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The differential diagnosis of ultrasonic imaging by automated breast volume scanning in breast cancer

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Summary

Background: This study aimed to evaluate the diagnostic efficiency of coronal ultrasonic characteristics by automated breast volume scanning (ABVS) in differentiating benign from malignant breast lesions, and further compare the differential diagnostic values of handheld ultrasound (HHUS), ABVS, HUUS combined with ABVS, and molybdenum target X-ray (MTXR) in benign and malignant lesions. *Materials and Methods:* This study was retrospectively performed in 84 patients with 87 breast lesions. All breast lesions were diagnosed by ABVS, HHUS, and MTXR, then confirmed using histopathologic examination. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated, as well as receiver operating characteristic (ROC) curve with the area under the curve (AUC) was analyzed to predict the diagnostic values of coronal ultrasonic characteristics by ABVS as well as HHUS, ABVS, HHUS combined with ABVS, and MTXR in breast benign and malignant lesions. *Results:* Convergence sign and lotus root sign of malignant lesions and the weeping willow sign of benign lesions could be observed in ABVS coronal image. Mass margin and surrounding halo also had high sensitivity, specificity, accuracy, PPV, and NPV. In addition, HHUS combined with ABVS, HHUS, ABVS, and MTXR had similar sensitivity, specificity, accuracy, PPV, NPV, and AUC in differentiating benign from malignant breast lesions. *Conclusions:* ABVS coronal image have high application value in differential diagnosis of benign and malignant breast lesions. In addition, HHUS combined with ABVS, HHUS, ABVS or MTXR have similar diagnostic efficiencies in differentiating benign and malignant lesions.

Key words: Automated breast volume scanning; Handheld ultrasound; Molybdenum target X-ray; Diagnostic efficiency; Breast lesions.

Introduction

Breast carcinoma (BC) is one of the most prevalent and the third leading cause of malignant diseases in women worldwide [1]. In China, approximately 1.6 million patients with BC are newly diagnosed and 1.2 million die of BC each year [2]. Although five-year survival rate reaches up to 90% in early-stage BC, five-year survival only is 23% in advanced stage BC [2]. Unfortunately, effective primary prevention (causal prophylaxis) measures are scarce to prevent BC so far. Therefore, it is imperative to strengthen secondary prevention measures and make great effort to improve survival rate by early discovery, early diagnosis, and treatment for BC.

Currently, molybdenum target X-ray (MTXR) has been considered as a standard breast lesions screening method due to easy operation, high accuracy, and normalized examinations [3, 4]. Approximately 30-50% microcalcification in early breast lesions can be detected using MTXR [5]. However, MTXR has some limitations such as poor sensibility and specificity in patients with smaller breasts or dense breast tissue, as well as involving pain and ionizing radiation [6].

In addition to mammography, handheld ultrasound (HHUS) is well recognized as a complementary screening technique for breast lesions [7, 8]. Significant advantages, such as well-tolerated, less affected by breast density, painless and no ionizing radiation, increase the detection rates of early BC [9, 10]. Nevertheless, in consideration of the dependence on operator, non-repeatability, and non-displayable lesion in the coronal plane, HHUS is limited to fully apply to BC evaluation [11]. Automated breast volume scanning (ABVS), a newly three-dimensional and automated US, can obtain reproducible and coronal images, and be operated by less trained personnel [12, 13]. Although several previous study have shown that ABVS has good feasibility and similar diagnostic efficiency in breast lesions compared with HHUS or mammography [14-16], few studies have assessed the coronal ultrasonic characteristics obtained from ABVS in benign and malignant lesions.

The aim of the present study was to evaluate the coronal ultrasonic characteristics by ABVS in breast lesions, investigate the diagnostic efficiency of coronal ultrasonic characteristics by ABVS in differentiating benign from malignant breast lesions, and further compare the differential diagnostic values of HUUS, ABVS, HUUS combined with ABVS, and MTXR in benign and malignant lesions, with

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histopathologic examination as the golden standard.

