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PRONE 3D ABUS VS HHUS: DIAGNOSTIC ACCURACY AND POTENTIALITIES

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Abstract

Purpose: Aim of the study is to evaluate the accuracy of SOFIA: automated 3D prone breast US vs hand held manual ultrasonography in breast cancer prevention.
Material and Methods: 57 female patients have been involved in this prospective study; the first in Italy and one of the first across Europe. All patients underwent clinical exam, hand held ultrasonography, 3D automated breast ultrasonography in prone position, mammography if >40 yo, in selected cases breast MRI.
Results: Compared to mammography, the association with 3D automated breast ultrasonography in prone position improved the diagnostic accuracy (respectively 8%, CI 2.22-19.23% vs 98.25%, CI 90.61-99.84%).
41 benign lesions and 15 cancers have been detected; one case of breast cancer has been missed because of the position (axillary region) on SOFIA.
Conclusion: 3D automated breast ultrasonography in prone position might be helpful to improve cancer detection in dense breasts, even if a little tendency towards the size underestimation of benign lesions has been demonstrated.

Keywords: *automated breast ultrasound, breast cancer screening, dense breasts.*

Introduction

It is well known that screening breast cancer programs are performed to decrease mortality on one side, and to find out earlier diagnosis on the other one. According to American College of Radiology, "mammography is the recommended method for breast cancer screening of women in the general population" [1, 2]. In women with dense breasts, mammographic sensitivity may be as low as 30–48% [3, 4] with much higher interval cancer rates and worse prognosis for resulting clinically detected cancers [5-8].

Therefore, mammography only does not perform as well as mammography plus supplemental screening in high-risk women [1]. In 2015, American Cancer Society framed up breast density in strong level of risk, as much as personal history of cancer, more than one family member, BRCA-1 and-2 gene expression.

"Mammographic breast density itself is an independent risk factor for developing breast cancer, with estimates of relative lifetime risk ranging from 1.8 to 6.0" [9].

Dense breast tissue is quite common, with over half of all premenopausal women, as do at least one third of elderly women having either heterogeneously dense C (visually estimated as >50 <75% glandular tissue) or extremely dense D (visually estimated as >75% glandular tissue) breasts [10-12].

It has been estimated that 28–30% of breast cancers are associated with breast density [13-15], in comparison with approximately 5–10% attributed to mutations in the BRCA-1 or -2 gene [16,17].

Tailoring of screening regimens on the basis of breast density and additional risk factors has been proposed [18].

Regarding breast cancer screening in asymptomatic women, the addition of HHUS to FFDM has improved screening benefit especially in women with dense breast tissue [19-23].

Corsetti et al. retrospective cohort study shows that including ultrasound as adjunct screening in women with C-D breasts brings the Interval Cancer rate to similar levels as IC in non-dense breasts. Hand held screening breast US significantly increases detection of small, node-negative breast cancers in women with dense breasts [24]. In women with dense breasts FFDM-negative, HHUS can detect mammographically occult breast carcinoma. From prospective, multicentric, randomized ACRIN 6666 study, "Women with dense breast tissue may benefit from adjunct screening imaging modalities, such as ultrasonography"; in annual breast cancer screening in women at elevated risk, adding screening US performed by the physician for dense breast patients results in 70.6% higher cancer detection rate in first year and 45.6% in second and third year compared to FFDM alone. Another technique with potential to become a valuable adjunct to mammography is Digital Breast Tomosynthesis (DBT), but with the disadvantage of further radiation dose given to the woman. ASTOUND study, the first prospective trial comparing directly HHUS and DBT, assessed the US supremacy vs DBT in terms of cancer detection rate in the same population of women with mammography-negative dense breasts. Based on these evidences, industry has intercepted the need to create an automated ultrasound that could also be used by the technician in screening dense breast setting. Thus, Automated Breast Ultrasound was born and the studies on its use as screening were not late in coming; several authors agree on the fact that additional 3D ABUS to mammography improved the performance of mammographic interpretation [25-30].

