



Automated Breast Ultrasound Screening for Dense Breasts

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Mammography is the primary screening method for breast cancers. However, the sensitivity of mammographic screening is lower for dense breasts, which are an independent risk factor for breast cancers. Automated breast ultrasound (ABUS) is used as an adjunct to mammography for screening breast cancers in asymptomatic women with dense breasts. It is an effective screening modality with diagnostic accuracy comparable to that of handheld ultrasound (HHUS). Radiologists should be familiar with the unique display mode, imaging features, and artifacts in ABUS, which differ from those in HHUS. The purpose of this study was to provide a comprehensive review of the clinical significance of dense breasts and ABUS screening, describe the unique features of ABUS, and introduce the method of use and interpretation of ABUS.

Keywords: Dense breast; Automated breast ultrasound; Screening; Early detection of cancer; Breast cancer

INTRODUCTION

In the eight randomized controlled trials conducted so far, mammography detected breast cancers in the early stages and thereby reduced breast cancer mortality by up to 20%. Mammography is the primary screening method for breast cancers (1-3).

The sensitivity of mammographic screening is lower for dense breasts, which are an independent risk factor for breast cancers (4, 5). Supplemental breast ultrasound (US) screening is expected to detect mammographically occult breast cancers (6). With the increasing demands

of supplemental US screening, radiologists are unable to widely use handheld US (HHUS) because of limited human resources and heavy workload. Automated breast US (ABUS) has been developed to overcome the limitations of operator dependency and lack of reproducibility in HHUS, and it is time-efficient for radiologists (7-10). ABUS has been approved in the United States and Europe as an adjunct to mammography for screening, especially for asymptomatic women with dense breasts (8, 10).

In this study, we addressed the clinical significance of dense breasts and effectiveness of ABUS screening of breast cancers for women with dense breasts. In addition, we introduced the method of use and interpretation of ABUS. The reader will gain comprehensive knowledge of the effective applications and unique imaging features of ABUS for women with dense breasts.

Dense Breasts

Dense breasts are associated with low mammographic sensitivity and breast cancer development. The frequency of dense breasts in the screening population over the age of 40 years was 43.3% in the United States and 54.8% in Korea. Moreover, among young women in their 40s, it increased to 56% and 83.2%, respectively (11, 12).

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Presence of dense breast tissue may lead to reduction in the sensitivity of mammography. According to the Breast Cancer Surveillance Consortium reports, the sensitivity of mammography decreased from 85.7–88.8% in patients with breast tissue composed almost entirely of fatty tissue (non-dense breast tissue) to 62.2–68.1% in patients with extremely dense breast tissues (13).

Breast density is an independent risk factor for breast cancers (13, 14). Dense breasts are in the intermediate risk category for breast cancers (lifetime risk: 15–20%) (1). Women with breast density \geq 75% had 4–6 times greater risk for developing breast cancers compared to women with breast density \leq 10% (15, 16), and women with breast density of 50–74% had 2.9 times greater risk compared to women with breast density \leq 10% (17). Park et al. (18) reported increased risks for breast cancer with greater breast densities in Korean women. Compared to women with breasts composed almost entirely of fatty tissue, women with extremely dense breasts had a five times higher risk of breast cancer, and women with heterogeneously dense breasts had a 3.8 times higher risk (18).

There is insufficient evidence for reduction in mortality with US screening, so no recommendations have been established for the screening guidelines. However, in the United States, legislative changes require healthcare providers to notify women of their breast tissue density and advise supplemental screening to women with dense breasts (19). The American College of Radiology (ACR) states that supplemental US screening is an option for women with dense breasts and supplemental magnetic resonance imaging may be performed depending on risk factors, such as a history of lobular carcinoma *in situ* in women

with intermediate risk for breast cancers (20). The Korean guidelines neither recommend nor oppose US as a screening modality (21).

Effectiveness and Diagnostic Performance of ABUS Screening

Although the evidence on long-term benefits is limited, supplemental US screening has high sensitivity for cancer detection, especially in early-stage invasive cancers, and reduces the frequency of interval cancers (6, 22, 23).

