

## Original Article



# Evaluation of the Role of Axillary Lymph Node Fine-Needle Aspiration Cytology in Early Breast Cancer With or Without Neoadjuvant Chemotherapy

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## ABSTRACT




**Purpose:** Fine-needle aspiration cytology (FNAC) of axillary lymph nodes (AxLNs) is performed to diagnose nodal metastasis in patients with breast cancer. Although the sensitivity of ultrasound-guided FNAC for identifying AxLN metastasis is in the range of 36%–99%, whether sentinel lymph node biopsy (SLNB) should be performed for neoadjuvant chemotherapy (NAC) patients with negative FNAC results is uncertain. This study aimed to determine the role of FNAC before NAC in the evaluation and management of AxLN in early breast cancer patients.

**Methods:** We retrospectively analyzed 3,810 clinically node-negative (a lymph node with no clinical metastasis without FNAC or radiological suspicion of metastasis with negative FNAC results) patients with breast cancer who underwent SLNB between 2008 and 2019. We compared the positivity rate of sentinel lymph nodes (SLNs) between patients who received and those who did not receive NAC with negative FNAC results or without FNAC and axillary recurrence rate in the neoadjuvant group with negative SLNB results.

**Results:** In the non-neoadjuvant (primary surgery) group, the positivity rate of SLNs in patients with negative FNAC results was higher than that in patients without FNAC (33.2% vs. 12.9%;  $p < 0.001$ ). However, the SLN positivity rate of patients with negative FNAC results (false-negative rate for FNAC) in the neoadjuvant group was lower than that in the primary surgery group (3.0% vs. 33.2%;  $p < 0.001$ ). After a median follow-up of 3 years, one axillary nodal recurrence was observed, which was a case from the neoadjuvant non-FNAC group. None of the patients in the neoadjuvant group with negative FNAC results had axillary recurrence.

**Conclusion:** The false-negative rate for FNAC in the primary surgery group was high; however, SLNB was the proper axillary staging procedure for NAC patients who have clinically suspicious AxLN metastases on radiologic examination but negative FNAC results.

**Keywords:** Biopsy, Fine-Needle; Breast Neoplasms; Neoadjuvant Therapy; Sentinel Lymph Node Biopsy

Nanae Horisawa <https://orcid.org/0000-0001-8457-5781>Yuri Ozaki <https://orcid.org/0000-0001-8382-7473>Yuka Endo <https://orcid.org/0000-0002-8415-3885>Kazuki Nozawa <https://orcid.org/0000-0002-0277-8196>Hiroji Iwata <https://orcid.org/0000-0002-0242-4718>**Conflicts of Interest**

The authors declare that they have no competing interests.

**Author Contributions**

Conceptualization: Iwata H; Investigation: Yoshimura A, Sawaki M, Hattori M, Kotani H, Kataoka A, Horisawa N, Ozaki Y, Endo Y, Nozawa K; Supervision: Iwata H; Visualization: Takatsuka D. Writing - original draft: Takatsuka D; Writing - review & editing: Takatsuka D.

