In-vivo imaging of breast cancer with ultrasound tomography: Probing the tumor environment

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ABSTRACT

We report on the use of ultrasound tomography (UST) to characterize breast cancer and study the local and distant tumor environments. We have imaged the tumor and its environment in 3 cases of breast cancer using a UST prototype and its associated image reconstruction algorithms. After generating images of reflection, sound speed and attenuation, the images were fused in combinations that allowed visualization and characterization of the interior of the tumor as well as the tissue immediate to the tumor and beyond. The reflection UST images demonstrated the presence of spiculation, and architectural distortion, indicators of both local tumor invasion and distant involvement with surrounding tissues. Furthermore, the sound speed images showed halos of elevated sound speed surrounding the tumors, indicating a local environment characterized by stiff tissues. The combination of sound speed and attenuation images revealed that the tumor interiors were the stiffest tissues in the region studied. These features and characteristics are commensurate with the known biomechanical properties of cancer and may be manifestations of the desmoplastic process that is associated with tumor invasion. We propose that UST imaging may prove to be a valuable tool for characterizing cancers and studying the tumor invasion process.

Keywords: Breast imaging, breast masses, image fusion, ultrasound tomography

1. INTRODUCTION

Ultrasound tomography (UST) is an emerging modality that offers the potential to overcome the operator dependence of current ultrasound imaging while maintaining its advantages of low cost and safety. Examples of systems built for breast imaging include those of Carson et al (U. Michigan)[1], Andre et al (UCSD)[2], Johnson et al (TechniScan Medical Systems)[3], Marmarelis et al (USC)[4], Ruiter et al (Karlsruhe)[5] Liu and Waag (U. Rochester)[6] and Duric and Littrup et al (KCI)[7-8]. UST's clinical relevance is based on its measurements of the biomechanical properties of human tissue which relies on the strong interaction between the acoustic waves and the tissue through which the waves propagate. At low frequencies (~ 2 MHz) this interaction includes diffraction and refraction as well as scatter. UST measures the effects of this interaction by recording the modified signals and, through a comparison with the emitted signals, provides a solution to the inverse problem that yields the variations in the biomechanical properties of tissue. Commonly rendered measurements include pulse-echo strength (reflection), sound speed and attenuation. These measurements have yielded parameters that can be used to characterize breast cancer. Stavros et al, for example, proposed that analysis of mass margins, shape and echo-properties, based on conventional, *reflection* ultrasound images, could lead to highly accurate differentiation of benign masses from cancer[9]. These observations led to the development of the "Stavros Criteria" which evolved into the Breast Imaging Reporting and Data System (BIRADS) for ultrasound. Similarly, in 1976, Greenleaf et al made the seminal observation that *sound speed* and *attenuation* measurements, made with transmission ultrasound, could also be used to characterize breast cancer[10]. However, since transmission ultrasound has not yet been adopted

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clinically these criteria are not currently part of the BIRADS lexicon. Nevertheless, the potential adoption of such criteria, in combination with currently adopted BIRADS criteria, would be attractive because the combined lexicon would provide a more complete view of the biomechanical properties of breast cancer and enhance the ability to differentiate cancer from benign lesions and normal tissues. UST offers the opportunity to link the measurable parameters of sound speed, attenuation and reflection to the biomechanical properties of tissue. For example, it is known historically that breast cancer can be palpated by virtue of its higher stiffness relative to background tissues. Sound generally travels faster through stiff tissues than soft tissues. Consequently there is a strong acoustic impedance change at the tumor boundary. The tumor therefore appears as a feature in reflection ultrasound imaging as well as a region of strongly elevated sound speed. Furthermore, because the structure of the tumor is different at the cellular level, it scatters acoustic energy differently from normal tissue, leading to a unique attenuation signature.

Our laboratory has focused on the development of ultrasound tomography for breast imaging. To that end we have been developing and testing a clinical prototype in KCI's breast center. We have demonstrated the feasibility of breast cancer detection with ultrasound tomography and set the stage for a variety of clinical research projects aimed at the life cycle of breast cancer, from risk assessment[11-12] to detection[13] to therapy monitoring[14]. The purpose of this paper is to report on a preliminary study aimed at extending the use of the UST prototype to not only characterize breast cancer but also study its environment in order to gain insight into the tumor invasion process.

