### Original Article Conventional ultrasound, ultrasound elasticity imaging, and acoustic radiation force impulse imaging for prediction of malignancy in breast masses

Jing-Jing Gong<sup>1,2,3\*</sup>, Zhao-Xia Wan<sup>4\*</sup>, Ming-Hua Yao<sup>1,2</sup>, Li-Xia Zhao<sup>1,2</sup>, Guang Xu<sup>1,2</sup>, Hui Liu<sup>1,2</sup>, Rong Wu<sup>1,2</sup>

<sup>1</sup>Department of Medical Ultrasound, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, China; <sup>2</sup>Ultrasound Research and Education Institute, School of Medicine, Tongji University, Shanghai 200072, China; <sup>3</sup>Department of Medical Ultrasound, Shanghai Changning Maternity and Infant Health Hospital, Shanghai 200051, China; <sup>4</sup>Department of Medical Gynaecology, Nantong Traditional Chinese Medical Hospital, Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, Nantong 226001, Jiangsu, China. <sup>\*</sup>Equal contributors.

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Abstract: Purpose: To evaluate the value of conventional ultrasound (US), US elasticity imaging (EI), and acoustic radiation force impulse (ARFI) imaging in predicting breast malignancy. Methods: A total of 323 breast masses from 302 patients underwent conventional US, EI, and ARFI before operation. Multivariate logistic regression analysis was performed to identify the predictors for malignancy. Diagnostic performance was evaluated with receiver operating characteristic (ROC) curve analysis. Results: 231 benign and 92 malignant masses were found. On conventional US, irregular shape, poorly defined margin, > 1 cm in size, inhomogeneous echotexture, contact with the capsule, microcalcification, and Adler II-III on color Doppler US were closely related to breast malignancy. Furthermore, an elasticity score of > 3, a Virtual Touch Tissue Imaging (VTI) grade of > III, and a clear margin on VTI were more common in the malignant group. The average shear wave velocity (SWV) of malignant lesions (7.56 ± 2.54 m/ sec) was higher than that of benign lesions (3.40 ± 1.96 m/sec). Multivariate logistic regression analysis showed that SWV, mass boundary on VTI, mass boundary on conventional US, microcalcification, and blood flow distribution were risk factors for predicting breast cancer. When the cut-off SWV value of 6.99 m/s was applied for the diagnosis of breast cancer, the area under the ROC curve for SWV was 0.859, and the sensitivity and specificity were 78.3% and 90% respectively. The accuracy was the highest in various US features. Conclusion: ARFI imaging is promising for malignant breast mass prediction, with a higher diagnostic performance compared with conventional US or El. Therefore, ARFI can be used to supplement conventional US to diagnose breast masses.

Keywords: Breast masses, conventional ultrasound, ultrasound elasticity imaging, acoustic radiation force impulse imaging

#### Introduction

Breast cancer is a common cause of female cancer deaths and seriously threatens the physical and mental health of women. Early detection and diagnosis are important for the treatment planning and prognosis evaluating for breast cancer [1, 2]. Ultrasound (US) is a key diagnostic method for breast cancer. Due to the diversity and similarity of US features for benign and malignant breast tumors, US may lead to misdiagnosis in some cases. In recent years, new technologies, such as elastography, have been emerging, thereby making the diagnosis of complicated breast diseases more accurate. Different from traditional elastographic techniques which have difficulties in applying pressure to deep tissue and are easily affected by the environment, Acoustic Radiation Force Impulse (ARFI) elastography is a new technology that applies pressure to tissue via ultrasound. ARFI technology, including Virtual Touch Tissue Imaging (VTI) and Virtual Touch Tissue Quantification (VTQ), can present elastograms and elastic values at the same time. Therefore, ARFI can evaluate the stiffness of lesions in a more objective and comprehensive way [3, 4]. Since ARFI technology is developing and being widely supported, it can provide clinicians with more valuable quantitative stiffness informa-



**Figure 1.** Elastographic and pathological findings of breast fibroadenoma. A. Conventional US demonstrates a regularly shaped tumor with even echoes and a compression UE score of 3. B. VTI demonstrates a tumor of Grade III with undefined boundaries. C. VTQ demonstrates a SWV value of 2.68 m/s. D. The pathological diagnosis (HE × 200) is fibroadenoma.

tion for the diagnosis and treatment of breast cancer [5-7].