In several studies, screening ABUS yielded a high diagnostic performance (Table 1), similar to screening HHUS (1, 9, 24–27). Supplemental ABUS screening increased breast cancer detection by 1.9–7.7 cases per 1000 women. Sensitivity increased by 21.6–41.0%, but specificity varied. Recall and biopsy rates increased while positive predictive value-3 (PPV3) decreased by 4.2–15.8%. The largest ABUS study additionally detected 1.9 cases of breast cancer per 1000 women (25), which was similar to the results of Japan Strategic Anti-cancer Randomized Trial (J-START) (22) but lower than the results of American College of Radiology Imaging Network 6666 (23) (Table 2). Differences in the cancer detection rate were thought to be because of the different inclusion criteria. The largest ABUS study had a proportion of invasive cancers of 93.3%, mean breast lesion size of 12.9 mm, and proportion of node-negative cancers of 92.6% (25), which were similar to the results of HHUS screening (22, 23). ABUS screening was effective in detecting small, invasive, and predominantly node-negative breast cancers, similar to HHUS screening.

Table 1. Diagnostic Performance of Supplemental ABUS Screening

Prospective Studies	Population (Numbers)	US Only Detected Cancers	Sensitivity (%)		Specificity (%)		Recall Rate (%)		CDR Per 1000		Biopsy Rate (%)		PPV3 (%)	
			US + MMG	MMG	US + MMG	MMG	US + MMG	MMG	US + MMG	MMG	US + MMG	MMG	US + MMG	MMG
Kelly et al. (24)	Women with dense breast/at elevated risk (4419)	23	81.0	40.0	98.7	95.1	9.6	4.2	7.2	3.6	N.R.	N.R.	N.R.	N.R.
			41.0		3.6		5.4		3.6		N.R.		N.R.	
Brem et al. (25)	Women with dense breast (15318)	30	100.0	73.2	72.0	85.4	28.4	15.0	7.3	5.4	7.4	3.8	9.8	14.0
			26.8		-13.4		13.4		1.9		3.6		-4.2	
Wilczek et al. (26)	Women with dense breast (1688)	4	100.0	63.6	98.4	99.0	2.2	1.3	6.6	4.2	1.3	0.6	47.8	63.6
			36.4		-0.6		0.9		2.4		0.7		-15.8	
Giuliano et al. (27)	Women with dense breast (3418 test/4076 control)	N.R.	97.6	76.0	99.7	98.2	N.R.	N.R.	12.3	4.6	N.R.	N.R.	N.R.	N.R.
			21.6		1.5		N.R.		7.7		N.R.		N.R.	

ABUS = automated breast ultrasound, CDR = cancer detection rate, MMG = mammography, N.R. = not reported, PPV3 = positive predictive value-3, US = ultrasound

Interpretation Criteria for ABUS Screening

There are no screening US guidelines applicable worldwide. To date, only one guideline and a few studies on the interpretation and management of screening US have been published (28-31). J-START adopted screening US guidelines from the Japanese Association of Breast and Thyroid Sonology (JABTS) (22), which was different from ACR breast imaging-reporting and data system (BI-RADS) in the lexicon (28, 29) (Table 3). The biggest difference was inclusion of a description of non-mass lesions, which was done only in the JABTS guidelines. Furthermore, the

categorization and management were different (Table 3). In the flow chart for assessing masses provided by the JABTS guidelines (Fig. 1), masses without an interrupted interface or echogenic halo were divided based on the size and depth-to-width ratio. JABTS guidelines reflected that lesions smaller than 5 mm had low PPVs. Ban et al. verified the usefulness of this guideline (29).

