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The value of quantitative shear wave elastography combined with conventional ultrasound in evaluating and guiding fine needle aspiration biopsy of axillary lymph node for early breast cancer: implication for axillary surgical stage

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Abstract

Objectives To investigate the value of conventional ultrasonography (US) combined with quantitative shear wave elastography (SWE) in evaluating and identifying target axillary lymph node (TALN) for fine needle aspiration biopsy (FNAB) of patients with early breast cancer.

Materials and methods A total of 222 patients with 223 ALNs were prospectively recruited from January 2018 to December 2021. All TALNs were evaluated by US, SWE and subsequently underwent FNAB. The diagnostic performances of US, SWE, UE_{or} (either US or SWE was positive) and UE_{and} (both US and SWE were positive), and FNAB guided by the above four methods for evaluating ALN status were assessed using receiver operator characteristic curve (ROC) analyses. Univariate and multivariate logistic regression analyses used to determine the independent predictors of axillary burden.

Results The area under the ROC curve (AUC) for diagnosing ALNs using conventional US and SWE were 0.69 and 0.66, respectively, with sensitivities of 78.00% and 65.00% and specificities of 60.98% and 66.67%. The combined method, UE_{or}, demonstrated significantly improved sensitivity of 86.00% ($p < 0.001$ when compared with US and SWE alone). The AUC of the UE_{or}-guided FNAB [0.85 (95% CI, 0.80–0.90)] was significantly higher than that of US-guided FNAB [0.83 (95% CI, 0.78–0.88), $p = 0.042$], SWE-guided FNAB [0.79 (95% CI, 0.72–0.84), $p = 0.001$], and UE_{and}-guided FNAB [0.77 (95% CI, 0.71–0.82), $p < 0.001$]. Multivariate logistic regression showed that FNAB and number of suspicious ALNs were found independent predictors of axillary burden in patients with early breast cancer.

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Conclusion The UE_{or} had superior sensitivity compared to US or SWE alone in ALN diagnosis. The UE_{or}-guided FNAB achieved a lower false-negative rate compared to FNAB guided solely by US or SWE, which may be a promising tool for the preoperative diagnosis of ALNs in early breast cancer, and had the potential implication for the selection of axillary surgical modality.

Keywords Breast neoplasms, Lymph nodes, Ultrasound, Elasticity imaging techniques, Fine needle aspiration biopsy

Introduction

Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide [1]. Preoperative identification of axillary lymph node (ALN) involvement plays a crucial role in determining the appropriate surgical approach and can potentially enhance the effectiveness of breast cancer treatment [2, 3]. Conventional ultrasound (US) is non-radioactive, inexpensive, and capable of assessing the morphological features of the lymph nodes such as cortical thickness and hilar status in real-time, thus it is widely used to evaluate the axilla preoperatively for early breast cancer [4].

According to the National Comprehensive Cancer Network (NCCN) guidelines, patients who have clinical node-negative axilla evaluated by conventional US were recommended to undergo axillary sentinel lymph node biopsy (SLNB), whereas patients with suspicious ALNs should undergo US-guided fine needle aspiration biopsy (FNAB) which is a popular and versatile method to diagnose ALNs before surgery [5]. Several studies have shown that patients with positive FNAB results would have a high axillary burden, which will further guide the selection of axillary surgical modality [6, 7]. However, the false-negative rate (FNR) of preoperative US-guided FNAB has been reported to be as high as 31% in early breast cancers, which caused unnecessary SLNBs and prolonged surgical time [8]. Therefore, improving the diagnostic efficacy of preoperative imaging to guide the choice of FNAB with the aim of reducing the false negative rate of FNAB was essential to optimize the management of the axilla [9, 10].

Shear wave elastography (SWE) can quantitatively measure tissue stiffness associated with tumorigenesis and disease progression. It has been shown to be helpful in assessing sentinel lymph nodes for breast cancers [11, 12]. Previous studies have demonstrated that qualitative and quantitative SWE can differentiate between metastatic and non-metastatic ALNs in breast cancer, with an area under the receiver operating characteristic curve (AUC) of 0.61–0.94 [13–15]. However, most of these studies focused on qualitative elastography analysis rather than quantitative SWE [16, 17]. It is important to note that qualitative elastography exhibited poorer interobserver and intraobserver reproducibility compared to quantitative SWE [18]. Some previous studies compared the performance of the combination of conventional US and elastography with conventional US alone in evaluating the ALNs for breast cancer, and demonstrated that measuring tissue stiffness by SWE could be utilized as a complementary tool to improve detection of ALN metastasis [11, 19, 20]. Based on these findings, it is hypothesized that combining conventional US and quantitative SWE could potentially achieve a favorable performance with higher sensitivity, thereby effectively identifying the target ALN (TALN) for fine-needle aspiration biopsy (FNAB). However, there is a limited number of prospective studies that have investigated the use of SWE combined with conventional US to determine TALN for FNAB selection. Therefore, the objective of this study is to assess the value of combining conventional US and quantitative SWE in diagnosing ALNs and evaluate whether this combined approach can identify TALN for FNAB, and enhance the diagnostic performance of FNAB for ALN metastasis in early breast cancer patients.

