COMPUTERIZED ULTRASOUND RISK EVALUATION (CURE): FIRST CLINICAL RESULTS

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Abstract: The Karmanos Cancer Institute has developed an ultrasound (US) tomography system, known as Computerized Ultrasound Risk Evaluation (CURE), for detecting and evaluating breast cancer, with the eventual goal of providing improved differentiation of benign masses from cancer. We report on our first clinical findings with CURE.

A preliminary study imaged 19 patients with CURE between October 1 and December 1, 2004. Patients were recruited on the basis of having a suspicious mass after mammography and follow-up ultrasound. The CURE exam was interposed between the standard US exam and subsequent biopsy. Biopsy results were therefore available for all 19 patients. Typically, 45 tomograms were taken of each patient with the CURE device. For each tomogram, images of reflectivity and sound speed were made with automated algorithms. In five cases, attenuation images had to be produced by a manual technique due to gain instability of the current transducer ring.

Based on the preliminary CURE data we have currently utilized six CURE diagnostic criteria for cancer. In this small sample, when each criterion is given equal weight, it appears that women with higher scores are more likely to have cancerous masses. More definitive results await the conclusion of a larger, ongoing study

Keywords: Ultrasound tomography, breast cancer, diagnostic criteria, tissue characterization

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1. INTRODUCTION

Ultrasound tomography may provide a more operator independent alternative to current breast ultrasound, while presenting hope for a highly specific , non-ionizing screening adjunct to mammography. Mammography screening has been shown to reduce the mortality rate up to 30% in multiple screening trials. However, mammography also generates many abnormal findings not related to cancer which leads to additional, costly imaging procedures and up to 80% benign biopsies. If marked improvements in tissue-specific imaging could be achieved, up to one million benign biopsies could be eliminated each year in the United States[1], saving several billion dollars[2]. Recent studies have demonstrated the effectiveness of ultrasound (US) imaging in detecting breast cancer[1], particularly for women with dense breasts. At the same time, other studies have raised questions about the efficacy of mammography[2]. However, despite these developments, US is used only as an adjunct to X-ray mammography. A major reason for ultrasound's adjunctive role is its limited imaging capabilities. Specifically, the operator dependence, limited resolution and contrast, the presence of speckle noise and artifacts are key factors which have prevented US imaging from playing a greater role in standard diagnostic evaluation.

Efforts to improve the diagnostic accuracy of current US may be best represented by the success of the 'Stavros/Colorado' criterion for mass margin evaluation[3]. Further advances have led to compound imaging[5] (SonoCT, ATL/Phillips) resulting in better mass margin identification by reduction, of speckle, clutter and ultrasound artifacts [6]. As a result of these advancements, US is increasingly being studied for its potential as a screening tool. The ongoing ACRIN 6666 study, funded by the Avon foundation and the National Cancer Institute, represents a definitive trial evaluating the potential of US as a screening tool[7,8,9]. However, its anticipated positive results could also highlight the difficulties of mass acceptance and replication at the community level due to the persistent operator dependent nature of conventional US.

Several investigators demonstrated the early promise of ultrasound tomography but lacked the appropriate hardware/software technology advances that are currently available to make a fast, practical system (10–12). Current work is being carried out on a number of fronts and includes Johnson et al[13] (TechniScan Inc), Marmarelis' group at USC[14], and the work at the Karmanos Cancer Institute (KCI) in Detroit[15–21]. However, due to continued practical constraints of hardware and/or software combinations, we are the only group that has obtained full breast data acquisition in approximately 1 minute or less for both reflection and transmission imaging.

1.1 Ultrasound Tomography and CURE

We are developing the Computerized Ultrasound Risk Evaluation System (CURE)[14–20] to be a fast, operator independent data acquisition tool with a high degree of flexibility for continued incremental improvement on both hardware and software aspects as dictated by initial outcomes. Its current operating characteristics are summarized in Table 1.

Table 1. Summary of CURE performance characteristics.

Operating frequency	Number of data acquisition channels	Data acquisition time (one slice)	Data acquisition time for entire slice set (50 slices)	Spatial Resolution (reflection–in plane)	Minimal detectable sound speed variations	Minimal detectable variations in attenuation	Patient in and out time
1.5 MHz	256	0.1s	30s	0.4−0.7 mm	5 m/s	10%	5 min

Our approach differs from those cited earlier[13–14] for two major reasons. First, because CURE embodies a ring transducer that surrounds the breast, we collect the entire 2-D scattered field, which allows us to perform both transmission tomography and reflection tomography. As detailed below, this approach allows for measurement of a larger number of cancer detection criteria than is possible with transmission or reflection only. Second, the high data acquisition speed of the CURE scanner completely eliminates inter and intra-slice image motion artifacts. We believe that these two unique aspects of our approach will allow us to fully probe the clinical potential of US tomography.

