Ultrasound Tomography for Breast Cancer Screening

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ABSTRACT

Both mammography and standard ultrasound (US) rely upon subjective criteria within the breast imaging reporting and data system (BI-RADS) to provide more uniform interpretation of outcomes, as well as differentiation and risk stratification of associated abnormalities. We have been developing a new technique for breast imaging that is based on ultrasound tomography which has the potential to provide extended detection and/or diagnostic criteria. Informed consent was obtained from all patients, prospectively recruited in an IRB-approved protocol following HIPAA guidelines. Images were produced by tomographic algorithms for reflection, sound speed and stiffness, then reviewed by a board-certified radiologist. In the first phase of the study, UST images were compared to multi-modal imaging to determine the appearance of lesions and breast parenchyma. In the second phase of the study, correlative comparisons with MR breast imaging were used to establish basic operational capabilities of the UST system including the identification and characterization of parenchymal patterns. Our study demonstrated a high degree of correlation of breast tissue structures relative to fat subtracted contrast enhanced MRI. With a scan duration of ~1-3 minutes, no significant motion artifacts were observed. Initial clinical results suggest an ability to characterize masses. Experience with the SoftVue system indicates that rendering of parenchymal structures and masses is similar to MRI while providing unique metrics for lesion characterization.

Keywords: Times Roman, image area, acronyms, references

1. INTRODUCTION

In the USA, breast cancer is the most common cancer among women, accounting for 1/3 of cancers diagnosed. Statistically, ~230,000 new cases of invasive breast cancer and ~63,000 in situ breast carcinomas are diagnosed annually in the US; breast cancer is the third leading cause of cancer death among women, causing ~40,000 deaths in the US every year [1]. According to SEER statistics, approximately 61% of women are found to have localized breast cancers at the time of diagnosis; about 31% are found to be regional disease; another 5% are diagnosed with distant metastases while about 3% are unstaged [2]. The 5-year survival rate for women with localized cancer is 98%; for those with regional disease, it drops to 84%; for those diagnosed with distant stage, the survival rate drops dramatically to 23%; while for unstaged cancers the 5-year survival rate is about 58%. Figure 1 illustrates the dependence of survival on cancer stage.

Improved breast cancer detection would have the greatest effect on the statistic of nearly 1 in 3 women who are diagnosed each year with later stage (regional or greater) breast cancer, totaling approximately 60,000 women per year in the United States. The net effect would be an increase in survival time and a corresponding decrease in mortality rates. This is also suggested in a recent meta-analysis, whereby increased participation and sensitivity lead to additional invasive cancer detection and greater mortality reduction [3].

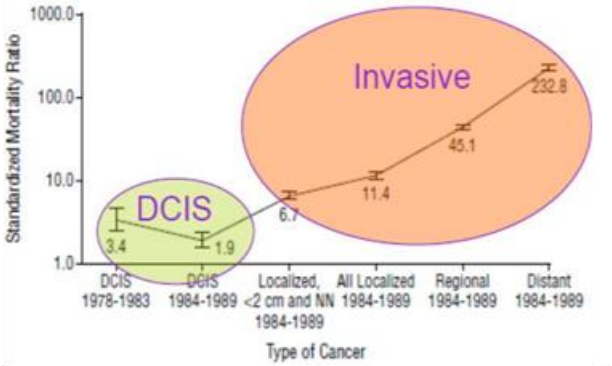
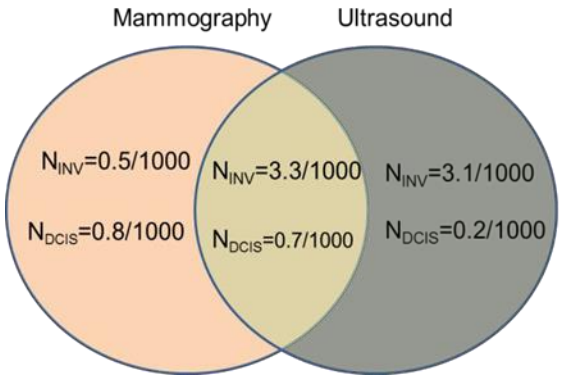


Figure 1. The dependence of mortality rates on cancer type and stage. From Kerlikowske et al, Arch Intern Med/Vol 160, April 10, 2000.

