Breast density measurements using ultrasound tomography for patients undergoing tamoxifen treatment

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ABSTRACT

Women with high breast density have an increased risk of developing breast cancer. Women treated with the selective estrogen receptor modulator tamoxifen for estrogen receptor positive breast cancer experience a 50% reduction in risk of contralateral breast cancer and overall reduction of similar magnitude has been identified among high-risk women receiving the drug for prevention. Tamoxifen has been shown to reduce mammographic density, and in the IBIS-1 chemoprevention trial, risk reduction and decline in density were significantly associated. Ultrasound tomography (UST) is an imaging modality that can create tomographic sound speed images of the breast. These sound speed images are useful because breast density is proportional to sound speed. The aim of this work is to examine the relationship between UST-measured breast density and the use of tamoxifen. So far, preliminary results for a small number of patients have been observed and are promising. Correlations between the UST-measured density and mammographic density are strong and positive, while relationships between UST density with some patient specific risk factors behave as expected. Initial results of UST examinations of tamoxifen treated patients show that approximately 45% of the patients have a decrease in density in the contralateral breast after only several months of treatment. The true effect of tamoxifen on UST-measured density cannot yet be fully determined until more data are collected. However, these promising results suggest that UST can be used to reliably assess quantitative changes in breast density over short intervals and therefore suggest that UST may enable rapid assessment of density changes associated with therapeutic and preventative interventions.

Keywords: Ultrasound tomography. Breast density. Tamoxifen

1. INTRODUCTION

Breast cancer is the most common type of cancer among women in North America, accounting for approximately 1 in 3 cancers diagnosed in US women. In the US in 2012, it is estimated that approximately 227,000 women were diagnosed with invasive breast cancer and that 40,000 women died from breast cancer [1]. Fortunately, breast cancer mortality has decreased secondary to improved treatment, increased early detection and potentially other factors. Early detection is accomplished primarily through screening mammography. Improved risk assessment could improve population-based screening and prevention strategies by identifying women at elevated risk who might benefit most from targeted treatment and prevention, while also identifying low-risk women who can be spared the costs, inconveniences and risks of excessive interventions. Thus, improving breast cancer risk assessment is an important public health goal. Toward that aim, several risk assessment models have begun to incorporate measures of breast density, which is known to confer up to a six-fold increase in breast cancer risk (dense vs. fatty breasts) [2-4].

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The current gold standard in the early detection of breast cancer is the use of mammography screening. Breast density can be measured from a mammogram by the calculation of a computer-generated value known as mammographic percent density (MPD). MPD reflects the ratio of the area of fibroglandular tissue to total breast area as measured on a mammogram. These areas can be calculated by using several different programs, including Cumulus, which is a semi-automated method [5]. MPD is related to breast tissue density, but the relationship is indirect because mammographic density corresponds to the X-ray attenuation characteristics of the breast. Also, the two-dimensional nature of mammographic images limits its ability to analyze three-dimensional anatomy and the degree of breast compression by mammography paddles may influence measurements.

Ultrasound tomography (UST) uses non-ionizing ultrasound waves to create three dimensional sound speed images of the breast anatomy without breast compression. The longitudinal sound speed of any material is given by:

$$v = \sqrt{\frac{C}{\rho}}$$

where C is the bulk modulus and ρ is the density of the material in question. Studies have shown that the bulk modulus of breast tissue scales with the cube of its density [6-8]. This suggests that for breast tissue, the velocity has a direct relationship with density. Therefore, the average density of the breast can be measured via UST by calculating the volume averaged sound speed (VASS), which is a quantitative measurement of breast density.

Tamoxifen is a selective estrogen receptor modulator (SERM) that has been shown to reduce the incidence of breast cancer in women who have had breast cancer by up to 50% [9, 10]. It is commonly used as a breast cancer preventative agent. Not only does tamoxifen reduce the risk of breast cancer, it also decreases breast density, particularly in premenopausal women. Several studies have shown that tamoxifen decreases breast density, measured either qualitatively or quantitatively on a mammogram, in up to approximately 50% of patients [9, 11-16]. The effects of tamoxifen on density have yet to be measured using UST sound speed measurements. Other studies have shown the relationship between UST density measurements and mammographic density measurements to be strong and promising [17]. Since UST uses non-ionizing radiation to create images, it can potentially be used to safely monitor and track changes in density over short time intervals, which may represent an attractive strategy for monitoring the effects of agents for which therapeutic or preventive effects might be linked to changes in density, such as tamoxifen.

