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ORIGINAL ARTICLE

Reliability of Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy in Breast Cancer Patients

Ahram Han[1,*], Hyeong-Gon Moon[1,*], Jisun Kim[1], Soo Kyung Ahn[1], In Ae Park[2], Wonshik Han[1,3], Dong-Young Noh[1,3]

Departments of [1]Surgery and [2]Pathology, Seoul National University Hospital, Seoul; [3]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

Purpose: Sentinel lymph node biopsy (SLNB) is an accurate and effective means of axillary nodal staging in early breast cancer. However its indication after neoadjuvant chemotherapy (NAC) is under constant debate. The present study evaluates the reliability of SLNB in assessing axillary nodal status after NAC. **Methods:** Data from 281 patients who had received NAC and subsequent SLNB were reviewed. The identification and false negative rates of SLNB were determined and the clinicopathologic factors associated with false negative results were investigated using univariate analysis. **Results:** The identification rate of SLNB after NAC was 93.6% and the false negative rate was 10.4%. Hormone receptor status, especially progesterone receptor positivity, was significantly associated with false negative results. The accuracy of intraoperative frozen section examination of sentinel lymph nodes was 91.2%. **Conclusion:** The identification rate of SLNB and the accuracy of intraoperative frozen section examination after NAC are comparable to the results without NAC in patients with early breast cancer. However considering the high false negative rates, general application of SLNB after NAC should be avoided. Patients with progesterone-positive tumors and non-triple-negative breast cancers may be a select group of patients in whom SLNB can be employed safely after NAC, but further studies are necessary.

Key Words: *Breast neoplasms, Neoadjuvant therapy, Sentinel lymph node biopsy*

INTRODUCTION

Axillary lymph node (ALN) status is an important prognostic factor in breast cancer [1]. Accurate lymph node staging and adequate locoregional control can be achieved by axillary lymph node dissection (ALND), which, however, is often followed by significant morbidities including lymphedema and nerve injury [2]. Sentinel lymph node biopsy (SLNB) has been suggested as an alternative method, associated with fewer complications. Over the years, the accuracy of SLNB has been confirmed in several studies, and SLNB has now become a standard surgical procedure for axillary staging in clinically node-negative primary breast cancer [3].

However, the effectiveness of SLNB after neoadjuvant chemotherapy (NAC) is less clear. Conflicting results on the accuracy of SLNB have been reported and ALND remains the standard of care for nodal staging and evaluation of local control after NAC [4-8]. The possibility of high false negative rates is a major concern in implementing SLNB in patients who receive NAC. The reported rate of sentinel node identification failure is another matter of contention [9,10].

In the present study, we evaluated the reliability of SLNB in predicting axillary lymph node status in breast cancer patients after NAC by assessing its identification and false negative rates. We also examined the accuracy of intraoperative frozen section examination of sentinel lymph nodes (SLNs) after NAC.

METHODS

From January 2008 to December 2011, 350 pathologically proven breast cancer patients underwent NAC and subsequent definitive surgery at Seoul National University Hospital. Among these patients, 281 underwent SLNB for axillary stag-

Correspondence to: **Dong-Young Noh**
Department of Surgery, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-2921, Fax: +82-2-3673-4250
E-mail: dynoh@snu.ac.kr

*These authors contributed equally to this work.

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ing during surgery and were included in the final analysis. The reliability of SLNB after NAC was examined by evaluating the sentinel node identification rate and false negative rate. During the study period, subsequent axillary dissection after SLNB was performed at the discretion of the responsible surgeon, because of a lack of safety data on SLNB in patients who receive NAC. Thus, axillary dissection was frequently performed even in SLN-negative patients. The false negative rate of SLNB in this study was evaluated only in patients who underwent subsequent ALND. This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB number: H-1309-098-522).

