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ORIGINAL RESEARCH

Accuracy and Influencing Factors of Axillary Lymph Node Ultrasound Assessment After Neoadjuvant Chemotherapy in Breast Cancer

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Background: Breast cancer is one of the most common malignancies among women worldwide. Neoadjuvant chemotherapy (NAC) has become a standard treatment for locally advanced breast cancer, offering several advantages. However, accurate assessment of axillary lymph node status after NAC is crucial for surgical planning and prognosis. Although the role of ultrasound in axillary staging has been studied, its accuracy in the post-NAC setting remains controversial.

Research Gaps: Previous studies have small sample sizes and do not comprehensively analyze factors influencing ultrasound performance. This study aims to evaluate the accuracy of ultrasound in assessing axillary lymph node status after NAC in breast cancer patients and identify clinicopathological factors affecting its performance.

Methodology: This retrospective cohort study analyzed data from 171 breast cancer patients who underwent NAC followed by surgery at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, between January 2015 and December 2019. Ultrasound assessments of axillary lymph nodes were compared with final pathological results. The impact of various clinicopathological factors on ultrasound accuracy was evaluated using univariate and multivariate logistic regression analyses.

Results: The overall accuracy of ultrasound in predicting axillary lymph node status after NAC was 76.2%, with a sensitivity of 68.4% and specificity of 83.7%. Factors significantly affecting ultrasound accuracy included tumor size reduction rate, lymph node cortical thickness change, and tumor biological subtype.

Conclusion: This study shows that ultrasound has moderate accuracy in assessing axillary lymph node status after NAC, but ultrasound alone is not sufficient for definitive assessment, and surgical confirmation is still necessary. The identified significant factors can optimize the use of ultrasound in post-NAC axillary staging.

Keywords: breast cancer, neoadjuvant chemotherapy, axillary lymph nodes, ultrasound, accuracy

Introduction

Breast cancer remains one of the most common malignancies affecting women worldwide, with an estimated 2.3 million new cases diagnosed in 2020.[1] In recent years, neoadjuvant chemotherapy (NAC) has emerged as a standard treatment approach for locally advanced breast cancer, offering several advantages including tumor downstaging, increased rates of breast-conserving surgery, and the opportunity to assess treatment response in vivo.[2,3] Accurate assessment of axillary lymph node status after NAC is crucial for surgical planning and prognosis.[4]

The management of axillary lymph nodes in breast cancer has evolved significantly over the past few decades. While axillary lymph node dissection (ALND) was traditionally the standard procedure for nodal staging, it is associated with significant morbidity, including lymphedema, sensory changes, and shoulder dysfunction.[5,6] The advent of sentinel lymph node biopsy (SLNB) has revolutionized axillary management, offering a less invasive alternative with reduced

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morbidity.[7] However, the accuracy and feasibility of SLNB after NAC have been subjects of debate, particularly in patients who were initially node-positive.[8–10]

In this context, non-invasive imaging modalities, particularly ultrasound, have gained increasing attention as potential tools for assessing axillary lymph node status after NAC. Ultrasound is widely available, cost-effective, and does not involve radiation exposure.[11] Several studies have investigated the role of ultrasound in axillary staging, but its accuracy in the post-NAC setting remains controversial.[12,13]

The potential of ultrasound to accurately assess axillary status after NAC is particularly important given the paradigm shift towards less invasive axillary management. The concept of axillary de-escalation, where patients with excellent response to NAC might avoid ALND, has gained traction.[14] However, this approach relies heavily on accurate identification of patients with residual nodal disease.

Previous studies have reported varying accuracies for ultrasound in post-NAC axillary assessment. Hieken et al found an overall accuracy of 74.1%,[12] while Baumgartner et al reported an accuracy of 71.8%.[13] However, these studies were limited by smaller sample sizes and did not comprehensively analyze factors that might influence ultrasound performance.

The primary objective of this study is to evaluate the accuracy of ultrasound in assessing axillary lymph node status following NAC in breast cancer patients and to identify clinicopathological factors that may influence its performance. By analyzing a comprehensive set of patient data, including tumor characteristics, treatment response, and ultrasound findings, we aim to provide insights that can help optimize the use of ultrasound in post-NAC axillary staging.[15]

The findings of this study have the potential to impact clinical practice by refining the role of ultrasound in post-NAC axillary assessment, potentially sparing some patients from unnecessary invasive procedures while ensuring adequate treatment for those with residual nodal disease.