2. METHODS AND MATERIALS

2.1 Patient Enrollment

The study protocol calls for an enrollment of 150 patients receiving tamoxifen. UST will be used to assess volumetric breast density within the first year of tamoxifen for patients with invasive or *in-situ* breast cancer and high-risk women receiving the drug for prevention. To assess whether tamoxifen-related declines in mammographic density found at 12 months can be identified earlier with UST, multiple repeat exams will be performed. An additional 150 women with negative mammographic screens who are not receiving tamoxifen will also be examined to ensure that the changes in UST density associated with tamoxifen use are greater than changes in density we might expect over time (i.e. aging). In order to assess whether early changes in density from tamoxifen are predictive of the changes at one year, the patients receiving tamoxifen will also undergo additional UST exams. These two additional exams will occur at approximately 1-3 months and 3-6 months post-tamoxifen initiation.

2.2 UST and Mammographic Density Measurements

Tomographic breast sound speed images were created using the UST system [18-23]. During these exams, the patient lies prone on a canvas with the breast of interest suspended pendulously through a hole in the canvas into the imaging tank. The tank is filled with water and contains an acoustic transducer ring of 256 elements that moves from the chest wall to the nipple region on a motorized gantry. Sound speed images are based on the arrival times of the acoustic signals as they travel through the patient anatomy. Patients were scanned at 1 mm intervals, which resulted in approximately 40-100 positions per patient. Sound speed tomograms were then reconstructed at each position to produce an image stack. Each image is composed of a matrix of values that stores the sound speed value of each pixel in km/s.

Analysis of the images was done with the public domain software package *ImageJ* [24]. The VASS of each patient's breast was measured by first removing the surrounding water bath from the image using a semi-automated elliptical approximation of the breast. Once this mask of the breast was created, the remaining pixel values were then averaged to produce the VASS.

The MPD of each patient was analyzed by one expert reader (NFB) using the CUMULUS 4 Software. The software uses a semi-automated algorithm where an observer manually selects the breast and a threshold between dense and fatty tissue. The software then measures the dense and total breast area which was used to calculate the percent density and non-dense areas.

2.3 Common Volume and Image Artifact

The whole volume of breast tissue that is imaged in each UST scan is highly dependent on the patient positioning during the scan. Therefore, when patients receive multiple scans, there is no guarantee the same volume will be imaged at each scan. A common volume was therefore determined for patients with multiple scans to track changes in roughly the same breast tissue. This volume was determined by choosing slices in the more detailed reflection images that contained similar landmarks and then using the sound speed images for those slices. Figure 1 shows an *exaggerated* example of the differences between the whole volume (WV) and common volume (CV) for a patient that has come in for multiple scans.

