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Can axillary surgery be omitted in breast cancer using ultrasound-guided needle aspiration or biopsy? CORPA trial: a phase 1 prospective study

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ABSTRACT

Introduction: Fine-needle aspiration or core needle biopsy guided by ultrasound of the axilla can provide crucial information for the treatment of breast cancer. **Methods:** This prospective phase 1 real-world study evaluated the effectiveness of the triple test, physical examination (PE), ultrasound (US), and ultrasound-guided fine-needle aspiration (USFNA) or ultrasound-guided core needle biopsy (USCNB) in predicting axillary metastases. It also explored the possibility of omitting axillary surgery based on negative results. The study included patients with high-penetrance mutations, ductal carcinoma in situ, or invasive breast cancer (cT1–4, axillary cN0–2), all of whom underwent aspiration or biopsy along with lymph node marking (using charcoal or clips), followed by sentinel lymph node biopsy and/or axillary dissection. **Results:** A total of 363 lymph nodes were dissected in 43 patients. The sensitivity of PE and US was 33.3% and 53.3%, respectively. When combining USFNA/USCNB with PE and US, sensitivity increased from 66.67% to 80%. Among patients with mutations or ductal carcinoma in situ or invasive cancer (cT1–4), when all three methods (PE, US, and USFNA/USCNB) were negative, the rate of positive lymph nodes was only 10%. **Conclusions:** Relying solely on PE, US, or USFNA/USCNB has limitations in detecting axillary metastases. Incorporating USFNA/USCNB significantly improved sensitivity and decreased false-negative rates. When all three methods were negative, the rate of axillary involvement was only 10%, indicating that axillary surgery could potentially be omitted. However, further studies are needed to validate these methods as reliable predictive tools for treatment decisions.

KEYWORDS: breast neoplasms, ultrasonography, fine-needle biopsy, large-core needle biopsy, sentinel lymph node.

INTRODUCTION

In recent decades, there has been a sharp increase in cancer incidence, with breast neoplasms showing high rates of both incidence and mortality[1,2]. Challenges in accessing new technologies, particularly for axillary assessment, remain a significant barrier in clinical practice.

Among the commonly used methods for axillary evaluation, physical examination (PE) is prone to errors, even when performed by experienced professionals[3-5]. Ultrasonography (US) is an operator-dependent technique with variable sensitivity, ranging from 23 to 87%[6,7], and false-negative rates ranging between 34% and 46.7%[8,9]. This method is also limited in detecting low-volume disease, particularly after neoadjuvant chemotherapy[10]. Sentinel lymph node biopsy (SLNB), considered the gold standard for axillary assessment, is associated with lower morbidity and improved quality of life[11], while offering overall survival rates comparable to axillary dissection[12]. However, this technique carries potential complications, including anaphylactic reactions and sensory neuropathies.

With advancements in the understanding of tumor biology and genomic profiling, combined with the development of novel chemotherapeutic and radiotherapeutic approaches, the possibility of de-escalating or even omitting axillary surgery has emerged[13-17]. Combining ultrasonography with fine-needle aspiration (USFNA) or core needle biopsy (USCNB) has emerged as a promising alternative, demonstrating improved sensitivity, specificity, and accuracy[18-20]. In this context, the question arises:

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is it possible to develop a low-cost axillary assessment method, based on USFNA/USCNB, that accurately predicts the degree of axillary involvement and informs treatment decisions? Thus, the aim of this study was to evaluate the concordance of USFNA/USCNB in predicting axillary metastasis and to investigate the potential of omitting axillary surgery in patients with high-penetrance mutations or in situ/invasive breast cancer, when the triple test (PE, US and USFNA/USCNB) is negative.

METHODS

Study design and population

This is a prospective, phase 1, analytical, single-arm clinical trial conducted in a real-world setting to evaluate the effectiveness of the triple test (PE, US, and USFNA/USCNB) in predicting axillary metastases and explore the possibility of omitting axillary surgery based on negative results. The inclusion criteria were: women over 18 years old, carriers of high-penetrance mutations indicated for prophylactic mastectomy, and those with in situ (DCIS) or invasive carcinoma classified as cT1–4 and cN0–2. The following were considered exclusion criteria: pregnant women, patients with previous breast or axillary cancer treatment, inflammatory or metastatic tumors, and those with positive axillary nodes (cN2) after neoadjuvant chemotherapy.

The study was conducted at two mastology services in the municipality of Sobral, state of Ceará, Brazil, between 2023 and 2024. All participants signed the informed consent form, and the trial was approved by the Ethics Committee of Universidade Vale do Acaraú (Report: 6.493.146; CAAE: 175394423.4.0000.5053).

Axillary evaluation and biopsy techniques

The axillary evaluation was performed by a single mastology specialist with expertise in US and breast biopsies, using a high-frequency linear transducer. All participants underwent PE and US, and USFNA or USCNB, followed by axillary surgery.