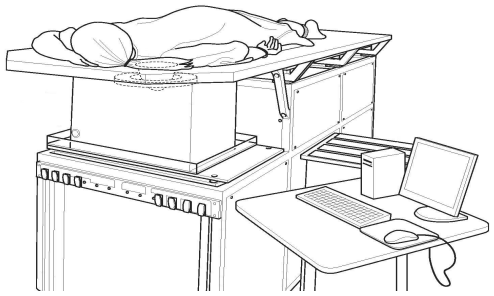

Figure 1: The UST clinical prototype (left). A patient lies in the prone position such that the breast is suspended inside a water tank that contains the ultrasound sensor.

A cancer interacts more strongly with its surroundings than benign lesions often leading to a desmoplastic reaction where the properties of the surrounding tissues are altered causing them to also be stiffer. This reaction explains why a palpated mass is often reported to be larger than the mass visualized with standard ultrasound. On a mammogram the tumor often appears to be spiculated and the alteration of the surrounding tissues is often visualized as architectural distortion. Since these effects are strongly tied to the presence of cancer the ability to measure these effects is critical to detecting and diagnosing cancer. In this paper we report on the use of UST to image breast cancer and its environment and to measure the effects of the desmoplastic reaction.

2. METHODS

The study described in this paper were carried out with a UST prototype developed at the Karmanos Cancer Institute (Figure 1).

The prototype:

The prototype is described fully in pervious publications. Here we summarize the basic operating characteristics.

- With data acquisition time of 0.03s per slice, the prototype scans patients without intra-slice motion artifacts. To the best of our knowledge, this is the fastest UST scanner collecting clinical data.
- Operating at a central frequency of 2 MHz, where signal scattering is relatively low, consistent penetration of the whole breast is assured.
- The scanner has an integrated transducer array that yields simultaneous data for reconstructions of reflectivity, attenuation, and sound speed parameters of tissue throughout the breast. This capability yields automatic image registration, facilitating image fusion, which greatly aids clinical analysis.
- The prototype has demonstrated fully operator-independent breast exams.

Patient recruitment and data collection

All imaging procedures were performed under an Institutional Review Board-approved protocol, in compliance with the Health Insurance Portability and Accountability Act, with informed consent obtained from all study subjects. Patients were selected if they exhibited a suspicious mass after mammography and/or follow-up ultrasound. The ultrasound tomography exam was scheduled after these conventional examinations, but before biopsy. A typical whole breast exam takes about 1 minute to perform. The total time the patient spends in the exam room is about 5 minutes. A patient exam begins with the patient lying prone on the scanner table. The table consists of flexible sailcloth, which contours to the patient's body, thereby increasing access to the axilla regions of the breast and increasing patient comfort. The breast is suspended in the imaging tank that lies below the table, through a hole in the table. The imaging tank is filled with warm, clean water. The ultrasound sensor, in the shape of a ring, surrounds the breast and moves from the chest wall to the nipple region of the breast on a motorized gantry, gathering data along the way (as shown in Figure 2). Typically, data are gathered at 1 mm intervals at 50-100 positions of the sensor, depending on the size of the breast.

