

Application of a second opinion ultrasound in Breast Imaging Reporting and Data System 4A cases: can immediate biopsy be avoided?

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Abstract

Objective: The probability of malignancy in women who are diagnosed with a Breast Imaging Reporting and Data System (BI-RADS) 4A score is low. Application of a second opinion ultrasound (SOUS), which is low in cost and minimally invasive, may lower the biopsy rate for patients who fall into this category. This study aimed to apply SOUS to patients with a BI-RADS score of 4A and predict the pathological results of a biopsy.

Methods: One hundred seventy-eight patients were analyzed. Univariate and multivariate analyses were performed to screen for predictive factors that are associated with malignancy. Categorical alteration of downgraded, unchanged, or upgraded was made after SOUS results. Changes in category were compared with biopsies to determine their predictive value of benignancy or malignancy.

Results: Independent factors associated with malignancy were age (>50 years), tumor size (≥ 20 mm), margin (not circumscribed), orientation (not parallel), and peripheral location, and an upgraded categorical alteration from SOUS. Downgraded categorical alterations were associated with benignancy.

Conclusions: In BI-RADS 4A cases, a biopsy is recommended when independent factors are associated with malignancy. A downgraded result from an SOUS examination is a protective factor, supporting the likelihood of benignancy in these patients.

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Keywords

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Introduction

Ultrasound is commonly used as a tool of breast cancer screening. Results from ultrasound screening are usually dependent on the operator, and are related to clinical experience and sometimes personality. Overestimates or underestimates of lesions can either lead to a misdiagnosis of cancer or an unnecessary biopsy.

The first version of the Breast Imaging Reporting and Data System (BI-RADS) was developed in 2003, aiming to standardize characterization of breast lesions with ultrasound and improve communication between general surgeons and radiologists.¹ The newest version of this system was updated in 2013.² Factors of lesions, including the shape, orientation, margin, boundary, echo pattern, posterior acoustic features, and surrounding tissue alterations, are defined as descriptors. The status of factors is considered and assigned a BI-RADS score from 0 to 6 to predict the likelihood of malignancy. In this system, category 4 is divided into three subcategories of 4A, 4B, and 4C. For category 4B and 4C, the likelihood of malignancy is >50% and a biopsy is commonly recommended. Patients with a BI-RADS 4A score have a 3% to 10% probability of malignancy and are defined as mild suspicion of malignancy.³ A dilemma in breast cancer is that unnecessary invasive biopsies can occur in benign cases and undiagnosed lesions can occur in malignant cases. In clinical practice, a biopsy is usually recommended to avoid misdiagnosis of cancer in 10% of patients. Therefore,

90% of patients suffer from unnecessary invasive manipulation.

Typically, ultrasound results are based on real-time videos and images of screenshots noted by a radiologist during the original examination. These screenshots are static and isolated, which may lead to uncertain or unobjective assessment in characterizing the BI-RADS stage of lesions.⁴ An SOUS is low cost and may benefit the majority of these patients if predictive factors that correlate with malignancy and benignancy can be identified. An SOUS is defined as re-evaluation of a lesion(s) via ultrasound within 2 weeks, with total independence from the first examination and evaluation by a different radiologist. Multiple studies in various cancer centers have shown that having a radiologist take a second look at previously obtained ultrasounds can decrease the risk of unnecessary surgery.⁵⁻⁷

This study aimed to identify clinical factors and assess the ability of an SOUS to predict pathological results of initially diagnosed BI-RADS 4A in patients, and increase the accuracy of detecting breast cancer and minimizing unnecessary biopsies.

Methods

Patients

Patients who were initially diagnosed with BI-RADS 4A by ultrasound in our center between September 2017 and September

2020 were included in this study. An SOUS was performed within 1 week of the initial diagnosis and was reviewed by a radiologist specializing in breast imaging (with >5 years of experience) without reference to the previous results. All patients received a biopsy and were then grouped as benign or malignant according to pathological reports.

