Ultrasound tomography imaging with waveform sound speed: Parenchymal changes in women undergoing tamoxifen therapy

Mark Sak[1], Neb Duric[1], Peter Littrup[1], Mark Sherman[2], Gretchen Gierach[3]

[1]Delphinus Medical Technologies, 45525 Grand River, Novi, MI, 48374

[2]Mayo Clinic, Jacksonville Florida, 32224

[3]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr. MSC 9774, Bethesda, Maryland 20892

ABSTRACT

Ultrasound tomography (UST) is an emerging modality that can offer quantitative measurements of breast density. Recent breakthroughs in UST image reconstruction involve the use of a waveform reconstruction as opposed to a ray-based reconstruction. The sound speed (SS) images that are created using the waveform reconstruction have a much higher image quality. These waveform images offer improved resolution and contrasts between regions of dense and fatty tissues. As part of a study that was designed to assess breast density changes using UST sound speed imaging among women undergoing tamoxifen therapy, UST waveform sound speed images were then reconstructed for a subset of participants. These initial results show that changes to the parenchymal tissue can more clearly be visualized when using the waveform sound speed images. Additional quantitative testing of the waveform images was also started to test the hypothesis that waveform sound speed images are a more robust measure of breast density than ray-based reconstructions. Further analysis is still needed to better understand how tamoxifen affects breast tissue.

1. INTRODUCTION

Mammographic breast density is a well-known breast cancer risk factor and it is established that women with higher breast density are at an increased risk of developing breast cancer relative to women with lower breast density[1-3]. Breast density has traditionally been measured using mammography, but more recently, ultrasound tomography (UST) sound speed images have also been shown to be an effective measure of breast density[4, 5]. UST has previously used a ray-based reconstruction method to produce sound speed images from which to make breast density measurements. However, recent improvements in UST imaging include the use of waveform reconstructions of sound speed images[6, 7]. These waveform images are of a much higher image quality than the ray-based reconstructions and offer better resolution of breast parenchyma (Figure 1).

UST is an emerging breast imaging modality that produces quantitative measures of breast density. It uses sound waves to produce three-dimensional images of breast tissue using the transmission and reflection properties of breast anatomy. The tissue sound speed is a useful property that can be used for breast density measurements. 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[8-10]. This therefore suggests that for breast tissue, the measured tissue sound speed has a direct relationship with the tissue density.

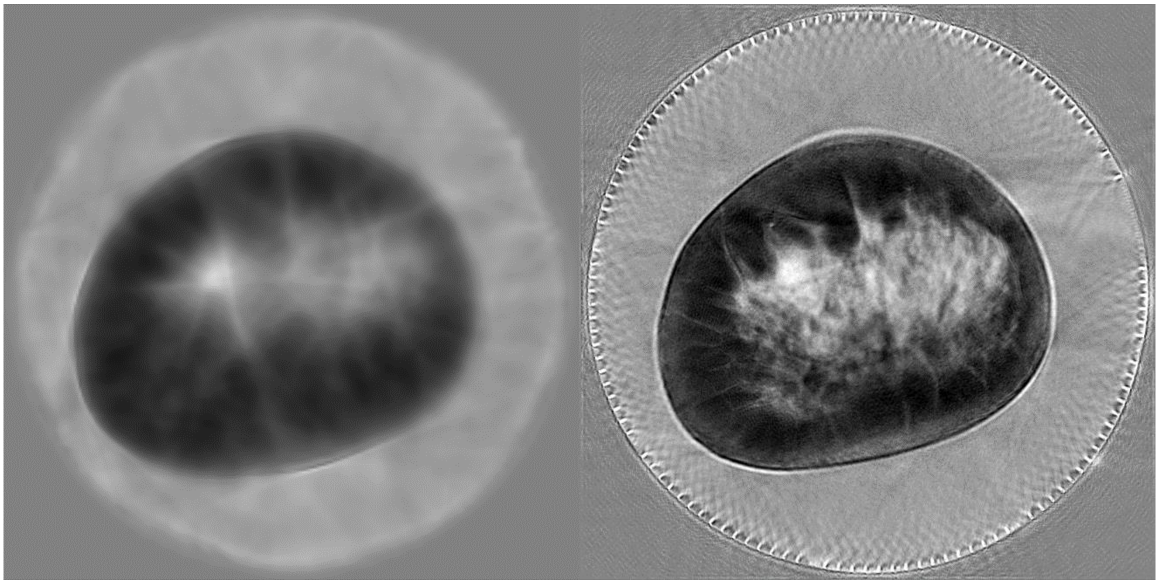

Figure 1 – (Left) An example of the ray-based sound speed image. (Right) An example of the same slice reconstructed using the waveform reconstruction. The detail and increases in the texture of the parenchymal patterns are much more apparent for the waveform images.

Tamoxifen is a selective estrogen receptor modulator (SERM) that has been shown to be effective in both the chemopreventive and adjuvant settings for reducing breast cancer incidence and mortality[11]. 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[12].

The higher resolution waveform UST images present a new way to measure the distribution of dense and non-dense breast tissue. This means that waveform images may be better used to both qualitatively and quantitatively track changes in the parenchymal patterns than the ray-based images. This work will use the waveform sound speed images to qualitatively observe changes in the parenchymal patterns for a subset of women undergoing therapy with tamoxifen. The qualitative results will be paired with additional quantitative measures of breast density that can be easily extracted from the sound speed images.

