Evaluation of a combined automated breast ultrasound and tomosynthesis system

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The FUSION-X-US-II is the latest prototype version of a system that combines 3D-automated breast ultrasound (ABUS) and digital breast tomosynthesis (DBT) and allows images from both modalities to be acquired in a single examination without any decompression or repositioning of the breast between the two acquisitions. This article describes the results of a prospective feasibility study designed to evaluate the performance of the system in a real life clinical setting. The results showed that there is a direct correspondence between lesions detected on the ABUS and tomosynthesis images and that malignant and suspicious breast lesions can be accurately identified. Additional technical modifications will further enhance the performance of the system, which has the potential to significantly improve breast cancer screening in the future.

Dense breast tissue leads to a reduction in the sensitivity of mammography and is also an independent risk factor for the development of breast cancer [1, 2], For these reasons, breast ultrasound is frequently used as a supplemental imaging modality in addition to mammography in cases of dense breasts [3-5]. However, the technique of hand-held ultrasound (HHUS) is highly operator-dependent and also time-consuming. To overcome these drawbacks, 3D-automated breast ultrasound (ABUS) has been developed and extensively evaluated [6-10].

Both ABUS and digital breast tomosynthesis have been shown to improve the sensitivity of breast cancer screening in women with dense breast tissue [11-14]. Over the last few years, hybrid systems have been developed which combine ultrasound and mammography/tomosynthesis in a single device. These developments included the FUSION-X-US-I prototype which incorporates ultrasound and tomosynthesis [15-20]. A subsequent version the FUSION-X-US-II has now been developed to overcome some limitations in the extent of ABUS coverage and in image quality in the earlier version.

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STUDY DESIGN

We assessed the performance of the new model for the detection and classification of breast lesions in a prospective single-center study involving 101 patients. Full characteristics of these patients can be found in reference 21. The patients were recruited into the study depending on the availability of the prototype and of personnel experienced in the operation of the new system. All patients underwent a standard diagnostic workup. This involved a clinical examination, 2D-digital mammography using a MAMMOMAT Inspiration system, (Siemens Healthineers), HHUS using an ACUSON S2000 or S3000 ultrasound unit and tomosynthesis using the FUSION-X-US-II prototype (Siemens Healthcare). The prototype is a research-only device and is not commercially available. In the study arm of the trial ABUS was in addition carried out directly after tomosynthesis by a radiology technologist without changing the breast position. Ultrasound-guided biopsies were carried out in BI-RADS 4 or 5 (n=47) cases.

The primary endpoint of our study was the breast cancer detection rate. Secondary endpoints were the detection and classification of benign lesions, image quality, breast coverage and the time of acquistion and interpretation of ABUS and tomosynthesis images

EQUIPMENT/IMAGING PROTOCOL

The FUSION-X-US-II prototype is based on the ACUSON S2000 Automated Breast Volume Scanner from Siemens and the MAMMOMAT Inspiration tomosynthesis system from Siemens, both of which are FDA approved and CE certified. In comparison to the earlier FUSION-X-US-I prototype, the latest version has a compression paddle that has been adapted in terms of weight and size to allow improved breast positioning. The breast is compressed in contact with a specially woven gauze, which provides sufficient ultrasound coupling and yields more constant tension and equal pressure distribution in ABUS. The gauze is transparent to the X-rays used

in tomosynthesis. A special air cushion attached to the housing of the X-ray detector can be inflated manually by the radiology technologist to push the peripheral parts of the breast homogenously towards the gauze.
After tomosynthesis, the breast remains compressed in the same position until the ABUS scan is complete. ABUS and tomosynthesis images are then transferred to a digital workstation where the corresponding coordinate systems are aligned so that the images from both modalities are linked and can be analyzed side by side.
ABUS acquisition in the current prototype differs from regular ABUS in that it covers an increased area of maximum 30 x 15.4 cm with a maximum penetration depth of 10 cm, resulting in 585 slices for one volume. In comparison, standard ABUS covers an area of 16.8 x 15.4 cm with a penetration depth of 6 cm and 318 slices.