Materials and methods

Patients

This prospective study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All patients signed informed consent for study participation and data collection. From January 2018 to December 2021, patients who met the following inclusion criteria were included: (i) Women with an age range from 18 to 80 years old; (ii) Patients with breast cancer newly diagnosed by core needle biopsy within 2 weeks; (iii) The size of the breast lesion is not more than 50 mm (cT1-2) (iv) The ipsilateral ALNs were not palpable. (v.) Without distant metastasis; (vi.) Patients who underwent axillary conventional US and SWE examinations. (vii) Patients who underwent FNAB for assessing ALN status. Exclusion criteria include: (i) Multifocal breast cancer; (ii) Patients who had undergone breast-conserving therapy for ipsilateral breast cancer, or neoadjuvant chemotherapy or radiotherapy; (iii)Patients refused surgical treatment for breast cancer, or surgical pathology results for ALNs were not available; (iv) Unqualified SWE images (the whole quality map was coded red or yellow). The flowchart exhibiting the patient enrollment was shown in Fig. 1.

Conventional US and identifying TALN

Two board-certified radiologists (J.L and Y.N.H,) with at least 3 years of experience in breast ultrasound performed the conventional US (grey-scale and color

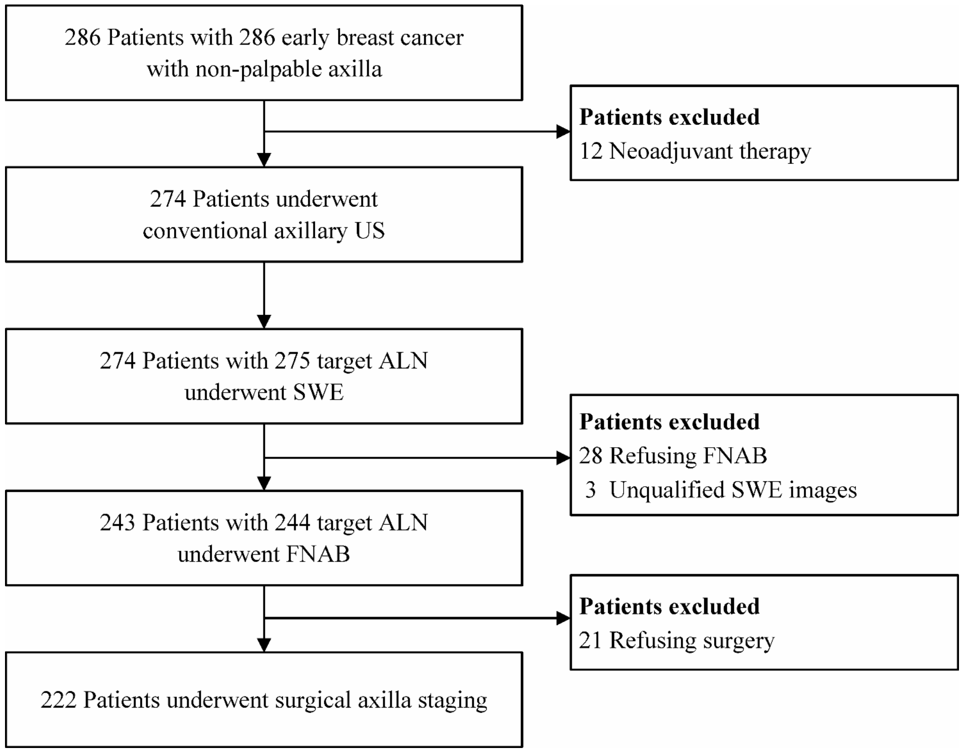

Fig. 1 The flowchart of patient recruitment

doppler) for axilla using a Siemens S2000 ultrasound machine (Siemens Healthcare, Mountain View, California) equipped with a 9L4 linear array transducer.

Axillary conventional US was performed firstly to screen the ALNs and obtained the images of all suspicious ALNs. The ALNs that met any of the following criteria were considered suspicious [21]: (i) Diffuse or eccentric cortical thickening (>3 mm), or focal cortical bulge. (ii) Rounded hypoechoic node. (iii) Complete or partial effacement of the fatty hilum. (iv) Non-hilum Blood Flow (NHBF) on color Doppler images. (v) Complete or partial replacement of the node with an ill-defined or irregular mass. (vi) Microcalcifications in the node. Only one TALN was selected from the ipsilateral axillary lymph nodes of each patient. The TALN was determined based on the morphological features observed on grey-scale US. The node that was completely or partially replaced by the ill-defined or irregular masses was prioritized as the target ALN. If no such masses were present, a rounded hypoechoic node was considered, followed by the node with the thickest cortex. If the patient had no suspicious ALN, the ALN with a comparatively thick cortex was determined as TALN [22]. All suspicious ipsilateral TALNs' features for each patient were recorded for analysis, including long and short diameter, Long/Short diameter ratio, cortical thickness.