This study applies conventional US, US Elasticity Imaging (EI), and ARFI technology to the analysis of breast cancer. The aim was to explore the relationship between breast cancer and US characteristics, and present the risk factors for breast cancer.

#### Materials and methods

#### Materials

A total of 304 breast tumor cases (one male patient and 303 female patients), which were examined through US and confirmed by pathol-

ogy between February 2013 and June 2014 in a tertiary hospital, were selected for the current study. The chosen patients are between 18 years old and 90 years old, with an average age of 45.2 ± 15.5 years old. The tumors are between 8 mm and 88 mm long, with an average diameter of 18.29 ± 10.0 mm. The selecting standards included: (1) no biopsy of lesions, surgery, or chemotherapy was conducted before the operation; (2) the two-dimensional (2D) color Doppler US, compression ultrasound elastography (UE), and ARFI technology were applied in the preoperative examinations; (3) the complete data were reserved; and (4) there were pathological results from the surgery or biopsy. The exclusion standards included: (1)



**Figure 2.** Elastographic and pathological findings of infiltrative ductal breast cancer. A. US demonstrates an irregularly-shaped tumor with uneven echoes and a compression UE score of 4. B. VTI demonstrates a tumor of Grade IV with clearly-defined boundaries. C. VTQ demonstrates a SWV value of X.XX m/s. D. The pathological diagnosis (HE × 200) is infiltrative ductal carcinoma of Grade II.

the minimal diameter of the tumor was shorter than 5 mm; (2) the maximal diameter of the tumor was shorter than 8 mm; (3) the 2D US demonstrated cystic tumors; (4) elastographic signals were absent.

#### Methods

*Instruments:* With instruments, including a color Doppler ultrasound device (Siemens Acuson S2000) and a 5-14 MHz linear probe, this study applies UE and ARFI technology.

*Examination method:* Examiners observed the breast tumor via 2D conventional US. We referred to the description provided by Del et al [8] upon examination of the ultrasonic signs of

the tumor. For tumor examination via US, we studied the size (taller than wide), shape (regular or irregular), boundary (clear or unclear), internal echo (even or uneven), cystic component (cystic or non-cystic), and calcification (non-calcification, coarse calcification, or microcalcification). The peripheral and internal blood flow signals were observed via the color Doppler ultrasound device. The richness of the blood flow signals were classified from Grade 0 to Grade III based on the semiquantitative method provided by Alder et al [9].

When compression UE was applied for the examination, the probe was placed perpendicularly and softly on the surface of the tumor. The

Benign Tumor	Number of Lesions	Malignant Tumor	Number of Lesions
Fibroadenoma	156	Infiltrative Ductal Carcinoma	78
Mastopathy	51	Papillocarcinoma	3
Intraductal Papilloma	16	Infiltrative Breast Cancer	3
Complex Adenoma	1	Intraductal Carcinoma	3
Mastitis	1	Infiltrative Lobular Carcinoma	2
Phyllodes Tumor	3	Well-differentiated Adenocarcinoma (Tubular Carcinoma)	1
Atypical Ductal Hyperplasia	1	Mucinous Carcinoma	2
Hamartoma	2		
Total	231	Total	92

 Table 1. Pathological types of 323 breast lesions

Table 2. Basic characteristics of patients and lesions

Characteristics	Benign Lesions	Malagment Lesions	P Value
Number of Cases	231	92	
Average Age (years)	$40 \pm 14$	58 ± 13	.026
Maximum of Average Length-diameter (mm)	$17 \pm 10$	22 ± 9	.286
Location of Lesions			.281
Left Breast	108 (111)	47 (44)	
Right Breast	123 (120)	45 (48)	
Distribution of Lesions			< .001
Solitary Cases	90 (106)	58 (42)	
Multiple Cases	141 (125)	34 (50)	

tumor was located in the center of the image area that was twice as big as the size of the tumor. Real-time observation of the 2D image and the elastogram were conducted. When the Quality factor (QF) value in the screen was higher than 65 and the lesion color in the elastogram was fixed, the image was frozen and saved. Color-coding was used to measure the elastic properties of the tissue. Most elastographic examinations conducted abroad [10-13] were performed based on the UE scoring system proposed by the University of Tsukuba in Japan.