IMAGE ANALYSIS

A physician with more than 10 years experience of ABUS evaluated the images using the syngo.breast ultrasound software from Siemens together with an additional software tool for side-by-side matching of ABUS and tomosynthesis slides (XUS Viewing Prototype, Siemens). The physician was blinded to the results of the standard diagnostic workup. The image quality of ABUS was rated subjectively on a scale ranging from 1 (quality below diagnostic usefulness) to 5 (quality equal to or greater than that of HHUS). Details of the image quality rankings are provided in reference 21.
All lesions detected were classified according to BI-RADS scores [18]. To quantify the breast coverage in ABUS and tomosynthesis the depicted breast area at the level of the nipple region was measured using Fiji ImageJ software in both techniques. The breast coverage of tomosynthesis was used as a reference standard for the coverage of ABUS.
Statistical analysis was performed using RStudio software. For the primary endpoint of cancer detection, we correlated malignant breast lesions identified in the standard diagnostic workup with those from the prototype ABUS/tomo combination and compared the localization, size and BI-RADS classification of the lesions.

RESULTS

152 patients were examined by tomosynthesis using the prototype. In 51 out of 152 cases, the ABUS scan could not be completed because of software glitches or hardware problems. No ABUS scan was cancelled for safety reasons or because of patient discomfort. The scan time of ABUS ranged between 40 and 60 seconds, depending on the breast volume. The total time to acquire the ABUS and tomosynthesis images ranged from 90 – 130 secs. The average time for the interpretation of both ABUS and tomosynthesis images was 277 ± 113 sec.

Coverage

The median breast area measured in tomosynthesis was 162.54 cm^2 and 123.37 cm^2 in ABUS so the median ABUS coverage was 80.0% of that of the tomosynthesis coverage.

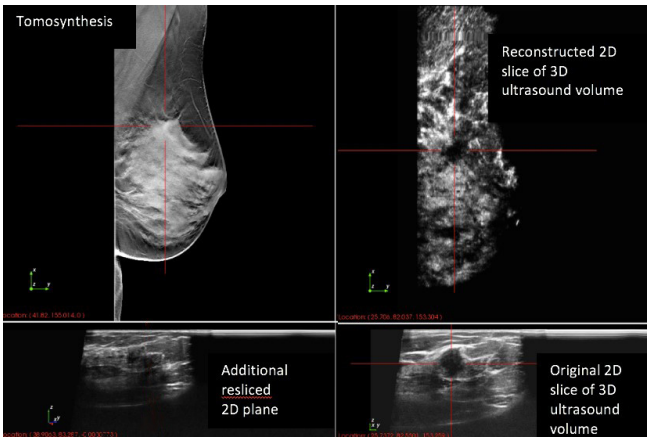

Figure 1. Mammographically and sonographically suspicious lesion in the correlated tomosynthesis and ABUS images. The patient had presented with a palpable lesion. In the standard diagnostic workup the lesion was highly suspicious at tomosynthesis and at hand-held ultrasound. Histology confirmed the diagnosis of invasive carcinoma (NST, ER+, PR-, Her2 neu-, G3, Ki-67 90%).

Image quality

In 86 out of 101 cases (85.1 %), the ABUS image quality was rated as diagnostically useful. In 18 out of 101 scans (17.8 %) the image quality was described as being close to that of HHUS, that is category 4 on the scale ranking the image quality.

Detection of breast lesions

From the data and images generated by the standard diagnostic workup of our patients, lesions in 48 out of 101 cases were classified as unclear or suspicious (BI-RADS 4 - 5) with a recommendation for histological analysis of a core biopsy. Histology confirmed 34 carcinomas.
Using the prototype ABUS and tomosynthesis images, 33 of these 34 carcinomas (97.1%) were identified and classified as suspicious (BI-RADS 4 or 5) or unclear, with a need for further diagnostic workup (BI-RADS 0). Of these 33 carcinomas, 26 (78.8%) were identified in tomosynthesis and ABUS [Figure 1], six (18.2%) were identified only in tomosynthesis and one carcinoma (3.0%) only in ABUS.
This lesion was described in ABUS as suspicious (BI-RADS 4) but was not visible in tomosynthesis (histology confirmed the diagnosis of an invasive lobular carcinoma).
In three cases, which were histologically confirmed as non-special type carcinoma (NST), ABUS gave a correct upgrading of the BI-RADS classification established at tomosynthesis: twice from BI-RADS 4b to BI-RADS 5 and once from BI-RADS 4a to BI-RADS 4b.
Retrospective evaluation of the seven carcinomas not detected in ABUS revealed that five (71.4%) were located outside of the area covered by the ABUS images.
Out of the total of 101 cases, 67 (66.3%) were classified as unsuspicious (BI-RADS 1-3) in the standard diagnostic workup.
Of these unsuspicious lesions, the BI-RADS classifications established by ABUS/tomosynthesis agreed with those established from the standard diagnostic workup in 42 cases. In six cases, lesions were classified as unclear in

