Volumetric breast density comparisons between waveform UST sound speed imaging and mammography

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ABSTRACT

Ultrasound tomography (UST) is a breast imaging modality that creates volumetric maps of breast anatomy without requiring ionizing radiation. Waveform sound speed reconstructions are a recent improvement to UST that offer much higher resolution images of dense and non-dense breast tissue. Volpara produces volumetric measures of breast density from two-dimensional mammograms. UST ray sound speed measurements have been shown to correlate strongly with measures of mammographic density. This work compares waveform sound speed measures with the volumetric mammographic density measures of Volpara. Very strong correlations of mean sound speed between the ray and waveform reconstructions were observed ($r_s = 0.950$). Measures of Volpara percent density versus UST waveform mean sound speed also showed strong correlations ($r_s = 0.848$), stronger than previously measured with two-dimensional mammographic density percent density. The higher resolution of waveform sound speed images allowed for clearer separation of dense and non-dense tissue and led to stronger correlations of dense volume with Volpara compared to the ray measures. These results show that UST waveform sound speed images offer improved performance in the measurement of dense breast tissue compared to ray sound speed images.

1. INTRODUCTION

Ultrasound tomography (UST) is an emerging breast imaging modality that is able to create three-dimensional maps of breast anatomy without the use of ionizing radiation[1–3]. UST sound speed images have been shown to correlate strongly with mammographic percent density measurements and show that UST sound speed is an excellent measure of breast density[4–6]. Recent improvements made to UST reconstruction algorithms have introduced waveform reconstructions of sound speed[7–9]. These waveform reconstructions have much higher image quality than previous ray-based reconstructions and offer much greater detail of the distribution of dense and fatty tissues inside the breast.

Volpara is an automated breast density assessment software that was designed to consistently produce quantitative volumetric measures of breast density using mammography[10,11]. With Volpara, breast density can be estimated by measuring the volume of fibroglandular tissue in the breast. It has been shown that women with high mammographic density also have a higher risk of developing breast cancer[12–14].

UST sound speed imaging has been shown to be a robust measure of breast density that correlates strongly with two-dimensional measurements of mammographic breast density[5,6]. However, all sound speed measurements have been made using ray-based reconstructions. Attempts to separate dense tissue from fatty tissue in the ray based images have produced limited results[15] and initial attempts to use waveform images to help separate tissue have shown promise[2].

2. METHODS

2.1 Patient Selection

A group of 100 women with benign and malignant findings in their breast underwent both a UST breast scan and had a Volpara reading of a mammogram at the Karmanos Cancer Institute (KCI) located in Detroit, MI. The raw data for the UST scan needed to be saved as the waveform reconstructions required the original data in order to be created. In order to limit the temporal changes in breast density, only those patients with that received a UST scan within one year relative to the Volpara mammogram reading were selected. The UST scans occurred over a period ranging from May 2014 to February 2016 as Volpara was only used at KCI during 2015.

2.2 Volpara Measurements

As part of the normal screening protocol, during most of the 2015 year, patients that underwent a mammogram also had a Volpara reading done. The measures of total dense volume, total breast volume, percent density and the density grade were recorded from the breast that was scanned with UST (Figure 1).

