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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

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ABSTRACT

Purpose: The aim of this study was to evaluate the impact of the 3D automated breast ultrasound (3D ABUS) when added to full field digital screening mammography (FFDSM), on breast cancer detection and recall rates in asymptomatic women with dense breasts examined in a high-volume breast cancer screening mammography center.

Methods and material: 1668 asymptomatic women, age 40–74 years, with heterogeneously dense parenchyma (ACR3) or extremely dense breast (ACR4) were included in the study. FFDSM was performed using standard craniocaudal (CC) and mediolateral oblique (MLO) views followed by anteroposterior (AP); lateral (LAT) and medial (MED) acquisitions of 3D ABUS in both breasts. All mammograms were double read by two dedicated breast radiologists. The 3D ABUS was read by the first radiologist immediately after reading the mammograms. The second reader looked at the 3D ABUS only if there was a need for consensus discussion because of unclear or abnormal mammograms or 3D ABUS.

Results: The combined FFDSM and 3D ABUS generated a total of 6.6 cancers per 1000 women screened (95% CI: 3.0, 10.2; $p < 0.001$) compared with 4.2 cancers per 1000 women screened (95% CI) for FFDSM alone. The difference in yield was an additional 2.4 detected cancers per 1000 women screened (95% CI: 0.6, 4.8; $p < 0.001$). The corresponding recall rate per 1000 women screened was 13.8 (95% CI: 9.0, 19.8) for FFDSM alone and 22.8 for combined FFDSM and ABUS (95% CI: 16.2, 30.0), yielding a difference of an additional 9.0 recalls per 1000 women screened (95% CI: 3.0, 15.0; $p = 0.004$).

Conclusion: The addition of 3D ABUS to FFDSM in women with ACR3 or ACR4 breast density significantly improved invasive breast cancer detection rate with an acceptable recall increase.

1. Introduction

In the last 25 years, several studies have demonstrated a gradual decrease in mortality in women with breast cancer, primarily due to more widespread implementation of screening mammography programs leading to a decline in numbers of late stage cancers [1]. Cause-specific mortality reductions of up to 45% have been reported for women attending breast screening programs [1].

Increased mammographic breast density has been shown to be an independent determinant of breast cancer and possibly prognosis [2]. Dense breasts are quite common, with approximately 2/3 of all premenopausal women and approximately 30% of elderly women having 50% or higherbreast density [3]. In clinical practice, the sensitivity of any form of mammography is limited in women with mammographically dense breast tissue. In women with more than 75% breast parenchymal dense tissue, the sensitivity has been shown to be as low as 48% [3,4]. Moreover, reports have shown the number of mammographically missed cancers as well as the number of interval cancers to be higher in parenchymal dense breast than in fatty breasts. The false–negative mammographic screening

Abbreviations: 3D ABUS, 3 dimensional automated breast ultrasound system; ACR, American College of Radiology; BI-RADS, breast imaging reporting and data system; FFDM, full-field digital mammography; FFDSM, full-field digital screening mammography; HHUS, manual handheld ultrasound; CC, craniocaudal; MLO, mediolateral-oblique; AP, antero-posterior; LAT, lateral; MED, medial; DCIS, ductal carcinoma in situ; IDC, invasive ductal cancer; LCIS, lobular cancer in situ; PAD, pathological anatomical diagnosis.

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rate has been shown to fluctuate as much as 10-fold from the lowest to the highest categories of breast density [4].

Breast lesions initially detected by physical examination or on mammography are also often examined with HHUS, a technique that since long has been used as an adjunctive diagnostic tool because it is not hampered by the limitation of breast density [5]. However, HHUS is operator dependent, time-consuming and difficult to reproduce [6]. In Caucasian women, no study has so far been able to conclusively show that HHUS could replace mammography as a screening method [7] although in the very recently published ACRIN study, Berg et al. [8] found the cancer detection rate by HHUs to be similar to FFDM with more calcified DCIS detected by FFDM and more likely invasive node negative cancer detected by HHUS. Nonetheless, HHUS still has the drawback of yielding more false positive findings.

In contrast to HHUS, 3D automated breast ultrasound system (ABUS) has a standardized acquisition protocol that can be performed by medical personnel after short training without the need for highly trained radiologists during the examination. 3D ABUS acquires large 3D volumes that overlap and can be evaluated multiplanar: coronal, transverse and sagittal.

Contrary to standard HHUS, 3D ultrasound technology can visualize each sectional plane of the saved volume because of its digital character. This practice enables temporal comparison which is a key factor in breast cancer screening. It can also depict cancers in the coronal plane thanks to the retraction sign. Breast cancer often appears as a stellate lesion with desmoplastic reaction disrupting the normal parallel soft tissue plane by producing a contraction of breast tissue towards the mass. The finding can be seen on several slices which makes the perception easier [9]. It must, however, be borne in mind that the retraction sign is not shown in every cancer.

Because of its capabilities, 3D ABUS enables reproducibility and can in essence eliminate the investigator-dependent and non-standardized documentation [10]. These are characteristics that could make 3D ABUS a very useful addition to the diagnostic breast screening armamentarium as suggested by Brem et al. [11].

The objective of this study was to evaluate the impact of the 3D ABUS when added to FFDSM on breast cancer detection and recall rate in asymptomatic women with dense breasts examined in a high-volume breast cancer screening mammography center.

2. Material and methods

The study was approved by the Regional Ethical Review Board and written informed consent was obtained from all patients.