Materials and Methods

This study was retrospectively performed in 84 patients with space occupying breast lesion (total 87 lesions) referred to the present hospital between March 2013 and October 2014. All patients were female and aged from 17 to 102 years (mean age with 43.2 ± 14.5). All breast lesions were diagnosed by ABVS, HHUS, and MTXR, then confirmed using pathology after surgical excision or US-guided percutaneous biopsy. No treatment was carried out prior to ultrasound examination. Based on operative and pathological findings, all breast lesions were assigned into benign group and malignant group. The study was endorsed by Ethical Committee of the present hospital and all patients gave their written informed consent.

A color Doppler ultrasound diagnostic system with the ABVS attachment was used to perform automated breast US with a frequency bandwidth of 7−14 MHz (11 MHz as the center frequency). All patients were maintained in a supine position and positioned with the hands behind the head. Enough couplant was smeared on surface of the breast. Then customized presets were set based on patients' cup size to optimize overall gain, depth, and focal zone placement. A conventional examination included 65 scans in the anterior-posterior and lateral positions, while additional scans in the medial, superior or inferior positions were required for interested breast area. Data with a volume of 15.4×16.8×6.0 cm (1,552.32 cm^3) were captured using a 14L-5BV linear array transducer at slice intervals of 0.5 mm. The nipple needed to be contained in each scan. After volume data acquisition, the transverse image series was sent to dedicated workstation that displayed reconstructed images in coronal and transverse and sagittal planes, as well as multiplanar reconstruction (MPR).

HHUS: HHUS was performed using a system with a 9L4-linear array transducer with a bandwidth of 7-11 MHz. Patients' position was similar to ABVS examination. The entire breast was scanned with the center of the nipples based on the appropriate presets.

MTXR: Conventional MTXR was performed in both sides of mammary gland axis and oblique views. For patients with nipple discharge, galactography was performed prior to MTXR.

Imaging examination results, including location, size, shape, the direction of major axis, edge, margin, internal echo, calcification, posterior echo, and the change of the surrounding tissue of the mass, were recorded. Tumor blood supply was evaluated with three-level scale according to semi quantitative classification described by Adler *et al.* [17]. In addition, some ultrasonic characteristics by ABVS such as convergence sign, lotus root sign (first defined because the echo is similar to the lotus root in the cross section), weeping willow sign (first defined because the echo is similar to weeping willow), malignant halo, minor calcification, enhanced anterior fat echo, and retromammary cellular space were also collected. Artery blood flow spectrum and hemodynamics were recorded.

The images were analyzed and diagnosed by two experienced board-certified radiologists in breast diagnostics. Breast Imaging Reporting and Data System (BI-RADS) established by American College of Radiology (ACR) [18] was used to evaluate the lesions as following: 1 grade: negative, 2 grade: benign, 3 grade: probably benign (malignancy suspicion < 3%), 4a grade: low malignancy suspicion (3-8%), 4b grade: intermediate malignancy suspicion (9-49%), 4c grade: moderate malignancy suspicion (50-94%), 5 grade: probably malignancy (> 95%), 6 grade: malignancy confirmed by pathology. BI-RADS grade of 2, 3 or 4a was considered as benign lesion, and BI-RADS grade of 4b, 4c or 5 was considered as malignant lesions.

Data analysis was performed by using SPSS 19.0 software. Continuous and categorical variables were expressed as mean ± SD and percentages, and analyzed by *t*-test and chi-square test, respectively. The comparison of ultrasonic characteristics of ABVS between benign group and malignant group were analyzed by chi-square test or rank sum test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated to predict the diagnostic values of coronal ultrasonic characteristics by ABVS as well as HHUS, ABVS, HHUS combined with ABVS, and MTXR in breast lesions, with pathological diagnosis as the reference standard. The authors also performed the receiver operating characteristic (ROC) curve with the area under the curve (AUC) to evaluate the diagnostic accuracy. *P* values less than 0.05 were considered statistically significant.