There were two studies validating the detection of BI-RADS category 3 on screening US. The malignancy rate of category 3 lesions was 0.8%, and only 0.1% of the cases had suspicious changes at the 6-month follow-up (30). Multiple bilateral circumscribed masses showed no signs of

Table 2. Additional Cancer Detection and Proportion of Invasive Cancers in Supplemental Ultrasound Screening

Study	SomoInsight (25)	J-START (22)	ACRIN 6666 (23)
Modality	ABUS	HHUS	HHUS
Study population	Asymptomatic women with dense breast 15318	Asymptomatic women in their 40's 36752	Asymptomatic women at high risk 2809
Period	2009–2011	2007–2011	2004–2006
Additional cancer detection	1.9/1000 women	1.84/1000 women	5.3/1000 women
Proportion of invasive cancer (%)	93.3	82.0	93.7
Mean size of invasive cancer (mm)	12.9	14.2	10.0
Proportion of node negative cancer (%)	92.6	85.5	96.7

ACRIN = American College of Radiology Imaging Network, HHUS = handheld ultrasound, J-START = Japan Strategic Anti-cancer Randomized Trial

Table 3. Comparison of Guidelines

Mass	JABTS	ACR BI-RADS
Shape	Oval/round, lobulated, polyponal, irregular	Oval, round, irregular
Margin	Well defined–smooth, rough Indistinct–with/without echogenic halo Obscure	Circumscribed Not circumscribed–indistinct, angular, microlobulated, spiculated
Orientation	Small (depth/width ratio < 0.7), large (≥ 0.7)	Parallel, non-parallel
Echogenicity	Echolevel–anechoic, hyper-, hypo-, isoechoic Homogeneity–heterogeneous, homogeneous	Anechoic, hyper-, hypo-, isoechoic, complex cystic and solid, heterogeneous
Non-mass	Ductal dilatations with internal echoes, hypoechoic area in mammary gland, architectural distortion	
Final assessment	JABTS	ACR BI-RADS
Category 0		0: Incomplete
Category 1	1: Negative	1: Negative
Category 2	2: Benign or abnormal findings that further examination is not necessary	2: Benign
Category 3, 4	3a, 3b: Benign but malignancy not ruled out 4a, 4b: Suspicious abnormality	3: Probably benign 4a, 4b, 4c: Suspicious
Category 5	5: Highly suggestive malignancy	5: Highly suggestive of malignancy

ACR = American College of Radiology, BI-RADS = breast imaging-reporting and data system, CNB = core needle biopsy, FNAB = fine needle aspiration biopsy, FU = follow-up, JABTS = Japanese Association of Breast and Thyroid Sonology

malignancy in the biopsy specimen or on follow-up US (31). Therefore, we concluded that category 3 lesions, including multiple bilateral circumscribed masses, required a follow-up of 1 year with screening.

A prospective multicenter Korean ABUS screening trial is underway. It aimed to evaluate cancer detection on ABUS alone in asymptomatic women in their 40s. Based on previous studies (30, 31), we modified BI-RADS and JABTS guidelines to develop interpretation criteria for ABUS screening (Table 4). Some solid masses assessed as BI-RADS category 3 have been classified under category 2 in this guideline. To date, a total of 846 people were screened with ABUS, and 5 cases of cancer were diagnosed. The recall rate was 7.56%. PPV for biopsy was 27.7%, and the cancer

detection rate was 5.9 cases per 1000 women. Interim results were better compared to previous ABUS screening trials (24-27); however, verification of the interpretation criteria using more follow-up data is required.

Wise Use of ABUS

ABUS is technically different from HHUS (Table 5). Comprehensive knowledge of indications for ABUS and technical differences between ABUS and HHUS is essential for its appropriate use.

