

Automated breast ultrasound: basic principles and emerging clinical applications

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Abstract Automated breast ultrasound (ABUS) is a recently introduced ultrasonography technique, developed with the purpose to standardize breast ultrasonography and overcome some limitations of handheld ultrasound (HHUS), such as operator dependence and the considerable amount of medical time necessary to perform and interpret HHUS. This new ultrasonography technique separates the moment of image acquisition (that may be performed also by a technician) from that of its interpretation, increasing reproducibility, reducing operator-dependence and physician time. Moreover, multiplanar reconstructions, especially the coronal view, introduce new diagnostic information. ABUS, with those advantages, has the potential to be used as an adjunctive tool to screening mammography, especially in the dense breast, where mammography has a relatively low sensitivity. Women's awareness of risks related to breast density is a hot topic, especially in the USA where legislative breast density notification laws increase the demand for supplemental ultrasound screening. Therefore, ABUS might have the potential to respond to this need. The purpose of this article is to present a summary of current state-of-the-art of ABUS technology and applications, with an emphasis on breast cancer screening. This article discusses also how to overcome some ABUS limitations, in order to be familiar with the new technique.

Keywords Automated breast ultrasound · Screening · Breast cancer · Ultrasonography

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Introduction

Breast cancer is the most common malignant disease of the female population [1] and mammographic screening is an effective proven method for reducing mortality, through early diagnosis [2]. Despite this, in dense breasts, mammographic sensitivity can be very low, even less than 50% [3]. For this reason and because of breast density has been established as an independent risk factor for breast cancer, the need for an additional tool is gaining ever greater interest [4]. Handheld ultrasound (HHUS) is a valid supplemental screening tool being widely available and cheap. Several studies evaluated HHUS as a screening tool in women with dense breast [5–9], the most significant is the large multi-institutional trial published by Berg et al. [5], reporting a supplemental yield of 4.2 per 1000 women screened. This study, however, revealed some “weak points” of HHUS screening, such as the high number of false positives (FP) and the considerable effort in terms of physician time for exam execution and interpretation [5]. Due to these limitations, technological research tried for years to propose ultrasonography machines able to standardize and simplify US examination. Automated breast ultrasound (ABUS), also known as automated volumetric scanner (ABVS), depending on the vendor, was introduced with the purpose to overcome the operator-dependence of HHUS, increasing the reproducibility of the examination. ABUS is a technological advance, which provides ultrasonography 3D representation of the breast tissue, with the advantage of multiplanar reformations and the capability to review images retrospectively once the examination has been acquired [4, 10]. The concept of automated breast ultrasound dates back to the 70s [11]; however, old generation scanners had transducers with relatively low frequency (4–7 MHz) and image quality was not sufficiently good. Interest in ABUS research further increased with the

development of modern scanners, provided with high-frequency transducers [12]. Therefore, several studies were performed mostly for the evaluation of ABUS as a supplemental screening tool [13–15] and in recent years some studies also considered its use in the clinical setting [12, 16–19].

In the present review, we performed a computerized search by using the PubMed database (www.ncbi.nlm.nih.gov/pubmed/), including articles listed up to 30 April 2017. The following search terms were used: automated breast ultrasound/ultrasonography, automated breast volume scanner/scanners/scanning and automated whole breast ultrasound/ultrasonography. Only articles in English were included. Titles and abstracts of search results were examined. When considered suitable, the full text was reviewed. The references of retrieved studies were examined to identify additional papers.

Articles regarding the use of ABUS in the screening or clinical setting were included. Excluded were studies (1) on non-human subjects, (2) that evaluated newly developed prototype devices (e.g. fusion devices) or (3) testing computerized applications for ABUS (e.g. image segmentation, density analysis or Computer Aided Detection).

Equipment and technique

Nowadays, several types of automated breast ultrasound systems are available, including two main categories: prone- and supine-scanners [4].

The first device, a supine-type scanner, was a hybrid system (SonoCine, Reno) provided with a conventional ultrasound transducer mounted on a computer-guided articulating arm [20]. This system received FDA clearance as an adjunct to screening mammography in 2008 [21]. The transducer moves automatically over the breast, in a way similar to that of HHUS, acquiring transverse images in cranio-caudal linear overlapping rows. A hydrogel nipple pad is applied to allow proper contact with the skin and a trained operator is responsible for appropriate vertical orientation of the probe and adequate contact pressure with the skin. Overall examination time is about 20–30 min (10–20 min for scanning, 5–10 min for preparing the patient) [13]. Following 2D axial scan's acquisition, the automated whole breast ultrasound software creates a cine loop, containing 2000–5000 images each [13]. Initially, such systems did not allow 3D reconstructions of the row data [4]; however, new 3-D whole breast multiplanar reconstruction software has recently been announced.

Modern automated breast scanners were subsequently developed (Somo-V, GE Healthcare; ACUSON S2000, Siemens Medical Solutions); both received FDA clearance in 2012 [21] and operate differently from previous hybrid machines. Those systems are provided with special

high-frequency and large footprint transducers (15 × 17 cm), similar in size to a mammography compression paddle and mounted on a mechanical arm. One of those modern systems is provided with a curved transducer designed to follow the contour of the breast [4]. The acquisition starts after placing the probe over the breast with only mild compression. A replaceable membrane covers the transducer surface to allow adequate contact with the skin of the entire area. In this system, the patient lies in the supine position with the arm of the side under examination over the head. Conventionally, three 1 min scans are sufficient for scanning the entire breast, excluding the axilla. However, in case of larger breast, more than one scan may be required to cover the entire field of interest. The average total time to complete the examination is approximately 15 min. Trained technicians are able to perform examination. Of note, learning to perform ABUS, with correct positioning and adequate compression power, requires time; therefore, training is a relevant part for image quality [22]. Compression errors can create artifacts that interfere with the interpretation (Fig. 1). After image acquisition, row data are stored on the systems' hard disk and then transferred to a dedicated workstation, where images, displayed both in the native axial plane of acquisition and reformatted coronal and sagittal planes, can be reviewed for further interpretation and analysis. The coronal plane, also known as the "surgical view" (in which the breast is positioned in the same way that it is oriented on the surgical table), introduces new diagnostic information, i.e. the retraction phenomenon [23]. The main limitations of ABUS systems are exclusion of axillary regions from the field of view and the absence of tools to assess vascularity and tissue elasticity [4].