2.1. Enrollment of research participants

All women invited for breast cancer service screening mammography between November 1, 2010 and February 3, 2012 were considered for inclusion. Inclusion criteria were ages 40 or older, asymptomatic, ACR3 and ACR4 density on assessment by radiographer in the screening situation. Women were excluded if they were currently pregnant or breastfeeding, had undergone breast surgery or had a history of cancer diagnosis and/or breast cancer treatment during the preceding 12 months.

Health status for all participants was surveyed from study entry until the completion of a 24 month follow-up period. This involved a routine FFDSM if the determination at study entry was normal or if the outcome of an abnormal determination was benign.

2.2. FFDSM

The equipment used was in all cases either a FFDM Microdose Senographe (Philips Solna, Sweden) or a Senographe DS FFDM (GE Healthcare, Milwaukee WI, USA). Examination images included two views, mediolateral oblique (MLO) and craniocaudal (CC) views in both breasts.

2.3. 3D ABUS

The equipment was provided by U-Systems, Inc. Sunnyvale, CA USA. Prior to commencement of the study, two radiographers received specific training in the operation of the imaging system after which they educated the remaining radiographers. Before taking part in the study, all radiologists participating in the trial had to review minimum 100 teaching cases and attend a one day tutorial session. The 3D ABUS examination was performed immediately after the FFDSM was completed. The 3D ABUS was equipped with a linear broadband transducer 6–14 MGHZ. The original acquisitions were performed in the transverse plane as HHUS perpendicular to the chest wall and reconstructed in the sagittal and coronal planes. Imaging was done from the chest wall to the skin in 2 mm thick slices covering areas of approximately $15 \times 17 \times 5$ cm. The depth mentioned is the maximum obtainable depth.

The 3D ABUS examination was carried out with the patient in a supine position and the fibroglandular tissue being flattened by applying gentle compression to the chest wall. The radiographer held the transducer during the examination and always performed at least 3 views of each breast: lateral (LAT), anteroposterior (AP) and medial (MED). The 3D ABUS examination took 15 min per patient.

2.4. 3D ABUS image reading

Five dedicated breast radiologists with experience from 2 to 30 years of mammography reading and 2–12 years of breast HHUS were involved in the interpretation of the images. The 3D ABUS review protocol stipulated the review of 3D coronal and transverse views.

The first reader interpreted the FFDSM with a reading time of 1–2 min followed by 5–7 min reading time for 3D ABUS. The second reader interpreted the FFDSM blinded to the first reader's assessment. If any of the readers expressed reading concerns, this was discussed to achieve consensus. In that situation, the second reader checked the entire 3D ABUS knowing that the first reader had a suspicious finding either on FFDSM or 3D ABUS images or on both examinations but without the knowledge of the location. Otherwise the 3D ABUS examination was not double read.

2.4.1. Interpretation of 3D ABUS findings and recalls

The radiologist described the 3D ABUS findings and, in recall cases, the findings of HHUS according to the following parameters: shape (round, oval, irregular), orientation (parallel, not parallel), margins (spiculated, microlobulated), angularity (indistinct, circumscribed), and echogenicity (hyper, iso, hypo). The likelihood of a finding being malignant was reported according to our current nationwide praxis using a five step coding: (1) normal, (2) benign, (3) probably benign, (4) highly suspicious of malignancy, (5) malignant.

All women with suspicious findings on either FFDSM or 3D ABUS were recalled and subjected to mammography work–up with complementaryviews and HHUS. The HHUS was performed by an experienced breast radiologist using an IU22 (Philips medical systems, Bothell, WA; USA). Women who got code 1–2 at the work-up examination, were verbally informed that their breast examination did not show any sign of malignancy and that no additional measures were needed, but that they would be invited to the next screening examination after the appropriate time interval. At the time of the study, our National Board of Health and Welfare recommended that women aged 40–49 years should undergo screening each 18 month, because younger patients often had more rapidly

