Volumetric breast density evaluation by Ultrasound Tomography and Magnetic Resonance Imaging: A preliminary comparative study

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ABSTRACT

Since a 1976 study by Wolfe, high breast density has gained recognition as a factor strongly correlating with an increased incidence of breast cancer. These observations have led to mammographic density being designated a "risk factor" for breast cancer. Clinically, the exclusive reliance on mammography for breast density measurement has forestalled the inclusion of breast density into statistical risk models. This exclusion has in large part been due to the ionizing radiation associated with the method. Additionally, the use of mammography as valid tool for measuring a three dimensional characteristic (breast density) has been criticized for its *prima facie* incongruity. These shortfalls have prompted MRI studies of breast density as an alternative three-dimensional method of assessing breast density. Although, MRI is safe and can be used to measure volumetric density, its cost has prohibited its use in screening. Here, we report that sound speed measurements using a prototype ultrasound tomography device have potential for use as surrogates for breast density measurement. Accordingly, we report a strong positive linear correlation between volume-averaged sound speed of the breast and percent glandular tissue volume as assessed by MR.

I. INTRODUCTION

On a standard mammogram, the patterns of radiographic density are driven by the fibroglandular tissue content of the breast. Mammographic percent density (MPD) is a quantitative measure of the relative content of dense tissue[1]. Since a 1976 study by John Wolfe, high MPD has gained recognition as a factor strongly correlating with an increased incidence of breast cancer[2]. Subsequent studies have shown that women with high MPD have upwards of a six-fold higher incidence of breast cancer compared to women with fatty breasts[3-.5]. These observations have led to MPD to be considered as a strong "risk factor" for breast cancer. Because it is believed that the MPD is a reflection of actual dense breast tissue, general terms such as "breast density" have been used to describe the MPD although the relationship between MPD and physical density is not well defined.

Clinically, the exclusive reliance on mammography for such breast density measurement has forestalled the inclusion of breast density into statistical risk models. This exclusion has in large part been due to the limitations of the mammographic method. Although MPD is likely to bear some relationship with true breast density, this relationship has not been clearly elucidated. On this point, the use of mammography as valid tool for measuring a three dimensional characteristic (breast density) has been criticized for its *prima facie* incongruity, volumetric approaches being deemed more logical[1,6]. Finally, both intra- and interobserver variability have made it difficult to accurately stratify the population based on this parameter. And though computer aided segmentation has been more accurate, it has limitations[1,7] and has proven cumbersome and time consuming, thereby making larger studies impractical.

These shortfalls have prompted magnetic resonance (MR) and ultrasound tomography (UST) studies of breast density as alternative tri-dimensional methods of assessing breast density[8-10]. Computed Tomography (CT) and Tomosynthesis have also been considered appropriate for such an application[1], though it must be noted that neither CT nor tomosynthesis have been explored for their use in assessing density. Also, as X-ray based modalities, neither obviates the problem of radiation exposure. MRI has been considered suitable for breast density analysis because it is non-

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ionizing and it offers a volumetric assessment of the breast. Furthermore, MRI provides strong contrast between fibroglandular and fatty tissues which facilitates the segmentation process[8]. MR analysis of percent glandular tissue volume (PGTV) has been shown to be highly correlated with MPD, with groups reporting Pearson coefficients from 0.75 to 0.91 depending on the exact methodology[11,12] .

Although MRI is effective at measuring volumetric breast density, its high inherent cost is likely to be an obstacle to any future implementation for density screening. In the absence of an effective, practical measurement, it will be difficult to screen young women for this strong risk factor and to carry out studies that would lead to the development of effective chemopreventive strategies to reduce the incidence of breast cancer.

