Original Article

The value of the improved percutaneous and intravenous contrast-enhanced ultrasound diagnostic classification in sentinel lymph nodes of breast cancer

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Background: Metastatic burden of sentinel lymph node (SLN) in breast cancer patient is the basis for the decision to choose SLN biopsy or axillary lymph node dissection (ALND). However, the diagnostic performance of the previous percutaneous contrast-enhanced ultrasound (P-CEUS) and intravenous contrast-enhanced ultrasound (IV-CEUS) pattern were not satisfied. This study aimed to establish new classification based on structural characteristics for P-CEUS and IV-CEUS of SLN in breast cancer and evaluate the diagnostic efficacy.

Methods: This retrospective study included consecutive breast cancer patients who had not received neoadjuvant therapy in the First Affiliated Hospital of Sun Yat-sen University between June 2019 and December 2021. Conventional ultrasound, P-CEUS and IV-CEUS were performed. The new classification methods for P-CEUS and IV-CEUS of SLN were established based on structural characteristics of SLN. Pathology was considered as the gold standard, the diagnostic efficacy of P-CEUS, IV-CEUS and combined contrast-enhanced ultrasound in SLNs was analyzed.

Results: The detection rate of SLN by P-CEUS in 368 patients was 95.42%. The P-CEUS pattern of SLNs was divided into six types. The IV-CEUS sequence was divided into three types. The IV-CEUS mode was divided into four types. Among the 438 SLNs detected by P-CEUS, 105 (23.97%) were malignant and 333 (76.03%) were benign. Among the previously classified P-CEUS, P-CEUS, IV-CEUS and combined contrast-enhanced ultrasound, the latter had the highest diagnostic efficacy ($P<0.05$), with sensitivity, specificity, positive predictive value, negative predictive value, accuracy and area under curve (AUC) of 81.90% (86/105), 97.30% (324/333), 90.53% (86/95), 94.46% (324/343), 93.61% (410/438) and 0.896 (0.864–0.923), respectively.

Conclusions: The new classification of the P-CEUS and IV-CEUS features of SLNs was performed based on structural characteristics of lymph nodes. Compared with the previously classified P-CEUS, the new

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classification method has higher diagnostic performance. The combination of new classified P-CEUS and IV-CEUS is helpful to further improve the diagnostic performance of SLNs.

Keywords: Breast cancer; ultrasound; contrast media; sentinel lymph node (SLN)

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Introduction

Breast cancer is one of the most common malignant tumors in women worldwide (1). Axillary lymph node (ALN) status is an important prognostic factor for breast cancer and it contributes to clinical treatment decisions (2,3). Sentinel lymph nodes (SLNs) are the initial metastatic sites, and cancer cells may bypass the SLNs and enter the vascular channels directly to spread to the systemic sites (4). Breast cancer patients following with further radiotherapy and systemic treatment can be exempted from axillary lymph node dissection (ALND) without increasing the risk of locoregional recurrence and decreasing disease-free survival, if sentinel lymph node biopsy (SLNB) shows two or fewer metastatic SLN (5). SLNB has replaced ALND as the preferred therapy for treating early-stage breast cancer with two or less metastatic SLNs, providing adequate axillary node staging information with minimal morbidity, and it has become the treatment standard for breast cancer management (6-10).

SLN detection methods mainly include blue dye-guided method, radioisotope method, indocyanine green fluorescence imaging, and contrast-enhanced ultrasound (CEUS) (11-13). CEUS is performed preoperatively, while other methods are performed intraoperatively. Percutaneous contrast-enhanced ultrasound (P-CEUS) is a non-invasive method used for detecting SLN in breast cancer patients with high predictive efficiency (14,15). The status of SLN could be diagnosed with this technique by dividing the P-CEUS pattern into three types (16-19). Intravenous contrast-enhanced ultrasound (IV-CEUS) is also used to diagnose SLN according to the pattern of homogeneous enhancement and uniform regression, or non-uniform regression (20). However, the diagnostic performance of the previous P-CEUS and IV-CEUS pattern were not satisfied, may be due to the neglect of structural characteristics of lymph nodes. The pattern classification of contrast-enhanced ultrasound usually did not combine the structural characteristics of lymph nodes, and only classified the enhancement patterns of the whole lymph nodes.

In this study, the structure of lymph nodes was considered and a new evaluation system was constructed by subdividing the pattern of heterogeneous enhancement. The diagnostic efficiency of the new system was tested by comparing with the original system. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1210/rc).

Methods

Patients

This retrospective study included consecutive 537 female breast cancer patients in the First Affiliated Hospital of Sun Yat-sen University from June 2019 to December 2021. The inclusion criteria were: (I) patients with pathological breast cancer; (II) patients with conventional ultrasound, P-CEUS and IV-CEUS of SLNs before surgery or puncture; (III) patients underwent puncture or surgery to obtain the histopathological data of SLNs. Patients with history of performed radiotherapy or chemotherapy were excluded. Eventually, 368 patients were included (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [(2020)316] and informed consent was taken from all the patients.