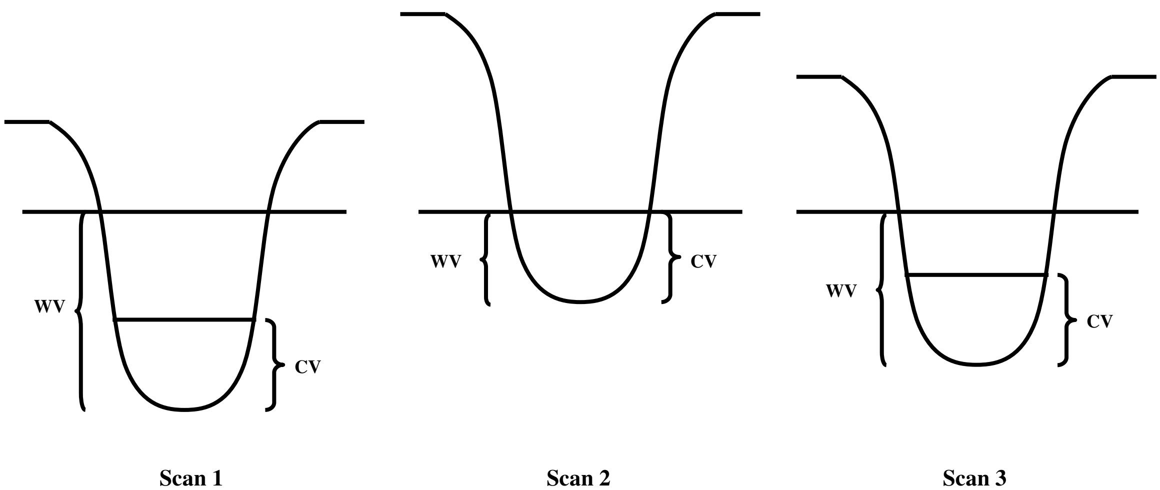

Figure 1 - An exaggerated example of a patient receiving three separate scans and the differences in calculating the whole volume (WV) and common volume (CV) between them.

Further complicating the measurement of the sound speed was an artifact that appeared in some sound speed images. This artifact presented itself as a dark ring or donut near the surface of the breast. When it is present, it appears in slices near the chest wall. This artifact is likely due to a slow moving surface wave that is measured by the transducers as the wave travels along the boundary of the chest wall and water bath. Since the wave is slow moving, it manifests itself as a dark region of low sound speed that does not correspond to any physical characteristic of the breast. Therefore, removal of this donut artifact is required to study only the breast anatomy. This creates the donut removed (DR) sound speed measurements, both for the whole volume (DRWV) and for the common volume (DRCV). Since the removal of this artifact leaves only the pixels that correspond to the breast, the DR sound speed measurements should more accurately reflect the density of the breast.

3. RESULTS AND DISCUSSION

3.1 Current Enrollment Summary

A total of 52 patients have been enrolled into the study so far. Of these 52 patients, 26 are case patients who will receive tamoxifen and 26 are untreated comparison subjects with negative screening mammograms. All 26 case patients have received their baseline scan. Of these 26 case patients, 20 of them have also received a second scan (1-3 month follow up) and 15 of these patients have also received a third scan (3-6 month follow up). The second scan was obtained an average of 51 days after tamoxifen initiation and the third scan was obtained an average of 143 days after starting treatment. After enrollment, one of the case patients decided to not begin taking tamoxifen after completing her baseline scan. All 26 comparison patients have only received their baseline scan. No patient has yet to receive their 12 month scan. These results are summarized below in Table 1.

Table 1 – Summary of Patient Scans

	# of Patients that Received the Scan				
Scan	**Case**	**Comparison**	**Total**	**Average Scan Time in Days (SD)**	**Earliest/Latest Time (Days)**
Baseline Scan	26	26	52	N/A	N/A
1-3 Month Scan	20	N/A	20	51 (16)	(33 – 97)
3-6 Month Scan	15	N/A	15	143 (34)	(85 – 193)
12 Month Scan	0	0	0	N/A	N/A

3.2 Baseline Density Measurements

For the majority of patients, a baseline UST scan and mammogram were obtained and analyzed (n = 46). Figure 2 shows the relationship between the UST VASS measurement and the MPD for each patient. A Spearman correlation coefficient of $r_s = 0.736$ (p-value < 0.001) was measured, which indicates a strong correlation between the two different density measurements. The relationship appears to be linear between the two modalities, which is likely due to the linear response of the digital X-ray detectors.

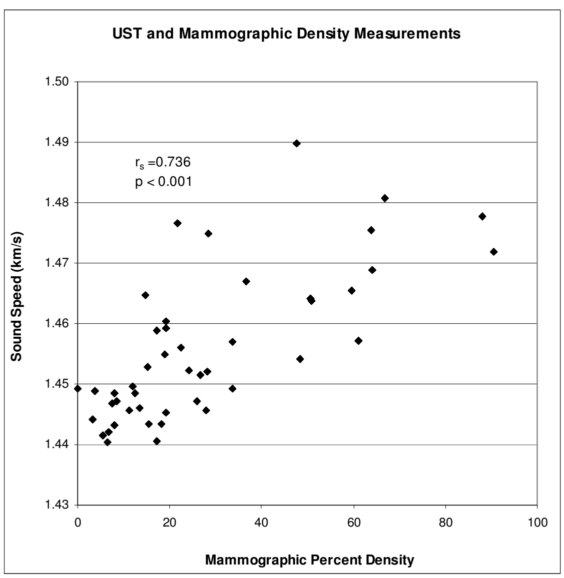

Figure 2 - Plot of baseline volume averaged sound speed versus mammographic percent density, n = 46.

