in vivo *38*: 2523-2530 (2024)
doi:10.21873/invivo.13724

Management of the Axilla After Neoadjuvant Chemotherapy: Can Axillary Needle Biopsy Replace Sentinel Node Biopsy?

EMINE YILDIRIM[1], PELIN BASIM[2], NESE UCAR[3], SIBEL BEKTAS[4], KUTAY ISCEN[1], EBRU KARCI[5] and ASENA AYCA OZDEMIR[6]

[1]*Department of General Surgery, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey;*
[2]*Department of General Surgery, Istanbul Medipol University, Faculty of Medicine, Istanbul, Turkey;*
[3]*Department of Radiology, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey;*
[4]*Department of Pathology, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey;*
[5]*Department of Oncology, Istanbul Medipol University, Faculty of Medicine, Istanbul, Turkey;*
[6]*Department of Medical Education, Faculty of Medicine, Mersin University, Mersin, Turkey*

Abstract. *Background/Aim: The aim of the study was to investigate whether it is possible to evaluate the axilla after treatment without performing sentinel lymph node biopsy (SLNB) in breast cancer patients with biopsy-proven axillary lymph node metastases who received neoadjuvant chemotherapy (NAC). Patients and Methods: This prospective, randomized, clinically designed study included patients with clinical T_{1-3} and biopsy-proven N_1 breast cancer. Prior to the surgery scheduled after NAC, the patients were randomized into two groups. A biopsy sample was obtained from the clipped axillary lymph node, which was preoperatively known to be metastatic, using fine needle aspiration (FNAB) in the first group and core needle biopsy (CNB) in the second group. The predictive ability of the two biopsy methods for the SLNB results was evaluated. Results: The study included 50 female patients with breast cancer, with a mean age of 48.4±10.72 years. In both groups, metastasis was detected in nine patients, and no metastasis was seen in 14 patients. In intergroup comparisons, all patients with metastasis in the FNAB group also had metastasis according to SLNB, while 21.4% of the cases without metastasis in this group were metastatic according to SLNB. In the CNB group, metastasis was observed in all patients with metastasis according to SLNB, while no metastasis was detected in those who were reported to have no metastasis by SLNB. The accuracy, specificity, and sensitivity values for the prediction of SLNB results were all found to be 100% for CNB, whereas they were 87%, 100%, and 75%, respectively, for FNAB. Conclusion: Both CNB and FNAB could potentially replace SLNB due to their high accuracy rates in evaluating the axilla after NAC. The sensitivity and accuracy of CNB were determined to be higher.*

Correspondence to: Emine Yildirim, MD, Assoc Prof. (ORCID: 0000-0003-2733-402X), Department of General Surgery, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Karayollari Mah., Osmanbey Cad., 621 Sokak, 34255 Gaziosmanpasa, Istanbul, Turkey. Tel: +90 5056234825, e-mail: opdreyildirim@gmail.com

Key Words: Breast cancer, neoadjuvant chemotherapy, sentinel lymph node biopsy, axillary lymph node dissection, axillary management.

The standard treatment for locally advanced and node-positive breast cancer is neoadjuvant chemotherapy (NAC) followed by surgery (1). NAC can reduce advanced stage tumors and biologically aggressive subtypes, making initially inoperable patients suitable for surgery, increasing the feasibility of breast-conserving surgery, and avoiding lymph node dissection in axillary surgery (2, 3). Many studies have reported a pathological complete response (pCR) of up to 60% in the axilla after NAC (4). Previous beliefs that fibrosis and tumor emboli in the lymphatic channels after NAC would alter lymphatic drainage have been challenged by studies such as the clinical trial conducted by the American College of Surgeons Oncology Group (ACOSOG) Z1071 and the SENTINA study, which investigated the performance of sentinel lymph node biopsy (SLNB) after

NAC in patients with proven axillary lymph node involvement by initial biopsy and demonstrated its feasibility when more than two lymph nodes were removed and dual mapping was performed (5, 6).