Limited performance of mammography. For women with dense breast tissue, who are at the highest risk for developing breast cancer [4-7], the performance of mammography is at its worst [8]. Consequently, many

cancers are missed at their earliest stages when they are the most treatable. Improved cancer detection for women with denser breasts would decrease the proportion of breast cancers diagnosed at later stages, which would significantly lower the mortality rate.

The Breast Screening Challenge. X-ray mammography detects about 5 cancers per 1000 screens [9]. However, its positive predictive value (PPV) is low and its sensitivity is greatly reduced in women with dense breast tissue [9]. Although digital breast tomosynthesis (DBT) may improve upon some of the limitations of standard mammography, it is unlikely to create a paradigm shift in performance [10] while generating potentially higher levels of ionizing radiation [11]. MRI can significantly improve on these limitations by its volumetric, radiation- free imaging. Studies have shown that MRI can have a positive impact in the breast management continuum ranging from risk assessment to diagnosis and treatment monitoring [11-22]. However, MRI can have a high false positive rate, requires contrast injection and the exams can be both long and costly [13]. Furthermore, MR has long been prohibitively expensive for routine use and there is a need for a low-cost equivalent alternative.



Recent studies have demonstrated the effectiveness of hand held ultrasound imaging in detecting breast cancer, particularly for women with dense breasts [23-33]. We have examined the data from these studies to extract the statistics of cancer detection by imaging mode. The results are summarized in Figure 2. It is striking to note that ultrasound (US) almost doubles the detection rate of invasive cancers in dense breasts. However, despite these successful study outcomes, handheld ultrasound is unlikely to be adopted for screening because it is operator- dependent, and its imaging aperture is small, which hinders whole breast imaging. Furthermore, ultrasound's increased sensitivity to invasive cancer is offset by lowered sensitivity to DCIS since mammography detects more microcalcifications [34]. Although such a trade-off may be justified by the fact that mortality from invasive cancers is much higher than that from DCIS, a combined screening (mammography plus US) would provide a comprehensive screen. It has therefore been proposed that US be used for screening, supplemental to mammography.

To that end, automated breast ultrasound (ABUS) has been introduced as a way of overcoming these issues, mainly by reducing operator dependence and increasing the field of view. For example, the GE Invenia ABUS ultrasound system for breast cancer screening, originally developed by U-Systems., recently received screening approval, adjunctive to mammography, from the FDA, because it demonstrated an ability to detect cancers missed by mammography in dense breasts. The SomoInsight screening study [23], indeed showed that ABUS plus mammography outperformed mammography alone, leading to the first FDA approval for ultrasound screening for breast cancer.

The fundamental quandary of breast screening today is the knowledge that (i) mammography misses cancers in dense breasts, (ii) that Automated Breast ultrasound (ABUS) detects cancers that mammography misses and yet (iii) screening continues largely with mammography only. This paradox is amplified even further by the proliferation of state breast density notification laws in the USA which mandate that this information be available to women undergoing breast cancer screening. The primary reason this paradox exists today is that ABUS screening increases call back rates (up to a factor of 2 in case of the SomoInsight study [22]). The improvement in classification performance, measured by the area under the ROC curve, is modest because the increase in sensitivity is partially offset by an increase in false positives thus slowing its adoption. Technically, with its basic B-mode capability, ABUS has the same issue with false positives as hand held ultrasound. It is therefore unlikely that ABUS will be widely adopted for screening in the foreseeable future without more tissue-specific imaging capability. Improved lesion characterization would help lower the barriers to adoption of screening ultrasound.

Ultrasound Tomography (UST) is an emerging technique that has the potential for quantitative, tissue specific imaging and characterization, by virtue of its transmission imaging capability [35-60]. Improved specificity would lower call back rates and lower barriers to adoption. An adjunctive use of UST would have the potential to improve specificity relative to current ABUS and provide a comprehensive screen that would uncover invasive cancers otherwise missed by mammography. Detection of such early stage invasive cancers would provide women with curative treatment, the opportunity for which might be otherwise lost.