For breast cancer diagnosis and staging, core needle biopsy and multiple imaging studies were performed. Initial imaging studies included breast and axilla sonography, mammography, chest computed tomography, breast magnetic resonance imaging (MRI), and bone scanning. Pathologic examination of biopsied tissue included immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR), c-erbB-2, p53, Bcl-2, and Ki-67. Formalin-fixed, paraffin-embedded tissue blocks were serially sectioned at 4-μm thickness and slides were subjected to our previously described IHC method [11]. Briefly, after deparaffinization in xylene and dehydration in a graded alcohol series, sections were treated to enhance antigen retrieval. The following mouse monoclonal antibodies were used as primary antibodies: ER (1:50; Dako Co., Carpinteria, USA), PR (1:50; Dako Co.), c-erbB-2 (1:200; Novocastra Laboratories Ltd., Newcastle, UK), p53 (1:1,200; Dako Co.), Bcl-2 (1:50; Dako Co.), and Ki-67 (1:800; Dako Co.). The antigen-antibody complex was detected using the labeled streptavidin-biotin method, using anti-mouse antibody and streptavidin horseradish peroxidase (Zymed Laboratories Inc., San Francisco, USA). Tumors were considered ER and PR positive if 10% or more nuclei were positively stained in 10 high-power fields. Human epidermal growth factor receptor 2 (HER2) overexpression was defined as a c-erbB-2 membrane staining score of 3+ (uniform, strong membranous staining in more than 30% of cancer cells) or a positive result on fluorescence *in situ* hybridization.

Neoadjuvant chemotherapy

Patients received 3 to 12 cycles of NAC before surgery. NAC regimens were mainly anthracycline- and/or taxane-based. Most patients received 3 to 8 cycles of chemotherapy unless their tumors were inoperable. Clinical response was determined on the basis of physical and radiologic examinations [12]. Complete clinical response (cCR) of the primary tumor was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. In most cases, MRI measurements were used to assess tumor regression. For 35 cases for which MRI measurements were not available, sonographic size estimates were used instead. ALN status was evaluated before and after NAC with high-resolution ultrasonography performed by experienced radiologists, and was categorized according to the maximum thickness of the cortex and the appearance of the fatty hilum [13]. Pathologic complete response (pCR) of the primary tumor was defined as the absence of invasive cancer cells in the breast and axilla; a residual *in situ* lesion in the breast was permitted. When referring to the response in the breast separately, we designated this as "TpCR."

Sentinel lymph node biopsy

SLNs were detected using a blue dye and/or a radioisotope technique. Subareolar intradermal injection of 0.8% indigo carmine (1 cc) dye in four areas around the areola was performed immediately before the surgery. For the radioisotope technique, Tc-99m antimony sulfur colloid (0.4 mCi) was intradermally injected 1 to 6 hours prior to surgery, in the quadrant where the tumor was located. Lymphoscintigraphic images were obtained approximately 40 minutes after injection, and SLNs were intraoperatively detected using a gamma probe (NEO2000; Neoprobe Co., Dublin, USA). SLNs were identified as any blue-stained nodes or any nodes with radioactive counts of 10% or greater than the count of the most radioactive node. SLNs and grossly enlarged non-SLNs suspicious for metastasis were harvested and were, in most cases, bisected and examined intraoperatively by hematoxylin and eosin staining of frozen sections. Postoperatively, SLNs were formalin-fixed, paraffin-embedded, and sectioned in 4 μm thickness for pathologic examination.

Definitions and statistical analysis

The identification rate was defined as the proportion of patients with successful detection of SLNs among the total number of patients who underwent SLNB (identification rate = number of patients in whom SLNs were detected/number of patients in whom SLNB was attempted). The false negative rate was defined as the number of patients with confirmed ALN metastasis but with negative SLN divided by the total number of patients with positive nodes (false negative rate = SLN-negative patients with ALN metastasis/total number of ALN-positive patients).

The chi-square test or Fisher exact test was used to assess the association between the false negative rate and various clinicopathologic factors. All statistical analyses were performed using SPSS Statistics version 18.0 software (SPSS Inc., Chicago, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

Patient demographic and tumor characteristics

Clinicopathologic characteristics at the time of initial diagnosis are illustrated in Table 1. The median age of patients was 46 years (range, 24-73 years). Among the 281 patients studied, 204 underwent breast-conservation surgery (72.6%). Most patients had cT2 (n=168, 59.8%) or cT3 (n=84, 29.9%) tumors, with a mean tumor size of 4.8 cm (range, 1.0-13.5 cm). Two hundred fifty-two patients (89.7%) had clinically positive lymph nodes at diagnosis. In 85 patients, the presence of lymph node metastasis was confirmed by needle biopsy. Among 281 patients, 150 (53.4%) were ER positive, 92 (32.7%) were PR positive, and 87 (31.0%) showed HER2 overexpression. Sixty-seven patients (23.8%) had triple negative (ER negative, PR negative, HER2 negative) breast cancer.

