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Original Article

Sonographic features of dense breast imaging reporting and data system 4 (BI-RADS-US4) for non-palpable breast lesions

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Abstract: The aim of this study was to investigate the diagnostic value of various features for differentiating between malignant and benign lesions by using the sonography for dense breast imaging reporting and data system 4 (BI-RADS-US4) for non-palpable breast lesions (dBI-RADS-US4-nPBL). The sonographic features and pathological results of a total of 102 dBI-RADS-US4-nPBLs were retrospectively analyzed so as to evaluate the diagnostic values of sonography for such patients. Among the 102 lesions included, 47 cases were benign and 55 cases were malignant, and the overall positive predictive value was 53.9%; the positive predictive values of the subcategories BI-RADS-US4A, 4B, and 4C were 18.2%, 55.0%, and 93.1%, respectively. The diagnostic performance for BI-RADS-US classification was determined using ROC curve analysis. For the cut-off point of 4B (sensitivity, 57.4%; specificity, 89.1%), the area under the receiver operating characteristic curve was 81.8%. The diagnostic sensitivity for lesions with an irregular shape was the highest (89.1%), and features such as burr, sublobe, microcalcification, rear echo attenuation, and mass walking pattern had higher diagnostic specificities for this category of lesions (95.7%, 87.2%, 89.4%, 80.9%, and 87.2%, respectively). Mass walking pattern (odds ratio [OR]=5.861, 95% confidence interval [1.862, 20.846], P=0.006) and margin (OR=4.462, [0.932, 4.462], P=0.000) were the two most significant predictors of malignant lesions in multivariate analysis. For BI-RADS-US4-nPBLs, the feature of irregular shape had the highest diagnostic sensitivity, and features such as burr, sublobe, microcalcification, rear echo attenuation, and mass walking pattern had higher diagnostic specificities. Patients with BI-RADS-US4B and 4C-nPBLs should be recommended to undergo biopsy, but those with BI-RADS-US4A-nPBLs should be appropriately cautious about the need for a biopsy.

Keywords: Breast cancer, non-palpable lesions, sonography, BI-RADS category 4

Introduction

Non-palpable breast lesions refer to masses that cannot be palpated by routine clinical examination but can be revealed by radiographic examination, and their malignancy rate can be 15% to 30% [1]. Breast cancer is the most common malignancy in women and has a relatively higher incidence in developed countries [2, 3]; because it is one of the main causes of cancer deaths among women, early diagnosis is an important means of reducing mortality. With people's increased awareness of tumors and the progress in breast cancer screening, clinical non-palpable early breast cancer can be detected on high-frequency ultrasound, and clinical integrated breast cancer sonographic protocols can have high diagnostic yields, in particular among young Asian women with dense breasts [4].

The sonographic qualitative diagnosis of breast imaging reporting and data system 4 (BI-RADS-US4) for breast lesions is quite difficult to use. In 2003, the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) was adapted for ultrasound rating [5], and breast ultrasound diagnosis became more standardized, which not only reduces the subjective judgments of the sono-

Table 1. Basic information and clinic feature of patients

	Malignancy	Benign	Total
Number	55	47	102
Age (years)	32.54±4.48	34.21±4.26	33.31±4.44
Diseased side			
Left	34	25	59
Right	21	22	43
Visiting reason			
Breast tenderness	23	22	45
Routine examination	20	12	32
Breast discomfort	9	7	16
Nipple discharge	3	5	8
Areola fester	0	1	1
Size area			
Width (cm)	0.74±0.23	0.76±0.26	0.75±0.24
Length (cm)	1.39±0.23	1.31±0.21	1.35±0.24
Area (cm^2)	1.04±0.44	1.02±0.48	1.03±0.45
BI-RADS-US classification			
4A	6	27	33
4B	22	18	40
4C	27	2	29

Table 2. Pathological results of the sonography-diagnosed BI-RADS-US4-nPBLs (case)

Pathological result	4A	4B	4C	Sum
Malignancy	6	22	27	55
Invasive ductal carcinoma	1	16	21	38
Squamous cell carcinoma	1	1	0	2
Angiosarcoma	1	0	0	1
Neuroendocrine carcinoma	1	3	5	9
Intraductal carcinoma	2	1	1	4
Benign	27	18	2	47
Fibroadenoma	12	3	0	15
Breast cystic hyperplasia	8	3	0	11
Intraductal papilloma	5	4	1	10
Sclerosing adenosis	2	6	1	9
Benign phyllodes tumor	0	1	0	1
Granulomatous mastitis	0	1	0	1
Sum	33	40	29	102

graphers but also increases the diagnostic accuracy of non-palpable breast lesions.