Motivated by these factors, our group has been developing a breast density measurement method based on the concept of ultrasound tomography (UST). We reported UST data showing a positive correlation between the volume-averaged sound speed (VASS) of the breast and MPD[10]. This previous work has suggested that sound speed can be used as a potential marker of breast density. In light of the fact that MRI and UST provide 3-D measures of density and that VASS and PGTV both correlate with MPD, we hypothesize that VASS estimates of the breast, derived from UST measurements, correlate strongly with PGTV estimates derived from MR analysis.

II. METHODS AND MATERIALS

IIA. In vivo dataset

Patient data were acquired from patients recruited into ongoing studies in accord with a Karmanos Cancer Institute (KCI) and Wayne State University approved research protocol. Recruited patients were set up for a UST breast exam in a manner markedly different from that of current methods. During a UST exam the patient lies prone on a canvas with the breast of interest hanging pendulously through a hole in the canvas where it is suspended in water. The latter acts as a coupling medium for the transducer. This positioning allows the ring transducer to begin data collection near the patient's chest wall.

Standard MRI breast exams were performed at KCI using a 3T Siemens Trio. The MRI imaging was supported by our MRI research facility and KCI's imaging core. MRI PGTV analysis was performed using pre-contrast T1-weighted images without fat saturation. The population selection criteria restricted our analysis to women for whom we possessed both UST reconstructions and breast MR sequences. There were 23 women satisfying these criteria. Three women were not included because of partial data corruption.

IIB. Magnetic resonance assessment of percent glandular tissue volume

MRI percent parenchyma analysis was performed in 20 patients using pre-contrast T1-weighted images without fat saturation as described in the literature[8]. Magnetic Resonance images were obtained axially and subsequently resliced in the coronal plane using ImageJ's built-in "reslice" function. Because UST analysis does not include the chest wall, we attempted to ensure the assessment of analogous sections of the breast by restricting our MRI analysis to the image slices between the chest wall (first slice) and the nipple (last slice). The first slice was delineated as the slice closest to the chest wall that did not merge with chest wall tissue (Figure 1). Additionally, the cutaneous layer of the breast was not included in our MRI analysis as it is not analogous to any component of our sound speed reconstructions and consistently increased the PGTV value. The dense tissue content of the breast was determined by applying an observer determined global threshold that included the majority of the glandular tissue (Figure 2). This global threshold analysis was performed by three independent observers to reduce the subjectivity associated with the method. The number of voxels above this threshold was then divided by the total number of voxels comprising the breast and multiplied by 100 for an MR PGTV value.

Though a global thresholding technique has its limitations, manual methods have been shown to be comparable to semi-automated methods such as fuzzy-means clustering[12]. The K-means routine was not performed on the pre-contrast T1 images because glare-artifacts in some of the images resulted in the routine classifying fatty tissue as glandular in some instances.

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IIC. Tomographic volume-averaged sound speed by ultrasound

Analysis of the UST sound speed reconstructions was performed in a stepwise manner. First, the water surrounding the breast was cropped out of the image using a semi-automated elliptical approximation of the breast region (Figure 3). Next, the mean sound speed of the breast for the entire image stack (chest wall to areolar region) was acquired using ImageJ's built-in "Histogram" function. In this case, the first slice was defined as the image obtained closest to the chest wall i.e. the image reconstructed from the first slice of the scan. The last slice was defined as the final slice in the areolar region with distinct boundaries (Figure 4). Because of the more limited out-of-plane resolution of the UST device, some peri-areolar slices were discarded for the confounding sound speed effect of water. Accordingly, the 'final slice'of our analysis was usually not the last image in which breast was visible.

III. RESULTS

Table 1 shows the VASS and PGTV values obtained with the methods described above. Table 1 also displays the inter-observer variation in PGVT determination from global threshold analysis. Among three independent observers we found that the standard error of the mean in PGVT was less than 2.5%. Notably, this is a considerably smaller inter-observer variation than that reported elsewhere[12]. The values listed in Table 1 were plotted against each other and a Pearson correlation was calculated. Figure 5 shows a strong positive linear correlation between Global sound speed (VASS) of the breast and MR PGTV (r=0.955). Our hypothesis that VASS and PGTV correlate linearly was established by our results.

