Original Article

Can negative axillary ultrasound reliably predict pathologically negative axillary lymph node status in breast cancer patients with cT ≤3 cm, cN0, and HER2-positive?—a retrospective, single-institution study

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Background: Breast cancer (BC) is the leading cancer in women globally, with human epidermal growth factor receptor 2 (HER2)-positive subtype accounting for 15–20% of cases and exhibiting aggressive behavior. The standard of care for operable BC has evolved to include neoadjuvant systemic therapy, which can guide treatment decisions and improve outcomes, particularly in HER2$^+$ BC. This study aims to investigate whether axillary ultrasound has a good negative predictive value (NPV) for early HER2 BC patients and to identify clinicopathological factors that can impact the axillary lymph node metastasis.

Methods: This retrospective, single-center study evaluated the medical records of 135 patients with HER2$^+$ BC, cT ≤3 cm, and clinically negative axillary lymph nodes from 2018 to 2020. The study aimed to determine the NPV of axillary ultrasound for pathologically negative axillary lymph node status and to identify factors associated with axillary lymph node metastasis.

Results: The NPV of axillary ultrasound was 78.5%, increasing to 89.6% and 93.3% when considering 0–1 and 0–2 metastatic lymph nodes, respectively. Lymphovascular invasion (LVI) was significantly associated with axillary lymph node metastasis, with a 2.2-fold increased risk.

Conclusions: Axillary ultrasound shows good predictive value for axillary lymph node negativity in HER2$^+$ BC patients with small tumors. However, the presence of LVI increases the risk of metastasis, suggesting a need for neoadjuvant chemotherapy. These findings contribute to personalized treatment strategies for early HER2$^+$ BC, emphasizing the role of axillary ultrasound in clinical decision-making.

Keywords: Human epidermal growth factor receptor 2-positive breast cancer (HER2$^+$ BC); axillary ultrasound; lymphovascular invasion (LVI); neoadjuvant therapy; axillary lymph node metastasis prediction

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Introduction

Breast cancer (BC) has emerged as the most prevalent cancer among women and the leading cause of mortality globally (1). BC is categorized into distinct subtypes based on the expression levels of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, including luminal A, luminal B, HER2$^+$, and basal-like. Notably, HER2$^+$ BC comprises approximately 15–20% of all subtypes (2) and

exhibits a more aggressive biological behavior, often leading to shorter recurrence-free and disease-free survival rates (3).

Thanks to the rapid advancement in therapeutics and enhanced multidisciplinary team care for BCs, the treatment paradigm for operable BC has shifted towards receiving neoadjuvant systemic therapy as the initial approach. Preoperative systemic therapy serves multiple purposes: it can downstage the breast tumor, facilitating breast-conserving surgery (BCS); reduce the burden of axillary metastasis, thus preserving peripheral nerves and lymphatic reflux in the arm; provide prognostic information at an individual level; and guide adjuvant regimens based on residual disease (4,5). Numerous clinical trials have demonstrated that achieving a pathological complete response (pCR) following neoadjuvant therapy can significantly improve disease-free survival and overall survival, particularly in HER2$^+$ BCs (6,7).

Anti-HER2 drugs encompass three main categories: monoclonal antibodies (e.g., trastuzumab and pertuzumab), tyrosine kinase antibodies (e.g., lapatinib and neratinib), and antibody-drug conjugates (e.g., trastuzumab emtansine and trastuzumab deruxtecan). Shen *et al.* conducted a meta-analysis of 15 prospective studies involving 2,190 patients to investigate the efficacy of neoadjuvant systemic therapy in HER2$^+$ BC. Their findings revealed a correlation between HER2 positivity and increased odds of achieving pCR when combining anti-HER2 agents with chemotherapy. Furthermore, HER2 status was predictive of higher pCR rates, regardless of the HER2-targeted regimens, chemotherapy regimens, endocrine therapy, or hormone receptor status (8).

