Enhancing early breast cancer detection with multimodal imaging techniques: A comparative analysis

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ABSTRACT

Background: Breast cancer is a leading health threat to women, and early diagnosis is essential for effective treatment and improved survival rates. This study evaluates the efficacy of multimodal imaging techniques in the early diagnosis of breast cancer, focusing on the comparative analysis of ultrasound, mammography, and magnetic resonance imaging (MRI). ***Materials and Methods:*** The study included 75 patients with breast lesions diagnosed between April 2019 and May 2023. Preoperative imaging was performed using X-ray mammography, ultrasound, and MRI. The lesions were categorized using the BI-RADS classification system, and diagnostic sensitivity, specificity, positive and negative predictive values were compared. Additionally, the study assessed the consistency of imaging techniques through Kappa testing. ***Results:*** Pathological analysis revealed 39 malignant and 36 benign cases. Imaging diagnosis using multimodal techniques showed that contrast-enhanced ultrasound (CEUS), MRI, and their combination had higher sensitivity and negative predictive value compared to mammography ($P < 0.05$). CEUS demonstrated a sensitivity of 92.31%, which was consistent with combined ultrasound imaging but higher than mammography. Kappa values indicated that CEUS had superior consistency among the imaging modalities evaluated. ***Conclusion:*** Multimodal imaging, particularly CEUS and MRI, significantly enhances the early diagnosis of breast cancer. While each modality presents unique advantages, the choice of imaging technique should be based on individual patient characteristics, lesion features, and consideration of practicality and cost-effectiveness.

INTRODUCTION

Breast cancer remains a significant health concern for women worldwide, with early diagnosis being crucial for effective treatment and improved patient outcomes [1]. The cornerstone of early detection lies in imaging techniques, which have evolved to become more sophisticated and sensitive over time [2]. Traditional imaging modalities such as ultrasound, X-ray, positron emission tomography (PET-CT), computed tomography (CT), and magnetic resonance imaging (MRI) have been the mainstays in diagnosing breast cancer [3]. However, the limitations of each individual technique have become increasingly apparent, necessitating the development and application of multimodal imaging approaches [4].

A single imaging modality often falls short due to its inherent limitations in imaging capabilities. For instance, a study that included a substantial number of subjects found that the area under the receiver operating characteristic (ROC) curve for ultrasound diagnosis was relatively low, indicating its limited sensitivity and specificity in detecting breast cancer [5]. Furthermore, the quality of ultrasound imaging is heavily dependent on the technical skill of the operator and the specific imaging protocols used [6].

Multimodal imaging technology, which combines multiple imaging techniques to integrate different modalities of image information, has emerged as a powerful tool to overcome these limitations [7]. This approach allows for the cross-verification and mutual supplementation of information, thereby enhancing diagnostic accuracy and efficiency. In recent years, significant progress has been made in breast cancer imaging. Multimodal imaging techniques that combine different modalities, such as the integration of 18F - fluorodeoxyglucose (FDG) PET/CT, PET/MRI, and single - photon emission computed tomography (SPECT)/CT, have shown great potential in improving diagnostic accuracy [8]. Additionally, emerging imaging methods like diffuse optical imaging (DOI) [9], contrast - enhanced ultrasound (CEUS) [10], and ultrasound elastography (UE) [11] have also been increasingly explored in breast cancer diagnosis. However, there are still limitations. For instance, the integration of multiple imaging modalities in real - world clinical settings remain challenging due to differences in equipment availability, cost, and the complexity of combining data from various sources. Also, while many studies have evaluated the performance of individual imaging techniques, a comprehensive comparison of a wide range of imaging methods, including both traditional and emerging ones, in a single, well - controlled study is lacking. This makes it difficult for clinicians to make evidence - based decisions on the most suitable imaging approach for each patient.

This study innovatively and comprehensively compared the application of multiple imaging technologies in breast cancer diagnosis, including not only traditional technologies such as ultrasound, mammography and MRI, but also emerging technologies such as DOI, CEUS and UE. By evaluating these techniques in a single cohort, we provide a more in - depth understanding of their individual and combined diagnostic performance. This fills a gap in the current literature as most studies focus on one or a few imaging modalities. Additionally, we assess the consistency among different imaging methods through Kappa testing, which offers new insights into their reliability. This research is intended to help clinicians select the most appropriate imaging method based on patient-specific factors, ultimately improving the accuracy of breast cancer diagnosis and patient prognosis.

