with non-TNBC subtype

Factor[a]	Odds ratio	95 % Confidence interval	*P*
Tumor response to NCT (nonresponse)	10.149	2.549–40.401	0.001
Node response to NCT (nonresponse)	2.425	1.040–5.654	0.040
Lymphovascular invasion (present)	5.699	1.125–28.866	0.036
Estrogen receptor (positive)	1.042	0.296–3.663	0.949
Progesterone receptor (positive)	1.494	0.544–4.104	0.436
HER2 (negative)	4.052	1.458–11.262	0.007

NCT neoadjuvant chemotherapy, *TNBC* triple-negative breast cancer, *HER2* human epidermal growth factor receptor 2

[a] This model was calculated using parameters significantly associated with final nodal status in the univariate analysis among 135 non-TNBC subtypes

Luminal B, HER2-enriched and TNBC subtypes had nodal pCRs of 51.6–58.8 % without statistical difference among non–luminal A subtypes. However, SLNB performance was quite different by molecular subtypes. In particular, TNBC showed better performance, that is, an acceptable FNR of 7.1 % and an accuracy of 97.1 % than luminal B and HER2-enriched subtypes (Table 4). This result suggests SLNB could be safely performed for locally advanced TNBC subgroups after NCT. An independent study with a larger population is required to validate our findings and to determine the nature of the association between tumor biology and SLNB performance.

A small number of authors have indicated the need for imaging- or biomarker-based response evaluations for the assessment of SLNB performance, although no comprehensive analysis has been conducted.[11,15,29] In our non-TNBC subpopulation, we considered clinicopathologic parameters associated with final node response to identify potential candidates for SLNB. Tumor and nodal response, the absence of LVI and HER2-positivity were found to predict final node-negative disease significantly among 135 non-TNBC subtypes and in a small number of patients who met all these factors, the performance of SLNB was increased. Nonetheless, further studies are needed to confirm our findings.

NCTs containing targeted agents are more effective at achieving tumor remission.[8] In the present study, a nodal pCR of 8 patients receiving HER2-blocking agents doubled. All 8 patients had a negative SLNB finding. After surgery, 7 were found to be TN and one was FN. Anticipation of the wide use of targeted therapies underlines the importance of the clinical value of SLNB in HER2-positive subgroups. Currently, clinical trials in clinically node-positive patients are investigating the role of SLNB (ACOSOG Z1071 and German SENTINA trial).[33,34] The results from these trials are expected to increase understanding of the value of SLNB after NCT in clinically node-positive patients.

In conclusion, SLNB using radioisotope was found to be technically feasible after NCT in LABC patients with initially biopsy-proven node metastasis. Furthermore, the high FNR observed in the present study cautions against the routine use of SLNB in LABC patients. On the other hand, significantly better SLNB performance was found for the TNBC subtype, and thus, our findings indicate SLNB could be considered in selected locally advanced TNBCs after NCT.

DISCLOSURE The authors declare that they have no conflicts of interest to disclose.

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