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SOLICITED REVIEW / *Breast imaging*

Three-dimensional automated breast ultrasound: Technical aspects and first results

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KEYWORDS
3D automated breast ultrasound;
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Dense breasts;
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Abstract Three-dimensional automated breast ultrasound system (3D ABUS) is an innovation in breast ultrasound that has been developed to uncouple detection from image acquisition and to address the limitations of handheld ultrasound (HHUS). 3D ABUS provides a large field of view using high frequency transducers, producing high-resolution images and covering a large portion of the breast with one sweep. As more data become available on breast density and the impact of supplemental screening, 3D ABUS has gained wider acceptance as an adjunct tool to mammography. Computer-aided detection software significantly reduces interpretation time, improving the workflow for the utilization of 3D ABUS as a supplemental screening tool. In the diagnostic setting, 3D ABUS offers valuable impact in the detectability of breast lesions and the differentiation of malignant from benign lesions, with a high inter-observer agreement. State-of-the art technique, including uniform compression and proper positioning, tends to reduce artifactual posterior shadowing, while combined 3D ABUS-mammography interpretation improves radiologists' diagnostic performance. Promising results have supported the enhanced efficiency of 3D ABUS in detecting the extent of breast cancer and assessing response to neoadjuvant chemotherapy, whereas its correlation with molecular subtypes of breast cancer is remarkable. Future perspectives include the integration of radiomics and deep learning in the further development of 3D ABUS.

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Abbreviations

3D ABUS	three-dimensional automated breast ultrasound system
BI-RADS	Breast Imaging-Reporting and Data System
CAD	computer-aided detection
EASY	European Asymptomatic Screening Study
EUSOBI	European Society of Breast Imaging
HHUS	handheld ultrasound
FFDM	full-field digital mammography
ICDR	incremental cancer detection rate
MRI	magnetic resonance imaging

Introduction

Mammography has been globally adopted as the primary screening examination for the early detection of breast cancer. The strongest evidence supporting the benefit of mammography has been provided by the long-term randomized controlled trials that have shown a reduction in the mortality rate by at least 20% [1,2].

However, not all women have the same benefits from mammography. It has been acknowledged that the sensitivity of mammography is lower in women with dense breasts, due to masking of non-calcified cancers, leading to an increase in the interval cancer rate and potentially delaying diagnosis with worse outcomes [3—5]. Supplemental screening with handheld ultrasound (HHUS) as an adjunct to mammography in women with dense breasts has been shown to increase the cancer detection rate by 1.8—4.6 cancers per 1000 women screened [6—10]. As more data has been available on the implications of breast density and the impact of HHUS in breast cancer detection, the 3D automated breast ultrasound system (3D ABUS) was developed to improve the availability of supplemental screening ultrasound in women with dense breasts. Historically, the concept and construction of the first automated scanner started in Australia in 1965; the latest 3D ABUS devices are equipped with a high frequency (7—15 MHz) transducer and a large probe 15.3 cm long, enabling the reconstruction of 3 million pixels a second at high frame rates to compute a full 3D breast volume from one single sweep.

More importantly, the reproducible, standardized acquisitions are uncoupled from data interpretation, and the capability of 3D multiplanar reconstruction improves the diagnostic accuracy in differentiating breast lesions. An improvement has been related to the value of the coronal plane in the visualization of architectural distortion which has also been named ''retraction phenomenon sign'' [11].

Various studies have evaluated the performance of 3D ABUS in cancer detection, when applied as an adjunct to mammography in women with dense breasts [12—14]. The results of a large prospective multicentre study which evaluated 15,318 women showed that 3D ABUS was associated with an incremental cancer detection rate (ICDR) of 30 cancers (1.9 per 1000 women screened) and the cancers detected were small invasive carcinomas with negative nodes [14]. Additionally, a study from Sweden, the European Asymptomatic Screening (EASY) Study showed an ICDR of 2.4 per 1000 women screened when 3D ABUS was performed in addition to mammography [13]. The reported required interpretation time has varied in different studies between 3—7 min. Recently, studies have shown that computer-assisted detection reduces the interpretation time needed without compromising the diagnostic accuracy [15,16].

The purpose of this review article was twofold: first, to discuss the current status of 3D ABUS utilization in clinical practice and second, to present an overview of the first results of the performance of 3D ABUS.

3D ABUS technique

Two main categories of automated breast ultrasound are available: the supine [14,17] and the prone [18,19] position systems. The newest supine-type 3D ABUS equipment devices consist of a flexible arm attached to a transducer, a touch-screen monitor and a dedicated workstation for interpretation of images. The system houses a 15.3 cm long transducer that is automatically adjusted between 6—15 MHz producing 3D data sets with 340 images per acquisition. Each acquisition captures a $15.3 \times 17 \times 5.0$ cm breast volume at slice intervals of 2-mm without overlap [20]. Technical advances of 3D ABUS architecture involve a flexible hardware with software beamforming and wide beams where the electrical signals are recorded from multiple transmissions, producing optimized quality images with high resolution and uniformity throughout the image due to automated adjustment of settings (gain, frequency, depth, time gain compensation, speed of sound, harmonics, nipple shadow and speckle reduction imaging) [21].

The sequence of the technique consists of three steps: patient positioning, image acquisitions and interpretation of data. The patient lies in the supine position with the ipsilateral hand raised above the head. Meanwhile, a rolled towel is placed under each shoulder that helps keep the breast stable with the nipple pointing to the ceiling. A hypoallergenic lotion is spread out evenly on the breast with an additional amount on the area of the nipple. A disposable membrane is used to aid coupling and to uniformly compress the entire breast, enabling greater penetration, improving detail resolution at depth and eliminating the creation of artifacts at the periphery. An option between three levels of compression and a selection between three breast sizes is available for optimization of image quality and patient comfort. A nipple marker is placed in every examination for accurate correlation of the reformatted views.

The total examination which includes patient preparation and acquisitions lasts approximately 10—15 minutes. The scan is performed automatically from the inferior part of the breast towards the superior area; as the transverse images are generated, the transducer sweeps the breast to create a volume. Three basic volumes are obtained for each breast: the anteroposterior, lateral and medial. In women with larger breasts additional volumes are acquired to cover the entirety of the breast (superior, inferior, upper outer quadrant). All examinations are performed by well-trained technologists. When the examination is completed, the volume data is processed automatically in multiplanar reconstruction (coronal and sagittal plane) and is transferred to a workstation for interpretation (Fig. 1) [22].