MATERIALS AND METHODS

Study subjects

The study cohort comprised 75 patients with confirmed breast diseases, diagnosed between April 2019 and May 2023 at The Yancheng School of Clinical Medicine of Nanjing Medical University. Preoperative diagnosis was performed using X-ray mammography, ultrasound (US), and magnetic resonance imaging (MRI). The age range of the patients was from 28 to 86 years, with an average age of 41.21±12.01 years. A total of 75 lesions were evaluated, all of which were single and unilateral, with the maximum diameter of the lesions varying from 7 to 56 mm and an average diameter of 20.12 ± 9.26 mm (table 1). This study has been approved by the Ethics Committee of Yancheng Third People's Hospital (YCTP-2023-06-12).

Table 1. Patients' demographic information.

Demographic Parameter	Details
Number of Patients	75
Age (years)	41.21 ± 12.01
Number of Lesions	75
Lesion Characteristics	All Single and Unilateral
Maximum Lesion Diameter Range (mm)	7 - 56
Mean Lesion Diameter (mm)	20.12 ± 9.26

Conventional ultrasound imaging

Conventional ultrasound examinations were conducted using Toshiba Aplio 500 (Toshiba, Japan) and GE Logiq 9 (General Electric, USA) color Doppler ultrasound diagnostic instruments, with probe frequencies ranging from 7 to 10 MHz. Patients were positioned supine, and the breast was scanned using a radial multisectional approach to assess the location, size, shape, edge, capsule, internal echo, calcification, and relationship with surrounding tissues of the breast mass. Additionally, the internal and surrounding color Doppler blood flow was evaluated, along with the bilateral axillary lymph nodes.

Diffuse optical imaging (DOI)

The Optimus-II type ultrasound light scattering imaging system (New Aobo, China) was utilized for DOI. The optical acquisition system was initiated to collect optical parameters, such as the maximum hemoglobin concentration (MHC) within the mass, to automatically generate a benign or malignant grading. An MHC of 140 μmol/L was used as the threshold value, with MHC < 140 μmol/L indicating a likely benign condition and MHC ≥ 140 μmol/L indicating a likely malignant condition. The system automatically provides corresponding BI-RADS classification results based on the imaging findings.

Elastography

Elastography was performed using the Toshiba Aplio 500 color (Toshiba, Japan) Doppler ultrasound diagnostic instrument, with the lesion confirmed and switched to the ultrasound elastography mode. The probe was applied with uniform pressure over the lesion area, performing slight to moderate-speed vibration and release maneuvers. The modified 5-point scale by Zhi *et al.* [12] was employed to evaluate the lesion's elastography image. This study correlated the 1-5 scoring system with the BI-RADS classification to determine the ultrasound elastography (UE) BI-RADS classification.

Contrast-enhanced ultrasound (CEUS)

CEUS was conducted using the GE Logiq 9 (General Electric, USA) color Doppler ultrasound instrument with a linear probe at a frequency of 12.0 MHz and a contrast probe frequency of 9.0 MHz. The contrast agent used was SonoVue (Bracco Company, Italy), which was mixed with 5 ml of physiological saline and shaken. After selecting the contrast mode, 2.4 ml of SonoVue was administered via an antecubital vein bolus injection. The dynamic distribution and behavior of the contrast agent microbubbles within the lesion were observed simultaneously. Post-contrast, the imaging process was reviewed to analyze the contrast agent's perfusion characteristics and enhancement degree within the mass. For the first time in this study, cases were classified based on CEUS findings and referenced to the BI-RADS classification, considering factors such as enhancement time, intensity, direction, size post-enhancement, uniformity, boundary post-enhancement, presence of filling

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defects, crab feet appearance, and presence of feeding vessels. The higher the CEUS findings leaned towards malignancy, the higher the BI-RADS classification score assigned by the physician.

Mammography

Mammography was performed using the GE Senographe DS (General Electric, USA) full-field digital mammography unit in an automatic exposure mode. Images were taken in axial, lateral, and oblique views, with additional views and local magnification as necessary. The examination assessed lesion characteristics, including location, size, shape, edge, density, internal calcification, nipple, surrounding tissue, and axillary lymph nodes. A diagnosis was provided by a mammography physician.