Other patient information was also obtained, including factors such as age, measured weight, height and body mass index (BMI). Correlations involving these factors and both density measurements were assessed and the results are shown below in Table 2. The correlations that were measured behaved as they had previously been observed with mammographic density measurements [17, 25-32]. Here, density, as measured by both UST and MPD, was weakly and inversely correlated with age, weight and BMI.

Table 2 – Density Correlations with Patient Factors

	Spearman Correlation Coefficient (p-value)	
Patient Characteristic	**Correlation with VASS (n = 52)**	**Correlation with MPD (n = 46)**
Age (years)	-0.389 (0.004)	-0.312 (0.035)
Weight (lbs)	-0.287 (0.039)	-0.272 (0.067)
Height (inches)	0.060 (0.674)	0.114 (0.452)
BMI (kg/m^2)	-0.296 (0.033)	-0.308 (0.037)

BMI – body mass index; MPD – mammographic percent density; VASS – volume averaged sound speed

3.3 Effects of Tamoxifen over Time

Taking the averages of the different scans can give us an estimate of how much of an effect tamoxifen has on breast density. The first scan (baseline) is assumed to start at time t = 0 even if the scan took place well before tamoxifen treatment began. The average time of the second scan (1-3 months) was 51 days after treatment began and the average time of the third scan (3-6 months) was 143 days after treatment began. For the 20 patients with two scans, when using the whole volume sound speed (WVSS), the baseline average sound speed was 1.4514 km/s and the second scan average was 1.4507 km/s. The results for the remaining methods of sound speed calculation are shown below in Table 3 and plotted in Figure 3. A different method of viewing the change over time is to average the difference from the baseline scan for each patient. This essentially normalizes the changes such that the baseline scan for each different method of calculation gives a change of zero. This plot is also shown below in Figure 3.

Table 3 – Results for Patients with Two Scans (n = 20)

Measurement	**Baseline Average (km/s)**	**Second Scan Average (km/s)**	**Change (m/s)**
WVSS	1.4514	1.4507	-0.7
CVSS	1.4518	1.4509	-0.9
DRWVSS	1.4530	1.4518	-1.2
DRCVSS	1.4523	1.4513	-1.0

WVSS – whole volume sound speed; CVSS – common volume sound speed; DRWVSS – donut removed whole volume sound speed; DRCVSS – donut removed common volume sound speed

Of the 15 patients with three scans, when using the whole volume sound speed, the baseline average sound speed was 1.4510 km/s, the second scan average was 1.4508 km/s and the third scan average was 1.4509 km/s. Once again, this overall change was negligible and too small to indicate any overall trend as a result of tamoxifen treatment. These results, along with the results for the other methods of measurement are shown below in Table 4 and plotted in Figure 3. The difference from the baseline scan for each method was also plotted in Figure 3.

Table 4 – Results for Patients with Three Scans (n = 15)

Measurement	Baseline Average (km/s)	Second Scan Average (km/s)	Third Scan Average (km/s)	Change From Baseline(m/s)
WVSS	1.4510	1.4508	1.4509	-0.1
CVSS	1.4513	1.4511	1.4504	-0.9
DRWVSS	1.4524	1.4518	1.4516	-0.8
DRCVSS	1.4512	1.4511	1.4505	-0.7

WVSS – whole volume sound speed; CVSS – common volume sound speed; DRWVSS – donut removed whole volume sound speed; DRCVSS – donut removed common volume sound speed