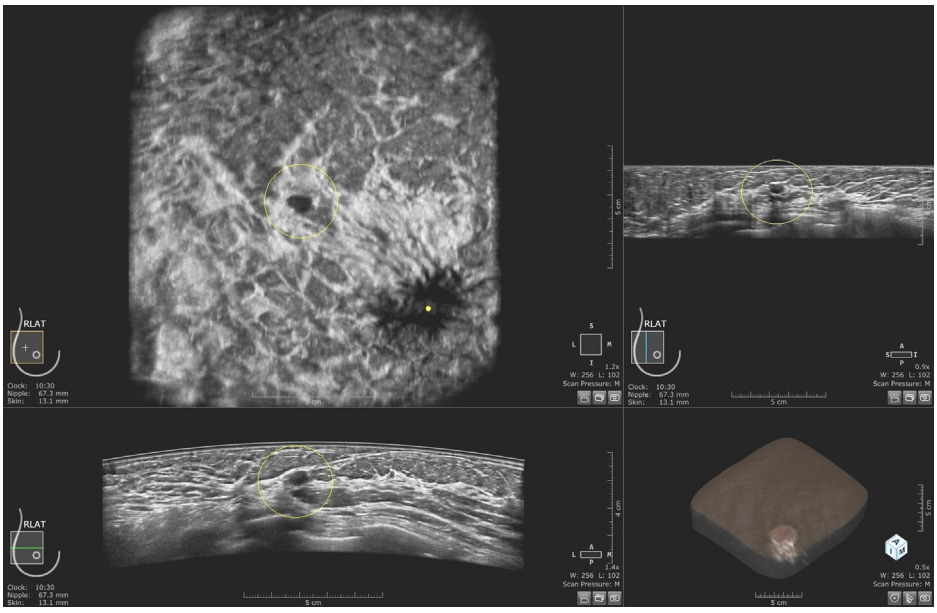

Figure 1. Three-dimensional automated breast ultrasound system images in a 56-year-old woman (right lateral volume); coronal, axial and sagittal plane illustrating a simple cyst (in the yellow circle).

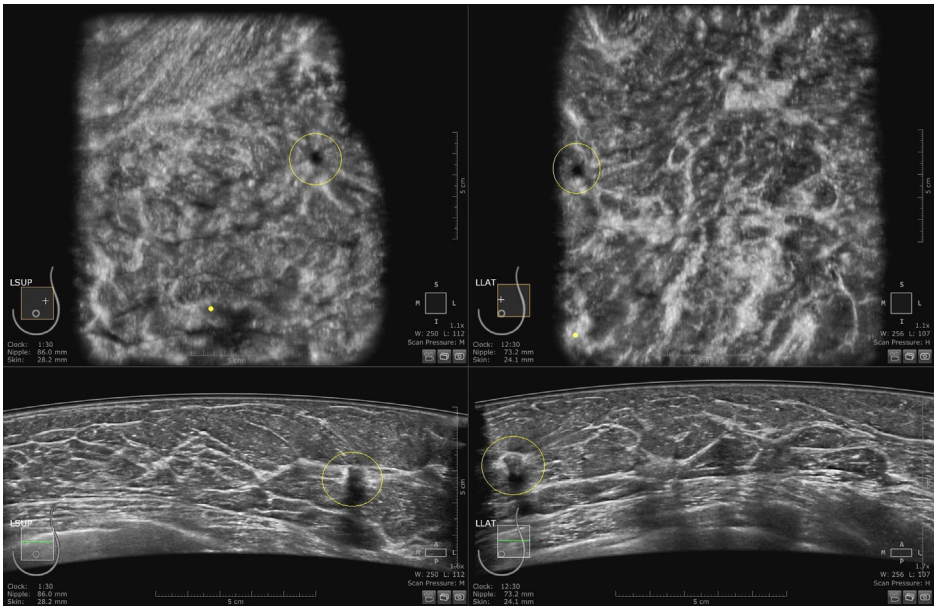

Figure 2. A 58-year-old woman with dense breasts. Three-dimensional automated breast ultrasound (left superior and left lateral volumes) revealed a black defect with acoustic shadowing, spicules and echogenic rim (in the yellow circle). Histopathological analysis of biopsy specimens revealed invasive ductal carcinoma of 7-mm in diameter, with negative sentinel node.

Automated software programs have been increasingly used with mammograms to provide quantitative measurement of breast density in a more objective and accurate way. Recently approved by the FDA, are the Volpara® and the Quantra® software programs [23]. Ongoing studies have suggested that 3D ABUS could also reliably quantify breast density, but integration of the quantitative techniques into clinical practice is still under investigation [24,25].

Image interpretation

The automated breast ultrasound technique has been developed to separate acquisition from interpretation, decreasing variability, improving reproducibility and allowing rapid review of images virtually right after the data has been acquired, without the patient's presence [26]. Once the image acquisitions have been performed, all the volumes are

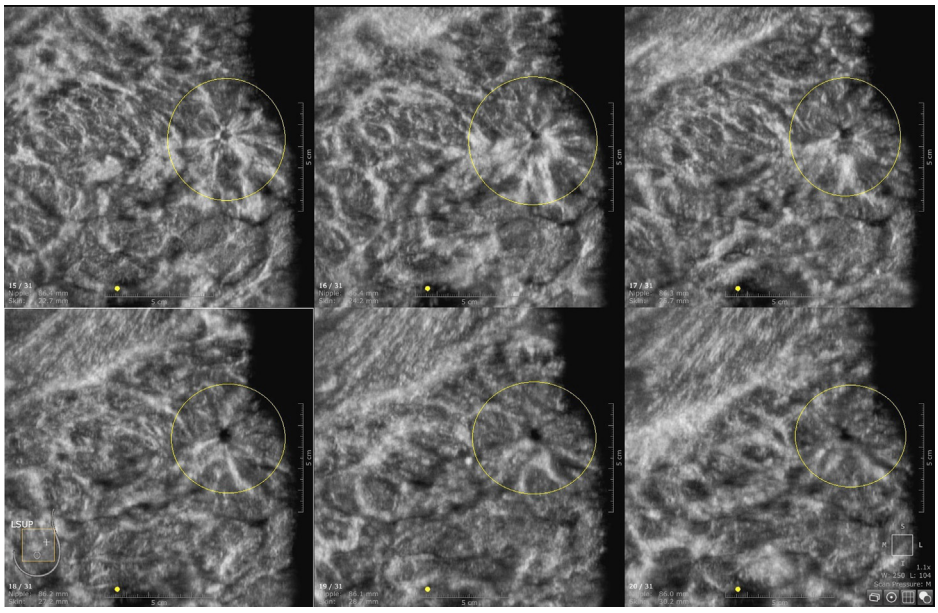

Figure 3. Retraction phenomenon sign (yellow circle) visualized on the reconstructed left superior coronal 2 mm ultrasound slices in a 49-year-old woman. Pathology showed an invasive ductal carcinoma measuring 0.5 cm in diameter.

transferred into a dedicated workstation for interpretation. Images are displayed in the raw transverse plane and reconstructed in coronal and sagittal plane for interpretation and further study. Moreover, patient history and clinical information are necessary before interpreting 3D ABUS examination [27,28].

Skaane et al. compared the reader performance and inter-observer variability of five radiologists reviewing 3D ABUS alone versus 3D ABUS in combination with mammography [29]. The 3D ABUS-mammography combination had higher inter-observer agreement in comparison to 3D ABUS alone. Additionally, all radiologists improved their diagnostic performance leading to the conclusion that combined reading should be adopted when 3D ABUS is incorporated in the screening of women with dense breasts.

Although there is no existing protocol on how to review the datasets, a standardized review process has been suggested, including the review of the coronal plane with the use of the scroll mode followed by review of the transverse plane with the use of the survey mode [27,30]. The coronal plane appears as the shape of a donut that includes the denser area of the breast and is used as a roadmap to navigate sequentially from the level of the skin posteriorly to the thoracic wall [31]. Reviewing all planes and all scans of every case is essential. Wide acquisition fields provide better visualization of the normal anatomy and any abnormality that is presented as a black defect (Fig. 2), with or without effect on the surrounding tissue. Any alteration of the normal breast structure and dilated ducts with or without solid component are easily depicted. In case of a suspicious abnormality the coordinates on both the coronal and the transverse views, as well as the sagittal view, are obtained automatically [30,32].