Per the ACR, BI-RADS4 lesions do not have clear diagnostic criteria between typical benign and malignant lesions due to its wide range of malignancy prevalence (from 3% to 94%), so patients with BI-RADS4 lesions are normally recommended to undergo biopsy or appropriate surgical resection [6].

This study analyzed and investigated the ultrasonographic features and pathological data of a total of 102 dense BI-RADS-US4 non-palpable breast lesions (dBI-RADS-US4-nPBL) treated at the Breast Center of Shaanxi Cancer Hospital, aiming to improve the sonographic diagnostic accuracy of lesions in the dense breasts of young women.

Methods

General data

A total of 102 BI-RADS-US4-nPBLs in young female patients were biopsied using 16G needle puncture or surgical resection and their diagnoses were confirmed by pathological results in the Breast Center of Shaanxi Cancer Hospital from March 2013 to February 2016. The patients' age, visiting reason, diseased side, and lesion sizes are shown in **Table 1**. All of the pathological reports were based on histological diagnoses. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Yan'an University. Written informed consent was obtained from all participants.

Treatment

The Netherlands, PHILIPS iu22, and MY lab Twice color Doppler ultrasound devices (Esaote, Italy) were used, along with a high frequency linear array probe (probe frequency 7.5-13 MHz). Based on the factory default breast ultrasonographic conditions, focus and gain were further adjusted according to the depth of lesions so as to ensure the best image quality. Intact image data (2D, blood flow, elasticity, or angiography) were all reviewed. The characteristic description and diagnostic classification of the lesions were obtained by using the BI-RADS classification standards (4th edition, 2003) established by the ACR as well as the new grading standards recommended by Kim *et al.* [7], which supplemented and refined the standardized classification of breast ultrasound. All the patients underwent ultrasound-guided biopsy or wire-localized resection. The pathological classification of breast cancer used the classi-

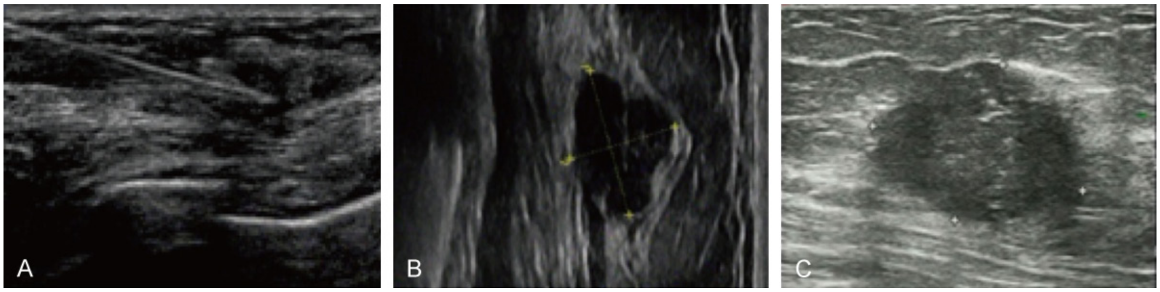

Figure 1. A: F, 38 years old, 0.9 cm×1.0 cm hypoechoic lesion at the anterolateral side of left breast, exhibiting irregular shape and no blood flow, BI-RADS-US4A; this patient was performed wire-localized resection, and the pathological results revealed adenosis combined with epithelial hyperplasia. B: F, 25 years old, 1.7 cm×1.3 cm hypoechoic nodule at the anterior side of left breast, sublobe-like, BI-RADS 4B; the pathological results revealed adenosis + fibroadenoma + ductal epithelial hyperplasia. C: 34 years old, right breast mass with angular margin and punctate calcification, under BI-RADS4C, this patient was performed ultrasound-guided biopsy, and the pathological results revealed infiltrating ductal carcinoma grade II.