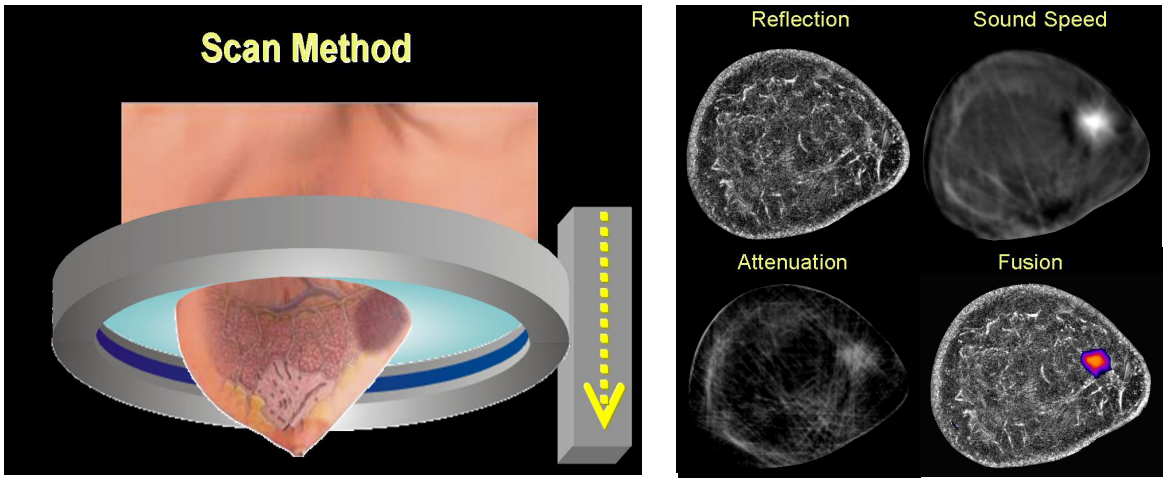

Figure 2: The ultrasound ring array (grey) surrounds the breast as it moves on a vertical trajectory from the chest wall to the nipple, acquiring data at discrete steps along the way. Each such dataset yields cross-sectional coronal images of reflectivity, sound speed and attenuation, as shown. Since the images are constructed from the same data, they are intrinsically registered, allowing fast and accurate image fusion, as shown.

Image Reconstruction and Analysis

Three types of images are produced from the raw data using previously described tomographic reconstruction algorithms[8,15]: (i) sound speed, (ii) attenuation and (iii) reflection. *Sound speed* images are based on the arrival times of acoustic signals. Previous studies have shown that cancerous tumors have enhanced sound speed relative to normal breast tissue[10], a characteristic which can aid the differentiation of masses, normal tissue, and fat. *Attenuation* images are tomographic reconstructions based on acoustic wave amplitude changes. Higher attenuation in cancer causes greater scatter of the ultrasound (US) wave, so attenuation data in conjunction with sound speed provides a potentially effective means for determining malignancy. *Reflection* images, derived from changes of acoustic impedance, provide echo-texture data and anatomical detail for the entire breast. Reflection images are valuable for defining tumor margins which can be used to characterize lesions through the Stavros criteria[10]. These 3 types of images can be combined without geometric discrepancy by means of image fusion, allowing for multi-parameter visual and quantitative characterization of masses.

A macro developed for *ImageJ* was used to fuse reflection (I_R), attenuation (I_A) and sound speed (I_S) UST images and to adjust image thresholds. Image fusion allows for improved visualization so that multiple characteristics can be viewed as one image, and breast tissue features can be evaluated more comprehensively. In addition to accentuating the lesion, the fused image depicts the local and distant tumor environment, including parenchyma and other components of breast architecture. For this study, the tumor and its environment were accentuated through the use of the thresholding technique described by equation 1,

$$I_F = I_R + I_{S>a} + \left[I_{S>b} \bullet I_{A>c} \right],$$

where $\bullet$ denotes the logical .AND. operation, and *a,b,c* are variable threshold values. In equation 1, I_R represents the reflection image used, I_S is the sound speed image and I_A is the attenuation image. The threshold values, *a,b* and *c* are used to set the displayed range of sound speed and attenuation.

The underlying reflection imaging is presented without thresholding and is used to visualize the tumor margin along with any associated spiculations and/or architectural distortion. It is noted that these images are reconstructed from the raw RF data. No envelope detection is used. Consequently, the reflecting filaments are characterized by sinusoidal cross sections that reflect the shape of the probing acoustic signal. This artifact represents a trade-off between resolution and image contrast. In this case the resolution (~0.5 mm) gain is about a factor of 2, which is enough to reveal the mass spiculation that would not otherwise be visible in our reflection images.

The sound speed image is thresholded ($S>a$) to bring up any elevated sound speed regions that are in the immediate tumor environment and is rendered in grey scale. The logical AND operation in the last term of equation 1 is used to display the sounds speed values of those pixels that simultaneously exceed the respective sound speed and attenuation values, *b* and *c*. The latter operation is motivated by the observations of Greenleaf, suggesting that the interiors of cancerous masses have high sound speed and attenuation. The results of this operation are displayed in color.