USFNA was performed using 22-gauge needles attached to a 10 mL syringe (Figure 1A). For each patient, 3–5 slides were prepared, fixed in 99% alcohol, and stained using the Papanicolaou method. The cytological criteria for a satisfactory sample included

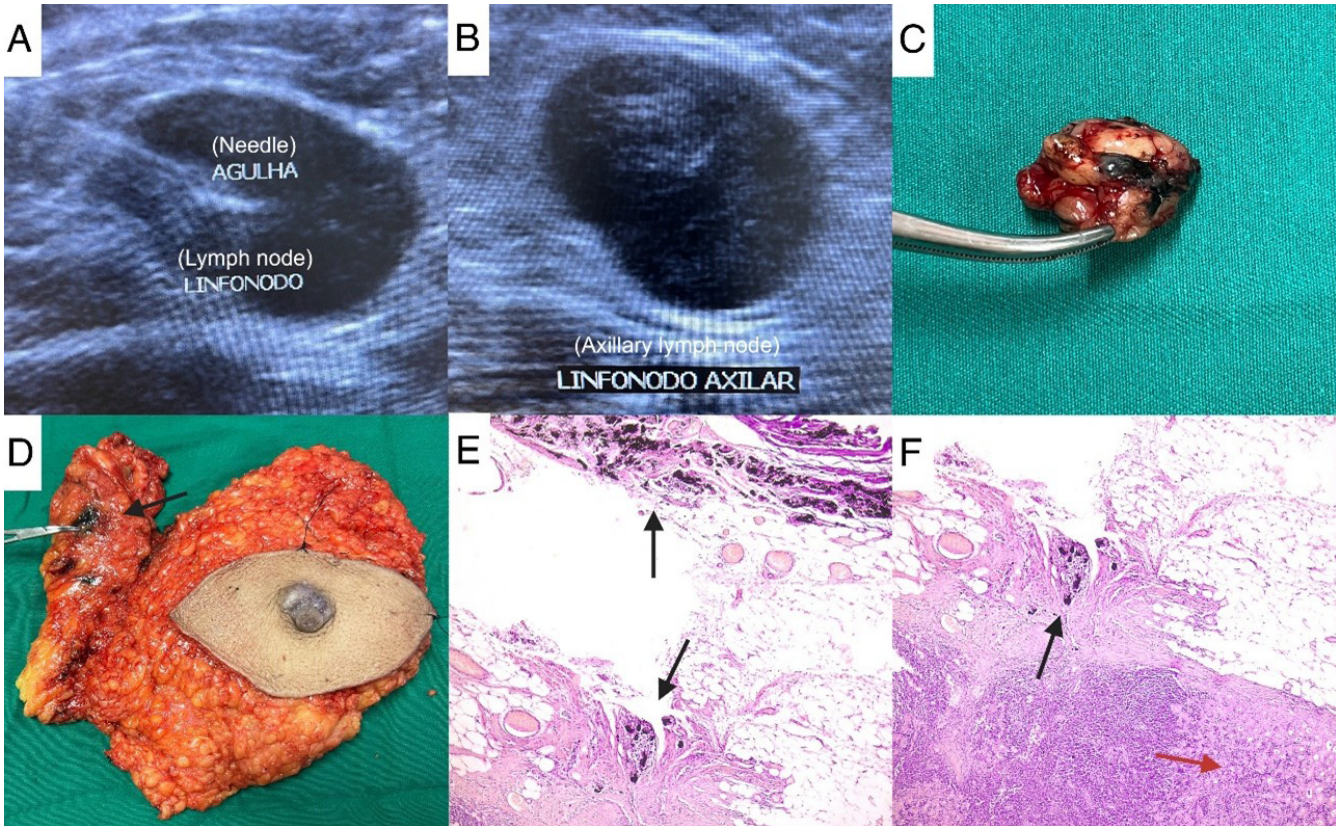

Figure 1. (**A**) Ultrasound-guided biopsy performed. (**B**) Ultrasound image showing an altered lymph node with loss of the hilum. (**C**) Surgical specimen with sentinel lymph node stained with patent blue and charcoal. (**D**) Axillary lymph node stained with charcoal and patent blue dye (black arrow). (**E**) Microscopic image of an axillary lymph node displaying charcoal in the adipose tissue and capsule (black arrows), stained with hematoxylin-eosin. (**F**) Axillary lymph node with metastatic carcinoma (red arrow), highlighted by charcoal (black arrow), and stained with hematoxylin-eosin.

highly cellular smears, without technical artifacts of desiccation or cell overlap, and a non-hemorrhagic background. In the background, a polymorphic lymphoid population was present, represented by lymphocytes at different stages of maturation and histiocytes. Samples were classified as positive for metastasis when they contained at least three groups or 10–20 neoplastic cells. USCNB was performed using an 18-gauge needle, with samples fixed in 10% formalin, embedded in paraffin, sectioned into 4–5 μm slices, and stained with hematoxylin-eosin. Both procedures were performed up to 15 days before surgery or during anesthetic induction.

All aspirated or biopsied lymph nodes (LNs) were marked with 0.5 to 1 mL of 4% charcoal in the outer fat zone (near the cortex) or with a metallic clip. In patients who underwent treatment with neoadjuvant chemotherapy, both the USFNA/USCNB and the marking procedure were performed after the completion of chemotherapy. The slides were classified as follows: negative for malignancy, positive for malignancy, suspicious (indicating cellular atypia), or unsatisfactory. The USFNA/USCNB was considered positive if the results were categorized as positive for malignancy, suspicious, or showing cellular atypia. The ultrasonographic criteria for classifying LNs as suspicious (US positive) included loss of the hilum (Figure 1B), cortical thickness ≥3 mm, shape alterations, or longitudinal diameter >2 cm.

Pathological assessment

In the immunohistochemical analysis, hormone receptors (HR) were considered positive when estrogen receptor (ER) or progesterone receptor (PR) expression was greater than 1%. The subtypes were classified as follows: luminal (HR positive and HER2 negative), HER2-positive (immunoexpression >30% or HER2 gene amplification), and triple-negative (ER negative, PR negative, and HER2-negative).