Prone-type scanners are still under development; however, one of these systems received FDA clearance in 2014 [21]. A circumferential transducer performs the scan with the patient lying prone on the table with the breast suspended in a warm-water bath beneath an opening in the table top [22, 24]. The transducer has a ring configuration and collects data by rotating 360°. After acquisition, data are processed and reconstructed to allow volumetric rendering [22, 24].

ABUS interpretation

Automated breast ultrasound technology allows the radiologist to interpret ultrasonography images in a separate time after acquisition. Different interpretation times have been reported, ranging from 5 to 10 min [14, 23, 25–29], probably according to differences in readers' experience and complexity of each case.

Regarding the reading technique there is no uniform protocol: some authors used a reading protocol starting from transverse plane [26], while other authors preferred starting from coronal plane [28, 30, 31].

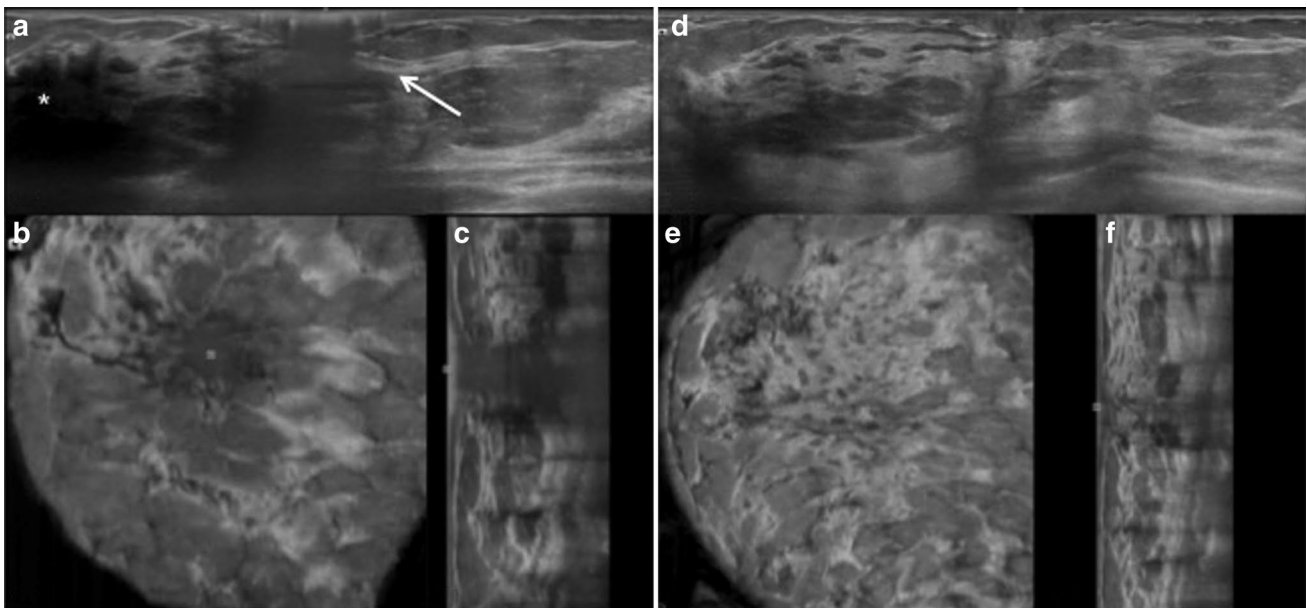


Fig. 1 Artifacts: nipple shadowing (*arrow*) and dense breast parenchyma artifacts (*asterisk*) displayed on automated breast ultrasonography using Siemens ABVS (**a** axial view, **b** coronal view, **c** sagittal view). Re-scanning the same patient and increasing scanning pres-

sure, these artifacts were eliminated (**d** axial view, **e** coronal view, **f** sagittal view) allowing to obtain an optimal visualization of the entire breast parenchyma

Clinical applications

Screening

The application of automated breast ultrasound was initially focused on the screening setting and first works aimed to test the new technique in dense breast. Interest has continued to increase in past years due to a greater awareness for the problem of breast density, especially in the USA where legislative breast density notification laws increase the demand for supplemental US screening [22, 26].

First screening works were performed using a hybrid system [13, 25]. Kelly et al. [13], in a multicenter study, compared mammography alone versus automated whole breast ultrasound (AWBU) plus mammography in 4419 women with dense breasts and/or at elevated risk of breast cancer. The above mentioned authors found an improvement in cancer detection of 3.6 per 1000 women screened with the addition of AWBU [13]. Sensitivity increased from 40% for mammography alone to 81% for the combined modalities, while AWBU alone reached a sensitivity of 67% [13]. The detection of invasive ductal cancers and smaller lesions (≤ 10 mm) was significantly higher for AWBU alone than mammography (sensitivities for cancers ≤ 10 mm of 81 and 33%, respectively) [13]. Of note, recalls increased from 4.2% for mammography alone to 9.6% adding AWBU [13]. Specificity based on recalls was 89.9% for AWBU, 95.15% for mammography and 98.7% for the combined modalities

[13]. Previous authors published another study evaluating radiologists' performance in breast cancer detection using mammography alone versus mammography plus AWBU in women with dense breast [25]. By adding AWBU to mammography, the sensitivity of breast cancer detection increased from 50 to 81% and all readers in this study significantly improved the identification of asymptomatic cancers [25]. Indeed, the cancer detection for true positive cases showed an increase of 63%, with only a 4% decrease in correct identification of the true negative cases [25]. By adding AWBU the detection of cancers ≤ 1 cm increased to 65%, while with mammography alone the detection of those cancers was 26% [25]. Of note, mean interpretation time per AWBU was 7 min 58 s [25], shorter than the time reported in the ACRIN 6666 trial regarding HHUS screening (19 min) [5].