Currently, the approach to both the breast and the axilla in the treatment of breast cancer is becoming less invasive. In recent years, some studies have shown that, in selected patient groups with triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (Her-2) enriched subtypes, which typically have high pCR rates, breast surgery can be omitted if pCR is demonstrated on percutaneous image-guided vacuum-assisted core biopsy and radiotherapy is planned (7). This raises the question of whether there may also be a patient group in which SLNB can be avoided after NAC.

In this study, we sought a new method for evaluating the axilla after NAC in patients with breast cancer known to have axillary involvement. To this end, before the surgery scheduled after NAC, we performed an ultrasonography-guided needle biopsy on the clipped axillary lymph node, which was known to have metastasis before treatment, and tested whether the axilla could be assessed after treatment without SLNB. We also investigated patient groups exhibiting stronger predictions based on molecular subtypes and clinicopathological characteristics.

The study aimed to determine whether SLNB could be avoided in certain patient groups and to evaluate the axilla less invasively after NAC in patients with breast cancer. The potential benefits of this new approach may include identifying specific patient subgroups in which it would be appropriate to avoid SLNB and reduce the use of invasive techniques.

Patients and Methods

Study design and data collection. This study, designed as a prospective, randomized clinical trial, was conducted in two participating centers to evaluate the predictive ability of fine-needle aspiration biopsy (FNAB) and core needle biopsy (CNB) under axillary ultrasonography guidance after preoperative treatment in breast cancer patients with histopathologically proven axillary lymph node metastasis whose treatment was initiated with NAC. The study commenced in March 2023 following the approval of the local ethics committee (date: March 6, 2023; number: E-10840098-772.02-1685) and was registered at ClinicalTrials.gov (identifier: NCT06096545). Written informed consent was obtained from all patients.

Female patients aged over 18 years who received NAC with clinical T_{1-3} and biopsy-proven N_1 breast cancer were included in the study. The exclusion criteria were axillary surgery history, SLNB history, and axillary excisional lymph node surgery history. Furthermore, patients with N_{2-3} disease for whom the initial treatment decision was axillary lymph node dissection (ALND), those with a diagnosis of inflammatory breast cancer, those with distant metastases, those who had not completed chemotherapy, and pregnant and lactating women were also excluded.

Initially, patients with biopsy-proven axillary metastases were equally randomized into two groups using the randomizer.org website. Patients in the first group underwent lymph node sampling with ultrasound-guided FNAB after completion of NAC, and those in the second group underwent lymph node sampling with ultrasound-guided CNB after completion of NAC.

To prevent any effect on research results, the patient's name was kept confidential while sending the biopsy samples for histopathological examination, and the surgeon was blinded to the biopsy results. During the surgery, clipped and stained lymph node were removed using SLNB, and frozen section evaluation was performed. Thus, the predictability of axillary metastasis with preoperative FNAB and CNB was tested.

Chemotherapy. All the patients included in the study received four cycles of AC+T (doxorubicin and cyclophosphamide followed by paclitaxel) as part of the NAC regimen. Trastuzumab and pertuzumab were added to the treatment of patients positive for Her-2 neu, while carboplatin and pembrolizumab were added to the treatment of some of the triple-negative cases.

Radiological evaluation, biopsy method, and histopathological evaluation. All patients underwent imaging with breast ultrasonography (US), mammography, and magnetic resonance imaging (MRI) before NAC. Using axillary ultrasonography, asymmetrical focal lymph nodes and those with diffuse cortical thickness (>3 mm); lymph nodes with lobulated contours, a hypoechoic/anechoic cortex compared to subcutaneous tissue, and obliterated lymph nodes; and those with a distorted fatty hilum that were not clearly visible were evaluated as suspicious for malignancy and biopsied before treatment (8). In patients with more than one suspected lymph nodes, a biopsy was taken from the radiologically most suspicious lymph node and this lymph node was clipped. After NAC, ultrasonography-guided CNB or FNAB was performed seven days before surgery on the clipped lymph nodes that had been histopathologically proven to be metastatic at the time of diagnosis. The clipped lymph node was visualized with US in all patients. At least two samples in FNAB and three to four samples in CNB were performed. After the biopsy, the histopathological results were grouped as negative, positive, suspicious, and non-diagnostic in terms of metastasis.

