# Association and predictive value of contrast-enhanced ultrasound features with axillary lymph node metastasis in primary breast cancer

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**Abstract.** Primary breast cancer is the most common malignant tumor in women worldwide, and axillary lymph node metastasis (ALNM) is an important marker of disease progression in patients with breast cancer. The objective of the present study was to analyze the association between contrast-enhanced ultrasound (CEUS) features and ALNM in primary breast cancer and its predictive value. A total of 120 patients with breast cancer were assigned to the non-metastatic group (n=70) and metastatic group (n=50). The factors influencing ALNM were explored by multivariate logistic regression analysis. The consistency of CEUS, ordinary ultrasonography and pathological examination in the diagnosis of the ALNM of breast cancer was evaluated by consistency testing. The sensitivity, specificity and consistency rate of CEUS features and ordinary ultrasonography were analyzed by receiver operating characteristic curve and four-fold table analyses. High enhancement amplitude, centripetal enhancement sequence, increased maximum cortical thickness, high peak intensity and a larger area under the curve of lymph nodes were more commonly found in the metastatic group than in the non-metastatic group. The lymph node aspect ratio and time to peak were lower in the metastatic group than the non-metastatic group. The time to peak was a protective factor for ALNM in patients with breast cancer. The sensitivity, specificity and coincidence rate with pathological examination of CEUS in the diagnosis of ALNM were 92.00, 90.00 and 90.83%, while these of ordinary ultrasonography were 76.00, 80.00 and 78.33%, respectively. The consistency test indicated that CEUS and pathological examination were consistent in the diagnosis of ALNM in patients with breast cancer, with a κ value of 0.816, indicating a good consistency. The κ value of ordinary ultrasonography and pathological examination was 0.763, also indicating a good consistency. However, these results indicate that CEUS is more valuable than ordinary ultrasonography in the diagnosis of ALNM in cases of breast cancer. In conclusion, the present study indicates that CEUS features were influencing factors associated with ALNM in patients with breast cancer and may serve as an important reference for the preoperative prediction of ALNM in breast cancer.

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*Key words:* ultrasonographic sonographic features, primary breast cancer, axillary lymph node metastasis, correlation, predictive value

## Introduction

Breast cancer is a malignant tumor that occurs in the epithelial tissue of the breast gland, and its incidence rate accounts for 7-10% of all types of malignant tumors (1). Breast cancer mainly manifests as a painless movable lump in the breast with an unclear boundary. Most patients have no pain, a dull pain or only mild discomfort, and some experience nipple discharge. At present, the etiology of breast cancer is not clear, but it has been suggested to be associated with viruses, genetics and sex hormones (2). As the pressures and pace of life have increased, the number of patients diagnosed with breast cancer has risen yearly, and an increase in the incidence of breast cancer has been observed among patients in younger age groups (3). Early breast cancer is curable through surgery, and the five-year survival rate after treatment can reach ~90%. However, for patients with advanced breast cancer, the five-year survival rate is only ~20% with an overall median survival time of 2-3 years (4).

Axillary lymph nodes are one of the main sites to which breast cancer metastasizes. The condition of the axillary lymph nodes is of great importance to patients when breast cancer is first diagnosed, as it is an important reference standard for the evaluation and determination of treatment strategies, and a key indicator for the evaluation of patient prognosis (5). At present, the main method used for the clinical diagnosis of breast

cancer is imaging. Ordinary ultrasonography evaluates lymph node size, morphology, lymph hilum status, cortical thickness and blood flow to evaluate the axillary lymph node metastasis (ALNM) of breast cancer. Contrast-enhanced ultrasound (CEUS), as a more novel clinical imaging method, has the advantages of non-invasiveness and high accuracy. It is able to evaluate the shape, growth direction, internal structure and edge of lesions from multiple levels and directions, and determine the location and density of blood vessels in the breast cancer mass, the speed of blood flow, the amount of blood and more specialized hemodynamic parameters. Ultrasound has a high resolution and diagnostic rate in both fat-dominated and glandular dense breast (6).