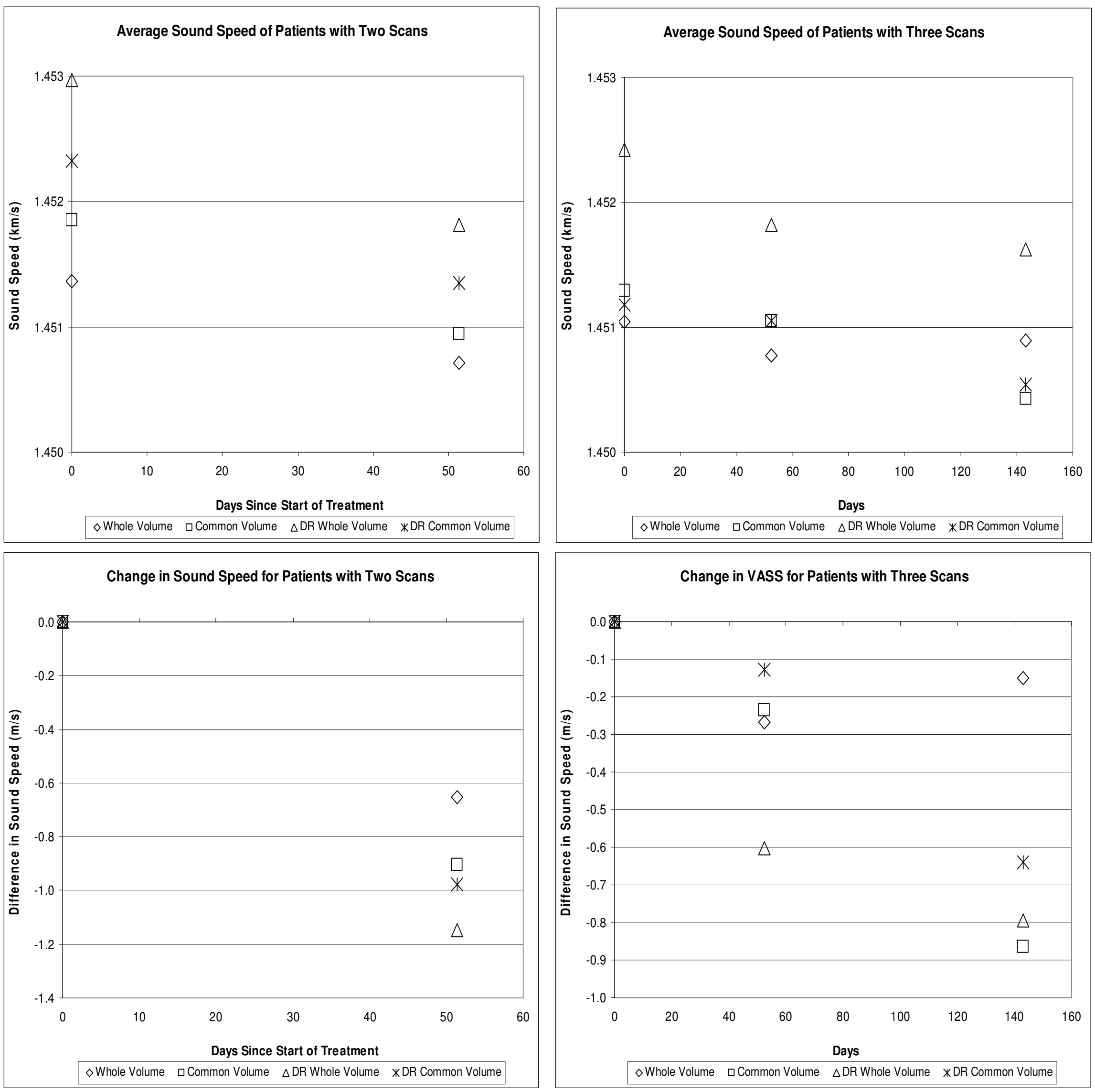

Figure 3 – Plots of the volume averaged sound speed (Top) and average change in sound speed (Bottom) for all patients with at least two scans (Left, n = 20) and three scans (Right, n = 15).

The changes in sound speed over this time frame are too small to draw firm conclusions, especially when compared to the uncertainty in the measurement of the average values. For the small number of patients used, the standard error of the average values calculated is on the scale of 3-4 m/s, so changes of less than 1 m/s may be lost in the noise. This uncertainty will decrease as more data are collected. Currently there is not any statistically significant trend that can be inferred from the overall average measurements of all the patients. However, among tamoxifen treated patients, approximately half appear to be density responders, so analysis of changes in density per patient may be more appropriate and provides the basis for further study.