Meanwhile, information indicating the location of the lesion with respect to the nipple and the skin , as well as distances among multiple masses are automatically documented. Assessing structures in multiple perspectives provides more information about the normal structure of the fibroglandular tissue and improves reading productivity in comparison to evaluating solely the transverse plane. Several studies have shown the added value of the coronal plane in demonstrating architectural distortion as spiculation, termed a ''retraction phenomenon sign'', often characteristic of a malignancy or radial scar (Fig. 3) [11].

Interpretation time varies in published series between 2.9 min and 9 min and the variation in the length of the interpretation time has been attributed to differences in radiologists' reading technique, experience and complexity of cases [13,14,27,33,34]. To improve reading time, a computer-aided detection (CAD) software for 3D ABUS (QVCAD^{TM}, QView Medical) has been developed and has received FDA approval [35]. A reader study has shown that this new technology has the potential to improve reading time with no loss in diagnostic accuracy. There has been an average of 33% improved reading time among 18 radiologists in this study; without the QVCAD system, the mean interpretation time was 3 minutes 33 seconds for each case, but decreased to 2 minutes 24 seconds when QVCAD was implemented, a difference that corresponds to 1 minute 9 seconds saved per case [15]. These results support use of the concurrent-read QVCAD system for interpretation of screening 3D ABUS studies in women with dense breast tissue to make interpretation significantly faster with non-inferior diagnostic accuracy compared to that of unaided conventional 3D ABUS reading (Fig. 4) [15,16].

Clinical implications

Screening setting

Breast density has emerged as an independent risk factor for breast cancer [36,37]. In the USA the ''Are you Dense'' campaign [38] and the website Dense-Breast-info.org [39]

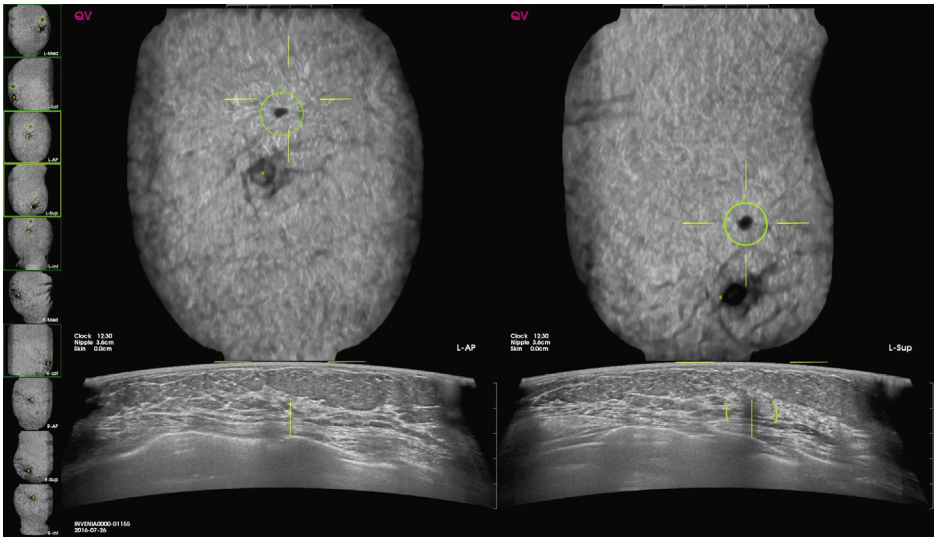

Figure 4. Computer-aided detection integrated in a three-dimensional automated breast ultrasound system examination (left anteroposterior and superior volumes). Dark areas (in green circles) representing a small invasive ductal carcinoma are highlighted on the computer-aided detection navigator images. Top images show coronal reconstructions and bottom images show transverse planes.

continue to raise awareness on breast density. As of March 2019, 36 States have passed ''density notification'' laws requiring women to be informed of their breast density. Women are therefore provided with the necessary information and can opt for further action and discussion with their physicians about supplemental screening if they have dense breasts. The aim of supplemental screening is to minimize the risk of missing a cancer at an early stage and to benefit the most from other available screening tools (Fig. 5) [39].

Recently the European Society of Breast Imaging (EUSOBI) issued recommendations for information to women and referring physicians concerning breast ultrasound. According to the EUSOBI recommendations, a possible indication for breast ultrasound pertains to women of average or intermediate risk with dense breasts, suggesting HHUS or 3D ABUS to be included as a supplemental screening modality following a negative mammogram; this combined approach increases cancer detection, but is also associated with a high false positive recall rate [34].

As more data become available on breast density and the impact of supplemental screening, 3D ABUS, which has overcome some of the limitations of HHUS, has gained wider acceptance as an adjunct tool to mammography. Several studies have investigated the impact of 3D ABUS as a screening modality when combined with mammography on cancer detection in women with dense breasts.

A large multicenter observational study (SomoInsight study) included 15,318 asymptomatic women aged 25—94 years with heterogeneously or extremely dense breasts who were followed-up for 1 year. The study evaluated the effect of 3D ABUS on breast cancer detection rates when 3D ABUS was implemented as a supplemental screening modality to full-field digital mammography (FFDM) versus FFDM alone. 3D ABUS detected 30 additional cancers showing an ICDR of 1.9 cancers per 1000 women (95% CI: 1.2—2.7; $P < 0.001$). Of the 30 cancers detected only with 3D ABUS, the vast majority (28 cancers, 93.3%) was invasive, of small size (mean size: 12.9 mm) and node negative (25/27 staged cancers, 92.6%). Accordingly, the combined arm offered an increase in sensitivity of 26.7%; on the other hand, there was an increase in recall rates (absolute increase: 13.5%) but recalls were additionally evaluated mainly with HHUS [14].

The EASY study was a single-center study conducted in Sweden, evaluating the impact of 3D ABUS when added to FFDM in a sample of 1668 asymptomatic women, aged 40—74 years. The EASY study highlighted an increase in ICDR by 2.4 detected cancers per 1000 women (95% CI: 0.6—4.8; $P < 0.001$) screened additionally by 3D ABUS; the sensitivity was improved by 36.4% in the combined examinations. The recall rate was 13.8 per 1000 women screened with FFDM and 22.8 screened with the combination of FFDM and 3D ABUS, reflecting an increase by 9.0 per 1000 women screened (95% CI: 3.0—15.0; $P = 0.004$) [13].

Giger et al. published a multi-reader, multi-case, sequential-design study evaluating FFDM supplemented by 3D ABUS versus FFDM alone in asymptomatic women with Breast Imaging-Reporting and Data System (BI-RADS) C or D breast density [21]. The study revealed a significant increase in the detection rate of breast cancer by 3D ABUS (absolute increase in sensitivity: 23.9% in mammography-negative cancers and 5.9% in mammography-positive cancers) without a substantial increase in the false positive rate [21].

Additionally, the ''ASSURE'' project has investigated methods to personalize breast cancer screening, based on risk and breast density markers; the impact of 3D ABUS in cancer detection was evaluated with the ultimate goal of decreasing mortality and improving the quality of life of women with breast cancer [40].