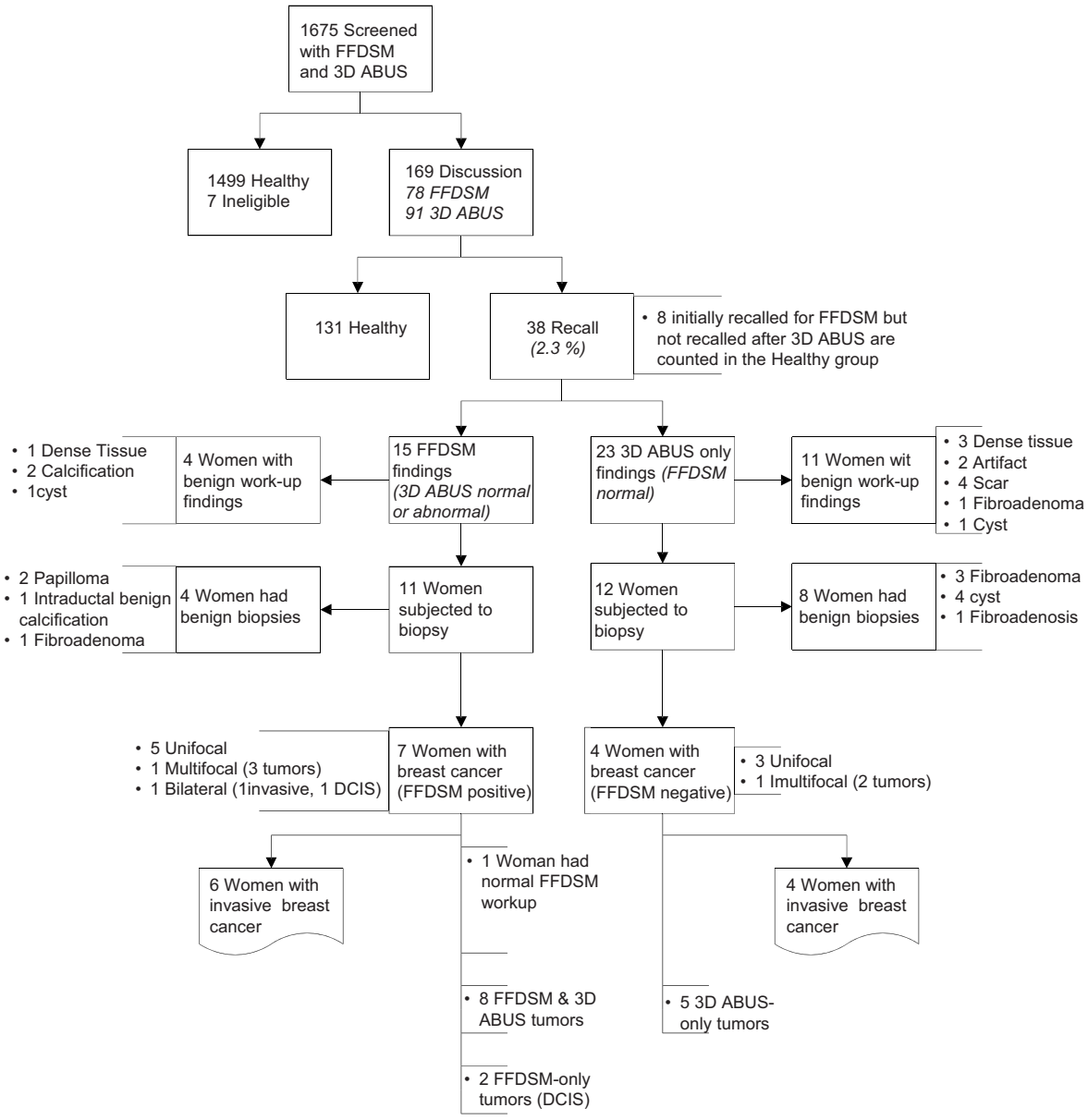

Fig. 1. Study flow chart. The figure presents 1675 study participants subjected to breast cancer screening with FFDSM and 3D ABUS.

growing cancers [12]. Not being a compulsory decree, it was not practiced all over the country but the recommendation was followed in our county.

Women with code 3–5 were all subjected to fine-needle biopsy and/or core biopsy in accordance with the praxis in our country. Surgically removed tissue was sent for pathological-anatomical analysis, and the final pathology was obtained for a concluding confirmation of diagnosis.

3. Statistics

Patient characteristics were compared by BI-RADS classification using the Pearson chi-square test and Student's *t*-test for categorical and continuous variables, respectively. For variables with low expected cell counts, the Fisher exact test and Wilcoxon test were used for categorical and continuous variables, respectively.

Of primary interest was to determine the increase in cancer detection with 3D ABUS added to FFDSM compared to FFDSM alone. Sensitivity and specificity for both FFDSM and FFDSM + ABUS were computed using 2×2 tables, and comparisons between modalities were drawn using the mid-P exact binomial test for sensitivity and the McNemar test for specificity [13,14].

Positive predictive value (PPV) was calculated for each modality among women who were recommended for recall using three ACR definitions: (1) the proportion of screen-detected cancers in all women with a recommendation other than routine screening (PPV_1), (2) the proportion of screen-detected cancers in women with a recommendation for a biopsy (PPV_2), and (3) the proportion of screen-detected cancers in women with a performed biopsy (PPV_3). Because all biopsies that were recommended were also performed, estimates for PPV_2 and PPV_3 were identical. Patients who were lost to follow-up were included in the denominators, yielding conservative PPV estimates.

The 95% confidence intervals around all diagnostic estimates and *p*-values were generated using 1000 bootstrap samples. All analyses were performed using SAS (SAS Institute, Cary, NC).

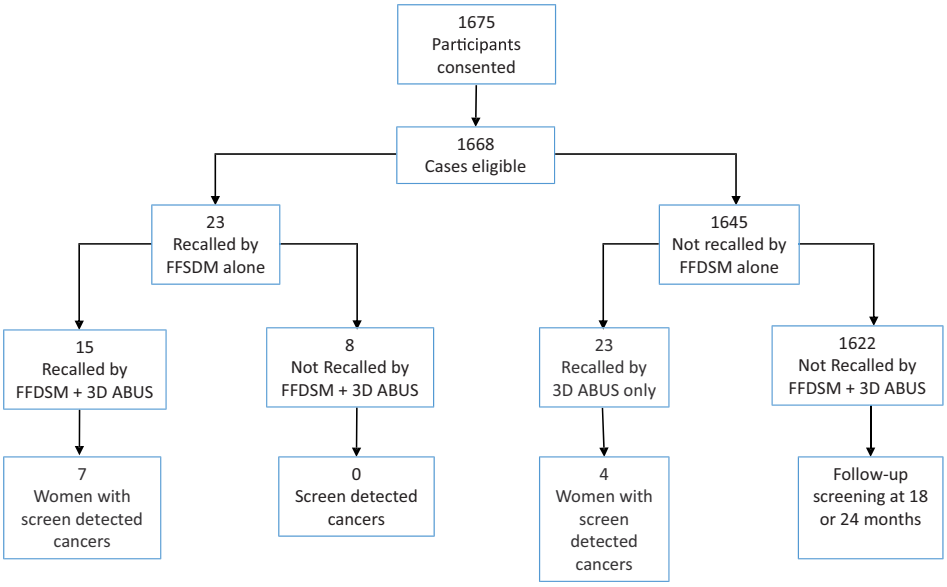

Fig. 2. Outcome of screening with FFDSM alone and screening with FFDSM and 3D ABUS.