Neoadjuvant chemotherapy was indicated for HER2-positive tumors with a diameter >2 cm, triple-negative tumors with a diameter >1 cm, tumors >5 cm that precluded breast-conserving surgery, and T4 cN1(f+), cN2 tumors. All participants underwent surgery, and SLNB was marked exclusively with patent blue. Axillary dissection was indicated according to the American College of Surgeons Oncology Group (ACOSOG) Z0011 criteria, or in the presence of positive SLNs after neoadjuvant chemotherapy.

During surgery, intraoperative frozen section analysis was performed when a pathologist was available. After fixation in 10% formalin, the LNs were isolated, sectioned at 2 mm, embedded in paraffin, and cut into 4–5 μm sections, which were stained with hematoxylin-eosin, with no additional immunohistochemical analysis. The LNs were categorized as follows: no tumor or isolated tumor cells (pN0); 1–3 positive LNs (pN1); 4–9 positive LNs (pN2); and 10 or more positive LNs (pN3). The American Joint Committee on Cancer (AJCC) Eighth Edition criteria were used for staging, cytological, and histological analyses[21].

Statistical analysis

In order to evaluate the concordance between the individual methods, Cohen's Kappa coefficient was used to assess the agreement of PE, US, and USFNA/USCNB with the final pathology assessment, which served as the gold standard. Sensitivity, specificity, accuracy, false-negative rates, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the caret package. Graphical illustrations were generated with the ggplot2 package. In the combined tests, a result was considered positive if any of the methods were positive, and negative if all methods were negative. All statistical analyses were conducted using R software (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical and pathological characteristics of participants

The median age of the participants was 57 years, and among the 43 women evaluated, 27 (64.2%) were postmenopausal and 14 (32.5%) received neoadjuvant chemotherapy. The luminal tumor subtype was the most common, present in 26 of 40 (60.4%) cancer cases. Clinical and pathological characteristics of patients are shown in Table 1.

A total of 40 women were assessed by USFNA, and 3 underwent USCNB. Across these patients, 72 procedures were performed, including 66 by USFNA and 6 by USCNB, with 72 LNs evaluated. Out of the 72 LNs, 68 were marked with charcoal (Figure 1C, 1D, and 1E), and 4 were marked with clips. No complications, such as bleeding, hematomas, infections, or neuropathies, were observed.

In the axillary surgeries, a total of 363 LNs were dissected from all cases, of which 69 were found to be positive for malignancy in the final pathology (Figure 1E). In the group that did not receive neoadjuvant chemotherapy, there were no unsatisfactory samples. However, 27.5% (8/29) of the patients who were classified as negative had hypocellular samples. In contrast, among patients who received neoadjuvant chemotherapy, 13.3% (2/15) of the samples were considered unsatisfactory after completing treatment.

Of the 43 patients evaluated through surgery, 15 were classified as positive and 28 as negative based on pathological assessment for cancer metastasis. This result was used as the reference standard for comparison with the other axillary evaluation methods.

Performance of diagnostic methods

Table 2 presents the results for sensitivity, specificity, accuracy, PPV, NPV, false-negative rates, and Kappa coefficient for the individual methods (PE or US or USFNA/USCNB) and the combined approaches (PE and US) and (PE and US and USFNA/USCNB).

In PE, 8 patients were classified as positive and 35 as negative, with 10 false negatives (Figure 2A). Among the false negatives, 5 were pN1a, 2 were pN2–3, 2 were ypN1a, and 1 was ypN3a.

PE alone demonstrated a sensitivity of 33.33%, a false-negative rate of 66.67%, and a fair level of agreement with pathological assessment (κ=0.253).

In US, 14 patients were classified as positive, with 9/14 (64.3%) exhibiting cortical thickness ≥3 mm, 3/14 (21.4%) showing loss of the hilum, 1/14 (7.15%) presenting shape alteration, and 1/14 (7.15%) showing a longitudinal diameter >2 cm. Additionally, 29 patients were classified as negative, of which 7 were false negatives (Figure 2B). Notably, 87.50% of the false-negative cases in US involved the luminal subtype and invasive pT2 tumors, including 3 pN1a, 1 pN3a, 2 ypN1a, and 1 ypN3a. US alone demonstrated a sensitivity of 53.33%, a false-negative rate of 46.67%, and fair agreement with pathological assessment (κ=0.324).

Table 1. Clinical and pathological characteristics of patients.

Feature/Classification	n	(%)
Age (years)		
<55	18	41.86
>55	25	58.14
Menopausal status		
Premenopausal	15	35.71
Postmenopausal	27	64.29
Clinical T		
T0/Tis/T1	20	46.51
T2	12	27.91
T3/T4	11	25.58
Pathological T		
pT0/ypT0/pTis/pT1/ypT1	23	53.48
pT2/ypT2	15	34.88
pT3/ypT3/pT4/ypT4	05	11.62
Axillary pathological N		
pN0/ypN0	28	65.12
pN1/ypN1	9	20.93
pN2–3/ypN2–3	6	13.95
Tumor subtype		
Luminal	26	60.47
HER2 positive	9	20.92
Triple negative	5	11.63
Non available	3	6.98
Histologic subtype		
Ductal	39	90.6
Lobular	02	4.6
Not classified (prophylactic surgery)	02	4.6
Grade		
G1–G2	26	63. 40
G3	15	36.60
Neoadjuvant chemotherapy		
No	29	67.44
Yes	14	32.56
Surgery		
Breast-conserving surgery	22	51.16
Mastectomy	21	48.84

T: tumor size; N: nodal status.