Indications

The main indication for ABUS screening is the presence

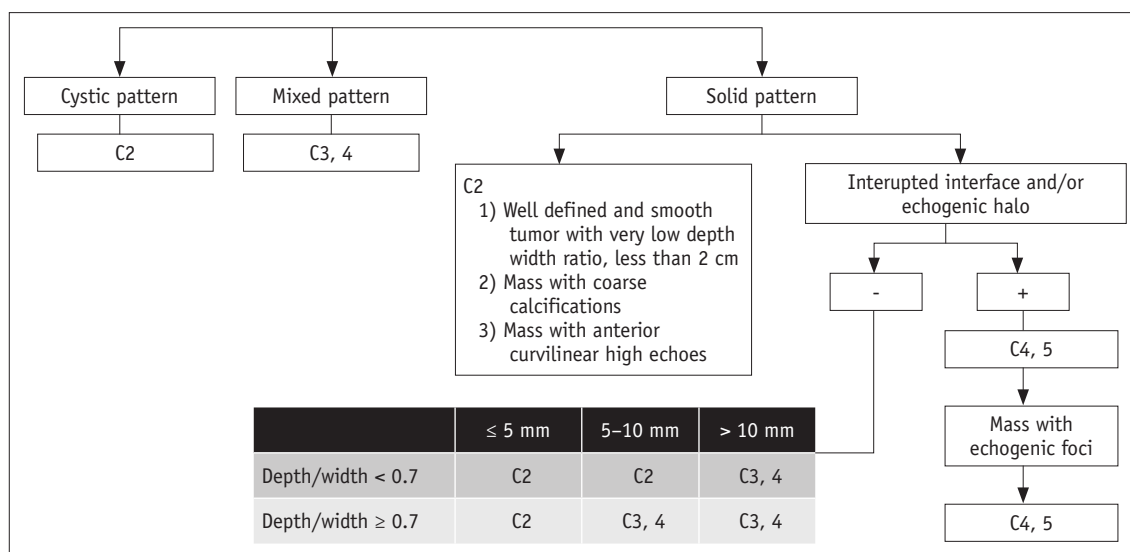


Fig. 1. Flow chart provided by Japanese Association of Breast and Thyroid Sonology for assessing mass lesions.

Table 4. Interpretation Criteria for ABUS Screening

Category	Finding	Size (mm)	Management
2	A: Simple cyst/IMN/calcified FA/fat-containing lesion		1 year FU
	B: Multiple, oval, circumscribed complicated cysts or masses		
	C: Non-simple cysts in setting of multiple or bilateral cysts (at least three cysts, with at least one in each breast)		
	D: Round, circumscribed, solid mass	≤ 5	
	E: Oval circumscribed, parallel solid mass	≤ 10	
3	Isolated complicated cyst		6 months FU
	Round circumscribed solid mass	> 5	
	Oval circumscribed parallel mass	> 10	
	Clustered microcysts		
	Fat necrosis		
4	Intraductal well defined lesion		Biopsy
	Others		
5	Irregular, spiculated mass		Biopsy

FA = fibroadenoma, IMN = intramammary lymph node

of dense breasts in asymptomatic women (8, 10). Currently, indications for ABUS in diagnosis remain unclear. However, there are no absolute contraindications (postoperative breasts or breasts with implants) (32). ABUS could document the multiplicity or bilaterality of breast cancers in cases of additionally suspicious lesion detected on magnetic resonance imaging (33). Furthermore, ABUS could help estimate the tumor extent precisely in cases of ductal carcinoma *in situ* (9, 34, 35) and monitor variations in tumor dimensions during the course of chemotherapy (9).

Technical Basics

ABUS comprises of a US scanner and special stationary device with a transducer, which moves automatically in a scan box (Fig. 2A). The slice thickness is adjustable from 0.5 mm to 8.0 mm (default value: 0.5 mm), and up to 448 axial slices are acquired.

The patient lies in a supine position, and ABUS of breasts is performed in anteroposterior, medial, and lateral views routinely and in the superior or inferior view additionally

in cases of large breasts (Fig. 2B). Image acquisition in six views takes approximately 10 minutes.

The axial image series is sent to a workstation where three-dimensional (3D) reconstructions of sagittal and coronal images occur. This ABUS-dedicated workstation with a dedicated software package provides an efficient and comprehensive analysis of the 3D data and facilitates easy reporting. The number of images varies with the slice thickness and depth (based on the breast cup size), but approximately 2000 images are usually generated. The display mode is chosen (Fig. 2C). When the cursor is placed on the mass in the axial view, coronal and sagittal views automatically display lesions. The average reading time is approximately 9 minutes (36), and the reading time varies with the presence/absence of abnormalities and display mode (9, 37). The storage capacity per patient is about 1 GB, so the representative images, instead of whole images, are selected and sent to a picture archiving and communication system.

