European Journal of Radiology 85 (2016) 1554–1563

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

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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ARTICLE INFO

Article history:
Received 16 November 2015
Received in revised form 27 May 2016
Accepted 6 June 2016

Keywords:
Breast cancer screening
Breast density
FFDSM
3D ABUS
Breast cancer detection
Recall rate

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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http://dx.doi.org/10.1016/j.ejrad.2016.06.004

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