2. METHODS AND MATERIALS

In an initial attempt to assess the potential of UST in breast imaging, studies were carried out at the Karmanos Cancer Institute, Detroit, MI, USA. Informed consent was obtained from all patients, prospectively recruited in an IRB-approved protocol following HIPAA guidelines. Patients were scanned at the Alexander J Walt Comprehensive Breast Center. Standard multi- modality imaging was available for all patients. The Walt Breast Center houses SoftVue, a UST system manufactured by Delphinus Medical Technologies, Inc (Novi, MI). SoftVue was used to scan the recruited patients for this study. Coronal image series were produced by tomographic algorithms for reflection, sound speed and stiffness. All images were reviewed by a board-certified radiologist with more than 20 years of experience in breast imaging and US-technology development. Symptomatic study participants were scanned with a SoftVue UST system. Pathological correlation was based on biopsy results and standard im- aging (e.g., US-definitive cyst). Tomographic algorithms were used to generate image stacks of reflectivity, sound speed and stiffness for each patient. Lesions were identified based on correlation with standard imaging so that the tumor sound speed (SS) and stiffness could be assessed.

In the first phase of the study, comparison with MR breast imaging was used to establish basic operational capabilities of the UST system including the identification and characterization of parenchymal patterns. The second phase of the study focused on lesion characterization using standard BIRADS criteria.

2.1 MR Concordance

UST and MR imaging were performed within weeks of each other. UST imaging was carried out with the SoftVue system (Delphinus Medical Technologies) and the MR exams with a Philips Achieva 3T system. As discussed above, UST images correlate best with MR images. Further inspection shows that of the three UST image types, the sound speed image correlates best with MR. Figure 3 shows a coronal view comparison between UST speed of sound and MR contrast enhanced fat subtracted images of representative parenchyma.

The parenchymal patterns are very similar with the only major difference relating to the shape of the breast. This difference can be explained by the fact that the SoftVue system utilizes water so that buoyancy foreshortens the breast while with MR, gravity lengthens the breast in the AP dimension (i.e. prone).

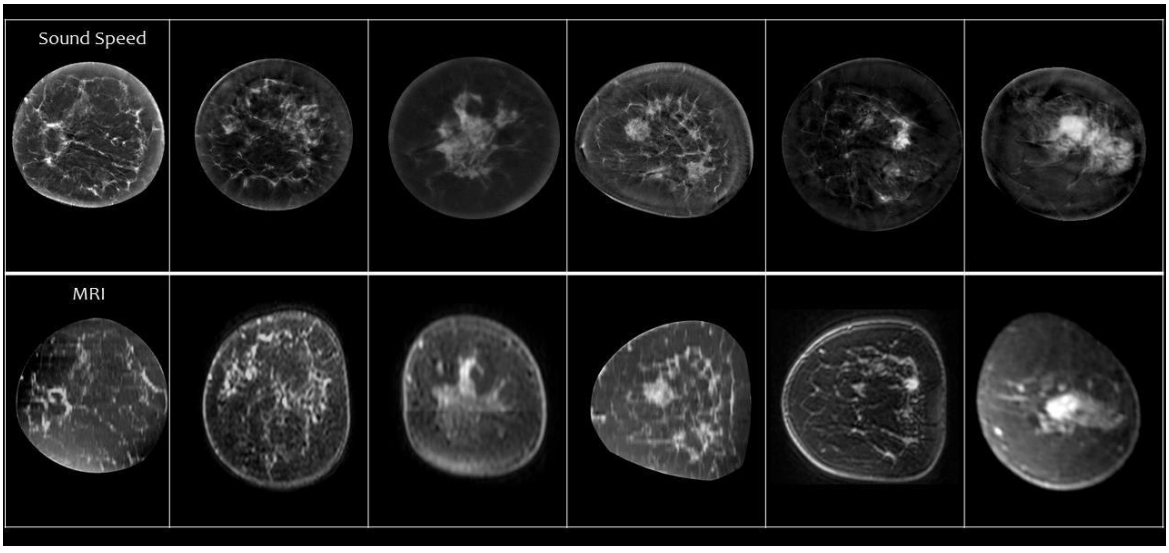


Figure 3. Top: Coronal UST sound speed images for 6 different patients. Bottom: Corresponding fat subtracted contrast enhanced MR images.