Instruments and methods

The contrast-enhanced ultrasound instruments included Siemens ACUSON (10L4 linear array probe), Mindray Resona 7 (L9-3 linear array probe) and Philips iU22 (L9-3 linear array probe), and the microbubble continuous real-time contrast-enhanced ultrasound imaging mode under low mechanical index (MI <0.15) was adopted. The ultrasound contrast agent was a suspension prepared by

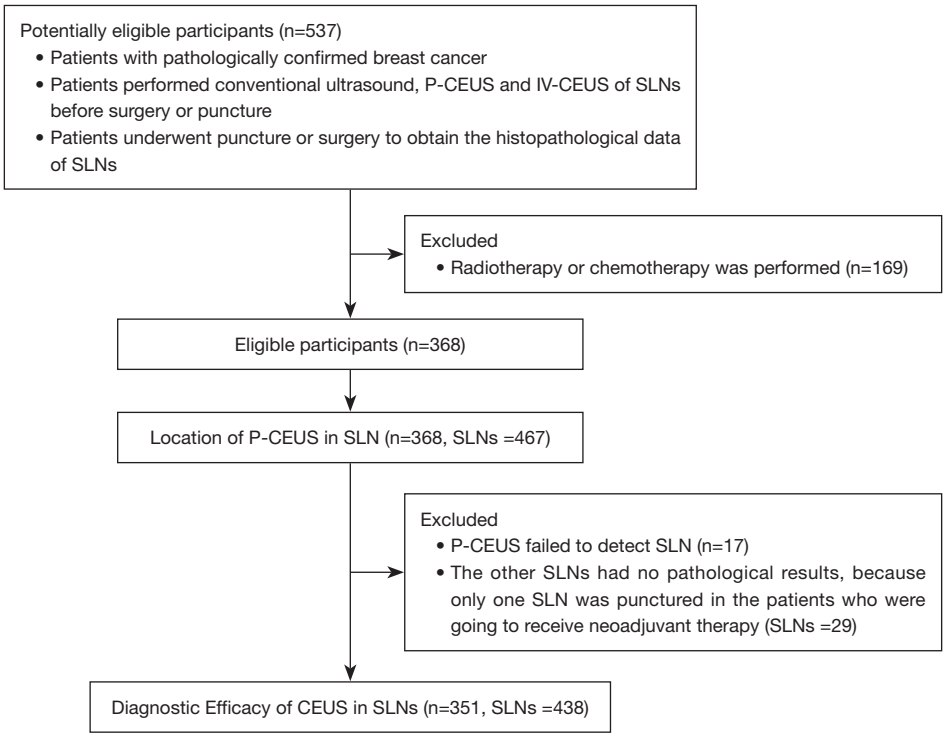


Figure 1 Flowchart of study subjects. P-CEUS, percutaneous contrast-enhanced ultrasound; IV-CEUS, intravenous contrast-enhanced ultrasound; SLN, sentinel lymph node; CEUS, contrast-enhanced ultrasound.

SonoVue (Bracco, Italy) lyophilized powder (59 mg sulfur hexafluoride microbubbles) and 5 mL normal saline, which had been shaken for 30 s for standby. The P-CEUS and IV-CEUS for SLN were commonly performed in our hospital. The ultrasound examination was performed by two physicians with more than 10 years of experience in CEUS. After approximately 20 cases, the physician became proficient in P-CEUS and IV-CEUS for SLN, reducing the scanning time from about 30 to 15 minutes. Physicians were unaware of the clinical information of the patients.

The patients lied in the supine position with the upper extremities abducted to fully expose the breast and axilla. After conventional ultrasound examination of the breast lesions and armpits of the patients, the skin was disinfected and 0.6–0.8 mL ultrasound contrast agent was injected into the upper abdomen around the affected side areola (*Figure 2A*). If the breast lesion was located in the nipple-areola complex, the contrast agent was injected away from the breast lesion. If the lymphatic vessel and SLN were not detected after a single injection, multi-point injection around the areola area was performed. Immediately after the injection of the contrast agent, the SLN was confirmed by observing the enhanced lymphatic drainage route. The lymphatic drainage route and SLNs on the skin surface were marked (*Figure 2B*). Then the SLN was observed under conventional ultrasound. After 2.4 mL ultrasound contrast agent was injected into the median elbow vein, the enhancement characteristics of SLN were observed. The number, size, cortical thickness, P-CEUS and IV-CEUS pattern of the SLNs were recorded.

Patients who planned to receive neoadjuvant therapy underwent SLN histological biopsy. For patients undergoing surgical treatment, 1 mL of 1% methylene blue solution was injected subcutaneously into the upper quadrant outside the areola area under general anesthesia during the operation (*Figure 2C*). After massaging the breast for 5–10 min, the blue stained lymphatics and blue stained SLNs were dissected at the marks on the body surface, and attention was paid to observe whether the blue stained lymphatics and blue stained lymph nodes were consistent with those marked by P-CEUS (*Figure 2D*). Blue stained lymph nodes were excised and sent to pathological examination. Micrometastases were defined as metastases of less than 2 mm (21).