In the VTI mode, the region of interest (ROI) was appropriately adjusted so that it covered the tumor and its peripheral breast tissue. The grey-scale coding was applied for the VTI image; the light areas indicated the soft tissues, whereas the dark areas corresponded to the hard tissues. With the reference of the previous VTI score standard [14-16], the VTI images of lesions were divided into five grades: Grade I demonstrated total white lesions; Grade II demonstrated total grey lesions; Grade IV demonstrated greyish black or primarily grey lesions; Grade V demonstrated black or blackish grey lesions. Boundaries of lesions in the VTI images were clearly defined or unclearly defined.

In the VTQ mode, the ROI (6 × 5 mm) was located within the lesion as well as in the gland tissue, which is 1-2 cm away from the lesion at the same depth. After the update button was pressed, the device automatically measured the VTQ value (m/s) of the area. Seven valid values were measured separately, and the images were saved on the hard drive. The average shear wave velocity (SWV) of the lesion and the surrounding gland tissue was calculated without the highest and lowest records. According to related works [17], the value "X.XX m/s" is replaced by "9 m/s" in this group. The small VTQ values indicate soft tissue, whereas the large VTQ values correspond to hard tissue. All the images were analyzed by four senior doctors.

#### Statistical analysis

Statistical analysis was performed by using SPSS software (version 13.0; SPSS, Chicago,

Ultrasonic Characteristics	Benign Lesions (n = 231)	Malignant Lesions (n = 92)	P Value
Conventional Ultrasound			
Shape			< .001
Regular	136 (106)	12 (42)	
Irregular	95 (125)	80 (50)	
Boundary			< .001
Clear	180 (144)	22 (58)	
Unclear	51 (86)	70(35)	
Taller than wide			< .001
≤1	226 (216)	76 (86)	
> 1	5 (15)	16 (6)	
Echo			< .001
Even	104 (79)	7 (32)	
Uneven	127 (152)	85 (60)	
Cystic Component			.015
Non-cystic	227 (223)	85 (89)	
Cystic	4 (8)	7 (3)	
Calcification			< .001
Non-calcification	186 (160)	37 (63)	
Coarse calcification	29 (35)	20 (14)	
Microcalcification	16 (37)	35 (14)	
Blood flow			< .001
Grade 0-I	205 (184)	52 (73)	
Grade II-III	26 (47)	40 (19)	
Compression Ultrasound			
Elastography			< .001
Elastography Score $\leq$ 3	165 (139)	29 (55)	
Elastography Score > 3	66 (92)	63 (37)	
ARFI Imaging			
VTI			< .001
Grade ≤ III	196 (157)	23 (62)	
Grade > III	35 (74)	69 (30)	
Boundary of VTI			< .001
Clear	45 (81)	68 (32)	
Unclear	186 (150)	24 (60)	
VTQ			
Average SWV of Lesion (m/s)	3.40 ± 1.96	7.56 ± 2.54	< .001
Average SWV of Peripheral Area of Lesion (m/s)	2.01 ± 0.73	2.30 ± 0.78	.725

 Table 3. Characteristics of conventional ultrasonogram, compression ultrasonic elastogram and ARFI image of benign and malignant breast lesions

III). A T-test was applied to the data with normal distribution, whereas a Non-parametric Wilcoxon Test was applied to the data with non-normal distribution. A Chi-square test was used to compare the clinical features of the benign and malignant tumors. A multivariable regression analysis was used to predict the risk factors for breast cancer. The ROC curve was used to explore the sensitivity and specificity of ultrasonic signs in the diagnosis of breast cancer. P < 0.05 was considered to be statistically significant.