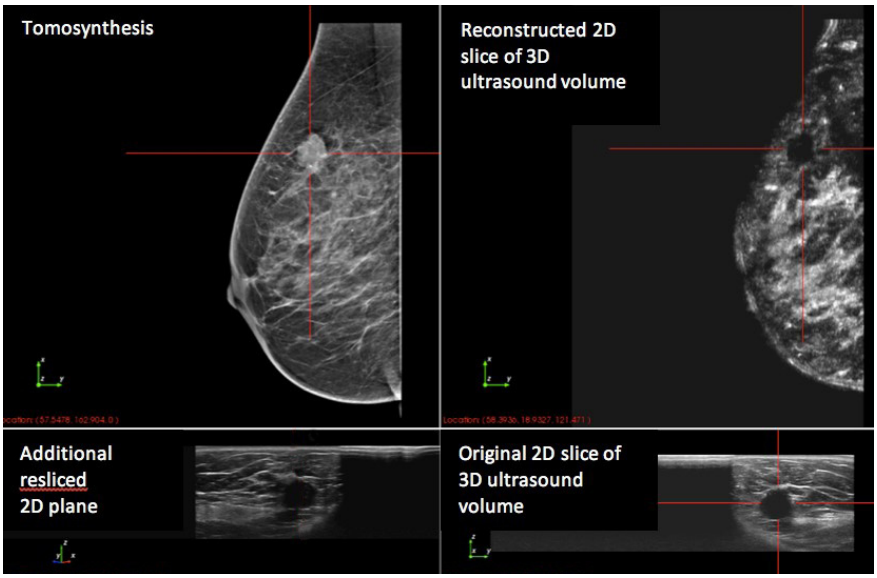

Figure 2. A case showing the additional benefit of ABUS. At tomosynthesis the lesion cannot be seen clearly, whereas in ABUS, the lesion is sonographically suspicious. Histology confirmed the diagnosis of invasive carcinoma (NST, ER+, PR+, Her2 neu-, G1, Ki-67 15%).

tomosynthesis (BI-RADS 0) but could be correctly downgraded through ABUS (BI-RADS 2).

Twelve cases were described as unclear or suspicious (BI-RADS 0 or 4) in the study-specific arm, but were unsuspicious (BI-RADS 1-3) in the standard diagnostic workup.

Qualitatively there seemed to be no apparent association between the breast density and cancers missed either by ABUS or by tomosynthesis, but the numbers were too low for meaningful statistical analysis.

A summary of the classification of lesions detected by the standard diagostic work-up versus the ABUS/tomosynthesis prototype is shown in Table 1.

Overall, the combined performance of tomosynthesis and ABUS led to a sensitivity of 97.1% (95% CI [91.4; 100]) and a specificity of 59.7% (95% CI [48.0; 71.4]) in the study- specific arm.

DISCUSSION

This is the first large prospective cohort study in a clinical setting of the use of a device combining ABUS and tomosynthesis. In the majority of cases the prototype instrument performed well and was reliable, although there were some technical difficulties that could be rectified on the spot. These technical problems were minor and do not invalidate the general principle of the clinical applicability of a hybrid ABUS/tomosynthesis device.

In 85.1% of the cases, the ABUS image quality was rated at category 3 or higher (i.e. diagnostically useful). Higher image quality could be achieved by adapting current high-end transducers to fit the requirements of the special prototype setup, especially as far as penetration depth and resolution are concerned.

It is important to note that the ABUS/tomosynthesis prototype is not intended to replace high-resolution HHUS as a tool for further investigation of unclear or suspicious lesions. Rather, it is intended to provide supplemental ABUS after tomosynthesis in a single procedure, with no breast decompression, in the large number of patients in screening programs who would otherwise not undergo any additional ultrasound examinations.