Magnetic resonance imaging (MRI)

MRI was conducted using a GE Signa EXCITE 1.5T (General Electric, USA) superconducting MR system. The protocol included transverse fat-suppressed SPGR sequence T1-weighted imaging (T1WI) and sagittal fat-suppressed FSE sequence T2-weighted imaging (T2WI) for plain scanning. VIBRANT dynamic contrast-enhanced scanning was performed after injecting the paramagnetic contrast agent gadopentetate dimeglumine (Gd-DTPA，Bayer Healthcare, Germany) at a rate of 0.1 mmol/kg body weight, analyzing the perfusion characteristics and enhancement pattern of the contrast agent within the mass.

Image analysis and evaluation criteria

Breast ultrasound analysis was independently performed by an experienced sonographer blinded to the study's purpose. Mammography and MRI images were analyzed by experienced radiologists. The BI-RADS classification criteria were referenced for diagnosis, where categories 1-3 were considered benign, and categories 4-5 were considered (possibly) malignant.

All surgical specimens of breast lesions were fixed in 10% neutral formalin, embedded in paraffin, sectioned at 4-5 μm thickness, and stained with hematoxylin-eosin (HE). Pathological diagnosis was independently made by two senior pathologists with over 10 years of experience in breast pathology, based on the World Health Organization (WHO) Classification of Tumors of the Breast (5th edition, 2019) criteria. In case of diagnostic discrepancy, a consensus was reached through joint consultation to confirm the final pathological type (benign or malignant).

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. Categorical data were expressed as rates, and intergroup comparisons were made using the chi -square test. Kappa consistency testing was applied to evaluate the agreement between different imaging modalities. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Pathological findings

A total of 75 lesions were evaluated, with pathological results indicating 39 malignant and 36 benign cases. The malignant cases included 18 cases of invasive ductal carcinoma, 5 cases of lobular carcinoma in situ, 6 cases of intraductal carcinoma, 3 cases of medullary carcinoma, 3 cases of mucinous carcinoma, 1 case of invasive ductal carcinoma with mucinous carcinoma, 2 cases of ductal carcinoma with lobular carcinoma, and 1 case of invasive non-special type carcinoma with focal squamous cell carcinoma. The benign cases consisted of 21 cases of fibroadenoma, 8 cases of hyperplasia, and 7 cases of mammary adenosis.

Imaging diagnosis grading results and comparison of diagnostic efficacies

Comparison of BI-RADS Grading Results from Various Imaging Diagnoses with Pathology

The BI-RADS grading results from different imaging diagnoses were compared with pathological findings as shown in table 2 and figure 1 illustrates a representative case of multimodal imaging diagnosis in a 42-year-old female patient.

Table 2. BI-RADS grading results of various imaging diagnoses and pathological comparison examples.

BI-RADS	DOI	UE	CEUS	XRM	MRI	DOI+UE +CEUS	DOI+UE+CEUS+XRM+MRI
Level1	0	0	0	3(3/0)	0	0	0
Level1	13 (1/12)	9(2/7)	10 (1/9)	6(2/4)	18 (0/18)	11 (1/10)	8(0/8)
Level1	19 (3/16)	23 (3/20)	22 (2/20)	27 (6/21)	10 (2/8)	20 (2/18)	18(1/17)
Level1	21 (16/5)	25 (18/7)	18 (13/5)	18 (11/7)	15 (7/8)	17 (10/7)	16(10/6)
Level1	22 (19/3)	18 (16/2)	25 (23/2)	21 (18/3)	32 (30/2)	27 (26/1)	33(28/5)

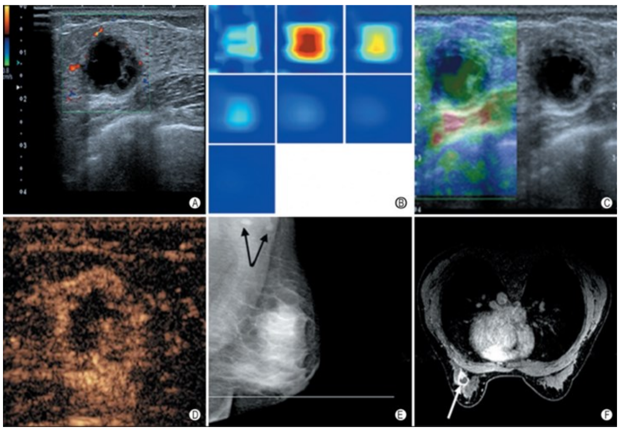

Figure 1. Multimodal imaging manifestations of breast cancer.