Table 1
Patient demographic and clinical characteristics at enrollment.

Characteristic	Total N = 1668	ACR density categories		P value*
		Heterogeneously (ACR3) N = 999	Extremely (ACR4) N = 669	
Age (y)				
n	1668	999	669	0.022
Mean (SD)	49.5 (7.9)	49.9 (7.9)	49.0 (7.8)	
Median	48.0	48.0	48.0	
Range (min, max)	40, 69	40, 69	40, 69	
Age group				
40–49 y	996 (59.7%)	579 (58.0%)	417 (62.3%)	0.183
50–59 y	446 (26.7%)	276 (27.6%)	170 (25.4%)	
60–69 y	226 (13.5%)	144 (14.4%)	82 (12.3%)	
Hormone replacement therapy				
Yes	248 (14.9%)	139 (13.9%)	109 (16.3%)	0.181
No	1420 (85.1%)	860 (86.1%)	560 (83.7%)	
History of biopsy				
Yes	63 (3.8%)	39 (3.9%)	24 (3.6%)	0.740
No	1605 (96.2%)	960 (96.1%)	645 (96.4%)	
History of breast cancer				
Yes	4 (0.2%)	4 (0.4%)	0 (0.0%)	0.154**
No	1664 (99.8%)	995 (99.6%)	669 (100.0%)	
Family history				
Yes	59 (3.5%)	37 (3.7%)	22 (3.3%)	0.653
No	1609 (96.5%)	962 (96.3%)	647 (96.7%)	

* P values derived from Student's t-test and chi-square test for continuous and categorical variables, respectively, unless otherwise noted.
** P values derived from Wilcoxon text and Fisher's exact test for continous and categorical variables, respectively.

4. Results

4.1. Patient characteristics

Fig. 1 presents the study flow. Of the 1675 asymptomatic women enrolled in the study, 7 women were excluded because of protocol violation. Thus, a total of 1668 women undergoing screening mammography (FFDSM) were eligible for analysis with 999 (60%) classified as ACR3 and 669 (40%) classified as ACR4 (Table 1). The mean age in eligible women classified as ACR4 was 49.5 years, on average almost one year older than women classified as ACR3. Other demographic and clinical characteristics were similar between women in the ACR3 and ACR4 groups. Among the 1668 eligible women, 248 (14.9%) had used either oral contraceptives or hormone replacement therapy. Sixty three women (3.8%) had a history of breast biopsy, 4 (0.2%) had a history of breast cancer, and 59 (3.5%) had a family history of breast cancer.

4.2. Screening performance

Among the 1668 eligible participants, findings on screening FFDSM alone called for a recall in 23 women. The addition of 3D ABUS supported the need for a recall in 15 of these women, and a recall could be avoided in 8 women (Fig. 2). Of the 1645 women who were not recalled on the basis of screening FFDSM alone, 23 were recalled on the basis of 3D ABUS only (Fig. 2). A total of 11 women with breast cancer were identified (Fig. 2, Table 2a). In cancer cases where recall recommendation differed, 4 of 4 cases were

Table 2a
Breast cancer detection by imaging method.

Characteristic	Any Detection with FFDSM	Detection with 3D ABUS only	Total
Number of women with cancer	7	4	11
ACR density categories, n (%)			
Heterogeneously	4 (57.1%)	2 (50.0%)	6 (54.5%)
Extremely	3 (42.9%)	2 (50.0%)	5 (45.5%)
Size of cancer (mm)			
Mean (SD)	22.4 (10.1)	21.8 (12.6)	22.2 (10.4)
Median (Q1, Q3)	20.0 (16.0, 24.0)	17.0 (13.5, 30.0)	20.0 (14.0, 24.0)
Range (Min, Max)	14, 44	13, 40	13, 44
Histological classification, n (%)			
Grade I	0 (0.0%)	2 (50.0%)	2 (18.1%)
Grade II	5 (71.4%)	1 (25.0%)	6 (54.5%)
Grade III	2 (28.6%)	1 (25.0%)	3 (27.3%)