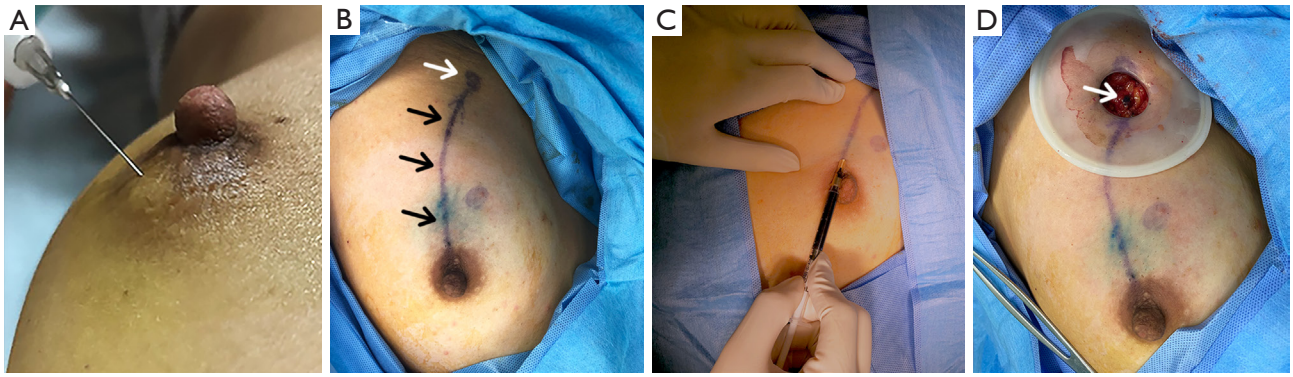


Figure 2 SLN location by percutaneous contrast-enhanced ultrasound and blue dye guided method. (A) Ultrasound contrast agent was injected into the upper outer quadrant of the affected side areola; (B) the lymphatic drainage pathway (black arrow) and sentinel lymph node (white arrow) were marked on the skin surface according to percutaneous contrast-enhanced ultrasound; (C) blue dye was injected in the upper outer quadrant of the ipsilateral areola; (D) sentinel lymph node marked by percutaneous contrast-enhanced ultrasound was consistent with the blue-stained lymph node shown by blue staining (white arrow). SLN, sentinel lymph node.

Statistical methods

Statistical software package SPSS 27.0 and Medcalc 19.5.6 were used in this study. If the localization mark of P-CEUS was consistent with blue dye, the P-CEUS localization mark of SLN and drainage lymphatic vessel was considered as correct. The status of SLN was based on pathological results. The receiver operating characteristic (ROC) curve was used to calculate the area under curve (AUC) of the diagnostic method. The diagnostic efficacy of the examination methods was compared with Delong test. The Cohen's kappa value was used to evaluate the consistency between observers and diagnostic methods. 0.6< AUC ≤0.8 was classified as good; 0.4< AUC ≤0.6 was classified as moderate. A two-sided P<0.05 was considered as a statistically significant difference.

Results

Participant characteristics

In this study, 368 female breast cancer patients were included, including three patients with bilateral breast cancer. The mean participant age was 51.1±11.2 years (age range was 25–86 years). The clinical characteristics of these patients are shown in *Table 1*. No patients experienced adverse reactions, such as allergies during the study.

Location of P-CEUS in SLNs

The detection rate was 95.42% (354 of 371) in the P-CEUS examination. Among these cases, four cases underwent suspicious lymph node puncture without blue staining, and the other 13 cases underwent blue staining, only 1 case of whom was not detected with blue-stained SLN. P-CEUS indicated that the average number of lymphatic vessels on each side was 1.23±0.53 (455/371), and the mean number of SLNs on each side was 1.26±0.71 (467/371) (*Table 1*). Only one SLN was punctured in the patients who were going to receive neoadjuvant therapy, and the other 29 SLNs had no pathological results. Thus, a total of 438 SLNs were included.

P-CEUS and IV-CEUS classification of SLN

P-CEUS pattern of SLNs was divided into six types (*Figures 3*,*4*):

- Type I: only part of the cortex was enhanced, others were non-enhanced, and the lymph node cortex was unevenly thickened;
- Type II: partial cortical filling defect;
- Type III: non-enhancement;
- Type IV: homogeneous high enhancement;
- Type V: diffuse inhomogeneous high enhancement;
- Type VIa: non/low enhancement of lymphatic hilus, homogeneous high enhancement of cortex;
- Type VIb: one half showed Type IV, V or VIa, and the other showed non-enhancement;
- Type VIc: only part of the cortex was enhanced, others were not enhanced, and lymph node cortex was evenly thickened.

Table 1 Participant characteristics and location of P-CEUS in SLNs

Parameter	Value
Age (years)	51.1±11.2
Histologic type	
Carcinoma *in situ*	34 (9.2)
Invasive breast carcinoma	336 (90.6)
Paget disease of the nipple	1 (0.3)
Pathological acquisition of lymph nodes	
Puncture	68 (18.3)
SLNB	249 (67.1%)
ALND	54 (14.6)
ALN status	
Positive	106 (28.6)
Negative	265 (71.4)
Lymphatic vessel (tracing by P-CEUS)	
0	8 (2.2)
1	282 (76.0)
2	71 (19.1)
3	9 (2.4)
4	1 (0.3)
SLN (tracing by P-CEUS)	
0	17 (4.6)
1	272 (73.3)
2	58 (15.6)
3	19 (5.1)
4	3 (0.8)
5	2 (0.5)
Total	371

Values are n (%) or mean ± standard deviation. P-CEUS, percutaneous contrast-enhanced ultrasound; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ALN, axillary lymph node.

- ❖ Type I–III were diagnosed as malignant lymph nodes, and Types IV–VI as benign lymph nodes.