2. METHODS AND MATERIALS

2.1 Patient Enrollment

As part of a larger study[13] that was designed to assess breast density changes using UST sound speed imaging among women undergoing therapy with tamoxifen for clinical indications, UST scans and mammograms were taken over a period of 12 months for approximately 70 women. For women diagnosed with breast cancer, UST scans were taken of the breast contralateral to the diagnosis. UST scanning was repeated up to 4 times during the 12 month period, with a baseline scan before the initiation of tamoxifen along with follow up scans at 1-3 months, 4-6 months and 12 months post-tamoxifen initiation.

2.2 Waveform Image Creation

The initial UST scans for these women were reconstructed using the ray-based sound speed images. Waveform reconstruction is a much more computationally intensive procedure and requires the use of the saved raw data. To compare the waveform reconstructions with the ray-based reconstructions, 22 women had their baseline scan reconstructed using waveform tomography. The quantitative results for these scans were compared to the ray-based results. In addition, 4 full sets of scans were analyzed both quantitatively and qualitatively. The scans were chosen to represent the full range of the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) breast density categories of almost entirely fatty, scattered fibroglandular densities, heterogeneously dense and extremely dense[14]. The breast density category was determined from the mammography report where it was recorded as part of the mammographic exam.

2.3 Density Measurements

Quantitative sound speed measurements for the waveform images were made in a similar manner to sound speed measurements made for ray based images. For each slice that contained breast tissue, the background water bath was manually segmented from the image, leaving behind only the breast tissue. Descriptive statistics were then calculated on the remaining voxels, including measures such as the mean value and standard deviation. This method of masking sound speed images to produce quantitative measurements has shown to be reliable between different users and repeatable[15].

In addition, using *ImageJ*, a k-means clustering algorithm was then applied to the masked waveform and ray sound speed images. The algorithm separated the image into two regions, one that corresponded to the dense tissue and one that corresponded to the non-dense tissue. Additional quantitative measures for these segmented subregions were then calculated. These measures included the mean sound speed of each subregion, the difference in the sound speed of the dense and non-dense subregions along with the volume of each subregion. Using the volume measurements, the percent volume density (USTPD) could be calculated by dividing the dense volume by the total volume. The same quantitative measurements were applied to both the waveform and ray UST images in order to directly compare the behavior of the two different reconstruction algorithms. Ray based measurements were made previously so any waveform image analysis was performed on the same slices.

Additonally, baseline mammograms were analyzed using CUMULUS[16] to determine the mammographic percent density (MPD), along with the relative amount of dense and non-dense mammographic areas visible.

3. RESULTS AND DISCUSSION

3.1 Comparison of Waveform and Ray-Based Quantitative Measurements

For the 22 participants that were analyzed, the quantitative measurements made using waveform imaging were compared to the quantitative measurements made using the ray based imaging. Only the baseline image was used in this comparison. The averaged results for several of the quantitative measures are shown below in Table 1. The listed p-value is from a paired t-test. Also, Spearman correlations were performed between the two different reconstruction methods.

Most of the quantitative measures show strong correlations between the ray and waveform reconstructions. However, comparing the mean values shows some differences between the reconstruction methods. The ray reconstructions create sound speed images with a slightly larger total volume than the waveform. When segmented, the dense volumes are the similar but the fatty tissue volume is larger in the ray reconstructions. Visual comparison of the ray and waveform images show that because of the higher resolution, the boundary between the breast tissue and the water bath is more clearly defined for the waveform images (Figure 2). This slight difference in the boundary definition accounts for the small but consistent increase in total volume and the fatty volume. In addition, there was much greater heterogeneity in depiction of dense tissue as noted by the significantly greater standard deviation for the waveform images relative to the ray-based images.

Table 1 – Quantitative Comparison of Waveform and Ray Reconstruction Methods (n=22)

UST Sound Speed Measure	**Waveform Mean Value**	**Ray Mean Value**	**t-test p-value**	**Spearman Coefficient**	**Spearman p-value**
Mean Sound Speed (m/s)	1456.5	1458.8	0.004	0.985	<0.001
Standard Deviation (m/s)	28.9	21.9	< 0.001	0.687	<0.001
Total Volume (cm^3)	610.7	661.4	< 0.001	0.995	<0.001
Dense Volume (cm^3)	171.7	176.9	0.709	0.837	<0.001
Fatty Volume (cm^3)	439.1	484.5	0.027	0.988	<0.001
USTPD (%)	31.9	32.9	0.697	0.782	<0.001
Mean Dense Sound Speed (m/s)	1490.4	1486.0	0.152	0.815	<0.001
Mean Fatty Sound Speed (m/s)	1439.5	1445.8	< 0.001	0.928	<0.001
Mean Sound Speed Subregion Difference (m/s)	51.0	40.2	0.003	0.309	0.1619