**INTRODUCTION**

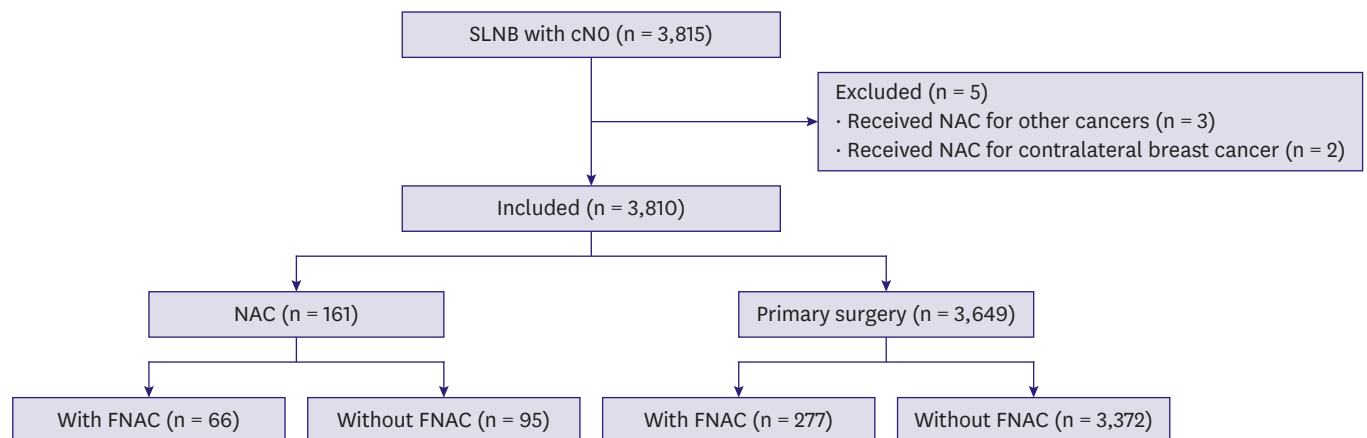
We often perform fine-needle aspiration cytology (FNAC) of radiologically suspicious axillary lymph nodes (AxLNs) in patients with early breast cancer (EBC) to diagnose nodal metastasis. The decision to perform axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) is based on the FNAC results. Studies report that the sensitivity of ultrasound-guided FNAC for identifying axillary lymph node metastasis in patients with breast cancer is in the range of 36%–99%, and the specificity ranges from 80%–100% [1-7].

Neoadjuvant chemotherapy (NAC) is administered for EBC before surgery to downstage tumors for breast-conserving surgery. Recently, it has been used for response-guided chemotherapy after surgery [8,9]. However, whether SLNB should be performed for NAC patients, especially with clinically suspicious AxLN metastases on radiologic examination and negative FNAC results, is uncertain, and no studies have reported SLNB results for these NAC patients with negative FNAC.

Hence, we aimed to assess the necessity of FNAC in such cases by analyzing the differences in the positivity rate of sentinel lymph node (SLN) in clinically node-negative (cN0) patients with and without FNAC stratified according to NAC.

**METHODS****Study population**

A total of 3,815 patients with cN0 EBC underwent SLNB at our hospital between January 2008 and December 2019. We retrospectively assessed the clinical and pathological data from the clinical records and counted two cases of synchronous or metachronous bilateral breast cancer. We excluded patients who received NAC for other cancers (three cases) and patients with non-invasive ductal carcinoma who received NAC for contralateral invasive breast cancer (two cases) (**Figure 1**). Thus, we analyzed 3,810 patients with cN0 EBC who underwent SLNB. This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Aichi Cancer Center Hospital (approval number: 2021-I-092). Written and oral informed consent was obtained from each patient before inclusion in the study.



**Figure 1.** Schema of this analysis.

SLNB = sentinel lymph node biopsy; NAC = neoadjuvant chemotherapy; FNAC = fine-needle aspiration cytology.

### Assessment of AxLN metastasis

To evaluate AxLN metastasis, all patients underwent palpation, followed by breast and axillary ultrasonography. Patients underwent additional radiological examinations before primary treatment (computed tomography, positron emission tomography/computed tomography, or magnetic resonance imaging), according to the physician's preference. Physicians performed FNAC for suspected cases of AxLN metastasis. FNAC was performed under ultrasonography guidance with a 21G needle. Cytology results were categorized in accordance with the Japanese guidelines (General Rules for Clinical and Pathological Recording of Breast Cancer, 18th edition) for quality assurance in breast cancer screening as follows: inadequate, normal or benign, indeterminate, suspicious for malignancy, or malignant [10]. Malignant lesions were defined as node-positive. In this study, cN0 was defined as a lymph node with no clinical metastasis without FNAC or radiological suspicion of metastasis with FNAC and cytology-negative lymph nodes.