In the past years other important studies have been published using modern automated ultrasound systems [14, 15, 32]. Wilczek et al. [14], in a single-center study, evaluated 1668 asymptomatic women, with heterogeneously/extremely dense breast parenchyma. The combination of digital mammography plus ABUS determined an increase in cancer detection of 2.4 per 1000 women screened [14]. The increase in sensitivity was 36.4% for combined modalities vs. mammography alone at study entry, while, including interval cancers, sensitivity increased by 25% [14]. Recall rates increased by 9.0 per 1000 (13.8 per 1000 for mammography alone and

22.8 for the combined imaging approach) and specificity decreased by 0.7% when ABUS was added to mammography [14]. The Somosight study [15], a multicenter prospective trial including 15,318 asymptomatic women with dense breast, compared mammography versus mammography plus ABUS. Combined imaging approach led to an increase in cancer detection rate of 1.9 per 1000 women with an increase in sensitivity of 26.7% [15]. Cancers detected only with ABUS were significantly more likely to be invasive in comparison to those detected by screening mammography alone (93.3 vs. 62.2%, $p = 0.001$) [15]. Moreover, ABUS alone detected cancers which presented with lower stage at diagnosis, suggesting positive prognostic implications [15]. In this study, recall rates increased from 150.2 per 1000 women with mammography alone to 284.9 per 1000 women by adding ABUS and the specificity decreased by 13.4% for the combined modalities (85.4% for mammography alone vs. 72% for mammography + ABUS) [15]. Giger et al. [32], in a multi-reader study on asymptomatic women with BI-RADS C or D breast density, showed an improvement in detection of both mammography-negative and mammography-positive breast cancers with the use of ABUS. The improvement in sensitivity was 23.9%, for mammography-negative breast cancers ($p = 0.004$) and 5.9% for mammography-positive breast cancers ($p = 0.234$) [32]. Specificity decreased non-significantly (from 78.1% for mammography alone to 76.2% for the combined modalities) due to a robust training program [32].

Table 1 presents the results of above presented screening studies. From all ABUS screening studies emerged an improvement in cancer detection rate, ranging from 1.9 to 3.6 per 1000 by adding ABUS to screening mammography [13–15]. These results are similar to those reported in the studies that used HHUS as an adjunct to screening mammography, in women with dense breast (from 1.9 to 5.3 additional cancer per 1000 women) [5, 7, 33–35]. On the other hand, an increase of recall rates was reported [13–15], a problem which emerged also from studies considering screening with HHUS [36, 37]. However, recall rate is expected to decrease progressively over the time as readers' experience increases [38]. In a retrospective study, Arleo et al. [38] evaluating ABUS as a screening tool in women with dense breasts, reported an overall recall rate of 19% during the 3-month study time period. Of note, recall rate trended down from 24.7% in the first study's month to 12.6% in the third study's month showing the clinical implication that ABUS has a learning curve [38]. Therefore, such a problem could be overcome improving readers' experience and by providing radiologists' training programs to help minimize false positives [32, 38].

Table 1 Results of studies comparing screening mammography alone versus mammography plus ABUS

Study	Kelly et al. [13]	Wilczek et al. [14] ^b	Brem et al. [15] ^b
Number (patients)	4419	1668	15,318
Sensitivity (%)			
Mammography	40	63.6	73.2
Mammography + ABUS	81	100	100
Difference ^a	41	36.4	26.7
Specificity (%)			
Mammography	95.15	99	85.4
Mammography + ABUS	98.7	98.4	72.0
Difference ^a	3.55	−0.7	−13.4
Recall rate per 1000 women			
Mammography	42	13.8	150.2
Mammography + ABUS	96	22.8	284.9
Difference ^a	54	9.0	134.6
Yield per 1000 women			
Mammography	3.6	4.2	5.4
Mammography + ABUS	7.2	6.6	7.3
Difference ^a	3.6	2.4	1.9

^a Data are the differences between the combined modalities vs. mammography alone

^b Sensitivity at study entry

Clinical setting

Automated breast ultrasound has been and still is actively studied for breast examination in different clinical scenarios. Most of the studies compared ABUS with HHUS in terms of detection [23, 28, 31, 39–42] and characterization [12, 43–48] of breast lesions, while others evaluated the diagnostic performance of ABUS [23, 29, 30, 39, 41, 43–46, 49, 50]. Some publications focused on the inter-observer agreement of ABUS [12, 16, 26, 30, 39, 41, 43, 51] and others evaluated ABUS in the pre-operative setting [17–19, 52], in the assessment of response to neoadjuvant chemotherapy [53] and as a second look procedure [10, 54, 55]. Furthermore, imaging-histologic correlation between ABUS semeiotics and molecular subtypes of breast cancer has been investigated [56].

Detection

Detection of breast lesions was reported to be similar between the two US modalities for most of the authors [23, 39–41], even if some studies reported higher detection rates for ABUS than HHUS (Table 2) [31, 42]. Chang et al.