Methods

Study Design and Patient Selection

This retrospective cohort study analyzed data from 171 female patients diagnosed with breast cancer who underwent neoadjuvant chemotherapy (NAC) followed by surgery at Shanghai Ruijin Hospital, Affiliated with the Medical School of Shanghai Jiaotong University, between January 2015 and December 2019. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shanghai Ruijin Hospital, Affiliated with the Medical School of Shanghai Jiaotong University, with the approval number: KLL-2024-570. The requirement for informed consent was waived due to the retrospective nature of the study.

Inclusion criteria were: (1) histologically confirmed invasive breast cancer, (2) completion of NAC followed by definitive breast surgery and axillary staging, (3) availability of pre- and post-NAC ultrasound assessments of axillary lymph nodes performed at our institution, and (4) complete pathological data from surgical specimens.

Exclusion criteria included: (1) male breast cancer, (2) bilateral breast cancer, (3) inflammatory breast cancer, (4) history of prior ipsilateral breast or axillary surgery, (5) patients who received partial NAC or discontinued treatment prematurely, and (6) patients with incomplete medical records or imaging data.

Data Collection

The following data were extracted from medical records: patient characteristics including age and menopausal status (premenopausal, postmenopausal); tumor characteristics such as location (outer upper, outer lower, inner upper, inner lower, other), presence of lymphovascular invasion (absent, present), biological subtype (Luminal-A, Luminal-B, HER2-Enriched, Triple Negative), and histological type (IDC, ILC, others); treatment details including surgical approach (ALND, SLNB); ultrasound measurements comprising pre-NAC tumor size, post-NAC tumor size, pre-NAC lymph node cortical thickness, post-NAC lymph node cortical thickness, and contralateral lymph node cortical thickness; and pathological findings such as post-surgical lymph node status (negative, positive), size of largest metastatic focus in lymph nodes, pathological tumor size, and histological grade (Low grade (I, II), High grade (III)).

Ultrasound Assessment

All patients underwent standardized axillary ultrasound examinations before initiating NAC and after completion of NAC but prior to surgery. The examinations were performed by board-certified radiologists with at least 5 years of experience in breast imaging, using high-resolution ultrasound equipment with linear transducers operating at 5–12 MHz.

The following parameters were assessed:

1) Primary tumor size: measured as the maximum diameter in two perpendicular dimensions. The larger of the two measurements was recorded as the tumor size.
2) Axillary lymph node status: evaluated based on cortical thickness (>3 mm considered abnormal), shape (round vs oval), echotexture (homogeneous vs heterogeneous), and hilum preservation (preserved, partially effaced, or completely effaced). Lymph nodes were classified as suspicious if they exhibited cortical thickening >3 mm, round shape, heterogeneous echotexture, or partial/complete hilum effacement.
3) Lymph node cortical thickness: measured at the thickest point perpendicular to the long axis of the lymph node. For each patient, the most suspicious lymph node (if present) or the largest visible lymph node was measured and recorded.

Pathological Assessment

Surgical specimens (both breast and axillary tissue) were evaluated by experienced breast pathologists according to standard institutional protocols. The entire specimen was serially sectioned at 5 mm intervals and carefully examined for residual tumor.

Lymph nodes were identified by palpation and visual inspection. Each lymph node was bisected along its long axis and entirely submitted for histological examination. Lymph nodes were sectioned at 2 mm intervals and examined microscopically. The presence of any metastatic deposit >0.2 mm was considered node-positive. Isolated tumor cells (≤0.2 mm) were classified as node-negative for the purpose of this study.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ultrasound in predicting axillary lymph node status were calculated using pathological findings as the gold standard.

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the distribution. Categorical variables were presented as frequencies and percentages.

The impact of various factors on ultrasound accuracy was assessed using univariate and multivariate logistic regression analyses. Factors included age, menopausal status, tumor location, biological subtype, histological type, lymphovascular invasion, tumor size reduction rate, lymph node cortical thickness change, and NLR (Neutrophil-to-Lymphocyte Ratio).

The tumor size reduction rate was calculated as (Pre-NAC size - Post-NAC size) / Pre-NAC size × 100% The lymph node cortical thickness change was calculated as: (Pre-NAC thickness - Post-NAC thickness) / Pre-NAC thickness × 100%

Receiver Operating Characteristic (ROC) curve analysis was performed to determine optimal cut-off values for continuous variables.

A p-value <0.05 was considered statistically significant.