For HER2$^+$ BC, the National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant systemic therapy over upfront surgery for cT2 or cN1 patients (9). This recommendation raises the question of whether upfront surgery or neoadjuvant chemotherapy is the preferred approach for clinically T ≤3 cm, N0, and HER2-positive BCs. For cT1N0 cases where upfront surgery is chosen, there is a concern regarding occult axillary lymph node disease, as reported in sentinel lymph node biopsy (SLNB). For a cT2 tumor that is 3 cm or smaller in size, neoadjuvant therapy is recommended, but upfront surgery can also be considered for BCS if patient preference is a factor. In such cases, the status of the axillary lymph nodes is crucial in determining whether upfront surgery or neoadjuvant therapy is appropriate.

Ultrasonography is a widely accessible and cost-effective method for evaluating the axilla. Recently, several ongoing prospective randomized clinical trials have been registered to investigate whether axillary ultrasound can replace SLNB in cN0 patients. These trials include two European studies (SOUND, INSEMA) and one Asian trial (NAUTILUS) (10). The SOUND trial recently released its results in 2023, indicating that omitting axillary surgery in cT1N0M0 patients with a negative axillary ultrasound is non-inferior to SLNB. This finding demonstrates the good negative predictive value (NPV) of axillary ultrasound in small BC. However, it is noteworthy that 87.8% of patients in the SOUND trial had the ER-positive, HER2-nonoverexpressing subtype. Only 95 cases were HER2-enriched, thus providing limited information on the applicability of negative axillary ultrasound in small HER2-enriched BC (11).

To avoid cT1N0M0, HER2-enriched patients missing the neoadjuvant treatment, McCaffrey *et al.* collected 38 patients and conducted a retrospective study. They found that 24% of patients had axillary lymph node metastasis in the postoperative pathology report, suggesting that patients with HER2-enriched early BC should undergo axillary ultrasound before surgery. This finding highlights the importance of axillary ultrasound in HER2-enriched BC to avoid missing the neoadjuvant treatment opportunity (12). Weiss *et al.* also examined the axillary lymph node status and the impact of neoadjuvant therapy on HER2$^+$ patients with cT <3 cm and cN0. They pooled data from two databases, totaling 947 patients. Their

Highlight box

Key findings

- Axillary ultrasound has a 78.5% negative predictive value for pathological axillary lymph node status in human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients with cT ≤3 cm and cN0. The presence of lymphovascular invasion (LVI) is a significant risk factor, doubling the risk of metastasis.

What is known and what is new?

- Axillary ultrasound is used to assess lymph node status in breast cancer.
- This study provides specific data for HER2-positive early-stage breast cancer, highlighting the impact of LVI on metastasis risk.

What is the implication and what should change now?

- Axillary ultrasound can guide treatment decisions, potentially reducing unnecessary axillary lymph node dissections. For patients with LVI, neoadjuvant chemotherapy is recommended. Change: practice should consider axillary ultrasound results and LVI status when planning treatment for HER2-positive breast cancer patients.

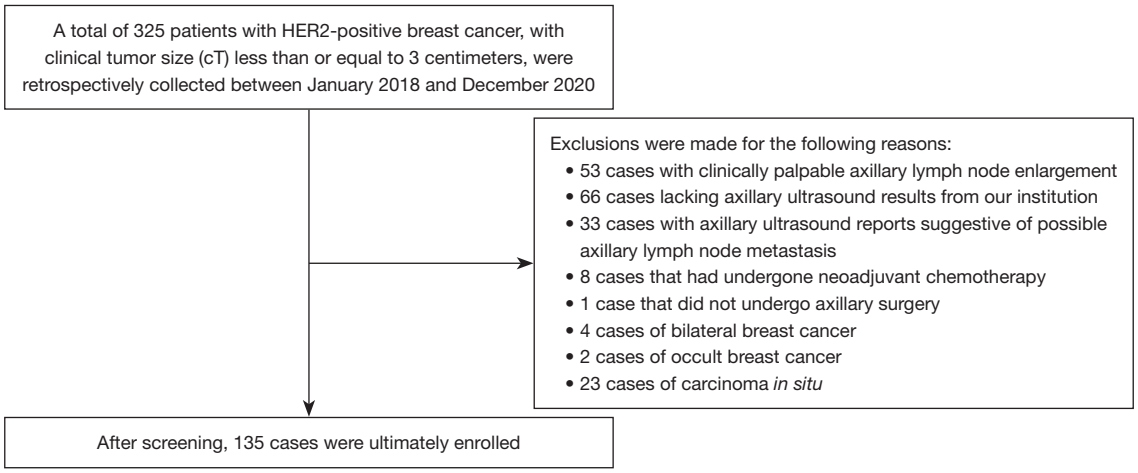

Figure 1 Flowchart for inclusion of patients from The First Affiliated Hospital of Guangxi Medical University. HER2, human epidermal growth factor receptor 2.