Table 2 Results of studies comparing ABUS and HHUS in breast lesion detection

Study	Number (patients, lesions)	HHUS detection rate (%)	ABUS detection rate (%)	<i>p</i>
Wang et al. [23]	213, 239	98.7	99.6	n. s.
Xiao et al. [31]	300, 417	78.2	100	<0.001
Wang et al. [39]	155, 165	95.8	97.6	n. s.
Lin et al. [40]	81, 95	100	100	n. s.
Kim et al. [41]	38, 66	93.9	84.8, 84.8, 86.3 ^a	n. s.
Zhang et al. [42]	81, 99	60.6, 85.8 ^b	89.9, 100 ^b	<0.05, n. s. ^b

n. s. not significant ($p > 0.05$)

^a Results for three readers

^b Results for two readers. The difference in the lesion detection was significant only for one of the two readers ($p = 0.0006$)

[28] retrospectively evaluated the detection performance of benign and malignant masses. Overall sensitivity and specificity of three readers were, respectively, 71.9 and 79.5%, and the sensitivity was higher for detection of malignant masses (87.5–95.8%) vs. benign masses (56.3–66.7%) [28]. Mass size, shape and surrounding tissue changes were the variables affecting detectability at ABUS [28]. Shin et al. [12] also demonstrated the relation between size and lesion detectability: the lesion detection rate increased along with the increase of lesion size.

Zhang et al. [42] and Xiao et al. [31] demonstrated that ABUS detected significantly higher number of breast lesions than HHUS. Furthermore, in the retrospective study by Xiao et al. [31], evaluating 300 patients with 417 breast lesions, ABUS was found to detect all malignant lesions (32/32) while HHUS identified 31/32 lesions ($p = 0.158$).

Characterization

Many studies focused on the comparison between ABUS and HHUS in the characterization of breast lesions according to BI-RADS lexicon [12, 43–47].

Agreement between ABUS and HHUS in final BI-RADS category assessment ranged from fair to almost perfect [12, 43–47]. Golatta et al. [43] found fair agreement between ABUS and HHUS in the comparison of BI-RADS scores ($k = 0.34$), but dichotomizing BI-RADS categories into suspicious (BI-RADS 4–5) vs. not suspicious (BI-RADS 1–2) agreement was substantial ($k = 0.68$). The same authors, 2 years later, performed another study on 983 patients showing fair agreement ($k = 0.31$) between ABUS and HHUS in assigning BI-RADS scores (dichotomized as “benign” for BI-RADS 1–2 and “unclear/suspicious” for BI-RADS 0, 4 and 5) [44]. Those results were caused probably by imbalanced blinding of readers (HHUS readers had clinical information and availability of mammography while ABUS readers did not) [44]. On the other hand, Shin et al. [12] found substantial agreement ($k = 0.64$) for final BI-RADS

assessment. In addition, good results were shown in the comparison of the two US modalities for the evaluation of clock-face position, distance from the nipple and largest diameter with intra-class correlation coefficients (ICC) of 0.75, 0.89 and 0.94, respectively [12]. Also Kim et al. [46], analyzing 106 solid breast masses (52 cancers, 54 benign lesions), found substantial agreement in BI-RADS final assessment ($k = 0.773 \pm 0.104$).

Regarding comparison between ABUS and HHUS for BI-RADS descriptors, fair to substantial agreement was shown [46]. Kotsianos-Hermle et al. [45] reported good correlation for the criterion “margin” ($\rho = 0.88$). In the study by Kim et al. [46] “posterior echo feature” presented the worst agreement ($k = 0.371 \pm 0.225$), while “orientation” the best ($k = 0.608 \pm 0.210$).

Automated breast ultrasound was also shown to detect calcifications better than HHUS [31] (Fig. 2) and to identify a new semeiotic feature, the retraction phenomenon (Fig. 3) [48]. Retraction phenomenon is a peculiarity of coronal plane, unique of ABUS, with high diagnostic accuracy for breast malignancy [31, 39, 40, 48]. Zheng et al. [48] found that retraction phenomenon and microlobulated margins were the best predictors for malignant masses, while Lin et al. [40] reported 100% specificity and 80% sensitivity for retraction phenomenon in detecting breast cancer with high accuracy to determine malignant and benign lesions (91.4%).

Diagnostic accuracy

Diagnostic accuracy in differentiation between malignant and benign lesions has been widely analyzed and most studies (Table 3) demonstrated high values for sensitivity and specificity, as reported in a recent meta-analysis (pooled values of 92.0 and 84.9%, respectively) [50].

Golatta et al. [44] compared ABUS, HHUS and mammography with a clinical gold standard, defined as the combination of mammography, HHUS and histology (if