IV-CEUS sequence was divided into three types based on the orders of bubbles entering the lymph nodes: centrifugal enhancement, centripetal enhancement and diffuse enhancement. IV-CEUS mode was divided into four modes (*Figure 5*): Type I: homogeneous high enhancement; Type II: diffuse inhomogeneous high enhancement; Type III: no/low enhancement of lymphatic hilus, homogeneous high enhancement of cortex; Type IV: part of the cortical filling defect, low enhancement or high enhancement, the rest showed the performance of Types I, II or III. Malignant lymph node was diagnosed as long as one of the following conditions was met: (I) centripetal enhancement; (II) diffuse enhancement; (III) the enhancement mode of IV-CEUS was type IV. SLN was diagnosed as malignant when P-CEUS and/or IV-CEUS diagnosed the SLN as malignant.

Diagnostic efficacy of CEUS in SLNs

Among the 438 SLNs, 105 (23.97%) were malignant and 333 (76.03%) were benign. Besides, skip metastasis was found in this study, four non-SLNs of two patients were malignant, while the SLNs located by P-CEUS and blue dye were non-metastatic.

The pathology and CEUS of 438 SLNs are shown in *Table 2*. There was excellent inter-observer consistency in P-CEUS, IV-CEUS enhancement sequence, and IV-CEUS pattern. The Kappa values were 0.884, 0.868, and 0.826, respectively (P<0.001).

The correspondence of P-CEUs and IV-CEUS of 438 SLNs are shown in *Table 3*. The McNemar test results showed that both methods were consistent in diagnosis (P=0.108), Kappa =0.812, P<0.001, indicating that both methods had good consistency in diagnosis results. Out of a total of 371 axillae, 261 axillae were free of lymph node metastases, of which 254 (97.32%) were negative for correctly diagnosed lymph node metastases, indicating that preoperative P-CEUS and IV-CEUS might potentially prevent unnecessary SLNB in patients without ALN metastasis.

The diagnostic performances of the previous classification of P-CEUS, P-CEUS, IV-CEUS and combined CEUS were compared (*Table 4*). The ROC curves of different diagnostic methods are shown in *Figure 6*. DeLong test results showed that the diagnostic performance of P-CEUS, IV-CEUS and combined CEUS was better than the previous classification of P-CEUS, respectively. There was no statistical difference in diagnostic performance between P-CEUS and IV-CEUS. The combined CEUS showed the best diagnostic performance. Surprisingly, the new combined CEUS pattern significantly increased the specificity and the accuracy than the previous