Table 3. Sonographic features of BI-RADS4Ls (n)

Sonographic feature	Number of lesions	Benign (47)	Malignant (55)	χ^2	P
Shape					
Regular	25	19	6	11.933	0.001
Irregular	77	28	49		
Margin					
Clear	17	12	5	21.969	0.000
Unclear	44	27	17		
Sublobe	19	6	13		
Burr	22	2	20		
Internal echo					
Even	25	16	9	4.281	0.039
Uneven	77	31	46		
Calcification					
Non- or coarse calcification	83	42	41	3.670	0.055
Microcalcification	19	5	14		
Posterior echo					
Enhanced	25	11	14	5.610	0.061
Non-changed	47	27	20		
Attenuated	30	9	21		
Mass walking pattern					
Parallel	77	41	36	6.497	0.011
Non-parallel	25	6	19		

fication method issued by the World Health Organization (WHO) in 2003.

Statistical analysis

SPSS16.0 was used for the data analysis; the measurement data were expressed as mean ± standard deviation ($\overline{x}$±s), and the count data were compared using the χ^2 test, with α=0.05 set as the test level. Diagnostic performance for BI-RADS-US classification was determined using receiver operating characteristic (ROC) curve analysis. The area under the receiver operating characteristic curve (AUC-ROC) was used to estimate the accuracy of predicting a malignant lesion. Multivariate analyses were performed to identify associations among malignant pathology diagnosis and sonographic features (P<0.05).

Results

Pathological and sonographic classifications

Pathological and sonographic classifications of the non-palpable breast lesions are shown in **Table 2** and **Figure 1**. The sonographic results identified 47 benign tumors as well as 55 malignant lesions, with a positive predictive value of 53.9%. The benign tumors included 27 4A cases, 18 4B cases, and 2 4C cases. The malignant lesions included 6 4A cases, 22 4B cases, and 27 4C cases. The positive predictive values for subcategories 4A, 4B, and 4C were 18.2%, 55.0%, and 93.1%, respectively, among which

Table 4. Diagnostic Value of malignant sonographic signs toward non-palpable breast cancer (%)

Sonographic signs	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Irregular shape	89.1	40.4	63.6	76.0
Unclear edge	30.9	42.6	38.6	34.5
Sublobe	23.6	87.2	68.4	49.4
Burr	36.4	95.7	90.9	56.3
Uneven internal echo	83.6	34.0	59.7	64.0
Posterior echo attenuation	38.2	80.9	70.0	52.8
Microcalcification	25.5	89.4	73.7	50.6
Non-parallel growth	34.5	87.2	70.4	53.2

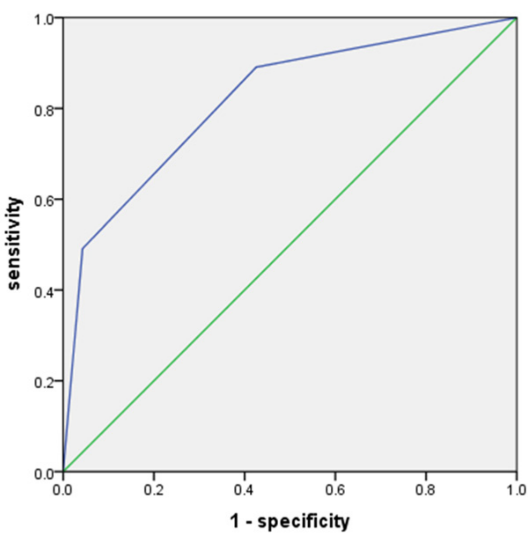

Figure 2. Receiver operating characteristic curve of BI-RADS-US classification to predict a malignant lesion in the cohort (n=102 patients).

malignant cases in stage 0 and I accounted for 67.3% (37/55).