From old generation equipped with low frequency transducer (4-7 MHz) to modern scanners with high-frequency (6-15 MHz), the image quality has improved. These 6-15 MHz, large (15-17cm) reverse-curved or linear-array transducers acquire the entirety of each breast, images are reconstructed coronally and viewed at a dedicated workstation [31, 32]. The coronal plane, also known as surgical view, is helpful not only to improve lesion detection and characterization, but also for pre-operative planning. In third last generation of 3D automated whole breast Ultrasound (Hitachi-ARIETTA 60-SOFIA) patient lies prone (as for MR scan). Each breast is placed on examination disc and a built-in transducer automatically revolves around the breast. The availability of multiplanar reconstructions on workstation combines both (supine and prone) Automated Breast US. The different patient position and the radial acquisition identifies SOFIA. This report expresses our preliminary results regarding the SOFIA system, the first installation in Italy and one of the earliest in Europe.

Methods

Patients

Between 1st June and 31st October 2017, 57 European female patients (mean age 52 yo, range 22-68 yo) with average breast cancer risk were involved in this prospective study.

Inclusion criteria were breast benign or malignant lesions diagnosis (cysts were not been taken into account in this study).

Exclusion criterion was previous oncological surgery and/or radiotherapy and BRCA 1 and/or 2 mutations [33]. All patients underwent clinical exam, hand held ultrasonography, mammography if ≥40 yo; in selected cases (19: 4 Fad, 15 K) breast MRI with intravenous contrast media has been performed. In all 57 patients, 3D automated breast ultrasonography in prone position has been performed.

Patients who agreed to participate to the study gave written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients underwent surgical excision and histological diagnosis has been obtained.

For each patient that undergoes to Mammography, breast Density has been classified according to American College Radiology (ACR) categories:

Category a - The breasts are almost entirely fatty.

Category b – There are areas of scattered fibro glandular density.

Category c – The breasts are heterogeneously dense, which may obscure small masses.

Category d – The breasts are extremely dense, which lowers the sensitivity of mammography .

Ultrasonography

HHUS exams were obtained on a dedicated breast US unit (GE Logiq S6) with a M12L 5-13MHz probe by first radiologist, who also made clinical examination. 3D Automated Breast prone US (SOFIA) acquisition were performed, in the same day, by one of the three technicians with appropriate training, under radiologist supervision in order to obtain a correct 360° automated exam.

SOFIA consists of a scanning table of 184 mm of diameter, into which the ultrasound transducer is embedded, and of a 3D review and documentation workstation. **FIG. 1** Operator distributes a thin layer of acoustic gel on the examination disc who have a built-in Hitachi probe. **FIG. 2a** Patient, applying some gel on the breast, gets on the examination table and places breast in the disc with the nipple positioned in the center. Patient lies prone with the contralateral leg bent in order to rotate slightly to center the nipple in the cone; arm can be by the patient's side. **FIG. 2b** 92 mm long L53L transducer automatically revolves around the breast and captures an entire breast in a single volume (30 seconds per breast). Pre-scan modality allows to confirm optimization of patient positioning (i.e. smallest drop-off artifact possible **FIG. 3**, or patient repositioning) and eventually modify scan parameters (gain, depth, focus, etc..). SOFIA acquisition required on average 10 minutes per patient. Finally, data were sent to workstation and independently reviewed by two dedicated breast radiologists.

Image analysis

First operator gave a positive or negative judgement on clinical exam, mammography, hand held and 3D automated breast prone ultrasonography; he also reported breast side, localization and diameter on hand held and SOFIA. First operator identified a BIRADS category for each lesion both on Hand Held US and on 3D automated prone US. Second operator reported breast side, localization and diameter on SOFIA and gave a BIRADS assessment only on 3D automated prone ultrasonography (SOFIA) blinded to the first operator's assessment. Both of them analyzed data on SOFIA workstation **FIG. 1B** (sagittal, coronal and axial plane, MPR, VR) within fifteen days from the examination. All interpretations were made in conjunction with mammograms when Mx were available. For first operator the decision of category was based on the highest level of mammographic or US findings; thus, in the case of a lesion that was morphologically probably benign on FFDM, but suspicious on US, the final assessment was based on the ultrasonography features (Hand Held and 3D AB prone). In 19 patients who underwent breast MRI, the localization of the lesion has been reported.