In the present study, 120 patients with breast cancer admitted to Affiliated Hangzhou First People's Hospital (Hangzhou, China) from March 2021 to March 2022 were selected, with the aim of analyzing the association between CEUS features and the ALNM of primary breast cancer and the predictive value of CEUS variables.

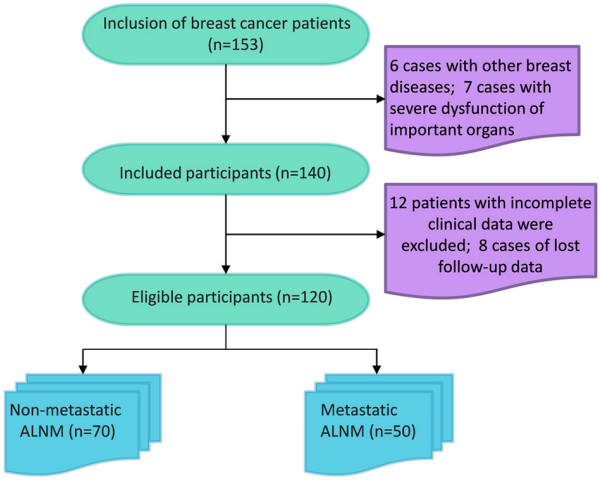


Figure 1. Selection process for patient data. ALNM, axillary lymph node metastasis.

## Materials and methods

*Patients*. A total of 120 patients with breast cancer admitted to Affiliated Hangzhou First People's Hospital from March 2021 to March 2022 were included in the present study, and the selection process is shown in Fig. 1. Inclusion criteria: i) Patients diagnosed with invasive breast cancer by pathological examination; ii) patients diagnosed with breast cancer for the first time, who had not received chemotherapy, radiotherapy or other associated treatment in the past; iii) patients whose clinical data was complete; and iv) patients and family members complied well with examination and treatment, and signed the informed consent form. Exclusion criteria: i) Patients with other malignant tumors; ii) patients with other breast diseases; iii) patients who were pregnant or lactating; iv) patients who were allergic to contrast media; and v) patients with severe dysfunction of important organs. According to the pathological results of axillary lymph node surgery, these cases were divided into a non-metastatic group (n=70) and a metastatic group (n=50). The age range of the 70 women in the non-metastatic group was 28-65 years, and the average age of this group was 43.16±6.85 years. The age range of the 50 women in the metastasis group was 30-64 years, and the average age of this group was 45.83±8.25 years. There was no significant difference in age and sex between the groups. The experimental procedure was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital (IIT-20210305-0024-01).

*Methods*. A Philips iU22 ELITE color ultrasound diagnostic system (Philips Healthcare) was used for CEUS examination. The patient was instructed to take a supine position and raise her upper arm above her head to fully expose both armpits. The axillary lymph nodes were scanned by conventional ultrasound and the size, internal echo and shape of the lymph nodes were recorded, for assessment of ALNM. Then, the L9-3 linear array probe was fitted and the system was switched to imaging mode. The skin in the areola area was sterilized, and 0.6 ml SonoVue (sulfur hexafluoride microbubbles for injection; Bracco Suisse SA; subpackaged by Shanghai Bracco Xinyi Pharmaceutical Co., Ltd.; approval no. for SonoVue: Guoyao Zhunzi J2018005) was injected into the skin at points corresponding with 3, 6, 9 and 12 o'clock, respectively, around the edge of the areola, and the cyber-physical fusion system [Zhongkesiou (Hefei) Technology Co., Ltd.] was started for real-time video recording. Scanning was performed from the areola to the axilla along the enhanced lymphatic vessels to observe the enhancement pattern of the axillary lymph nodes in each patient. CEUS features including blood flow classification, peripheral acoustic halo, perfusion sequence, enhancement mode, enhanced boundary, peripheral aggregation, increased range after enhancement, enlarged lymph node diameter line (the diameter line indicates the thickness of the lymph nodes in the plane on ultrasonography), edge radiation enhancement, enhancement amplitude, enhancement sequence, lymph node aspect ratio, maximum cortical thickness of lymph nodes, peak intensity, time to peak and the area under the curve (AUC) of the lymph nodes were evaluated and recorded.