Clinical information of patients was retrospectively obtained from an electronic medical record system, including age, lesion location and dimensions, BI-RADS classification, and a pathological report. The age of 50 years was used to divide patients into two groups. The location of lesions was grouped as central for retroareolar lesions and peripheral for all others. The following factors of an SOUS were recorded: tumor size, blood flow signal, margin, orientation, echo pattern, posterior features, and internal calcification. Tumor size was grouped in relation to the diameter of the lesion. Changes in ultrasound results were classified as downgraded, unchanged, or upgraded according to the results of the SOUS. A BI-RADS score of 0 from an SOUS scan was defined as upgraded.

This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital (approval no. 2016-147-T96). Written informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was performed with IBM SPSS 21.0 (IBM Corp., Armonk, NY, USA). Groups were compared using the chi-square test or Fisher's exact test. Multiple logistic regression analysis was used to determine independent risk factors of malignancy (variables with $P < 0.05$ in the univariate analysis were included). Pathological results of biopsies were set as the diagnostic standard for evaluating

SOUS. Statistical significance was defined as $P < 0.05$.

Results

A total of 178 patients with an initial ultrasound result that was categorized as BI-RADS 4A were included in this study. The mean age of patients was 47.7 ± 13.8 years and age ranged from 15 to 85 years old. The mean tumor size was 14.6 ± 9.8 mm and it ranged from 2 to 59 mm. All patients received a biopsy after an SOUS scan within 1 week and were then grouped as 143 benign cases and 35 malignant cases. The patients' demographics are shown in Table 1. The characteristics of SOUSs are shown in Table 2. Typical ultrasound images are shown in Figure 1.

Univariate and multivariate analyses of predictive factors are shown in Table 3. Univariate analysis of potential predictive factors related to pathological results showed that an age older than 50 years, a larger tumor size (≥ 20 mm), a positive blood flow signal on ultrasonography, no circumscribed tumor margin, an irregular tumor shape, no parallel orientation of the tumor, no internal calcification, a peripheral location of the lesion, and an upgraded SOUS were malignancy-related factors (all $P < 0.05$). These factors were included in multivariate analysis, which showed that age (> 50 years), tumor size (≥ 20 mm), no circumscribed tumor margin, no parallel orientation of the tumor, a peripheral location of the tumor, and an upgraded SOUS scan result were significant independent factors for malignancy (all $P < 0.05$). Only 8 of the 178 patients did not have any of these factors and all of their biopsy reports of lesions were proven to be benign. Among the 36 downgraded patients by an SOUS, no malignant cases were found.

Table 1. Patients' demographics.

Characteristic of the patients	Patients, n (%)
Age (years)	
≤50	101 (56.7)
>50	77 (43.3)
Pathological result	
Benign	143 (80.3)
Malignant	35 (19.7)
Location	
NAC	50 (28.1)
Peripheral	128 (71.9)

NAC, nipple and areola complex.

Table 2. Characteristics of an SOUS.

Characteristic of the patients	Patients, n (%)
Tumor size	
<20 mm	133 (74.7)
≥20 mm	45 (25.3)
Blood flow signal*	
Negative	90 (50.1)
Positive	76 (42.7)
Tumor margin	
Circumscribed	108 (60.7)
Not circumscribed	70 (39.3)
Tumor shape	
Regular	98 (55.1)
Irregular	80 (44.9)
Echo pattern	
Homogeneous	19 (10.7)
Heterogeneous	159 (89.3)
Tumor orientation	
Parallel	152 (85.4)
Not parallel	26 (14.6)
Posterior features of the tumor	
Negative	84 (47.2)
Positive	94 (52.8)
Internal calcification	
Yes	123 (69.1)
No	55 (30.9)
SOUS alterations	
Downgraded	36 (20.2)
Unchanged	116 (65.2)
Upgraded	26 (14.6)

*The status of the blood flow signal was not described in 12 pathological reports.

SOUS, second opinion ultrasound.