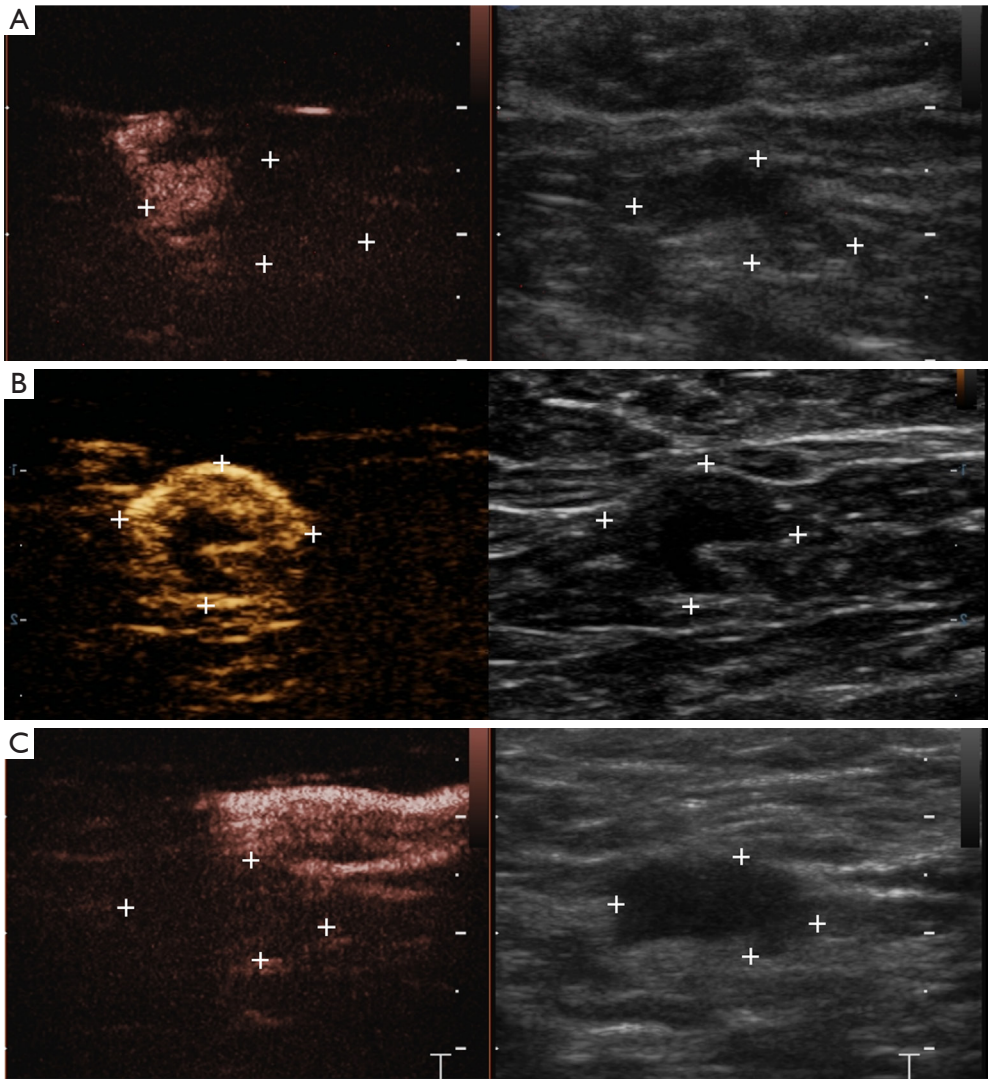
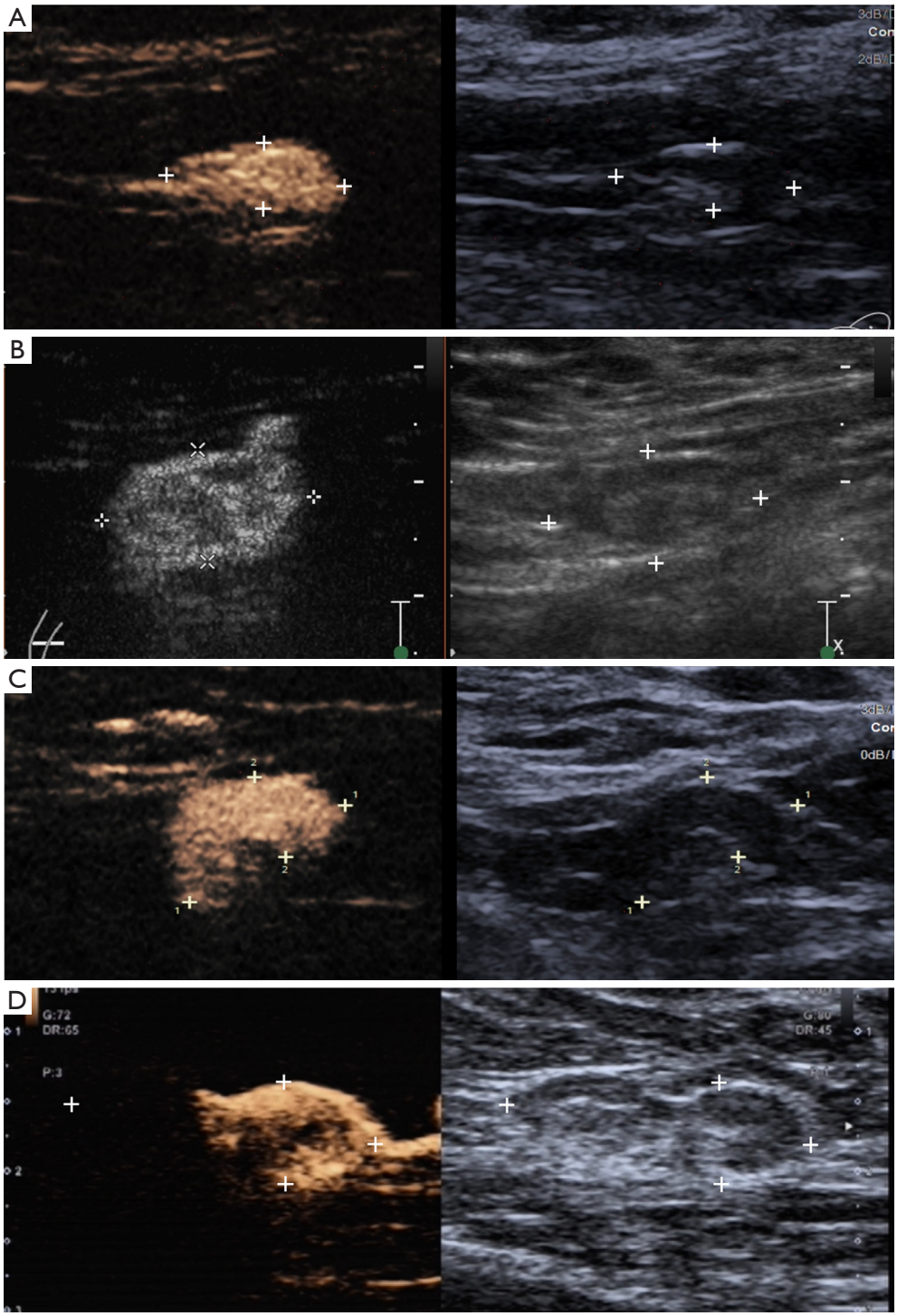


Figure 3 Different percutaneous contrast-enhanced ultrasound patterns of malignant lymph nodes are shown in the corresponding diagrams. (A) Type I: only part of the cortex was enhanced, others were non-enhanced, and the lymph node cortex was unevenly thickened; (B) Type II: partial cortical filling defect; (C) Type III: non-enhancement.

pattern, indicating that the structural characteristics of lymph node had significance in diagnosis.

Discussion

Accurate localization and assessment of SLN properties and ALN burden are critical for treatment decision-making and prognostic assessment in breast cancer patients. Failure of intraoperative SLN mapping indicates a significantly increased risk of breast cancer metastasis to the axillary lymphatic system (22,23). Different blue agent, injection volume, injection sites (injecting peri-tumorally, subareolarly, intradermally, subdermally) and waiting time might result in variations in the SLN detection rate of the blue dye method (11). When P-CEUS was performed, the injection points of contrast agent were mostly at 3, 6, 9, and 12 of the areola with SLN detection rate of 95.7–98.2% (16,17,19,20), or in the upper outer quadrant of the areola with SLN detection rate of 100% (24). In this study, only a single-point injection of contrast agent in the upper quadrant outside the areola region obtained a SLN detection rate of 95.42% with 17 cases failed to track