In USFNA/USCNB, after excluding the two patients with unsatisfactory results, 7 were classified as positive and 34 as negative, with 8 of these being false negatives (Figure 2C). All 8 false negatives were observed in USFNA, with none identified in USCNB. Among the false-negative cases, 87.50% involved the luminal subtype, and 62.50% were associated with pT2 tumors. These false negatives included 5 pN1a and 3 pN2–3 cases. The performance of USFNA/USCNB alone showed a sensitivity of 42.86% and a false-negative rate of 57.14%, with moderate agreement with pathological assessment (κ=0.445).

The combination of PE and US in the 43 patients demonstrated better performance than the individual tests, achieving a sensitivity of 66.67%, a false-negative rate of 33.33%, and fair agreement with pathological assessment (κ=0.346). In the 41 patients with satisfactory USFNA/USCNB samples, combining all three methods (Figure 2D) provided the highest sensitivity of 85.71%, a false-negative rate of 14.29%, and moderate agreement (κ=0.467). The only two false negatives in the combination of the three methods were both pN1a patients with the luminal subtype.

In the subgroup of 14 patients who received neoadjuvant chemotherapy, PE had a sensitivity of 40.0% and a false-negative rate of 60.0%, similar to the results obtained with US (Table 3). In these patients, after excluding two samples deemed unsatisfactory, USFNA/USCNB showed 100% sensitivity, a 0% false-negative rate and κ=1.

When comparing size, tumors in the cT2 subgroup (larger than 3 cm) showed 41.7% axillary involvement, whereas tumors in the cT1 subgroup (up to 2 cm) had a 13.6% positive rate. Additionally, the luminal subtype exhibited 46.2% positive axillary involvement, compared to 21.4% in the HER2/TN group.

Among the seven patients diagnosed with mutations or DCIS, only one (14.2%) had positive LNs (pN1a). This patient was a false negative case for USFNA/USCNB but had positive findings on PE and US.

In the cT1–2 stage group, 14 women had negative PE and US. Among them, 14.2% (2/14) had positive LNs (1 pN1a, 1 ypN1a). However, when USFNA was included in this subgroup, this number decreased to just one patient (7.14%).

DISCUSSION

It is debatable whether, and under what circumstances, other methods should be added to PE and US. Our study revealed that using individual methods alone is insufficient for accurately

Table 2. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, false negative rates, and Kappa coefficient for physical examination, ultrasound, and fine needle aspiration or core needle biopsy ultrasound-guided fine-needle aspiration/ultrasound-guided core needle biopsy in all patients.

Test	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	FNR (%)	Kappa
PE	33.33 (11.82–61.62)	89.29 (71.77–97.73)	69.77 (53.87–82.82)	62.50 (31.52–85.78)	71.43 (63.09–78.52)	66.67 (38.38–88.18)	0.254
US	53.33 (26.59–78.73)	78.57 (59.05–91.70)	69.77 (53.87–82.82)	57.14 (36.24–75.78)	75.86 (63.89–84.81)	46.67 (21.27–73.41)	0.324
USFNA/USCNB*	42.86 (17.66–71.14)	96.30 (81.03–99.91)	78.05 (62.39–89.44)	85.71 (44.41–97.83)	76.47 (67.24–83.73)	57.14 (28.86–82.34)	0.445
PE+US	66.67 (38.38–88.18)	71.43 (51.33–86.78)	69.77 (53.87–82.82)	55.56 (38.62–71.29)	80.00 (65.32–89.47)	33.33 (11.82–61.62)	0.364
PE+US+USFNA/USCNB*	85.71 (57.19–98.22)	66.67 (46.04–83.48)	73.17 (57.06–85.78)	57.14 (42.87–70.32)	90.00 (70.82–97.09)	14.29 (1.78–42.81)	0.467

The analysis included 41 patients with satisfactory results in USFNA/USCNB.
PPV: positive predictive value; NPV: negative predictive value; FNR: false negative rates; PE: physical examination; US: ultrasound; USFNA: ultrasound-guided fine-needle aspiration; USCNB: ultrasound-guided core needle biopsy.