Quantitative shear wave elastography

After conventional US, the same radiologist obtained shear wave elastography images using a Siemens S2000 ultrasound machine (Siemens Healthcare, Mountain View, California) equipped with a 9L4 linear array transducer for TALN before FNAB. The Virtual Touch Tissue Imaging and Quantification (VTIQ) with the high-quality control and perfect reproducibility is used to measure shear wave velocity (SWV) in ALNs [23].

The measurement depth of VTIQ was set to be less than 30 mm. This is because the shear wave signal measured at a depth exceeding 30 mm is prone to attenuation and may result in unreliable measurements [24]. At the beginning of ARFI, the patients were told to hold the breath for 3–5 s. The quality map, which was displayed in green-yellow-red representing high-intermediate-low quality, respectively, was obtained to guide the SWV measurement. Intermediate- and low-quality areas were avoided for the measurement of SWV. For each node, at least five regions of interest (ROIs) (2×2 mm) were placed on the most suspicious areas of ALN to measure SWVs, such as thickened or focally bulged cortex and hypoechoic areas in an irregular mass. The VTIQ was performed twice for each TALN. A detailed introduction to the calculation of quantitative SWE parameters provided in the Supplementary Information. There were two combination methods of US and SWE: (i) UE_{or}: ALN was considered as suspicious if either the result of conventional US or SWE was positive. (ii) UE_{and}: ALN was considered as suspicious if both the results of conventional US and SWE were positive.

FNAB procedures

All FNAB procedures were performed by one radiologist (J.L) with at least 10 years of experience in interventional US. Each TALN enrolled underwent FNAB against the TALN cortex guided by grey-scale US. The 23-gauge needles were used to obtain the sample from suspicious TALN area with SWE measurements: (1) FNAB of positive US TALNs was regarded as US-guided biopsy. (2) FNAB of positive SWE TALNs was regarded as SWE-guided biopsy. (3) FNAB of positive US and SWE TALNs was regarded as UE_{and}-guided biopsy. (4) FNAB of positive US or positive TALNs was regarded as UE_{or}-guided biopsy. In order to obtain enough cells for diagnosis, each TALN was punctured twice on average and placed directly into the CytoLyt solution. In our study, when lymph node cytology revealed metastatic involvement, the FNAB result was deemed positive.

Clinicopathological information

All patients underwent breast conserving surgery ($n=19$) or mastectomy ($n=204$). Histopathological diagnosis of ALN confirmed via SLNB or ALND was considered as the gold standard [25]. Clinical data including age, clinical T stage and tumor location were recorded. Pathological data including Ki67 index, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2) status, lymphovascular invasion, histologic type and histologic grade were also obtained from the pathology results of breast surgery.

Statistical analysis

The statistical analyses were performed using SPSS software (V.26.0) and MedCalc software (V.11.2). All continuous variables following normal distribution were presented as mean±standard deviation and all variables not following normal distribution were described as median (interquartile range [IQR]). All categorical variables were described by number and frequency. Using T test to compare the continuous variables following normal distribution between the metastatic and non-metastatic groups, using Mann-whitney U test to compare the continuous variables not following normal distribution between the two groups, and using Chi-square test to compare the categorical variables between the two groups. Using surgical axillary staging as the reference standard, Youden's method was used to determine the optimal cutoff points. The diagnostic performance of different methods was evaluated using AUC, sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV). DeLong test was used to compare the difference between AUCs. The univariate and multivariable logistic regression analysis was performed to find the independent predictors

Table 1 Clinical and pathological characteristics of 223 lesions in 222 breast cancer patients

Characteristics	Number of patients or lesions (%)
Age	
< 40 years old	38(17.12)
≥ 40 years old	184(82.88)
Tumor location	
Left	124(55.86)
Right	97(43.69)
Bilateral	1(0.45)
Clinical T stage	
T1	94(42.15)
T2	129(57.85)
Histologic type	
Invasive ductal carcinoma	193(86.55)
Invasive lobular carcinoma	4(1.79)
Others	26(11.66)
ALN status	
Metastatic	100(44.84)
Non-metastatic	123(55.16)
ER status	
Negative	59(26.46)
Positive	163(73.09)
Not available	1(0.45)
PR status	
Negative	75(33.63)
Positive	147(65.92)
Not available	1(0.45)
HER2 status	
Negative	143(64.13)
Positive	77(34.53)
Not available	3(1.34)
Ki-67	
≥ 14%	199(89.24)
< 14%	24(10.76)
Axillary surgery	
SLNB	97(43.50)
ALND	126(56.50)
Lymphovascular invasion	
Present	74(33.18)
Absent	127(56.95)
Not available	22(9.87)
Histologic grade	
I	2(0.90)
II	96(43.05)
III	95(42.60)
Not available	30(13.45)

ALN: axillary lymph node; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor; The age and tumor location were described based on number and percentage of patients. The remaining clinical and pathological characteristics were described based on number and percentage of lesions

Table 2 Conventional US characteristics of benign and metastatic axillary lymph nodes