#### Results

Pathological results for puncture and operation

Among all 304 cases, 323 lesions were examined. According to the pathological results,

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0.8.10				
Parameters	OR	95% CI	P Value	
Conventional Ultrasound				
Shape	2.10	0.61-7.24	.242	
Boundary	7.6	2.28-25.35	.001	
Aspect Ratio	1.27	0.23-7.08	.783	
Echo	1.02	0.262-4.00	.972	
Cystic Component	6.27	0.71-55.67	.099	
Calcification	6.25	1.76-22.16	.005	
Blood Flow	4.78	1.42-16.05	.011	
Compression Ultrasound				
El Score	1.54	0.55-4.33	.416	
ARFI Imaging				
VTI Grade	1.85	0.61-5.64	.278	
VTI Boundary	15.77	4.26-58.37	< .001	
VTQ	26.03	7.94-85.28	< .001	

Table 4. Logistic regression analysis of pre-
diction in breast cancer based on ultrasonic
signs

there were 231 benign tumors (**Figure 1**) and 92 malignant tumors (**Figure 2**). Details of pathological types can be found in **Table 1**.

## Comparison between pathological diagnosis and basic characteristics of lesions

The ages of patients and the distribution of lesions (P < 0.05) indicated the basic characteristics for the identification of benign and malignant breast tumors. We observed that breast cancer was more frequently seen in elderly patients or single-lesion cases. The maximal length-diameter and the location of the lesion showed no important differences in the identification of benign and malignant breast tumors (**Table 2**).

# Comparison of conventional US, compression UE, and ARFI images of benign and malignant breast lesions

Conventional US features, such as irregular shaped, unclear boundaries, taller than wide > 1, uneven echoes, cystic components, microcalcification, and Adler Grade (II-III) are closely related to the ultrasonic demonstrations of breast cancer (P < 0.05). An elastography score of > 3, VTI grade of > III, and clearly-defined boundaries in VTI images were more commonly seen in cases of malignant lesions (P < 0.05). In all cases with a *P* value lower than 0.05, the average SWV value of the malignant lesion (7.56 ± 2.54) was higher than that of the benign lesion (7.56 ± 2.54). The SWV value of the gland tissue, which is located around the lesion in the same depth, was not statistically different in the benign versus malignant cases (P = 0.725) (Table 3).

Multivariable regression analysis of ultrasonic signs

According to results of the Multiple Logistic Regression Analysis, the VTQ value, VTI boundary, tumor boundary, calcification, and blood flow in the conventional US indicate five risk factors for the US prediction of breast cancer (P < 0.05, see **Table 4**). The respective odds ratio (OR) was 26.03, 15.77, 7.6, 6.25, and 4.78, respectively, whereas the 95% Confidence Interval (CI) was 7.94-85.28, 4.26-58.37, 2.28-25.35, 1.76-22.16, and 1.42-16.05, respectively.

## Analysis of ultrasonic signs based on ROC curves

When the VTQ cut-off value was 6.99 m/s for the diagnosis of breast cancer, the area under the curve (AUC) was 0.859 with a sensibility of 78.3% and a specificity of 90.0%, which lead to the highest accuracy of breast cancer diagnosis (**Table 5**; **Figure 3**).

#### Discussion

Because the incidence of breast cancer is gradually increasing, it is very important to identify the population with a high-risk of developing breast cancer and persuade these individuals to conduct preventive measures and regular body check-ups. Therefore, researchers have proposed a large number of breast cancer prediction models [18-20]. By studying the risk factors for breast cancer among White Americans, the Gail Model established an individualized breast cancer prediction model, which is the most widely used model by physicians. The major risk factors include race, age, family history of breast cancer, breast biopsy frequency, menarche age, initial childbearing age, and existence of atypical hyperplasia in the biopsies of benign lesions. The present study aimed to provide clinical evaluation standards in terms of ultrasonic images to make the diagnosis and evaluation of breast cancer more accurate and objective.