Not all patients were candidates to the surgery; in surgical patients, histological diagnosis has been obtained.

In not surgical patients, follow-up has been done.

Statistical Analysis

Statistical analysis was performed using MedCalc Statistical Software Version 17.9.7. Accuracy and Positive Predictive Value has been calculated for Mammography exams (performed in 50 patients > 40 yo), for 3D automated ultrasonography and for Mammography associated with 3D automated ultrasonography. Mammography associated with hand held ultrasonography has been considered the gold standard, according to histological results. Size difference between hand held and 3D ultrasonography has been calculated in benign lesions, such as inter-observer variability using Cohen's Kappa.

Results

There is a significative difference in the diagnostic accuracy of mammography only compared with mammography and automated 3D prone breast US, using as gold standard HHUS and histopathology (**TABLE 1**). Positive finding at clinical examination was founded in six women, and in two of them, with also positive FFDM result, cancer was confirmed on histopathology. The remaining four cases were fibroadenomas. Out of fifty patients that underwent mammography, according to ACR Breast Density categories, ten were classified as D (20%), twenty-four as C (48%), fifteen as B (30%) and one as A (2%). Therefore, in 68% of our sample we have dense breasts. Among the four patients that showed positive findings on Mx exams (two B, two C), two were histologically confirmed as Fad, both without BIRADS intra- and inter-operator assessment differences (no MRI - diameters in mm on HHUS / SOFIA / FFDM = 18/18/17 in one case and 15/11/10 in the other one - range size difference intra-operator: 1 – 5 mm FFDM vs US, no size difference HHUS vs SOFIA in first case, 4 mm in second case). The other two were malignant lesions, also palpable at clinical exam, and size lesions on HHUS, SOFIA and FFDM (respectively mm 24/22/21 and 21/20/18) substantially corresponded. We refer to size measured on HHUS and SOFIA -and Mx if available-, not on the surgical removed specimen.

Regarding BIRADS assessment (Cohen's Kappa 0.65, in 53 patients there has been an absolute inter-operator agreement (Cohen's Kappa 0.65 **TABLE 2**). Only in 7% of our sample (4/57) BIRADS assessment difference between first operator and second reader occurred: one of this four cases showed both inter-readers (SOFIA-SOFIA) both intra-operator (HHUS-SOFIA) disagreement, another one presented only inter-readers and in the other two cases was observed intra-operator disaccord. All of these lesions were malignant and an exact correspondence between MRI location and HHUS and SOFIA was observed (in terms of breast quadrants).

Readers' BIRADS judgement matched with histopathology result in every patient's expected one, save the case of a 59 yo woman (ACR C - Clinical Exam and FFDM negative – MRI not performed) who presented a lesion in Left breast Upper Inner quadrant detected only with US (HHUS size 9 mm; SOFIA size 10 mm). This lesion, evaluated by both as BIRADS-5, revealed as a fibroadenoma at the exeresis [Cohen's Kappa 0.65].

Regarding intra-operator (HHUS-SOFIA) size difference measurement, we observed that maximal one was 8 mm (HHUS size 20mm, SOFIA size 12mm); but as highlighted in **TABLE 2** the average difference of the underestimation found with 3D AB prone US was 1.59 - 3.04 mm.

In 14% of our sample (8/57) neither reader have identified the lesion with automated prone three-dimensional breast US (SOFIA). Seven were histologically proven fibroadenomas, among these three were missed for position, due to the fact that these lesions were located in the axillary region and were out of SOFIA examination disc (SOFIA's Field Of View, as [24] already described with ABUS); two located in UI, one in UO and one in RA (in this region some authors already discussed about ABUS's skills in benign or malignant lesion characterization [26]). We hypothesize that these four fibroadenomas were missed because of their mantle region [26,31] or maybe for weak training. The last one of these eight cases was a 12 mm lobular invasive cancer (50 yo, ACR C, Clinical Exam and FFDM negative, positive-MRI; pT1a G2, HER2: neg, ER: 80%, PG: neg, Ki-67: 8%) detectable on Mx because of microcalcifications and missed on SOFIA due to the position (left axillary region) **FIG 4.**

Discussion

Radiologically dense breasts are associated with decreased mammography sensitivity and increased risk of an interval cancer in screened women, and density is also an independent risk factor for breast cancer [34-35].