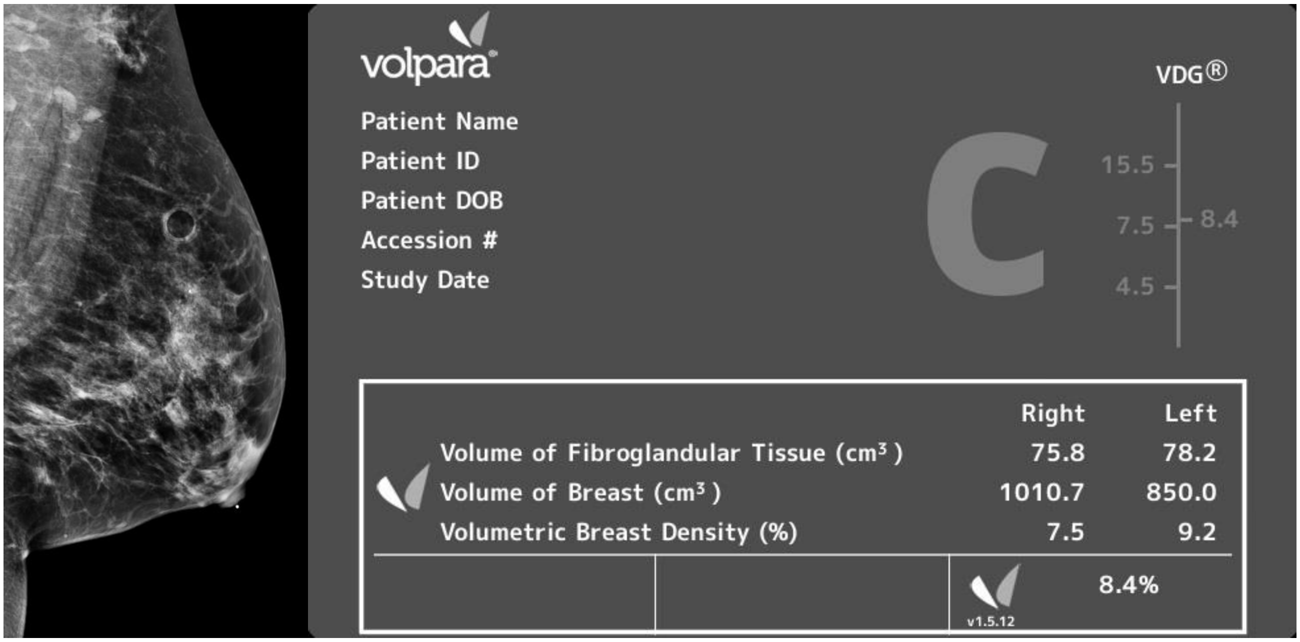

Figure 1 – An example mammogram along with the output screen after a Volpara reading. The relevant density measures could easily be read from this screen.

2.3 UST Sound Speed Image Creation and Analysis

At the time of the UST scan, the ray based sound speed images were created as part of the default reconstruction algorithm and the raw US data was saved. After the waveform reconstruction algorithm was created, it was used on the raw data to create the waveform sound speed images. Therefore, the waveform and ray based sound speed images were derived from identical scans.

Calculating the density statistics for the sound speed images requires the image to first be segmented from the background water bath. Unfortunately, the sound speed of the water bath is intermediate to that of the breast tissue, so simply thresholding the sound speed image does not separate water from breast tissue. Initially, the masking of the breast tissue was done manually on a slice by slice basis. However, this proved to be time consuming, especially when attempting to analyze hundreds of images at once. Previous attempts to develop automatic segmentation of breast tissue required the use of the additional images created by the UST reconstruction algorithm[16].

The ray based images were initially segmented by applying a threshold to the ray based attenuation image. Since the attenuation of the breast tissue was higher than that of water, a simple threshold was applied to the attenuation image and the corresponding mask was then used to separate sound speed from water. However, this method did not effectively segment all slices, so those slices where the masking was inadequate had their mask manually replaced. This reduced the time required to segment the images relative to the original method, but still required a user to identify and manually replace the inadequate masks.

In addition to creating higher resolution sound speed images, the waveform reconstruction also produced a slightly different reflection image known as Wafer (Waveform enhanced reflection). This image used the sound speed information to enhance the contrast at the breast tissue water bath boundary. Wafer images are therefore much easier to threshold to segment the breast tissue. The waveform masks were therefore created by first thresholding the Wafer image, applying several morphological operators to the initial mask to create the final mask for each slice.

Once the sound speed images were masked, the mean sound speed, the total volume of tissue along with other basic statistics were easily pulled from the quantitative images for each scan. A k-means segmentation algorithm was also run to separate the sound speed image into dense and non-dense regions (Figure 2). The same statistics were then recorded for each subregion of the breast for both sets of images. These statistics were then compared to each other along with the correlated Volpara mammography statistics using standard statistical techniques.