### Surgical treatment

SLNB was performed using technetium ( $^{99m}\text{Tc}$ ) and a blue dye (indigo carmine or indocyanine green).  $^{99m}\text{Tc}$  was injected into the areola, and lymphoscintigraphy was performed 3 hours after the injection on the day before surgery. Indigo carmine or indocyanine green was injected into the areola immediately before surgery. Resected SLNs were evaluated for metastases by a pathologist intraoperatively and postoperatively with hematoxylin and eosin-stained specimens. Positive or negative lymph node metastasis was defined according to the UICC (Union for International Cancer Control) 8th edition TNM staging system for breast cancer; therefore, isolated tumor cells were defined as negative. In the NAC group, all patients underwent SLNB at the same time as breast surgery after NAC. ALND was performed in all patients with positive SLNB results and omitted in all patients with negative SLNB results.

### Pathological assessment and definition of molecular subtypes

Breast cancer subtypes were evaluated from biopsy specimens before NAC, according to the immunohistochemical classification proposed by the 2011 St. Gallen Expert Panel as follows: Luminal: estrogen receptor (ER) and/or progesterone receptor (PgR) positive, and human epidermal growth factor receptor 2 (HER2)-negative; Luminal-HER2: ER and/or PgR positive, and HER2 positive; HER2: ER and PgR negative and HER2 positive; Triple negative: ER, PgR, and HER2 negative [11]. ER positivity was defined as an Allred score  $\geq 3$ . HER2-positive was defined as a Hercep test score of 3+ or fluorescent in situ hybridization positivity following a Hercep test score of 2+. Tumor stage was stratified according to the UICC for International Cancer Control 8th edition TNM staging system for breast cancer.

In this study, we defined pathological complete response (pCR) as pT0/is and pN0.

### Systemic and radiation therapies in the NAC group

In the NAC group, perioperative systemic treatment was performed according to the general guidelines. Patients who underwent breast-conserving surgery also underwent whole-breast radiotherapy. Additionally, patients with high-risk T3 or T4 tumors who underwent mastectomy received postmastectomy radiotherapy.

### Statistical analysis

We assessed the positivity rates of SLN with subgroups (primary surgery group and NAC groups, each divided into with or without FNAC). We compared patient characteristics, axillary recurrence rate (ARR), and 3-year distant recurrence-free survival (3-y DRFS) in

the NAC group with negative SLNB divided into those with or without FNAC. DRFS was defined as the time to distant recurrence or all-cause mortality. Differences in the positivity rates of SLN and patient characteristics were calculated using the  $\chi^2$  test. The Kaplan–Meier method was used to plot distant recurrence-free survival and cumulative incidence of axillary recurrence events. The log-rank test was used to test the differences in the Kaplan–Meier curves. Survival was calculated from the date of surgery to the date of the event or latest follow-up. A two-tailed  $p$  value  $< 0.05$  was considered significant. Statistical analysis was performed using the Stata software (version 15.0; StataCorp, College Station, TX, USA).

## RESULTS

We assessed 3,810 patients with cN0, a lymph node with no clinical metastasis without FNAC or radiological suspicion of metastasis with negative FNAC results, EBC who underwent SLNB; the analysis is schematically represented in **Figure 1**. Of the 3,810 patients, 161 received NAC (NAC group) and 3,649 did not (primary surgery group). In the NAC group, 66 patients underwent FNAC before chemotherapy, and 95 patients did not. In the primary surgery group, 277 patients underwent FNAC before surgery, and 3,372 patients did not. All these patients who underwent FNAC had negative FNAC results.

The patient and pathological tumor characteristics of the NAC group are shown in **Table 1**. Statistically significant differences were observed in clinical tumor size ( $p = 0.003$ ), progesterone receptor status ( $p = 0.021$ ), histological grade ( $p = 0.009$ ), and radiotherapy ( $p = 0.0013$ ) between patients with and without FNAC. However, other factors (ER status, HER2 status, subtype, surgery, chemotherapy, number of nodes removed, and pathological response) showed no significant differences between patients with and without FNAC.