Evaluating jointly the results of the studies assessing the screening context, 3D ABUS improves cancer detection rates when added to FFDM. The reported recall rate is comparable to HHUS when added to mammography. Similarl to time trends noted in HHUS [8,41], recall rates substantially decrease also in 3D ABUS as readers gain experience [42]. As with every imaging modality, there is a learning curve; intensive training and experience

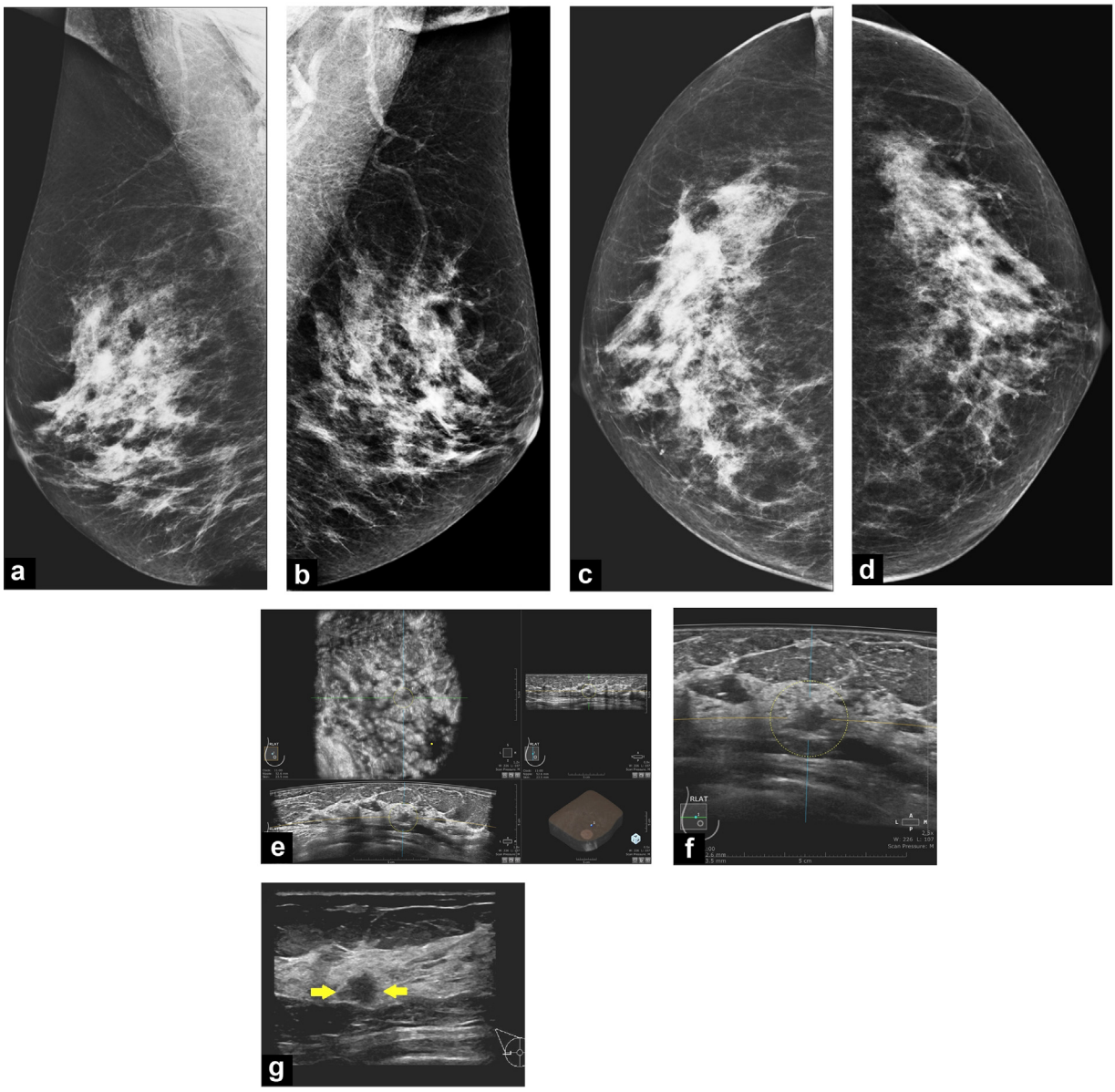

Figure 5. Digital mammography of a 56-year-old woman with dense breasts. Mediolateral (a: right, b: left) and craniocaudal (c: right, d: left) views were interpreted as normal. Supplemental three-dimensional automated breast ultrasound examination of the right lateral volume (e, f) revealed a hypoechoic mass (in a yellow circle) with angular margins at 9 o'clock position 52.6 mm from the nipple and 23.5 mm from the skin, that was confirmed (yellow arrows) with handheld ultrasound (g). Histopathological analysis showed an invasive ductal carcinoma associated with ductal carcinoma in situ.

establishing benchmarks, similar to the structure that has been designed for physician-performed screening HHUS, could improve the performance of radiologists. Additionally, well-trained technologists, acquiring state-of-the art image data, concentrating on including the entire breast within the field of view, adequately compressing the breast and meticulously applying the lotion, could reduce the false positive results and the recall rate; application of a computer-aided detection system could be helpful in the improvement of the workflow given the large volume of women in population screening centres [43]. Adopting a combined reading of 3D ABUS and mammography compared to 3D ABUS alone should be standard when implementing 3D ABUS in screening women with dense breasts [29]. The combination of all these aspects would substantially accelerate the application of 3D ABUS in high-volume screening with the goal of improving the detection of breast cancer.

Critically appraising the effectiveness of 3D ABUS in the context of supplemental screening, no randomized trials have been performed to assess the benefit in reducing mortality rates. Such randomized trials would necessitate a long-term follow-up period surpassing 10 years and would require considerable resources. Therefore, important surrogate measures, such as tumor size, percentage of invasive cancers, grade and nodal status [44], as well as interval cancer rates, would suggest an impact in the reduction of the mortality rate.

Table 1 Comparison of breast lesion detection between 3D ABUS and HHUS.

Study	Number of patients	Number of lesions	3D ABUS detection rate (%)	HHUS detection rate (%)
Kim et al. [49]	38	66	84.8 to 86.3 (across three radiologists)	93.9
Lin et al. [48]	81	95	100	100
Wang et al. [45]	213	239	99.6	98.7
Wang et al. [47]	155	165	97.6	95.8
Xiao et al. [46]	300	417	100	78.2
Zhang et al. [50]	81	99	89.9 to 100 (across two examiners)	60.6 to 85.9 (across two examiners)

3D ABUS: three-dimensional automated breast ultrasound system; HHUS: handheld ultrasound.

The screening setting can be considered the most important field of use for ABUS. Hence, after its approval for use, the integration of ABUS has also been assessed in the clinical, diagnostic setting. In the near future, further ongoing research results are anticipated to further establish its clinical value. In the next section, the available scientific evidence is put together to increase awareness.

Diagnostic setting

Besides the role of 3D ABUS in screening as an adjunct tool to mammography, several studies have addressed the utilization of 3D ABUS in the diagnostic setting. The diagnostic accuracy of 3D ABUS, as well as the comparison of the diagnostic performance of 3D ABUS versus HHUS have been evaluated in the detection and characterization of breast lesions in terms of BI-RADS assignment, shape, margins, orientation, posterior features and echogenicity assessment.