findings revealed that approximately 20% of patients who underwent upfront surgery had pathologically confirmed positive lymph nodes, while 10% of patients who received neoadjuvant therapy exhibited axillary lymph node positivity. Based on these results, they also recommend the use of ultrasound for axillary lymph node assessment in this patient population (13). However, there is a scarcity of clinical studies that specifically evaluate the utility of axillary ultrasound in early HER2$^+$ BC patients.

The primary aim of our study is to investigate whether axillary ultrasound has a good NPV for patients with cT ≤3 cm, cN0M0, and HER2$^+$ BC. This information is crucial to guide clinical decision-making on whether to prioritize neoadjuvant chemotherapy or surgical treatment for this subset of patients. Secondly, we aim to analyze the lymph node metastasis status of the collected cases and identify which clinicopathological factors have the greatest impact on axillary lymph node metastasis. By doing so, we hope to provide a more comprehensive understanding of the factors that influence the spread of cancer to the axillary lymph nodes and contribute to evidence-based decision-making in the management of early HER2$^+$ BC. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-140/rc).

Methods

Between January 2018 and December 2020, we retrospectively examined the medical records of patients diagnosed with cT ≤3 cm and HER2-enriched BC at The First Affiliated Hospital of Guangxi Medical University. From an initial pool of 325 patients, several exclusion criteria were implemented, which included clinical axillary lymph node positivity, lack of axillary ultrasound examination at our institution, ultrasound detection of lymph node metastasis, prior administration of neoadjuvant therapy, bilateral BC, occult BC, non-performance of axillary surgery, incomplete treatment documentation, and carcinoma *in situ* cases. The term "occult breast cancer" refers to a condition where metastatic cancer is found in the axillary lymph nodes without an identifiable primary tumor in the breast. Following the application of these exclusions, a final cohort of 135 patients was enrolled in this study (*Figure 1*). The study protocol received approval from the Ethical Review Committee of The First Affiliated Hospital of Guangxi Medical University (approval No. 2024-E264-01) and was conducted in accordance with the ethical principles enshrined in the Declaration of Helsinki (as revised in 2013). Since this is a retrospective study, the need for informed consent was waived by Ethical Review Committee of The First Affiliated Hospital of Guangxi Medical University.

For the enrolled patients, a comprehensive assessment was made of numerous parameters such as age at diagnosis, breast and axillary surgical procedures, histopathological tumor type, tumor grade, ER status, PR status, HER2 status, Ki-67 proliferation index, lymphovascular invasion (LVI), perineural invasion (PNI), the number of harvested axillary lymph nodes, and the count of metastatic lymph nodes. Furthermore, we scrutinized ultrasound-reported

attributes like axillary lymph node status, the maximum diameter of the primary breast tumor, and the location of the breast lesion.

The positivity of ER and PR statuses was defined as more than 1% of tumor nuclei demonstrating positive staining via immunohistochemistry techniques, as per established guidelines (14,15). A positive HER2 status was affirmed if the immunohistochemistry score was 3+ or if a 2+ score was coupled with definitive HER2 gene amplification ascertained through fluorescence in situ hybridization (FISH).

Axillary ultrasound was conducted utilizing a GE LOGIQ E9 ultrasound system (GE Healthcare, Chicago, IL, USA). The examination employed a high-resolution linear transducer with a probe frequency ranging from 6 to 15 MHz. There are two skilled sonographers with over 7 years of experience specializing in breast and axillary ultrasound examinations. They assessed the probability of axillary lymph node metastasis based on a variety of ultrasound features, including the longitudinal/transverse axis ratio, hilar architecture, cortical thickness, cortical echogenicity, and the presence of lymph node vascularity. *Figure 2A*,*2B* represent normal lymph nodes, while *Figure 2C* indicates a metastatic lymph node. Among the cases enrolled in this study, there were no instances of examinations that proved to be non-contributory to the diagnosis or treatment process.