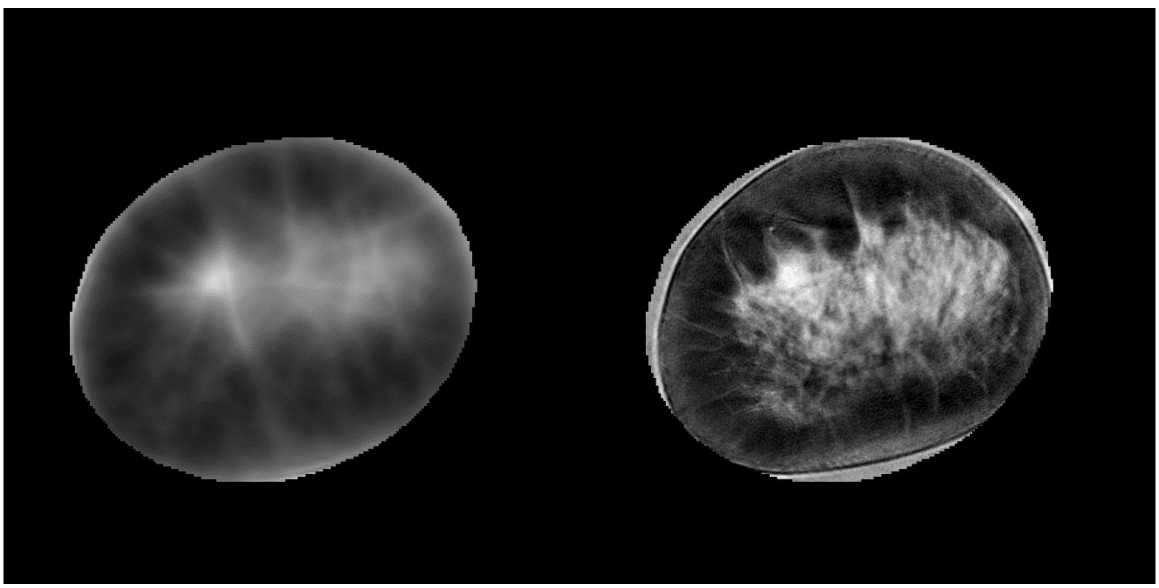

Figure 2 – To show the slight differences in the reconstruction of the breast/water bath boundaries, the mask for the ray image on the left was applied to the same waveform slice on the right. The ray mask is slightly larger than the waveform image due to the higher resolution of the waveform reconstruction more clearly defining the boundary of the breast tissue. The anatomic texture of the parenchymal patterns is also greater in the in waveform images. When the quantitative analysis was performed, the waveform images were therefore masked separately from the ray images.

The higher resolution waveform images also likely account for the differences in the mean sound speed values. The waveform images are able to more clearly separate dense tissue from fatty tissue which results in less volume averaging than in the ray images. In the ray images, the lower resolution causes the dense regions to blend into the fatty regions. This could explain why the difference in subregion mean sound speed is greater in waveform images compared to the ray images.

3.2 Qualitative And Quantitative Analysis of Changes in Parenchymal Patterns Over Time

The changes in the parenchymal patterns over the course of a year were examined on a qualitative and quantitative level for select cases. The same quantitative waveform UST values of mean sound speed, along with the subregion characteristics were calculated for each case using a common volume among all four scans. This ensured that the same volume was quantitatively analyzed for changes. Visual inspection was also performed to identify similar regions of tissue at each scan. Also, mammograms spaced approximately a year apart were also analyzed for density measurements for a comparison. A fatty, scattered, heterogeneous and dense breast were selected to highlight the ability of waveform imaging to track changes in parenchymal tissue. The breast density was determined by the BIRADS density score given to the breast in the mammography report by the radiologist.

3.2.1 Analysis of an Almost Entirely Fatty Breast (BI-RADS Density Category A)

The quantitative UST and mammographic breast density measures are shown below in Table 2 for the fatty breast. Waveform UST sound speed images of the same anatomy for each scan are shown in Figure 3 to directly show the changes in the parenchymal patterns. The quantitative mammographic measures indicate there is little change in density and that the mammographic percent density and dense breast area remain very low. The UST measures also show low mean sound speed but do indicate a small decrease in the mean sound speed at the 12 month follow up. The USTPD shows an initial decrease but rises at the 12 month mark. It appears that the decrease in the mean sound speed at 12 months is mostly driven by the decrease in the mean sound speed of the dense tissue.