Surgical technique and nodal evaluation. The surgical technique employed was mastectomy or breast-conserving surgery, depending on the mass in the breast, tumor location or multicentricity, the presence of radiotherapy contraindications, and patient preference. In axillary evaluation, the SLNB technique with the isosulfan blue dye was applied. In addition, the clipped lymph node was excised under ultrasound guidance through a guide wire in all patients before surgery.

Sentinel lymph node biopsy evaluation. During SLNB evaluation, multiple, 2-mm thick sections were taken from the removed lymph node and stained with hematoxylin and eosin. Lymph nodes with metastasis larger than 2 mm were defined as positive for metastasis according to the eighth edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC) (9). In the final pathological evaluation of the axilla, the presence of macrometastasis was considered positive, while lymph nodes with benign histopathological features were evaluated as negative. The

presence of micrometastases and isolated tumor cells was also noted. The size and diameter of the metastatic lymph node were included in the evaluation.

Breast resection materials. Breast resection materials were examined in terms of the largest tumor diameter, histopathological diagnosis, histological grade, estrogen, progesterone, Ki-67 and Her-2 receptor status. Breast cancer subtypes were classified into four groups: Luminal A, Luminal B, Her-2 enriched, and TNBC (10). Pathological staging was performed based on the eighth edition of the AJCC Cancer Staging Manual (9). The Nottingham modification of the Bloom-Richardson system was used for the determination of histological grade (11).

Intergroup comparison. For the patients included in the study, the results of the needle biopsy and SLNB performed after NAC were compared, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the needle biopsy methods for the prediction of SLNB results were determined. In addition, the effects of patient age, menopausal status, body mass index (BMI), radiological features of breast cancer and axillary lymph node, tumor and lymph node size, and the histopathological type, histological grade, and molecular subtype of the tumor on sensitivity, specificity, PPV, NPV, and accuracy were investigated.

Statistical analysis. The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. The independent-samples *t*-test was used for the comparison of the groups for variables that showed a normal distribution, and the Mann-Whitney *U*-test was used for those without a normal distribution. In the analysis of categorical variables, the chi-square and Fisher's exact tests were applied in accordance with the data type. Sensitivity, specificity, PPV, NPV, and accuracy values were calculated in the evaluation of needle biopsy after NAC in predicting the results of SLNB. TIBCO Statistica (TIBCO Software Inc., Palo Alto, CA, USA) and MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium) were used (12).

Ethical approval. All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This prospective study was conducted after receiving approval from the ethics committee of the Istanbul Medipol University Faculty of Medicine (number: E-10840098-772.02-1685; date: March 6, 2023). The study was registered at ClinicalTrials.gov (identifier: NCT06096545). Informed consent was obtained from all participants included in the study.

Results

Patient enrollment for the study began in March 2023 and was concluded in January 2024 upon reaching the target number of patients. The study was completed with 50 female patients with breast cancer, with a mean age of 48.4±10.72 years. Each group consisted of 25 patients. The mean time from chemotherapy to surgery was 3.86±1.05 weeks. All patients were taken into surgery after the lymph node, which was detected to have metastasis, was marked with a clip before NAC using a guide wire under preoperative ultrasound guidance. Sentinel lymph nodes were identified using the isosulfan blue dye in all patients. Blue-stained lymph nodes were not observed in the axilla of two patients in the FNAB group and one patient in the CNB group, and the clipped lymph node was sent for frozen section examination as a sentinel lymph node. In all the remaining patients, the clipped lymph node was also stained blue.

The most common histological type was invasive ductal cancer (84% in the FNAB group and 68% in the CNB group). The majority of patients were assigned in the luminal B subgroup. The Ki67 value was >20% in all patients. The clinicopathological data of the patients is shown in Table I.