*Outcome measures*. The clinicopathological characteristics of the patients were collected. The CEUS characteristics were compared between the two groups. Multivariate logistic regression was employed to analyze the factors that influenced ALNM in the patients with breast cancer. The sensitivity, specificity and coincidence rate of CEUS and ordinary ultrasonography with pathological examination in the diagnosis of the ALNM of breast cancer were evaluated by a four-fold table analysis. The consistency between CEUS and pathological examination in the diagnosis of breast cancer ALNM was examined using a consistency test. An internal consistency coefficient ($\kappa$) $\geq$0.75 indicated that the consistency between CEUS, ordinary ultrasonography and pathological examination was good.

*Statistical analysis*. SPSS20.0 software (IBM Corp.) was used to analyze the experimental data. Measurement data such as the age and the time to peak are shown as the mean ± standard deviation and were compared using an unpaired t-test. The blood flow grade, peripheral acoustic halo and other

Table I. Analysis of the clinicopathological characteristics of patients with breast cancer.

| Clinicopathological characteristics | N (%) |
|---|---|
| Lesion location | |
| Left breast | 53 (44.17) |
| Right breast | 67 (55.83) |
| Tumor histological type | |
| Lobular | 5 (4.17) |
| Ductal | 105 (87.50) |
| Mixed | 6 (5.00) |
| Others | 4 (3.33) |
| Operation mode | |
| Total mastectomy | 55 (45.83) |
| Breast conservative surgery | 65 (54.17) |
| TNM stage | |
| T1 | 7 (5.83) |
| T2 | 42 (35.00) |
| T3 | 59 (49.17) |
| T4 | 12 (10.00) |
| Imaging staging | |
| T1 | 42 (35.00) |
| T2 | 68 (56.67) |
| T3 | 10 (8.33) |

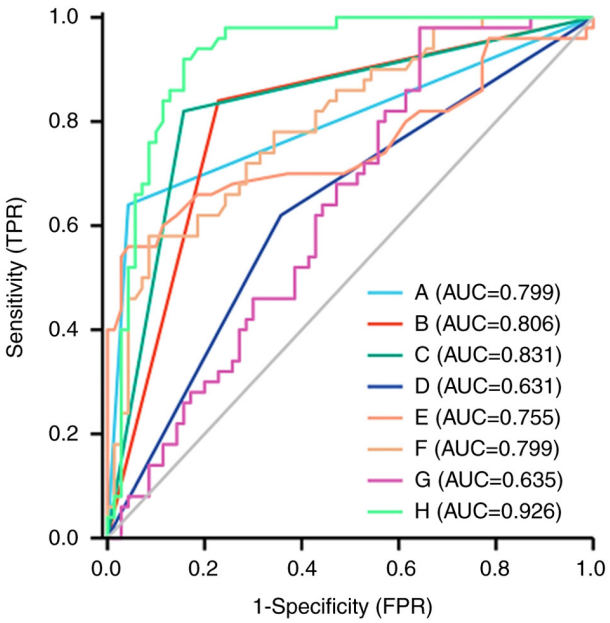


Figure 2. ROC curve analysis of the predictive value of single and combined CEUS characteristics for axillary lymph node metastasis in breast cancer. A, Blood flow classification of axillary lymph nodes; B, enhancement mode; C, range increase after enhancement; D, enhancement amplitude; E, maximum cortical thickness of the lymph nodes; F, peak intensity; G, time to peak; H, combined CEUS features. CEUS, contrast-enhanced ultrasound; AUC, area under the curve; TPR, true positive rate; FPR, false positive rate.

enumeration data are expressed as n (%) and were compared using a $\chi^2$ test. Multivariate logistic regression was performed to analyze the risk factors of ALNM in patients with breast cancer. Receiver operating characteristic (ROC) curve and four-fold table analyses were used to analyze the sensitivity, specificity and coincidence rate of CEUS in the diagnosis of ALNM of breast cancer. P<0.05 was considered to indicate a statistically significant difference.