2.2 Mass characterization using BIRADS

Characterization of Cancer. Figures 4 and 5 show two examples of breast cancer. The left side of each image provides a coronal view of tumor location and extent of accompanying dense tissue. The right side shows a zoomed-in view of each tumor showing more detailed morphology. Visual inspection using

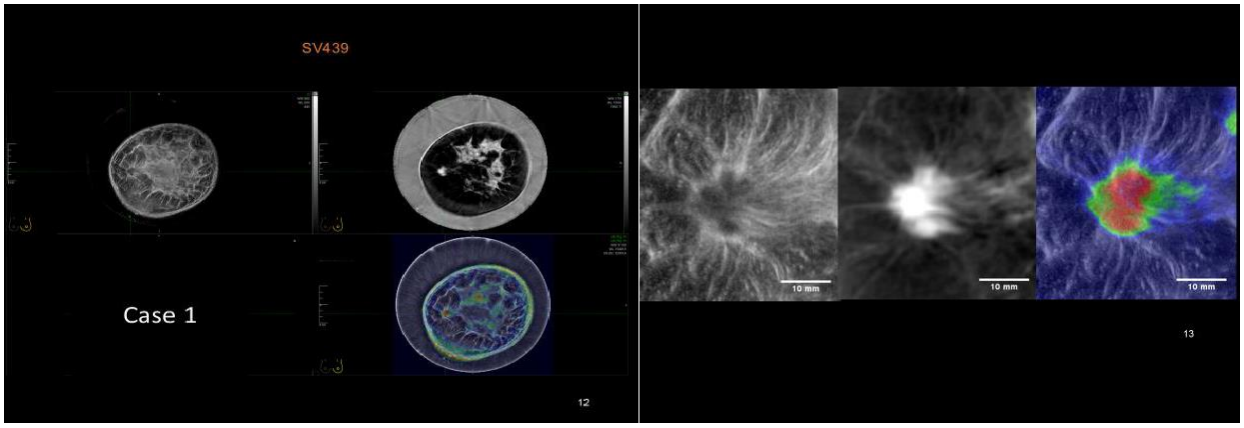


Figure 4. Left: A cancer at 9 o'clock. **Right**: Zoomed in views.

the standard BIRADS lexicon suggests that the cancers can be characterized as being irregular in shape in all three modalities, hypoechoic in reflection and spiculated in reflection and sound speed. Furthermore, the tumors have high sound speed and stiffness.