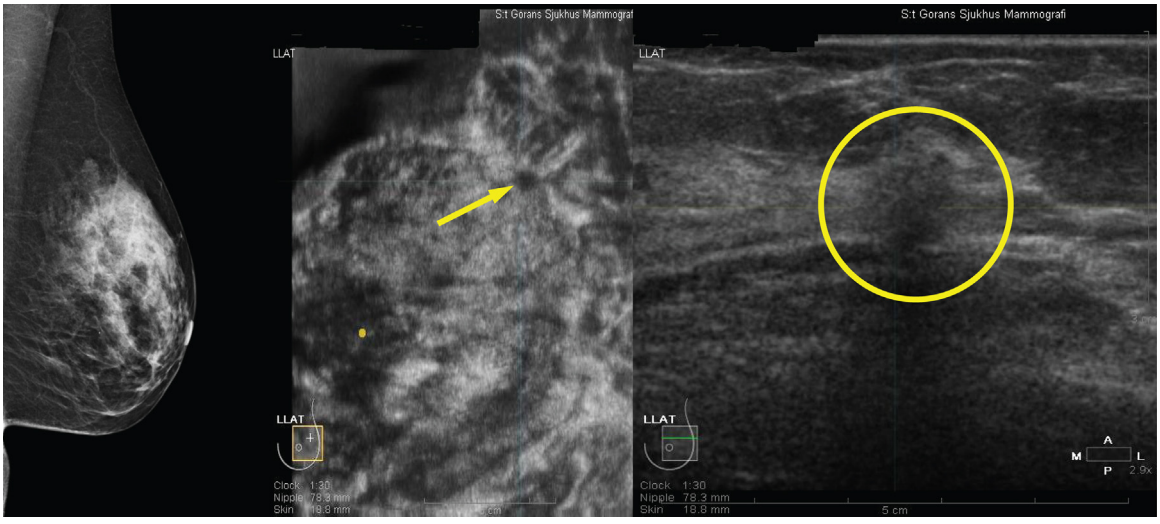

Fig. 3. Presentation of a unifocal node negative cancer in left breast visible only on 3D ABUS. Cancerous lesion indicated by arrow on central image (coronal plane) and circle on rightmost image (tranverse plane). No lesion visible on FFDSM (leftmost image).

detected with 3D ABUS and not with FFDSM alone ($p = 0.063$). Six cancers with an invasive growth were detected on both FFDSM and 3D ABUS and 2 ductal carcinomas in situ (DCIS) were seen only on FFDSM. One woman had cancer in both breasts; in one breast an IDC was detected on both FFDSM and 3D ABUS and in the other breast a DCIS was seen only on FFDSM. Five (45.5%) of the 11 women with breast cancer had at least one family member with breast cancer. One patient was unable to give any information concerning heredity. Findings by imaging method and characteristics of the cancers found in eleven women are shown in Tables 2a and 2b. Fig. 3 illustrates a unifocal node negative cancer seen on ABUS only.

4.3. Cancer detection

The combined read of FFDSM and 3D ABUS generated a total of 6.6 cancers per 1000 women screened (95% CI: 3.0, 10.2; $p < 0.001$) compared with 4.2 cancers per 1000 women screened (95% CI) for FFDSM alone (Table 3). The difference in yield was an additional 2.4 detected cancer per 1000 women screened (95% CI: 0.6, 4.8; $p < 0.001$), resulting in a relative increase of 57%.

4.4. Screening recalls

The recall rate per 1000 women screened was 13.8 (95% CI: 9.0, 19.8) for FFDSM alone and 22.8 for FFDSM combined with 3D ABUS (95% CI: 16.2, 30.0), yielding a difference of an additional 9.0 recalls per 1000 women screened (95% CI: 3.0, 15.0; $p = 0.004$). The recall rate from the combined FFDSM and 3D ABUS was 2.3% compared to 2.1% for FFDSM alone in our ordinary screening program in the year preceding the study.

4.5. Sensitivity and specificity

The increase in sensitivity at screening for FFDSM and 3D ABUS versus FFDSM alone was 36.4% (95% CI: 9.1%, 66.7%; $p < 0.001$), and when interval cancers were included, the increase in sensitivity was 25.0% (95% CI: 5.6%, 50.0%; $p < 0.001$). The difference in specificity was −0.7% (95% CI: −1.2%, −0.1%; $p = 0.018$). The increase in biopsy rate was 7.2 per 1000 women screened (95% CI: 3.6, 11.4; $p < 0.001$), and the increase in surgery rate was 2.4 per 1000 women screened (95% CI: 0.6, 4.8; $p < 0.001$). The PPVs for cancers found (PPV_1) and for biopsies recommended and performed (PPV_3) were numerically smaller for FFDSM and 3D ABUS compared to FFDSM alone with 28.9% (11 of 38) versus 30.4% (7 of 23) for PPV_1 and 47.8% (11 of 23) versus 63.6% (7 of 11) for PPV_3; although these differences were not statistically meaningful ($p > 0.10$ in both cases). Regardless of the inclusion of interval cancers, the increase in NPV for FFDSM and 3D ABUS versus FFDSM alone was 0.2% (95% CI: 0.1%, 0.5%; $p < 0.05$).

4.6. Interval cancers

In five women (0.3%) cancers were detected in the interval between their scheduled routine screening time-points. All interval cancers were detected after the patient had felt a palpable breast

Table 2b
Characteristics of breast tumors detected on both FFDSM and 3D ABUS in 11 women.