In the radiological evaluation of the breast before NAC, there was a mass with irregular borders in 64% of the patients according to the ultrasonography examination. This mass was not clearly delineated in 70% of the patients and was solid in 50%. Mammography revealed a mass with a speculated contour in the breast in 56% of the patients, and only 44% had microcalcification. On MRI, mass enhancement was present in 60% of the patients. Table II presents the imaging findings for the axilla.

In intergroup comparisons, metastasis was detected in the biopsy performed after NAC in nine patients in the FNAB group, while no metastasis was seen in 14 patients, and the result was considered non-diagnostic in the remaining two patients in this group. Surprisingly, the patient distribution was the same for the CNB group.

In the FNAB group, lymphovascular invasion was more common among the patients with malignant biopsy results, while in the CNB group, asymmetric density was more frequently detected in the mammographic image of those with malignant CNB results, and mass appearance was more prevalent among the benign cases. In the FNAB group, eight (88.9%) of the patients with malignant biopsy results and four (28.6%) of the benign patients had lymphovascular invasion (p=0.009). Regarding imaging findings, four (44.4%) of the patients with malignant biopsy results and one (7.1%) of the benign patients in the CNB group had asymmetric density on mammographic imaging. In the CNB group, three (33.3%) of the patients with malignant biopsy results and 12 (85.7%) of the patients with benign biopsy results had an increased mammographic mass appearance (p=0.034). In addition, four (44.4%) of the patients with malignant biopsy results and one (7.1%) of the patients with benign biopsy results in the CNB group were in the TNBC subgroup and three (33.3%) of the patients with malignant biopsy results and 12 (85.7%) of the patients with benign biopsy results were in the luminal B subgroup (p=0.034).

Upon examination of the consistency between needle biopsy and SLNB results, we determined that all patients with axillary lymph node metastasis detected by FNAB after NAC also had metastasis according to SLNB. However,

Table I. *Clinical and pathological characteristics of the patients*.

Characteristics	FNAB		CNB		Total		*p*-Value
	Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		
Age (year)	49.88±10.99	29-69	46.92±10.45	27-65	48.4±10.72	27-69	0.334[a]
BMI (kg/m^2)	28.56±4.05	22-41	26.48±2.95	21-32	27.52±3.66	21-41	0.064[b]
Tumor diameter (mm)	36.76±19.29	16-88	28.96±9.6	14-51	32.86±15.59	14-88	0.236[b]
Largest LN Diameter (mm)	19.64±7.97	9-34	18.96±7.39	9-41	19.3±7.62	9-41	0.838[b]
	n	%	n	%	n	%	*p*-Value
Menopause							
Present	17	68	12	48	29	58	0.152
Absent	8	32	13	52	21	42	
Clinical T stage							
T1	4	16	6	24	10	20	0.067
T2	14	56	18	72	32	64	
T3	7	28	1	4	8	16	
Tumor type							
Invasive ductal cancer	21	84	17	68	38	76	0.214
Invasive lobular cancer	3	12	3	12	6	12	
Other	1	4	5	20	6	12	
Tumor subtype							
Luminal B	14	56	16	64	30	60	0.542
Her-2-enriched	6	24	3	12	9	18	
TNBC	5	20	6	24	11	22	
Grade							
1	1	4	0	0	1	2	0.106
2	13	52	7	28	20	40	
3	11	44	18	72	29	58	
LVI							
Absent	14	56	15	60	29	58	0.774
Present	11	44	10	40	21	42	
Type of breast surgery							
Mastectomy	20	80.0*	8	32	28	56	0.001*
Breast-conserving surgery	5	20	17	68.0*	22	44	
Type of axillary surgery							
Only SLNB	12	48	14	56	26	52	0.571
ALND after SLNB	13	52	11	44	24	48	
Axillary pathological response							
Complete response	11	44	14	56	25	50	0.062
Partial response	9	36	11	44	20	40	
No response	5	20	0	0	5	10	