Table 5. Technical Differences between ABUS and HHUS

Techniques	ABUS	HHUS
3D view	3D reconstruction	-
FOV (cm)	15 x 17	4-6 x 4-6
Scan direction	Transverse	Transverse, longitudinal, radial, antiradial
Probe (MHz)	5-14 (average 10 MHz)	5-17, 18
Elastography, color Doppler	-	Available
Focal zone	Wide and fixed	Manual setting
Coupling agent	Lotion	Gel

FOV = field of view, 3D = three-dimensional

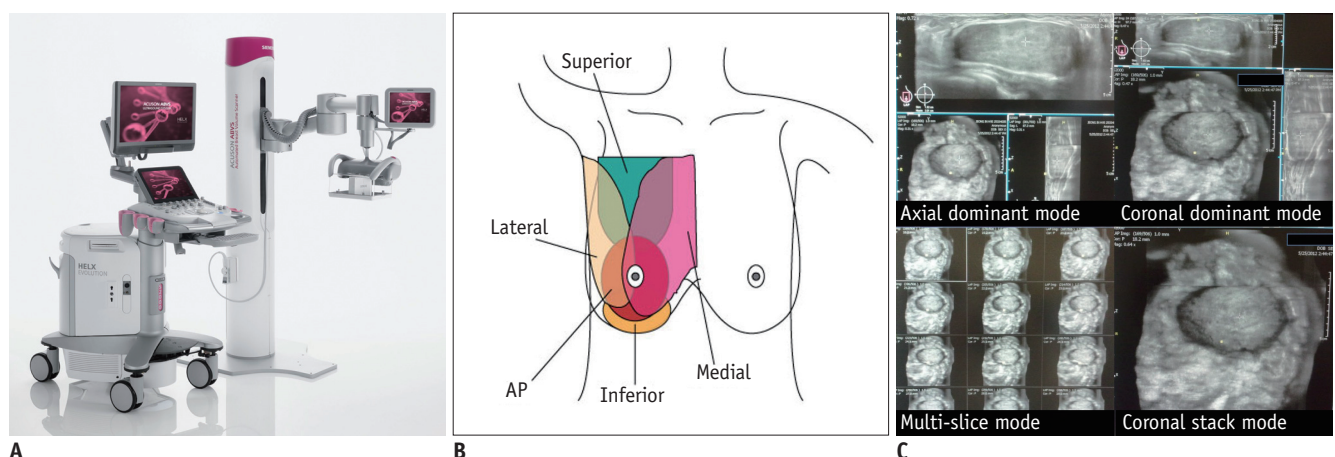


Fig. 2. ABUS with dedicated scanner and workstation.

A. ACUSON S2000 Automated Breast Volume Scanner (Siemens Healthineers) comprises of scanner and special stationary device with transducer. **B.** Images are obtained in three to five views per breast. **C.** Workstation provides three-dimensional reconstruction view, and display mode is chosen from four settings. ABUS = automated breast ultrasound, AP = anteroposterior

Qualified Interpretation of ABUS

ABUS has features that are different from HHUS. Computer-aided detection (CAD) has been introduced as an auxiliary software.

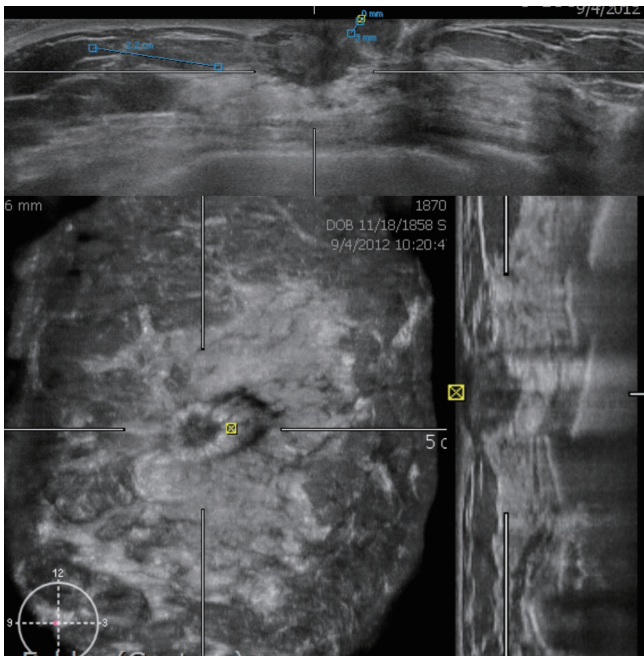


Fig. 3. ABUS image of 58-year-old woman with right breast cancer. Axial (upper column), coronal (right lower column), and sagittal (left lower column) images show irregular spiculated hypoechoic mass measuring 2.2 cm. Retraction phenomenon is seen in coronal view.