The sensitivity of mammography for non-calcified lesions decreases as the BIRADS breast density category increases. And as it has been already said by Corsetti et al [19] "additional cancer detection by ultrasound is likely to improve screening benefit in dense breasts." According to [19, 36-39] HHUS has led to an increase from 1.9 to 5.3 in the yield of further cancers detected for 1000 women screened. Over the last few years, three-dimensional automated breast US began to be investigated as a solution for intermediate-risk women with dense breasts. In 2015, a multicenter, prospective study including more than 15000 asymptomatic women with dense breast, showed that 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%; most of these cancers were clinically important. Value also confirmed by Wilczek et al. whom -anyway in C-D but smaller population- found "a difference in yield of an additional 2.4 detected cancers per 1000 women screened" [28]. Giger et al., in a multi-reader study on asymptomatic C-D, reported that the improvement in sensitivity was 23.9%, for mammography-negative breast cancers and 5.9% for mammography-positive breast cancers [27]. From all ABUS screening studies emerged an improvement in cancer detection rate, ranging from 1.9 to 3.6 per 1000 women adding ABUS to FFDM [25, 26] (**FIG.5**).

Thus, as pointed out previously literature, both manual US [36-39] both ABUS [40-43] allow to have an improved cancer detection rate compared to FFDM in women with dense breasts, and as argued by Giuliano even in cost-benefit terms [30]. Therefore, it is essential to complete the FFDM screening with Ultrasound, although the number of false positives may increase, as described for both the manual and the automated breast US -and in very truth also for MRI [44].

With regard to that, improving readers' experience and providing radiologists' training programs help to minimize false positives. Inevitably the addition of US in screening increased recall rates, both for ABUS and for HHUS [45]; based on a recent review "increasing readers' experience and improving the scanning technique could overcome this problem" [46]. Indeed a retrospective study drawn attention to 'ABUS learning curve', recall rate progressively decreased to half its value within three months [47].

Wang et al. have analyzed the most common pathologies that can induce False Positive or False Negative both at HHUS and ABUS (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 US features, such as smooth and circumscribed margins, at histology revealed phyllodes tumor, medullary carcinoma and invasive solid papillary carcinoma) (**FIG.6**). As stated by Chang "mass size, shape and surrounding tissue changes were the variables affecting detectability at ABUS" [29]; Shin widely described relation between size and lesion detectability [48]. From studies comparing automated breast and manual US in lesion detection, no significant difference emerged between manual and automated US methods, except for [49] and [50] whom assessed that ABUS detected significantly higher number of breast lesion than HHUS. In comparison with manual US, some authors found a better lesion size prediction with automated breast US; Xu comparing ABUS and HHUS measurements with tumor size and volume on pathology specimen after surgical excision, reported that all ABUS measurements (largest k diameter, k volume, k surface area) showed stronger correlation coefficient than those of HHUS [51]. Concerning lesion characterization, a meta-analysis showed high pooled values for diagnostic accuracy of ABUS in differentiation between malignant and benign lesions [52]. Zheng et al elaborated on correlation between ABUS imaging features and molecular subtypes of breast cancer [53].

With the understanding that above-mentioned results concern studies conducted with Automated supine Breast US, we may, in some ways, analogize these to ours. In other words, even though acquisition is different - indeed ABUS transducer scans transversally, while SOFIA Hitachi probe moves radially - both supine and prone Automated

Breast US systems give the availability of workstation with 3D multiplanar reconstructions, thus the possibility of a better visualization, especially in coronal and sagittal reconstructions, of the retraction phenomenon and other distinctive features of malignant lesions. The architectural distortion around a mass with larger diameters makes the lesion easier to detect than a smaller one without such evidence. This should be taken into consideration even more in women with dense tissue, in which stroma could mask initial surrounding tissue changes. However, it is needed to clarify that the retraction sign is not shown in every cancer. About the retraction phenomenon and its role in coronal reconstruction for determining malignant from benign lesions, it has been already said enough for ABUS; such margin could be seen in ABUS as well as in HHUS, the availability of workstation with 3D multiplanar reconstructions, a workstation with 3D reconstruction availability and axial, sagittal and coronal views enable an even better US lesions features (such as margin, shape, echogenicity, boundary, posterior shadowing in addition to architectural distortion) evaluation and characterization. This could enhance diagnostic performance, especially in dense breasts FFDM-negative [54].