Discussion

Ultrasound is widely applied for evaluating the risk of malignancy in relation to morphological features of breast lesions. Ultrasound has a special advantage in evaluating dense breast tissue, which is common in Eastern women, and is standardized by the BI-RADS lexicon.⁸ The advantages of ultrasound are that it is simple, cost-effective, and has radiation-free imaging, which is desirable by patients and physicians.⁹ Patients with BI-RADS 4A comprise the majority of BI-RADS 4 cases, which is the most controversial subcategory owing to its malignancy ratio. This controversy usually causes hesitation about whether to perform a biopsy or simply perform a follow-up. Although the BI-RADS lexicon was set to ensure that ultrasound diagnoses are standardized and objective, there are still influential characteristics, such as clinical experience by radiologists.¹⁰

An SOUS, also called a second-look ultrasound, has been described in several studies as an additional examination following a previous ultrasound, mammogram, or magnetic resonance imaging scan.¹¹ An SOUS may provide additional information for further characteristics of lesions, and may sometimes rectify incorrect conclusions of previous radiological examinations.¹² In our study, an SOUS was applied in patients with BI-RADS 4A with the aim of improving diagnostic accuracy of breast cancer, possibly avoiding unnecessary biopsies. We found that a downgraded SOUS scan result was a protective factor supporting the likelihood of benignity. Patients who had the following standards may also be considered as benign: ≤50 years and having a parallel and centrally located lesion <20 mm in diameter that displayed clear margins. These patients might safely benefit from avoiding an immediate biopsy, while follow-up is still recommended. BI-RADS

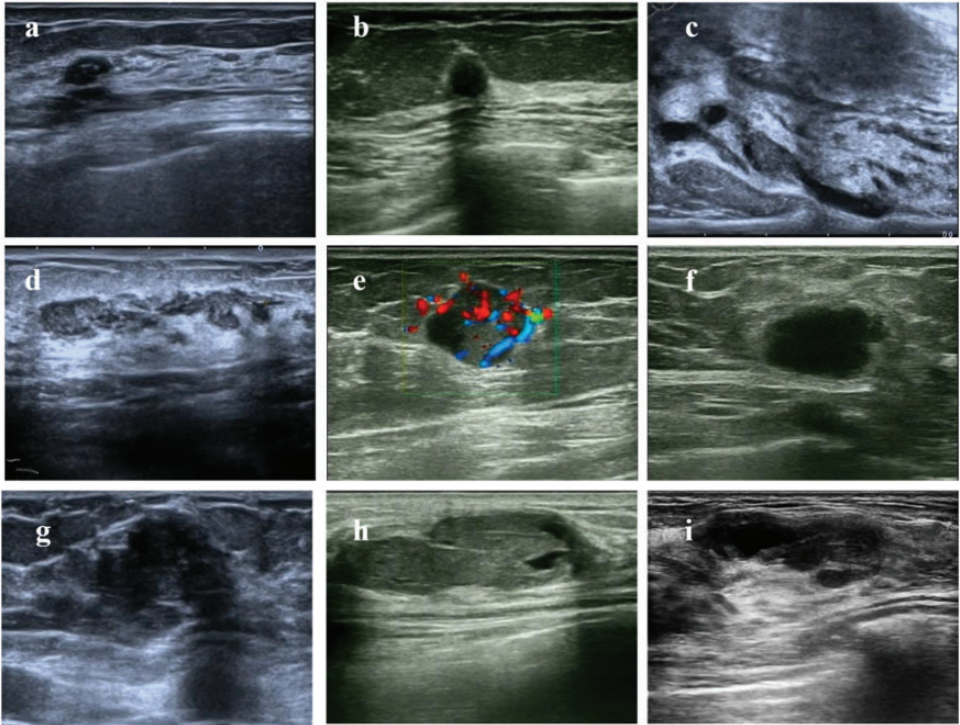


Figure 1. Typical ultrasound images for an SOUS. (a–c) Screenshots of downgraded lesions from an SOUS examination. The three lesions were initially diagnosed as BI-RADS. Internal calcification (a), not having a parallel orientation (b), and intraductal calcification (c) were considered major factors indicating the diagnosis of BI-RADS 4A. Pathological reports showed that the lesions were fibroma (a and b), and intraductal papilloma (c). (d–f) Images of lesions diagnosed as BI-RADS 4A by initial ultrasound and SOUS scans. An irregular shape and heterogeneous echo pattern can be seen in a lesion (d) and a pathological examination showed granulomatous inflammation. Lesions in panels e and f were suspected as malignant lesions because of visible blood flow in the lesions (most malignant tumors show a blood supply) (e) and an irregular shape (f). Both lesions were invasive carcinoma. (g–i) Images of lesions that were initially diagnosed as BI-RADS 4A and upgraded to BI-RADS 4B by an SOUS. The three lesions showed similar characteristics of an irregular shape and heterogeneous echo pattern. Final pathological results of the three lesions indicated a borderline lobulated tumor (g) and invasive carcinoma (h and i).