Patient age, maximal length-diameter ratios, and locations of tumors, as well as the occurrence of solitary or multiple lesions were con-

Parameters	AUC	95% CI	Cut-off Value	Sensibi- lity (%)	Specifi- city (%)	
Conventional Ultrasound						
Shape	0.729	0.67-0.79	Irregular	87.0	58.9	
Boundary	0.770	0.71-0.83	Unclear	76.1	77.9	
Taller than wide	0.576	0.50-0.65	> 1	17.4	97.8	
Echo	0.687	0.63-0.75	Uneven	92.4	45	
Cystic Component	0.53	0.46-0.60	Cystic	7.6	98.3	
Calcification	0.656	0.58-0.73	Microcalcification	38.0	93.1	
Blood Flow	0.661	0.59-0.73	II	43.5	88.7	
Compression Ultrasound						
El Score	0.700	0.64-0.76	4	68.5	71.4	
ARFI Imaging						
VTI Grade	0.799	0.74-0.86	IV	75.0	84.8	
VTI Boundary	0.772	0.71-0.83	Clear	73.9	80.5	
VTQ	0.859	0.80-0.91	6.99	78.3	90.0	

Table 5. Analysis of ultrasonic signs based on ROC curves

**ROC curve** 1.0 curve source shape boundary taller than wide 0.8 echo cystic component calcification blood flow Elscore VTI grade VTI boundary 0.6 sensibility VTQ 0.4 0.2 0.0 0.2 0.4 0.6 0.8 1.0 00 1 - specificity

Figure 3. The ROC of ultrasonic signs in the diagnosis of breast masses.

sidered in our study. The results showed that breast cancer was commonly seen in elderly patients with an average age of  $58 \pm 13$  years old and occured more often in single-lesion cases. The maximal length-diameter ratios and the locations of the lesions were equally important in the identification of benign and malignant breast lesions.

In the 2D US, the benign breast tumor was regularly shaped, with clearly-defined boundaries, even internal echoes, nonsignificant or rare blood flow, and a RI value lower than 0.7, whereas the malignant breast tumor was irregularly shaped, with burr-shaped edges, weak posterior echoes, microcalcification spots, a blood flow signal higher than Grade II, and a RI value higher than 0.7. However, clinical practice showed that a considerable number of benign and malignant breast tumors share similar 2D grey-scale images, which, in particular, leaded to a high misdiagnosis and missed diagnosis rates in the early stage of breast cancer due to non-significant symptoms [21]. Therefore, researchers focused on the identification of benign and malignant breast lesions.

Stiffness is one of the most important features of a tissue. In clinical practice, the stiffness of the tissue was examined via palpation, which was subjective, had a high misdiagnosis, and missed diagnosis rate. UE is a newly developed technology that identifies benign and malignant tumors by measuring their relative stiffness.

In terms of imaging patterns, UE can be classified into Compression UE and ARFI Elastography. ARFI technology is a new UE that uses acoustic radiation force impulse, with VTI and VTQ applied for clinical practice. The VTQ technology can quantify the tissue elasticity, thereby enabling the comparisons between neighboring tissue and among different patients.

Our results showed that the elastography scores of benign and malignant breast tumors

were different (P < 0.05). The benign tissue elastography scores were mostly equal to or lower than 3, whereas the malignant tissues were most always equal to or higher than 4. In our study, the AUC of breast cancer diagnosis was 0.700 with a sensibility of 68.5% and a specificity of 71.4%, which indicated that the elastography score had application value but still could not serve as an independent variable in the ultrasonic prediction of breast cancer (P > 0.05). Probably due to its strong dependence on manipulators, this technology can lead to deviation when different or even similar manipulators are used to examine the same lesion at different times. In addition, because of the diversity and complexity of the color elastograms, the five-point scoring system cannot cover all demonstrations of UE, thereby confusing examiners and making score classification difficult. Furthermore, all the above factors can lead to biased diagnosis results. As for other major limitations, the compression UE fails to provide quantitative standards for the measurement of tissue stiffness, probably due to the overlapping elastic coefficients among the different tissue. For example, medullary carcinoma is soft with a two-thirds area of solid substance, a small quantity of interstitial substance, and massive necrosis and bleeding. The cystosarcoma phylloide, has a large quantity of cancer cells and a small amount of fiber and collagen tissue that may not be diagnosed due to low elastography scores and tissue stiffness. The necrosis and liquidation in malignant lesions may also lead to low elastography scores and cause missed diagnosis. However, the complicated calcification, collagenization, and hyaline change as well as the rich interstitial cells in benign lesions are the major factors that cause false-positive results of elastography. Therefore, UE requires further improvement.