But - as highlighted in our results with four (3 Fad and 1 k) lesions missed for position axillary region is a weak point for all (supine and prone) Automated Breast US. 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". For this reason, vendor provides a dedicated probe for axillary region study. In contrast to ABUS, SOFIA allow to add complementary Doppler and elastosonography tools. The average acquisition time is similar, indeed we reported about 5 minutes per breast on SOFIA (radial scanning 30 seconds) and with ABUS 3-4 min (conventionally three 1 min scans are sufficient for scanning the entire breast, excluding the axilla). Kelly et al. reported circa 8 min as mean interpretation time with ABUS [55]. Radiologists' interpretation time for each woman at SOFIA workstation was 10 minutes. The average total time to complete the ABUS examination is approximately 15 min, near to 19 required in HHUS.

In our sample, we particularly observe a little tendency towards the size underestimation of benign lesions on SOFIA compared to manual US, as highlighted in **TABLE 2**. This could be explained by thinking on the radial scanning of the breast volume, considering that most benign lesions have a global oval shape, so that sometimes the radial transducer movement does not include their maximum diameter pertain orientation, which can instead be better estimated with HHUS due to the availability of anti-radial and transversal scan planes.

In conclusion, our thus partial results suggest that both manual and automated prone breast ultrasound improve diagnostic accuracy in mammography-negative women with dense breasts; as highlighted in **TABLE 1** an additional 90% accuracy was observed by adding Automated prone Breast US.

One bias of the study was a benign breast existing lesion.

Future development of this study will be to compare lesion's position detected on SOFIA with its corresponding MRI location in clock-face terms, eventually evaluation with a SOFIA second-look after MRI [56-62] and compare lesion's volume obtained on SOFIA with surgical specimen.

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Table 1. *Diagnostic accuracy and Positive Predictive Value (PPV) of Mammography and Mammography + 3D automated prone breast US (SOFIA) in the detection of malignant and benign lesions.*

		ACCURACY (%)	CI (%)	PPV
MX	TOT	8	2.22-19.23	100
	FAD	5.88	0.72-19.68	100
	K	12.50	1.55- 38.35	100
MX + 3D US	TOT	98.25	90.61-99.84	100
	FAD	100	91.4-100	100
	K	93.75	69.77-99.84	100

Table 2. Size difference benign lesions HHUS / SOFIA (*Two-tailed significance level: 0.00000*) *Cohen's Kappa inter-observer variability: 0.65*

		Mm
Mean diameter	HHUS	16.31 ± 3.41
	SOFIA	14.00 ± 3.73
	Mean (± DS)	2.31 ± 2.59
Difference	MIN	1.59
	MAX	3.04

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Figure 1. Automated three-dimensional prone breast US composition

a) scanning table, into which the ultrasound transducer is embedded;