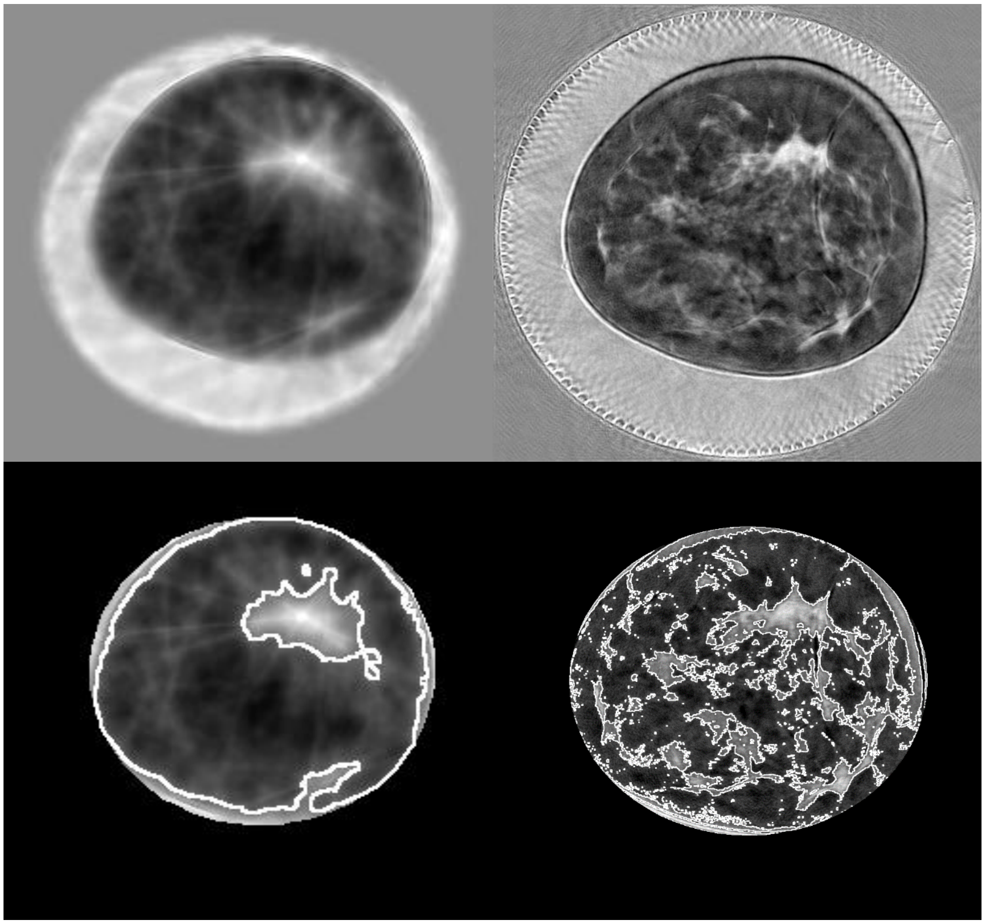

Figure 2 – (Top Left) The original ray sound speed image that was created at the time of the UST scan. (Top Right) The same slice of the same breast reconstructed using the waveform algorithm from the raw data that was collected at the time of the scan. (Bottom Left) The masked ray sound speed image with the results of the k-means segmentation algorithm imposed over top that separate dense tissue from non-dense tissue. (Bottom Right) The masked waveform sound speed image with the segmentation of the dense and non-dense tissue overlayed.

3. RESULTS

3.1 Ray and Waveform UST Measurement Comparisons

The same breast density measures along with volume measures between the UST ray and waveform sound speed images were compared and the results are shown below in Table 1. Paired t-tests were run on the same measures to show the differences in the mean values and Spearman correlations were also run to show how the two quantitative images related to each other.