Mass selection and rendering

Masses were selected by cross-correlating existing data with radiologist reports that indicated the presence of either spiculation or architectural distortion or both. In the end, three candidates were selected for the pilot study presented here. The masses were identified on the individual UST images by a certified radiologist (PJL) by correlating their location and size with those reported in the standard mammography and ultrasound exams. An ROI was chosen for each mass and equation 1 applied in three different ways. (i) The reflection image was presented by itself in order to clearly visualize the spiculations and/or architectural distortion. It is represented as a grey-scale image. (ii) A fused image was created by using only the first and last term of equation 1 in order to superimpose the tumor core. The image created from the last term of equation 1 is rendered with color contours of sound speed and superimposed on the grey scale rendering of the reflection image (first term of equation 1). (iii) A fused image was created using all three terms to add the sound speed characteristics of the immediate environment of the tumor. In this case the image resulting from the middle term of equation 1 was rendered in grey scale and superimposed on the images arising form the other terms.

3. RESULTS AND DISCUSSION

Application of equation 1, as described in the above section, yielded the images shown in Figure 3. The characteristics of the three masses chosen are summarized in Table 1.

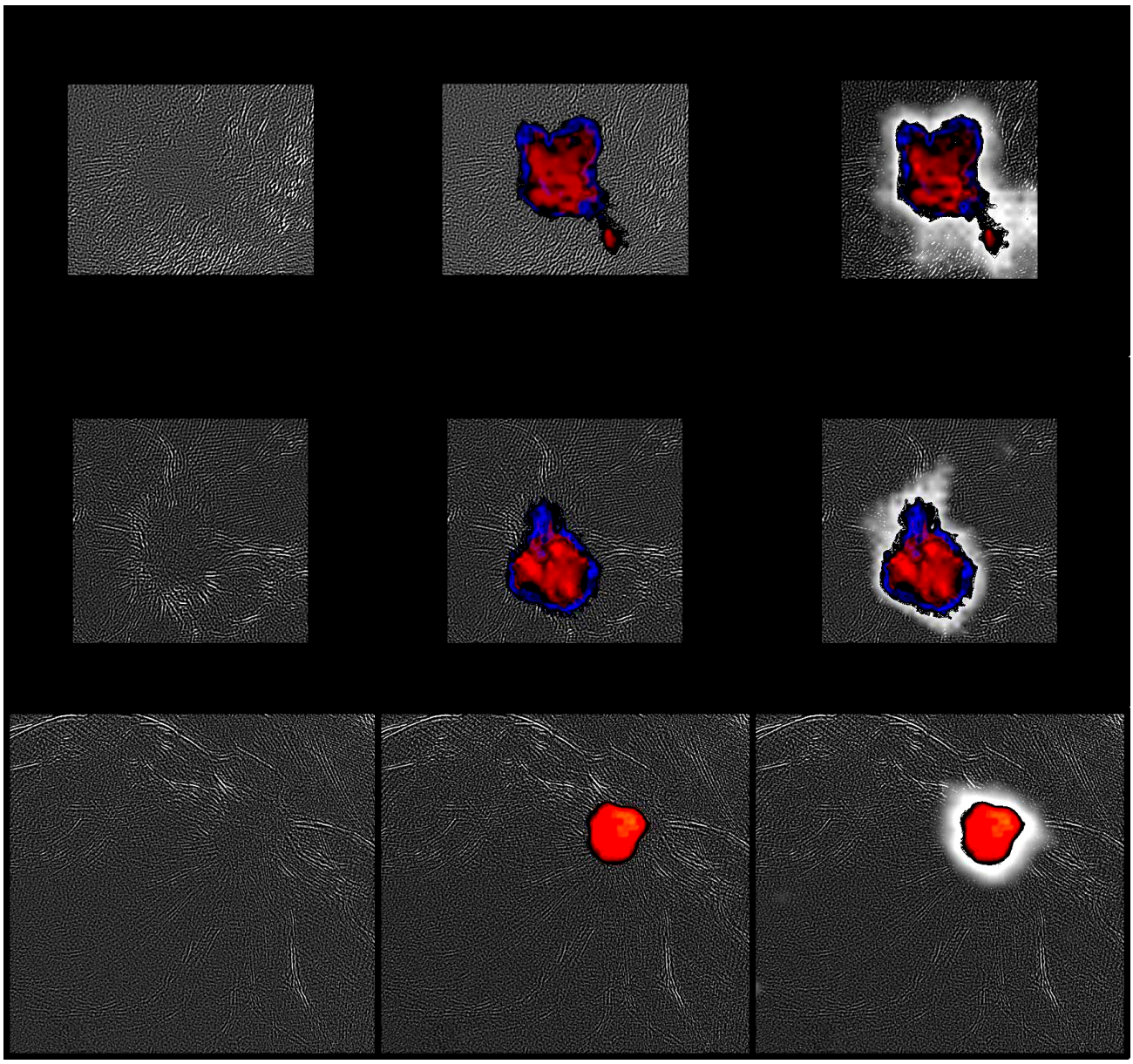

Figure 3: Left column: Reflection only image of cancer in three different patients. Middle column: Superposition of regions that represent high sound speed and attenuation (*S > 1.52 km/sec* **AND** *A > 0.15 dB/MHz/cm*). Right column: Additional superposition of regions with sound speeds, s > 1.45 km/sec. The bottom row shows an expanded view of a cancer in order to visuzlize the architectural distortion.

De-identified Patient Number	Cancer?	Spiculation reported?	Architectural Distortion reported?
235	Yes	Yes	No
257	Yes	Yes	No
339	Yes	Yes	Yes

Table 1. Characteristics of the masses chosen for study

As figure 3 shows, spiculation is seen in the three masses for which spiculation was originally reported from mammographic data. The spiculated masses appear as hyper-echogenic features radiating away from the interior of the tumor (left column). It is well recognized that spiculations are a manifestation of tumor invasion. In the case of the mass seen in the bottom row of figure 3, the more distant tumor environment shows clear signs of architectural distortion, also represented by highly echogenic filamentary structures that act as tracers of tissue distortion on larger scales.