The increase of the area of breast coverage in the current prototype as compared to the previous model can be attributed to the positive effect of the air cushion, especially at the mammillary area. Of the breast area that is still not covered, a large part is due to a blind gap of approximately 1 cm located towards the pectoralis muscle that is caused by interference from the housing of the ABUS device. This shortcoming could be easily overcome by the use of a dedicated ultrasound transducer with optimized housing. This will be tested in future prototypes.

		FUSION-X-US-II prototype		
		Unclear/suspicious	Unsuspicious	Total
Standard diagnostic workup (goldstandard)	Malignant	33	1	34
	Benign	27	40	67
	Total	60	41	101

The values are absolute frequencies.

Table 1. Classification of lesions detected with the FUSION-X-US-II prototype compared with the standard diagnostic workup (gold standard)

The prototype ABUS/tomosynthesis device showed a high cancer detection rate (33 out of 34 carcinomas, 97.1%). One of these carcinomas was only seen in ABUS and not in tomosynthesis. In this case, the combined use of ABUS and tomosynthesis is a clear advantage over tomosynthesis alone [Figure 2]. Only one carcinoma was missed by the ABUS/tomosynthesis prototype. Due to its localization close to the thoracic wall, this particular lesion was only visible in HHUS in the standard diagnostic workup.

The use of the ABUS modality in the ABUS/tomoynthesis system led to a correct downgrading of BI-RADS classifications in ten cases, which had been erroneously described as suspicious or as unclear in tomosynthesis. On the other hand, the ABUS/tomosynthesis prototype decreased the diagnostic precision or formally led to a false upgrading of twelve cases as determined by the standard diagnostic procedure.

CLINICAL IMPLICATIONS

The results of our study show that a combination of ABUS and tomosynthesis using the FUSION-X-US-II prototype in a clinical setting is feasible and time-efficient. The procedure could be fully integrated into the clinical workflow, so it is applicable in practice. Since the examination is carried out by a radiology technologist, with the radiologist interpreting the images afterwards, there is a potential cost saving compared to current ultrasound procedures.

In the future, automatization and standardization of image acquisition are likely to be of increasing importance as image recognition algorithms are increasingly used to support clinical decision-making. In this context, the standardized and automated procedures of ABUS combined with tomosynthesis could provide an important basis for the development of such algorithms in the near future.

Hybrid devices like the current prototype could potentially allow a greater number of patients to receive supplemental ABUS after mammography/tomosynthesis. Previous studies have suggested that a widespread use of ABUS can lead to the detection of additional carcinomas [22], but further evidence of the precise ultimate clinical benefit still has to be established.

Again, it should be remembered that ABUS is a potential screening tool and not a substitute for the use of HHUS in a diagnostic situation. Therefore, any unclear or suspicious lesions will still need to be examined further with HHUS.

LIMITATIONS OF OUR STUDY

We tried to simulate as far as possible a real-life clinical workflow where the aim is to have as much information available and presented at the same time to enable a comprehensive diagnosis to be established. Thus we did not separate or blind the readings of the tomosynthesis and ABUS images. Only the reading of tomosynthesis images was truly independent, whereas the reading of ABUS could have been influenced by a recall bias.

Also, since the images in our study were evaluated by only one reader, we were not able to calculate inter-observer agreement, which is an important factor when considering the applicability of the technology to screening situations. This aspect should be analyzed in future studies.

The image quality was also only assessed subjectively by one examiner, whose impression of image quality could have been influenced by several factors, e.g. image resolution, presence of artefacts, coverage and personal experience.

Similarly, the assessment of the ABUS breast coverage is difficult, because there is no method to measure the three-dimensional extension of each breast. It was for this reason that the measurements of the tomosynthesis coverage were used as a reference standard for ABUS.

Take-home messages

- The FUSION-X-US-II prototype allows the combination of automated breast ultrasound and digital breast tomosynthesis in a single device without decompression of the breast.
- Image quality and breast coverage of ABUS are sufficient to accurately detect malignant breast lesions.
- If tomosynthesis and ABUS were to become part of breast cancer screening programs, the combination of both techniques in one device could offer practical and logistic advantages.
- Further studies are needed to evaluate the ultimate clinical benefit of a combination of ABUS and tomosynthesis in screening programs.