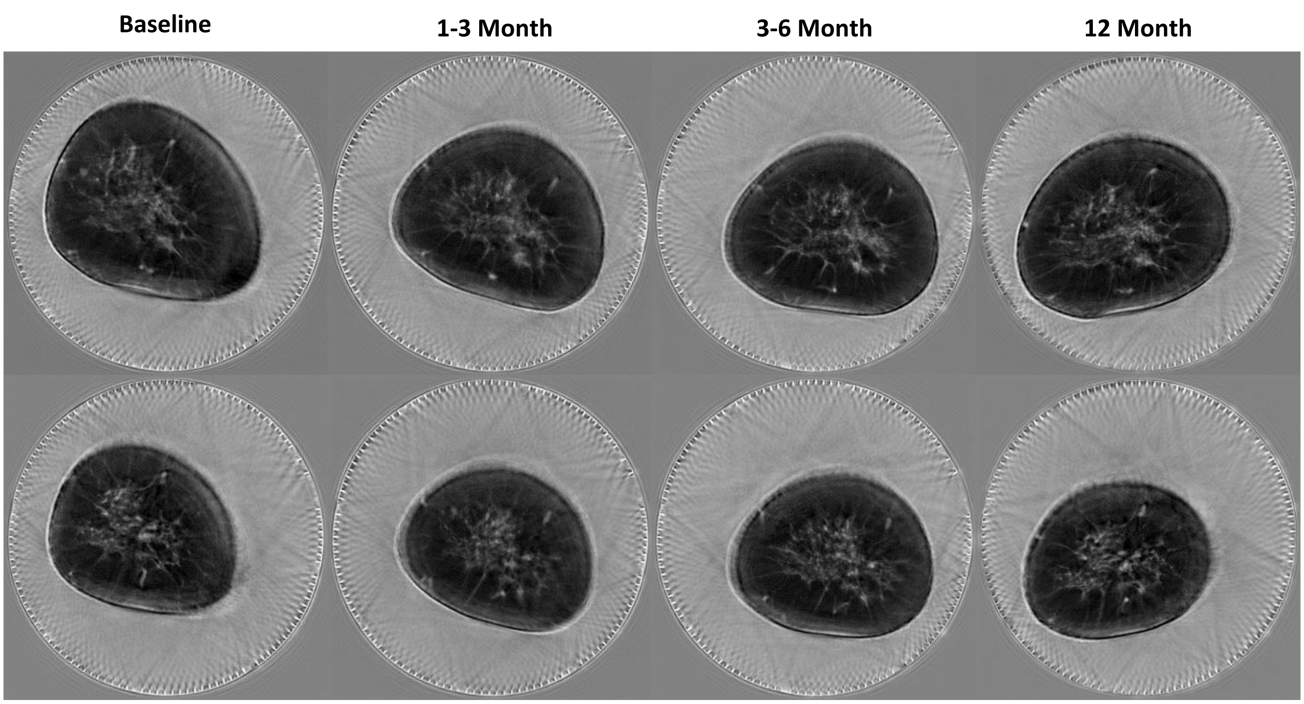

Figure 3 – UST sound speed images for a fatty breast. Each row shows a slice from each of the four scans that roughly represent the same anatomy. The far left images are the baseline, followed by the 1-3 month follow up, then the 3-6 month follow up with the far right images being from the 12 month follow up scan. The top row of images represents anatomy closer to the chest wall while the bottom row represents anatomy closer to the middle of the breast. The breasts are mostly fat so finding similar landmarks of dense regions was compensated for by approximating the underlying anatomy of fibrous bands.

Viewing Figure 3 it is apparent that the breast is mostly fatty tissue. There are few extended regions of dense tissue and most of the dense regions tend to be thinner strands of parenchymal tissue along with some prominent blood vessels. While the patient positioning between scans is variable, it is still possible to align anatomy within the breast from scan to scan. The internal anatomy does shift slightly, but similar structures can be seen. However, without the additional quantitative information obtained from UST imaging, a visual inspection would very likely be insufficient to determine whether or not any apparent change in breast density occurred.

Table 2 – Quantitative UST and Mammographic Density Measures for a Fatty Breast

UST Sound Speed Measures	**Baseline Scan**	**1-3 Month Follow Up**	**3-6 Month Follow Up**	**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-2	88	189	382
Mean Sound Speed (m/s)	1442.1	1443.1	1441.0	1439.8
Standard Deviation (m/s)	22.8	21.6	21.3	20.8
Total Volume (cm^3)	669.3	681.5	685.9	700.9
Dense Volume (cm^3)	140.6	120.5	122.6	176.0
Fatty Volume (cm^3)	528.7	561.0	563.3	524.9
USTPD (%)	21.0	17.7	17.9	25.1
Mean Dense Sound Speed (m/s)	1476.6	1478.9	1476.5	1467.2
Mean Fatty Sound Speed (m/s)	1433.0	1435.4	1433.2	1430.7
Mean Sound Speed Subregion Difference (m/s)	43.6	43.5	43.3	36.5
Mammographic Density Measures	**Baseline Scan**			**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-101			404
Mammographic Percent Density (%)	2.8	**N/A**		3.8
Dense Mammographic Area (cm^2)	8.7			11.2
Non-Dense Mammographic Area (cm^2)	297.6			284.8
Total Mammographic Area (cm^2)	306.3			295.9

3.2.2 Analysis of a Breast with Scattered Fibroglandular Densities (BI-RADS Category B)

The quantitative UST and mammographic density measures for the breast with scattered densities are shown in Table 3 and the aligned UST waveform sound speed images are shown in Figure 4. The USTPD measures along with the MPD measures show that there was a clear and consistent decrease in breast density over the observed time period. However, while the mean sound speed and mean subregion sound speeds also show an overall decrease, the changes are not consistent over the course of the year. The mean sound speeds show a large initial decrease over the first several months followed by a slight increase over the last 6 months.

When visually viewing the changes in Figure 4, there are easily visualized changes to the parenchymal patterns. In the first slice, there is an extended region of dense tissue at the 1 o'clock position that shrinks in size over the course of the year. At the 12 month scan, the region is a fraction of the size as it was at the baseline scan. In the second comparison slice, there are three small regions of density extending from the 7 o'clock to the 9 o'clock position. Once again, by the final scan, these regions are a much smaller size compared to the baseline scan. The waveform UST images therefore offer an excellent visual representation of the changes to the breast tissue itself.