The positivity rates of SLN are shown in **Table 2**. In the primary surgery group, the positivity rate of SLN in patients with negative FNAC results was significantly higher than that in patients without FNAC (33.2% vs. 12.9%;  $p < 0.001$ ). In the NAC group, there was no difference in the positivity rate of SLN in patients without FNAC (3.0% vs. 7.4%;  $p = 0.311$ ). Furthermore, in patients with negative FNAC results, the positivity rate of SLN in the NAC group was significantly lower than that in the primary surgery group (3.0% vs. 33.2%;  $p < 0.001$ ).

In the 152 patients with negative SLN who underwent NAC, we assessed ARR in each group (with FNAC [ $n = 64$ ] and without FNAC [ $n = 88$ ]). One patient (1.1%) without FNAC showed axillary recurrence 5.2 years after surgery, and no patient with negative FNAC results showed axillary recurrence (median follow-up, 3.0 [range 0.1–11.5]). The cumulative incidence of ARR is shown in **Figure 2** (log-rank  $p = 0.531$ ).

Among 147 patients (excluding patients with bilateral breast cancer), we assessed DRFS in each group (with FNAC [ $n = 63$ ] and without FNAC [ $n = 84$ ]); 3-y DRFS was 92.0% (95% confidence interval [CI], 80.0–97.0) and 97.8% (95% CI, 85.35–99.7) in patients with negative FNAC results and without FNAC, respectively. There was no statistical difference in the DRFS between the two groups ( $p = 0.242$ , **Figure 3**).

**Table 1.** Patient characteristics in neoadjuvant chemotherapy group

Variables	With FNAC	Without FNAC	p-value
All patients	66	95	
Age	49 (23-78)	51 (29-78)	
Clinical tumor size			0.003
cT1	3 (4.6)	17 (17.9)	
cT2	49 (74.2)	73 (76.8)	
cT3	9 (13.6)	3 (3.2)	
cT4	5 (7.6)	2 (2.1)	
Estrogen receptor status			0.286
Positive	28 (42.4)	50 (52.6)	
Negative	38 (57.6)	44 (46.3)	
Unknown	0	1 (1.1)	
Progesterone receptor status			0.021
Positive	13 (19.7)	37 (38.9)	
Negative	53 (80.3)	57 (60.0)	
Unknown	0	1 (1.1)	
HER2 status			0.178
Positive	32 (48.5)	58 (61.0)	
Negative	34 (51.5)	36 (37.9)	
Unknown	0	1 (1.1)	
Histological grade			0.009
1	2 (3.0)	3 (3.2)	
2	11 (16.7)	36 (37.9)	
3	53 (80.3)	53 (55.8)	
Unknown	0	3 (3.2)	
Subtype			0.243
Luminal	13 (19.7)	18 (18.9)	
Luminal-HER2	16 (24.2)	33 (34.7)	
HER2	16 (24.2)	26 (27.4)	
TN	21 (31.8)	17 (17.9)	
Unknown	0	1 (1.1)	
Surgery			0.057
Mastectomy	35 (53.0)	36 (37.9)	
Lumpectomy	31 (47.0)	59 (62.1)	
Chemotherapy			0.585
Anthracycline	8 (12.1)	13 (13.7)	
Taxane	3 (4.6)	8 (8.4)	
Anthracycline-taxane	55 (83.3)	74 (77.9)	
Number of nodes removed			0.185
1	25 (37.9)	42 (44.2)	
2	26 (39.4)	35 (36.8)	
3	7 (10.6)	13 (13.7)	
4	7 (10.6)	2 (2.1)	
5	1 (1.5)	3 (3.2)	
Radiotherapy			0.013
PMRT	9 (13.6)	3 (3.2)	
WBRT	29 (44.0)	59 (62.1)	
None	28 (42.4)	33 (34.7)	
Pathological response			0.618
pCR (pT0/is pN0)	29 (43.9)	38 (40.0)	
Non-pCR	37 (56.1)	57 (60.0)	