<u>Table 1 – Waveform and Ray UST Sound Speed Characteristic Comparisons</u>

UST Density Characteristic	**Ray Mean Value**	**Waveform Mean Value**	**t-test p-value**	**Spearman Coefficient**	**Spearman p-value**
Mean Sound Speed (m/s)	1444.3	1446.9	< 0.001	0.950	< 0.001
Standard Deviation (m/s)	19.1	34.1	< 0.001	0.831	< 0.001
Total Breast Volume (cm^3)	817	1003	< 0.001	0.789	< 0.001
Dense Tissue Volume (cm^3)	210	191	0.149	0.296	0.003
Fatty Tissue Volume (cm^3)	607	812	< 0.001	0.821	< 0.001
USTPD (%)	28.8	22.6	< 0.001	0.683	< 0.001
Mean Dense Sound Speed (m/s)	1469.1	1504.0	< 0.001	0.573	< 0.001
Mean Fatty Sound Speed (m/s)	1433.8	1430.9	< 0.001	0.851	< 0.001
Mean Sound Speed Subregion Difference (m/s)	35.3	73.0	< 0.001	0.266	0.008
Skewness	1.3	1.4	0.178	0.829	< 0.001
Kurtosis	7.6	4.2	< 0.001	0.885	< 0.001

There is a very strong correlation between the waveform and ray based mean sound speed images (Figure 3) despite there being a small, but statistically significant difference in the average values. While the total volume of dense tissue measured between the two images is statistically similar, the average sound speed of the waveform dense region is much higher than for the ray images. This suggests that waveform images are able to more clearly separate the dense tissue from the fatty tissue and reduce the amount of volume averaging that occurs in this region.

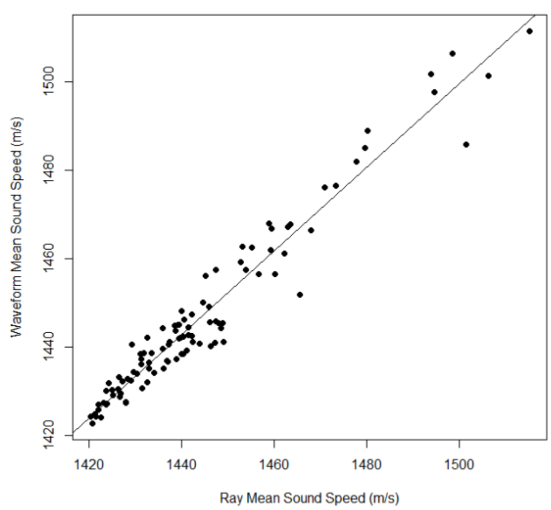

Figure 3 – Plot of the Waveform mean sound speed value versus the Ray mean sound speed value for each scan along with the line of best fit. The Spearman correlation coefficient was $r_s = 0.950$.

3.2 Mammographic and UST Volume Comparisons

The most direct comparison between Volpara and UST imaging is the volume of tissue imaged. The average volume of breast tissue that was measured in both mammography and UST were compared and the results are shown below in Table 2. The percent density measurements are derived from the volume measurements and are also shown in the same table.

Volpara measures the largest total breast volume but the smallest volume of dense tissue which therefore also gives it the smallest percent density value. Paired t-test were also performed on between the UST and Volpara measures (wave-Volpara and ray-Volpara) and all measures showed statistically significant differences in the average values with all $p < 0.001$.

Table 2 – Direct Breast Volume Comparisons

Volume Measure	Volpara Average	Ray UST Average	Waveform UST Average
Total Breast Volume (cm^3)	1103	817	1003
Dense Tissue Volume (cm^3)	80	210	191
Fatty Tissue Volume (cm^3)	1023	607	812
Percent Dense Tissue (%)	8.8	28.8	22.6

Spearman correlations were also run between the Volpara volume measurements and the UST volume measurements. The results are shown in Table 3 and show very strong correlations between Volpara and either UST image when measuring the total volume and the fatty volume. There is a moderate correlation between the volumes of dense tissue, but the waveform images give a slightly stronger correlation than the ray images. This suggests that waveform imaging does a better job of defining dense and non-dense tissue compared to ray based images.

Table 3 – Spearman Correlation Coefficients for UST and Volpara Comparisons

Volume Measure	Spearman Coefficient Between Volpara and	
	Ray UST	Waveform UST
Total Breast Volume	0.896	0.803
Dense Tissue Volume	0.496	0.589
Fatty Tissue Volume	0.899	0.824

3.3 Mammographic and UST Density Measures Comparisons

Comparisons between the UST breast density measures of mean sound and percent density with Volpara measure of breast density were then taken. The Spearman coefficients between the ray and waveform sound speed measures with the Volpara measures are shown below in Table 4 and the plots of these values can be seen in Figure 4. The mean sound speed has a similar strength correlation with Volpara percent density for both the waveform and ray image. However, when UST percent density is used as the density measure, the waveform imaging shows stronger correlations than the ray imaging. This once again suggests that the waveform imaging is better able to separate dense tissue from non-dense tissue.