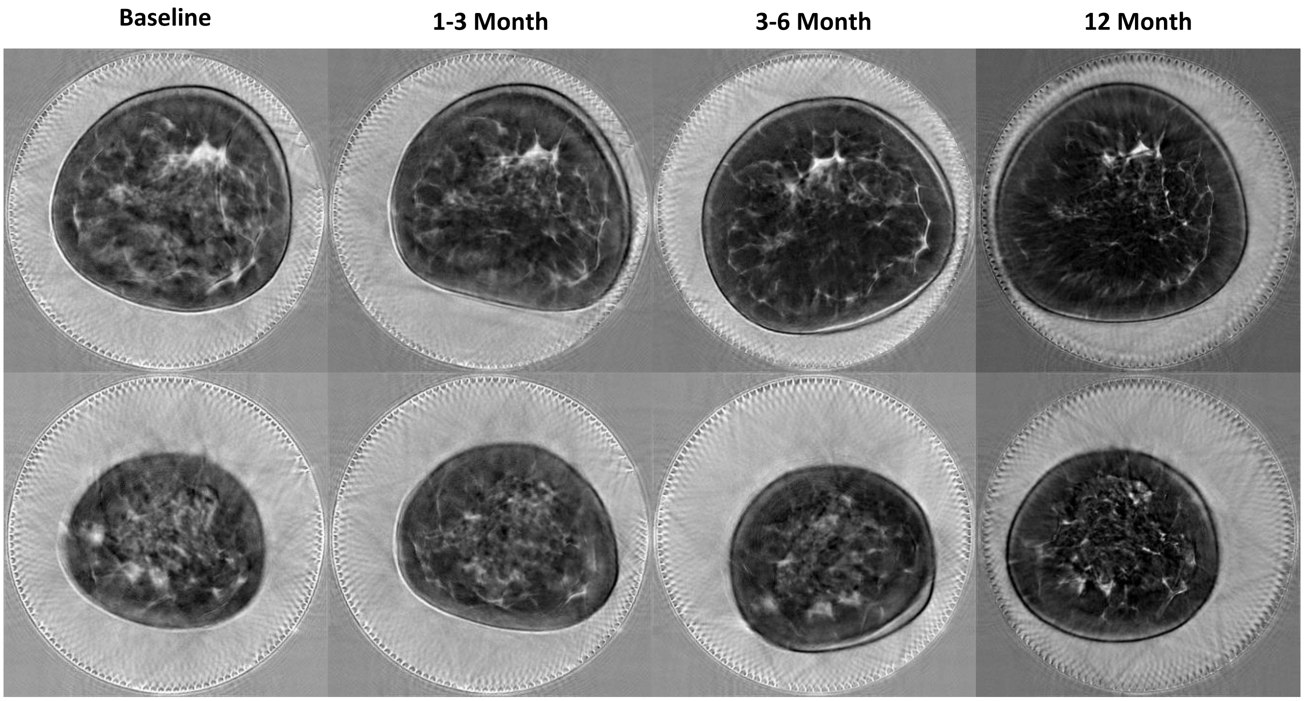

Figure 4 – UST sound speed images for the scattered density breast. Each row shows a slice from each of the four scans that roughly represent the same anatomy. The far left images are the baseline, followed by the 1-3 month follow up, then the 3-6 month follow up with the far right images being from the 12 month follow up scan. The top row of images represents anatomy closer to the chest wall while the bottom row represents anatomy closer to the middle of the breast. There are some small dense regions scattered throughout the breast so identifying similar landmarks is easier. It is also easily seen that these dense regions are shrinking in size.

Table 3 - Quantitative UST and Mammographic Density Measures for a Scattered Density Breast

UST Sound Speed Measures	**Baseline Scan**	**1-3 Month Follow Up**	**3-6 Month Follow Up**	**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-4	101	177	372
Mean Sound Speed (m/s)	1454.7	1445.9	1436.9	1443.2
Standard Deviation (m/s)	24.7	23.1	20.3	21.0
Total Volume (cm^3)	1133.6	1123.0	1142.7	1144.3
Dense Volume (cm^3)	307.9	308.4	274.3	249.8
Fatty Volume (cm^3)	825.7	814.6	868.4	894.5
USTPD (%)	27.2	27.5	24.0	21.8
Mean Dense Sound Speed (m/s)	1486.2	1474.3	1464.1	1472.7
Mean Fatty Sound Speed (m/s)	1443.0	1435.1	1428.3	1434.9
Mean Sound Speed Subregion Difference (m/s)	43.2	39.3	35.8	37.7
Mammographic Density Measures	**Baseline Scan**			**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-171			380
Mammographic Percent Density (%)	17.6	**N/A**		3.5
Dense Mammographic Area (cm^2)	59.6			12.7
Non-Dense Mammographic Area (cm^2)	277.9			350.2
Total Mammographic Area (cm^2)	337.4			362.9

3.2.3 Analysis of a Heterogeneously Dense Breast (BI-RADS Density Category C)

The quantitative density and sound speed measures for a heterogeneously dense breast are shown below in Table 4. The UST sound speed measurements are not entirely consistent with the mammographic density results. The UST sound speed measurements show a decrease up to 6 months followed by a slight increase over the last 6 months. While there is a net decrease in sound speed over the 12 month time frame, the decrease is relatively small compared with the decrease observed in MPD. Also, the USTPD along with the relative amounts of dense and non-dense tissue remained relatively consistent. However, the MPD measurements show there was a moderate decrease in density. This change was evidenced as both decreases in the MPD but also with the amount of dense mammographic area.

By viewing the UST sound speed images themselves in Figure 5, the changes in parenchymal patterns are difficult to notice by eye. It is still possible to identify similar regions at each scan, even with a large portion of the breast being composed of dense tissue. There is a fatty region embedded in the dense tissue for the first selected slice, but observing whether it is increasing or decreasing in size cannot be done easily by eye. Also, in the second selected slice, there is a large dense region in the six o'clock position that can easily be identified but is difficult to estimate the magnitude of change. Any change in density occurs on a quantitative basis for this patient.