Neoadjuvant chemotherapy and tumor response after treatment

All patient received NAC prior to definitive surgery. Twenty-seven patients (9.6%) presented no evidence of residual tumor on physical and radiologic examination after NAC. The incidence of pCR was higher than that of cCR with a rate of 21.7% (61 patients). Regarding nodal status, among 252 clinically node positive patients at diagnosis, 162 (64.3%) became clinically node negative after chemotherapy. According to the final pathologic results, NAC resulted in complete nodal sterilization in 49.2% (125) of initially clinically node-positive breast cancer patients.

SLN identification rate and related factors

After NAC, the overall SLN identification rate was 93.6% (263/281). SLN identification rate was 93.0% (186/200) in 200

Table 1. Patient and tumor characteristics

Characteristic	No. (%)	Characteristic	No. (%)
Age category (yr)		Ki-67 activity	
<50	169 (60.1)	Low (≤10%)	155 (55.2)
≥50	112 (39.9)	High (>10%)	108 (38.4)
Clinical T stage		Missing	17 (6.0)
cT1	12 (4.3)	p53 expression	
cT2	168 (59.8)	Low (<25%)	163 (58.0)
cT3	84 (29.9)	High (≥25%)	99 (35.2)
cT4	17 (6.0)	Missing	19 (6.8)
Clinical nodal status		Clinical response of primary tumor to NAC (n=281)	
Negative	29 (10.3)	cCR	27 (9.6)
Positive	252 (89.7)	cPR	199 (70.8)
cN1	170 (60.5)	cSD	48 (17.1)
cN2	52 (18.5)	cPD	0
cN3	30 (10.7)	Not available	7 (2.5)
ER status		Pathological response of primary tumor to NAC (n=281)	
Negative	128 (45.6)	pCR	61 (21.7)
Positive	150 (53.4)	Otherwise	220 (78.3)
Missing	3 (1.1)	Clinical nodal status after NAC	
PR status		Initially clinically node negative patients (n=29)	
Negative	186 (66.2)	Negative	25 (86.2)
Positive	92 (32.7)	Equivocal	2 (6.9)
Missing	3 (1.1)	Positive	2 (6.9)
HER2 overexpression		Initially clinically node positive patients (n=252)	
Negative	191 (68.0)	Negative	162 (64.3)
Positive	87 (31.0)	Equivocal	48 (19.0)
Missing	3 (1.1)	Positive	42 (16.7)
TNBC		Pathological nodal status after NAC	
TNBC	67 (23.8)	Initially clinically node negative patients (n=29)	
Non-TNBC	212 (75.4)	Metastatic LN present	8 (27.6)
Not known	2 (0.7)	Negative	21 (72.4)
Bcl-2 expression		Initially clinically node positive patients (n=252)	
Negative	96 (34.2)	Metastatic LN present	124 (49.2)
Positive	169 (60.1)	Negative	128 (50.8)
Missing	16 (5.7)		

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; TNBC=triple negative breast cancer; NAC=neoadjuvant chemotherapy; cCR=clinical complete response; cPR=clinical partial response; cSD=clinical stable disease; cPD=clinical progressive disease; pCR=pathological complete response; LN=lymph node.

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patients who underwent intraoperative lymphatic mapping with blue dye alone. When both blue dye and radioactive colloid were used, SLNs were successfully detected in 96.2% (76/79) of cases. In two patients in whom only radioactive colloid was used, SLNs were identified in one patient (50%). According to univariate analysis, no clinicopathologic factors including age at diagnosis, clinical T stage, initial nodal status, hormonal receptor status, and degree of clinical/pathological response to NAC was significantly related to the SLN identification rate (Table 2).