The middle column of Figure 3 illustrates the relationship between the tumor core and the tumor environment. It is evident that the stiffest tissues are confined to the interior of the tumor and quantify what has long been known qualitatively from palpation. The stiffness is believed to arise from the failure of the local lymphatic system which results in greater stiffness from the effects of edema which further implies higher sound speeds. Furthermore, our observation that the tumor core is also highly attenuating is consistent with the anomalous cellular structures known to exist in cancer and which are likely to scatter acoustic energy differently from normal tissue. Since scattering is the dominant source of attenuation at our operating frequency of ~ 2 MHz, the elevated attenuation is not surprising (and is observed in conventional ultrasound as shadowing).

When regions of somewhat lower sound speed are added to the image in grey scale (rightmost column of Figure 3) it is evident that these regions are coincident with the immediate environment of the tumor. Although these regions have lower sound speed compared to the interior of the tumor, the values are still higher compared to the distant background tissue. A possible interpretation of this observation is that the local environment is characterized by relatively dense tissue which is an expected manifestation of a desmoplastic reaction. Furthermore, such an interpretation is consistent with the long known observation that palpation often overestimates the size of a mass, presumably because the stiff local environment of the tumor is included in the measurement.

The ability to visualize the local and distant tumor environments with UST represents a new tool for characterizing tumors and for studying tumor invasion. However, not all cancers exhibit spiculated margins and architectural distortion. For that reason, consistent mass characterization requires a greater range of measurable parameters. Some of these parameters are provided by the sound speed and attenuation parameters and are discussed further in other papers[8,13].

4. CONCLUSIONS

We have studied the tumor environment in 3 cases of breast cancer using a UST prototype and its associated image reconstruction algorithms. Fused UST images demonstrate the presence of spiculation, architectural distortion, stiff local environments and very stiff tumor cores. These features are consistent with the presence of cancer and the associated invasion into the surrounding tissues, including the manifestation of desmoplastic processes. We propose that UST measurements may prove valuable in characterizing cancers and studying the tumor invasion process. This ongoing work will expand into a study of a larger number of invasive tumors and will be the subject of future papers.

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