The patients included in this study were all operated on by surgeons who have over 5 years of experience and have performed more than 200 SLNBs and axillary lymph node dissections (ALNDs). Additionally, the sentinel lymph nodes (SLNs) were localized using a dye tracing method to ensure accurate removal during surgery. Most patients underwent SLNB, and if intraoperative pathology indicated SLN metastasis, further ALND was performed. A minority of patients received ALND treatment directly.

Statistical analyses

In this study, statistical analyses were carried out utilizing IBM SPSS Statistics version 25.0. Continuous variables were depicted through medians alongside their respective ranges, whereas categorical variables were expressed as counts accompanied by their corresponding percentages. To identify clinical factors with potential predictive power for axillary lymph node metastasis, a two-step logistic regression approach was adopted. Firstly, a series of univariate logistic regressions were run for an initial screening of relevant variables. Subsequently, a multivariate logistic regression analysis was conducted to refine the selection based on the initial findings.

All statistical tests applied herein were two-tailed, and a P value threshold of less than 0.05 was established to denote statistical significance.

Results

The median age of the 135 patients enrolled in this study was 49 years (range, 30–79 years), with 21 patients (15.6%) aged <40 years and 114 patients (84.4%) aged ≥40 years. The median maximum tumor diameter reported by breast ultrasonography was 1.9 cm (range, 0.8–3.0 cm), with 82 patients (60.7%) having a cT ≤2 cm tumor stage and 53 patients (39.3%) having a 2< cT ≤3 cm tumor stage. Pathological reports showed a median maximum tumor diameter of 1.8 cm (range, 0.2–2.9 cm), with 94 patients (69.6%) having a pT ≤2 cm tumor stage and 41 patients (30.4%) having a 2< pT ≤3 cm tumor stage.

Thirty-nine patients (28.9%) had breast tumors located in the upper outer quadrant, followed by 29 patients (21.5%) in the upper inner quadrant. The number of patients with breast tumors located at the 12 o'clock position and in the lower outer quadrant was the same, with 13 patients (9.6%) each. The remaining patients were distributed as follows: 11 patients (8.1%) in the 6 o'clock direction, 10 patients (7.4%) in the 3 o'clock direction, 9 patients (6.7%) in the lower inner quadrant, and 4 patients (3%) each in the 9 o'clock direction and at the center of the breast.

The pathological type was primarily invasive ductal carcinoma (IDC), with 134 patients (99.3%) having this type, while 1 patient had myeloid breast cancer (MBC). A total of 60 patients (44.4%) had a pathological report indicating the presence of ductal carcinoma in situ (DCIS) in addition to invasive cancer, while 75 patients (55.6%) did not have DCIS. Ninety-six patients (71.1%) had a pathological grade II, 26 patients (19.3%) had a pathological grade III, and 3 patients (2.2%) had a pathological grade I. Eight patients (5.9%) had multifocal tumors, and 1 patient (0.7%) had multicentric tumors. Twenty-nine patients (21.5%) had pathologically confirmed LVI, and 8 patients (5.9%) had neural invasion. ER was positive in 91 patients (67.4%) and negative in 44 patients (32.6%). PR was positive in 76 patients (56.3%) and negative in 59 patients (43.7%). Fifty-nine patients (43.7%) had a Ki-67 level greater than 30%, while 74 patients (54.8%) had a Ki-67 level of 30% or less. Two patients (1.5%) had missing Ki-67 data. Sixty-two patients (45.9%) underwent