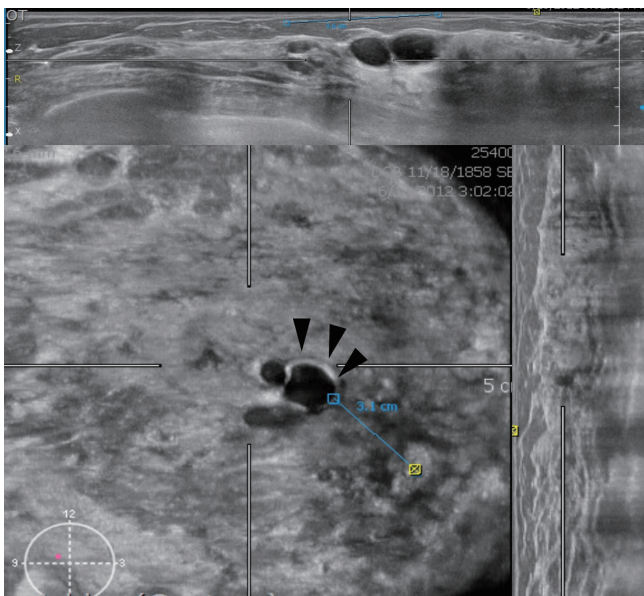


Fig. 4. ABUS image of 44-year-old woman. Axial and coronal images show few cysts. White-wall sign is seen in coronal view (arrowheads).

Display Mode and Unique Features of ABUS

The coronal view is the unique display mode of ABUS, which shows the entire breast anatomy. The analysis is fast and comprehensive (37, 38). A single-center retrospective study compared the detection rates of coronal and transverse display modes and reported that the transverse view was better than the coronal view for lesion detection (37). However, most screening studies use the coronal view rather than the transverse view. Further studies are needed to verify whether or not the coronal view alone is sufficient.

The retraction phenomenon on ABUS is a sign of malignancy, which presents as a stellate pattern around the lesion (Fig. 3) (35). It showed a sensitivity of 80–89% and specificity of 96–100% for cancer detection (9, 35, 39). It was best visualized in the coronal view (40) and might be absent in fast-growing cancers (35).

The white-wall sign presents as an echogenic wall in the coronal view and corresponds to the acoustic enhancement on HHUS (Fig. 4). It is mainly seen in benign lesions, such as simple cysts, fibroadenomas, and papillomas, and rarely associated with cancers (9, 38).

The coronal view had the potential to detect non-mass

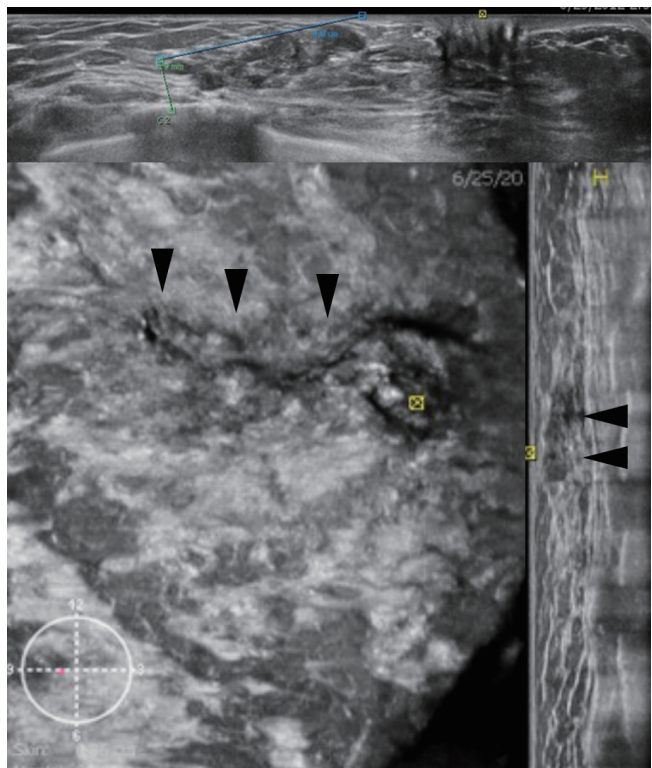


Fig. 5. ABUS image of 49-year-old woman with atypical papilloma. Three orthogonal views reveal segmental non-mass lesion of intraductal masses measuring 4.8 cm (arrowheads).