Detectability

Analysis of various studies have reported higher or equal detectability results of breast lesions by 3D ABUS when compared to HHUS; detection rates by 3D ABUS have varied between 84.8% and 100%, whereas the respective rates for HHUS have ranged from 60.6% to 100% [45—50]. However, a small study on 14 cancer cases showed that only 57.1—78.6% of cancers initially detected with HHUS were identified with 3D ABUS, a fact that according to the authors could be attributed to the lack of readers' experience with 3D ABUS [51]. The results of studies comparing detection rates in 3D ABUS in comparison to HHUS are summarized in Table 1.

A factor contributing to the improved detection rates is the additional information obtained by 3D ABUS on the coronal plane as lesions may be identified only in one of the three orthogonal planes [11,52]. The factors that could affect detectability at 3D ABUS are the size, shape and location of the lesion, the composition of breast parenchyma, surrounding tissue changes and technical parameters [43,53].

Malignant vs. benign differentiation

Chou et al. examined 182 lesions (47 carcinomas and 135 benign lesions) and presented a sensitivity equal to 98% and a specificity equal to 85% [54]. Kotsianos-Hermle et al. evaluated 107 lesions in 97 patients and reported a sensitivity of 96.5% and a specificity of 92.3% [55]. Wang et al. evaluated 239 lesions and found a high sensitivity (95.3%) and specificity (80.5%) in the differentiation of benign and malignant lesions [45]. Similar diagnostic accuracy was shown by Lin et al. who exhibited a 100% sensitivity and 95% specificity of 35 pathologically proven lesions [48].

Golatta et al. reported a sensitivity of 82% and a specificity of 68% [56]. In a subsequent study, Golatta et al. reported a sensitivity of 74% and a specificity of 85%; factors impeding the identification of lesions by 3D ABUS were the retroareolar location and the non-inclusion of the entire breast in the field of view and interpretation errors due to missing clinical information [57]. The results of studies examining the differentiation of malignant versus benign lesions with 3D ABUS are shown in Table 2.

Regarding BI-RADS classification, Wenkel et al. reported a good agreement between 3D ABUS and HHUS for five participating examiners with kappa (κ) values between 0.83 and 0.87 [58]. Shin et al. presented a substantial agreement between 3D ABUS and HHUS in final BI-RADS assessment category ($\kappa = 0.63$), shape of the mass ($\kappa = 0.71$), orientation ($\kappa = 0.72$) and margins of the lesions ($\kappa = 0.61$) [59]. Kim et al. showed a substantial agreement regarding shape ($\kappa = 0.707$) and moderate agreement on type (κ=0.592), margins ($\kappa = 0.438$), orientation of the mass ($\kappa = 0.472$), echogenicity ($\kappa = 0.524$), posterior acoustic features ($\kappa = 0.541$) and only a slight agreement for the final BI-RADS assessments yielded ($\kappa = 0.397$) [60]. In a series of 1886 women, Vourtsis and Kachulis reported high overall agreement in BI-RADS assessment between 3D ABUS and HHUS; 3D ABUS outperformed HHUS in detecting architectural distortions on the coronal plane [27]. One of the greatest advantages of 3D ABUS pertains to the identification of the 'retraction phenomenon sign' on the coronal plane [52,61], which reflects architectural distortion and has high sensitivity and specificity for malignancy, although it can be seen with radial scars and post-lumpectomy scars as well [48].

A robust diagnostic training program to standardize description and reporting of lesions is required as adhering to HHUS to increase the reliability and consistency when implementing 3D ABUS technique in diagnostic setting.

Table 2 Characterization of breast lesions (malignant vs. benign) with 3D ABUS.

Study	Number of patients	Description of the study population	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Comparative evaluation versus HHUS
Chou et al. [54]	182 lesions	Taipei, Taiwan; histologically proven breast lesions	98	85	70	No comparison
Golatta et al. [56]	42	Heidelberg, Germany; women referred for further diagnostic evaluation concerning symptoms, screen-detected abnormalities or follow-up after breast cancer	82	68	81	No comparison
Golatta et al. [57]	983	Heidelberg, Germany; monocentric, prospective, cohort study. The indication for examination included routine check-up, follow-up, preoperative staging of breast cancer, evaluation of palpable lumps and work-up of abnormalities found in HHUS or mammography	74	85	24	No comparison
Kim et al. [49]	38	Seoul, Korea; consecutive breast cancer patients who were scheduled for breast MRI; patients who were scheduled for chemotherapy and patients who refused a breast operation were excluded	88—96 (across three radiologists)	81.3—93.8 (across three radiologists)	Not reported	No significant differences

Table 2 (*Continued*)

Study	Number of patients	Description of the study population	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Comparative evaluation versus HHUS
Kotsianos-Hermle et al. [55]	97	Munich, Germany; patients who had a clinical reason to have a mammogram (either breast pain, findings on palpation or found sonographically suspect lesions); lesions had to be morphologically classified as solid tumors or complicated cyst and have a margin of normal tissue	96.5	92.3	Not reported	No significant differences
Lin et al. [48]	81	Guangzhou, China; patients who had a clinical reason to undergo sonography (either breast pain, unusual findings on palpation or preoperative diagnosis)	100	95	Not reported	3D ABUS had a higher diagnostic accuracy than HHUS for breast neoplasms, but no statistical tests were presented for this comparison
Wang et al. [45]	213	Beijing, China; women scheduled for open biopsy; lesions had to be morphologically classified as solid tumors or complex cysts and have a margin of normal tissue	95.3	80.5	73	No significant differences
Wang et al. [47]	155	Beijing, China; consecutive patients scheduled to undergo ultrasound-guided core needle biopsy due to suspicious breast lesions detected during screening mammography or manual ultrasound	96.1	91.9	95.2	No significant differences

3D ABUS: three-dimensional automated breast ultrasound system; HHUS: handheld ultrasound; MRI: magnetic resonance imaging.

Table 3 Between-observer agreement for BI-RADS categorization with 3D ABUS.

Study	Number of patients	Number of examiners	BI-RADS categories used in the study	Kappa value
Golatta et al. [56]	42	6	Two categories: BI-RADS 1—2; 4—5	0.52
Kim et al. [49]	38	3	Five categories: 1; 2; 3; 4; 5	0.57
Shin et al. [59]	55	5	Six categories: BI-RADS 1—2; 3; 4A; 4B; 4C; 5	0.63
Skaane et al. [29]	90	5	Five categories: BI-RADS 1; 2; 3; 4; 5	0.07—0.34, across participating radiologists
Vourtsis and Kachulis [27]	1886	2	Five categories: BI-RADS 1; 2; 3; 4; 5	0.99
Wang et al. [47]	155	2	Two categories: BI-RADS 1—3; 4—5	0.44
Wojcinski et al. [64]	100	2	Two categories: BI-RADS 1/2; 0/3/4/5	0.36
Zhang et al. [65]	208	2	Three categories: BI-RADS 3; 4; 5	0.70

3D ABUS: three-dimensional automated breast ultrasound system; BI-RADS: Breast Imaging-Reporting and Data System.