Sonographic features

There were significant differences in the sonographic features of tumor shape, walking pattern, edge, posterior echo, microcalcifications, internal echo classification, and percentage of malignant tumors between benign and malignant tumors (P<0.05). The sensitivity, specificity, positive predictive value, and negative predictive value of sonographic features in diagnosing tumors revealed that for tumors with an irregular shape, the highest diagnostic sensitivity was 89.1%, but the specificity was low (40.4%); the specificities in diagnosing tumors with burr, sublobe, microcalcifications, and non-parallel growth were high (**Tables 3** and **4**).

Results of ROC and multivariate analysis

The AUC of the BI-RADS-US classification to predict the likelihood of correctly predicting a malignant lesion was 0.818 (95% CI 0.736-0.900; **Table 2** and **Figure 2**). The Youden index of 4B was 0.465, which was the highest among the three classifications, so the selected cut-off point was 4B, with a sensitivity of 57.4% and a specificity of 89.1%. In multivariate analyses, mass walking pattern (odds ratio [OR]=5.861, 95% CI [1.862, 20.846], P=0.006) and margin (OR=4.462, [0.932, 4.462], P=0.000) were the two most significant predictors of malignancy on multivariate analysis. Shape was close to the significance level, but internal echo, posterior echo, and calcification had no significant effect on predicting a malignant lesion. Mass walking pattern had the largest OR, which means that non-parallel was 5.861 times more accurate than that of parallel in predicting a malignant lesion (OR=5.861). The results are shown in **Table 5**.

Discussion

With wide application of ultrasound in dense breast cancer screening, increasing numbers of non-palpable breast lumps have been found because its sensitivity is higher than that of mammography for dense breasts. High-resolution ultrasound can identify lesions in 17% of patients with non-palpable or radiography-negative breast cancer [8].

In 2003, the ACR developed the BI-RADS-US so as to standardize the reporting and classification of conventional ultrasound for breast lesions, thus improving its diagnostic efficiency in the USA [5]; these classification criteria can effectively distinguish between benign and malignant solid tumors [9-12]. However, due to the wide span of BI-RADS category 4 malignant lesions (4th edition) in 2003 (2% to 94%), and because the cut-off point for benign and malignant lesions is limited between category 3 and 4, the specificity and diagnostic accuracy based

Table 5. Multivariate analyses of predictors of incidence of malignant

Sonographic feature	Regression coefficient	*P*-value	OR (95% CI)
Shape	1.496	0.061	4.462 (0.932-21.372)
Margin	1.577	0.000	4.841 (2.239-10.467)
Internal echo	-0.707	0.365	0.493 (0.107-2.279)
Calcification	0.565	0.416	1.760 (0.451-6.872)
Posterior echo	-0.529	0.210	0.589 (0.258-1.346)
Mass walking pattern	1.767	0.006	5.851 (1.642-20.846)

on the 4th edition are still not high enough, and the clinical problem to be faced is over-biopsy of such lesions.

In the 2nd century AD, Gallen described the appearance of breast cancer as a "crab", namely the modern diagnostic sign of burr. However, for dBI-RADS-US4-nPBLs, their sonographic features are not sufficiently exposed but mammography has a higher misdiagnosis rate for lesions in dense breasts. Although ultrasound has advantages in dense breasts, previous ultrasound diagnoses lacked uniform standards, so the diagnosis often depended on the clinical experience of the sonographers, but it is difficult to provide a standardized and clear basis for clinical diagnosis.

Yoon et al. [13] and the new BI-RADS (5th edition, ACR, 2013) [14] specified the malignant ranges of the three subcategories of BI-RADS4 lesions based on their shape, walking pattern, edge, and posterior echo, namely 4A (2%-10%), 4B (10%-50%), and 4C (50%-95%), with positive predictive values of 7.6%, 37.8%, and 81.9%, respectively. In this study, the positive predictive values for 4A, 4B, and 4C were 15.6%, 56.1%, and 93.1%, respectively. Obviously, the new subcategorization significantly increases the positive predictive value, so these classification criteria will help to standardize the application of ultrasound terms and clinical decisions about management of lesions.