Table 2. Sentinel lymph node identification rate according to clinicopathologic characteristics

Characteristic	SLN identification rate*	%	*p*-value
Age category (yr)†			
<50	157/169	92.9	0.599
≥50	102/112	94.6	
Clinical T stage†			
cT1	12/12	100.0	0.823
cT2	157/168	93.5	
cT3	78/84	92.9	
cT4	16/17	94.1	
Clinical nodal status†			
Negative (cN-)	29/29	100.0	0.137‡
Positive (cN+)	234/252	92.0	
Pathologic nodal status†			
Metastasis proven by needle biopsy	79/85	92.9	0.768
Otherwise	184/196	93.9	
ER status†			
Negative	118/128	92.2	0.402
Positive	142/150	94.7	
PR status†			
Negative	171/186	91.9	0.126
Positive	89/92	96.7	
HER2 overexpression†			
Negative	172/182	94.5	0.360
Positive	88/96	91.7	
Triple negative breast cancer			
TNBC	61/67	91.0	0.246‡
Non-TNBC	200/212	94.3	
Clinical response of primary tumor to NAC			
cCR	27/27	100.0	0.153‡
Otherwise (cPR, cSD, cPD)	236/254	92.9	
Clinical nodal status after NAC (sonographic)			
Negative	173/187	92.5	0.116
Equivocal	50/50	100.0	
Positive	40/44	90.9	
Pathologic response of primary tumor to NAC			
TpCR	58/61	95.1	0.424‡
Otherwise	236/254	92.9	
Pathologic nodal status after NAC			
Negative	140/149	94.0	0.790
Positive	123/132	93.2	

SLN=sentinel lymph node; cN-=clinically node negative; cN+=clinically node positive; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; TNBC=triple negative breast cancer; NAC=neoadjuvant chemotherapy; cCR=clinical complete response; cPR=clinical partial response; cSD=clinical stable disease; cPD=progressive disease; TpCR=pathological complete response of primary tumor.
*SLN identification rate=number of patients in whom SLNs were detected/number of patients in whom sentinel lymph node biopsy was attempted; †Clinicopathologic variables at the time of initial diagnosis; ‡*p*-values from Fisher exact test.

For 18 patients in whom SLNs were not identified, subsequent axillary dissection revealed the presence of metastatic cancer cells in nine cases (50%).

False negative rate of SLNB and related factors

Among 263 patients with identified SLNs, 202 (76.8%) underwent subsequent ALND (Figure 1). No further ALND was performed on the other 61 patients who had negative frozen section results. The false negative rate of SLNB was determined in the 202 patients who underwent SLNB followed by ALND (Table 3). According to patients' final pathology reports, SLNB results accurately predicted ALN status in 190 of 202 patients. However, in 12 patients with residual cancer cells after NAC, SLNB failed to identify the metastatic nodes, resulting in a false negative rate of 10.4%.

The false negative rate was significantly higher in patients with PR-negative tumors than in those with PR-positive tumors (16.7% vs. 3.7%, $p=0.024$) (Table 4). Although ER status and HER2 expression were not significant factors affecting the false negative rate, triple-negative breast cancer (TNBC) patients showed a significantly higher false negative rate than non-TNBC patients (26.3% vs. 7.4%, $p=0.028$). No other investigated factors including age, response to NAC, and nodal status were positively associated with the false negative rate, as shown in Table 4. Multivariate logistic regression analysis showed that TNBC was an independent predictor of false negative SLNB in patients who received NAC (hazard ratio [HR], 0.155; $p=0.045$).

Table 3. Axillary lymph node status after neoadjuvant chemotherapy in patients who underwent sentinel lymph node biopsy followed by axillary lymph node dissection (n=202)

	Axillary LN	
	Positive	Negative
SLN		
Positive	103	0
Negative	12*	87
Total	115	87

LN=lymph node; SLN=sentinel lymph node.
*False negative rate=SLN-negative patients with axillary lymph node (ALN) metastasis/total number of ALN-positive patients=12/(103+12)=12/115 (10.4%).