Characteristics	Benign (123)	Metastatic (100)	*p* Value
Cortical thickness (mm)	2.6 (1.5) *	4.5 (3.9)	< 0.001
Long-diameter (mm)	14.4 (9.8)	13.8 (8.6)	= 0.308
Short-diameter (mm)	6.2 (2.5)	8.0 (4.6)	< 0.001
Short / Long diameter ratio	0.44 (0.22)	0.57 (0.25)	< 0.001
Hilum			< 0.001
Present	117 (95.12%)	57 (57.00%)	
Absent	6 (4.88%)	43 (43.00%)	
Blood Flow			< 0.001
Non- or Normal	116 (94.31%)	54 (54.00%)	
NHBF	7 (5.69%)	46 (46.00%)	

* median (interquartile range [IQR]); US: Ultrasound; NHBF: Non-hilum Blood Flow

Table 3 Diagnostic performance of conventional US, SWE, UE_{and}, and UE_{or} in predicting ALN status

Method	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	AUC
US	78.00 [68.61–85.67]	60.98 [51.77–69.64]	61.90 [56.00–67.47]	77.32 [69.66–83.50]	68.61	0.69 [0.63–0.75]
SWE	65.00 [54.82–74.27]	66.67 [57.60–74.91]	61.32 [54.30–67.90]	70.09 [63.56–75.88]	65.92	0.66 [0.59–0.72]
UE_{and}	57.00 [46.71–66.86]	85.37 [77.86–91.09]	76.00 [66.67–83.37]	70.95 [65.83–75.58]	72.65	0.71 [0.65–0.77]
UE_{or}	86.00 [77.63–92.13]	42.28 [33.42–51.51]	54.78 [50.52–58.96]	79.45 [68.66–86.30]	61.89	0.64 [0.57–0.70]

US: ultrasound; SWE: shear wave elastography; UE_{or}: US positive or SWE positive; UE_{and}: US positive and SWE positive; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristic curve

Data in brackets are the 95% confidence intervals

of axillary burden. All statistics were two sided and the p values < 0.05 was considered statistically significant.

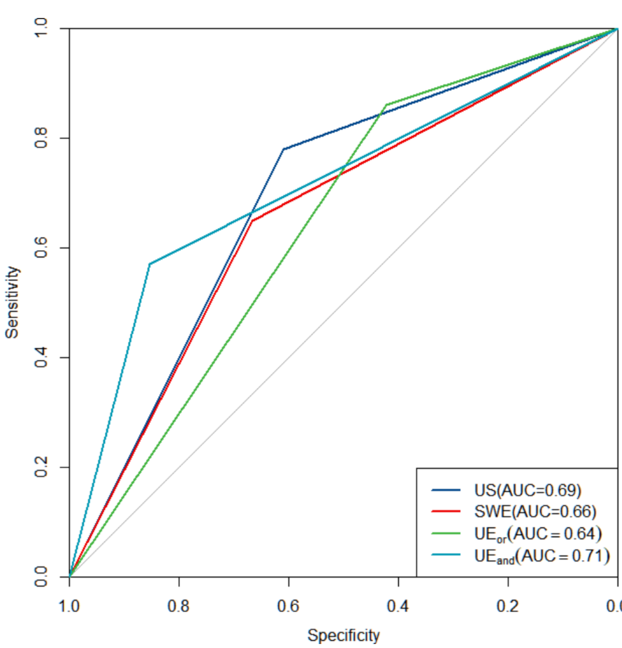

Fig. 2 The receiver operating characteristic (ROC) curve for using conventional US, SWE, UE_{and}, and UE_{or} in predicting ALN (axillary lymph node) status

Results

Study population

From January 2018 to December 2021, 286 female patients were included in this study, of whom 64 were excluded. At last, a total of 222 patients aged from 23 to 78 (Median, 50; IQR, 14) years old with 223 target ALNs were eligible for this study, of whom one had bilateral breast cancer. According to the surgical histopathology results, 44.84% (n = 100) of ALNs were metastatic, whereas 55.16% (n = 123) were benign. Of metastatic axilla, 53 were with less than 3 metastatic ALNs and 47 were with 3 or more metastatic ALNs. Table 1 details clinical and pathological characteristics of the patients and lesions.

The performance of axillary conventional US, SWE and conventional US combined with SWE

The Conventional US characteristics of benign and metastatic ALNs were shown in Table 2. The performance of Conventional US, SWE, and Conventional US combined with SWE were shown in Table 3; Fig. 2.