Pat	Age (years)	Side	ACR-density	Tumor size on HHUS[a] (mm)	Tumor size on FFDSM (mm)	Clinicopathological features						Comments
						Tumor size on PAD (mm)	Histo-logical cancer type	Elston Grade	Estrogen receptor	Progesteron receptor	Prolife-ration factor (KI67)	Human epidermal growth factor receptor	
1	42	R	3	9.4, 10	0	32	IDC	1	100%	100%	>5%	Negative	First screen, 40 mm between tumors
2	40	R	4	6, 6, 5, 6	0	44	IDC	2	80%	–	12%	Negative	First screen, <10 mm between tumors 9, 13, 14, 10
3	67	R	4	11.3	15	14	IDC	2	100%	97%	10%	Negative	Radio frequency therapy preop
4	67	L	3	10	0	20	IDC	3	100%	90%	>40%	Negative	Lobular growing pattern, ductally invasive
5	61	R L	3	25 0	20 25	22 19	IDC DCIS	2 2	90%	<5%	30%	Positive	Bilateral cancer
6	59	R	3	9	9	16	IDC	3	100%	100%	50%	Negative	Waited 1 year for op because of psychiatric illness
7	59	L	4	19	18	24	IDC	2	80%	20%	50%	Negative	
8	40	L	3	30, 8, 5	40	85	DCIS	2	95% (on biopsy)	80%	15%	Negative	First screen, >10 mm between tumors. Preop chemotherapy
9	56	L	3	10	25	40	IDC	2	45%	90%	15%	Negative	Fibrotic unchanged pattern at several FFDSM, 1 axillary met
10	47	R	4	14	0	13	IDC	1	90%	30%	14%	Negative	Skin retraction, 1 axillary met
11	48	L	3	0	12.5	17 9	DCIS LCIS	2	n.a.	n.a.	n.a.	n.a.	

Calc calcifications, met metastasis, n.a. not applicable, R right breast, L left breast, ACR American College of Radiology, HHUS manual handheld ultrasound, FFDSM full-field digital mammography, PAD pathological anatomical diagnosis, IDC invasive ductal dancer, DCIS ductal cancer in situ, LCIS lobular cancer in situ.

[a] Tumor size on HHUS was in all cases concordant with tumor size on 3D ABUS.

Table 3
Results of asymptomatic women breast cancer screened with FFDSM alone and combined read (FFDSM and 3D ABUS).

Characteristic	FFDSM alone	Combined read FFDSM and 3D ABUS	Difference (FFDSM and 3D ABUS) − FFDSM alone
Number of women recalled	23	38	15
Number of women with screening cancer found	7	11	4
Sensitivity at study entry (%)	63.6 (33.3, 90.9)	100 (−, −)	36.4 (9.1, 66.7)
Sensitivity including interval cancers (%)[a]	43.8 (20.0, 69.2)	68.8 (43.3, 92.3)	25.0 (5.6, 50.0)
Specificity (%)	99.0 (98.5, 99.4)	98.4 (97.8, 98.9)	−0.7 (−1.2, −0.1)
Cancer detection rate per 1000 women screened	4.2 (1.2, 7.2)	6.6 (3.0, 10.2)	2.4 (0.6, 4.8)
Recall rate per 1000 women screened	13.8 (9.0, 19.8)	22.8 (16.2, 30.0)	9.0 (3.0, 15.0)
Biopsy rate per 1000 women screened	6.6 (3.0, 10.8)	13.8 (8.4, 19.8)	7.2 (3.6, 11.4)
PPV_1 (%)	30.4 (12.3, 49.1)	28.9 (14.3, 42.3)	−1.5 (−16.1, 12.8)
PPV_2 and PPV_3 (%)[b]	63.6 (33.3, 90.0)	47.8 (27.0, 66.7)	−15.8 (−37.5, 5.8)
Number of women not recalled	1645	1630	−15
NPV at screening (%)	99.8 (99.5, 99.9)	100 (−, −)	0.2 (0.1, 0.5)
NPV including interval cancers (%)[a]	99.5 (99.1, 99.8)	99.7 (99.4, 99.9)	0.2 (0.1, 0.5)

Note: numbers in parentheses are 95% confidence intervals.
[a] Includes interval cancers.
[b] Because all recommended biopsies were also performed, PPV_2 and PPV_3 are identical.

lump. Three cases were "clear-cut" interval cancers that were not previously visible by any method. In retrospect, two of the interval cancers could have been detected earlier. In one instance the FFDSM was misinterpreted as unchanged microcalcifications with no suspicion of malignancy on three earlier FFDSM. This case was one of the 3D ABUS "discussion cases" where the 3D ABUS was double read. At the retrospective review of the patient's earlier 3D ABUS no suspicious malignant findings were seen.

The second case had very subtle signs (only seen on one view) on both FFDSM and 3D-ABUS that were initially interpreted as benign (Fig. 4). Characteristics of the interval cancers are shown in Table 4.

5. Discussion

The aim of our study was to evaluate the additive value of 3D ABUS to FFDSM. The study was not designed to compare neither FFDSM nor HHUS to 3D ABUS. Our findings clearly show that it is feasible to implement 3D ABUS into a high volume FFDSM center and increase the cancer detection rate in women aged 40–74 years, while maintaining an acceptable low recall rate well within the recommendations of the European guidelines for quality assurance in breast cancer screening and diagnosis [15]. Our recall rate also compares favorably to the reported recall rate of 10.7% in the ACRIN study and the 8.8% in the J-Start study [8,16].

In our study, the addition of 3D ABUS screening in women with dense breast tissue at FFDSM demonstrated a cancer detection rate of 6.6 cancers per 1000 women screened. The improved incremental cancer detection rate of 2.4 cancers per 1000 women screened was comparable to the rates observed in studies of mammography screening supplemented by HHUS in women with dense breasts, ranging from 1.9 – 5.3 additional cancers per 1000 reported [5,8,17,18]. Adding HHUS has also been shown to increase the cancer detection rate in women under age 50 with dense breasts [16,19].