SOUS, second opinion ultrasound; BI-RADS, Breast Imaging Reporting and Data System.

4A cases may be subcategorized into a low-risk group and normal-risk group according to the results of SOUS, regardless of whether the results are downgraded.

The rate of malignancy in BI-RADS 4A cases was 19.7% in this study, which is much higher than that found in most other studies (3%–10%).¹³ This finding could be mainly explained by bias from patient selection. A biopsy was

recommended to all patients who were diagnosed with BI-RADS 4A by a first or second ultrasound. Ultimately, the patient made the decision of whether to receive an immediate biopsy or close follow-up. Patients usually choose follow-up instead of a biopsy for the following reasons: (1) mental resistance of invasive manipulation; (2) having received a biopsy of the same lesion previously with a benign result; (3)

Table 3. Univariate and multivariate analyses of predictive factors.

Characteristic	Benign, n (%)	Malignant, n (%)	Univariate P value	Multivariate P value
Age			0.026	0.009
≤50 years	87 (86.1)	14 (13.9)		
>50 years	56 (72.7)	21 (27.3)		
Tumor size			<0.001	<0.001
<20 mm	117 (88.0)	16 (12.0)		
≥20 mm	26 (57.8)	19 (42.2)		
Blood flow signal			0.001	0.280
Negative	82 (91.1)	8 (8.9)		
Positive	54 (71.1)	22 (28.9)		
Tumor margin			<0.001	<0.001
Circumscribed	102 (94.4)	6 (5.6)		
Not circumscribed	41 (58.6)	29 (41.4)		
Tumor shape			<0.001	0.702
Regular	88 (89.8)	10 (10.2)		
Irregular	55 (68.8)	25 (31.2)		
Echo pattern			0.095	
Homogeneous	18 (94.7)	1 (5.3)		
Heterogeneous	125 (78.6)	34 (21.4)		
Tumor orientation			0.002	0.001
Parallel	128 (84.2)	24 (15.8)		
Not parallel	15 (57.7)	11 (42.3)		
Posterior features of the tumor			0.184	
Negative	71 (84.5)	13 (15.5)		
Positive	72 (76.6)	22 (23.4)		
Internal calcification			0.003	0.311
Negative	92 (74.8)	31 (25.2)		
Positive	51 (92.7)	4 (7.3)		
Location of the tumor			0.001	0.011
Central	53 (94.6)	3 (5.4)		
Peripheral	90 (73.8)	32 (26.2)		
SOUS alterations				0.016
Downgraded	36 (100.0)	0 (0.0)	0.002*	
Unchanged	94 (81.0)	22 (19.0)	Ref	
Upgraded	13 (50.0)	13 (50.0)	0.002**	

*Comparison between downgraded and unchanged from the result of an SOUS by the chi-square test.

**Comparison between upgraded and unchanged from the result of an SOUS by the chi-square test.

SOUS, second opinion ultrasound.

a stable lesion is confirmed by several follow-ups; and (4) contraindication of biopsies. The composition of breast tissue varies with individual hormonal status and is associated with the menstrual cycle, which may lead to different results. Additionally, the interpretation by the

radiologist may also slightly affect the classification of ultrasound results when making the decision between BI-RADS 3 and 4A.

Multivariate analysis in this study showed that age, tumor size, margin, orientation, and location, and upstaging by an

SOUS scan were independent factors related to malignancy. Fu et al.¹⁴ compared the age of patients with BI-RADS 3, 4, or 5 and found that age was significantly higher in groups 4A and 4B than in the other groups. Similar conclusions were found in a study by Leblebici et al.¹⁵ With increased age, mammary gland tissue tends to degenerate and blend with adipose tissue.¹⁶ Additionally, decreased levels of hormones cause replacement of original mammary gland tissue with atrophic epithelial and adipose cells. These factors increase difficulty in evaluating the status of lesions as a function of age.¹⁷ Qualitative changes in mammary tissue also increase the risk of malignant transformation and may explain the significantly higher rate of malignancy in patients older than 50 years.