The first clinical prototype has been integrated into the normal patient flow of the Walt Comprehensive Breast Center located at KCI. The purpose of this paper is to report on the initial clinical tests.

2. DATA COLLECTION AND ANALYSIS

2.1 Phantom Studies

The prototype device was installed in August, 2005 and first evaluated with phantoms. The breast phantom was built by Dr. Ernie Madsen of the University of Wisconsin and represents tissue-equivalent scanning characteristics of highly scattering, predominantly parenchymal breast tissue. It also mimics the presence of benign and cancerous masses embedded in glandular tissue, including a subcutaneous fat layer. The

phantom was scanned with CURE and representative images are shown in Fig. 1a–d.

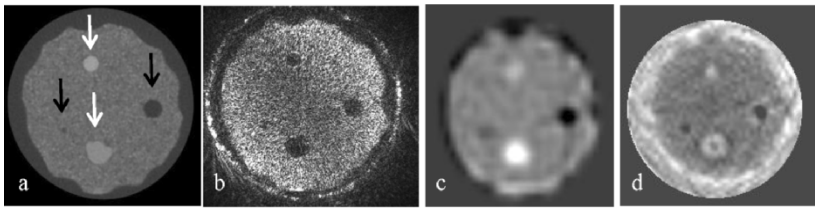

Figure 1. CURE Imaging of the breast phantom. From left to right: (a) an X-ray CT slice containing two fat spheres (black arrows) and two "cancerous tumors" (white arrows). The corresponding CURE images show (b) reflection, (c) sound speed and (d) attenuation. All four masses are detected in the three CURE images. Note the significantly different sound speed and attenuation of the benign and cancerous masses (c and d). Sound speed and attenuation values increase from black to white.

The phantom mass assessment was largely successful. The resolution, contrast and location accuracy met our milestone targets of 0.5 mm, SNR > 3 and +/- 5 mm, respectively. The sound speed characterization of the various phantom components also met the milestone targets, reaching an accuracy of 5 m/s. The targeted goal of measuring accurate mass attenuation, however, was not met. The primary reason for this was an unforeseen design flaw in the first transducer that led to random gain variations among the elements that make up the transducer. Since these gain variations were a function of time, it was not possible to calibrate them. Therefore, relative attenuation values were determined from manual calculations along each ray projection. Despite the labor-intensive nature of these manual calculations, proof of principle was demonstrated by generating attenuation images for 5 of the patients and the breast phantom (Figure 1d). Fortunately, these images serve as good estimates of future attenuation imaging capabilities with our new transducer ring, which is better matched to the attenuation algorithm. If necessary for the next series of patients, the flexible system architecture will allow continuous incremental design implementations upon the transducer and/or algorithm software in order to make any further design modifications a minor adjustment, rather than an impediment to further clinical progress.

Overall, CURE performance reached or exceeded most of our milestone targets, allowing us to proceed with the in-vivo testing. The clinical implications of these in-vivo tests are now described.

2.2 In-Vivo Testing

Patients were selected if they exhibited a suspicious mass after mammography and/or follow-up ultrasound at the Karmanos Cancer Institute (Walt Comprehensive Breast Center). The CURE exam was interposed between these conventional examinations and subsequent biopsy. Biopsy confirmation was therefore available for all recruited patients. Typically, 45 tomograms were taken of each patient with the CURE device. (Fig. 2a–f).

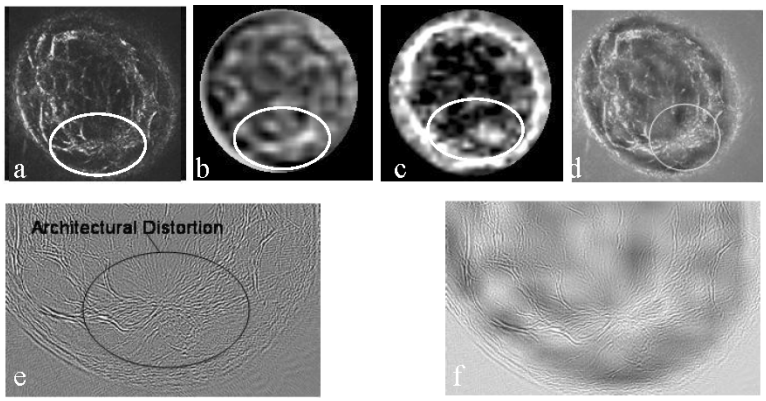

Figure 2. Images showing a 1 cm Invasive Ductal Carcinoma. (a) The reflection intensity image showing the region of architectural distortion, (b) the sound speed image showing elevated sound speed, (c) the attenuation image showing elevated attenuation, (d) reflection – sound speed overlay, (e) close up of edge reflection image showing the details of the architectural distortion and (f) detailed reflection – sound speed overlay showing the correlation of architectural distortion with elevated sound speed. The grey scale on the sound speed and attenuation images reflects quantitative changes in values. White indicates high sound speed/attenuation while black indicates low values. The CURE images reveal architectural distortion, elevated sound speed and elevated attenuation in the region of the tumor, all risk factors for cancer.