## Results

*Clinicopathological characteristics of the patients with breast cancer.* Among the 120 patients in this study, the majority of the tumors (67/120, 55.83%) were located in the right breast. The most common histological type of tumor was ductal type, which was present in 105 patients, accounting for 87.50% of all cases. Breast conservative surgery was the most frequently performed type of surgery, which was applied to 65 patients (54.17%). T1 and T2 were the most common TNM stages, accounting for 35.00 and 49.17% of cases, respectively. T1 and T2 were the most common imaging stages, accounting for 35.00 and 56.67% of cases, respectively (Table I).

*Comparison of CEUS features*. The proportion of cases with an axillary lymph node blood flow of grade II-III, peripheral acoustic halo and perfusion sequence from cortical to portal was higher in the metastatic group compared with the non-metastatic group. In addition, the metastatic group had a higher incidence of inhomogeneous enhancement, peripheral aggregation, increased range after enhancement, enlargement of the lymph node diameter line and non-marginal radiation enhancement than the non-metastatic group. A high enhancement amplitude and centripetal enhancement were all more commonly found in the metastatic group than in the non-metastatic cases. Also, the maximum cortical thickness, peak intensity and AUC of the lymph nodes were larger, while the lymph node aspect ratio and time to peak were clearly lower in the metastatic group compared with the non-metastatic group (all P<0.05; Table II).

*Logistic regression analysis of risk factors of ALNM in patients with breast cancer.* Logistic regression analysis revealed that there were several risk factors associated with ALNM in patients with breast cancer, namely a blood flow grade of the axillary lymph nodes of II-III, enhancement mode (inhomogeneous), increased range after enhancement, high enhancement amplitude, maximum cortical thickness of the lymph nodes and peak intensity. The time to peak was a protective factor for ALNM in patients with breast cancer (all P<0.05; Table III).

*ROC curve analysis of single and combined CEUS characteristics for the prediction of ALNM in breast cancer.* ROC curve analysis showed that the AUC of ALNM in breast cancer was 0.799, 0.806, 0.831, 0.631, 0.755, 0.799 and 0.635, respectively, for prediction by blood flow classification, enhancement mode, range increase after enhancement, enhancement amplitude, maximum cortical thickness of the lymph nodes, peak intensity and the time to peak. For combined CEUS features the AUC was 0.926, the sensitivity was 92%, the specificity was 90.0% and the Youden index was 0.820. The combined CEUS features had high clinical predictive value (Table IV and Fig. 2).

Table II. Comparison of contrast-enhanced ultrasound features between metastatic and non-metastatic breast cancer.

| Indicators | Non-metastatic group (n=70) | Metastatic group (n=50) | $t/\chi^2$-value | P-value |
|---|---|---|---|---|
| Blood flow grade, n (%) | | | 50.341 | <0.001 |
| Grade 0-I | 67 (95.71) | 18 (36.00) | | |
| Grade II-III | 3 (4.29) | 32 (64.00) | | |
| Peripheral acoustic halo, n (%) | | | 66.109 | <0.001 |
| No | 63 (90.00) | 8 (16.00) | | |
| Yes | 7 (10.00) | 42 (84.00) | | |
| Perfusion sequence, n (%) | | | 3.939 | 0.047 |
| Portal to cortical | 29 (41.43) | 12 (24.00) | | |
| Cortical to portal | 41 (58.57) | 38 (76.00) | | |
| Enhancement mode, n (%) | | | 72.614 | <0.001 |
| Homogeneous | 63 (90.00) | 6 (12.00) | | |
| Inhomogeneous | 7 (10.00) | 44 (88.00) | | |
| Enhanced boundary, n (%) | | | 1.761 | 0.184 |
| Clear | 32 (45.71) | 21 (42.00) | | |
| Indistinct | 38 (54.29) | 29 (58.00) | | |
| Peripheral aggregation, n (%) | | | 51.571 | <0.001 |
| No | 61 (87.14) | 11 (22.00) | | |
| Yes | 9 (12.86) | 39 (79.00) | | |
| Increased range after enhancement, n (%) | | | 52.189 | <0.001 |
| No | 11 (15.71) | 41 (82.00) | | |
| Yes | 59 (84.29) | 9 (18.00) | | |
| Enlargement of lymph node diameter line, n (%) | | | 72.310 | <0.001 |
| No | 65 (92.86) | 8 (16.00) | | |
| Yes | 5 (7.14) | 42 (84.00) | | |
| Marginal radiation enhancement, n (%) | | | 25.682 | <0.001 |
| No | 13 (18.57) | 32 (64.00) | | |
| Yes | 57 (81.43) | 18 (36.00) | | |
| Enhancement amplitude, n (%) | | | 8.097 | 0.004 |
| High enhancement | 25 (35.71) | 31 (62.00) | | |
| Other enhancements | 45 (64.29) | 19 (38.00) | | |
| Enhancement sequence, n (%) | | | 44.203 | <0.001 |
| Centripetal | 12 (17.14) | 39 (78.00) | | |
| Diffuse coevolution | 58 (82.86) | 11 (22.00) | | |
| Lymph node aspect ratio | 2.39±0.26 | 1.86±0.23 | 11.542 | <0.001 |
| Maximum cortical thickness of lymph nodes, cm | 0.25±0.08 | 0.51±0.23 | 8.757 | <0.001 |
| Peak intensity, db | 5.78±2.69 | 8.93±2.47 | 6.541 | <0.001 |
| Time to peak, sec | 28.15±15.33 | 22.46±12.45 | 2.163 | 0.033 |
| AUC of lymph nodes | 278.96±152.36 | 389.27±210.33 | 3.333 | 0.001 |