Table 4 - Quantitative UST and Mammographic Density Measures for a Heterogeneously Dense Breast

UST Sound Speed Measures	**Baseline Scan**	**1-3 Month Follow Up**	**3-6 Month Follow Up**	**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	0	112	175	371
Mean Sound Speed (m/s)	1457.3	1454.1	1450.8	1454.6
Standard Deviation (m/s)	31.1	27.4	27.0	30.7
Total Volume (cm^3)	608.7	621.2	642.1	631.1
Dense Volume (cm^3)	154.2	172.2	159.6	160.8
Fatty Volume (cm^3)	454.5	449.0	482.5	470.3
USTPD (%)	25.3	27.7	24.9	25.5
Mean Dense Sound Speed (m/s)	1500.3	1489.6	1488.4	1495.3
Mean Fatty Sound Speed (m/s)	1442.7	1440.5	1438.4	1440.7
Mean Sound Speed Subregion Difference (m/s)	57.6	49.1	50.0	54.5
Mammographic Density Measures	**Baseline Scan**			**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-114			482
Mammographic Percent Density (%)	27.8	**N/A**		19.9
Dense Mammographic Area (cm^2)	61.7			45.2
Non-Dense Mammographic Area (cm^2)	160.6			181.7
Total Mammographic Area (cm^2)	222.3			226.9

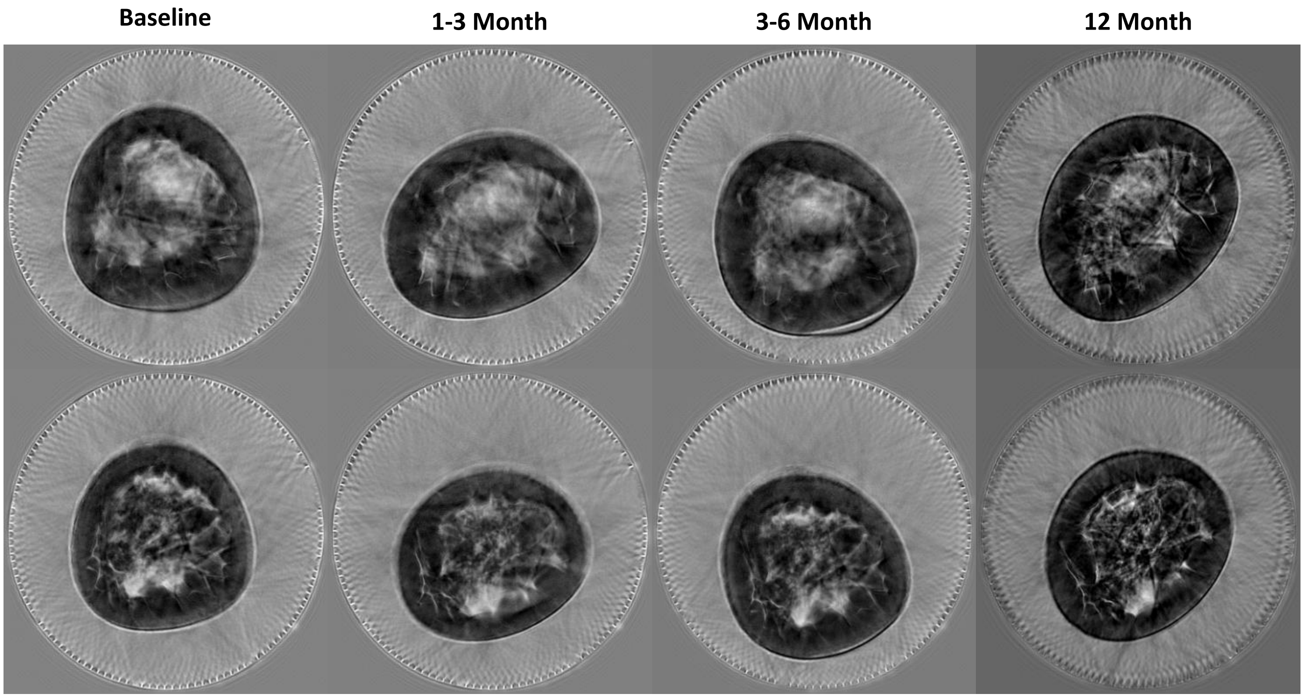

Figure 5 – UST sound speed images for the heterogeneously dense breast. Each row shows a slice from each of the four scans that roughly represent the same anatomy. The far left images are the baseline, followed by the 1-3 month follow up, then the 3-6 month follow up with the far right images being from the 12 month follow up scan. The top row of images represents anatomy closer to the chest wall while the bottom row represents anatomy closer to the middle of the breast. There is much more dense tissue but similar looking landmarks can still be easily identified. Despite being a higher density, the changes in the dense regions are difficult to visually identify over the 12 months.

3.2.4 Analysis of an Extremely Dense Breast (BI-RADS Density Category D)

An extremely dense breast was analyzed (TAM243) and the mammographic and UST breast density measures are shown in Table 5. The UST sound speed measures are the highest for any of the breasts measured here and they do indicate that there was a significant decrease in breast density. There appeared to be an initial increase in density at 1-3 months, but that was followed up by a dramatic decrease in density between the 3 and 12 month time frame. There were large decreases in all sound speed measures along with the USTPD and the volume of dense tissue over this time. This seemingly large decrease in UST measurements is tempered by smaller decreases in mammographic measurements. While both MPD and dense breast area do show a decrease, the magnitude of the change is much smaller.

The visual inspection of the UST sound speed images is shown in Figure 6. Whereas with the fattier breasts, dense structures were identified within the fatty background, here it is easier to identify similar regions of fatty tissue within the dense tissues. Over the final three scans, the increases in the fatty regions are visually apparent. In the second comparison slice, there is a fat lobule located at about 7 o'clock inside an extended dense region of tissue that increases in size, eating away into the dense tissue. There is a central region of dense tissue within the breast that slightly decreases in size. However, there is also a fatty ring that surrounds this dense region that appears to both grow in size while becoming more homogeneously fatty.