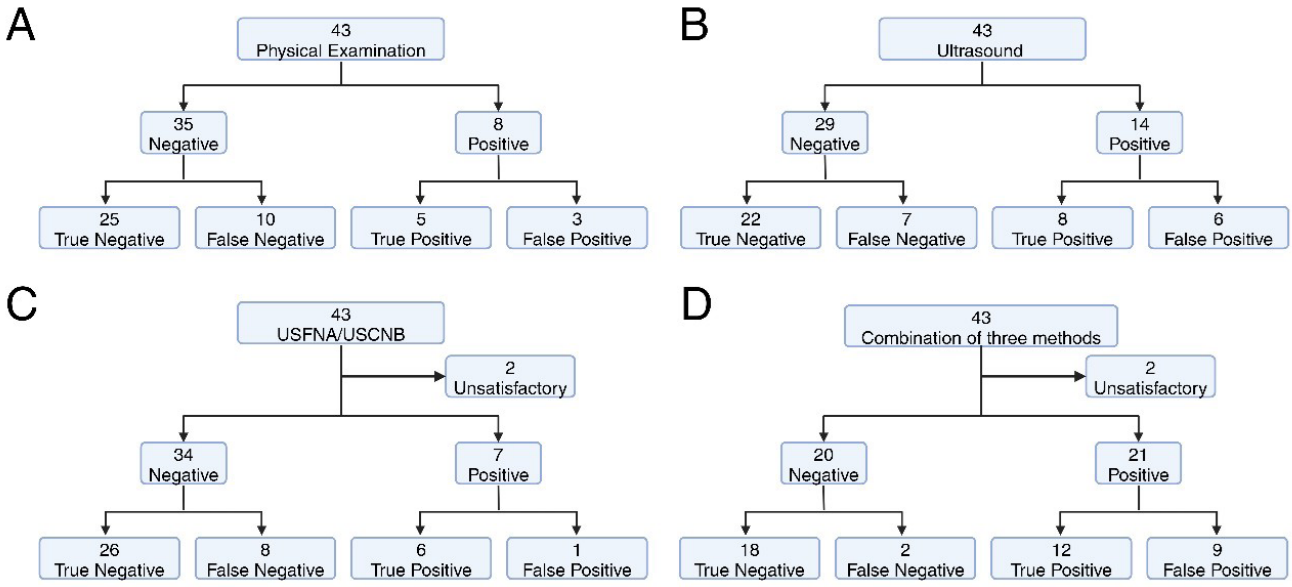

Figure 2. Diagram illustrating the results of physical examination (**A**), ultrasound (**B**), ultrasound-guided fine-needle aspiration/ultrasound-guided core needle biopsy – ultrasound-guided fine-needle aspiration/ultrasound-guided core needle biopsy (**C**), and the combination of all three methods (**D**).

Table 3. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, false negative rates, and Kappa coefficient of physical examination, ultrasound, and fine needle aspiration or core needle biopsy ultrasound-guided fine-needle aspiration/ultrasound-guided core needle biopsy in patients who underwent chemotherapy. All results refer to tests conducted after the completion of chemotherapy.

Test	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	FNR (%)	Kappa
PE	40.00 (5.27–85.34)	100 (66.37–100)	78.57 (49.20–95.34)	100 (15.81–100)	75.00 (59.46–85.99)	60.00 (14.66–94.73)	0.461
US	40.00 (5.27–85.34)	88.89 (51.75–99.72)	71.43 (41.90–91.61)	66.67 (19.09–94.43)	72.73 (55.69–84.98)	60.00 (14.66–94.73)	0.317
USFNA/USCNB*	100 (63.06–100)	100 (39.76–100)	100 (73.54–100)	100 (63.06–100)	100 (39.76–100)	0 (0.00–60.24)	1,000

The analysis included 12 patients with satisfactory results in USFNA/USCNB.
PPV: positive predictive value; NPV: negative predictive value; FNR: false negative rates; PE: physical examination; US: ultrasound; USFNA: ultrasound-guided fine-needle aspiration; USCNB: ultrasound-guided core needle biopsy.

detecting axillary involvement, whereas combining multiple methods significantly enhances sensitivity.

When analyzed separately, PE showed the worst result among the three methods, with sensitivity of 33.33%, aligning with previous studies reporting values between 32.0% and 33.0%[4,5]. This highlights that the absence of palpable LNs does not ensure a disease-free axilla, as morphological changes often occur at later stages[10].

US is a widely used and cost-effective method for axillary evaluation, with sensitivity ranging from 23.0 to 73.0%[22]. However, its accuracy can be influenced by factors such as the size of metastatic LNs, tumor burden, obesity, histological grade, and HER2 status[6,9,23]. Larger LNs are more easily detected, whereas smaller metastases may be missed, which can lead to lower sensitivity. In our analysis, US showed a limited sensitivity of 53.33%, emphasizing the challenge of relying on US alone for axillary metastasis detection. Combining US with other methods, like PE or USFNA/USCNB, could improve diagnostic accuracy. For instance, the combination of PE and US performed better than the individual tests, achieving a sensitivity of 66.67%, a false-negative rate of 33.33%, and fair agreement (κ=0.346)

A high sensitivity of USFNA/USCNB has been demonstrated in recent meta-analyses, which found sensitivity ranging from 73% to 79% for USFNA and 85% to 88% for USCNB[24,25]. However, in our analysis, USFNA/USCNB had only 42.86% sensitivity when used alone. This suggests that, while USFNA and USCNB can be valuable tools, their performance might be limited when not combined with other methods, such as PE or US. Indeed, combining PE, US, and USFNA/USCNB provided a sensitivity of 85.71%, a false-negative rate of 14.29%, and moderate agreement with surgical pathology (κ=0.445), outperforming even the combination of PE and US without USFNA/USCNB. This highlights the importance of integrating multiple diagnostic approaches to enhance sensitivity and reduce false-negative rate, ultimately improving diagnostic accuracy and clinical decision-making.

In recent years, numerous studies have emphasized the possibility of axillary surgical de-escalation. Trials such as ACOSOG-Z0011[12], the International Breast Cancer Study Group (IBCSG) 23-01[14], Sentinel Node vs Observation after axillary Ultrasound (SOUND)[17], and Sentinel Node vs Mastectomy/Axillary Clearance (SENOMAC)[26] demonstrated that, in early-stage tumors with 1–2 positive SLNs, the removal of only the SLN achieved a local recurrence rate of less than 2.0% and an overall survival rate of 95.0%. Recent studies have evaluated the omission of axillary surgery in various scenarios. In patients with high-penetrance mutations, the probability of detecting an occult tumor is less than 6.4%, and in invasive tumors, it is only 1.0%, suggesting that SLNB could be omitted, especially if the pre-surgical magnetic resonance imaging is normal[27-29]. In a meta-analysis involving 4,338 patients with DCIS, Davey et al. found that among the 3,156 patients who underwent SLNB, 4.9% had an absolute risk of positive SLNB[30]. Similarly, in a report by Li et al., including 8,279 patients with DCIS and microinvasion, 8.0% had axillary metastasis[31].

Among the seven patients in our study diagnosed with mutations or DCIS, only one (14.2%) had positive LNs, which were detected by US and PE. Patients with all three negative tests were classified as pN0 in the final pathology, suggesting that axillary surgery could potentially be omitted in this group. However, factors such as tumor size, histological grade, and microinvasion should be carefully evaluated when determining whether to incorporate USFNA/USCNB, proceed with SLNB, or omit axillary surgery.