IV. DISCUSSION

The rationale for establishing a volumetric, sonographic method for measuring breast density is multi-faceted. The most immediate benefit of such a modality would be the potential of improving the outcomes of breast cancer screening programs. Mammographic breast cancer screening has gained notoriety for its poor sensitivity in women with dense breasts. The improved sensitivity of MRI in breast cancer detection has been noted in the literature[13]. Still, this improvement is mitigated by the approximate 10-fold increase in the cost of breast MRI over that of mammography[14].

To bridge this gap, it has been suggested that women in a pre-specified high density category might be referred to a more sensitive screening modality such as MR. Though some have put forward mammographic density to fill this function[15], it appears to us that a non-ionizing, volumetric method such as the one here described would be preferred for such a role.

Although generally it is breast density that best correlates with breast cancer incidence, currently no information exists in using MRI to screen for cancer in women with dense breasts (16). Fiduciary considerations aside , our sonographic method is an advance over MR breast density measurements because 1) the speed of sound of a breast is a property based on actual mechanical properties of the breast and 2) provides an absolute quantity as a result i.e. is not a derivative quantity such as PGTV.

Additionally, such a method would allow for more robust interest in interventions aimed at stemming breast cancer incidence by reducing breast density. The efficacy of such prophylaxis could then be more readily and safely assessed by the UST method. Recently, studies have suggested that there is a relative decrease in breast density of women using Tamoxifen as well as soy and green tea consumers[16,17]. It is our future goal to assess patient response to such prophylaxis by means of the breast density surrogate. Such discrimination early in the course of treatment would help obviate futile interventions and spur the search for more effective measures.

These methods for breast density analysis have far reaching implications for both epidemiological and screening applications. Aside from the cost-effectiveness of such methods, we anticipate valuable research applications which may address the etiological import of breast density in cancer development. For instance, our method would provide the feasibility for assessing and further studying breast density in young women. The evaluation of mammographic density in young women is not practical due to the hazard associated with exposing young women to ionizing radiation. The UST method would circumvent this obstacle and allow for more thorough studies of breast density as an etiological

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factor in breast cancer development from an early age. Additionally, such three-dimensional surrogates could fulfill an important role in stratifying the population according to more strictly defined "risk" categories which would allow for more individually targeted breast cancer screening protocols.

The shortfalls of the UST method include its inability to fully access the axillary tail. A further setback of our study was the use of an operator-dependent threshold technique to assess the fibroglandular tissue content of the breast in our pre-contrast T1-weighted MR images. This approach was chosen over a clustering method because of the difficulties described in our Methods section. Future studies involving MRI measurements will utilize standard measurement methods such as those described by Boyd[9]. Another weakness of this study is the small number of patients in the study.

V. CONCLUSION

In summary, the VASS of the breast as derived from our UST sound speed reconstructions showed remarkable correlation with PGTV values derived by MR analysis. Here, we report for the first time a strong linear correlation between MR-derived PGTV and the VASS of the breast. The implication of such a strong correlation is that UST may be as effective as MRI in estimating breast density. Given the intrinsically low cost of ultrasound technology, there is potential for UST to bridge the gap between inexpensive MPD measurements and the potentially more accurate but expensive MRI methods. Future, larger studies will be aimed at substantiating these conclusions.

VI. ACKNOWLEDGMENTS

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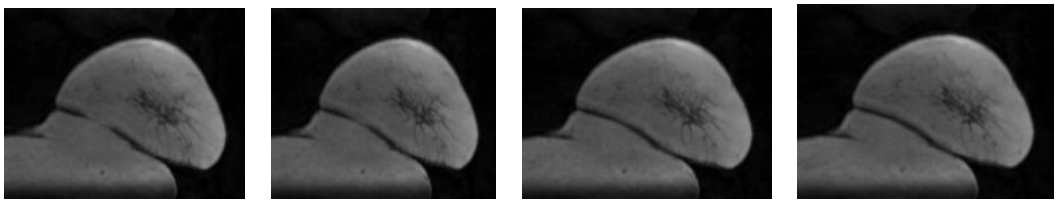
A. 