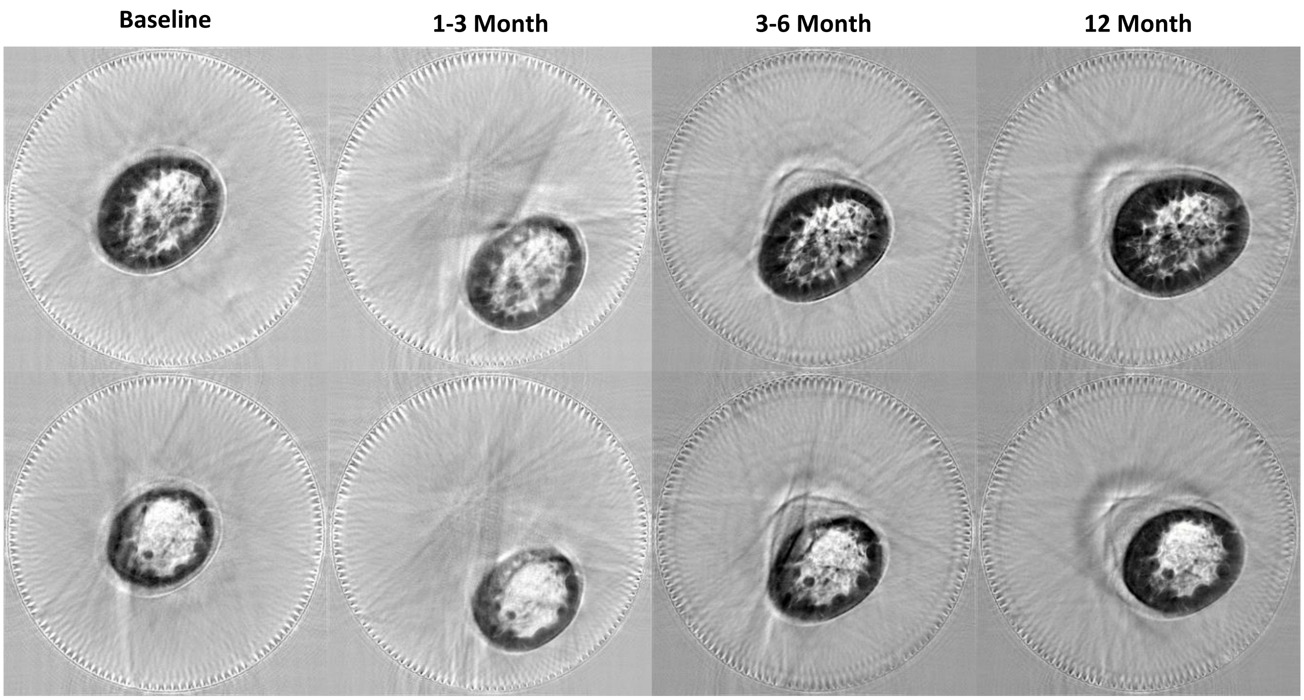

Figure 6 – UST sound speed images for the extremely dense breast. Each row shows a slice from each of the four scans that roughly represent the same anatomy. The far left images are the baseline, followed by the 1-3 month follow up, then the 3-6 month follow up with the far right images being from the 12 month follow up scan. The top row of images represents anatomy closer to the chest wall while the bottom row represents anatomy closer to the middle of the breast. For the densest breasts, it is much easier to match similar fatty regions within the dense tissue rather than trying to align the dense regions themselves. Here, the fatty regions appear to be growing in size and growing into the dense regions over the time frame, compatible with the total volume of dense tissue decreasing by both USTPD and MPD.

Table 5 - Quantitative UST and Mammographic Density Measures for an Extremely Dense Breast

UST Sound Speed Measures	**Baseline Scan**	**1-3 Month Follow Up**	**3-6 Month Follow Up**	**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	0	94	196	371
Mean Sound Speed (m/s)	1481.0	1490.5	1479.1	1475.7
Standard Deviation (m/s)	44.2	38.7	45.8	46.7
Total Volume (cm^3)	171.0	174.2	169.9	169.5
Dense Volume (cm^3)	72.2	78.4	63.4	55.7
Fatty Volume (cm^3)	98.8	95.7	106.5	113.7
USTPD (%)	42.2	45.0	37.3	32.9
Mean Dense Sound Speed (m/s)	1525.9	1527.7	1530.7	1534.5
Mean Fatty Sound Speed (m/s)	1448.2	1460.1	1448.3	1446.9
Mean Sound Speed Subregion Difference (m/s)	77.7	67.6	82.3	87.7
Mammographic Density Measures	**Baseline Scan**			**12 Month Follow Up**
Time From Tamoxifen Initiation (Days)	-153			345
Mammographic Percent Density (%)	35.0	**N/A**		32.6
Dense Mammographic Area (cm^2)	33.9			27.6
Non-Dense Mammographic Area (cm^2)	62.9			57.2
Total Mammographic Area (cm^2)	96.8			84.8

4. CONCLUSIONS

Waveform reconstructions of UST sound speed images were repeatedly made on a group of women who underwent tamoxifen therapy over the course of approximately one year. Using the waveform images, similar regions of breast parenchyma could easily be identified at various points throughout the follow-up period. For some of the participants, changes to the breast parenchyma could also be identified visually. Where changes were not readily apparent, the quantitative UST measurements could also be used to identify whether or not any significant changes to breast sound speed, a surrogate of volumetric breast density, likely occurred. These results show that waveform UST sound speed images are an excellent tool to obtain high resolution maps of breast parenchyma. These images can supplement the quantitative information that is already contained in the image.