3.4 Patients Responding to Treatment

The data plotted above show the average change in sound speed of all patients undergoing treatment with tamoxifen. The small overall change in sound speed across all patients may mask heterogeneity in responses because change in sound speed was averaged across patients whose density declined, remained unchanged or increased. To further examine the effects of tamoxifen on UST-measured breast density, the response of the patients was grouped into three categories:

1. Those that showed a decrease of more than 1 m/s (Decrease)
2. Those that showed an increase of more than 1 m/s (Increase)
3. Those that showed an increase or decrease of less than 1 m/s (No change)

Since the average change was greatest for the DRWVSS measurements, this metric was used to determine which patients fit into each category. Of the 20 patients that received two scans, 8 showed a decrease, 6 showed no change and 6 showed an increase in sound speed, while of the 15 that received three scans, 7 showed a decrease, 3 showed no change and 5 showed an increase in sound speed. Table 5 gives the results for the average sound speed of the patients that showed a decrease while Figure 4 plots the changes for the different methods used to calculate sound speed. When observing these patients, the changes in sound speed are much more apparent than when changes are averaged across the entire group. Also, the changes measured here are also greater than the uncertainties in the measurements, suggesting that the visible trends may be more statistically relevant.

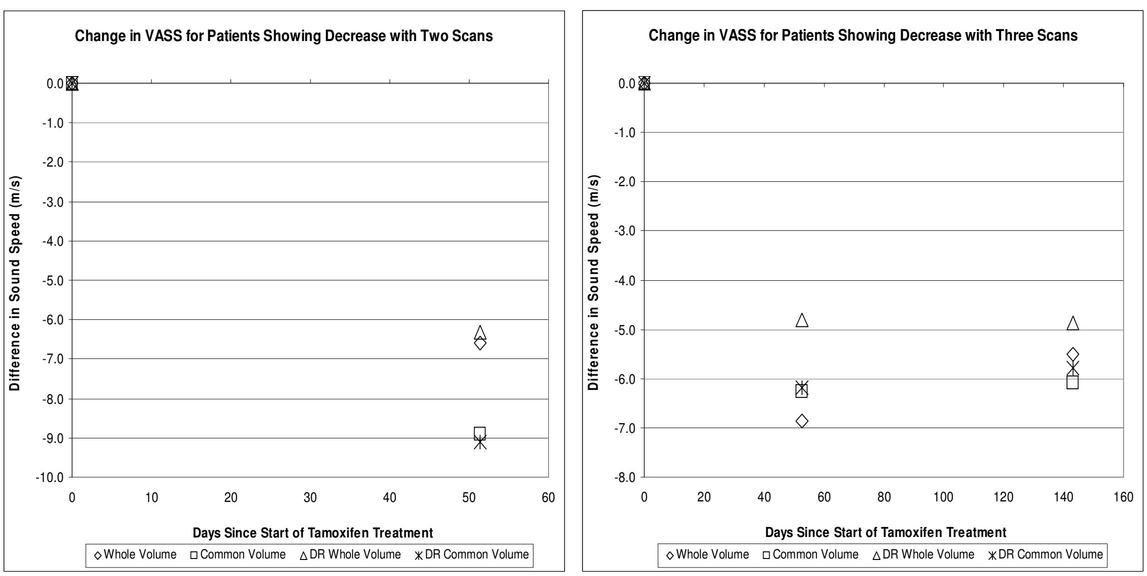

Figure 4 - Plots of the average change in sound speed measured using all separate measures of sound speed for patients that showed at least a 1 m/s decrease who had two UST scans (Left, n = 8) and three UST scans (Right, n = 7).

Table 5 - Average Sound Speed of Patients Showing a Decrease in Sound Speed

	Measurement	Baseline Average (km/s)	Second Scan Average (km/s)	Third Scan Average (km/s)	Change from Baseline(m/s)
Patients With Two Scans (n=8)	WVSS	1.4571	1.4505	N/A	-6.6
	CVSS	1.4569	1.4480	N/A	-8.9
	DRWVSS	1.4587	1.4524	N/A	-6.3
	DRCVSS	1.4581	1.4490	N/A	-9.1
Patients With Three Scans (n=7)	WVSS	1.4560	1.4491	1.4505	-5.5
	CVSS	1.4544	1.4482	1.4484	-6.0
	DRWVSS	1.4543	1.4494	1.4494	-4.9
	DRCVSS	1.4544	1.4482	1.4486	-5.8

WVSS – whole volume sound speed; CVSS – common volume sound speed; DRWVSS – donut removed whole volume sound speed; DRCVSS – donut removed common volume sound speed

To make the effects of the patients whose breast density decreased with tamoxifen treatment more evident, the average sound speed of each response group (i.e. those showing an increase, no change or decrease in sound speed) was plotted as a function of time. This plot is shown below in Figure 5 for patients with two and three scans. Once again, the DRWV measurements were used as they provided the greatest overall changes in sound speed and the removal of the artifact provided the most accurate measure of the breast's true sound speed.