Another key discussion regarding the omission of axillary surgery involves early-stage invasive tumors. We evaluated 14 women with cT1–2 invasive tumors who had negative PE and US. Among them, 14.2% had positive LNs. However, when considering only patients with a negative triple test, the rate of positive LNs dropped to 8.3%, suggesting that SLNB could potentially be omitted in cT1–2 patients with a negative triple test. The safety of this approach is further supported by the Insentinel Node vs Mastectomy/Axillary Surgery (INSEMA) trial, which included 4,858 patients with cT1–2 tumors and negative double testing, showing an axillary recurrence rate of only 1.0% in the group that omitted surgery[32]. Our study also revealed that in tumors larger than 3 cm, 41.7% of the LNs were involved, and luminal tumors had 46.2% positive axillae, suggesting that surgical decisions for tumors above 3 cm and luminal subtypes should be made on an individual basis.

Of the total number of patients, 25 had negative US and PE; of these, 20.0% (5/25) had axillary involvement. In contrast, among 20 of the 41 patients with the same characteristics and with negative triple test, only 10.0% (2/20) exhibited axillary involvement. Previous studies have reported a higher sensitivity of USFNA than the 42.86% found in the present analysis, suggesting the potential to omit SLNB based on USFNA results. For instance, Astvatsaturyan et al. identified a sensitivity of 78.0% and a specificity of 98.0% for USFNA in a cohort of 228 women, suggesting that it could potentially avoid SLNB in 36.0% of cases[33]. Similarly, Sallout et al., with 354 patients, found a false-negative rate of only 11.6% and a specificity of 99.2% for USFNA, concluding that USFNA could be an alternative to SLNB in a significant proportion of patients[34]. However, our results suggest that while USFNA/USCNB may play a crucial role, the accuracy of the combined tests is essential to make a safe decision about omitting SLNB, as relying on just one or two tests may not provide enough certainty regarding axillary involvement.

Axillary evaluation in the context of neoadjuvant chemotherapy is another important topic. In our study, US alone demonstrated a false-negative rate of 60.0% in patients after neoadjuvant chemotherapy. When US was negative, 27.2% (3/11) of patients showed axillary involvement in surgery, and similar limitations have been reported in other studies. The Z1071 trial, for instance, found that among 461 cases with preserved fat in the hilum after neoadjuvant chemotherapy, 59.0% (273/461) had residual disease, and among 344 patients with cortical thickness ≤3 mm, 55.8%

(192/344) had positive pathology[35]. The Sentinel Neoadjuvant (SENTINA) trial, which focused on the cN1 group that converted to ycN0 after neoadjuvant chemotherapy, found that 53.4% had residual disease on histopathology, with US demonstrating a sensitivity of only 23.9% and an NPV of 50.3%[36]. Additionally, the Sentinel Node Fine-Needle Aspiration Cytology (SN FNAC) study showed a sensitivity of 52.8% for US in 145 patients[37]. These findings highlight the challenges of using US alone for axillary evaluation after neoadjuvant chemotherapy, emphasizing the need for more reliable methods or combined approaches to improve diagnostic accuracy in this setting.

In our study, which included cT1–4 patients with negative PE and US findings after neoadjuvant chemotherapy, 27.2% (3/11) exhibited positive axillary LNs. Notably, in this subgroup, USFNA/USCNB demonstrated 100% sensitivity with no false-negative results, outperforming US. This suggests that SLNB could potentially be omitted in these cases, as USFNA/USCNB was a reliable diagnostic tool. This finding was unexpected, as chemotherapy-induced fibrosis was anticipated to compromise the sensitivity of USFNA/USCNB. The results demonstrated the potential of adding USFNA/USCNB as a reliable predictor in guiding management decisions for this specific subgroup.

Another important consideration is the relationship between axillary involvement rates and the response of both the breast and axilla to chemotherapy. Barron et al. reported that among 30,821 patients (cT1–2, cN0–1) who achieved a pathological complete response (pCR) and remained cN0, axillary involvement was less than 2.0%. This suggests that axillary surgery could potentially be omitted in this group[38]. Additionally, studies on the de-escalation of surgery after chemotherapy, such as the Imaging-guided Conservative Axillary Management (ICARO) study, revealed a 2.0% axillary recurrence rate at three years in cases with isolated tumor cells (ypN0i+) identified in surgical pathology following neoadjuvant chemotherapy[39]. In our study, 28.5% (4/14) of patients who underwent neoadjuvant chemotherapy achieved pCR, and all had negative LNs, highlighting the influence of tumor biology and chemotherapy advancements on axillary response.

This trial has limitations that must be considered. These include a small sample size, macroscopic evaluations performed by different technicians, the use of patent blue dye as the sole method for identifying sentinel LNs, the use of charcoal (resulting in two dark-colored markers), a limited number of USCNB procedures, and a confidence interval above 5%. Retrospective studies also related false-negative rates higher than 30.0% for USFNA, underscoring its limitations as a method for detecting micrometastasis or a small number of positive LNs[40].

CONCLUSIONS

This study highlights the limitations of PE, US, and USFNA/USCNB when used individually for detecting axillary metastases. However, combining PE and US with USFNA/USCNB improved sensitivity from 66.67% to 85.71%. Notably, axillary surgery could potentially be avoided in women with negative results across all three methods. Nevertheless, further research is required to validate this approach as a reliable predictive tool for guiding treatment decisions in breast cancer patients.