Results

Of the 87 breast lesions, there were 54 (62%) benign lesions with the lesion size of 7 mm × 4 mm−91 mm × 56 mm, and 33 (38%) malignant lesions with the lesion size of 3 mm × 2 mm−91 mm × 61 mm. Pathological diagnosis results included 23 invasive ductal carcinomas, four ductal carcinomas in situ, three mucinous carcinomas, one invasive lobular carcinoma, one invasive papillary carcinoma, and one intracystic papillary carcinoma in the malignant group, as well as 27 fibroadenomas, 21 cyclomastopathies, five intraductal papillomas, and one chronic mucopurulent inflammation in the benign group. The average age of onset was 37.29 ± 10.00 years in the benign group and 53.00 ± 15.59 years in the malignant group with a significant statistical difference ($p = 0.00$). No significant difference was found in the distribution of the left and the right breast lesions between the benign and malignant groups. In addition, tumor blood supply according to semiquantitative classification was analyzed: 0-III levels, respectively, in 22.2% (12/54), 29.6% (16/54), 24.1% (13/54), and 24.1% (13/54) of the benign lesions, and 0-III levels, respectively, in 12.1% (4/33), 3.0% (1/33), 9.1% (3/33), and 75.7% (25/33) of the malignant lesions. Resistant index in the benign group was lower than that in the malignant group (0.67 ± 0.10 *vs.* 0.79 ± 0.12, $p = 0.01$).

Lesion detection rates of HHUS, ABVS and MTXR were 96.5% (84/87), 98.9% (86/87), and 89.6% (78/87), respectively. The detection rates had no significant difference between HHUS and ABVS, while detection rates using HUUS and ABVS were remarkably higher than that using MTXR ($p = 0.02$). One lesion was not detected by ABVS due to the edge of mammary gland, and then was successfully detected through the combination of clinical data, palpation, and ABVS. Three undetected lesions by HUUS were detected using ABVS and comprised two malignant lesions with ductal carcinoma in situ and one benign lesion with intraductal papilloma. Nine undetected lesions by MTXR all located in dense mammary tissue and then were

Table 1. — *Coronal ultrasonic characteristics by automated breast volume scanning between benign and malignant lesions.*

Ultrasonic characteristics	Malignant group (n = 33)	Benign group (n = 54)	*p* value
Shape			0.00
Irregularity	27	15	
Inerratic	6	39	
Margin			0.00
Clear	6	44	
Fuzzy	27	10	
Edge			0.00
Smooth	7	29	
Angulate	9	10	
Lobulated	4	11	
Spiculated	13	4	
Direction of major axis and skin			0.00
Unparallel	24	9	
Parallel	9	45	
Calcification			0.00
No or thick	12	46	
Punctate	21	8	
Convergence sign			0.00
Yes	10	3	
No	23	51	
Lotus root sign			0.00
Yes	9	0	
No	24	54	
Weeping willow sign			0.02
Yes	0	10	
No	33	44	
Surrounding halo			0.95
Yes	12	20	
No	21	34	
Uniform and continuous halo			0.00
Yes	1	19	
No	11	1	
Enhanced anterior fat echo		0.00	
Yes	17	2	
No	16	52	
Change of posterior echo			0.00
No	14	35	
Enhanced	11	17	
Reduced	8	2	
Retromammary cellular space			0.00
Clear	11	0	
Fuzzy	22	54	

Table 2. — *Diagnostic efficiency of ultrasonic characteristics by automated breast volume scanning for malignant lesions.*

Ultrasonic characteristics	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Shape	81.8	72.2	64.3	86.7	75.9
Margin	81.8	81.5	73.0	88	81.6
Edge	78.8	53.7	51.0	80.6	63.2
Direction of major axis	72.7	83.3	72.7	83.3	79.3
Calcification	63.4	85.2	72.4	79.3	77.0
Convergence sign	30.3	94.4	76.9	68.9	78.2
Lotus root sign	27.3	100	100	69.2	72.4
Weeping willow sign	0	81.5	0	57.1	50.5
Uniform and continuous halo	91.2	95	91.2	95	93.8
Enhanced anterior fat echo	51.5	96.3	89.5	76.5	79.3
Change of posterior echo	57.5	64.9	50	71.4	62.1
Retromammary cellular space	66.6	100	100	83.1	87.4

PPV, positive predictive value; NPV, negative predictive value.