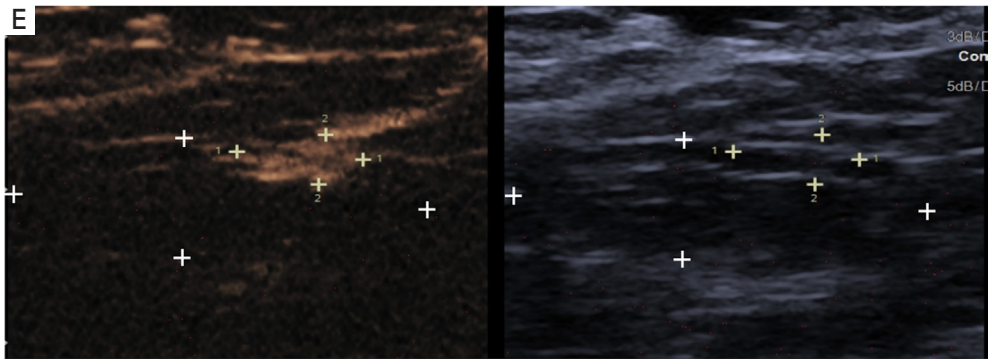


Figure 4 Different percutaneous contrast-enhanced ultrasound patterns of benign lymph nodes are shown in the corresponding diagrams. (A) Type IV: homogeneous high enhancement; (B) Type V: diffuse inhomogeneous high enhancement; (C) Type VIa: non/low enhancement of lymphatic hilus, homogeneous high enhancement of cortex; (D) Type VIb: one half showed Type IV, V or VIa, and the other showed non-enhancement; (E) Type VIc: only part of the cortex was enhanced, others were not enhanced, and lymph node cortex was evenly thickened.

SLNs. The lymphatic drainage pathway could be visualized with only one injection, which could reduce the patients' pain and simplify the operation process. Discontinuous lymphatic channel and non-enhanced SLN on CEUS might be a sign of SLN metastasis, in which case SLNB is not recommended (25). The failure to trace SLN in 17 cases might be related to stenosis and obstruction of the lymphatic channel. In this study, more SLNs were traced by blue staining than CEUS, which might be due to smaller tracer molecules and longer waiting time after injection. It is also difficult to distinguish SLNs from closely adjacent non-SLNs which could take up the blue dye, resulting in unnecessary resection of extensive lymph nodes (26,27). In this study, two patients had metastasis to four non-SLNs and non-metastatic SLNs (located by P-CEUS and blue staining). It was considered as skip metastasis or SLN connected to another lymphatic channel which was ignored in P-CEUS. This was one of the reasons for the false negative diagnosis of SLNs by P-CEUS.

P-CEUS could help diagnose the status of SLNs while locating SLNs (16-19). In previous studies, P-CEUS enhancement modes of SLNs were divided into three types, and there were great differences in diagnostic efficiency among them (16-19). In this study, the P-CEUS enhancement pattern of SLN was combined with corresponding structural characteristics and a total of six P-CEUS types was classified based on the variety of histological and pathological manifestations of SLNs. In previous studies, the P-CEUS patterns of SLN were often divided into three types: homogeneous enhancement, heterogeneous enhancement, and no enhancement (16-19). Where, homogeneous enhancement SLN was deemed as benign, and the latter two were diagnosed as malignant. In this study, it was also found that 93.12% of homogeneously enhanced SLNs were benign lymph nodes, and 95.83% of non-enhanced SLNs were malignant lymph nodes. However, in this study, the heterogeneously enhanced SLNs were divided into types I–II and types V–VI. Where, the P-CEUS manifestations of Type I–II were diagnosed as malignant SLN, and the diagnosis of Type V–VI was diagnosed as benign SLN. The results in this study showed that 88.24% of Type I and 85.71% of Type II SLN were malignant by pathology; 88.89% of Type V, 91.07% of Type VIa, 95.83% of Type VIb and 100.00% of Type VIc SLN were benign by pathology. Therefore, subdivision of SLNs showing heterogeneous enhancement by P-CEUS could help to more accurately diagnose the nature of SLNs. Compared with the previous three-type classification, the large gap in diagnostic performance might be related to differences between different observers and different populations included in the study.

Benign lymph nodes with heterogeneous enhancement on P-CEUS might be associated with intralymphatic fibrofatty tissues or might be due to relatively little contrast media access to sentinel nodes. Human lymph nodes begin to degenerate after puberty, with signs of adipocyte accumulation and fibrosis in degenerative lymph nodes (28). In conventional ultrasound, the involutional lymph nodes are slightly hyperechoic fatty, fibrous connective tissue near the lymphatic hilum, and hypoechoic lymphoid tissue near the cortex. For lymph nodes with only partial cortical enhancement, i.e., Type I and Type VIc on P-CEUS, it is