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In figure 1 multimodal imaging manifestations of breast cancer. A: Conventional ultrasound shows a mixed cystic and solid lesion in the left breast, approximately 14cm × 22cm in size, with clear boundaries and regular morphology. Color Doppler flow imaging shows punctate and strip-like blood flow signals around the lesion. B: Optical scattering imaging shows significant abnormalities in blood distribution, with slightly lower local blood oxygen levels, classified as BI-RADS 4C. C: Elastic imaging shows blue and green within the lesion, with an elasticity score of 3 points, classified as BI-RADS 3. D: Contrast imaging shows high enhancement around the lesion with no contrast agent entering the center, with a lesion size of approximately 16cm × 25cm. The enhancement pattern is rapid entry and slow exit, classified as BI-RADS 4C. E: X-ray mammography shows BI-RADS 2 type breast, with no mass shadow seen within the gland, and two enlarged lymph nodes can be seen in the left axillary region (indicated by the arrow), considered as BI-RADS 1. F: Dynamic contrast-enhanced MRI shows significant ring enhancement around the lesion during the arterial phase (indicated by the arrow), classified as BI-RADS 4B. The pathological examination result is invasive non-special type cancer with local squamous cell carcinoma.

Comparison of diagnostic efficacies

The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value for ultrasound, mammography, and MRI are presented in table 3.

The sensitivity and negative predictive value of contrast-enhanced ultrasound (CEUS), MRI, and the combination of all three imaging modalities were superior to those of mammography, with statistically significant differences ($P < 0.05$). The sensitivity of CEUS and combined ultrasound imaging was consistent, at 92.31%, slightly higher than that of elastography and diffuse optical imaging, with no statistically significant difference ($P > 0.05$), but with a statistically significant difference compared to mammography ($P < 0.05$).

Table 3. diagnostic sensitivity, specificity, positive predictive value, and negative predictive value.

Imaging diagnosis	sensitivity	specificity	Positive predictive value	Negative predictive value
DOI	89.74	77.78	81.40	87.50
UE	87.18	75.00	79.07	84.38
CEUS	92.31*	80.56	83.72	90.63*
DOI+UE+CEUS	92.31*	77.78	81.82	90.32
XRM	74.36	69.44	72.50	71.43
MRI	94.87*	72.22	78.72	92.86*
US+XRM+MRI	97.44*	69.44	77.55	96.15*

Compare to XRM, *P<0.05

Kappa consistency testing

Kappa consistency testing was performed for each imaging diagnosis. The Kappa values for diffuse optical imaging, elastography, CEUS, combined ultrasound, mammography, MRI, and combined imaging were 0.678, 0.624, 0.732, 0.705, 0.439, 0.677, and 0.676, respectively. The consistency of CEUS was superior to that of other imaging modalities.

DISCUSSION

Breast cancer is one of the most common malignancies among women, and imaging plays a crucial role in early detection and definitive diagnosis, significantly impacting clinical management [13]. This study aimed to compare and discuss the commonly used imaging diagnostic methods to enhance the accuracy of breast tumor diagnosis.

Breast ultrasound is instrumental in the differentiation, diagnosis, and staging of breast cancer. It offers high resolution for breast tissue, unrestricted by the density of the gland, thus compensating for the limitations of mammography [14]. Mammography often struggles with imaging dense glandular tissue, where lesions can be obscured. High-frequency ultrasound has been shown to detect more small and occult breast cancers within dense glandular tissue with greater accuracy [15]. In this study, three lesions missed by mammography were all dense breasts classified as BI-RADS 4, and the lesions were clearly visualized in ultrasound, with the smallest measuring approximately 7 mm in the greatest dimension. Mammography identified microcalcifications in 16 cases, 13 of which were malignant and presented in a clustered distribution, while three were benign, showing coarse granular calcifications. All calcifications were evident in ultrasound [16].