Table 3. — *Diagnostic value of HHUS, ABVS, HHUS combined with ABVS, and MTXR in differentiating benign and malignant lesions.*

Diagnostic method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
ABVS	81.8	85.2	77.1	88.5	83.9
HHUS	78.8	83.3	74.3	86.5	81.6
HHUS + ABVS	87.9	87.0	80.6	92.2	87.4
MTXR	81.8	83.3	75	88.2	83.9

ABVS: automated breast volume scanning, HHUS: handheld ultrasound, MTXR: Molybdenum target X-ray, PPV: positive predictive value, NPV: negative predictive value.

detected by HUUS or ABVS, including three malignant lesions and six benign lesions.

As shown in Table 1, significant differences were found in terms of coronal ultrasonic characteristics by ABVS, including shape, edge, margin, the direction of major axis, calcification, uniform and continuous halo, anterior fat echo, posterior echo, convergence sign, lotus root sign, weeping willow sign, and retromammary cellular space, between the benign and malignant groups (all $p < 0.05$, Figure 1). Interestingly, lotus root sign only appeared in malignant lesions, while weeping willow sign only found in benign lesions. No significant difference was found in whether surrounding halo or not between the benign and malignant groups. For lesions with surrounding halo, the thickness of halo in malignant lesions was higher than that in benign lesions (3.80 ± 1.80 mm *vs.* 1.11 ± 0.37 mm, $p = 0.01$). Coronal ultrasonic characteristics by ABVS had different diagnostic efficiency in differentiating benign and malignant lesions (Table 2). Mass margin (clear or fuzzy) and surrounding halo (uniform and continuous or not) had high sensitivity (81.8% and 91.2%), specificity (81.5% and 95%), accuracy (81.6% and 93.8%), PPV (73.0% and