False negative rates (FNR) ranging from 35 to 44% in diagnosing ALN metastasis using different SWE parameters. Among all parameters, SWVmax with a cut-off value of 2.46 m/s had the superior sensitivity (65%) and lowest FNR (35%), which was chosen to be the performance of SWE (Fig. 3). The diagnostic performance of

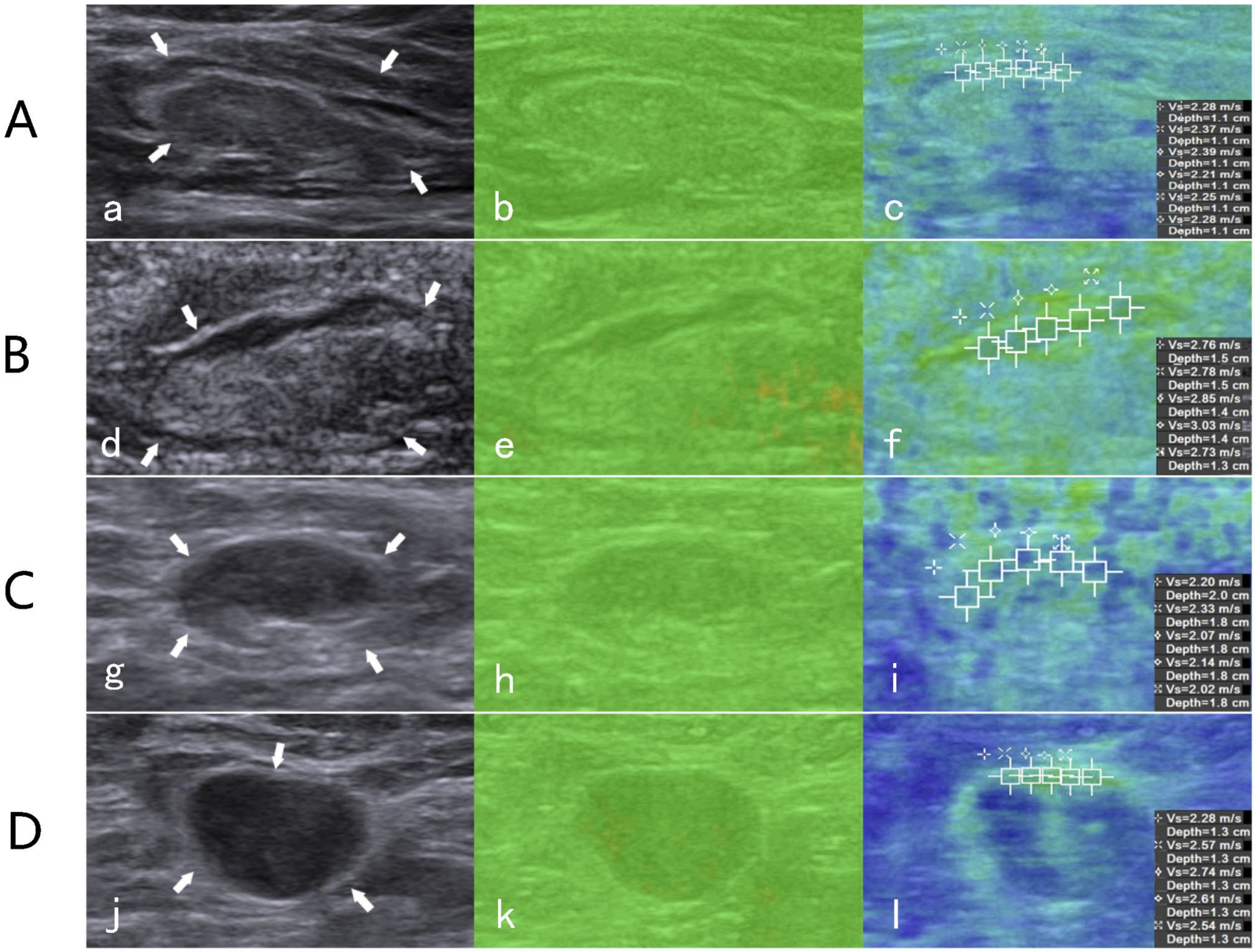

Fig. 3 A 49-year-old patients with breast carcinoma. **a** Conventional US image of negative ALN with normal cortex (1.2 mm) and hyperechoic hilum. **b** Quality map of quantitative SWE. **c** Velocity map of quantitative SWE, and SWVmax is negative as 2.37 m/s. Fine needle aspiration biopsy and surgical pathology of the node revealed benign ALN. **B** 56-year-old patients with breast carcinoma. **d** Conventional US image of negative ALN with normal cortex (2.6 mm) and hyperechoic hilum. **e** Quality map of quantitative SWE. **f** Velocity map of quantitative SWE, and SWVmax is suspicious as 2.80 m/s. Fine needle aspiration biopsy and surgical pathology of the node revealed metastatic ALN. **C** 59-year-old patients with breast carcinoma. **g** Conventional US image of suspicious ALN with diffuse cortical thickening and eccentric hilum. **h** Quality map of quantitative SWE. **i** Velocity map of quantitative SWE, and SWVmax is negative as 2.37 m/s. Fine needle aspiration biopsy and surgical pathology of the node revealed benign ALN. **D** 51-year-old patients with breast carcinoma. **j** Conventional US image of suspicious ALN with a rounded hypoechoic node. **k** Quality map of quantitative SWE. **l** Velocity map of quantitative SWE, and SWVmax is suspicious as 2.56 m/s. Fine needle aspiration biopsy and surgical pathology of the node revealed metastatic ALN

SWE parameters in evaluating the ALN status with reference to surgical staging was shown in the Supplementary Table.