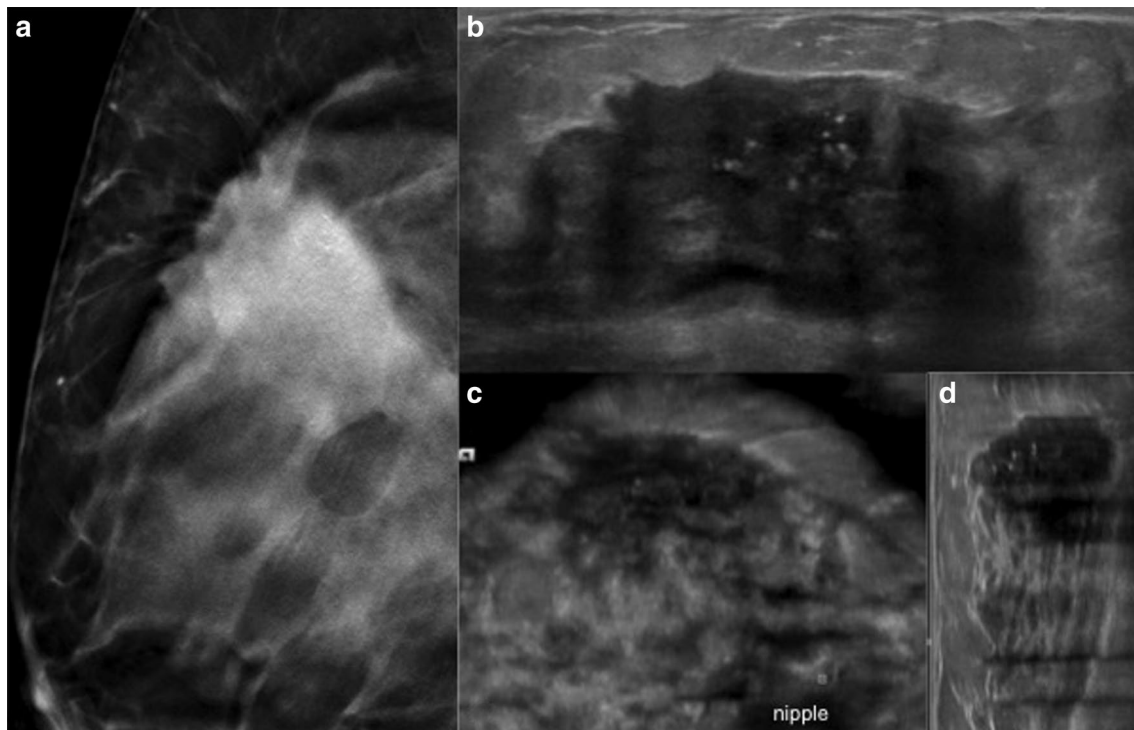


Fig. 2 A case of 48-year-old woman with invasive ductal carcinoma (IDC) of the right breast, diagnosed on US-guided core needle biopsy. Tomosynthesis (**a** MLO view) showed an irregular opacity with spiculated/lobulated margins and fine pleomorphic calcifica-

tions. Automated breast ultrasonography, performed using Siemens ABUS, detected a heterogeneous hypoechoic mass, with lobulated margins containing calcifications, which are well seen as hyperechoic spots (**b** axial view, **c** coronal view, **d** sagittal view)

indicated), on a population of 983 patients. They reported values of negative predictive value (NPV) of 98%, specificity of 85% and sensitivity of 74% for ABUS [44]. In this study 31 of 119 malignant lesions were rated as BI-RADS 1-2 by ABUS; of those, 12 lesions were seen after re-reading ABUS examinations and 8 lesions were primarily seen with MRI or mammography, therefore found on second look [44]. Remaining 11 of 119 lesions were definitively not seen by ABUS because of their location (behind the nipple or too peripheral), difficulties to perform examination (presence of ulcerated cancer) or in image interpretation (due to the lack of clinical information, e.g. previous surgical treatments) [44]. Imbalanced blinding caused those results, since radiologists evaluating HHUS were aware of patients' history and mammography while ABUS readers were not [44]. Relevant problems concerning the image quality emerged from the study, such as the presence of artifacts and lacking data due to inadequate contact between the transducer and the skin [44].

Most of published studies did not find significant differences between HHUS and ABUS in diagnostic performance (Table 3) [23, 39, 41, 45, 49]. However, Choi et al. [29] evaluated a large population of asymptomatic women who were subdivided into two groups (1866 patients for

ABUS and 3700 patients for HHUS) and showed that diagnostic accuracy and specificity were significantly higher for ABUS than HHUS (respectively, diagnostic accuracy 97.7 vs. 96.5% and specificity 97.8 vs. 96.7%). On the other hand, Kim et al. [46] found a significantly higher accuracy, in terms of areas under the ROC curve, for ABUS than for HHUS when considering the mean values by multi-reader analysis (respectively, 0.963 vs. 0.991); differences between ABUS and HHUS did not reach statistical significance when considering each reader.

Examining FP and false negatives (FN) Wang et al. [23] showed that most common pathology types for FP (19.5% with ABUS and 17.5% with HHUS) were adenosis, intraductal papilloma, fibroadenoma and mastitis. FN (4.7% with ABUS and 9.4% with HHUS) were lesions not detected because of small size or not suspicious ultrasonography features, such as smooth and circumscribed margins (at histology: phyllodes tumor, medullary carcinoma and invasive solid papillary carcinoma) [23]. One of the FN of HHUS (misinterpreted as adenosis) was a 6.5 cm invasive ductal carcinoma, presenting as an extensive hypoechoic area but correctly detected by ABUS, thanks to its wide scanning area [23].