AUC, area under the curve.

*Value of CEUS and ordinary ultrasonography in the diagnosis of ALNM in breast cancer.* Four-fold table analysis confirmed that the sensitivity, specificity and coincidence rate with pathological examination of CEUS in the diagnosis of ALNM were 92.00, 90.00 and 90.83%, while these of ordinary ultrasonography were 76.00, 80.00 and 78.33%, respectively (Tables V and VI). The consistency test suggests that CEUS and pathological examination were consistent in the diagnosis of ALNM of breast cancer, with a κ value of 0.816, indicating good consistency (P<0.05; Table V). The κ value of ordinary ultrasonography and pathological examination for the diagnosis of ALNM in breast cancer was 0.763, also indicating good consistency (P<0.05; Table VI). However, CEUS is markedly more valuable than ordinary

Table III. Logistic regression analysis of risk factors of axillary lymph node metastasis in patients with breast cancer.

| Indicators | β | SE | Wald | P-value | OR | 95% CI |
|---|---|---|---|---|---|---|
| Blood flow grade of axillary lymph nodes II-III | 0.785 | 0.239 | 3.568 | 0.048 | 2.015 | 1.136-3.769 |
| Peripheral acoustic halo | 1.326 | 0.466 | 2.893 | 0.269 | 1.395 | 1.045-1.975 |
| Perfusion sequence (cortical to portal) | 1.058 | 0.419 | 2.748 | 0.285 | 1.278 | 1.001-1.867 |
| Enhancement mode (inhomogeneous) | 1.265 | 0.316 | 21.582 | <0.001 | 3.859 | 2.154-4.968 |
| Peripheral aggregation | 0.562 | 0.298 | 3.261 | 0.078 | 2.154 | 1.567-2.044 |
| Increased range after enhancement | 1.396 | 0.315 | 26.154 | <0.001 | 4.165 | 2.136-6.487 |
| Enlargement of lymph node diameter line | 0.512 | 0.296 | 2.274 | 0.316 | 1.378 | 1.028-2.657 |
| Without marginal radiation enhancement | 2.165 | 0.895 | 2.069 | 0.415 | 1.368 | 1.025-3.761 |
| Enhancement amplitude (high) | 1.236 | 0.317 | 5.369 | 0.018 | 3.078 | 1.596-5.874 |
| Enhancement sequence (centripetal) | 2.138 | 0.947 | 2.016 | 0.433 | 1.216 | 1.058-1.359 |
| Lymph node aspect ratio | -0.869 | 0.478 | 3.295 | 0.065 | 0.826 | 0.749-0.932 |
| Maximum cortical thickness of lymph nodes | 0.968 | 0.316 | 14.268 | <0.001 | 3.089 | 1.278-6.038 |
| Peak intensity | 0.438 | 0.158 | 4.237 | 0.029 | 1.826 | 1.246-3.068 |
| Time to peak | -0.816 | 0.362 | 3.979 | 0.036 | 0.895 | 0.678-0.958 |
| AUC of lymph nodes | 0.418 | 0.268 | 2.968 | 0.215 | 1.625 | 1.173-3.087 |

SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the curve.