Table 4 – UST and Volpara Density Correlations

Type of UST Imaging	Correlation	Spearman Coefficient
Waveform	Mean Sound Speed versus Volpara Percent Density	0.848
	Mean Sound Speed versus UST Percent Density	0.819
	UST Percent Density versus Volpara Percent Density	0.859
Ray	Mean Sound Speed versus Volpara Percent Density	0.834
	Mean Sound Speed versus UST Percent Density	0.557
	UST Percent Density versus Volpara Percent Density	0.665

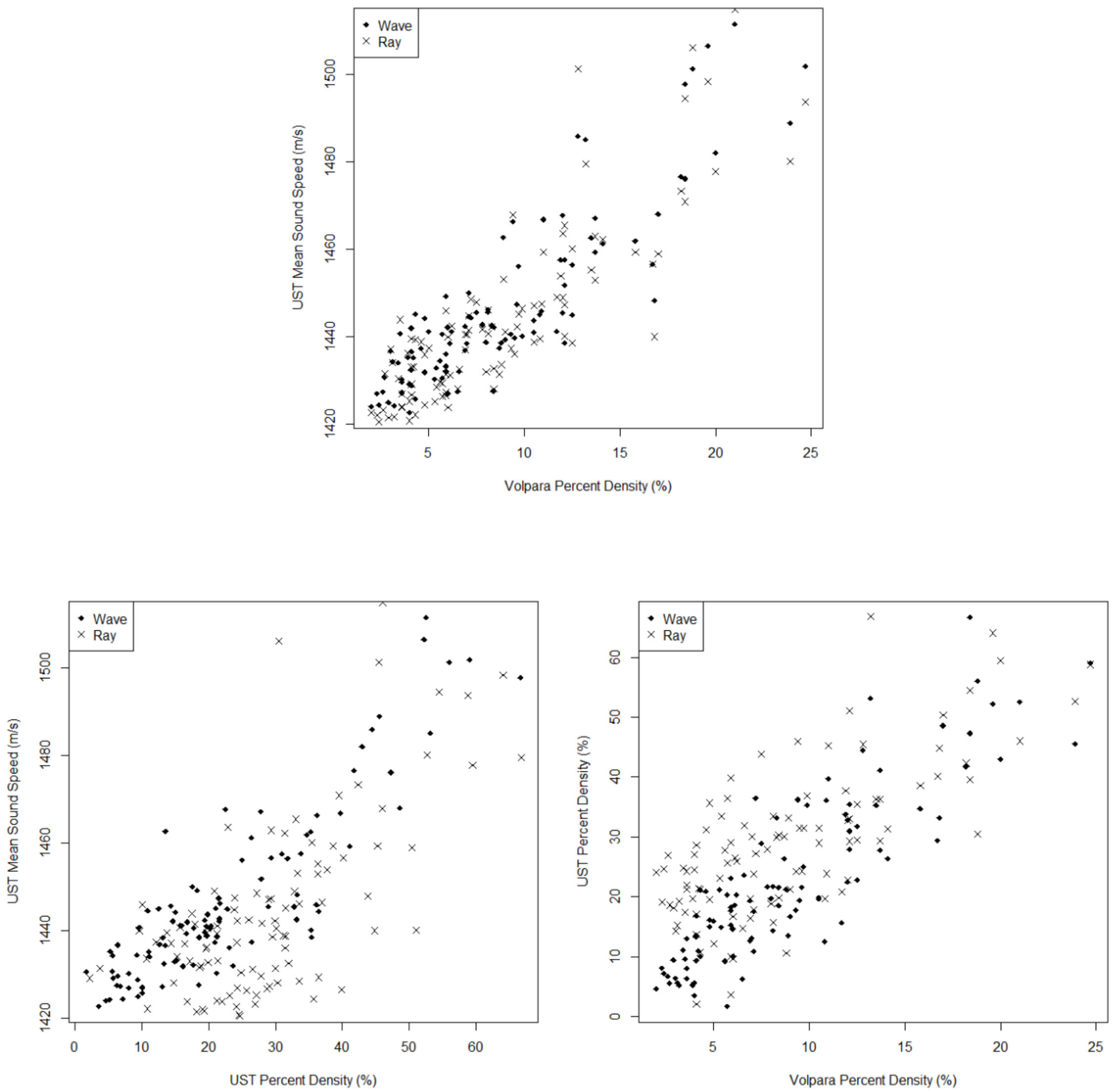

Figure 4 – Plots of (Top) the waveform and ray mean sound speed versus the Volpara PD, (Bottom Left) the waveform and ray mean sound speed versus the USTPD and (Bottom Right) the waveform and ray USTPD versus the Volpara PD

3.4 Volpara Density Grade Comparisons

Volpara also scores each breast's density on a four-point scale based on its percent density measure. The mean percent density measures and dense volume measures were calculated for each group and the results are shown in Table 5. Boxplots of the percent density and dense volumes versus the Volpara group are shown in Figure 5. These results show that the Volpara density score is the most tightly correlated with the Volpara grade, although waveform USTPD also shows strong correlations to the groupings. The total volume of dense tissue rises as the density increases until the breasts get very dense, then there is a plateau. Also, these results show that the ability of the ray sound speed images to identify dense tissue is poor compared to the waveform sound speed images.

Table 5 – Average Percent Density and Dense Volume Measures Grouped by Volpara Density Grade

Volpara Grade	Number of Breasts	Volpara PD (%)	Ray USTPD (%)	Waveform USTPD (%)	Volpara Dense Volume (cm^3)	Ray Dense Volume (cm^3)	Waveform Dense Volume (cm^3)
A	23	3.4	20.0	8.8	51.7	227.9	106.0
B	28	6.1	24.1	16.2	74.8	216.9	183.2
C	36	10.7	31.3	27.7	100.3	196.3	239.6
D	13	19.2	47.8	46.9	83.7	199.7	220.7