b) 3D review and documentation workstation

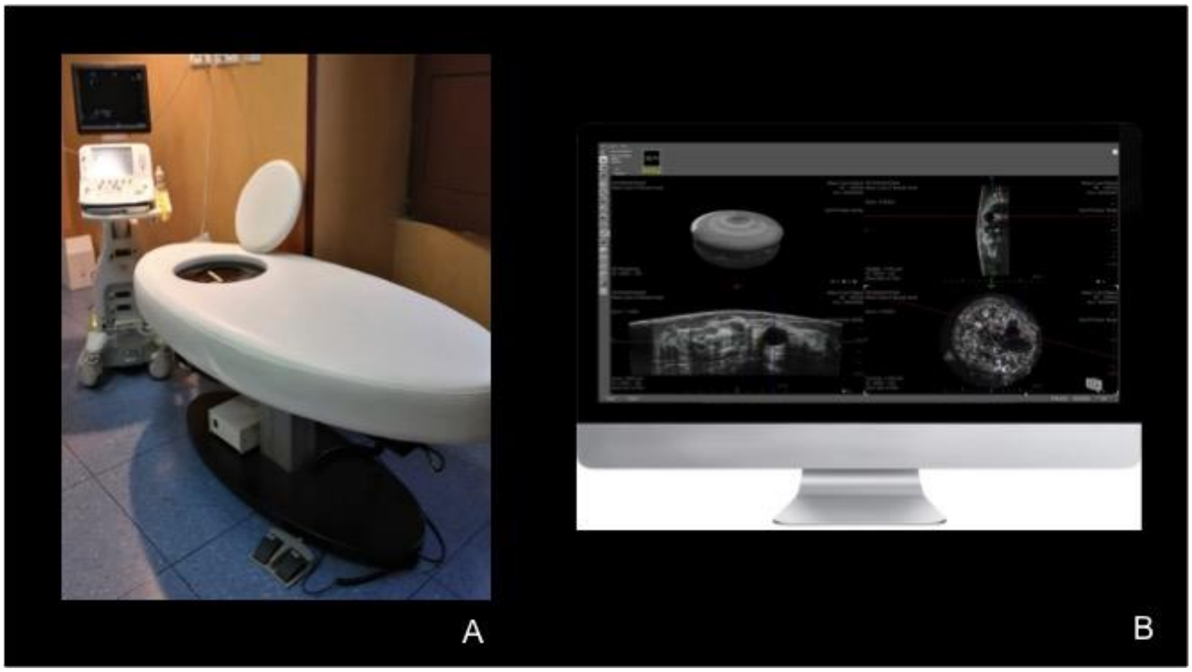

Figure 2. a) Automated three-dimensional prone breast US probe**.**
Position of the patient to allow left (b) and right (c) breast scanning

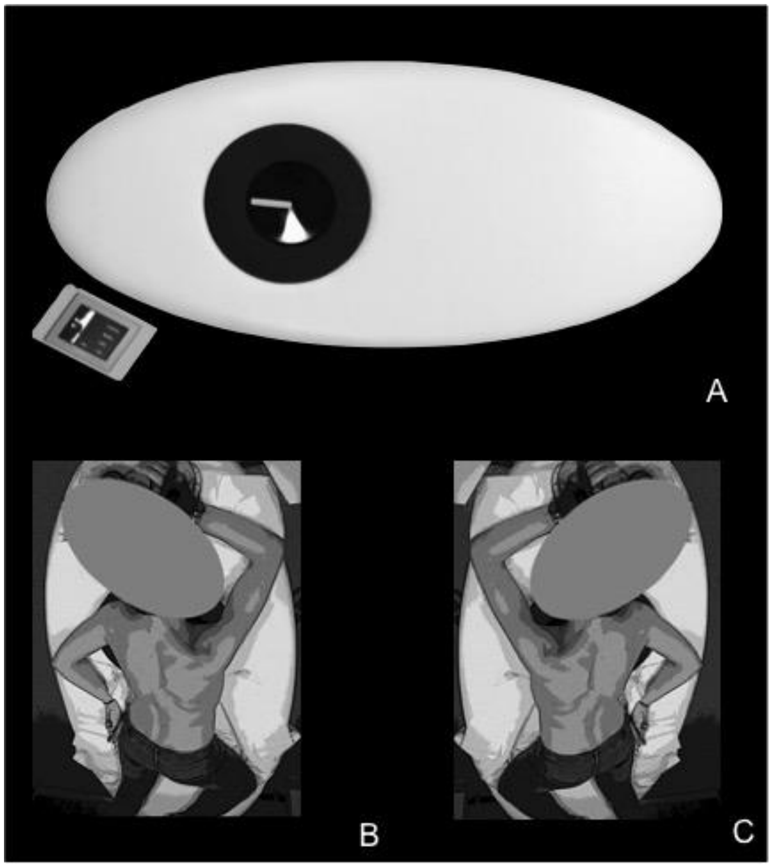

Figure 3. 3D automated US artifacts
Acceptable (A) vs unacceptable (D) drop-off and probe position during pre-scan (B, C)

