Journal of Medical Imaging

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Abstract. Image-guided core needle biopsy is the current gold standard for breast cancer diagnosis. Microcalcifications, an important radiographic finding on mammography suggestive of early breast cancer such as ductal carcinoma *in situ*, are usually biopsied under stereotactic guidance. This procedure, however, is uncomfortable for patients and requires the use of ionizing radiation. It would be preferable to biopsy microcalcifications under ultrasound guidance since it is a faster procedure, more comfortable for the patient, and requires no radiation. However, microcalcifications cannot reliably be detected with the current standard ultrasound imaging systems. This study is motivated by the clinical need for real-time high-resolution ultrasound imaging of microcalcifications, so that biopsies can be accurately performed under ultrasound guidance. We have investigated how high-frequency ultrasound imaging can enable visualization of microstructures in *ex vivo* breast tissue biopsy samples. We generated B-mode images of breast tissue and applied the Nakagami filtering technique to help refine image output so that microcalcifications could be better assessed during ultrasound-guided core biopsies. We describe the preliminary clinical results of high-frequency ultrasound imaging of *ex vivo* breast biopsy tissue with microcalcifications and without Nakagami filtering and the correlation of these images with the pathology examination by hematoxylin and eosin stain and whole slide digital scanning.

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Keywords: ultrasonics; imaging; tissues; transducers; acoustics; image processing.

Paper 15111R received Jun. 1, 2015; accepted for publication Oct. 27, 2015; published online Dec. 10, 2015.

1 Introduction

Image-guided needle biopsy is the gold standard for cancer diagnosis. These biopsies are generally performed under ultrasound guidance for masses and stereotactic guidance for microcalcifications.^{1,2} Ultrasound-guided biopsy is the preferred method of choice since it is more comfortable for patients and does not require ionizing radiation. Stereotactic-guided biopsy, however, is chosen over ultrasound-guided biopsy for microcalcifications since current standard ultrasound systems cannot reliably visualize microcalcifications, the presence of which can suggest early breast carcinoma such as ductal carcinoma *in situ* (DCIS). Thus, there is a clinical need for an ultrasound imaging tool that can be used in conjunction with the external ultrasound system to guide the needle during the biopsy of microcalcifications for accurate tissue sampling.

1.1 Clinical Need Background

Clinical ultrasound imaging has been validated as an effective tool in guiding percutaneous needle procedures such as central

venous catheterization³ and other needle biopsy procedures including transbronchial⁴ and pancreatic fine needle aspiration.⁵ Standard clinical ultrasound imaging relies on transmitting and receiving ultrasound energy. The redistribution of this energy from a transmitted wave occurs through either reflection, when the wavelength is smaller than the object it encounters, or scattering, when the wavelength is greater than or comparable to the dimension of the object. This is particularly relevant in breast imaging as the ability to identify and sample microcalcifications increases the probability of sampling potentially malignant tissue. The wavelengths of current clinical imaging systems (5 to 15 MHz) with respective wavelengths of 300 to 100 μm , limit the ability of receiving strong echo signals from microcalcifications. The size of microcalcifications, usually <100 μm , then entails that “scattering” becomes the dominant mode of energy redistribution obscuring their identification.⁶ Since the fundamental limitation of wavelength cannot be changed for these clinical imaging systems, attempts to improve image processing of ultrasound echo data to highlight these microcalcifications has been implemented by systems such as the Toshiba Aplipure System.⁷ The Aplipure system uses compound imaging to

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improve the contrast of breast images, which helps the user visualize microcalcifications within the tissue.⁸ Providing enhanced microcalcification visualization enables physicians to better target tissues they hope to sample with the core biopsy needle. As sampling error is the primary cause for false negative results, improving the resolution of specific structures (i.e., microcalcifications) that may represent DCIS is a promising solution that will improve the sensitivity of breast cancer biopsy procedures under ultrasound guidance. In summary, radiologists need an ultrasound system that can provide high-resolution images of tissue and structures such as microcalcifications in real-time to guide the biopsy needle, improve diagnostic accuracy, and reduce sampling error.

We have evaluated external and internal imaging arrays to address this clinical need. Given the small size of microcalcifications and the fact that lesions within the breast can be several centimeters below the skin's surface, imaging systems require axial and lateral resolutions that correspond to center frequencies above 50 MHz to resolve these individual structures. An external imaging probe is not a viable solution here since acoustic energy attenuation in tissue would be prohibitively large. Ultrasound probes that image the lesion from within the tissue, through an interventional tool such as a core biopsy needle, becomes a more viable solution. Under these conditions, the requirement for depth of penetration is limited to the tissue sampling distance of the core biopsy needle, which is <4 mm for most existing core biopsy needles. We have built and are currently evaluating this internal interventional imaging array and have designed a clinical imaging study to validate that high-frequency ultrasound imaging is useful for identifying tissue features such as microcalcifications to guide the tissue biopsy.