Although the lesion boundary was associated with malignancy in this study, the state of the lesion boundary was removed from the newest version of the BI-RADS lexicon. This deletion was based on the low diagnostic value of the presence of an echogenic transition zone or echogenic rim versus an abrupt margin transition zone of a mass to discriminate.¹⁸ However, the description of the margin is still standardized, leaving the option open for the potential of the state of the lesion boundary to return in future, updated lexicons.

Retroareolar benign lesions are easily suspected to be malignant because of signs of ductal ectasia, vascularity, and a cystic-solid mixture, leading to an increased possibility of a false diagnosis. A denser distribution of glandular tissue, blood vessels, and central location of the mammary duct might partially explain this phenomenon. In contrast, patients with a sparse distribution of the mammary gland and duct, and lesions in peripheral locations showing a more typical appearance and are more likely to be grouped into BI-RADS 3 or higher than BI-RADS 4A. Cai et al.¹⁹ also found that sonographic features favoring

malignancy included the location of the lesion. These authors showed that a peripheral location favored a malignant process, whereas a central location favored a benign process, but the reason for this finding remains unexplained.

Traditionally, internal calcification is recognized as a potential risk factor for malignancy. Interestingly, the results from our study are different from conventional perception. The ratio of malignant lesions to internal calcification was low, which indicated that internal calcification was a potential factor of benignancy. In the second version of the BI-RADS ultrasound lexicon published in 2013, "macrocalcification" was removed from calcification terminology, but the term "intraductal" was added.¹⁹ Among the 51 benign cases with internal calcification in our study, a pathological examination showed that most lesions were fibroadenomas (28, 54.9%), mastopathies (18, 35.3%), and intraductal papillomas (5, 9.8%). These were not subcategorized on the basis of macrocalcification, microcalcification, or intraductal calcification. When macrocalcification is considered as a risk factor of malignancy, benign lesions with macrocalcification are likely to be overestimated. These lesions may comprise the majority of fibroadenomas with calcification, which should actually be grouped into BI-RADS 3 instead of 4A. Reports of ultrasound should be standardized by subcategorization of internal calcification according to the newest BI-RADS lexicon. This subcategorization would avoid overestimation of lesions and unnecessary invasive biopsy or surgery.

This study is the first to investigate pathologically relevant clinical and sonographic factors, and the value of an SOUS in predicting malignancy or benignancy in BI-RADS 4A cases. Multivariate analysis showed that age, tumor size, margin, orientation, and location, and upstaging by an

SOUS scan were independent factors associated with malignancy and the necessity of a biopsy. A downgraded SOUS scan result with a previous BI-RADS 4A result indicated a benign process and relatively safety for these patients to have follow-up performed instead of an immediate biopsy. These findings should be further confirmed in large-scale studies.

This study has some limitations. This was a retrospective study, and therefore, selection bias was inevitable. Information of patients with BI-RADS 4A who did not receive a biopsy was not included, which may have affected the data analysis. Most patients received other radiological examinations, including mammography and magnetic resonance imaging before a biopsy. Because our study focused on the clinical value of an SOUS, the results of mammography and magnetic resonance imaging were not included. The importance of multimodal radiological examination should be analyzed in future studies.

Conclusion

In this study, an SOUS was performed in patients who were initially diagnosed with BI-RADS 4A in a previous ultrasound examination. Our study shows that age, tumor size, margin, orientation, and location, and upgraded results of SOUS are independent factors associated with malignancy, and biopsy is still highly recommended. A downgraded SOUS result is a protective factor for the likelihood of benignancy and these patients should avoid an immediate biopsy. Our findings suggest that an SOUS is an accurate and feasible technique, which can greatly increase the diagnostic accuracy in patients who are initially diagnosed with BI-RADS 4A. Although further large-scale studies are required for confirm our results, these results are encouraging.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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