The addition of 3D ABUS to FFDSM resulted in an increase in sensitivity of 36.4% compared to FFDSM alone and 25% when interval cancers were included in the analysis. This finding is in line with other studies reporting that sensitivity increases when adding ABUS. Kelly et al. [20] reported an increase in sensitivity from 40% for mammography alone to 81% with the addition of ABUS. In a recent study comparing FFDM with 3D ABUS to FFDM alone for mammography-negative cancers, the addition of 3D ABUS caused a 23.9% sensitivity increase [21]. The small loss of specificity in our study (−0.7%) compares favorably to the −13.4% specificity loss reported in the Somoinsight study [11].

The tumors seen on both examination modalities were larger than the ones generally found in our screening program. One explanation is that in our standard screening program we also include women with fatty breasts, where very small tumors are more easily detected by FFDSM. In accordance with the study by Leong et al. [22], we saw more DCIS on FFDSM than on ultrasound supporting the conclusion by Jeh et al. [23] that detection of microcalcifications without a mass provides difficulties even with a 3D ABUS system. Surprisingly, the tumors detected by 3D ABUS only were not as small as the ones found in a study by Kaplan [17]. However, in Kaplan's study tumor size was measured on HHUS while we refer to the histopathological size measured on the surgically removed specimens.

Tumor stage at diagnosis still appears to significantly affect overall survival in women afflicted with breast cancer, even with today's modern and more effective treatment methods, as indicated by a recent large Dutch population-based study [24]. In our study, 2 of the 4 women with cancers visible on 3D ABUS only had axillary metastases indicating later stage cancers. This is contrary to the findings by Corsetti et al. [19], who reported a significantly higher proportion of early stage cancers detected by HHUS only as compared to mammography only (65% and 36%, respectively). However, our figures have to be interpreted with caution because of the small numbers.

In our material, we did not have any lobular invasive cancers but one ductal malignancy with lobular growth pattern. One explanation for this could be the small sample size in our study and the fact that all known palpable lumps were excluded from the trial. Calcifications can lead to misinterpretation and erroneous diagnosis. The one cancer in our study that was diagnosed as an interval cancer because of misinterpretation of calcifications on the FFDSM gives a misinterpretation rate of 20%. This is lower than the 30% missed cancers caused by misinterpretation of calcifications reported by Birdwell et al. [25]. However, because of the large difference in numbers of malignancies between our two studies a comparison must be interpreted with caution.

Clearly, new diagnostic tools are needed that can help to identify malignancies also in dense breasts. MRI with a short pass technique is promising but not widely available, still somewhat expensive and involves an intravenous injection of contrast media [26,27].

Another technique with the potential to become a valuable adjunct to mammography is tomosynthesis. However, adding tomosynthesis to FFDSM will increase the radiation dose given to the woman. In comparison, 3D ABUS has the advantage of no additional radiation but the disadvantage of being a more time-consuming procedure.

Table 4
Characteristics of five patients with interval cancers. All interval tumors were invasive ductal cancers (IDC).

Pat	Age (years)	Side	ACR- density	Tumor size at HHUS (mm)	Tumor size at FFDSM (mm)	Clinicopathological features						Comments
						Tumor size on PAD (mm)	Elston Grade	Estrogen receptor	Progesteron receptor	Prolife-ration factor (KI67)	Human epidermal growth factor receptor	
1	69	L	3	17, 21	70[a]	15, 21 (60 with DCIS)	2	+	+	40%	Negative	15 months post-screening. Suspicious sign at FFDSM at last screening
2	47	L	3	20	20[b]	21	2	+	+	30%	Negative	10 months post-screening. Minimal sign at FFDSM and ABUS at last screening
3	46	R	4	10, 15, 30	35[a]	55	2	+	+	15%	Positive	11 months post-screening
4	53	R	4	10	0	19 (30 with DCIS)	2	+	+	15%	Positive	13 months post-screening, vascular invasion 1 axillary metastasis.
5	47	R	3	7, 30	0	8, 37	3	+	+	30%	Negative	23 months post-screening normal FFDM and normal HHUS 1 year post-screening, vascular invasion 2 axillary metastases

R right breast, L left breast, ACR American College of Radiology, HHUS manual handheld ultrasound, FFDSM full-field digital mammography, PAD pathological anatomical diagnosis, DCIS ductal cancer in situ.
[a] Densities and calcifications.
[b] Densities.