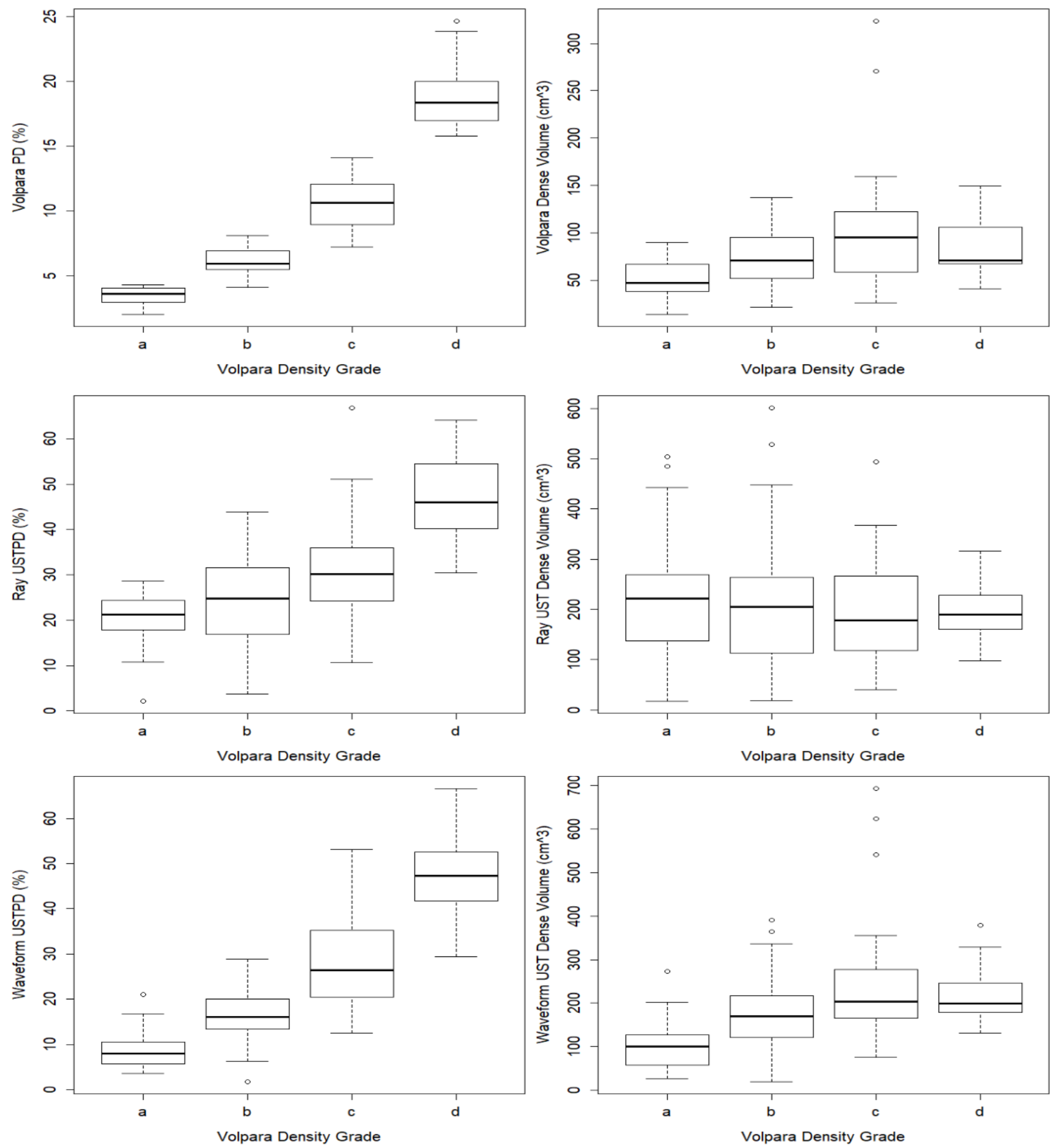

Figure 5 – Boxplots of the percent density (Left) and dense volume (Right) as grouped by the Volpara Density Grade.

4. DISCUSSION

The very strong correlation between the waveform and ray mean sound speed values (Figure 3) indicate that the main UST breast density measure is likely not affected by the change in image type. Ray based mean sound speed has been shown to be a good correlate with mammographic density[5,6] so it should follow that waveform sound speed should also correlate strongly.

The statistically significant differences in the averaged mean sound speed, total volume and subsequently USTPD between the waveform and ray images can likely be attributed to the masking methods. The ray based images did have a user manually remove or add masks to slices that corresponded to the breast tissue[16]. Therefore, the ray images had slices which contained some chest wall removed and had slices beyond the nipple also removed. The masking that was performed for the waveform images was completely automated. There were no attempts to go back to ensure that every mask on every slice was acceptable or to remove slices that corresponded to the unwanted anatomy. This explains why the total volume for the waveform images is higher as there were more slices included in the measurements.

Furthermore, the chest wall slices are more likely to contain regions of higher sound speed as the pectoralis muscles has a higher sound speed than most breast tissue. Also, the additional slices past the nipple that may have been included in the waveform masking would have a higher sound speed than the fatty tissue that mostly comprises these breasts. This explains the slight increase in the average sound speed of approximately 2 m/s. However, since the plot of the waveform versus ray mean sound speed showed no dramatic outliers (Figure 3), the current method of automated masking of waveform sound speed images appears to acceptable.

Despite waveform imaging measuring a higher total volume of breast tissue than ray imaging, the UST volume was still less than that measured by Volpara. This difference is likely explained by the fact that the positioning of the breast is dramatically different for a UST image than for a mammogram. For UST patient positioning can vary from scan to scan and not every scan completely reaches the chest wall. Therefore, UST scans are likely to underestimate the total volume of breast tissue compared to mammography which is able to more consistently image the chest wall. Recent improvements to patient positioning in UST scans seek to maximize the volume of breast that is seen.