Two different combination methods of US and SWE were used to explore the diagnostic performance for metastatic ALNs, which were defined as UE_{or} and UE_{and}. The method of UE_{or} showed the highest sensitivity compared with conventional US alone (86.00% vs. 78.00%, $p<0.001$), SWE alone (86.00% vs. 65.00%, $p<0.001$) and the method of UE_{and} (86.00% vs. 57.00%, $p<0.001$), while the UE_{and} showed the highest specificity among the conventional US alone (85.37% vs. 60.98%, $p<0.001$), SWE alone (85.37% vs. 66.67%, $p<0.001$) and method of UE_{or} (85.37% vs. 42.28%, $p<0.001$).

The performance of FNAB in different sub-populations

The performance of FNAB in different sub-populations were shown in Table 4. FNAB achieved superior performance (accuracy>90%) in the US+, US+SWE+and SWE+sub-population. In the US- SWE- sub-population, FNAB showed lowest sensitivity (7.14%) and highest specificity (100%).

The performance of different methods to guide FNAB of axilla and FNR

The performance of different methods to guide FNAB was shown in Table 5; Fig. 4. The AUC of the UE_{or}-guided FNAB [0.85 (95% CI, 0.80–0.90)] was significantly higher than that of US-guided FNAB [0.83 (95% CI, 0.78–0.88),

Table 4 The performance of FNAB in different sub-populations

Sub-populations	*n*	Sensitivity % (No. of cases)	Specificity % (No. of cases)	PPV % (No. of cases)	NPV % (No. of cases)	Accuracy %
ALL	223	73.00(73/100)	98.37(121/123)	97.33(73/75)	81.76(121/148)	87.00
US +	126	87.18 (68/78)	95.83 (46/48)	97.14 (68/70)	82.14 (46/56)	90.48
US + SWE +	75	96.49 (55/57)	88.89 (16/18)	96.49 (55/57)	88.89 (16/18)	94.67
US + SWE –	51	61.90 (13/21)	100.00 (30/30)	100.00 (13/13)	78.94 (30/38)	84.31
US –	97	22.73 (5/22)	100.00 (75/75)	100.00 (5/5)	81.52 (75/92)	82.47
US – SWE +	31	50.00 (4/8)	100.00 (23/23)	100.00 (4/4)	85.18 (23/27)	87.10
US – SWE –	66	7.14 (1/14)	100.00 (52/52)	100.00 (1/1)	80.00 (52/65)	80.30
SWE +	106	90.77 (59/65)	95.12 (39/41)	96.72 (59/61)	86.67 (39/45)	92.45

FNAB: Fine-needle aspiration biopsy; US: ultrasound; SWE: shear wave elastography; PPV: positive predictive value; NPV: negative predictive value; +: positive; –: negative; Data in brackets are present as the number of FNAB/ Surgery cases

$p=0.042$], SWE-guided FNAB [0.79 (95% CI, 0.73–0.84), $p=0.001$], and UE_{and}-guided FNAB [0.77 (95% CI, 0.71–0.82), $p<0.001$]. The FNR of the UE_{or}-guided FNAB was lowest with a value of 28.00%, and the FNR of US-guided FNAB, SWE-guided FNAB and UE_{and}-guided FNAB were 32.00%, 41.00% and 45.00%, respectively. Four patients were detected by the UE_{or}-guided FNAB but missed by the method of US-guided FNAB, 3 of whom had high burden disease (≥3 lymph node metastases).

Preliminary exploration of independent predictors of axillary burden in early breast cancer patients

The univariate and multivariate logistic regression analyses based on clinical and ultrasound characteristics were performed to explore the independent predictors of axillary burden in early breast cancer patients. As shown in Table 6, clinical T stage (T2, $p=0.011$), the number of suspicious ALNs (>2, $p<0.001$), SWE (>2.46 m/s, $p<0.001$), positive FNAB ($p<0.001$) and characteristics of TALN (short axis [>6.6 mm, $p<0.001$], Hilum [lymphatic hilum shifted or disappeared, $p<0.001$], Blood signal [mixed-blood flow or peripheral blood flow, $p<0.001$], Cortical thickness [>3.0 mm, $p<0.001$] were detected to be significantly associated with axillary burden. Furthermore, multivariable analysis showed that the enrolled patients with positive FNAB result (odds ratio [OR],36.034, 95% CI, 7.618-170.434; $p<0.001$) and more than 2 suspicious ALNs (odds ratio [OR],21.257, 95% CI, 4.584–93.082; $p<0.001$) were observed to be the independent factors of axillary burden.