The new classification criteria focus on defining 4A and 4B as the cut-off point for diagnosing benign and malignant lesions. In this study, we identified the cut-off point as 4B according to the ROC. The AUC was 0.818, which has diagnostic significance. Only six cases out of the 55 malignant lesions belonged to 4A (10.9%), indicating that this category can appropriately avoid a biopsy or follow-up, but 4B and 4C should undergo a biopsy.

In this study, a total of 49 4B and 4C malignant lesions showed irregular shapes, non-parallel growth, burrs, or sublobes [15-18]. The results of this study suggest that non-palpable lesions have significant differences in their shape, edge, internal echo, posterior echo, and microcalcifications ($P<0.05$). The results indicate that morphological changes are effective sonographic changes for the differentiation of benign and malignant breast lesions. The malignant lesions in this study exhibited irregular shapes, with a sensitivity of 89.1%, but the specificity was low (40.4%). The specificity of posterior echo attenuation was 80.9% with a positive predictive value of 70.0%, and therefore, posterior attenuation has great value in diagnosing malignant breast cancers. In multivariate analyses, only the mass walking pattern and margin were significant predictors of malignancy. Shape was close to the significance level, while internal echo, posterior echo, and calcification were not significant predictors of malignant lesions.

Vibert and Valleron defined descriptors such as irregular shape, hybrid echo, posterior attenuation, fine burr, non-parallel growth, microcalcification, and ductal ectasia as the sonographic features suspicious for malignancy [19]. The results of this study showed the sensitivity and positive predictive value of burr were 95.7% and 90.9%, respectively; therefore, the risk of malignancy if a burr is present is high, and thus, it exhibits a high value for the diagnosis of breast cancer [17]. Microcalcification is one specific significant sign of breast cancer or ductal carcinoma [18].

It has been thought for a long time that coarseness and microcalcifications are the most useful signs for identifying benign and malignant tumors [19]. The 5th edition of the ACR removed the definition of coarse calcifications as benign calcifications, and states that any kind of calcification, no matter how coarse or fine, increases the risk of malignancy. In this study, the sensitivity of microcalcifications for diagnosing malignancy was 25.5%, with a specificity of 89.4%. This study included only one case of

BI-RADS 4A invasive ductal carcinoma (2.6%), and the rest were 16 cases of 4B (42.1%) and 21 cases of 4C (55.3%), indicating that identification of microcalcificationsis the main sonographic feature of invasive breast cancer.

The following new concepts were identified in this study: flow signals are not specific for identifying benign and malignant breast tumors; for example, certain malignant lesions lack a blood supply or peripheral blood, but some benign lesions such as inflammatory lesions have a rich blood supply. Furthermore, detection of flow is closely related to the equipment sensitivity and operators' techniques, and therefore, the emphasis placed on flow signals should be reduced. Elastography has various results, is very dependent on the operator, and has more overlapping features, and we conclude that the effectiveness of elastography cannot be recognized, but it can be used as a secondary reference.

Rare cases such as breast angiosarcoma, neuroendocrine tumors, and medullary carcinoma lack imaging and ultrasound specificities [20], and they belong to BI-RADS category 4A and are difficult to distinguish from benign lesions. In addition, among the non-palpable lesions, intraductal carcinomas accounted for 16.4% (9/55), and were in stage 0 or I, a significantly higher diagnosis rate than that found by traditional palpation.

In summary, BI-RADS4 malignant lesions have a wide range of malignancy prevalence, and therefore, a biopsy is usually required for pathological diagnosis. Irregular shape has a higher sensitivity for the diagnosis of breast cancer, and burr, sublobe, posterior echo attenuation, microcalcification, and mass walking pattern have higher specificities in diagnosing breast cancer. The influence of flow signals should be reduced, and the effectiveness of elastography cannot be recognized. High-resolution ultrasound is the preferred ultrasound screening method for young women with dense breasts, and its use for screening, diagnosis, and resection can be expected to occupy a dominant position in the future.

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Disclosure of conflict of interest

None.

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