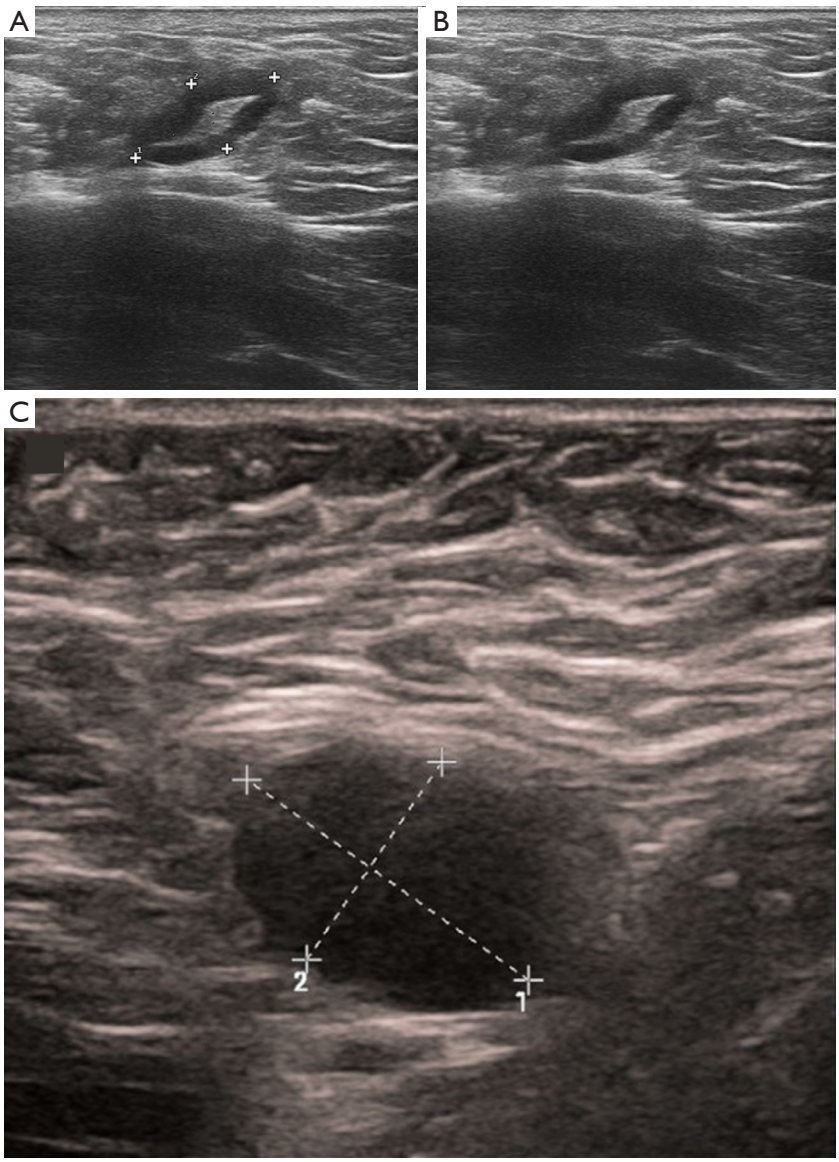

Figure 2 Axillary ultrasound for lymph node detection illustration. (A,B) The sonogram of normal axillary lymph nodes; (C) the sonogram of a metastatic axillary lymph node.

BCS, while 73 patients (54.1%) underwent a mastectomy. Among the axillary surgeries, 106 patients only received SLNB, 22 patients (16.3%) received SLNB + ALND, and 7 patients received ALND (5.2%). The median number of SLNs harvested was 4. Pathologically confirmed axillary lymph node metastasis was present in 29 patients (21.5%). It should be noted that among the patients who received SLNB, 3 patients with positive SLNs did not receive further ALND. The baseline data of the patients was presented in *Table 1*, while the status of axillary lymph node metastasis was exhibited in *Table 2*.

By comparing the metastatic status reported in pathological axillary lymph node biopsies with the negative axillary findings reported by ultrasound, it can be determined that the NPV of axillary ultrasound for patients with cT <3 cm, $HER2^+$ status, and clinically negative axillary lymph nodes is 78.5%. However, the axillary lymph node metastasis rate among this cohort of patients is 21.5%. When excluding three patients who did not undergo further ALND and considering 0–1 metastatic lymph node as a