Table 4. False negative rate of sentinel lymph node biopsy according to clinicopathologic characteristics

	FNR*	%	*p*-value		FNR*	%	*p*-value
Age category (yr)				ER status			
<50	6/68	8.8	0.545	Negative	6/33	18.2	0.090†
≥50	6/47	12.8		Positive	6/81	7.4	
Clinical tumor size (MRI, initial)				PR status			
<5 cm	6/61	9.8	0.823	Negative	10/60	16.7	0.024
≥5 cm	6/54	11.1		Positive	2/54	3.7	
Clinical tumor size (MRI, post-NAC)				HER2			
<3 cm	7/59	11.9	0.607	Negative	10/86	11.6	0.727†
≥3 cm	5/56	8.9		Positive	2/28	7.1	
cCR				TNBC			
Yes	2/5	40.0	0.084†	TNBC	5/19	26.3	0.028†
No	10/110	9.1		Non-TNBC	7/95	7.4	
TpCR				Ki-67 expression			
Yes	2/5	40.0	0.084†	Low (≤20%)	7/87	8.0	0.219†
No	10/110	9.1		High (>20%)	4/21	19.0	
Clinical nodal status (US, initial)				p53 expression			
Negative (cN-)	1/7	14.3	0.548†	Low (<25%)	8/81	9.9	0.501†
Positive (cN+)	11/108	10.2		High (≥25%)	4/28	14.3	
Clinical nodal status (US, post-NAC)				Bcl-2 expression			
Negative	7/89	7.9	0.139†	Negative	3/27	11.1	0.545
Equivocal or positive	5/26	19.2		Positive	8/82	9.8	
Clinically complete nodal regression							
Yes	5/59	8.5	0.480				
No	7/56	12.5					

FNR=false negative rate; MRI=magnetic resonance imaging; NAC=neoadjuvant chemotherapy; cCR=clinical complete response; TpCR=pathological complete response of primary tumor (regardless of axillary status); US=ultrasonography; cN-=clinically node negative; cN+=clinically node positive; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; TNBC=triple negative breast cancer.
*FNR=sentinel lymph node-negative patients with axillary lymph node (ALN) metastasis/total number of ALN-positive patients; †*p*-values from Fisher exact test.

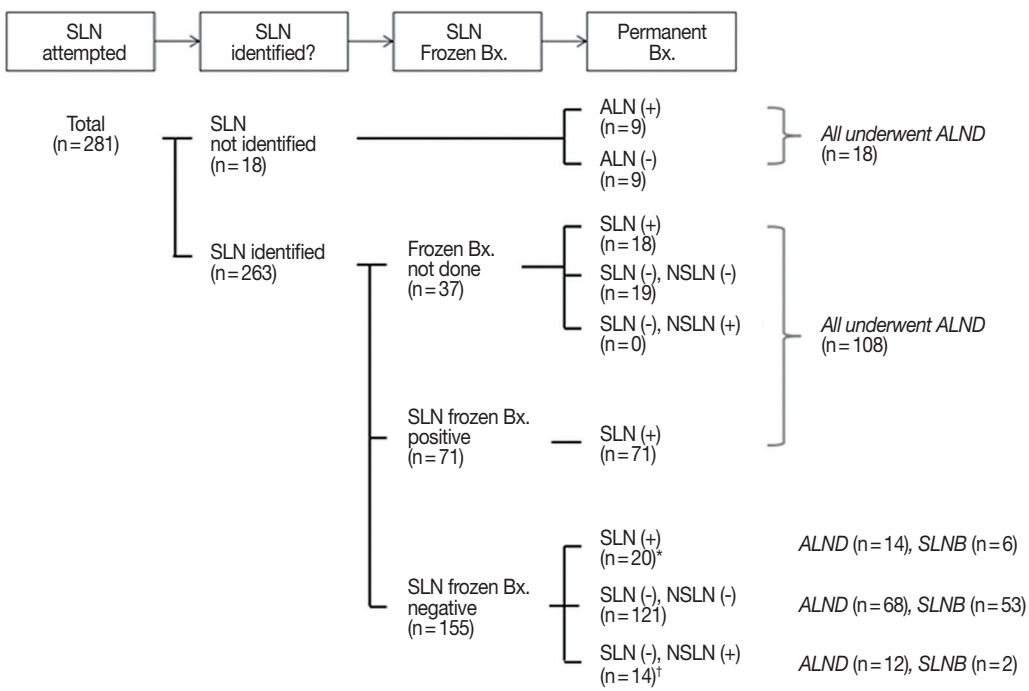

Figure 1. Description of the study population by treatment/procedure performed.
SLN=sentinel lymph node; Bx=biopsy; ALN=axillary lymph node; ALND=axillary lymph node dissection; SLNB=sentinel lymph node biopsy. *Frozen biopsy and permanent biopsy discordant cases; †False negative cases (based on permanent biopsy results).