FNAB: Fine-needle biopsy group; CNB: core needle biopsy group; SD: standard deviation BMI: body mass index; LN: lymph node; T: tumor; Her-2: Human epidermal growth factor receptor 2; TNBC: triple-negative breast cancer; LVI: lymphovascular invasion; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; [a]Independent-samples *t*-test; [b]Mann-Whitney *U*-test; *Chi-squared test, statistically significant.

three of the 14 cases that were not identified as metastatic in the FNAB group were reported to have metastasis according to SLNB, and there were two non-diagnostic cases in the FNAB group SLNB results indicated metastasis in all patients with axillary lymph node metastasis detected by CNB, and the non-metastatic results were also completely consistent between CNB and SLNB. Table III shows the sensitivity, specificity, PPV, NPV, and accuracy values of FNAB and CNB after NAC in predicting SLNB results.

There were two patients in each group whose axillary needle biopsy performed after NAC was not diagnostic. The reason for the non-diagnostic results was the insufficient number of cells obtained from the biopsy material taken from two patients in the FNAB group and the high-grade chemotherapy response observed in two patients in the CNB group. SLNB detected metastasis in all patients whose needle biopsy results were non-diagnostic. The diameter of the metastasis in the axillary lymph node in these patients

Table II. *Ultrasonographic characteristics of axillary lymph nodes (LNs).*

Ultrasonographic characteristics	FNAB		CNB		Total		
	n	%	n	%	n	%	*p*-Value
Cortex							
Normal	0	0	9	36.0*	9	18	0.004*
Diffuse thickening	18	72.0*	11	44	29	58	
Asymmetric thickening	7	28	5	20	12	24	
Cystic necrotic area							
Absent	21	84	19	76	40	80	0.725**
Present	4	16	6	24	10	20	
Fatty hilum							
Absent	19	76	17	68	36	72	0.529
Present	6	24	8	32	14	28	
Number of suspected LNs							
1	9	36	12	48	21	42	0.566
2	12	48	11	44	23	46	
3	4	16	2	8	6	12	

FNAB: Fine-needle biopsy group; CNB: core needle biopsy group; p: Chi-squared test; **Fisher's exact test; *statistically significant.

Table III. *Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of needle biopsy after neoadjuvant chemotherapy in predicting sentinel lymph node biopsy (SLNB) results.*

	FNAB		CNB		Total	
	%	95%CI	%	95%CI	%	95%CI
Sensitivity	75	42.8-94.5	100	100-100	85.7	63.7-96.9
Specificity	100	100-100	100	100-100	100	100-100
PPV	100	100-100	100	100-100	100	100-100
NPV	78.6	57.9-91.7	100	100-100	89.3	74.5-95.9
Accuracy	87	66.4-97.2	100	100-100	93.5	82.1-98.6

FNAB: Fine-needle aspiration biopsy group; CNB: core needle biopsy group; CI: confidence interval.

varied between 2.5 and 5 mm. Nondiagnostic results of lymph node biopsies, either with FNAB or CNB, were not repeated as they were not reported to the observers until the study was completed and were not included in the statistical evaluation as they were thought to increase the true positive values and cause bias in the study results.

In both groups, patients who did not have metastasis according to needle biopsy showed a reduction of more than 50% in the diameter of clipped metastatic lymph nodes and a decrease in cortex thickness (<3 mm) in axillary ultrasound findings evaluated after NAC.

When examining the impact of clinicopathological variables and radiological findings on the sensitivity, specificity, and accuracy of needle biopsy in predicting SLNB results, among all patients, the highest specificity was found for those without lymphovascular invasion, while the sensitivity value was higher for patients with lymphovascular invasion. Similarly, in the FNAB group, specificity was higher for the patients without lymphovascular invasion, whereas sensitivity was higher for those with lymphovascular invasion. In the CNB group, there was higher sensitivity for the TNBC subgroup compared to the luminal B subgroup. The findings are illustrated in Figure 1.

Discussion

Less invasive techniques are being developed for axillary surgery in addition to de-escalation in primary tumor surgery for breast cancer. Several studies conducted to avoid the morbidity of axillary dissection indicated the feasibility of SLNB after NAC, first in early-stage breast cancer and then in locally advanced tumors (5, 6).