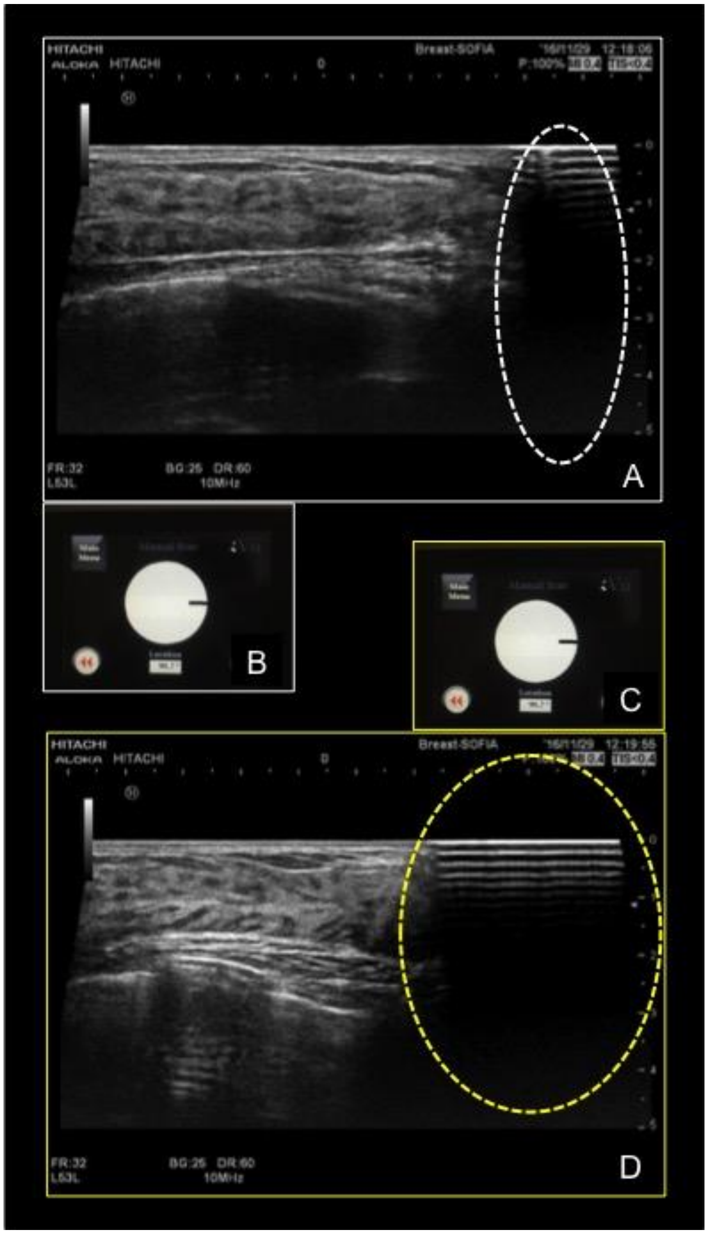

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Figure 4. F, 50 yo. the figure shows the case missed at 3D automated breast ultrasonography due to the position of the lesion.
MLO mammography projection (a) and the magnification (b) shows a suspect cluster of microcalcifications in axillary region.