According to our study, when the VTQ cut-off value was 6.99 m/s during breast cancer diagnosis, the AUC was 0.859 with a sensibility of 78.3% and a specificity of 90.0%, which lead to the highest accuracy of breast cancer diagnosisamong all ultrasonic signs. The VTI grade (AUC = 0.799, sensibility = 75.0%, specificity = 84.8%) and VTI boundary (AUC = 0.772, sensibility = 73.9%, specificity = 84.8%) resulted in the second and third highest accuracy, respectively, in the diagnosis of breast cancer. In terms of the research results proposed by Mitsuhiro et al [22], when the VTQ cut-off value

was 3.59 m/s during breast cancer diagnosis, the respective sensibility, specificity, and accuracy was 91%, 93%, and 92%, respectively. A total of 56% of cases (51/91) refer to scirrhous infiltrative ductal carcinoma, with the VTQ cutoff value lower than 3.59 m/s in this study. Reasons for a lower VTQ cut-off may refer to the fact that 84.8% of the cases (78/92) are identified as Infiltrative Ductal Carcinoma, with only two mucinous carcinoma cases and no related medullary carcinoma cases.

The present study showed that the boundaries of some benign tumors were clearly defined in the grey-scale image, but difficult to identify in the VTI image. However, the boundaries of many malignant tumors were undefined in the grey-scale image, but clearly-defined in the VTI image with demonstrations of characteristic changes, such as the burr-shaped edges and crab claw-shaped infiltration. The results of the current study showed that the boundaries of malignant breast lesions were much clearer than benign lesions in the VTI image (P < 0.01), which is similar to previous results proposed by Carra et al [23]. Reasons for these results may be due to the fact that the elasticity difference between the malignant breast lesion and the surrounding breast tissue is more significant than the acoustic impedance difference of the conventional US, whereas the elasticity difference between the benign breast lesion and the surrounding breast tissue is similar to the acoustic impedance difference of the conventional US.

In the present study, the VTQ was the strongest independent variable (OR = 26.03) for the prediction of breast cancer risk factors. Other risk factors include the VTI boundary (OR = 15.77), tumor boundary (OR = 7.6), microcalcification (OR = 6.25), and distribution of blood flow (OR = 4.78). These results play an important role in practical work. On the one hand, a larger quantity of risk factors indicates a higher risk of developing breast cancers; on the other hand, the VTQ is the strongest for predicting breast cancer risk factors among all ultrasonic signs, the VTO and the VTI boundary are more convincing than the sonographic signs of conventional US, such as unclearly-defined tumor boundaries, microcalcification, and rich blood flow in the identification of malignant tumors. According to some previous reports, irregular shape, unclear boundaries, angle-shaped edges, or burr-shaped edges of the tumor can

serve as independent risk factors for breast cancer. However, this conclusion was drawn based on the Multivariable Regression Analysis of conventional US. Therefore, the combination of conventional US and ARFI technology has high clinical value in the prediction of breast cancer. A previous study conducted by Yoon et al [24] showed that with the combination of conventional US and ARFI technology, the sensibility, specificity, accuracy, positive predictive value, and negative predictive value during examination could reach 97.5%, 92.3%, 93.6%, 79.6%, and 99.1%, respectively, based on the calculation of the strain ratio.

#### Conclusions

VTQ is the strongest for predicting breast cancer risk factors and has the highest accuracy for breast cancer diagnosis among all ultrasonic signs. As an assisting technique for conventional US, ARFI technology possesses a good prospect for the identification of benign and malignant breast tumors.

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#### Disclosure of conflict of interest

None.

Address correspondence to: Dr. Rong Wu, Department of Medical Ultrasound, Shanghai Tenth People's Hospital, Ultrasound Research and Education Institute, School of Medicine, Tongji University, Shanghai, China. Tel: 86-21-66301031; E-mail: wurong7111@163.com

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