Between-observer agreement

Several studies have evaluated the inter-observer reliability in BI-RADS assessment, with heterogeneous results according to a recent systematic review [62]; kappa values varied considerably [27,29,47,49,56,59,63—65]. In the study by Vourtsis and Kachulis, the inter-observer agreement in BI-RADS classification between the two assessors was very high (99.8%, $\kappa = 0.996$) [27]. The results of studies evaluating inter-observer agreement in BI-RADS categorization in 3D ABUS are presented in Table 3.

Similarly, heterogeneous results have been published regarding the between-observer concordance on BI-RADS descriptors (echo pattern, margins, orientation, posterior acoustic feature, shape) and information about location, distance from the nipple, as well as from the skin and the size of the lesion [49,59,63,65].

Artifacts

Although the resolution and quality of 3D ABUS images have been significantly improved in the newest scanners, possible artifacts still exist. The most common artifact has been described as corrugation, which is due to respiratory motion; this artifact can be avoided when women breathe calmly and do not speak or cough [66]. Another common artifact, dropout shadowing deep to the skin, is caused by insufficient lotion application and extreme compression [67,68]. Shadowing caused by an artifact diminishes by rotating and tilting the crosshairs on the coronal plane. Uniform compression of the breast and proper positioning tend to diminish artifactual posterior shadowing that develops at the interface of fat lobules. Shadowing apparent in the area behind the nipple can be avoided by applying a sufficient amount of lotion without any bubbles and close contact between the scanner and the nipple [69]. Clinical information and patient history contribute to distinguishing post-operative changes from a malignant lesion. In the study by Vourtsis and Kachulis, a ''zig zag'' sign was produced by disruption of the scanning process in 61.5% of women with palpable lesions; such a sign could be alarming for the radiologist to seek an underlying lesion [27].

Detection of the extent of the disease

Breast magnetic resonance imaging (MRI) has been extensively used for the preoperative staging of multifocality and multicentricity of the disease. On the other hand, 3D ABUS, due to the global visualization of the breast is also an emerging modality for operative planning [70]; lesion size measured by 3D ABUS correlates well with MRI [71] and histopathological [48,63] measurements. Additionally, the coronal plane offers special value for surgical planning due to better imaging of the segmental approach and the similar orientation as the patient is positioned for surgery [31]. 3D ABUS is capable of visualizing also satellite lesions smaller than 1 cm, offering more information than HHUS in the assessment of multifocal cancer [27,45].

Assessment of response to neoadjuvant chemotherapy

Another potential indication of 3D ABUS pertains to the assessment of response to neoadjuvant chemotherapy; Wang et al. showed a high sensitivity and specificity of 3D ABUS in predicting complete response rate after four cycles of chemotherapy [72]. Similar results have been reported in a prospective study of 35 women [73].

Second-look examination

3D ABUS can be useful in the further evaluation of MRI findings as a second-look tool [74—77]. 3D ABUS outperformed HHUS as a second-look examination after breast MRI, detecting additional lesions that were not identified on HHUS [74,77]; according to Girometti et al. HHUS and 3D ABUS showed equivalent results in a cohort of 131 patients [76].

Molecular subtypes of breast cancer

The potential correlation between molecular subtypes of breast cancer and 3D ABUS morphological features is a topic under investigation. Combinations of present or absent retraction sign, post-acoustic shadowing, echogenic halo and calcifications seem capable of predicting the molecular subtype of breast cancer [78,79]. Correlations between the retraction phenomenon sign and lesion of small size, low grade, estrogen and progesterone receptor positivity have also been reported, signalling favourable prognosis [80].

Future perspectives

Ongoing are intensive exploration of novel developments and research in additional applications of the 3D ABUS technology. 3D ABUS could be utilized in the surveillance of benign lesions due to its standardized technique and the precise documentation of lesion location and distance from the nipple [63]. Evaluation of breast density with 3D ABUS is another promising field [24,25].

Research is active in the field of deep learning to develop advanced algorithms and to optimize the workflow of breast imaging. Radiomic 3D ABUS signature, encompassing combinations of imaging features, could accurately differentiate between malignant and benign breast lesions [81].

A prospective feasibility study is investigating the fusion-X-US prototype, which combines the 3D ABUS and tomosynthesis in one device; this may be a future clinical modality to improve workflow in breast imaging [82].

Conclusions

Studies have shown that 3D ABUS is a standardized and reproducible modality that overcomes the limitations of HHUS, while it offers valuable impact in the detectability of breast lesions, the differentiation of malignant from benign lesions, with a high inter-observer agreement. Computer-aided detection software significantly reduces interpretation time, improving the workflow for the utilization of 3D ABUS as a supplemental screening tool. Promising results have supported the enhanced efficiency of 3D ABUS in detecting the extent of the disease, assessing response to neoadjuvant chemotherapy and correlating with molecular subtypes of breast cancer. Future perspectives include the integration of radiomics and deep learning in the further development of 3D ABUS.

Informed consent

Written informed consent was not required for this review article.

Author statement

AV: conceptualization; data curation; investigation; methodology; roles/writing — original draft.

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References

[1] Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA 2015;314:1599—614.
[2] Tabar L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011;260:658—63.
[3] Bae MS, Moon WK, Chang JM, Koo HR, Kim WH, Cho N, et al. Breast cancer detected with screening US: reasons for nondetection at mammography. Radiology 2014;270:369—77.
[4] Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. Radiology 2012;265:59—69.
[5] Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002;225:165—75.
[6] Corsetti V, Houssami N, Ghirardi M, Ferrari A, Speziani M, Bellarosa S, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: interval breast cancers at 1-year follow-up. Eur J Cancer 2011;47:1021—6.
[7] Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Bohm-Velez M, et al. Combined screening with ultrasound and mammography vs. mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151—63.
[8] Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307:1394—404.
[9] Buchberger W, Niehoff A, Obrist P, DeKoekkoek-Doll P, Dunser M. Clinically and mammographically occult breast lesions: detection and classification with high-resolution sonography. Semin Ultrasound CT MR 2000;21:325—36.