Among the three ultrasound diagnostic methods, elastography had the lowest diagnostic efficacy. Misdiagnoses were attributed to the specificity of pathological components such as calcification and increased stromal elements, leading to overestimation of scores. In three cases of invasive ductal carcinoma with internal necrotic liquefaction and two cases of medullary carcinoma, the hardness of the lesion was underestimated due to the presence of anechoic areas. Elastography is also susceptible to operator influence, which can reduce the accuracy of scoring. Compared to other elastography techniques, shear wave elastography does not require compression and provides a quantitative measurement of tissue elasticity through the Young's modulus value.

Diffuse optical imaging (DOI) predicts the benign or malignant nature of a mass with a high rate of concordance for breast cancer diagnosis. However, there were false-positive and false-negative cases in

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the study. DOI diagnosed 43 malignant lesions, of which 35 were confirmed malignant postoperatively, and eight were misdiagnosed. The reasons for this include increased neovascularization in inflammatory conditions, the rich capillary network in intraductal papillomas, and the relationship between tumor size and blood flow. Additionally, heterogeneous breast tissue can affect the path of light scattering, and deeper lesion locations can also impact the results (17).

Contrast-enhanced ultrasound (CEUS) uniquely provides information on the distribution and morphology of breast lesion vasculature, showing superiority in detecting tumor blood flow information. This study showed that its sensitivity was slightly higher than elastography and DOI, consistent with combined ultrasound imaging at 92.31%, and significantly different from mammography in terms of sensitivity and negative predictive value. CEUS detected 36 out of 39 malignant lesions, with slightly higher specificity than other imaging modalities, and a Kappa value superior to other examinations. Malignant lesions typically showed intense enhancement post-contrast, with fast-in and fast-out or fast-in and slow-out enhancement patterns. The lesion size appeared larger than on 2D ultrasound, and branched vessels were visible, especially in mixed lesions dominated by necrotic components, providing a clear view of the solid lesion. Dynamic observation of lesion blood perfusion characteristics further aids in the diagnosis of breast cancer (18).

Mammography is internationally recognized as an effective method for detecting breast cancer. However, some studies report that mammography does not reduce breast cancer mortality rates. MRI has been used for screening high-risk populations for breast cancer. The results of this study showed that breast MRI with contrast enhancement had a sensitivity and specificity of 94.87% and 72.22%, respectively, with higher sensitivity than other imaging diagnostic methods and the highest detection rate for malignant lesions. Enhanced MRI has been proven to be highly sensitive in detecting asymptomatic and symptomatic high-risk women for breast cancer. However, MRI is less sensitive to calcifications and has a higher overlap rate between benign and malignant lesions, leading to lower specificity. The combined application of imaging techniques improves sensitivity but reduces specificity, especially for lesions with complex pathological components, where there is an overlap between benign and malignant features, leading to potentially overestimated BI-RADS classifications (19).

In recent years, a large number of studies have explored the diagnostic value of various imaging methods for breast cancer. One study found that breast ultrasound, a widely used imaging method, can effectively distinguish cystic lesions from solid lesions (20). Its high-resolution imaging of breast tissue, especially in dense glandular tissue where mammography has limitations, is consistent with our findings. Studies have reported that high-frequency ultrasound can indeed detect more small and occult breast cancers in dense glandular tissue, which was also confirmed in our study. Three lesions missed by mammography in dense breasts were clearly visible under ultrasound.

However, this study has several limitations. First, the sample size of 75 patients is relatively small, which may limit the generalizability of the results. Second, the study was conducted in a single center, which may introduce selection bias. Future large - scale, multi - center studies are needed to validate our findings. Additionally, the cost - effectiveness analysis in this study was only briefly mentioned. A more in - depth economic evaluation of different imaging modalities is necessary to better guide clinical practice.

CONCLUSION

Each imaging modality has unique advantages in breast disease diagnosis. CEUS and MRI, either alone or in multimodal combinations, significantly enhance early breast cancer detection. Clinical selection should prioritize individual patient characteristics, lesion features, practicality, and cost-effectiveness to optimize diagnostic accuracy.

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Ethical Consideration: This study has been approved by the Ethics Committee of Yancheng Third People's Hospital (YCTP-2023-06-12). All procedures were carried out in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients before the study.

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***AI Usage*:** No artificial intelligence was used in the preparation of this manuscript.

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