Table 1 Baseline characteristics of enrolled HER2-enriched patients

Characteristics	N (%) or median [range]
Age group	
<40 years	21 (15.6)
≥40 years	114 (84.4)
Ultrasonic T stage	
cT ≤2 cm	82 (60.7)
2< cT ≤3 cm	53 (39.3)
Pathological T staging	
pT ≤2 cm	94 (69.6)
2< pT ≤3 cm	41 (30.4)
Tumor location	
Upper outer quadrant	39 (28.9)
Lower outer quadrant	13 (9.6)
Upper inner quadrant	29 (21.5)
Lower inner quadrant	9 (6.7)
Other position	42 (31.1)
Missing value	3 (2.2)
Histologic subtype	
IDC	134 (99.3)
MBC	1 (0.7)
Histologic grade	
Grade I	3 (2.2)
Grade II	96 (71.1)
Grade III	26 (19.3)
Missing value	10 (7.4)
With DCIS[†]	
Present	60 (44.4)
Absent	75 (55.6)
Multifocal disease	
Present	8 (5.9)
Absent	127 (94.1)
Multicentric disease	
Present	1 (0.7)
Absent	134 (99.3)
Lymphovascular invasion	
Present	29 (21.5)
Absent	106 (78.5)
Neural invasion	
Present	8 (5.9)
Absent	127 (94.1)
ER status	
Positive	91 (67.4)
Negative	44 (32.6)
PR status	
Positive	76 (56.3)
Negative	59 (43.7)
Ki-67	
>30%	59 (43.7)
≤30%	74 (54.8)
Missing value	2 (1.5)
Breast surgery	
mastectomy	73 (54.1)
BCS	62 (45.9)
Axillary surgery	
SLNB	105 (77.8)
ALND	7 (5.2)
SLNB + ALND	23 (17)
No. of obtained sentinel lymph nodes	4 [1–11]
Axillary lymph node status	
With metastasis	29 (21.5)
Without metastasis	106 (78.5)

[†], invasive cancer with associated DCIS. HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; MBC, myeloid breast cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 2 Axillary lymph node metastasis status of enrolled patients

Axillary lymph nodes status	Values
Pathological positive SLN, n	
0	103
1	17
2	7
3	1
>3	0
Subsequent ALND achieved positive lymph nodes, n	
0	16
1	4
2	0
3	0
>3	2
Direct ALND achieved positive lymph nodes, n	
0	3
1	3
2	0
3	0
>3	1
NPV of axillary ultrasound, %	78.5

SLN, sentinel lymph node; ALND, axillary lymph node dissection; NPV, negative predictive value.

Table 3 Univariate logistic analysis of preoperative factors potentially influencing axillary lymph node metastasis

Factors	P value
Age	0.26
Ultrasonic tumor diameter	0.32
Tumor location	0.90
Histologic subtype	>0.99
Histologic grade	0.43
With ductal carcinoma *in situ*	0.23
Multifocal disease	0.27
Multicentric disease	>0.99
Lymphovascular invasion	0.059
Neural invasion	0.27
Estrogen receptor	0.49
Progesterone receptor	0.58
Ki-67	0.43

Table 4 Multivariate logistic regression analysis identifying significant preoperative indicators of axillary lymph node metastasis

Factors	B	Wald	OR (95% CI)	P
With DCIS	−0.381	0.714		0.40
Present			0.684 (0.283–1.652)	
Absent			1	
Lymphovascular invasion	0.788	2.727		0.009
Present			2.2 (0.863–5.607)	
Absent			1	

OR, odds ratio; CI, confidence interval; DCIS, ductal carcinoma in situ.

negative outcome, the NPV of axillary ultrasound increases to 89.6%. When setting the cut-off at 0–2 metastatic lymph nodes for a negative result, the NPV of axillary ultrasound rises to 93.3%.

To identify preoperative factors associated with axillary lymph node pathology positivity, we conducted univariate binary logistic regression analysis between preoperatively available patient clinical characteristics and axillary lymph node pathology outcomes. The results are presented in *Table 3*. Based on literature reports, the tumor invasiveness in invasive BC with concurrent carcinoma *in situ* is lower compared to those without carcinoma *in situ*. Additionally, numerous studies have suggested that the presence of LVI is a pathological feature indicating stronger invasiveness in BC. Therefore, we chose two factors with P<0.25, namely "lymphovascular invasion" and "with DCIS", for further multivariate logistic regression analysis (*Table 4*). The results revealed that LVI had statistical significance in predicting axillary lymph node metastasis (P=0.009). Furthermore, the risk of metastasis was 2.2 times higher in cases with LVI compared to those without [95% confidence interval (CI): 0.863–5.607].