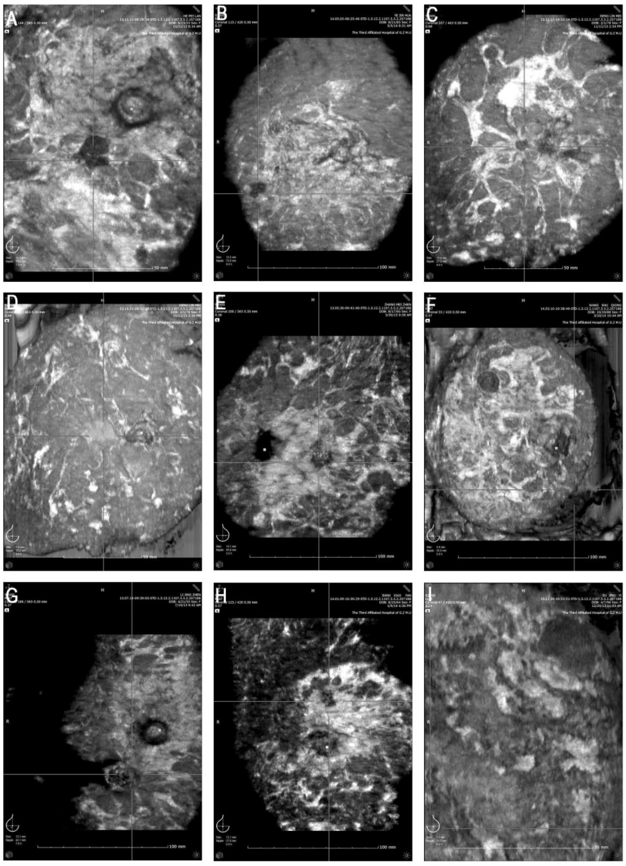

Figure 1. — Coronal ultrasonoscopy by automated breast volume scanning in benign and malignant lesions.
A) Irregularity mass with angulate edge is present in invasive ductal carcinoma. B) Irregularity mass with lobulated edge is present in fibroadenoma. C) Convergence sign appears in invasive ductal carcinoma. D) Enhanced fat echo is observed in the anterior of mass in invasive ductal carcinoma. E) Punctate calcification is found in mass of invasive ductal carcinoma. F) Uniform and continuous halo is present in fibroadenoma. G) Non-uniform thickness and discontinuous halo is observed in invasive ductal carcinoma. H) Lotus root sign appears in ductal carcinoma in situ. I) Weeping willow sign appears in fibroadenoma.

91.2%), and NPV (88% and 95%).

The sensitivity, specificity, accuracy, PPV, and NPV of ABVS combined with HUUS in differentiating benign and malignant lesion were 87.9%, 87.0%, 87.4%, 80.6%, and 92.2%, respectively, which were slightly higher than those of ABVS, HUUS, and MTXR but without statistical differences (all $p > 0.05$, Table 3). ROC analysis (Figure 2) also showed that the AUC for HHUS, ABVS, HHUS combined with ABVS, and MTXR gave a good and similar discriminatory power of 0.869 (95% confidence interval (CI): 0.787-0.951, $p = 0.042$), 0.879 (95% CI: 0.799-0.959, $p = 0.041$), 0.886 (95% CI: 0.806-0.966, $p = 0.041$), and 0.864 (95% CI: 0.779-0.948, $p = 0.043$), respectively.

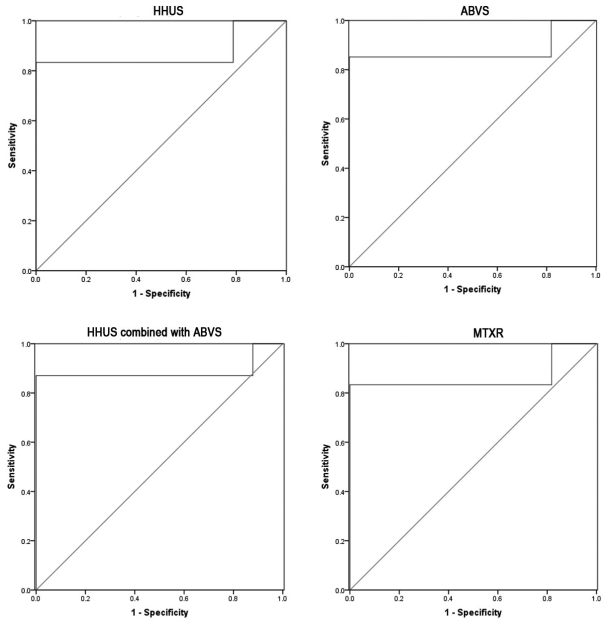

Figure 2. — The receiver operating characteristic curve of HHUS, ABVS, HHUS, combined with ABVS and MTXR in differentiating benign and malignant lesion. ABVS: automated breast volume scanning, HHUS: handheld ultrasound, MTXR: Molybdenum target X-ray.

Discussion

Due to poor prognosis of advanced stage BC, early diagnosis and treatment are necessary [19]. In the present study, the authors retrospectively analyzed the diagnostic value of HHUS, ABVS, HHUS combined with ABVS, and MTXR in 54 benign and 33 malignant lesions, and the results showed higher lesion detection rate of HUUS or ABVS than that of MTXR. Previous study showed that detection rates of breast lesions were 95.8%, 97.6%, and 87.8%, respectively, using HUUS, ABVS, and mammography [15], which was similar to the present results (96.5%, 98.9%, and 89.6%). All nine lesions missed by MTXR was found in dense mammary tissue, while all were detected by HUUS or ABVS, suggesting the diagnostic advantage of HUUS and ABVS in patients with dense breast tissue. Three missed lesions by HUUS might have been caused by less mass and high scanning speed. In addition, one misdiagnostic lesion by ABVS was found to be located in the edge of mammary gland, which indicated a disadvantage of ABVS due to blinding of clinical situation.