Results

Patient and Tumor Characteristics

A total of 171 female patients were included in the study. The patient and tumor characteristics are summarized in Table 1. The mean age of the patients was 48.8 ± 11.7 years (range: 21–77 years). Majority of the patients were premenopausal (52%). The most common tumor location was the outer upper quadrant (49.7%), and the predominant

Table 1 Patient and Tumor Characteristics

Characteristic	N (%)
Age (years)	
Mean ± SD	48.8± 11.7
Range	21-77
Menopausal status	
Premenopausal	89(52.0)
Postmenopausal	82(48.0)
Tumor location	
Outer upper	85(49.7)
Outer lower	19(11.1)
Inner upper	25(14.6)
Inner lower	10(5.8)
Other	32(18.7)
Pre-neoadjuvant chemotherapy T staging	
T1	16 (9.3)
T2	116 (67.8)
T3	32 (18.7)
T4	7 (4.0)
Pre-neoadjuvant chemotherapy N staging	
N0	8 (4.7)
N1	60 (35.1)
N2	61 (35.7)
N3	42 (24.6)
Post-neoadjuvant chemotherapy T staging	
T0	4 (2.3)
T1	77 (45.0)
T2	78 (45.6)
T3	12 (7.0)
Post-neoadjuvant chemotherapy N staging	
N0	44 (25.7)
N1	80 (46.8)
N2	27 (15.8)
N3	20 (11.7)
Pathological T staging after neoadjuvant chemotherapy	
T0	68 (39.8)
Tis	5 (2.9)
T1	43 (25.1)
T2	42 (24.6)
T3	13 (7.6)
Pathological N staging after neoadjuvant chemotherapy	
N0	92 (53.8)
N1	26 (15.2)
N2	32 (18.7)
N3	21 (12.2)
Biological subtype	
Luminal-A	49(28.7)
Luminal-B	57(33.3)
HER2-Enriched	44(25.7)
Triple Negative	21(12.3)

(*Continued*)

Table 1 (Continued).

Characteristic	N (%)
Histological type	
IDC	143(83.6)
ILC	7(4.1)
Others	21(12.3)
Lymphovascular invasion	
Present	53(31.0)
Absent	118(69.0)

biological subtype was Luminal-B (33.3%). Invasive ductal carcinoma (IDC) was the most common histological type (83.6%).

Treatment Details

All patients received NAC followed by surgery. The surgical approach was ALND in 162 patients (94.7%) and SLNB in 9 patients (5.3%). The decision to perform ALND was primarily based on persistently abnormal ultrasound findings of the axillary lymph nodes post-NAC.

Ultrasound and Pathological Findings

The ultrasound measurements before and after NAC, as well as the pathological findings, are presented in Table 2. There was a significant reduction in both tumor size and lymph node cortical thickness following NAC ($p<0.001$ for both). The mean contralateral lymph node cortical thickness was 1.8 ± 0.6 mm. Post-surgical pathology revealed positive lymph nodes in 84 patients (49.1%) and negative lymph nodes in 87 patients (50.9%). The cortical thickness of the affected lymph nodes was significantly greater than that of the contralateral lymph nodes before operation, and significantly lower than that of the contralateral lymph nodes after operation.

Accuracy of Ultrasound Assessment

The performance of ultrasound in predicting axillary lymph node status after NAC is summarized in Table 3. The overall accuracy of ultrasound in predicting axillary lymph node status post-NAC was 76.2%, with a sensitivity of 68.4% and specificity of 83.7%.

Table 2 Ultrasound and Pathological Findings

Characteristic	Pre-NAC	Post-NAC	t	p-value
Tumor size (mm, mean ± SD)	40.2±19.0	22.8±14.5	12.611	<0.001
Axillary lymph node cortical thickness on affected side (mm, mean ± SD)	9.93±5.96	3.99±4.09	15.551	<0.001
Pathological tumor size	-	≤20 mm:18 (10.5%) >20-50 mm: 120(70.2%) ≥50 mm: 33 (19.3%)		-
Pathological conditions		Positive: 84 (49.1%) Negative: 87 (50.9%)		
Histological grade	-	Low (I or II): 79 (62.7%) High (III): 47(37.3%)		-
Axillary lymph node cortical thickness	Affected Side:9.93±5.96 Contralateral Side:3.87±1.43		13.215	<0.001
Axillary lymph node cortical thickness		Affected Side:3.99±4.09 Contralateral Side:5.81±7.02	−2.329	0.021

Table 3 Accuracy of Ultrasound Assessment

Measure	Value (95% CI)
Accuracy	76.2% (67.2–83.3%)
Sensitivity	68.4% (52.5–80.9%)
Specificity	83.7% (72.7–90.8%)
Positive Predictive Value	68.4% (52.5–80.9%)
Negative Predictive Value	83.7% (72.7–90.8%)

Factors Influencing Ultrasound Accuracy

Univariate analysis identified several factors significantly associated with ultrasound accuracy: tumor size reduction rate (p=0.003), lymph node cortical thickness change (p<0.001), biological subtype (p=0.018), histological grade (p=0.042), and neutrophil-to-lymphocyte ratio (NLR) (p=0.037). All these factors demonstrated statistically significant associations with the accuracy of ultrasound assessment, with lymph node cortical thickness change showing the most significant correlation.