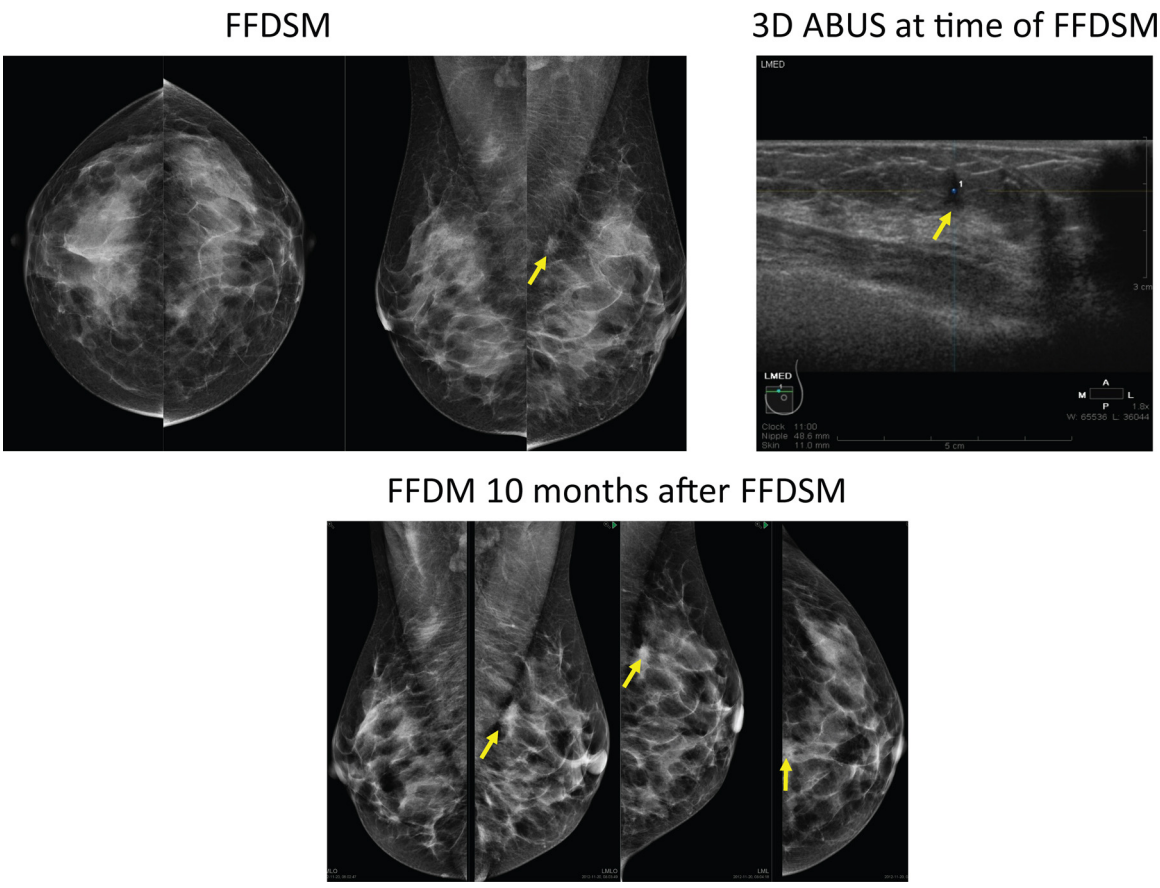

Fig. 4. Images showing one interval cancer that was initially misinterpreted and retrospectively seen on FFDM and 3D ABUS. Cancerous lesion indicated by arrow.

In the Oslo Tomosynthesis Screening Trial [28] comprising 12621 eligible subjects, the addition of tomosynthesis to the mammography screening program improved cancer detection by 31% in women with dense breasts, but it did also increase the recall rate by 0.7% (2.1% to 2.8%). Recently, a prospective comparative Italian multicenter trial showed that HHUS had better incremental breast cancer detection than tomosynthesis in mammography negative dense breasts at similar false-positive recall rate [29].

The setup of our study was similar to the Somoinsight study by Brem et al. [11] and the reader performance studies by Skaane et al. [30] and GIGER et al. [21]. In all three studies the first reader assessed the mammogram and then 3D ABUS. All three studies concluded that adding 3D ABUS to mammography improved the performance of mammographic interpretation.

One challenge in using 3D ABUS is the time needed to perform and examine the images. In our study the examination done by the radiographer took 15 min and the radiologist's interpretation of 3D ABUS 5–7 min. This interpretation time is longer than the 2.9 min reported in the Somoinsight study [11], but less than the 9 min reported in the study by Skaane et al. [30]. The reason for the observed differences may depend on differences in learning curves, individual radiologic experience and the way protocols and reports are filled out.

Our study has some limitations: First, all dedicated breast radiologists involved in the study had to undergo tutorials prior to study initiation but even so each one had to familiarize themselves with this new modality leading to individual learning curves. Another limitation is that the 3D ABUS was double red only in case of discussions, while FFSDM was always double red. Also, we did not have access to a computer-aided detection system for 3D ABUS. Such a system could possibly have been of help to reduce reading time and improve early cancer detection. Further studies in this area are needed. Second, the number of study participants was relatively small in the context of breast screening trials. Third, the study was not designed to detect mortality which prevented us from analysing a potentially beneficial effect of the enhanced cancer detection.

6. Conclusion

3D-ABUS appears to be a promising adjunct method to FFDSM programs for women with dense breasts, and our study shows that it is possible to well integrate the technique into the program of a high-volume screening center. Besides increasing the cancer detection rate, it has the advantage of maintaining an acceptable recall rate without affecting the radiation dose given to the patient. Nevertheless, in order to find the best strategies and methods to detect more breast cancers and reduce the number of investigated benign lesions further studies are needed. Comparative studies with tomosynthesis and MRI with a short pass technique including cost-effectiveness aspects would be of interest. Such studies can maybe provide us with answers as how to define which women would benefit most from which method, and also help to decide how to best integrate those methods into the screening program of women with dense breasts.

Conflict of interest

During the writing of this manuscript, Lawrence Rasouliyan was an employee of ICON Clinical Research, a company that received funding from GE Healthcare to provide biostatistical services. Brigitte Wilczek, Karin Leifland and Henryk E. Wilczek have no conflicts of interest to disclose.

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Authors' contributions

Brigitte Wilczek and Karin Leifland initiated the working hypothesis and participated in the study design, performance of the study and data acquisition, the analysis and interpretation of data, and writing the article. Henryk E. Wilczek participated in the analysis and interpretation of data and in writing the article. Lawrence Rasouliyan performed the statistical analysis, participated in the interpretation of the data and revisions of the manuscript, and provided valuable input on the content. All authors were active in reviewing and finalizing the article.

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