Table IV. Receiver operating characteristic curve analysis of single and combined CEUS characteristics for the prediction of axillary lymph node metastasis in breast cancer.

| CEUS characteristics | AUC | 95% CI | P-value | Sensitivity (%) | Specificity (%) | Youden index |
|---|---|---|---|---|---|---|
| Blood flow grade of axillary lymph nodes | 0.799 | 0.727-0.870 | 0.015 | 64.0 | 95.7 | 0.597 |
| Enhancement mode | 0.806 | 0.734-0.877 | 0.001 | 84.0 | 77.1 | 0.611 |
| Increased range after enhancement | 0.831 | 0.763-0.900 | 0.001 | 82.0 | 84.3 | 0.663 |
| Enhancement amplitude | 0.631 | 0.543-0.720 | 0.036 | 62.0 | 64.3 | 0.263 |
| Maximum cortical thickness of lymph nodes | 0.755 | 0.658-0.852 | 0.019 | 56.0 | 95.7 | 0.517 |
| Peak intensity | 0.799 | 0.719-0.879 | 0.015 | 58.0 | 91.4 | 0.494 |
| Time to peak | 0.635 | 0.537-0.734 | 0.037 | 90.0 | 35.7 | 0.257 |
| Combined detection | 0.926 | 0.877-0.975 | <0.001 | 92.0 | 90.0 | 0.820 |

CEUS, contrast-enhanced ultrasound; AUC, area under the curve; 95% CI, 95% confidence interval.

ultrasonography in the diagnosis of ALNM associated with breast cancer (Tables V and VI).

## Discussion

Breast cancer is the most common malignant tumor in women worldwide, which seriously threatens the lives and health of patients (7,8). With medical research developments, the early diagnosis and treatment of breast cancer have greatly improved, and the mortality rate has decreased; however, the high incidence of breast cancer remains a public health problem globally (9). ALNM is a common type of breast cancer metastasis, and epidemiological statistics show that the probability of ALNM occurring in patients with breast cancer is as high as 15%. ALNM is very important in newly diagnosed cases of breast cancer, as it can determine the treatment and prognosis of patients (10,11). Therefore, methods for the early and effective evaluation of axillary lymph status and metastasis in patients with breast cancer are the current focus of breast surgery professionals.

In CEUS, which is considered the third revolution of ultrasound medicine, a liquid-air interface is generated by the injection of a microbubble contrast agent into the body, which enables images of organs and lesions to be clearly observed. It not only increases the contrast resolution of the image, but also enables dynamic observation of the tissue microvessels and blood perfusion in real time, and has a greatly improved detection rate and accuracy. It is widely used in the diagnosis, guidance of curative effect and evaluation of prognosis in patients with breast cancer (12,13). It has been suggested that

Table V. Value of CEUS in the diagnosis of axillary lymph node metastasis in breast cancer.

| | Pathological examination, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| CEUS detection | Metastasis | No metastasis | Sensitivity, % | Specificity, % | Coincidence rate, % | κ | P-value |
| Metastasis | 46 (38.33) | 7 (5.83) | 92.00 | 90.00 | 90.83 | 0.816 | <0.001 |
| No metastasis | 4 (3.33) | 63 (52.50) | | | | | |
| Total | 50 (41.67) | 70 (58.33) | | | | | |

CEUS, contrast-enhanced ultrasound.