1.2 High-Frequency Imaging Array Development

This clinical study serves as a proof of concept that high-frequency imaging can provide clinically useful images to improve tissue visualization during ultrasound-guided breast biopsy. We are currently in development and have a prototype miniaturized high-frequency linear array integrated within a core biopsy needle to provide ultra-high-resolution images of breast tissue. Such images obtained within tissue may allow radiologists to identify features such as microcalcifications not previously seen during conventional biopsy guidance, thus procuring tissue with a higher diagnostic yield for malignancy and a lower false negative rate. The concept of integrating an ultrasound imaging array within a breast cancer biopsy needle has been demonstrated by Cochran et al.⁹ where they fabricated a 15-MHz linear array that can fit within a 2-mm diameter biopsy needle. This device is still limited, however, as imaging at 15 MHz cannot reliably provide the necessary resolution to differentiate small structures within the breast, such as lobules, ducts, or microcalcifications. We have thus embarked on building a much higher frequency array that can resolve these fine structures and does so from within the slender housing of a biopsy needle.

1.3 Motivation for Clinical Imaging Study

To validate the utility of a miniaturized high-frequency imaging array, we will demonstrate that high-frequency ultrasound imaging enables differentiation of cancerous tissue from normal tissue by analyzing tissue obtained during a clinical breast tissue study. Our clinical study's endpoints are designed to assess high-frequency ultrasound imaging's ability to visualize

microcalcifications in breast tissue by comparing high-frequency ultrasound images of breast biopsy tissue with digital pathology images, the gold standard for breast cancer diagnosis. In our study, the microstructures within breast tissue that are relevant to image-guided breast biopsy and breast cancer diagnosis are microcalcifications and necrotic tissue. The presence of microcalcifications has been shown to highly correlate with malignancy when cancer is present, and thus is a very useful feature during the biopsy guidance procedure.⁶

2 Methods

2.1 Clinical Study Design

The primary aim of this study is to confirm the presence of microcalcifications within breast tissue using high-frequency ultrasound imaging. To provide this confirmation, each biopsy specimen underwent histopathological sectioning and imaging, producing hematoxylin and eosin (H&E) pathology images that serve as a reference for the ultrasound images. Both high-frequency ultrasound and pathology image sets were generated in parallel imaging planes using a specimen handling and imaging technique described in the following sections. By generating ultrasound and pathology image sets with parallel image planes, features identified in the ultrasound image slices could be confirmed by matching them with those in the pathology image slices.

The method used to determine matches between ultrasound and pathology images was possible because of the orientation of both the ultrasound and pathology image planes and the presence of clear landmark features within the images (microcalcifications), which confirmed that the ultrasound and pathology image slices were correctly matched. The image sets were matched in the following way. First, the ultrasound and pathology image sets were arranged side-by-side. Next, landmark features, such as microcalcifications, were identified on the pathology images. Since the microcalcifications are three-dimensional objects, the pathology image slices where they first become visualized and when they no longer appear mark the extent of the width of the structure. The position of the structure within the biopsy specimen is noted in relation to its top and bottom surfaces and left and right ends. Once the width and position within the biopsy specimen of this microcalcification is known, the same structure is searched for in the ultrasound image set. Since the image sets are in parallel and the position and approximate width of the structure within the biopsy specimen is known, the microcalcifications can be identified in the high-frequency ultrasound image. Finally, the ultrasound and pathology image slices that both depict the microcalcification are arranged next to each other and displayed.

Ultrasound images were generated using a single element transducer with a press-focused, 2.25-mm diameter aperture, and a 3.4-mm focal depth, giving an f-number of 1.5. The transducer had a center frequency and a -6 dB bandwidth of 74 MHz and 27 MHz, respectively. The transducer's piezoelectric material was lead magnesium niobate-lead titanate (PMN-PT) (HC Materials, Bolingbrook, IL) and was backed by E-Solder 3022 conductive epoxy (Von Roll USA, New Haven, Connecticut). The first matching layer was made of 2 to 3- μ m diameter silver particles (Sigma Aldrich, St. Louis, Missouri) mixed with Insulcast 501 epoxy (ITW Polymers Coatings North America, Montgomeryville, Pennsylvania). The second matching layer was vapor-deposited parylene. The ground connection was made via a chrome/gold electrode plated across the front surface

of the 2 to 3 μm silver epoxy matching layer to the brass transducer housing. A SubMiniature version A (SMA) coaxial connector threaded into the back of the brass housing, completing the ground connection. The signal connection through the center signal port of the SMA connector shorted to the conductive silver

epoxy backing of the transducer. This SMA connector then connected to the pulser/receiver (Panametrics 5900PR, Olympus, Inc., Waltham, Massachusetts) via a coaxial cable and was secured in a fixture attached to the three-axis motorized positioner stage.