It is apparent that the methods used to separate dense tissue from non-dense tissue are dramatically different for UST and for Volpara. UST is able to identify more dense tissue than Volpara. The volumetric imaging of UST allows for the breast anatomy to be visualized much more clearly than the compressed projection image that is used in mammography and this is likely why the measured volumes of dense tissue for UST are higher.

Previous work done that compared UST sound speed measurements to mammographic breast density used a mammographic percent density that was based on the area of dense tissue that was seen[5,6]. Correlations between these two values were on the order of $r_s = 0.7$. Here, the correlation between sound speed and Volpara percent density was on the order of $r_s = 0.84$, which is greater. This suggests that Volpara's ability to determine volumetric properties from a two-dimensional mammogram is more effective than relying only on two-dimensional measures itself.

The women in this group had density measures analyzed on breasts that contained both benign and malignant findings. It has previously been shown that the presence of these findings is unlikely to greatly affect the ability to accurately classify breast density using UST. Previous work shows similar strength correlations for women with and without findings in their breasts[6].

5. CONCLUSION

Waveform UST imaging offers much more detailed sound speed imaging than previous ray based imaging. The quantitative aspects of waveform sound speed imaging is also preserved, allowing for much greater detail in the distribution of dense and non-dense tissue. Volpara volumetric breast density measures correlate very strongly with UST density measures. These results show that waveform UST sound speed imaging can be an effective tool to help clearly define and visualize distributions of dense tissue throughout the breast.

6. REFERENCES

[1] N. Duric, et al., "Breast Imaging with the SoftVue Imaging system: First results," Proc. SPIE 8675 (2013).

[2] M. Sak, Duric, N., Littrup, P., Sherman, M., Gierach, G., "Ultrasound tomography imaging with waveform sound speed: parenchymal changes in women undergoing tamoxifen therapy," Proc. SPIE 10139, (2017).

[3] E.A. O'Flynn, et al., "Ultrasound Tomography Evaluation of Breast Density: A Comparison With Noncontrast Magnetic Resonance Imaging," Invest. Radiol. 52, 343–348 (2017).

[4] M. Sak, et al., "Current and future methods for measuring breast density: a brief comparative review," Breast Cancer Manag. 4, 209–221 (2015).

[5] N Duric, et al., "Breast density measurements with ultrasound tomography: A comparison with film and digital mammography," Med. Phys. 40, 013501-12 (2013).

[6] M Sak, et al., "Using Speed of Sound Imaging to Characterize Breast Density," Ultrasound Med. Biol. 43, 91–103 (2017).

[7] G Y Sandhu, C Li, O Roy, S Schmidt, N Duric, "Frequency domain ultrasound waveform tomography: breast imaging using a ring transducer," Phys. Med. Biol. 60, 5381 (2015).

[8] G Y Sandhu, et al., "Frequency-domain ultrasound waveform tomography breast attenuation imaging," Proc. SPIE 9790, (2016).

[9] G Y Sandhu, Erik West, Cuiping Li, Olivier Roy & Neb Duric., "3D frequency-domain ultrasound waveform tomography breast imaging," Proc. SPIE 10139, (2017).

[10] J. Wang, et al. "Agreement of Mammographic Measures of Volumetric Breast Density to MRI," PLOS ONE 8, e81653 (2013).

[11] A Gubern-Mérida, et al. "Volumetric Breast Density Estimation from Full-Field Digital Mammograms: A Validation Study," PLOS ONE 9, e85952 (2014).

[12] C. W. Huo, et al. "Mammographic density—a review on the current understanding of its association with breast cancer," Breast Cancer Res. Treat. 144, 479–502 (2014).

[13] A. Pettersson, et al. "Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis," J. Natl. Cancer Inst., (2014).

[14] V.A. McCormack, "Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis," Cancer Epidemiol. Biomarkers Prev. 15, 1159–1169 (2006).

[15] M Sak, Neb Duric, Peter Littrup, Mark E. Sherman & Gretchen L. Gierach. "Using ultrasound tomography to identify the distributions of density throughout the breast," Proc SPIE 9790, (2016).

[16] M Sak, Neb Duric, Peter Littrup & Katelyn Westerberg. "A comparison of automated versus manual segmentation of breast UST transmission images to measure breast volume and sound speed," Proc SPIE 10139, (2017).