This study found that coronal ultrasonic characteristics obtained from ABVS showed different differential diagnostic efficiency in breast lesions. Previous studies showed that convergence sign had high sensitivity (80-89%) and specificity (96-100%) in differentiating benign and malignant lesions [11, 20, 21]. However, this study showed convergence sign had low sensitivity (30.3%) and high specificity (94.4%). The reasons might be that convergence sign often occurred in tumors with a size < 2 cm, while large tumors showed less convergence sign due to rapid growth and incomplete or missing hyperplastic tissue [22]. Enhanced anterior fat echo was found in 17 (17/33) malignant lesions and only in two (2/54) benign lesions, with a 51.5% sensitivity and 96.3% specificity in differentiating benign and malignant lesions in this study. Enhanced anterior fat echo occurring in malignant lesions might be caused by fibrous tissue hyperplasia in subcutaneous fat of tumor margin and different cell arrangement and distribution, which led to different echo reflectance [23, 24]. The present study found that surrounding halo had high sensitivity, specificity, accuracy, PPV, and NPV. Warm *et al.* [25] analyzed 186 breast lesions and showed that uniform and continuous halo occurred in benign lesions, while discontinuous halo was found in malignant lesions, which was similar to the present study. In addition, mass margin (clear or fuzzy) also had high sensitivity, specificity, accuracy, PPV, and NPV. Several studies had demonstrated that margin characteristics were related to the highest diagnostic value in differentiating benign and malignant lesions [26, 27]. Similarly, Wang *et al.* [15] found a continuous hyperechoic rim occurring in most benign lesions, and spiculated and stellate margins appeared in malignant lesions. Interestingly, the present authors found that lotus root sign only was observed in malignant lesions with 27.3% sensitivity, 100% specificity, and 72.4% accuracy, while weeping willow sign was only observed in benign lesions with 0% sensitivity, 81.5% specificity, and 50.5% accuracy. This result prompted the differential diagnostic values of lotus root sign in malignant lesions and weeping willow sign in benign lesions, while further study is necessary. Furthermore, the present authors found that HHUS, ABVS, HHUS combined with ABVS, and MTXR had similar diagnostic efficiency in differentiating benign and malignant lesions. Some studies suggested that both HHUS and ABVS had better diagnostic sensitivity than MTXR for breast lesions [15, 28]. However, the present study showed similar sensitivity and specificity between HHUS or ABVS and MTXR, which might be caused by smaller sample size, different pathological types, and lack of clinical experience. In addition, consistent with this study, some scholars reported that ABVS had higher diagnostic accuracy and specificity than HHUS, but without significant statistical difference [15, 16, 28], suggesting the similar diagnostic efficiency of HHUS and ABVS. Despite all of these, ABVS still had promising diagnostic value in differentiating benign and malignant lesions due to investigator-independent, better observation of lesion margin and standardized documentation. However, the present study has several limitations. The first limitation is the small sample size, further study with larger sample size should be performed to confirm the results of this study. Second, due to a shorter application time and deficient experience of ABVS in clinical practice, ABVS may have a high diagnostic accuracy.

Conclusions

Convergence and lotus root sign of malignant lesions and the weeping willows sign of benign lesions can be observed, as well as mass margin (clear or fuzzy) and surrounding halo (uniform and continuous or not) in ABVS coronal image which have high application value in the differential diagnosis of benign and malignant breast lesions. In addition, HHUS combined with ABVS, HHUS, ABVS, or MTXR have similar diagnostic efficiencies in differentiating benign and malignant lesions.

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