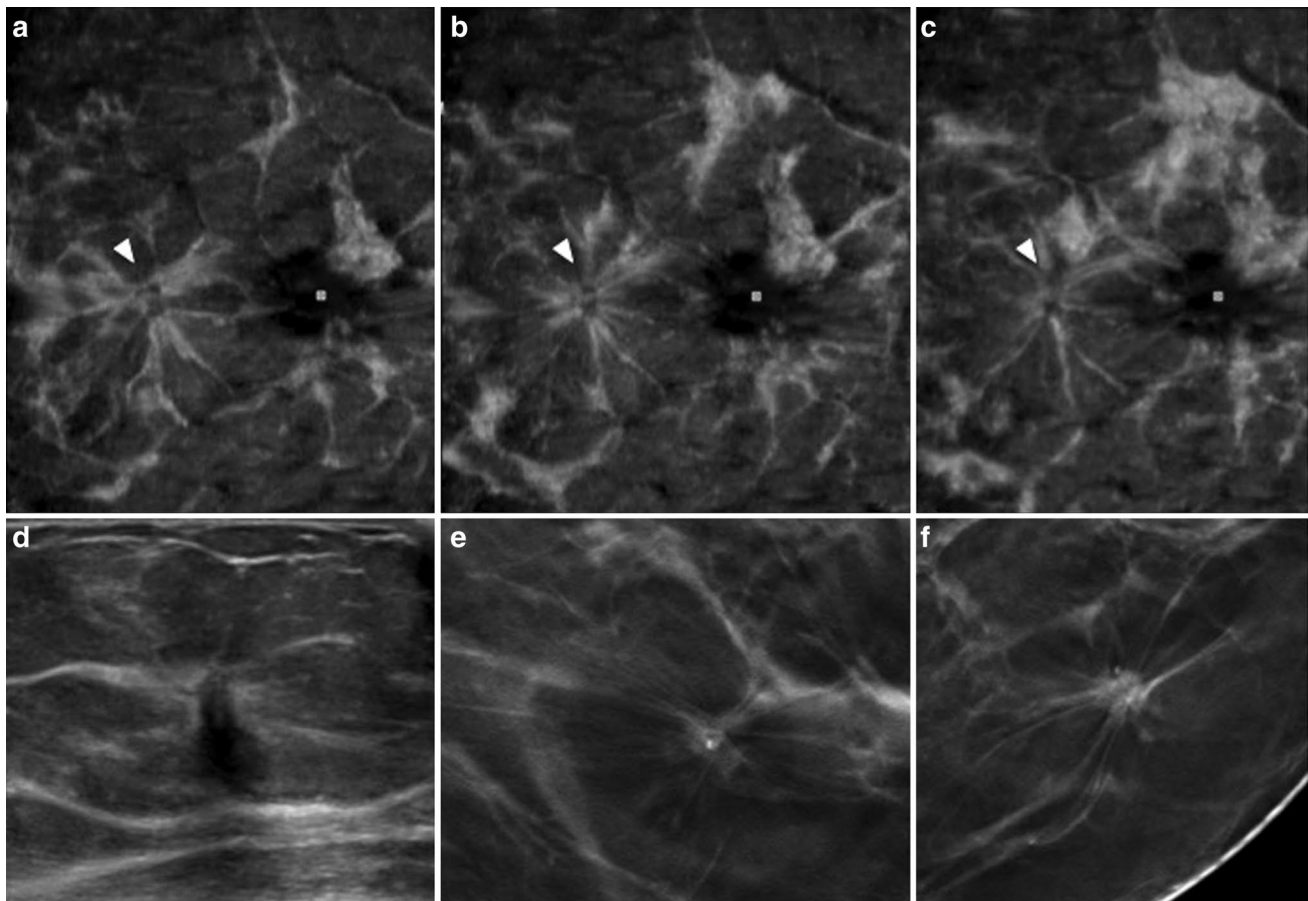


Fig. 3 A case of 55-year-old woman with invasive ductal carcinoma (IDC) of the left breast diagnosed on US-guided CNB. Automated breast ultrasonography detected a small (8 mm) hypoechoic mass presenting the retraction phenomenon, which is a useful feature vis-

ible on coronal plane (**a, b, c** three contiguous coronal images, **d** axial view). Tomosynthesis (**e** MLO view, **f** CC view) showed a small spiculated opacity

Inter-observer reliability

Inter-observer reliability has a fundamental role in determining the diagnostic accuracy of ABUS with a significant impact on its clinical practice [50]. Agreement between readers has been tested for description of BI-RADS features, BI-RADS final category assessment, location and size of lesions. Key results from main studies are summarized in Table 4.

Data regarding the agreement in assigning BI-RADS scores were heterogeneous, ranging from slight to substantial [12, 26, 30, 39, 41, 43, 51]. Agreement proved to increase by dichotomizing BI-RADS scores into benign and suspicious groups [30, 43] and also by adding mammography to ABUS [26]. Skaane et al. [26] in their retrospective study comparing reader performance (5 radiologists) of ABUS vs. ABUS plus mammography found a considerable inter-observer variability in giving BI-RADS assessment scores. Reader agreement improved

for mammography plus ABUS (mean k ranged from 0.14 to 0.44) compared to ABUS alone (mean k ranged from 0.07 to 0.34) [26].

Few studies considered BI-RADS feature assessment showing fair to substantial agreement for the main descriptors [12, 41, 51], while agreement in size, location and distance from the nipple varied from moderate to excellent [12, 16, 41], whereas only “lesion depth from the skin” showed low reliability (ICC = 0.342) [16]. Chang et al. [16] analyzing 24 patients with ABUS two times before biopsy or surgery (within a mean interval of 1.3 days) found that the different values of depth were probably related to variations in positioning and scanning pressure of the probe. Compression may also affect lesion characteristics; in particular, some benign lesions are more deformable than the stiffer solid masses and could flatten [16]. Therefore, margins and shape of benign lesions could change by increasing compressive pressure [16].

Table 3 Results of studies evaluating diagnostic accuracy of ABUS

Study	Number (patients)	SE (%)	SP (%)	PPV (%)	NPV (%)	Accuracy (%)	Reference standard	Comparison with HHUS
Wang et al. [23]	213	95.3	80.5	73	93.3	85.8	Histology	n.s. (HHUS: SE 90.6%, SP 82.5%, PPV 74%, NPV 94.1%, accuracy 85.3%)
Choi et al. [29]	5566 ^a	77.8	97.8	14.6	99.9	97.7	Histology and follow-up imaging (≥ 12 months)	Significant differences for: Specificity (HHUS 96.7%) Accuracy (HHUS 96.5%)
Wojcinski et al. [30]	100	83.3 ^b	78.1 ^b	–	–	79 ^b	HHUS	–
Wang et al. [39]	155	96.1	91.9	95.2	93.4	94.5	Histology	n. s. (HHUS: SE 93.2%, SP 88.7%, PPV 93.2%, NPV 88.7%, accuracy 91.5%)
Kim et al. [41]	38	88.0, 90, 96.0 ^c	81.3, 87.5, 93.8 ^c	–	–	–	Histology	n. s. (HHUS: SE 98%, SP 62.5%)
Golatta et al. [43]	42	82	68	81	69	–	Histology	–
Golatta et al. [44]	983	74	85	24	98	–	Combination of HHUS, mammography and histology (if indicated)	–
Kotsianos-Hermle et al. [45]	97	96.5	92.3	–	–	–	Histology	n. s. (HHUS: SE 97.5%, SP 88.5%)
Kim et al. [46]	87	89.2	79	81.31	94.1	0.963 ^d	Histology or follow-up ≥ 2 years (before the study start)	Significant difference for accuracy (HHUS: 0.991) ^d
Schmachtenberg et al. [49]	28	93.3	83.3	77.8	95.2	87.2	MRI and histology (if available)	n. s. (HHUS: SE 100%, SP 83.3%, PPV 78.9%, NPV 100%, accuracy 89.7%)