AUTHORS' CONTRIBUTIONS

EFC: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft. JJL: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. LGR: Data curation. SCO: Formal analysis. FDOM: Formal analysis. VOCF: Formal analysis, Writing – original draft. LGPP: Writing – review & editing. FNC: Data curation. DIMC: Data curation.

REFERENCES

1. World Health Organization. Câncer de mama agora a forma mais comum de cancer: OMS tomando medidas [Internet]. 2021 [cited on Feb 03, 2021]. Available from: https://www.who.int/pt/news/item/03-02-2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al . Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
3. Lanng C, Hoffmann J, Galatius H, Engel U. Assessment of clinical palpation of the axilla as a criterion for performing the sentinel node procedure in breast cancer. Eur J Surg Oncol. 2007;33(3):281-4. https://doi.org/10.1016/j.ejso.2006.09.032
4. Majid S, Tengrup I, Manjer J. Clinical assessment of axillary LNs and tumor size in breast cancer compared with histopathological examination: a population-based analysis of 2,537 women. World J Surg. 2013;37(1):67-71. https://doi.org/10.1007/s00268-012-1788-5
5. Feng Y, Huang R, He Y, Lu A, Fan Z, Fan T, et al. Efficacy of physical examination, ultrasound, and ultrasound combined with fine-needle aspiration for axilla staging of primary breast cancer. Breast Cancer Res Treat. 2015;149(3):761-5. https://doi.org/10.1007/s10549-015-3280-z
6. Dihge L, Grabau DA, Rasmussen RW, Bendahl PO, Rydén L. The accuracy of preoperative axillary nodal staging in primary breast cancer by ultrasound is modified by nodal metastatic load and tumor biology. Acta Oncol. 2016;55(8):976-82. https://doi.org/10.3109/0284186X.2016.1146826

7. Alvarez S, Añorbe E, Alcorta P, López F, Alonso I, Cortés J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. AJR Am J Roentgenol. 2006;186(5):1342-8. https://doi.org/10.2214/AJR.05.0936
8. Riedel F, Schaefgen B, Sinn HP, Feisst M, Hennigs A, Hug S, et al. Diagnostic accuracy of axillary staging by ultrasound in early breast cancer patients. Eur J Radiol. 2021;135:109468. https://doi.org/10.1016/j.ejrad.2020.109468
9. Man V, Luk WP, Fung LH, Kwong A. The role of pre-operative axillary ultrasound in assessment of axillary tumor burden in breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat. 2022;196(2):245-54. https://doi.org/10.1007/s10549-022-06699-w
10. Weber WP, Gentilini OD, Morrow M, Montagna G, Boniface J, Fitzal F, et al. Uncertainties and controversies in axillary management of patients with breast cancer. Cancer Treat Rev. 2023;117:102556. https://doi.org/10.1016/j.ctrv.2023.102556
11. Karampelias V, Koukouras D, Tzorakoleftherakis E, Mariolis-Sapsakos T, Chrysikos D. Breast cancer section analysis correlates with sentinel lymph node biopsies: precision and topographic anatomy. Breast Dis. 2019;38(1):1-5. https://doi.org/10.3233/BD-180355
12. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA. 2017;318(10):918-26. https://doi.org/10.1001/jama.2017.11470
13. van Roozendaal LM, Vane MLG, van Dalen T, van der Hage JA, Strobbe LJA, Boersma LJ, et al. Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial (BOOG 2013-08). BMC Cancer. 2017;17(1):459. https://doi.org/10.1186/s12885-017-3443-x
14. Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-93. https://doi.org/10.1016/S1470-2045(18)30380-2
15. Tran HT, Pack D, Mylander C, Martino L, Rosman M, Tafra L, et al. Ultrasound-based nomogram identifies breast cancer patients unlikely to harbor axillary metastasis: towards selective omission of sentinel lymph node biopsy. Ann Surg Oncol. 2020;27(8):2679-86. https://doi.org/10.1245/s10434-019-08164-3
16. Lee MK, Montagna G, Pilewskie ML, Sevilimedu V. axillary staging is not justified in postmenopausal clinically node-negative women based on nodal disease burden. Ann Surg Oncol. 2023;30(1):92-7. https://doi.org/10.1245/s10434-022-12203-x
17. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol. 2023;9(11):1557-64. https://doi.org/10.1001/jamaoncol.2023.3759
18. Pessoa EC, Rodrigues JR, Pessoa CKCP, Véspoli HML, Uemura G. Punção aspirativa de linfonodo axilar guiada pela ultrassonografia é eficaz como método de predição de acometimento linfonodal em pacientes com câncer de mama? Rev Bras Ginecol Obstet. 2014;36(3):118-23. https://doi.org/10.1590/S0100-72032014000300005
19. Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018;105(10):1244-53. https://doi.org/10.1002/bjs.10920
20. Huang Y, Zheng S, Lin Y. Accuracy and utility of preoperative ultrasound- guided axillary lymph node biopsy for invasive breast cancer: a systematic review and meta-analysis. Comput Intell Neurosci. 2022;2022:3307627. https://doi.org/10.1155/2022/3307627
21. American Joint Committee on Cancer. Cancer staging manual. 8th ed. New York: Springer International Publishing; 2016.
22. Le Boulc'h M, Gilhodes J, Steinmeyer Z, Molière S, Mathelin C. Pretherapeutic imaging for axillary staging in breast cancer: a systematic review and meta- analysis of ultrasound, MRI and FDG PET. J Clin Med. 2021;10(7):1543. https://doi.org/10.3390/jcm10071543
23. Tucker NS, Cyr AE, Ademuyiwa FO, Tabchy A, George K, Sharma PK, et al. Axillary ultrasound accurately excludes clinically significant lymph node disease in patients with early stage breast cancer. Ann Surg. 2016;264(6):1098-102. https://doi.org/10.1097/SLA.0000000000001549
24. Zheng H, Zhao R, Wang W, Liu X, Wang X, Wen C, et al. The accuracy of ultrasound guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph nodes in women with breast cancer: a systematic review and meta-analysis. Front Oncol. 2023;13:1166035. https://doi.org/10.3389/fonc.2023.1166035
25. Xu Q, Wang J, Wang J, Guo R, Qian Y, Liu F. The effectiveness of ultrasound-guided core needle biopsy in detecting lymph node metastases in the axilla in patients with breast cancer: systematic review and meta-analysis. Clinics (Sao Paulo). 2023;78:100207. https://doi.org/10.1016/j.clinsp.2023.100207
26. Boniface J, Tvedskov TF, Rydén L, Szulkin R, Reimer T, Kühn T, et al. Omitting axillary dissection in breast cancer with sentinel-node metastases. N Engl J Med. 2024;390(13):1163-75. https://doi.org/10.1056/NEJMoa2313487
27. Madan V, Mamounas EP. Is sentinel lymph node biopsy necessary in patients who undergo prophylactic mastectomy? Clin Breast Cancer. 2023;23(2):231-6. https://doi.org/10.1016/j.clbc.2022.12.003
28. Wong SM, Ferroum A, Apostolova C, Alhassan B, Prakash I, Basik M, et al. Incidence of occult breast cancer in carriers of brca1/2 or other high-penetrance pathogenic variants undergoing prophylactic mastectomy: when is sentinel lymph node biopsy indicated? Ann Surg Oncol. 2022;29(11):6660-8. https://doi.org/10.1245/s10434-022-11916-3
29. Fat SC, Weed C, Samaha Y, Chung A, Boyle MK, Giuliano A, et al. Incidence of cancer and role of sentinel lymph node biopsy in BRCA mutation carriers undergoing prophylactic mastectomies. Am Surg. 2023;89(10):4066-71. https://doi.org/10.1177/00031348231175498