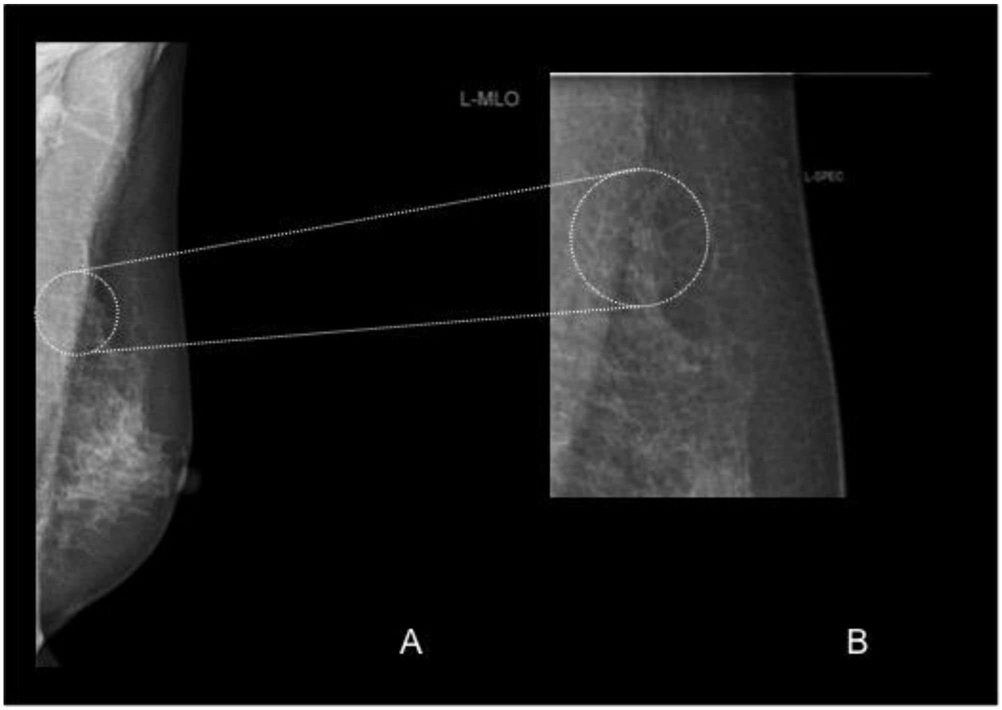

Figure 5. F, 67 yo. the figure shows a case of cancer in left Upper Inner quadrant.
Mammography: A) left cranio-caudal projection, B) magnification in left cranio-caudal projection, C) left medio-lateral projection HHUS: D, E 3D Automated Prone Breast Ultrasonography:
F) axial plane during moving scan, G) axial plane on workstation, H) coronal plane, I) sagittal plane

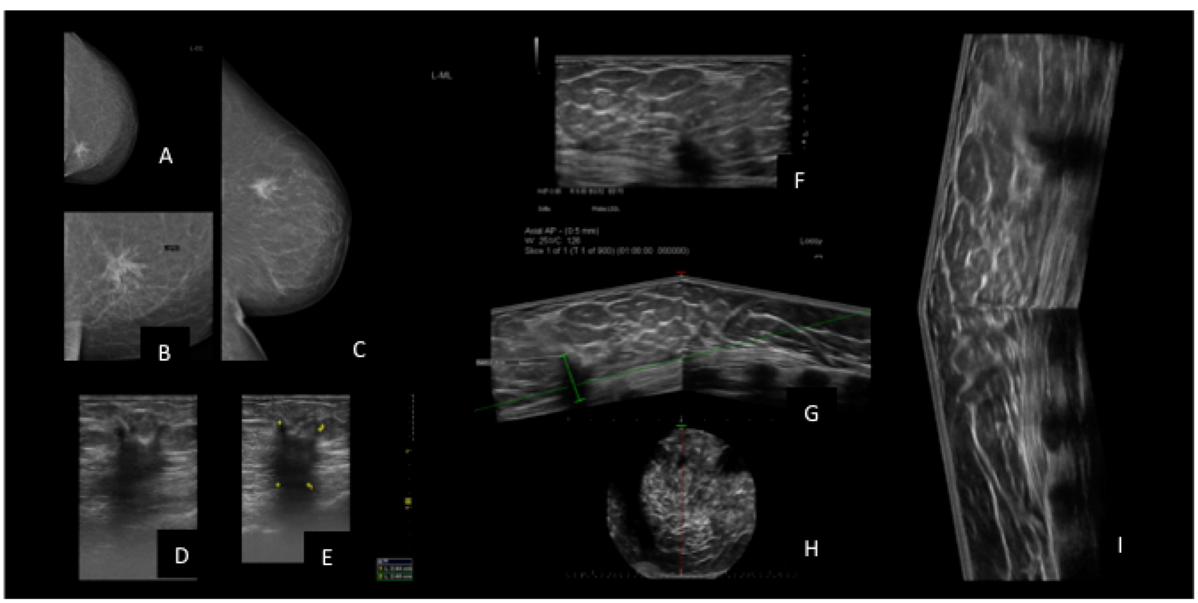

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Figure 6. F, 38 yo. the figure shows a case of benign lesion (fibroadenolipoma) in right outer equatorial Region HHUS: A, B
3D Automated Prone Breast Ultrasonography: c) axial plane during moving scan, D) sagittal plane