Table 5 The performance of different modality-guided FNAB in predicting ALN status

Different modality-guided FNAB		Metastatic Axilla (*N* = 100)	Non-metastatic Axilla (*N* = 123)	AUC	Sensitivity %	Specificity %	PPV%	NPV%	Accuracy %
US-guided FNAB	Positive (*N* = 70)	68	2	0.83[a] [0.78–0.88]	68.00 [57.92–76.98]	98.37 [94.25–99.80]	97.14 [89.52–99.27]	79.08 [73.95–83.43]	84.75
	Negative (*N* = 153)	32	121						
SWE-guided FNAB	Positive (*N* = 61)	59	2	0.79[b] [0.72–0.84]	59.00 [48.71–68.74]	98.37 [94.25–99.80]	96.72 [88.08–99.16]	74.69 [69.97–78.89]	80.72
	Negative (*N* = 162)	41	121						
UE_{and}-guided FNAB	Positive (*N* = 57)	55	2	0.77[c] [0.71–0.82]	55.00 [44.73–64.97]	98.37 [94.25–99.80]	96.49 [87.30–99.10]	72.89 [68.38–76.98]	78.92
	Negative (*N* = 166)	45	121						
UE_{or}-guided FNAB	Positive (*N* = 74)	72	2	0.85 [0.80–0.90]	72.00 [62.13–80.52]	98.37 [94.25–99.80]	97.30 [90.06–99.31]	81.21 [75.92–85.55]	86.55
	Negative (*N* = 149)	28	121						

FNAB: Fine-needle aspiration biopsy; US: ultrasound; SWE: shear wave elastography; UE_{or}: US positive or SWE positive; UE_{and}: US positive and SWE positive; AUC: area under the receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value; +: positive; –: negative; Data in brackets are the 95% confidence intervals

[a] indicates $p=0.042$, Delong et al. in comparison with UE_{or}-guided FNAB

[b] indicates $p=0.001$, Delong et al. in comparison with UE_{or}-guided FNAB

[c] indicates $p<0.001$, Delong et al. in comparison with UE_{or}-guided FNAB

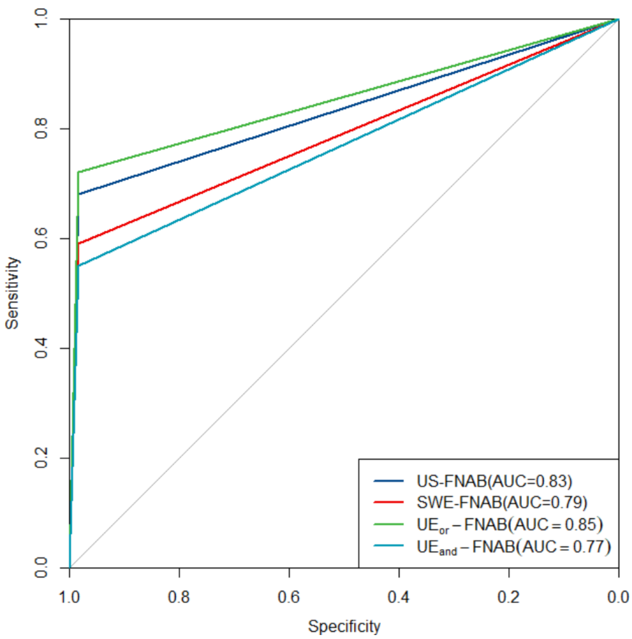

Fig. 4 The receiver operating characteristic (ROC) curve for using different modality-guided FNAB in predicting ALN (axillary lymph node) status

Discussion

Accurate identification of axillary lymph node (ALN) involvement before surgery will facilitate the management of axilla for early breast cancer. This study found that the combination method of UE_{or} (meets the diagnostic criteria of either US or SWE) achieved high sensitivity of 86.00% in diagnosing the ALN metastasis, which could be used to identify target ALN for FNAB with an AUC value of 0.85 with the lowest FNR (28.00%). Compared with conventional US-guided FNAB and SWE-guided FNAB, the UE_{or}-guided FNAB could detect more patients with metastatic ALNs. FNAB in the three sub-populations of US+, US+SWE+and SWE+demonstrated the favorable diagnostic performance.

Conventional US is widely used as the first-line imaging method to evaluate ALNs [26]. Nevertheless, it exhibits only modest performance, with AUCs ranging from 0.59–0.72 [27]. In this study, axillary US exhibited an AUC of 0.69 in detecting ALN involvement, aligning with findings from previous studies [28]. Moreover, conventional US demonstrated a sensitivity of 78%, slightly surpassing the previously reported range of 26–76% [29, 30].

Previous studies had shown that combining quantitative SWE with conventional US can enhance the diagnostic performance for metastatic ALNs [14, 31]. A previous study has shown that the combination method of US and SWE can improve the specificity compared to US alone (90.9% vs. 81.8%) at the expense of drop in sensitivity (65.8% vs. 73.7%) [12]. In this study, the combination method of UE_{and} (meets the both diagnostic criteria of US and SWE) exhibited high specificity (85.37%) but low sensitivity (57.00%) in diagnosing ALNs, potentially resulting in missed diagnoses for many patients. Conversely, the method of UE_{or} achieved superior sensitivity (86%) compared to US (78%), SWE (65%), and UE_{and} (57%), consistent with previous research [19, 32].

In the current clinical practice, conventional US-guided FNAB stands as a prevalent approach for ALN diagnosis before surgery [32]. Nonetheless, the moderate sensitivity of conventional US may result in a relatively elevated rate of false negatives during FNA guidance [33, 34]. A previous study has shown that the sensitivity and FNR of US-guided FNAB for detecting metastatic ALNs in early breast cancer were 45% and 55%, respectively [35]. In our study, the FNR of US-guided FNAB was still as high as 32%, resulting in underestimation of the stage in some patients before treatment.