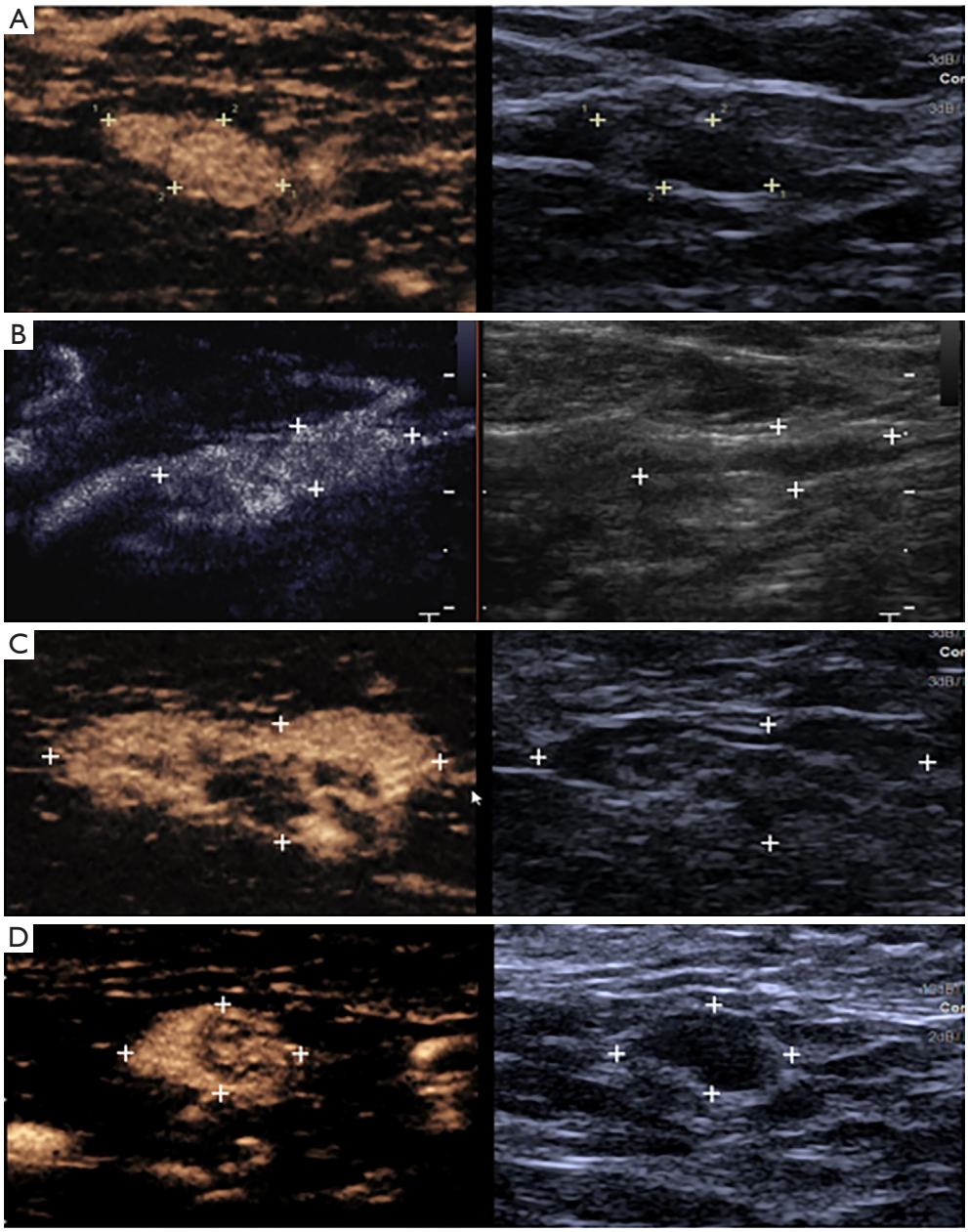


Figure 5 Different types of intravenous contrast-enhanced ultrasound patterns are shown in the corresponding diagrams. (A) Type I: homogeneous high enhancement; (B) Type II: diffuse inhomogeneous high enhancement; (C) Type III: no/low enhancement of lymphatic hilus, homogeneous high enhancement of cortex; (D) Type IV: part of the cortical filling defect, low enhancement or high enhancement, the rest showed the performance of Types I, II or III.

necessary to distinguish whether the lymph node cortex is unevenly thickened. Malignant SLN manifested as P-CEUS Type I–III might be related to cancer cells invading lymph nodes; the tumor tissue continues to grow, and gradually occupies the SLN. Tumor cells can enter the lymphatics using a chemokine gradient as a guide, either through the intercellular space between endothelial cell junctions, or possibly by inducing larger discontinuities in the endothelial cell layer, into the lymphatics, and through the afferent lymphatics lymph nodes (29,30). Cancer cells first seed in

Table 2 CEUS and pathology of SLN

Diagnostic method	Pathology		Total
	Malignant	Benign	
P-CEUS			
Type I	17 (89.47%)	2 (10.53%)	19
Type II	39 (88.64%)	5 (11.36%)	44
Type III	23 (95.83%)	1 (4.17%)	24
Type IV	15 (6.88%)	203 (93.12%)	218
Type V	3 (18.75%)	13 (81.25%)	16
Type VIa	5 (7.58%)	61 (92.42%)	66
Type VIb	1 (2.56%)	38 (97.44%)	39
Type VIc	2 (16.67%)	10 (83.33%)	12
IV-CEUS enhancement sequence			
Centrifugal	34 (9.37%)	329 (90.63%)	363
Centripetal	13 (100.00%)	0 (0.00%)	13
Diffuse	58 (93.55%)	4 (6.45%)	62
IV-CEUS pattern			
Type I	68 (20.67%)	261 (79.33%)	329
Type II	9 (47.37%)	10 (52.63%)	19
Type III	14 (18.67%)	61 (81.33%)	75
Type IV	14 (93.33%)	1 (6.67%)	15
IV-CEUS diagnosis			
Malignant	73 (93.59%)	5 (6.41%)	78
Benign	32 (8.89%)	328 (91.11%)	360
Combined CEUS			
Malignant	86 (90.53%)	9 (9.47%)	95
Benign	19 (5.54%)	324 (94.46%)	343
Total	105	333	438

Values are n or n (%). Combined CEUS, combined percutaneous and intravenous contrast-enhanced ultrasound; SLN, sentinel lymph node; P-CEUS, percutaneous contrast-enhanced ultrasound; IV-CEUS, intravenous contrast-enhanced ultrasound.