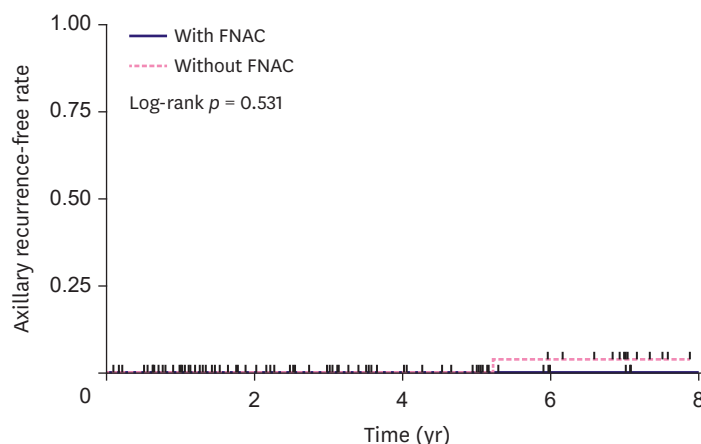
Values are presented as number (%) or median (range).

FNAC = fine-needle aspiration cytology, HER2 = human epidermal growth factor receptor-2, PMRT = postmastectomy radiotherapy, WBRT = whole-breast radiotherapy, pCR = pathological complete response.

**Table 2.** Positivity rate of sentinel lymph node with/without fine-needle aspiration cytology

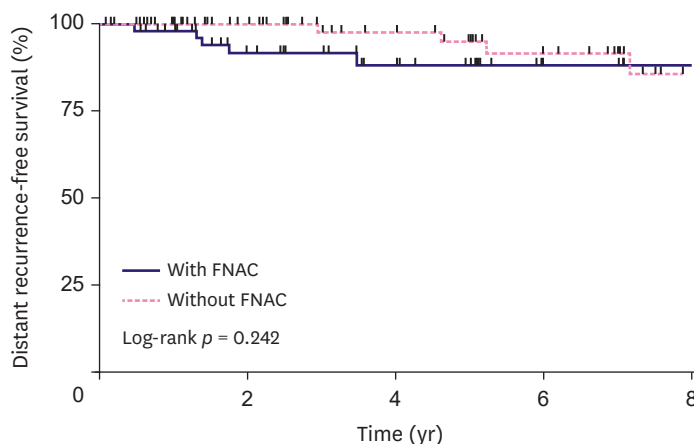
Variables	NAC	Primary surgery	p-value
With FNAC	3.0%	33.2%	< 0.001
Without FNAC	7.4%	12.9%	0.109
p-value	0.311	< 0.001	

NAC = neoadjuvant chemotherapy; FNAC = fine-needle aspiration cytology.



No. at risk					
With FNAC	64	40	23	7	3
Without FNAC	88	60	39	26	11

**Figure 2.** Axillary recurrence-free rate in the neoadjuvant chemotherapy group. FNAC = fine-needle aspiration cytology.



No. at risk					
With FNAC	63	40	23	7	3
Without FNAC	84	57	39	26	11

**Figure 3.** Distant recurrence-free survival in the neoadjuvant chemotherapy group. FNAC = fine-needle aspiration cytology.

## DISCUSSION

In our study, the positivity rate of SLN in the primary surgery group with negative FNAC results was statistically higher than that in the group without FNAC. These results indicate that lymph nodes suspected to be clinically or radiologically metastatic are more likely to be metastasis-positive, even if they are diagnosed as metastasis-negative using FNAC. In this study, the false-negative rate for FNAC and the positivity rate of SLN in patients who underwent FNAC were synonymous, and the false-negative rate for FNAC in the primary surgery group (33.2%) was similar to that reported in a previous study (31%) [7]. However, in patients who underwent FNAC, the SLN positivity rate in the NAC group was significantly lower than that in the primary surgery group. This may indicate that AxLN metastasis