In this study, we performed comparisons considering the possibility that axillary evaluation might be possible without SLNB after NAC in patients with $T_{1\text{-}3}N_1M_0$ breast cancer and determined that the SLNB frozen section examination results

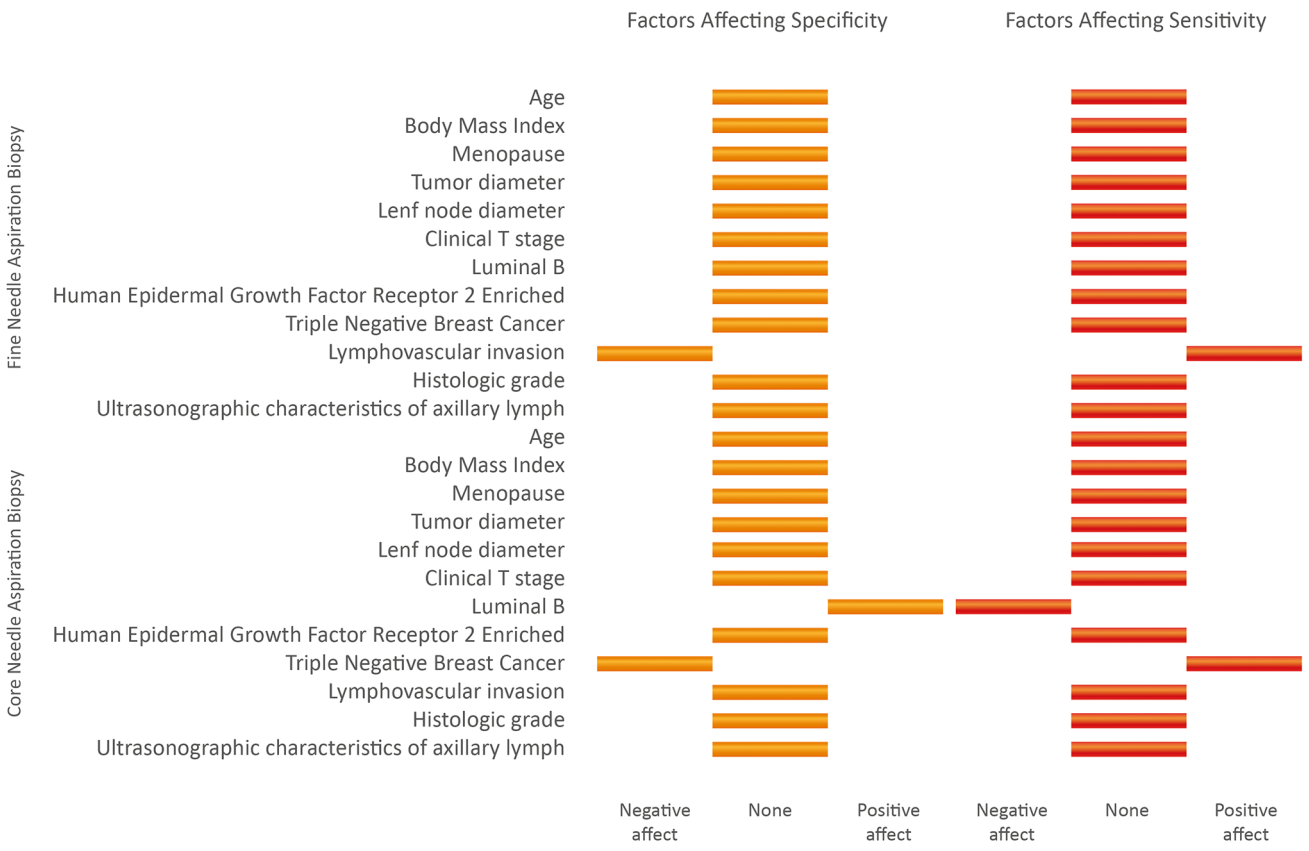

Figure 1. *Factors affecting sensitivity and specificity.*

could be accurately predicted with a needle biopsy sample from the clipped lymph node histopathologically proven to be metastatic before treatment. In particular, the SLNB results were accurately predicted in all patients in the CNB group.