Table 3 P-CEUS and IV-CEUS diagnosis of SLN

P-CEUS	IV-CEUS		Total
	Malignant	Benign	
Malignant	69	17	86
Benign	8	344	352
Total	77	361	438

P-CEUS, percutaneous contrast-enhanced ultrasound; IV-CEUS, intravenous contrast-enhanced ultrasound; SLN, sentinel lymph node.

the medulla and/or marginal sinus of lymph nodes through the afferent lymphatic vessels to form micrometastases with a diameter of less than 2 mm (31). Micrometastases are more difficult to be identified than macrometastases when performing P-CEUS (32). This is one of the reasons for false negatives. Due to the invasive procedure performed on the patient, reactive hyperplasia of axillary lymph nodes might be resulted, resulting in thickening of the nodal cortex. P-CEUS at this time could help differentiate cortical thickening from tumor growth in the malignant SLNs.

Table 4 Comparison of diagnostic efficacy of different diagnostic methods for SLN

Diagnostic method	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	AUC (95% CI)
Previous classification of P-CEUS	85.71%	60.96%	40.91%	93.12%	66.89%	0.733 (0.689-0.774)
P-CEUS	75.24%	97.60%	90.80%	92.59%	92.24%	0.864 (0.828-0.895)
IV-CEUS	69.52%	98.50%	93.59%	91.11%	91.55%	0.840 (0.802-0.873)
Combined CEUS	81.90%	97.30%	90.53%	94.46%	93.61%	0.896 (0.864-0.923)

SLN, sentinel lymph node; AUC, area under curve; CI, confidence interval; P-CEUS, percutaneous contrast-enhanced ultrasound; IV-CEUS, intravenous contrast-enhanced ultrasound; Combined CEUS, combined percutaneous and intravenous contrast-enhanced ultrasound.

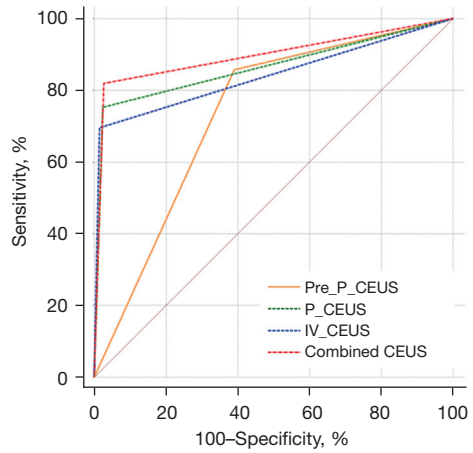


Figure 6 ROC curves of different diagnostic methods. Pre-P-CEUS, previous classification of percutaneous contrast-enhanced ultrasound; P-CEUS, percutaneous contrast-enhanced ultrasound; IV-CEUS, intravenous contrast-enhanced ultrasound; Combined CEUS, combined percutaneous and intravenous contrast-enhanced ultrasound; ROC, receiver operating characteristic.

P-CEUS could reflect the lymphatic drainage of lymph nodes, while IV-CEUS could reflect the blood supply of SLN. When lymph node metastasis occurs, the metastatic tumor tissue destroys the normal lymphatic drainage pathway, and its blood supply might be different from that of normal lymphoid tissue according to the pathological type and progression of the disease. The blood supply of early metastatic lymph nodes dose not change significantly, and the diagnostic sensitivity is poor. Different from previous study (20), this study presented a new classification of IV-CEUS enhancement order and patterns for SLNs. For malignant lymph nodes, the IV-CEUS enhancement sequence of lymph nodes was non-centrifugal due to the presence of blood supply to the metastatic tumor tissue. In Type IV SLNs, the enhancement degree of part of the cortex was inconsistent with the surrounding cortex, and the blood supply of the metastatic tumor tissue was considered as being inconsistent with the surrounding normal lymph node tissue. Combining P-CEUS and IV-CEUS, while maintaining high specificity, positive predictive value, negative predictive value and accuracy, the sensitivity could reach 81.90%. Both types of angiography could provide effective information for accurate diagnosis of SLN properties from the two aspects of lymphatic drainage and blood supply characteristics.

This study was a single-center study, which might have selection bias. When the SLN is too small, it is more difficult to accurately judge the CEUS classification, but the classification criteria for CEUS enhancement patterns of SLNs of different sizes were consistent. In addition to the possibility of skip metastasis, the reasons for false negatives in the study included the very small size of metastases in malignant lymph nodes and overlapping enhancement patterns of benign and malignant lymph nodes. Therefore, how to more effectively diagnose breast cancer SLN remains to be further studied.

Conclusions

The new classification of the P-CEUS and IV-CEUS features of SLNs was performed based on structural characteristics of lymph nodes. Compared with the previous classification method of P-CEUS, the new classification method has higher diagnostic performance. The combination of P-CEUS and IV-CEUS is helpful to further improve the diagnostic performance of SLN.

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Footnote

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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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [(2020)316] and informed consent was taken from all the patients.

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