resolves after NAC, or that the result of SLNB was a false negative. Previous systematic reviews reported that the false-negative rate of SLNB in patients undergoing NAC was 6% (95% CI, 3–8) [12]. In either case, it is important that the ARR was very low in this study and that ALND could have been avoided in many cN0 patients after NAC. Therefore, SLNB should be performed even in patients with negative FNAC results prior to NAC. On the other hand, SLNB before NAC is one option to accurately evaluate AxLN metastasis; however, SLNB before NAC is considered unnecessary because no patients with negative FNAC results have had axillary recurrence despite the high false-negative rate for FNAC before NAC. Thus, we could perform FNAC instead of SLNB before NAC in the evaluation and management of AxLN from the point of view of minimally invasive procedures.

In contrast, FNAC in some patients with radiologically suspected AxLN metastasis may cause overdiagnosis. ALND after NAC for patients with positive FNAC results before NAC may be overtreated because currently, in majority of Japanese institutions, patients with cN1 who convert to cN0 after NAC still undergo ALND, to account for the false-negative rates in accordance with the Japanese Breast Cancer Society Clinical Practice Guidelines, 2018 edition [13]. However, at the 17th St. Gallen International Breast Cancer Consensus Conference in 2021, expert panelists considered that patients with cN1 who convert to cN0 after NAC are potential candidates for SLNB. If these patients have no residual nodal disease when clipped lymph nodes or at least three SLNs are identified and resected, they do not require ALND [14]. To begin with, the definition of ‘cN0’ used by physicians, countries, and clinical trials is ambiguous; therefore, we need to keep in mind that FNAC may cause overdiagnosis. Thus, it may be unnecessary to perform FNAC in the NAC group. To prove this hypothesis, we compared the ARRs of patients with negative FNAC results and those with positive FNAC results who converted to cN0 after NAC. However, we could not evaluate the latter patients because all patients underwent ALND in our hospital if they converted to cN0 after NAC. We will consider omitting ALND in these patients in the future and investigating this hypothesis.

In a previous study with a design similar to ours, the positivity rate of SLN in the NAC group was 19.1%, which was higher than that in our study (3.0% and 7.4%) [15]. This difference may be because previous studies included more Luminal patients and fewer TN and HER2 patients than in our study. According to another report [16], the pCR rates of TN and HER2 breast cancer were higher than those of Luminal breast cancer; thus, in this study, pre-existing AxLN metastasis could have been resolved with NAC, especially in TN and HER2 patients. Therefore, we should carefully choose patients with TN and HER2 breast cancers to undergo FNAC.

This study had several limitations. This was a single-center retrospective study, and the decision to perform FNAC was based on physician preference. We would recommend defining objective criteria for FNAC, such as diffuse cortical thickening, focal cortical mass, and/or effacement or replacement of the fatty hilum of the lymph node [17]; further prospective studies are required. Another limitation is the short median follow-up time (3.0 years); a long follow-up period could have been more informative. However, our study demonstrated few early AxLN recurrences in cN0 patients who underwent SLNB after NAC. Few early recurrences are important for high-grade tumors, such as TN and HER2, because previous studies have reported that patients with TN and HER2 breast cancer had a high risk of early recurrence [18,19]. Furthermore, we did not show the patient and pathological tumor characteristics in the primary surgery group. More Luminal patients were included in the primary surgery group than in the NAC group. However, Vane et al. [20] reported no significant difference in the sensitivity of axillary ultrasonography between the subtypes.

In conclusion, our findings showed that SLNB was the proper axillary staging procedure for NAC patients, even in those with clinically suspicious AxLN metastases on radiologic examination and negative FNAC results. Thus, we do not need to perform SLNB before NAC, although the false negative rate for FNAC before NAC is high. Conversely, in some 'cN1' cases, FNAC before NAC may cause overdiagnosis and ALND may lead to overtreatment. Thus, it may be unnecessary to perform FNAC in the NAC group; however, further studies are needed in the future.

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