Analysis of the CURE images of the 19 patients in our initial sample, suggested that we could image a number of attributes relating to the mass shape, acoustic mass properties and architecture of the surrounding tissue. These attributes are listed below.

1. **Aspect** ratio (width to height) < 1.4: The mass appears more round than elliptical.
2. Irregular **Shape**: The tumor has an irregular contour, including a branching pattern or ductal extension.
3. Irregular **Margins**: includes spiculation, angular margins and/or microlobulation.

4. Architectural **Distortion**: Surrounding tissue shows altered anatomy (e.g. mass effect and/or retraction).
5. Elevated **Sound Speed**: Higher sound speed than surrounding tissue is noted within the mass. Typically the sound speed is elevated by 50 to 150 m/s relative to fat.
6. Elevated **Attenuation**: Higher attenuation than surrounding tissue is noted within the mass. The amount of enhancement varies but is typically about 0.5 dB/cm relative to fat at 1.5 MHz.

The first three attributes are linked to the acoustic shape of the mass as defined by the appearance of the mass in the CURE reflection images. They represent straightforward applications of the "Stavros" criteria[3]. The fourth attribute is linked to the architecture of the tissue surrounding the tissue. Architectural distortion is an attribute commonly measured in mammography. In the CURE data it is defined by the appearance of the tissue in our reflection images. The fifth and sixth attributes are unique to transmission ultrasound and were first defined by Greenleaf[10]. They represent the internal acoustic properties of the mass and are defined by the quantitative values measured in the CURE transmission images.

The above attributes are defined such that the probability of cancer increases with the number of attributes that are present. Despite the relatively small sample of patients in our data and the limits on attenuation measurements a trend is beginning to emerge in the application of these attributes. For the masses known to exist in each patient we determined, from the CURE images, whether a given attribute was present or not. The presence of each attribute was denoted qualitatively with a binary decision; 1 = "yes" or 0 = "no". The numbers assigned to the six attributes were then summed to provide a total score; the higher the score the greater the chance that a mass is cancerous. The results are shown in Fig. 3.

Figure 3 shows that an apparent separation exists in the cancer and benign patient distributions. The 9 patients with cancer have an average CURE score of 4.9 ± 0.8, while those with benign masses have an average score of 0.8 ± 0.6, ($p<0.0001$). These numbers suggest that a reasonable cutoff value for separating the two populations is 3. Despite the low number of patients analyzed thus far, a highly significant difference between the average probability score for benign and malignant masses was identified. Obviously, this is a highly selective series for patients with relatively large masses. A larger series appears likely to define a distinct cut-point in the probability score for differentiating benign from malignant masses.

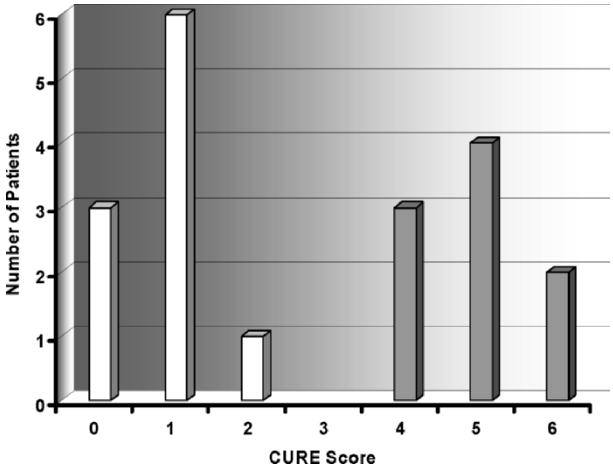

Figure 3. CURE scoring results.

Although the small sample size precludes a rigorous statistical analysis, these results demonstrate the feasibility of diagnostic imaging of breast lesions using the first-generation CURE device and justify its continued development as guided by the clinical results from our continuing studies. Future studies will focus on fine tuning of the CURE machine for reflection, sound speed and attenuation measurements as well as the statistically rigorous development of prognostic tables relating imaging findings to tissue characterization and differentiation of benign from malignant findings.

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