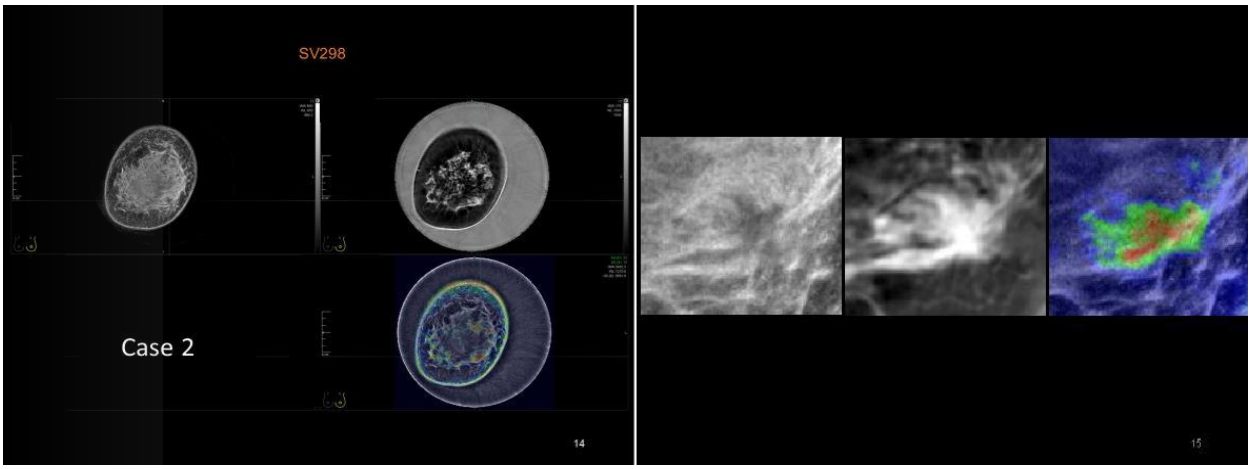
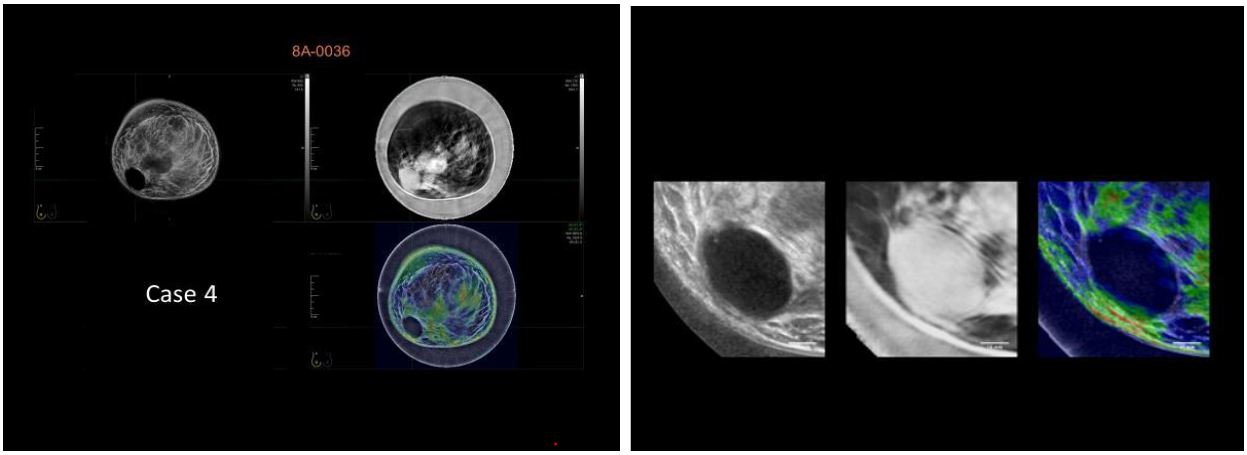


Figure 5. Left: A cancer at 4 o'clock. **Right**: Zoomed in views. .

Characterization of benign lesions. Figures 6, 7 and 8 show examples of benign masses. The left side of each image provides a coronal view of tumor location and extent of accompanying dense tissue. The right side shows a zoomed-in view of each mass for more detailed morphology. Visual inspection using the standard BIRADS lexicon suggests that cysts can be characterized as being well circumscribed in all three modalities and anechoic in reflection (Figure 10). Furthermore, the cysts have sound speeds similar to water and no stiffness signature. Fibroadenomas (FAs)are characterized as being well circumscribed in all three modalities and hypoechoic in reflection (Figure 6). Furthermore, FAs have sound speeds higher than that of water and have variable stiffness. Some FAs are stiff (Figure 7) and some are very soft (Figure 8).

US-BI-RADS criteria are predominantly devoted to assessment of tumor shape, margins and interaction with adjacent tissue [61,62]. However, criteria such as shadowing or enhanced through transmission are not applicable to UST's circular geometry. UST, operating at 3 MHz, appears more sensitive to specular reflectors of benign mass capsules, or the spiculations and/or architectural distortions of many cancers. Measurement of physical properties like sound speed are unique to UST [63-68]. Moreover, the whole-breast feature of localized tissue stiffness also opens the possibility of improved cancer detection for screening. These differences in characterization are being investigated as part of a predictive model to determine how much improvement in specificity over conventional ultrasound can be expected.