30. Davey MG, O'Flaherty C, Cleere EF, Nohilly A, Phelan J, Ronane E, et al. Sentinel lymph node biopsy in patients with ductal carcinoma in situ: systematic review and meta-analysis. BJS Open. 2022;6(2):zrac022. https://doi.org/10.1093/bjsopen/zrac022

31. Li X, Zhou C, Xu T, Ren Y, Li M, Shang J. Meta-analysis on axillary lymph node metastasis rate in ductal carcinoma in situ with microinvasion. Cancer Med. 2024;13(12):e7413. https://doi.org/10.1002/cam4.7413

32. Reimer T, Stachs A, Veselinovic K, Kühn T, Heil J, Polata S, et al. Axillary surgery in breast cancer – primary results of the INSEMA trial. N Engl J Med. 2025;392(11):1051-64. https://doi.org/10.1056/NEJMoa2412063

33. Astvatsaturyan K, Ramazyan A, Bose S. Is ultrasound-guided fine needle aspiration biopsy of axillary lymph nodes a viable alternative to sentinel lymph node biopsy? Diagn Cytopathol. 2021;49(10):1099-109. https://doi.org/10.1002/dc.24824

34. Sallout L, Tashkandi M, Moqnas A, AlMajed H, Al-Naeem A, Alwelaie Y. Fine- needle aspiration biopsy of axillary lymph nodes: a reliable diagnostic tool for breast cancer staging. Cancer Cytopathol. 2024;132(2):103-8. https://doi.org/10.1002/cncy.22770

35. Le-Petross HT, McCall LM, Hunt KK, Mittendorf EA, Ahrendt GM, Wilke LG, et al. Axillary ultrasound identifies residual nodal disease after chemotherapy: results from the American College of Surgeons Oncology Group Z1071 Trial (Alliance). AJR Am J Roentgenol. 2018;210(3):669-76. https://doi.org/10.2214/AJR.17.18295

36. Schwentner L, Helms G, Nekljudova V, Ataseven B, Bauerfeind I, Ditsch N, et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy – results from the multi-center SENTINA trial. Breast. 2017;31:202-7. https://doi.org/10.1016/j.breast.2016.11.012

37. Morency D, Dumitra S, Parvez E, Martel K, Basik M, Robidoux A, et al. Axillary lymph node ultrasound following neoadjuvant chemotherapy in biopsy-proven node- positive breast cancer: results from the SN FNAC study. Ann Surg Oncol. 2019;26(13):4337-45. https://doi.org/10.1245/s10434-019-07809-7

38. Barron AU, Hoskin TL, Day CN, Hwang ES, Kuerer HM, Boughey JC, et al. Association of low nodal positivity rate among patients with ERBB2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. JAMA Surg. 2018;153(12):1120-6. https://doi.org/10.1001/jamasurg.2018.2696

39. Montagna G, Laws A, Ferrucci M, Mrdutt MM, Sun SX, Bademler S, et al. Nodal burden and oncologic outcomes in patients with residual isolated tumor cells after neoadjuvant chemotherapy (ypN0i+): the OPBC-05/ICARO study. J Clin Oncol. 2025;43(7):810-20. https://doi.org/10.1200/JCO.24.01052

40. Topps AR, Barr SP, Pikoulas P, Pritchard SA, Maxwell AJ. Pre-operative axillary ultrasound-guided needle sampling in breast cancer: comparing the sensitivity of fine needle aspiration cytology and core needle biopsy. Ann Surg Oncol. 2018;25(1):148-53. https://doi.org/10.1245/s10434-017-6090-1