From the preliminary data shown here, the change in sound speed that occurred after the second scan, approximately 50 days after treatment began, resulted in the largest visible change. The change was maintained after the third scan. These preliminary data do not permit definitive conclusions regarding whether serial UST examinations may enable rapid identification of women who will show discernible declines in mammographic density at 12 months and beyond. However, it appears that it may be possible to use UST to detect changes in breast density associated with tamoxifen treatment after only approximately 50 days of treatment, at least in some women.

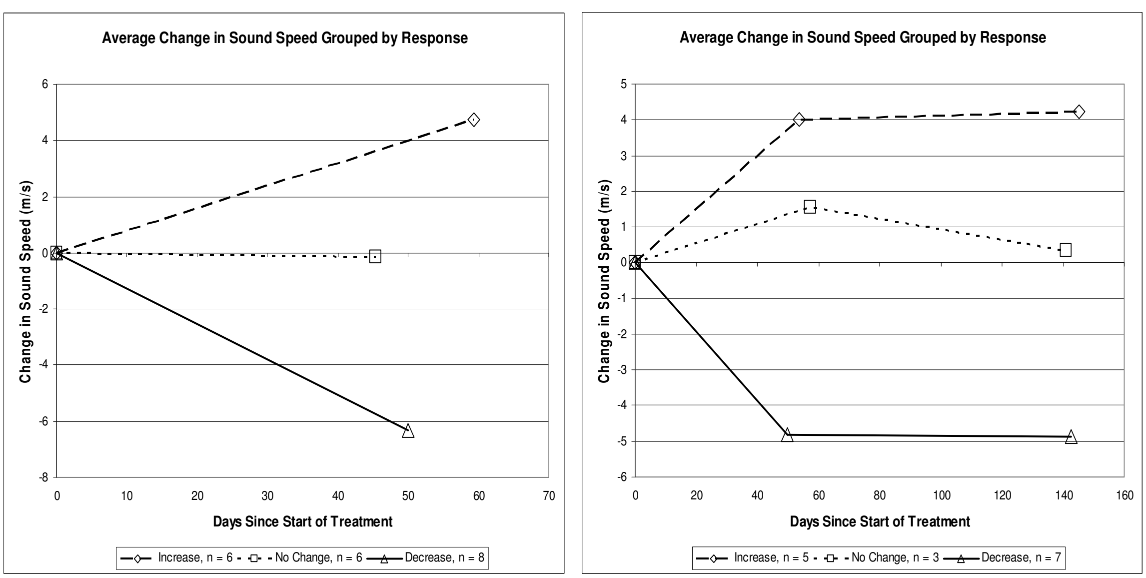

Figure 5 - The average change in sound speed grouped by response type for patients that received two scans (Left) and three scans (Right).

4. CONCLUSIONS

Ultrasound tomography was used to create sound speed images of the breast for women receiving tamoxifen. We analyzed the average sound speed in serial images using various methodologies to monitor the potential changes in breast density associated with tamoxifen treatment. Despite the preliminary nature of the data, the results that were obtained so far are promising. For the small number of women analyzed to date, 52 patients, relationships between both UST and mammographic breast density measurements with several patient characteristics behaved as expected. Sound speed correlated strongly and positively with MPD, while both density measures correlated negatively with age, weight and BMI. Decreases in sound speed have been detected in approximately 45% of the women undergoing tamoxifen treatment after only two months. However, the effect of tamoxifen on sound speed cannot yet be fully determined until the complete data set is collected. UST imaging shows promise as a safe and reliable method of serially measuring breast density changes over short periods of time.

5. ACKNOWLEDGMENTS

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