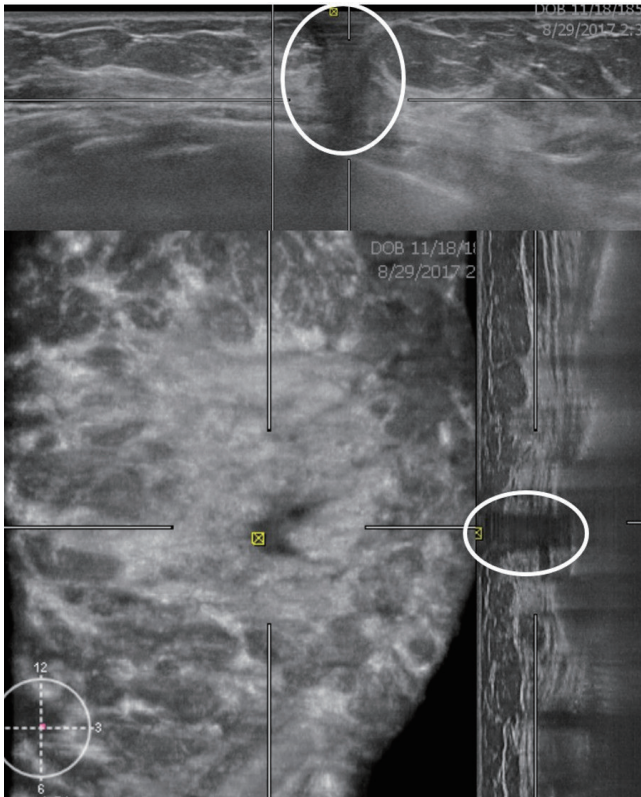


Fig. 6. ABUS image of 46-year-old woman. Axial and sagittal images demonstrate nipple shadow, and reverberation artifact is seen as hypoechoic area with shadowing and multiple parallel echogenic lines (circles). This was interpreted as space occupying lesion, but handheld ultrasound showed no focal lesions (not shown). Therefore, this is false-positive case.

lesions by depicting dilated ducts and intraductal echoes (Fig. 5). Ductal carcinomas *in situ* and papillary neoplasms are frequently seen as a non-mass lesion. ABUS in the coronal view allows a more precise evaluation of the lesion extent compared to HHUS (9, 34, 35).

Artifacts and Image Quality

The optimal image quality should be guaranteed for screening. However, the image quality and ultrasonic resolution diminish with poor contact, marked shadowing due to fibrotic breasts, and artifacts (10, 35, 41).

The nipple shadow and reverberation artifacts frequently occurred with ABUS (Fig. 6) (10, 35). Skip artifacts can be used to detect isoechoic masses. They present as a transverse anechoic line at the location of change in tissue stiffness due to a mass (Fig. 7) (10).

The training and experience of radiologists and technicians play an important role in obtaining high-quality images, resulting in qualified interpretation.