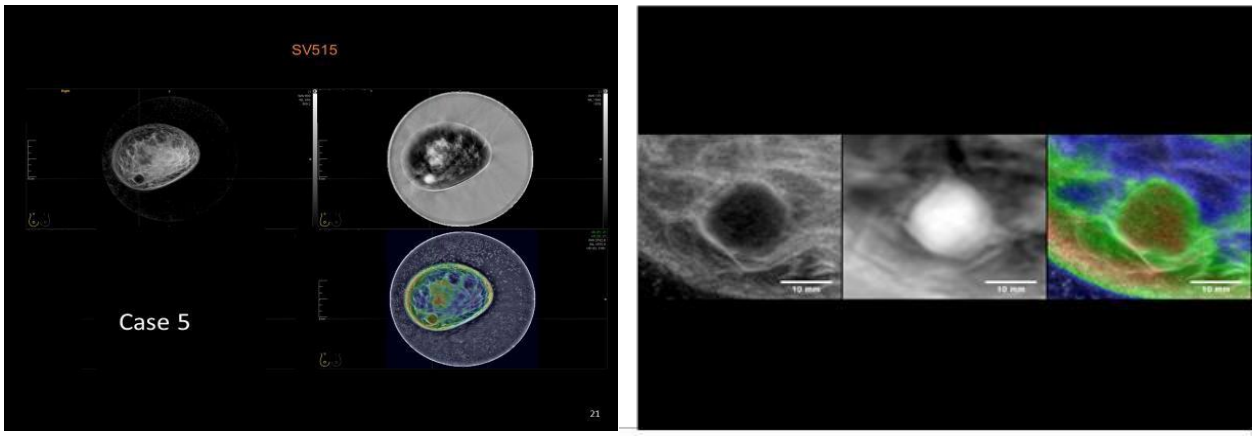


Figure 7. Left: A fibroadenoma at 7 o'clock. **Right**: Zoomed in views. .

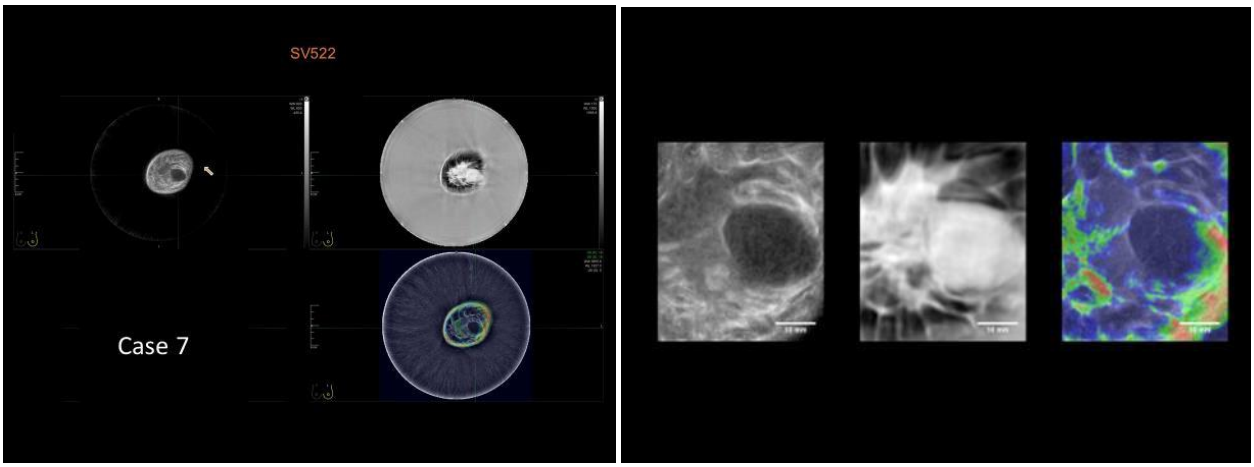


Figure 8. Left: A fibroadenoma at 3 o'clock. **Right**: Zoomed in view. .

3. CONCLUSIONS

In this study we reviewed the status of breast cancer screening and the potential role that ultrasound tomography (UST) could play in breast imaging. Several results from recent ongoing UST studies were used in this review. The main conclusions from those studies are:

(i) UST sound speed demonstrated a high degree of correlation of breast tissue structures relative to fat-subtracted, contrast enhanced MRI. This correlation of structures was most evident in coronal plane comparisons.

(ii) Initial clinical results suggest an ability to characterize lesions using Standard BI- RADS criteria of visual assessment of margins (in all 3 UST modalities), in combination with relative stiffness values. These parameters leverage all three imaging modes of UST (reflection, sound speed and stiffness).

UST is a promising new modality that has the potential to complement existing breast imaging methods to aid in lesion detection and characterization. Future larger scale studies will assess UST's role in diagnostic and screening settings.

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