SE sensitivity, SP specificity, NPV negative predictive value, PPV positive predictive value, n.s. not significant ($p > 0.05$)

^a Two study groups: 1866 patients examined with ABUS and 3700 examined with HHUS

^b Combined evaluations of two readers (data for reader 1 and reader 2 are, respectively, SE 83.3 and 100%; SP 68.3 and 51.2%; accuracy 71 and 60%)

^c Reported values are the data of three readers

^d Receiver operating characteristic (ROC) analysis: ROC—area index (Az). Az for HHUS and ABUS were not statistically significant for each reader ($n = 3$), but the mean Az values were significantly different

Other applications of ABUS

In the preoperative setting, one of the preliminary studies for ABUS, which was performed in a population of 40 patients including both in situ and invasive cancers, showed promising results in the extent of cancer assessment [19]. Li et al. [18], analyzing 33 patients with histologically proven DCIS, found that ABUS assessed the extent of disease better than HHUS (compared to histopathology) and that mean lesion

size assessed by ABUS did not differ significantly from that determined by histopathology. Moreover, Huang et al. [52] focusing on the pre-operative assessment of DCIS, found that ABUS is superior to HHUS in the detection of malignancies and it is also more accurate in the tumor largest diameter assessment.

Considering 3D evaluation of 51 invasive ductal carcinomas, Xu et al. [17] assessed largest tumor diameter, tumor volume and tumor surface area on HHUS and ABUS and

Table 4 Results of studies evaluating inter-observer agreement of ABUS in the assessment of different ultrasonography features

Study	Number (patients)	Number (readers)	Inter-observer agreement		Location and size (ICC)							
			BI-RADS assessment (k)		BI-RADS descriptors (k)			Location and size (ICC)				
			Shape	Orientation	Margin	Echogenicity	Posterior acoustic feature	Clock-face position	Distance from the nipple	Depth from the skin	Size (largest diameter)	
Shin et al. [12]	55	5	0.63, 0.71 ^a	0.71	0.72	0.61	0.45	0.42	0.77	0.89	–	0.92
Chang et al. [16]	24	2	–	–	–	–	–	–	0.994	0.926	0.342	0.98
Skaane et al. [26]	90	5	0.07–0.34 (range) 0.14–0.44 ^b (range)	–	–	–	–	–	–	–	–	–
Wojcinski et al. [30]	100	2	0.27, 0.36 ^c	–	–	–	–	–	–	–	–	–
Wang et al. [39]	155	2	0.443	–	–	–	–	–	–	–	–	–
Kim et al. [41]	38	3	0.57	0.45	0.50	0.25	0.65	0.45	0.74 ^d	–	–	0.43 ^d
Golatta et al. [43]	42	6	0.35 ^e 0.52 ^{c,e}	–	–	–	–	–	–	–	–	–
Zhang et al. [51]	208	2	0.70 ^f	0.79	0.74	0.76	0.69	0.68	–	–	–	–

k kappa value, ICC intra-class correlation coefficient

^a Agreement for grouped final assessments into three categories (1 or 2, 3, and 4A–C or 5)

^b Agreement for ABUS plus mammography

^c Agreement for dichotomized BI-RADS categories (negative = BI-RADS 1, 2 vs. positive = BI-RADS 0, 3, 4, 5 [30]; benign = BI-RADS 1, 2 vs. suspicious = BI-RADS 4, 5 [43])

^d Kappa value

^e Multiple kappa coefficient

^f Only BI-RADS 3, 4 and 5 categories were used in the study

compared these with tumor size and volume on pathology specimen after surgical excision (gold standard). All ABUS measurements showed stronger correlation coefficient than those of HHUS [17]. Furthermore, volumetric measurements determined by ABUS had significantly higher accuracy than those determined by HHUS [17].