5. ACKNOWLEDGEMENTS

The authors wish to thank Dr. Norman Boyd for his work in analyzing the mammograms and Lisa Bey-Knight and Vivian Linke for their work in scanning participants using the SoftVue UST scanner. This work was supported, in part, by the Intramural Research Program of the National Cancer Institute.

6. REFERENCES

1. Huo, C.W., G.L. Chew, K.L. Britt, W.V. Ingman, M.A. Henderson, J.L. Hopper, and E.W. Thompson, *Mammographic density—a review on the current understanding of its association with breast cancer.* Breast Cancer Research and Treatment, 2014. **144**(3): p. 479-502.
2. Pettersson, A., R.E. Graff, G. Ursin, I.d. Santos Silva, V. McCormack, L. Baglietto, C. Vachon, M.F. Bakker, G.G. Giles, K.S. Chia, K. Czene, L. Eriksson, P. Hall, M. Hartman, R.M.L. Warren, G. Hislop, A.M. Chiarelli, J.L. Hopper, K. Krishnan, J. Li, Q. Li, I. Pagano, B.A. Rosner, C.S. Wong, C. Scott, J. Stone, G. Maskarinec, N.F. Boyd, C.H. van Gils, and R.M. Tamimi, *Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis.* Journal of the National Cancer Institute, 2014.
3. McCormack, V.A. and I. dos Santos Silva, *Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis.* Cancer Epidemiology Biomarkers & Prevention, 2006. **15**(6): p. 1159-1169.
4. Duric, N., N. Boyd, P. Littrup, M. Sak, L. Myc, and C. Li, *Breast density measurmement with ultrasound tomography: a comparison with film and digital mammography.* Medical Physics, 2013. **40**.
5. Sak, M., N. Duric, P. Littrup, L. Bey-Knight, H. Ali, P. Vallieres, M.E. Sherman, and G.L. Gierach, *Using Speed of Sound Imaging to Characterize Breast Density.* Ultrasound in Medicine & Biology, 2017. **43**(1): p. 91-103.
6. Sandhu, G.Y., C. Li, O. Roy, S. Schmidt, and N. Duric, *Frequency domain ultrasound waveform tomography: breast imaging using a ring transducer.* Physics in Medicine and Biology, 2015. **60**(14): p. 5381.
7. Sandhu, G.Y.S., C. Li, O. Roy, E. West, K. Montgomery, M. Boone, and N. Duric. "Frequency-domain ultrasound waveform tomography breast attenuation imaging," Proc. SPIE 9790 Medical Imaging 2016: Ultrasound Imaging, 9790 (2016).
8. Mast, T.D., *Empirical relationships between acoustic parameters in human soft tissues.* Acoustics Research Letters Online, 2000. **1**(2): p. 37-42.
9. Masugata, H., K. Mizushige, S. Senda, A. Kinoshita, H. Sakamoto, S. Sakamoto, and H. Matsuo, *Relationship between myocardial tissue density measured by microgravimetry and sound speed measured by acoustic microscopy.* Ultrasound in Medicine & Biology, 1999. **25**(9): p. 1459-1463.
10. Weiwad, W., A. Heinig, L. Goetz, H. Hartmann, D. Lampe, J. Buchmann, R. Millner, R.P. Spielmann, and S.H. Heywang-Koebrunner, *Direct Measurement of Sound Velocity in Various Specimens of Breast Tissue.* Investigative Radiology, 2000. **35**(12): p. 721-726.
11. Cuzick, J., J. Warwick, E. Pinney, S.W. Duffy, S. Cawthorn, A. Howell, J.F. Forbes, and R.M.L. Warren, *Tamoxifen-Induced Reduction in Mammographic Density and Breast Cancer Risk Reduction: A Nested Case-Control Study.* Journal of the National Cancer Institute, 2011. **103**(9): p. 744-752.
12. Mullooly, M., R.M. Pfeiffer, S.J. Nyante, B.M. Heckman-Stoddard, M. Perloff, I. Jatoi, L.A. Brinton, E.J. Aiello Bowles, R.N. Hoover, A. Glass, A. Berrington de Gonzalez, M.E. Sherman, and G.L. Gierach, *Mammographic Density as a Biosensor of Tamoxifen Effectiveness in Adjuvant Endocrine Treatment of Breast Cancer: Opportunities and Implications.* Journal of Clinical Oncology, 2016. **34**(18): p. 2093-2097.
13. Sak, M., N. Duric, P. Littrup, C. Li, L. Bey-Knight, M. Sherman, N.F. Boyd, and G. Gierach. "Breast density measurements using ultrasound tomography for patients undergoing tamoxifen treatment," Medical Imaging 2013: Ultrasonic Imaging, Tomography, and Therapy, 8675 (2013).
14. D'Orsi, C.J., E.A. Sickles, E. Mendelson, and E. Morris, *ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. .* Reston, VA, American College of Radiology, 2013.
15. Khodr, Z.G., M.A. Sak, R.M. Pfeiffer, N. Duric, P. Littrup, L. Bey-Knight, H. Ali, P. Vallieres, M.E. Sherman, and G.L. Gierach, *Determinants of the reliability of ultrasound tomography sound speed estimates as a surrogate for volumetric breast density.* Medical Physics, 2015. **42**(10): p. 5671-5678.
16. Byng, J.W., N.F. Boyd, E. Fishell, R.A. Jong, and M.J. Yaffe, *The quantitative analysis of mammographic densities.* Physics in Medicine and Biology, 1994. **39**(10): p. 1629.