[10] Sprague BL, Stout NK, Schechter C, van Ravesteyn NT, Cevik M, Alagoz O, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. Ann Intern Med 2015;162:157—66.
[11] Van Zelst JC, Platel B, Karssemeijer N, Mann RM. Multiplanar reconstructions of 3D automated breast ultrasound improve lesion differentiation by radiologists. Acad Radiol 2015;22:1489—96.
[12] Kelly KM, Dean J, Comulada WS, Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol 2010;20:734—42.
[13] Wilczek B, Wilczek HE, Rasouliyan L, Leifland K. Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: report from a hospital-based, high-volume, single-center breast cancer screening program. Eur J Radiol 2016;85:1554—63.
[14] Brem RF, Tabar L, Duffy SW, Inciardi MF, Guingrich JA, Hashimoto BE, et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology 2015;274:663—73.
[15] Jiang Y, Inciardi MF, Edwards AV, Papaioannou J. Interpretation time using a concurrent-read computer-aided detection system for automated breast ultrasound in breast cancer screening of women with dense breast tissue. AJR Am J Roentgenol 2018;211:452—61.
[16] van Zelst JCM, Tan T, Clauser P, Domingo A, Dorrius MD, Drieling D, et al. Dedicated computer-aided detection software for automated 3D breast ultrasound; an efficient tool for the radiologist in supplemental screening of women with dense breasts. Eur Radiol 2018;28:2996—3006.
[17] Mundinger A. 3D supine automated ultrasound (SAUS, ABUS, ABVS) for supplemental screening women with dense breasts. J Breast Health 2016;12:52—5.
[18] Farrokh A, Erdonmez H, Schafer F, Maass N. SOFIA: a novel automated breast ultrasound system used on patients in the prone position: a pilot study on lesion detection in comparison to handheld grayscale ultrasound. Geburtshilfe Frauenheilkd 2018;78:499—505.
[19] O'Flynn EAM, Fromageau J, Ledger AE, Messa A, D'Aquino A, Schoemaker MJ, et al. Ultrasound tomography evaluation of breast density: a comparison with noncontrast magnetic resonance imaging. Invest Radiol 2017;52:343—8.
[20] US Food and Drug Administration. Premarket Approval (PMA) P110006; 2013 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P110006S001 [accessed on September 01, 2018].
[21] Giger ML, Inciardi MF, Edwards A, Papaioannou J, Drukker K, Jiang Y, et al. Automated breast ultrasound in breast cancer screening of women with dense breasts: reader study of mammography-negative and mammography-positive cancers. AJR Am J Roentgenol 2016;206:1341—50.
[22] Rella R, Belli P, Giuliani M, Bufi E, Carlino G, Rinaldi P, et al. Automated breast ultrasonography (ABUS) in the screening and diagnostic setting: indications and practical use. Acad Radiol 2018;25:1457—70.
[23] Destounis S, Arieno A, Morgan R, Roberts C, Chan A. Qualitative versus quantitative mammographic breast density assessment: applications for the US and abroad. Diagnostics (Basel) 2017;7 [pii: E30].
[24] Moon WK, Shen YW, Huang CS, Luo SC, Kuzucan A, Chen JH, et al. Comparative study of density analysis using automated whole breast ultrasound and MRI. Med Phys 2011;38:382—9.
[25] Chen JH, Lee YW, Chan SW, Yeh DC, Chang RF. Breast density analysis with automated whole breast ultrasound: comparison with 3-D magnetic resonance imaging. Ultrasound Med Biol 2016;42:1211—20.
[26] Thigpen D, Kappler A, Brem R. The role of ultrasound in screening dense breasts — a review of the literature and practical solutions for implementation. Diagnostics (Basel) 2018, [pii: E20];8.
[27] Vourtsis A, Kachulis A. The performance of 3D ABUS versus HHUS in the visualisation and BI-RADS characterisation of breast lesions in a large cohort of 1886 women. Eur Radiol 2018;28:592—601.
[28] Geisel J, Raghu M, Hooley R. The role of ultrasound in breast cancer screening: the case for and against ultrasound. Semin Ultrasound CT MR 2018;39:25—34.
[29] Skaane P, Gullien R, Eben EB, Sandhaug M, Schulz-Wendtland R, Stoeblen F. Interpretation of automated breast ultrasound (ABUS) with and without knowledge of mammography: a reader performance study. Acta Radiol 2015;56:404—12.
[30] Lander MR, Tabar L. Automated 3-D breast ultrasound as a promising adjunctive screening tool for examining dense breast tissue. Semin Roentgenol 2011;46:302—8.
[31] Dominique A, editor. Lobar approach to breast ultrasound. Cham, Switzerland: Springer-Nature; 2018.
[32] Aripoli A, Fountain K, Winblad O, Gatewood J, Hill J, Wick JA, et al. Supplemental screening with automated breast ultrasound in women with dense breasts: comparing notification methods and screening behaviors. AJR Am J Roentgenol 2018;210:W22—8.
[33] Huppe AI, Inciardi MF, Redick M, Carroll M, Buckley J, Hill JD, et al. Automated breast ultrasound interpretation times: a reader performance study. Acad Radiol 2018;25:1577—81.
[34] Evans A, Trimboli RM, Athanasiou A, Balleyguier C, Baltzer PA, Bick U, et al. Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. Insights Imaging 2018;9:449—61.
[35] US Food and Drug Administration. Premarket Approval (PMA) P150043; 2016 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150043 [accessed on September 01, 2018].
[36] Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007;356:227—36.
[37] Chiu SY, Duffy S, Yen AM, Tabar L, Smith RA, Chen HH. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev 2010;19:1219—28.
[38] Are You Dense Inc. Are you Dense?; 2018 https://www.areyoudense.org/ [accessed on Sep 01, 2018].
[39] Dense-Breast.Info. Legislation and regulations — what is required?; 2017 http://densebreast-info.org/legislation.aspx [accessed on Sep 01, 2018].
[40] Platel B. ASSURE Personalised breast cancer screening; 2012 http://www.assure-project.eu [accessed on Sep 01, 2018].
[41] Weigert JM. The Connecticut Experiment; the third installment: 4 years of screening women with dense breasts with bilateral ultrasound. Breast J 2017;23:34—9.
[42] Arleo EK, Saleh M, Ionescu D, Drotman M, Min RJ, Hentel K. Recall rate of screening ultrasound with automated breast volumetric scanning (ABVS) in women with dense breasts: a first quarter experience. Clin Imaging 2014;38:439—44.
[43] Mendelson EB, Berg WA. Training and standards for performance, interpretation, and structured reporting for supplemental breast cancer screening. AJR Am J Roentgenol 2015;204:265—8.
[44] Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of