Multivariate logistic regression analysis confirmed three independent factors affecting ultrasound accuracy, as shown in Table 4.

ROC curve analysis was conducted to determine optimal cut-off values for key parameters. For tumor size reduction rate, the optimal cut-off value was found to be 65%, with an Area Under the Curve (AUC) of 0.731, sensitivity of 72.7%, and specificity of 68.4%. For lymph node cortical thickness change, the analysis yielded an optimal cut-off value of 55%, demonstrating a higher AUC of 0.812, with improved sensitivity and specificity at 79.2% and 73.9% respectively.

Subgroup Analysis

The accuracy of ultrasound in different subgroups is presented in Table 5. When stratified by biological subtype, ultrasound accuracy was highest in Luminal-A tumors 85.7%) and lowest in Triple Negative tumors (71.4%).

In patients with tumor size reduction rate ≥65%, ultrasound accuracy was significantly higher (84.4%) compared to those with <65% reduction (67.3%).

Table 4 Factors Influencing Ultrasound Accuracy (Multivariate Analysis)

Factor	Odds Ratio	95% CI	p-value
Tumor size reduction rate	1.04	1.01–1.07	0.008
Lymph node cortical thickness change	1.06	1.03–1.09	<0.001
Biological subtype	0.68	0.48–0.96	0.029

Table 5 Subgroup Analysis of Ultrasound Accuracy

Subgroup	Accuracy
Biological subtype	
Luminal-A	85.7% (42/49)
Luminal-B	77.2% (44/57)
HER2-Enriched	70.5% (31/44)
Triple Negative	71.4% (15/21)
Tumor size reduction rate	
≥65%	84.4% (54/64)
<65%	67.3% (72/107)
Lymph node cortical thickness change	
≥55%	85.0% (96/113)
<55%	62.1% (36/58)

For patients with lymph node cortical thickness change ≥55%, ultrasound accuracy was markedly higher (85.0%) compared to those with <55% change (62.1%).

Discussion

This study evaluated the accuracy of ultrasound in assessing axillary lymph node status following neoadjuvant chemotherapy (NAC) in breast cancer patients and identified factors influencing its performance. Our findings demonstrate that ultrasound has moderate accuracy in this setting, with an overall accuracy of 76.2%, sensitivity of 68.4%, and specificity of 83.7%.

Compared with the results of the three large prospective trials (ACOSOG Z1071, SENTINA, and SN FNAC)[8,9,16] (Table 6), our false-negative rate of 52% is higher than their 12.6%–14.2%. This further highlights the limitations of using ultrasound alone to assess axillary lymph node status after NAC and supports our conclusion that surgical confirmation is necessary for axillary lymph node status after NAC, as ultrasound assessment alone is insufficient.

The accuracy observed in our study is comparable to previous reports in the literature. For instance, Baumgartner et al reported an accuracy of 71.8% for ultrasound in predicting axillary nodal status post-NAC.[13] Similarly, Hieken et al found an overall accuracy of 74.1%.[12] Our slightly higher accuracy might be attributed to advancements in ultrasound technology and increasing experience with post-NAC axillary assessment. However, it's important to note that while the specificity is reasonably high (83.7%), the sensitivity (68.4%) suggests that ultrasound alone may miss a substantial proportion of patients with residual nodal disease.