In real-world scenario, FNAB should be performed in the ALN that detected by the method with the highest sensitivity and lowest FNR. Therefore, the UE_{or} with high sensitivity was more suitable for identifying TALN for FNAB. This study showed that the performance of UE_{or}-guided FNAB was superior to that of US-guided FNAB. The FNR of UE_{or}-guided FNAB (28%) was lower than that of US-guided FNAB (32%), and 3 patients with high burden disease was missed by US-guided FNAB but could be detected by UE_{or}-guided FNAB, suggesting that UE_{or}-guided FNAB could detect more patients with axillary lymph node metastasis to avoid down-stage before surgery, which could reduce unnecessary SLNB and shorten the waiting time for surgery.

We also investigated the accuracy of FNAB in different subgroups of diagnostic method and found that the US+, US+SWE+and SWE+sub-populations exhibited greater suitability for FNAB due to their high diagnostic performance. Conversely, the US-SWE- sub-population may not be as suitable for FNAB due to its the lower sensitivity (7.14%) in identifying the ALNM.

Certainly, our study has some limitations. First, because we did not perform any clip placement of the lymph nodes performing FNAB, it was difficult to match the target ALN to the lymph nodes cleared by surgical axillary staging. Second, SWE would prolong the examination time, and the reproducibility of elastography was limited due to the influence of patient respiration and operator experience. However, when both conventional US and SWE are applied for evaluating lesions, reproducibility of SWE is highly reliable for quantitative assessment [18]. Third, the method of UE_{or} guidance did result in an increase of nonessential FNAB, and the cost-effective analysis or clinical benefit of UE_{or} may need to be further studied, which will require a large and multi-centered data sample in the future to further assess clinical benefit and validate the authenticity of the results.

Table 6 Univariate and multivariate logistic analyses to determine the independent predictors associated with axillary burden

Characteristics	Cut-off value	Univariate logistic Regression		Multivariate logistic Regression	
		Odds Ratio (95% CI)	*p* value	Odds Ratio (95%CI)	*p* value
Age			0.055		
cT stage		2.544 (1.239–5.224)	0.011		0.315
Number of suspicious ALNs at US	≤ 2	1.0		1.0	
	> 2	27.623 (9.580-79.649)	< 0.001	21.257 (4.854–93.082)	< 0.001
SWE	≤ 2.46 m/s	1.0			0.558
	> 2.46 m/s	7.931 (3.495–17.995)	< 0.001		
FNAB	Negative	1.0		1.0	
	Positive	48.375 (16.203–144.430)	< 0.001	36.034 (7.618-170.434)	< 0.001
Characteristics of TALN					
Long axis	≤ 15.9 mm		0.734		
	> 15.9 mm				
Short axis	≤ 6.6 mm	1.0			0.182
	> 6.6 mm	5.820 (2.652–12.770)	< 0.001		
Cortical thickness	≤ 3.0 mm	1.0			0.664
	> 3.0 mm	11.312 (4.270-29.965)	< 0.001		
Blood flow	Non- or normal	1.0			0.240
	Peripheral or mixed	6.006 (2.980-12.108)	< 0.001		
Hilum	Normal	1.0			0.502
	Shift or disappear	6.303 (3.094–12.838)	< 0.001		

US: ultrasound; ALNs: axillary lymph nodes; TALN: target axillary lymph node; CI: confidence interval; SWE: shear wave elastography; FNAB: fine-needle aspiration biopsy

Conclusion

The combination method of UE_{or} showed a better sensitivity than US alone for diagnosing the ALNs metastasis. The application of UE_{or}-guided FNAB had a better diagnostic performance than US-guided alone with a lower FNR, which may facilitate the management of axillary lymph nodes for early breast cancer patients.

Abbreviations

ALN	Axillary lymph node
US	ultrasound
NCCN	National Comprehensive Cancer Network
SLNB	Sentinel lymph node biopsy
FNAB	Fine needle aspiration biopsy
ALND	Axillary lymph node dissection
SWE	Shear wave elastography
FNR	false-negative rate
AUC	receiver operating characteristic curve
NHBF	Non-hilum Blood Flow
VTIQ	Virtual touch tissue imaging quantification
ARFI	acoustic radiation force impulse
SWV	Shear wave velocity
ROIs	Regions of interest
ER	Estrogen receptors
PR	Progesterone receptors
HER2	Human epidermal growth factor receptor 2
IQR	Interquartile range
PPV	Positive predictive value
NPV	Negative predictive value

Supplementary Information

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Supplementary Material 1

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Author contributions

J.L. and ZM.X. designed the research project, collected and collated imaging data. X.L. and YN.H. read imaging, analyzed the data statistically and prepared the figures and wrote manuscript text. YL.W. and XY.Z. collected and collated clinical and surgical data. X.L. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
This prospective study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All patients signed informed consent for study participation and data collection.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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