Table VI. Value of ordinary ultrasonography in the diagnosis of axillary lymph node metastasis in breast cancer.

| | Pathological examination, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| Ordinary ultrasonography | Metastasis | No metastasis | Sensitivity, % | Specificity, % | Coincidence rate, % | κ | P-value |
| Metastasis | 38 (31.67) | 14 (11.67) | 76.00 | 80.00 | 78.33 | 0.763 | <0.001 |
| No metastasis | 12 (10.00) | 56 (46.67) | | | | | |
| Total | 50 (41.67) | 70 (58.33) | | | | | |

CEUS, real-time elastography and hemodynamics have certain value in the diagnosis of breast cancer, and can provide great improvements in sensitivity and specificity (3). In addition, CEUS has been described as having a high diagnostic rate and strong sensitivity for breast cancer, which facilitates evaluation of the efficacy of chemotherapy for breast cancer and guides the therapeutic schedule (9). A previous study showed that CEUS features are associated with biological prognostic factors in patients with breast cancer, and play an important role in the diagnosis of breast cancer and evaluation of its prognosis (12). The logistic regression analysis in the present study demonstrated that most of the patients whose breast cancer was associated with ALNM had a lymph node blood flow grade of II-III, an inhomogeneous enhancement mode, increased range after enhancement, enhanced amplitude (high enhancement), increased maximum cortical thickness of the lymph nodes, high peak intensity and short time to peak. The real-time flow of contrast agent microbubbles in the lymphatic vessels can be observed using CEUS. Normal lymph node drainage is smooth and presents a homogeneous enhancement mode, while tumor cells may block the lymphatic vessels when they invade the lymph nodes, resulting in a heterogeneous enhancement mode. In addition, lymph nodes invaded by tumor generally show marginal or intermediate defects, so the enhancement amplitude often shows high enhancement. Tumor angiogenesis occurs to provide sufficient nutrients to tumor cell; therefore, an increased blood flow grade commonly indicates a high risk of ALNM. Normal lymph nodes tend to be oval in shape and movable, but as the tumor invades, cortical thickening can gradually occur. In addition, lymph node metastasis is accompanied by high peak intensity, increased range after enhancement and short peak time. Early monitoring is helpful for assessing the changes associated with breast cancer.

The diameter of SonoVue microbubbles, the ultrasound contrast agent used in the present study, is similar to that of human red blood cells. After injection into the human body, it provides a blood flow signal and red blood characteristics in lymph nodes to show the drainage path of lymph in breast tissue in real time (14). Moreover, the analysis of lymph node perfusion effectively differentiates the metastatic and inflammatory lymph nodes of the tumor and helps to determine the characteristics of axillary lymph nodes (15,16). In the present study, ROC curve and four-fold table analyses showed that CEUS features were of high clinical value in the diagnosis of ALNM in breast cancer. A consistency test was employed to determine the consistency between CEUS and pathological examination in the diagnosis of ALNM in patients with breast cancer; the value of κ was 0.816, which indicates good consistency. In addition, the analysis indicated that the value of CEUS in the diagnosis of ALNM in patients with breast cancer was markedly higher than that of ordinary ultrasonography. The results indicate that CEUS had high sensitivity and specificity in the identification of ALNM in patients with breast cancer, and suggest that it may be used as the main imaging method to evaluate the status of axillary lymph nodes, enabling doctors to devise treatment plans in the early stages. It has previously been demonstrated that CEUS can improve the diagnostic rate of axillary lymph nodes in breast cancer, and is important for the detection of sentinel lymph nodes in breast cancer (17). For suspected lymph nodes in clinical surgery, it is proposed that careful, repeated and multi-segment exploration should be carried out. If necessary, dual-mode or multimodal ultrasonic diagnosis can also be performed.

In summary, CEUS features have a certain association with ALNM in patients with breast cancer, which can be used to determine the characteristics of the axillary lymph nodes

and help in the diagnosis of the disease and the development of guidance programs. However, the results presented by CEUS are closely associated with the skill of the operator and/or the technology used by the operator, and may be affected by data bias. In addition, the sample size included in the study was limited. In future studies, the sample size and research duration will be expanded to obtain more in-depth results.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