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Table 5. Meta-analysis and recent reports on sentinel lymph node biopsy after neoadjuvant chemotherapy

	Year	No.	Study design/population	IR	Associated factors	FNR	Associated factors
Xing et al. [15]	2006	1,273	Meta-analysis	90		12	
van Deurzen et al. [7]	2009	2,148	Meta-analysis	90.9		10.5	
Kelly et al. [16]	2009	1,799	Meta-analysis	89.6		8.4	
Tan et al. [8]	2011	449	Meta-analysis, clinically node negative after NAC	94.3		9.4	
Classe et al. [17]	2009	195	Prospective, multicenter/Operable, noninflammatory, unifocal, large, N0 or N1	90.1	Initial cN0	11.5	-
Schwartz et al. [18]	2010	79	Retrospective/T0-T4, N0-N2	98.7	-	1/23	-
Ozmen et al. [19]	2010	77	Retrospective/Stage IIB, IIIA, IIIB, clinically node negative after NAC, NAC=FAC or AC/docetaxel	92	Residual tumor size	13.7	Initial N stage
Reitsamer et al. [20]	2010	185	Retrospective/Stage II or III, taxane-based NAC	81.1	-	8.3	-
Kang et al. [21]	2011	66	Retrospective/Pathologically proven positive ALN before NAC	87.9	cCR (NS)	17.1	-
Pecha et al. [22]	2011	343	Retrospective, multicenter	80.8	Young age, cN0, ER+, low Ki-67, LVI	19.5	LVI, ER- (NS)
Canavese et al. [23]	2011	64	Prospective, single center/T≥2 cm and clinically node positive, NAC=FEC/T	93.8	-	2.1	-
Takahashi et al. [24]	2012	96	Retrospective, single center/Stage II, III	87.5	-	24.5	Initial cN0, cCR (NS)
Alvarado et al. [25]	2012	150	Retrospective/Pathologically proven positive ALN before NAC	93		20.8	Initial cN0, tumor size, number of SLN removed
Takei et al. [26]	2012	105	Retrospective, single center/Clinically positive ALN at diagnosis	75.7	-	8.2	-

IR=identification rate; FNR=false negative rate; NAC=neoadjuvant chemotherapy; cN0=clinical nodal stage N0; FAC=fluorouracil, anthracyclin, cyclophosphamide; AC=anthracyclin, cyclophosphamide; ALN=axillary lymph node; cCR=clinical complete response; NS=not significant; ER=estrogen receptor; LVI=lymphvascular invasion; FEC/T=fluorouracil, epirubicin, cyclophosphamide/taxane; SLN=sentinel lymph node.

Discordance between intraoperative frozen section results and final permanent section results of SLNB

The final pathologic results of SLN status were not always in accordance with intraoperative frozen section findings. Among 226 patients receiving intraoperative SLN examination, frozen sections indicated no tumor cells in 155 patients (Figure 1). However, the final pathologic examination of the SLNs showed metastatic cells in 20 patients with negative frozen section results, yielding an accuracy of 91.2%, a sensitivity of 78%, and a specificity of 100% for the frozen section study.

DISCUSSION

The accuracy of SLNB after NAC remains controversial for several reasons. First, lymphatic fibrosis or tumor debris occurring after NAC may result in changes in the lymphatic drainage pattern, leading to a decrease in SLNB accuracy. Although direct comparison of the lymphatic drainage pattern before and after NAC has not been reported, Brown et al. [14] recently demonstrated histologic changes including fibrosis and obliteration of lymph node architecture after NAC. They performed SLNB and subsequent axillary dissection after NAC in patients with pathologically proven positive ALNs and demonstrated that SLNs from patients with sterilized ALNs generally exhibited the histologic changes mentioned above, indicative of treatment effect. Another possible explanation for the increased false negative rate is the nonsequential therapeutic effect of NAC on lymph nodes, which indicates SLNs may be sterilized before non-SLNs.