Discussion

Axillary SLNB has long been considered the gold standard for managing the axilla in BC patients with negative lymph nodes. It serves a critical role in staging lymph nodes for early-stage BC and significantly diminishes the risk of

complications that can severely impact the quality of life, including lymphedema and nerve damage. Nonetheless, SLNB is not without its risks, and there is a learning curve associated with the procedure for different surgeons. Consequently, the false-negative rate can vary among practitioners (16,17). Therefore, recent clinical studies (11,18,19) have suggested that for stage I–II BC patients with clinically negative axillary lymph nodes, axillary ultrasound might be an alternative to SLNB. The SOUND study (11) has demonstrated that axillary ultrasound is effective in predicting axillary status in early-stage BC patients and that those with axillary ultrasound-negative results can forego axillary surgery without inferior outcomes compared to SLNB treatment. However, these studies included a relatively small number of HER2-overexpressing early BC patients, whose axillary status is critical in determining whether to proceed with upfront surgery or neoadjuvant therapy.

In our study, among the HER2$^+$, clinically axillary lymph node-negative, cT $\leq$3 cm, and axillary ultrasound-negative BC patients, 21.5% had axillary lymph node metastasis, resulting in a NPV of axillary ultrasound at 78.5%. These figures suggest that even when axillary ultrasound indicates negativity, HER2-positive patients with small breast tumors still have a high likelihood of axillary lymph node metastasis. When making initial diagnostic decisions for this patient population, it is crucial to consider the benefits of neoadjuvant therapy. The CTNeoBC study (7) showed that HER2-positive BC patients who achieve a pCR after neoadjuvant treatment have better prognoses than those with residual disease, indicating long-term survival benefits associated with pCR. If trastuzumab and pertuzumab treatments do not lead to pCR in neoadjuvant therapy, the Katherine study (20) proposed that if pCR is not achieved with standard trastuzumab or trastuzumab plus pertuzumab neoadjuvant therapy, switching to trastuzumab emtansine (TDM1) escalation therapy after neoadjuvant treatment can reduce the risk of recurrence and death by 50% in these patients. This evidence underscores the significance of neoadjuvant therapy in HER2$^+$ BC, as it increases pCR rates, predicts prognosis, and informs decisions on whether secondary anti-HER2 therapy (TDM1) is needed.

Several studies have also reported on the diagnostic value of axillary ultrasound in predicting axillary metastasis in BC patients. Cools-Lartigue *et al.*'s study (21) included 167 stage 1–2 patients with no axillary lymph node metastasis reported on ultrasound, yielding an NPV for axillary ultrasound of 75%. Bedrosian *et al.* (22) studied 180 BC patients with clinically unpalpable axillary lymph nodes and negative axillary ultrasound results, finding that 39 patients were falsely diagnosed, leading to an NPV of 78.3%. Rezkallah *et al.* (23) included 128 BC patients, among whom 96 had normal axillary ultrasound findings; ultimately, 77 patients had negative SLNB results, while 19 had positive results, resulting in an axillary ultrasound NPV of 80.2%. All these studies report values similar to our derived NPV of 78.5%.

Upadhyaya *et al.* (24) investigated factors affecting the accuracy of axillary staging in BC patients through axillary ultrasound, including 605 BC patients. They found an NPV of 84.4% for axillary ultrasound and concluded that axillary lymph node metastasis was associated with larger tumor diameters, grade III pathological staging, multifocal tumors, HER2 positivity, LVI positivity, and invasive ductal carcinoma. Comparable results were seen in the SOUND study (11), which reported an axillary ultrasound NPV of 86.3%. The higher NPVs in these two studies may be attributed to their inclusion of more BC patients. Additionally, research suggests that HER2 positivity is a high-risk factor for axillary lymph node metastasis, and since all patients in our study were HER2$^+$, this could influence the NPV of axillary ultrasound, causing its decrease.