One of the key findings of our study is the identification of factors that significantly impact ultrasound accuracy. Tumor shrinkage rate, changes in lymph node cortical thickness, and biological subtype emerged as independent predictors of ultrasound performance. When these factors are combined, the accuracy of predicting axillary lymph node status can be enhanced. Particularly, when tumors respond well to NAC, characterized by substantial tumor shrinkage and marked reduction in lymph node cortical thickness, the accuracy of ultrasound assessment significantly improves. This can be explained by the fact that significant tumor size reduction often correlates with a better overall response to chemotherapy, including in metastatic lymph nodes.[17] Our findings align with those of Croshaw et al, who reported that patients with complete or near-complete responses to NAC were more likely to have accurate axillary ultrasound findings.[18] The substantial decrease in cortical thickness likely reflects the resolution of metastatic deposits in response to chemotherapy, making it easier to differentiate between benign and malignant nodes on ultrasound.[19] This is consistent with the work of Boughey et al, who found that changes in lymph node morphology on imaging correlate with pathological response.[20] Among different biological subtypes, Luminal-A tumors had the highest accuracy (85.0%), followed by Luminal-B (77.8%), while HER2-enriched and triple-negative subtypes had lower accuracies (69.6% and 69.2%, respectively). This variation can be attributed to differences in tumor biology and response patterns to NAC. HER2-enriched and triple-negative tumors are known for their higher pathological complete response (pCR) rates to NAC but also for their more aggressive behavior and potentially more complex lymph node involvement.[21] This heterogeneity may pose challenges for ultrasound assessment. Our results are in line with those of Nguyen et al, who reported varying accuracies of axillary staging across different breast cancer subtypes.[22] High-grade tumors, associated with more aggressive behavior and potentially more complex patterns of lymph node involvement, may affect ultrasound interpretation.[23] These findings suggest that for patients whose ultrasound examinations show no abnormalities in axillary lymph nodes after NAC and who have a good tumor response, it may be possible to consider avoiding surgical staging of the axilla. However, we must also recognize that currently no combination of clinicopathological and

Table 6 Summary of False Negative Rates in 1071, SENTINA, and SN FNAC Studies

Study Name	False Negative Rate (%)
1071[8]	12.6
SENTINA[9]	14.2
SN FNAC[16]	13.3

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ultrasound features provides sufficient accuracy to completely replace surgical staging, especially when facing potential residual nodal disease. Therefore, in clinical practice, we still need to proceed with caution and make individualized treatment decisions based on the specific circumstances and treatment responses of patients.

Our study results are of significant clinical importance. First, they show that ultrasound performance in post-NAC axillary assessment varies significantly based on tumor and treatment characteristics. This underscores the need for a personalized approach to interpreting ultrasound results. Second, identifying optimal cut-off values for tumor size reduction (65%) and lymph node cortical thickness change (55%) provides practical benchmarks for clinicians to gauge the reliability of ultrasound findings. Patients meeting or exceeding these thresholds may be candidates for less invasive axillary staging procedures, while those falling short may benefit from more comprehensive evaluation. Third, our results highlight the potential value of incorporating pre- and post-NAC ultrasound measurements into clinical decision-making. Notably, the change in lymph node cortical thickness is a strong predictor of ultrasound accuracy. This suggests that serial ultrasound examinations during NAC can provide valuable information about treatment response and help guide axillary management decisions.

Since our study period (2015–2019), clinical practice has shifted. We now routinely perform SLNB with dual mapping to obtain at least three sentinel lymph nodes, moving away from ALND as a standard approach. However, it's important to acknowledge the limitations of our study. As a single-center, retrospective study, our findings may not be generalizable to all populations. The moderate sample size, while larger than some previous studies, may still limit the power to detect some associations. Additionally, while we focused on ultrasound, other imaging modalities such as MRI or combined approaches (eg, ultrasound with fine-needle aspiration) might offer complementary information and warrant investigation.

Future research directions should include prospective, multi-center studies to validate our findings and explore the integration of ultrasound with other imaging modalities or molecular markers. The potential of artificial intelligence and machine learning in improving ultrasound interpretation, particularly in the complex post-NAC setting, is another exciting area for future investigation.

Conclusion

This study concludes that ultrasound demonstrates moderate accuracy in assessing axillary lymph node status after NAC in breast cancer patients, with an overall accuracy of 76.2%, sensitivity of 68.4%, and specificity of 83.7%. While ultrasound provides valuable information, its high false-negative rate (52%) and false-positive rate (16%) indicate that it is insufficient for definitive axillary staging post-NAC. Surgical confirmation remains essential. Additionally, we identified significant factors affecting ultrasound accuracy, including tumor size reduction rate, lymph node cortical thickness change, and tumor biological subtype. These findings can help optimize the use of ultrasound in post-NAC axillary staging. Future research should focus on improving the accuracy of non-invasive imaging techniques and exploring the integration of ultrasound with other diagnostic tools to enhance the management of breast cancer patients.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shanghai Ruijin Hospital, Affiliated With the Medical School of Shanghai Jiaotong University. Due to the nature of retrospective study and anonymized patient's information, informed consent is waived with the approval of the Ethics Committee of Shanghai Ruijin Hospital, Affiliated With the Medical School of Shanghai Jiaotong University.

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Disclosure

The authors report no conflicts of interest in this work.

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