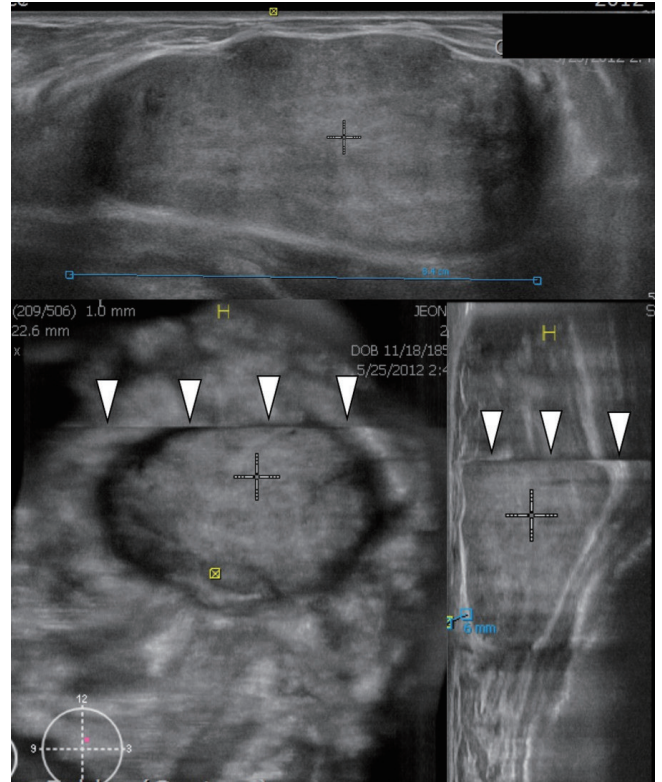


Fig. 7. ABUS image of 28-year-old woman with fibroadenoma. Three orthogonal views show circumscribed oval hypoechoic mass measuring 8.2 cm. Coronal and sagittal images demonstrate skip artifact as transverse line (arrowheads) above mass.

CAD Application

CAD improves the radiologist's diagnostic performance and shortens the reading time. The ABUS-dedicated CAD software improves the radiologist's performance, and the area under the receiver operating characteristic curve (AUC) has increased from 0.77–0.82 without CAD to 0.84 with CAD (42, 43). A study showed improved sensitivity with CAD for all tested readers (42). In another study, CAD significantly improved AUC only for radiologists without experience in ABUS interpretation (44). CAD significantly shortened the reading time in all studies (49.3 seconds without CAD and 44.7 seconds with CAD (44); 158.3 seconds without CAD and 133.4 seconds with CAD (45), and 3 minutes 33 seconds without CAD and 2 minutes 24 seconds with CAD (43)). A CAD software (QVCAD, Qview Medical Inc., Los Altos, CA, USA) was used in a few studies (42–45). This system employs several image pattern recognition processes and artificial neural networks to detect suspicious areas measuring 5 mm or more in diameter (Fig. 8).

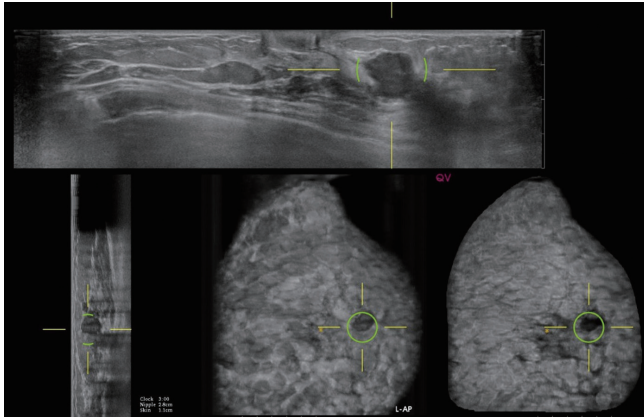


Fig. 8. ABUS image of 53-year-old woman with left breast cancer. Computer-aided detection with QVCAD (Qview Medical Inc.) system shows cancer and marks suspicious mass with green circles.

Limitations of ABUS Screening

ABUS screening is also limited by its high recall rate and biopsy rate with low PPV, similar to HHUS screening (9, 24-26). Screening US guidelines are required to reduce the frequency of false-positive results and improve PPV. In addition, a certain period of learning time is required to achieve the desirable PPV (46).

Biopsy methods under ABUS guidance have not been developed, so HHUS is performed in another step to re-examine the patients (9).

SUMMARY

ABUS is an effective screening modality to detect mammographically occult breast cancers in women with dense breasts. The coronal view is a unique display mode with high diagnostic accuracy. CAD helps detect breast cancers and reduce the interpretation time. Efforts should be made to reduce the hazards of ABUS screening, and further studies are required to verify the cost-effectiveness of ABUS for supplemental screening in women with dense breasts.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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