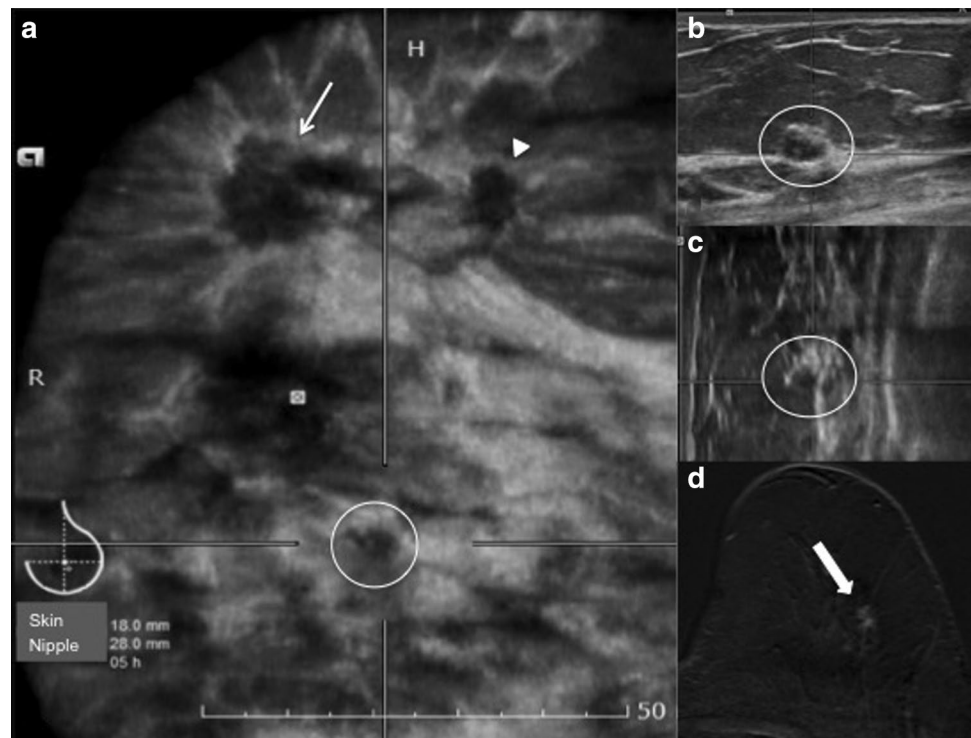
Automated breast ultrasound has been also evaluated in the assessment of response to neoadjuvant chemotherapy [53]. In a study by Wang et al. [53] ABUS was performed before treatment and after two cycles of chemotherapy in a population of 290 patients. The product change of two largest perpendicular diameters (PC) in axial and coronal planes and the longest diameter change in axial and coronal planes were the four prediction methods examined in the study [53]. The overall performance of ABUS in predicting complete response after four cycles of chemotherapy was high (area under the receiver operating characteristic curve [AUC]: 0.83–0.85) and all four prediction methods revealed high sensitivities (85.7–88.1%) while specificity was high only for PC (81.5–85.1%) [53]. Lower values of AUC were observed when mid-treatment ABUS was used to predict poor pathological outcomes [53].

Automated breast ultrasound showed promising results as a second look (SL) tool after breast MRI [10, 54, 55] (Fig. 4). Chae et al. [54] found 80 additional suspicious lesions on 58 preoperative breast MRI. ABUS-SL detected 70/80 lesions while HHUS-SL detected 65/80 lesions. Only 4% of HHUS detected lesions were not detected on ABUS while 10% of ABUS detected lesions were not

detected on HHUS [54]. Girometti et al. [10] compared HHUS with ABUS in the second-look scenario evaluating a population of 131 patients that had undergone breast MRI for different reasons beyond breast cancer staging (e.g. high risk of breast cancer, B3 lesions, evaluation of response to neoadjuvant chemotherapy etc.). They found comparable values of both techniques in terms of detection rates for MRI-detected lesions (69.3 vs. 71.5%, for ABUS and HHUS, respectively), with an almost perfect agreement in assessing them as significant or not ($k = 0.94$) [10]. Kim et al. [55], on a population of 40 patients undergoing preoperative breast MRI with 76 additional MRI findings, found significantly higher values of detection rate for ABUS than HHUS (94.7 vs. 86.8%, respectively; $p < 0.05$).

When evaluating the correlation between ABUS imaging features and molecular subtypes of breast cancer, Zheng et al. [56] demonstrated that the luminal-A, luminal-B, HER2 and triple-negative subtypes have specific predictive factors (luminal-A: retraction phenomenon, post-acoustic shadowing, echogenic halo, absence of calcifications; luminal-B: presence of calcifications, absence of retraction phenomenon; HER2: presence of calcifications, absence of retraction phenomenon, non-mass lesions, absence of echogenic halo, post-acoustic enhancement; triple negative: absence of retraction phenomenon, post-acoustic enhancement, absence of echogenic halo, absence of calcifications, regular shape). Retraction phenomenon showed a strong correlation with molecular subtypes resulting in the strongest

Fig. 4 A case of 70-year-old woman with multifocal and multicentric invasive lobular carcinoma (ILC) of the left breast. Automated breast ultrasonography (**a** coronal view, **b** axial view, **c** sagittal view) detected two hypoechoic lesions with retraction phenomenon on the upper quadrants of the left breast, well represented on coronal reconstruction (index lesions: *thin arrow*; multifocality: *arrowhead*). Another small hypoechoic area (*circle* on coronal, axial and sagittal views) was detected on automated ultrasonography second-look examination performed after staging breast MRI, due to the presence of suspicious mass like enhancement on the inferior-outer quadrant of the same breast (**d** *large arrow*). Coronal view well depicts all three neoplastic lesions in the same image



independent predictor for the luminal-A subtype when present and for the triple negative subtype when absent [56].

Conclusion

Automated breast ultrasound is an emergent ultrasonography technique, developed to support screening mammography, especially in dense breast, where mammography's sensitivity is relatively low. ABUS has the advantage to be more reproducible and less operator-dependent than HHUS. In addition, multiplanar reconstructions, a peculiarity of ABUS, are very useful for image interpretation. However, ABUS presents some limitations because of the lack of tools to assess vascularity and tissue elasticity; another possible limitation is the exclusion of axillary regions from the field of view. Furthermore, an increase of false positives has been reported when using ABUS. Increasing readers' experience and improving the scanning technique could overcome this problem. ABUS applications are currently under research, both in the screening setting and in the clinical setting. With the increase of screening demand, ABUS has the potential to be the method of choice as an adjunctive tool to screening mammography in women with dense breast tissue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent The images of automated breast volumetric scanner (ABVS) and MRI shown in the figures were retrospectively selected among examinations previously performed according to an Ethical Committee approved trial investigating the role for ABVS in clinical practice, with informed consent obtained from all individual participants.

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