LL and HY were involved in study conception, and analysis and interpretation of data. LZ and XK performed experiments and analyzed data. XK edited the manuscript. TH provided resources, analyzed data, and reviewed and revised the manuscript. XK and TH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital (IIT-20210305-0024-01). Written informed consent was obtained from all participants for participation in the study and all methods were carried out in accordance with the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Anders CK, Johnson R, Litton J, Phillips M and Bleyer A: Breast cancer before age 40 years. Semin Oncol 36: 237-249, 2009.
2. Hankinson SE, Colditz GA and Willett WC: Towards an integrated model for breast cancer etiology: The lifelong interplay of genes, lifestyle, and hormones. Breast Cancer Res 6: 213-218, 2004.
3. Li Y, Lu S, Zhang Y, Wang S and Liu H: Loco-regional recurrence trend and prognosis in young women with breast cancer according to molecular subtypes: Analysis of 1099 cases. World J Surg Oncol 19: 113, 2021.
4. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, Saggia C, Rubinelli S and Gennari A: Breast cancer survivorship, quality of life, and late toxicities. Front Oncol 10: 864, 2020.
5. Liang X, Li Z, Zhang L, Wang D and Tian J: Application of contrast-enhanced ultrasound in the differential diagnosis of different molecular subtypes of breast cancer. Ultrason Imaging 42: 261-270, 2020.
6. Huang Y, Le J, Miao A, Zhi W, Wang F, Chen Y, Zhou S and Chang C: Prediction of treatment responses to neoadjuvant chemotherapy in breast cancer using contrast-enhanced ultrasound. Gland Surg 10: 1280-1290, 2021.
7. Mann RM, Kuhl CK and Moy L: Contrast-enhanced MRI for breast cancer screening. J Magn Reson Imaging 50: 377-390, 2019.
8. Suter MB, Pesapane F, Agazzi GM, Gagliardi T, Nigro O, Bozzini A, Priolo F, Penco S, Cassano E, Chini C and Squizzato A: Diagnostic accuracy of contrast-enhanced spectral mammography for breast lesions: A systematic review and meta-analysis. Breast 53: 8-17, 2020.
9. Wang L, Li J, Qiao J, Guo X, Bian X, Guo L, Liu Z and Lu Z: Establishment of a model for predicting sentinel lymph node metastasis in early breast cancer based on contrast-enhanced ultrasound and clinicopathological features. Gland Surg 10: 1701-1712, 2021.
10. Lee YJ, Kim SH, Kang BJ and Kim YJ: Contrast-Enhanced ultrasound for early prediction of response of breast cancer to neoadjuvant chemotherapy. Ultraschall Med 40: 194-204, 2019.
11. Qiao J, Li J, Wang L, Guo X, Bian X and Lu Z: Predictive risk factors for sentinel lymph node metastasis using preoperative contrast-enhanced ultrasound in early-stage breast cancer patients. Gland Surg 10: 761-769, 2021.
12. Xu H, Xu GL, Li XD, Su QH and Dong CZ: Correlation between the contrast-enhanced ultrasound image features and axillary lymph node metastasis of primary breast cancer and its diagnostic value. Clin Transl Oncol 23: 155-163, 2021.
13. Mori N, Mugikura S, Miyashita M, Kudo Y, Suzuki M, Li L, Mori Y, Takahashi S and Takase K: Perfusion contrast-enhanced ultrasound to predict early lymph-node metastasis in breast cancer. Jpn J Radiol 37: 145-153, 2019.
14. Li J, Lu M, Cheng X, Hu Z, Li H, Wang H, Jiang J, Li T, Zhang Z, Zhao C, *et al*: How Pre-operative sentinel lymph node contrast-enhanced ultrasound helps intra-operative sentinel lymph node biopsy in breast cancer: Initial experience. Ultrasound Med Biol 45: 1865-1873, 2019.
15. Liu YB, Xia M, Li YJ, Li S, Li H and Li YL: Contrast-enhanced ultrasound in locating axillary sentinel lymph nodes in patients with breast cancer: A prospective study. Ultrasound Med Biol 47: 1475-1483, 2021.
16. Hu Z, Cheng X, Li J, Jiang J, Jiang Z, Li H, Li T, Zhang Z, Tan B and Lu M: Preliminary study of real-time three-dimensional contrast-enhanced ultrasound of sentinel lymph nodes in breast cancer. Eur Radiol 30: 1426-1435, 2020.
17. Du LW, Liu HL, Gong HY, Ling LJ, Wang S, Li CY and Zong M: Adding contrast-enhanced ultrasound markers to conventional axillary ultrasound improves specificity for predicting axillary lymph node metastasis in patients with breast cancer. Br J Radiol 94: 20200874, 2021.