mammographic screening for breast cancer. Radiol Clin North Am 1992;30:187—210.
[45] Wang HY, Jiang YX, Zhu QL, Zhang J, Dai Q, Liu H, et al. Differentiation of benign and malignant breast lesions: a comparison between automatically generated breast volume scans and handheld ultrasound examinations. Eur J Radiol 2012;81:3190—200.
[46] Xiao YM, Chen ZH, Zhou QC, Wang Z. The efficacy of automated breast volume scanning over conventional ultrasonography among patients with breast lesions. Int J Gynaecol Obstet 2015;131:293—6.
[47] Wang ZL, Xu JH, Li JL, Huang Y, Tang J. Comparison of automated breast volume scanning to handheld ultrasound and mammography. Radiol Med 2012;117:1287—93.
[48] Lin X, Wang J, Han F, Fu J, Li A. Analysis of eighty-one cases with breast lesions using automated breast volume scanner and comparison with handheld ultrasound. Eur J Radiol 2012;81:873—8.
[49] Kim SH, Kang BJ, Choi BG, Choi JJ, Lee JH, Song BJ, et al. Radiologists' performance for detecting lesions and the interobserver variability of automated whole breast ultrasound. Korean J Radiol 2013;14:154—63.
[50] Zhang Q, Hu B, Hu B, Li WB. Detection of breast lesions using an automated breast volume scanner system. J Int Med Res 2012;40:300—6.
[51] Chang JM, Moon WK, Cho N, Park JS, Kim SJ. Breast cancers initially detected by handheld ultrasound: detection performance of radiologists using automated breast ultrasound data. Acta Radiol 2011;52:8—14.
[52] Zheng FY, Yan LX, Huang BJ, Xia HS, Wang X, Lu Q, et al. Comparison of retraction phenomenon and BI-RADS-US descriptors in differentiating benign and malignant breast masses using an automated breast volume scanner. Eur J Radiol 2015;84:2123—9.
[53] Chang JM, Moon WK, Cho N, Park JS, Kim SJ. Radiologists' performance in the detection of benign and malignant masses with 3D automated breast ultrasound (ABUS). Eur J Radiol 2011;78:99—103.
[54] Chou YH, Tiu CM, Chen J, Chang RF. Automated full-field breast ultrasonography: the past and the present. J Med Ultrasound 2007;15:31—44.
[55] Kotsianos-Hermle D, Hiltawsky KM, Wirth S, Fischer T, Friese K, Reiser M. Analysis of 107 breast lesions with automated 3D ultrasound and comparison with mammography and manual ultrasound. Eur J Radiol 2009;71:109—15.
[56] Golatta M, Franz D, Harcos A, Junkermann H, Rauch G, Scharf A, et al. Inter-observer reliability of automated breast volume scanner (ABVS) interpretation and agreement of ABVS findings with handheld breast ultrasound (HHUS), mammography and pathology results. Eur J Radiol 2013;82:e332—6.
[57] Golatta M, Baggs C, Schweitzer-Martin M, Domschke C, Schott S, Harcos A, et al. Evaluation of an automated breast 3D ultrasound system by comparing it with handheld ultrasound (HHUS) and mammography. Arch Gynecol Obstet 2015;291:889—95.
[58] Wenkel E, Heckmann M, Heinrich M, Schwab SA, Uder M, Schulz-Wendtland R, et al. Automated breast ultrasound: lesion detection and BI-RADS classification — a pilot study. Rofo 2008;180:804—8.
[59] Shin HJ, Kim HH, Cha JH, Park JH, Lee KE, Kim JH. Automated ultrasound of the breast for diagnosis: inter-observer agreement on lesion detection and characterization. AJR Am J Roentgenol 2011;197:747—54.
[60] Kim EJ, Kim SH, Kang BJ, Kim YJ. Inter-observer agreement on the interpretation of automated whole breast ultrasonography. Ultrasonography 2014;33:252—8.
[61] Kim YW, Kim SK, Youn HJ, Choi EJ, Jung SH. The clinical utility of automated breast volume scanner: a pilot study of 139 cases. J Breast Cancer 2013;16:329—34.
[62] Meng Z, Chen C, Zhu Y, Zhang S, Wei C, Hu B, et al. Diagnostic performance of the automated breast volume scanner: a systematic review of inter-rater reliability/agreement and meta-analysis of diagnostic accuracy for differentiating benign and malignant breast lesions. Eur Radiol 2015;25:3638—47.
[63] Chang JM, Cha JH, Park JS, Kim SJ, Moon WK. Automated breast ultrasound system (ABUS): reproducibility of mass localization, size measurement, and characterization on serial examinations. Acta Radiol 2015;56:1163—70.
[64] Wojcinski S, Gyapong S, Farrokh A, Soergel P, Hillemanns P, Degenhardt F. Diagnostic performance and inter-observer concordance in lesion detection with the automated breast volume scanner (ABVS). BMC Med Imaging 2013;13:36.
[65] Zhang J, Lai XJ, Zhu QL, Wang HY, Jiang YX, Liu H, et al. Inter-observer agreement for sonograms of breast lesions obtained by an automated breast volume scanner. Eur J Radiol 2012;81:2179—83.
[66] Xiao Y, Zhou Q, Chen Z. Automated breast volume scanning versus conventional ultrasound in breast cancer screening. Acad Radiol 2015;22:387—99.
[67] Karst I, Henley C, Gottschalk N, Floyd S, Bailey J, Mendelson E.3D automated breast ultrasound facts and artifacts. Radiological Society of North America 2017 Scientific Assembly and Annual Meeting, November 26—December 1 2017, Chicago, IL. 2017.
[68] Karst I, Henley C, Gottschalk N, Floyd S, Mendelson E. 3D automated breast ultrasound: facts and artifacts. Radiographics 2019 [accepted for publication].
[69] Isobe S, Tozaki M, Yamaguchi M, Ogawa Y, Homma K, Satomi R, et al. Detectability of breast lesions under the nipple using an automated breast volume scanner: comparison with handheld ultrasonography. Jpn J Radiol 2011;29:361—5.
[70] Grady I, Gorsuch-Rafferty H, Hansen P. Sonographic tomography for the preoperative staging of breast cancer prior to surgery. J Ultrasound 2010;13:41—5.
[71] Schmachtenberg C, Fischer T, Hamm B, Bick U. Diagnostic performance of automated breast volume scanning (ABVS) compared to handheld ultrasonography with breast MRI as the gold standard. Acad Radiol 2017;24:954—61.
[72] Wang X, Huo L, He Y, Fan Z, Wang T, Xie Y, et al. Early prediction of pathological outcomes to neoadjuvant chemotherapy in breast cancer patients using automated breast ultrasound. Chin J Cancer Res 2016;28:478—85.
[73] D'Angelo A, Rinaldi P, Rella R, Giuliani M, Belli P, Carlino G, et al. Usefulness of automated breast volume scanner to evaluate the early response to neoadjuvant therapy in breast cancer patients: a prospective study. Abstract B-1419 in ECR 2018. Insights Imaging 2018;9:S481—2.
[74] Chae EY, Shin HJ, Kim HJ, Yoo H, Baek S, Cha JH, et al. Diagnostic performance of automated breast ultrasound as a replacement for a handheld second-look ultrasound for breast lesions detected initially on magnetic resonance imaging. Ultrasound Med Biol 2013;39:2246—54.
[75] Halshtok-Neiman O, Shalmon A, Rundstein A, Servadio Y, Gotleib M, Sklair-Levy M. Use of automated breast volumetric sonography as a second-look tool for findings in breast magnetic resonance imaging. Isr Med Assoc J 2015;17:410—3.
[76] Girometti R, Zanotel M, Londero V, Bazzocchi M, Zuiani C. Comparison between automated breast volume scanner (ABVS) versus handheld ultrasound as a second-look procedure after magnetic resonance imaging. Eur Radiol 2017;27:3767—75.
[77] Kim Y, Kang BJ, Kim SH, Lee EJ. Prospective study comparing two second-look ultrasound techniques: handheld ultrasound and an automated breast volume scanner. J Ultrasound Med 2016;35:2103—12.
[78] Zheng FY, Lu Q, Huang BJ, Xia HS, Yan LX, Wang X, et al. Imaging features of automated breast volume scanner:

correlation with molecular subtypes of breast cancer. Eur J Radiol 2017;86:267—75.
[79] Wang XL, Tao L, Zhou XL, Wei H, Sun JW. Initial experience of automated breast volume scanning (ABVS) and ultrasound elastography in predicting breast cancer subtypes and staging. Breast 2016;30:130—5.
[80] Jiang J, Chen YQ, Xu YZ, Chen ML, Zhu YK, Guan WB, et al. Correlation between three-dimensional ultrasound features and pathological prognostic factors in breast cancer. Eur Radiol 2014;24:1186—96.
[81] Papanikolaou N, Vourtsis A. The performance of Radiomic ABUS signature in the differentiation of benign from malignant breast lesions (Accepted Abstract). European Society of Breast Imaging (EUSOBI) Annual Scientific Meeting 2018, Athens. 2018.
[82] Schaefgen B, Heil J, Barr RG, Radicke M, Harcos A, Gomez C, et al. Initial results of the FUSION-X-US prototype combining 3D automated breast ultrasound and digital breast tomosynthesis. Eur Radiol 2018;28: 2499—506.