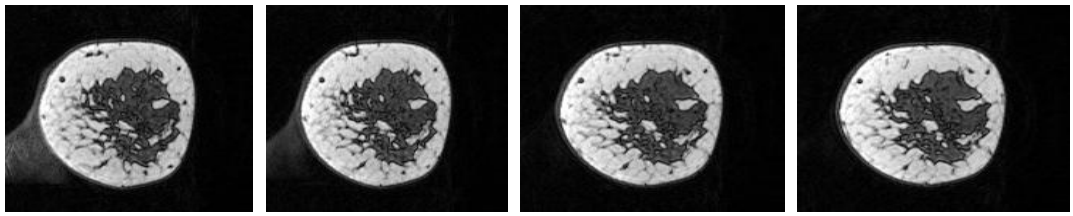
B. 

FIGURE 1. Example of methodology for determining "first slice." In panels (A) and (B) the third image in the series was considered the "first slice" based on clear delineation from surrounding tissue.

A. B.

FIGURE 2. Image (A) shows raw MR slice. Image (B) shows identical slice with observer applied threshold (yellow) defining glandular tissue

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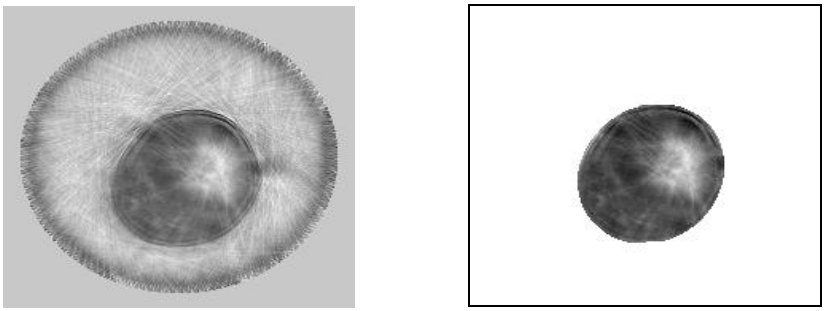

FIGURE 3. Image (A) shows raw sound speed slice. Image (B) shows identical slice with the ring and water regions cropped out by elliptical approximation of the breast borders.

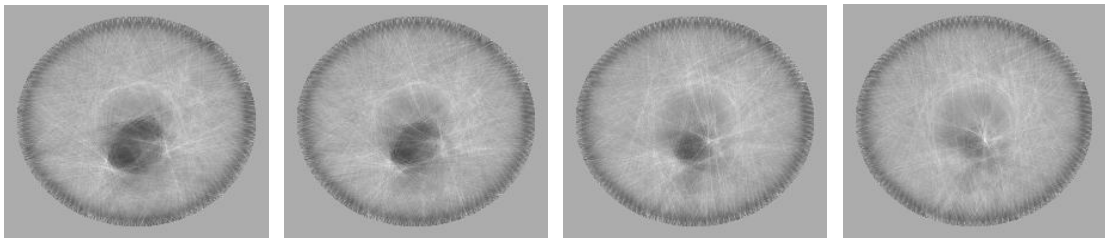

FIGURE 4. Example of methodology for determining "last slice" in the sound speed reconstruction sequences. In this panel the second image in the series was considered the "last slice" based on visibly distinct boundaries.

