3D Supine Automated Ultrasound (SAUS, ABUS, ABVS) for Supplemental Screening Women with Dense Breasts

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Introduction

The latest re-analysis of ACRIN 6666 data by Berg and co-workers 2016 showed that cancer detection rate with handheld ultrasound (HHUS) is comparable with mammography, with a greater proportion of invasive and node-negative cancers among US detections (1). Supplemental screening by HHUS in addition to mammography in women with dense breasts results in additional screen detected cancer rates between 1.8 and 4.6 per thousand examinations depending on the basic risk of the collectives (2). Three-dimensional supine automated ultrasound (SAUS) of the breast, also known as 3D automated breast ultrasound (ABUS; trademarks of General Electric company; Invenia and somo v˚ ABUS) or 3D automated breast volume scanning (ABVS, trademark of Siemens company; ACUSON S2000™ automated breast volume scanner), represents an innovative technology that has gained FDA approval for screening or early detection of breast cancer in women with dense breasts; claiming to find 35.7% more cancers in women with dense breasts than mammography alone (3, 4). Can ABUS/ABVS really catch up with HHUS and other supplementary imaging methods in screening women with dense breasts? What is the future of population-based supplemental imaging in women at intermediate risk?

3D supine automated ultrasound (SAUS: ABUS, ABVS) – what is it?

In contrast to HHUS a mechanical arm links the ABUS or ABVS transducer with the computing system. Patients lie supine. A technician performs several automated standardized scanning tracks of both breasts at a predefined speed. The resulting three-dimensional data sets co-register the US echo information with the corresponding voxel positions within the breast volume. Finally a physician reads the data on a workstation similar to reading a CT or MRI examinations in multiple planes and reconstructions (5). Multiplanar reconstructions of 3D automated breast ultrasound have been shown to improve lesion differentiation by radiologists (6). Modern prone water bath systems operate on the principles of ultrasound tomography. They incorporate multiple sound characteristics of reflection, sound speed, and attenuation of transmission ultrasound that can be sampled by a circular array surrounding the breast. Currently clinical studies have been initiated. However, population-based trials do not exist to date (4).

Advantages of 3D supine automated ultrasound (SAUS)

Older versions of the 3D supine automated ultrasound technology have been shown to be inferior to HHUS (5, 7), however updated technology has overcome previous problems to a large degree (8, 9). The newest generation of ABUS (Invenia ABUS; trademark of GE) is faster, achieves a higher resolution and generates less coupling artefacts between the curved transducer and the curved surface of the breast compared to older systems with a plane transducer surface (5). Compared to HHUS, 3D supine automated ultrasound of the breast provides for better detection of architectural distortions and hyperechoic rim in the coronal plane (10, 11). The complete, non-selective documentation of the 3D data allows better determination of the 3D localization of a lesion and a lower inter-observer variability. It promises a more reproducible and more examiner independent examination in an optimized reading environment (5, 8-11). Further, digital data enable computer-aided detection (CAD) and quantitative texture analysis of breast lesions (12).

The other side

More recent studies on HHUS and 3D supine automated ultrasound of the breast between 2007 and 2016 have shown that the advances in ultrasound technology have had little effect on the diagnostic performance of supplemental ultrasound and on patient outcomes compared to meta-analysis of older data on supplemental HHUS (2, 13-15).

Currently in most western countries, screening mammography is still considered the method of choice, because despite critical discussion of alternatives it is the world's most established compromise of advantages, disadvantages and costs (16). Recently IARC Working Group updated their assessment of various screening methods comparing their level of evidence regarding benefits and adverse effects. The authors judged the level of evidence "sufficient" for screening mammography to reduce breast cancer mortality in women between 50 and 74 years

(16). They also stated that the extent of the benefit outweighs the risk of radiation-induced cancer from mammography although over-diagnosis occurs. Population-based mammography programs can be cost-effective in countries with a high breast cancer incidence. Insufficient evidence for a reduction of breast cancer mortality has been found for supplemental ultrasound, tomosynthesis and all other methods including clinical breast examination, breast self-examination or MRI of high-risk women. Randomized trials with mortality as an endpoint, however, have only ever been performed with mammography. Breast self-examination has been studied and has shown to increase the rate of benign biopsies. IARC Working Group found sufficient evidence of increased false positive screening outcomes and limited evidence of increased cancer detection rates also for supplemental ultrasound in women with dense breasts and negative mammography (16).

In addition, opponents of 3D supine automated breast ultrasound may argue that previous ABUS and ABVS studies showed an average 10 percent lower detection rate, higher rate of false positives and higher recall rates compared to physician-performed whole breast HHUS (1, 2, 5). More shadowing artefacts created by angulated Cooper ligaments and fibrous structure, especially at the periphery of the breast are causing false positive cases and may need supplementary characterization to differentiate a pseudo lesion from a real lesion by use of HHUS, Doppler and elastographic techniques. Furthermore, final US-guided biopsy is based on HHUS-guidance, so as a result, "one-stop-shop" ABUS is only effective for negative cases (2, 15).

Dense breasts mask cancers during mammography and they are associated with an increased risk for developing breast cancer. The latter effect is less important than masking (17). Women with heterogeneous and extremely dense breast tissue show a 3-5 times higher relative risk than women with fatty breasts as referenced in meta-analysis, but only a 2 times higher relative risk than women with scattered fibroglandular tissue (18). Recommendations to overcome masking in women with dense breasts focus on MRI, ultrasound and, more recently digital tomosynthesis (2, 17).