Axillary ultrasound (AUS) and ultrasound-guided needle biopsy (AUS-FNAB/CNB) have been successfully used for years to evaluate the axilla in patients with early-stage breast cancer, and treatment decisions were based on the findings of these procedures. Patients with axillary metastases detected by ultrasound-guided needle aspiration biopsy are more likely to have more aggressive pathologic features than those with metastases detected by SLNB (13). Fayyaz *et al*. evaluated the predictive ability of US-FNAB for SLNB results in patients with early-stage breast cancer and reported an 85% accuracy rate (14). In a recent study conducted by Yildirim *et al*. AUS and AUS-FNAB performed by experienced personnel were shown to be valuable methods in excluding axillary disease, with accuracy rates of 77.39% and 68%, respectively, and specificity rates of 87.10% and 100%, respectively (8). However, that study and other similar research in the literature focused on evaluating the axilla in patients with early-stage tumors who had not received NAC.

Current guidelines recommend axillary dissection for clinical node-positive patients after NAC and those with N_{2-3} breast cancer at baseline, regardless of treatment response, while SLNB can be performed with low false negative rates in N_1 cases (5, 15, 16). Given these circumstances, it seems reasonable to investigate whether patients with N1 disease constitute a group in which SLNB can be omitted.

In a study in which axillary lymph node metastasis was initially known and radiological evaluation findings after NAC were compared with SLNB results, axillary nodal burden was successfully demonstrated with ultrasound and MRI. The authors also reported that the presence of axillary lymph nodes, especially after NAC, showed a strong correlation with residual disease (17). Ha *et al*. suggested that imaging after NAC was useful in evaluating axillary lymph node response, but that it could not replace SLNB or ALND in axillary staging (18). In another study, You *et al*. showed that the metastatic axillary lymph node could be evaluated with high sensitivity using the three methods together in imaging performed with ultrasound, MRI, and positron emission tomography-computed tomography (PET-CT) after NAC, and that PET-CT had high specificity in this

evaluation (19). Based on these studies, it is essential to perform further research to ascertain whether SLNB should be omitted in a selected group of patients with biopsy-proven axillary metastases that become negative after NAC.

After assessing the axilla with imaging during NAC, the next step may involve examining the axilla with a needle biopsy guided by ultrasonography. Our results indicated that, especially in the N1 patient group, where a clip was placed on the metastatic lymph node before treatment, AUS-CNB could be successfully applied to evaluate the axilla after NAC. Furthermore, FNAB was found to have high specificity, suggesting that ALND could be performed without SLNB in patients with metastasis detected by FNAB.

A limitation of this study is the small number of its target population. In addition, since ALND was not performed on SLNB-negative patients, non-sentinel metastasis could not be evaluated. US-guided needle biopsy is promising in N_1 patients with limited axillary involvement and clip placement in the metastatic lymph node before NAC. However, the clinical significance of this limited success rate is unclear. Further studies are needed to address the clinical impact of needle biopsy-related false-negative rates on the clinic to provide supporting data.

In conclusion, a needle biopsy taken from the lymph node marked with a clip after NAC may replace SLNB in patients with limited axillary metastases, if our results are supported by further studies involving a larger patient population. Our findings indicated that axillary CNB better predicted SLNB results than FNAB.

Funding

The Authors declare that they received no financial support for this study.

Conflicts of Interest

The Authors have no conflicts of interest to declare that are relevant to the content of this article.

Authors' Contributions

Surgical and Medical Practice: EY, PB, NU, SB; Concept: EY; Design: EY; Data Collection and/or Processing: EY, PB, KI, EK; Analysis and/or Interpretation: AAO, EY, PB; Literature Review: EY; Manuscript Writing: EY. AAO prepared Figure 1. All Authors agreed on all aspects of the final manuscript.

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Received April 15, 2024
Revised May 20, 2024
Accepted May 22, 2024