In the present study, we aimed to assess the reliability of SLNB after NAC by evaluating its identification rate and false negative rate.

The overall identification rate achieved in our study was 93.6%, similar to the pooled value from four previously published meta-analyses (Table 5) [7,8,15-26]. However, identification rates from recent independent reports show significant variation, ranging from 75.7% to 98.7%, which is often explained by study population heterogeneity. Clinicopathologic factors such as initial clinical nodal status [17,22], residual tumor size [19], degree of tumor response to NAC [21], age, ER status, proliferation index, and lymphovascular invasion [22] have been suggested to affect identification rates. However, no single clinicopathologic factor has consistently been shown to affect the identification rate of SLNB after NAC. In our study, none of the above factors were significantly associated with the identification rate. SLNs were successfully detected in all initially node-negative patients, thus resulting in an identification rate of 100%, but this result did not reach statistical significance ($p=0.137$). The insignificance may be due to the small study population size as suggested by the fact that the

proportion of initially node-negative patients was only 10.3% (29/281). Similarly, SLN detection was successful in all 27 patients who achieved clinical cCR after NAC, but this too was not statistically significant ($p=0.153$).

The false negative rate of SLNB after NAC was 10.4% in our study, which is substantially higher than that in primary breast cancer patients without NAC observed at our institution [27]. The reported false negative rates of SLNB after NAC from other recent studies range from 2% to 24%, and results of meta-analyses seem to converge to values of approximately 10%. Similar to our result, findings presented at the 2012 San Antonio Breast Cancer Symposium from the American College of Surgeons Oncology Group Z0171 trial, which included 756 breast cancer patients who received NAC, indicated a false negative rate of 12.8% [28]. Although the acceptable range of false negative results in patients receiving NAC remains controversial, a rate of over 10% of false negative results by SLNB warrants precaution when indicating the procedure in this patient population.

Our analysis suggests that patients with PR-positive tumors and non-TNBC might be a select group in which SLNB can be indicated after NAC. Pecha et al. [22] also reported a nonsignificant trend in the association between hormonal receptor status and the accuracy of SLNB. It is however difficult to explain why SLNB in patients with PR-negative tumors or in TNBC patients showed higher false negative rates in the current study. This finding may be explained by the diverse susceptibility to NAC by different breast cancer subtypes, as PR-negative tumors and TNBC each showed a higher CR rate than PR-positive tumors and non-TNBC (data not shown). A similar difference in response to NAC was reported among breast cancer subtypes in a meta-analysis by Houssami et al. [29]. Tumors with higher response may undergo greater changes in the lymphatic drainage pattern, which consequently leads to higher false negative results of SLNB.

Histologic changes after NAC pose potential challenges to the interpretation of SLN frozen sections, which prompted us to investigate the discordance rate between frozen section examination and permanent examination. Compared to the permanent examination results, intraoperative assessment of frozen sections from SLNB after NAC showed 91.2% accuracy. Although this discordance rate is similar to the observation in breast cancer patients who do not receive NAC at our institution [27], it may have larger implications. Missed cases on frozen section analysis mostly involve micrometastasis, which, in the NAC group, may be a result of an incomplete response of initial macrometastasis. As speculated in a report by Sahoo and Lester [30], such possibilities are supported by results from the National Adjuvant Breast and Bowel Project (NSABP) B-18. In NSABP B-18, patients with lymph node micrometastases who were not treated with chemotherapy before surgery had identical survival compared to those with negative nodes. However, in the NAC group, survival of patients with minimetastases and micrometastases in lymph nodes was significantly worse. Thus, considering the prognostic significance of micrometastasis in patients receiving NAC, we should be prudent in performing SLNB, which relies on the results of frozen sections. In recognition that these frozen section results can miss micrometastases in approximately 10% of the cases, patients should be informed about the possibility of additional axillary dissection after pathologic results of permanent sections.

In summary, our study suggests that SLNB after NAC and intraoperative examination of frozen sections is technically feasible. However, SLNB after NAC is associated with a higher risk of false negativity, which may vary depending on the molecular characteristics of the tumor such as PR expression and molecular subtype. Our results suggest that patients with PR positive and non-TNBC are the potential candidates for SNLB after NAC.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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