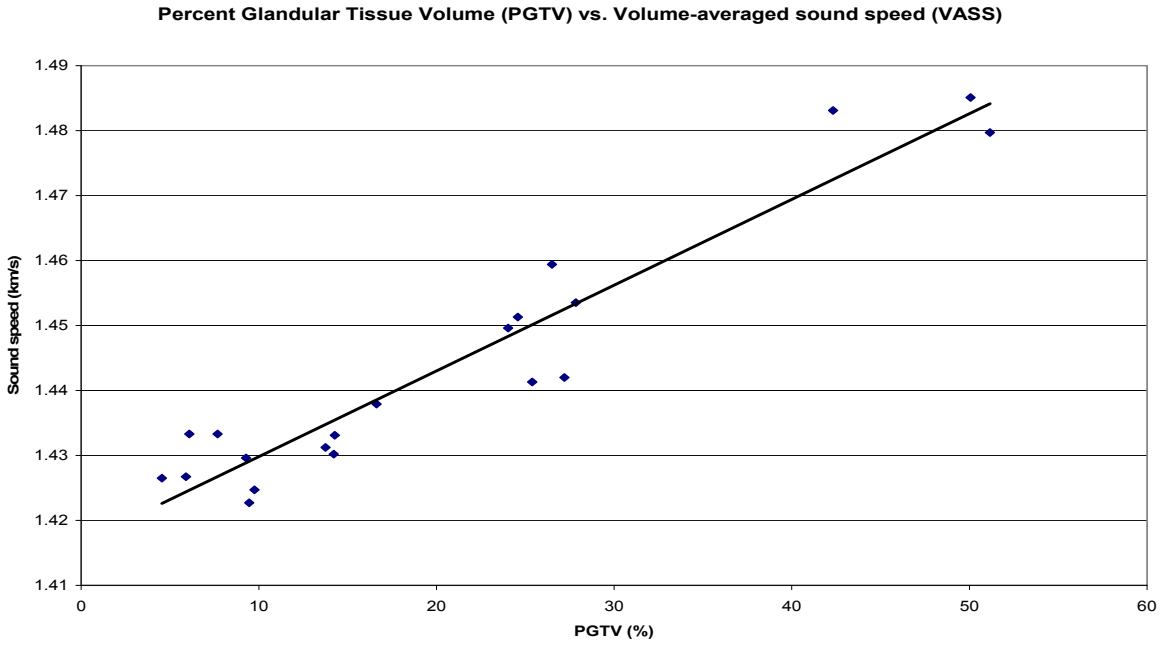

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FIGURE 5. Percent glandular tissue volume (PGTV) plotted against Volume-averaged Sound speed (VASS).

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TABLE 1. Inter-observer variation.

Patient	Obs. 1	Obs. 2	Obs. 3	Mean	Std. Dev.
147	7.685054	27.25053	23.36732	19.43430104	10.35874
152	24.03464	18.0158	16.75664	19.60236149	3.889757
160	42.32893	44.08581	48.78082	45.06518621	3.33558
161	14.28121	12.67651	13.81492	13.59087999	0.825478
172	6.085753	11.00121	11.00121	9.362722896	2.837939
177	9.278911	8.788214	10.38653	9.484551423	0.81876
180	14.22524	10.53599	14.49819	13.08647405	2.212998
182	24.58449	28.07418	28.60283	27.08716684	2.183441
191	9.463791	7.428433	7.683897	8.192040535	1.10875
198	25.385	32.65172	27.67242	28.56971273	3.715526
200	5.894736	14.32871	15.29731	11.84025117	5.171693
206	51.15792	53.26858	47.34584	50.59078076	3.001824
221	26.50753	28.62815	31.3175	28.8177275	2.410585
235	27.2075	22.80845	44.52479	31.51358094	11.4807
239	27.84754	40.78001	44.92001	37.8491845	8.905594
249	16.63209	18.84407	23.1926	19.55625606	3.337736
252	50.06725	43.12527	48.42008	47.20420028	3.627195
259	4.545759	7.575105	13.85833	8.659730604	4.750084
273	13.76085	19.80692	24.88806	19.48527754	5.570571
277	9.761767	14.36393	15.01472	13.04680628	2.863476
				Mean Std. Dev.	4.120321
				SEM	0.921332

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