Furthermore, Houvenaeghel's study (25) involved 1,771 HER2-positive patients with small breast tumors and found a correlation between LVI and pN status. Both this study and ours reached consistent conclusions about the association between LVI and axillary lymph node metastasis, supporting our finding that LVI is related to axillary lymph node metastasis in HER2$^+$ patients with small tumors. Similarly, another study (26) reported an association between LVI and non-SLN metastasis in BC patients. A further study (27) indicated that regardless of pathological molecular subtypes and axillary lymph node status, BC patients with LVI have poorer prognoses.

Given our conclusion that BC patients with LVI have a higher risk of axillary lymph node metastasis, we recommend that patients with HER2$^+$, small tumors, and ultrasound-negative axillary lymph nodes but with preoperative pathological evidence of LVI should first be considered for neoadjuvant therapy.

The negative predictive capacity of axillary ultrasound is significant in identifying patients with low axillary burden, potentially sparing them from ALND. The ACOSOG Z0011 clinical trial (28) proposed that for early-stage BC patients undergoing BCS and planned for breast field radiation, 1–2 positive SLNs could warrant exemption from

further ALND. The AMAROS clinical trial (29) found that for cT1–2 BC patients with 1–2 positive SLNs, there was no significant difference in 10-year axillary recurrence rates, disease-free survival, and overall survival between those receiving isolated axillary radiotherapy and ALND. In our study, when setting 0–2 axillary lymph node metastases as negative results, the NPV of axillary ultrasound was 93.3%, suggesting that axillary ultrasound can effectively distinguish patients with low axillary burden. Consequently, for BC patients anticipated to undergo BCS, axillary ultrasound negativity could potentially guide the decision to exempt the patient from ALND. A study involving 1,247 BC patients confirmed that axillary ultrasound combined with other preoperative clinical-pathological indicators can accurately predict axillary lymph node metastatic burden [area under the curve (AUC) =0.702] (30).

Breast surgical specialists do encounter a learning curve with techniques such as SLNB and ALND. Surgeons outside the field of breast surgery may face the risk of false-negative outcomes during SLNB, typically attributed to a limited surgical caseload and a lack of familiarity with the axillary anatomy. Nonetheless, at our institution, the annual tally of breast surgeries exceeds a thousand cases, thereby minimizing the influence of the learning curve on the findings of this study.

Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans significantly improve diagnostic accuracy and mitigate the impact of operator-induced variability in ultrasound diagnostics. Despite these advantages, they are less favorable when considering time and economic costs, as they necessitate extended appointment wait times and substantial patient preparation during the scanning process, with expenses significantly exceeding those of ultrasound examinations. Just as there is a learning curve associated with SLNB, ultrasound physicians, after completing a training period with axillary ultrasound, can achieve commendable diagnostic capabilities. Thus, the exploration of axillary ultrasound, as a means for the early detection of early-stage BC patients, presents a potentially superior alternative (31-33).

The limitations of our study include: (I) being a retrospective study, there may be biases in case data collection; (II) as a single-center study, the sample size was relatively small, potentially compromising representativeness; (III) although all ultrasonographers in our study had over 5 years of experience and diagnostic authorization for ultrasound, inconsistencies in diagnostic tendencies and technical operations might exist due to the involvement of multiple examiners.

Conclusions

Negative axillary ultrasound can effectively predict pathologically negative axillary lymph nodes in cT ≤3 cm, clinically axillary lymph node-negative, and $HER2^+$ BC patients, providing reliable information for $HER2^+$ patients with small tumors when deciding between neoadjuvant chemotherapy and direct surgery. However, for axillary ultrasound-negative patients with concurrent LVI, their risk of axillary lymph node metastasis increases (odds ratio =2.2), in which case, we should initially recommend neoadjuvant chemotherapy.

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Footnote

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Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-140/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-140/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol received approval from the Ethical Review Committee of The First Affiliated Hospital of Guangxi Medical University

(approval No. 2024-E264-01) and was conducted in accordance with the ethical principles enshrined in the Declaration of Helsinki (as revised in 2013). Since this is a retrospective study, the need for informed consent was waived by Ethical Review Committee of The First Affiliated Hospital of Guangxi Medical University.

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