Facts on HHUS
A systematic review of the literature to 2008 on supplemental breast ultrasound after negative mammographic screening reported diagnosis of primarily invasive carcinomas in 3.2 per thousand women with breast density type categories B-D of the American College of Radiology (ACR); mean tumour size for those identified was 9.9 mm, 90% with negative lymph node status (19). Most mammography-detected cancers occurred in dense breast ACR types C and D. Biopsy rates were in the range from 2.3% to 4.7%, with positive predictive values (ppV) for positive ultrasound findings from 8.4% to 13.7% (19). In five studies of more than 500 examinations per each study and a total of 28474 examined women with dense breasts between 2007 and 2016, the incremental cancer detection rate (ICDR) per examination of supplemental HHUS varies between 1.8 and 6.8/1000 examinations at a median of 2.7/1000 examinations (Incremental cancer detection rates - Parris 1.8; Girardi 2.2; Choi 2.7; Weigert 3.2; Hooley 4.6) (20-24). Girardi and co-workers performed breast HHUS in 22,131 asymptomatic women with negative mammography and showed an overall US detection rate of 1.85 per thousand (41/22.131) over all grades of breast density, 2.21 per thousand (22/9960) in dense breasts vs 1.56 per thousand (19/12,171) in fatty breasts (21). Incremental cancer detection rate per thousand examinations of supplemental HHUS is calculated as the number of cancers detected by US only divided by the total number of examinations (25).

Facts on SAUS
Incremental cancer detection rate per thousand examinations of supplemental SAUS in larger studies varies between 1.9 and 7.7 at a median of 3.6 (Brem 1.9, Leifland 2.3, Kelly 3.6, Giuliano 7.7, Choi 3.8) (25-28). Incremental biopsy rates of supplemental ABUS in heterogeneously and extremely dense breasts vary between 20 and 39 per thousand and showed an average of 36 per thousand in the large SomoInsight study (24-28). In contrast, the addition of ABUS to screening mammography did not demonstrate significantly increased recall rates in the Easy Study when compared to historic rates from screening mammography alone at the contributing sites. The Easy study demonstrated an additional ABUS incremental recall rate of 6 per thousand at a recall rate of 23 per thousand with combined mammography and ABUS examinations (26). In an average-risk population using an automated arm for screening US, a cancer detection rate of 3.6 per thousand was achieved, and only 3% of women were recommended for biopsy and 31% of biopsies showed cancer (28).

The average time to perform a 3D supine automated ultrasound study lies between 15 to 30 minutes; average time to read between 5 to 10 minutes. The ROC inter-observer variability has been reported between AUC 0.59 – 0.9; sensitivity varies between 35 to 100% (5, 8, 10, 24-28).

Evidence based medicine and coverage for supplemental screening
Ultrasound has been shown to detect node-negative invasive cancers at smaller average size and even higher sensitivity than mammography, but with also a higher false positive and biopsy rate (1-2, 13-15). The latest improvements in technology shows promise that 3D supine automated ultrasound will be catching up with HHUS regarding supplemental cancer detection rates for comparable collectives. A highly variable incremental recall rate at ABUS screening studies between 6 per thousand and 285 per thousand of the women screened with dense breasts needs further clarification (5, 24-28). Promise is not the same as hard evidence. Vendors have to rely on limited evidence when investing capital in modern economies including the health market. Currently, new technologies as 3D supine automated ultrasound (SAUS), digital breast tomosynthesis (DBT), contrast-enhanced digital mammography (CEDM), computer assisted detection (CAD), or hybrid and fusion imaging techniques are going to be incorporated into clinical practice without sufficient evidence of effectiveness in prospective studies, as MRI successfully did in the last decades. National health systems or corresponding private and statutory health insurance companies should be sure that health providers deliver maximum health benefits at reasonable costs to patients or collectives at risk. Only modalities without intravenous contrast injection are suitable for population-based studies (25). A mammography population-based screening programme can also be successfully integrated in a mid-lower income country and continues to be the only evidence–based screening tool to reduce breast-cancer-specific mortality (29). Increase of incremental cancer detection rate (around 2/1000 examinations) and absolute decrease of recall rate (about 1-1.5%) have been observed after implementation of 3D digital breast tomosynthesis in population-based screening trials (30-33). Many logistical issues and the role of potential over-diagnosis of DCIS need further evaluation to determine the potential implications and cost of supplemental HHUS, SAUS, combined 2D + supplemental 3D mammographic screening (30-36). At present, the available data strongly support investment in new large-scale population screening trials that should use a randomized and prospective design. Robust, reliable results should influence the future investments of national health systems and contribute to

the reimbursement of insurance for refined screening strategies. There is insufficient evidence to support the use of other imaging modalities, such as thermography, breast-specific gamma imaging, positron emission mammography, and optical imaging, for breast cancer screening (37). However, the future of supplemental imaging in women at intermediate risk for breast cancer looks bright.

Conclusion and next step

ABUS and digital tomosynthesis are the current most promising candidates to supplement population-based screening for breast cancer in women with heterogeneously and extremely dense breasts who do not meet high-risk criteria for screening MRI. The presumed incremental cancer detection rates of approximately 2 per thousand in addition to mammography of both modalities move in the same range. Ultrasound, however, is a tomographic modality that does not show adverse effects by ionizing radiation and detects a different spectrum of invasive cancers than tomosynthesis. The next step is a large-scale, prospective, randomized trial comparing HHUS, ABUS and digital tomosynthesis. The proposed end point for this study should be the reduced rate of interval cancers in women with dense breasts. Further, relevant surrogate parameters for a presumed mortality reduction should be sampled and analysed (38). The results will be helpful in making evidence-based political, economic and workflow decisions on refined population-based supplemental screening.

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