CONCLUSIONS

Overall, this study has shown that the combined performance of tomosynthesis and ABUS with the FUSION-X-US-II prototype can be successfully implemented in a clinical workflow. Malignant lesions were accurately detected. For a realistic clinical application, the ABUS coverage and image quality of the prototype should and can be improved. Further studies are needed to evaluate the ultimate clinical benefit of the approach in a screening program.

REFERENCES

1. Carney PA *et al.* Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography, Ann. Int Med. 2003; 138:168.
2. Buist DS *et al.* Factors contributing to mammography failure in women aged 40-49 years. J Nat Cancer Inst 2004; 96: 1432.
3. Berg WA *et al.* Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008; 299L 2151.
4. Ohuchi N *et al.* Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet 2016; 387: 341.
5. Berg WA & Vourtsis A., Screening Breast Ultrasound Using Handheld or Automated Technique in Women with Dense Breasts. J Breast Imaging 2019; 4: 283.
6. Giger ML *et al.* Automated Breast Ultrasound in Breast Cancer Screening of Women With Dense Breasts: Reader Study of Mammography-Negative and Mammography-Positive Cancers, AJR Am J Roentgenol 2016: 206:1341.
7. Halshtok-Neiman O. *et al.* Use of Automated Breast Volumetric Sonography as a Second-Look Tool for Findings in Breast Magnetic Resonance Imaging, Isr Med Assoc J 2015; 17: 410.
8. Golatta M *et al.* Interobserver reliability of automated breast volume scanner (ABVS) interpretation and agreement of ABVS findings with hand held breast ultrasound (HHUS), mammography and pathology results, Eur J Radiol 2013; 82 e332-6.
9. Golatta M *et al.* Evaluation of an automated breast 3D-ultrasound system by comparing it with hand-held ultrasound (HHUS) and mammography, Arch Gynecol Obstet 2015; 29: 889
10. Lin X. *et al.* The diagnostic performance of automated versus handheld breast ultrasound and mammography in symptomatic outpatient women: a multicenter, cross-sectional study in China. Eur Radiol. 2021; 3: 947.
11. Ciatto S. *et al.* Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study, Lancet Oncol. 2013; 14: 583.
12. Skaane P. *et al.* Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program, Radiology 2013; 267: 47.
13 Wojcinski S *et al.* Diagnostic performance and inter-observer concordance in lesion detection with the automated breast volume scanner (ABVS), BMC Med Imaging 2013;13: 36.
14. Dibble EH *et al.* Dense breast ultrasound screening after digital mammography vs after digital breast tomosynthesis, Amer. J Roentgenology 2019;213: 1397.
15. Kapur A *et al.* Combination of digital mammography with semi-automated 3D breast ultrasound, Technol Cancer Res Treat 2004; 3: 325.
16. Padilla F *et al.* Breast mass characterization using 3-dimensional automated ultrasound as an adjunct to digital breast tomosynthesis: a pilot study, J Ultrasound Med 2013; 32: 93.
17. Richter K *et al.* [Combination of mammography with automated ultrasound (Sono-X) in routine diagnosis?], Zentralbl Chir 1998; 123:37-41.
18. Sinha SP *et al.* Multi-modality 3D breast imaging with X-Ray tomosynthesis and automated ultrasound, Conf Proc IEEE Eng Med Biol Soc 2007; 2007: 1335.
19. Schaefgen B, *et al.* Initial results of the FUSION-X-US prototype combining 3D automated breast ultrasound and digital breast tomosynthesis, Eur Radiol 2018; 28: 2499.
20. Emons J *et al.* Initial clinical results with a fusion prototype for mammography and three-dimensional ultrasound with a standard mammography system and a standard ultrasound probe, Acta Radiol. 2018; 59:1406.
21. Schäfgen B et al Evaluation of the FUSION-X-US-II prototype to combine automated breast ultrasound and tomosynthesis. Eur Radiol. 2020 *doi: 10.1007/s00330-020-07573-3*
22. Kelly KM & Richwald GA. Automated whole-breast ultrasound: advancing the performance of breast cancer screening. Semin Ultrasound CT MR 2011; 32: 273/.

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