Fig. 1 (a) Outline of clinical study to examine efficacy of high-frequency ultrasound imaging in identifying cancer in breast biopsy core samples. (b) The ultrasound transducer scanned the biopsy samples while the specimen is secured in an agar gel block to maintain its orientation, enabling comparison between the ultrasound and the pathology image sets.

Fig. 2 Ultrasound B-mode images from (a)–(c) three consecutive image slices captured at 100 μm intervals. The circled feature is a highly echogenic specular reflector with acoustic shadowing directly below, which is consistent with a microcalcification.

We have obtained Institutional Review Board approval for this study and have collected and imaged tissue samples from our two institutions, the Norris Cancer Hospital, Keck Hospital of University of Southern California (USC) and the Los Angeles County-University of Southern California (LAC-USC) Medical Center. The study design is based on prior efforts to determine how well radiologists can classify tissue using ultrasound images obtained with clinical ultrasound machines and their correlation with known diagnoses determined by histopathological assessment.^{10,11}

Fresh biopsy specimens were obtained at both Norris Cancer Hospital and LAC+USC Medical Center, placed in plastic containers with phosphate-buffered saline solution and transported immediately to the ultrasound imaging lab on University Park Campus of USC. To standardize the plane of imaging for ultrasound image acquisition and the plane of sectioning for pathological assessment, biopsy specimens were encased in 3% agar gel (Fisher Scientific, Waltham, Massachusetts) within a Petri dish with the top portions exposed for ultrasound imaging. The agar gel served to keep the tissue specimen in a rigid position so that the pathology sectioning can be performed along parallel planes to the ultrasound image acquisition. Ultrasound B-mode images were collected at intervals of 100 μm . After the images were collected, a motorized stage with a razor blade attachment cuts smooth vertical walls into the agar gel. The agar gel with the encased biopsy specimen was then submerged in 10% neutral buffered formalin (pH 6.8 to 7.2 at 25) and transported to the Keck Hospital Pathology department where the gel-encased specimens were processed for pathology that included paraffin embedding, sectioning at 50 μm , and plating the tissue on glass slides for H&E staining. The pathology slides were then imaged with a Leica SCN400 digital pathology slide scanner (Leica Microsystems, Inc., Buffalo Grove, Illinois) and uploaded to the Leica digital image hub, an image storage database. The pathology images were then accessible for review, and comparison was made to the ultrasound images.

Pathology sections were taken from a plane parallel to that of the ultrasound images at 50 μm intervals instead of 100 μm

intervals to provide more pathology sections than ultrasound image slices. This oversampling of pathology image slices was implemented to account for the slight shrinkage of the specimen as it undergoes histopathological processing. In this study, it was not necessary to have exact 1:1 matching between ultrasound and pathology image slices because the features we were looking for, microcalcifications, were sufficiently wide that they spanned several ultrasound and pathology image slices. So the identification of these microcalcifications could be made by comparing several, adjacent ultrasound–pathology image pairs that all showed the microcalcification structure. Thus, oversampling the specimen with ultrasound and pathology image slices accounted for the fact that the ultrasound–pathology image set correspondence would not be exact.

2.2 Ultrasound Imaging System

The goal of the preliminary pilot study is to demonstrate that high-frequency ultrasound imaging enables radiologists to differentiate cancerous tissue from normal tissue using identifiable markers such as microcalcifications that have been associated with DCIS. Our clinical study endpoints are meant to provide a preliminary assessment of the effectiveness of high-frequency ultrasound imaging by comparing our newly acquired high-resolution ultrasound images of breast biopsy tissue with digital pathology images generated from the H&E sections of biopsy tissue. Figure 1 illustrates the clinical study design for imaging breast biopsy core tissue samples with ultrasound images using a single element transducer.

A Panametrics 5900PR pulser/receiver was used to send high-voltage pulses to and receive the low-voltage echo signals from the single element transducer. The receiver applied a 26 dB gain to the received echo signals. A digitizer (DynamicSignals LLC, Lockport, Illinois) with 1 GHz sampling frequency captured the radio frequency (RF) echo signal and transferred the data to a PC. A single pulse/echo signal formed each scanline during the image data capture process and scanlines were captured at 10 μm intervals and the scanline data set was

Fig. 3 Hematoxylin and eosin stained digital pathology images of biopsy core tissue sectioned at intervals of 50 μm .

Fig. 4 Comparison between (a) histological and (b) ultrasound images of an *ex vivo* breast core biopsy tissue sample.

Fig. 5 (a) Ultrasound B-mode image with two regions (A and B) identified for parameter estimation using the Nakagami filtering technique along with their respective (c) gray scale histograms. The *m*-parameter plot (b) shows that the left and right halves of this biopsy specimen are constituted of fat on the left and tumor.

reconstructed to form a log compressed gray scale B-mode image. Once each B-mode image was captured, the transducer was translated 100 μm perpendicular to the imaging plane, and the image process was repeated until images were captured across the entire width of the biopsy specimen which ranged from 2 to 4 mm. This image capture pattern is shown in Fig. 1.

2.3 Nakagami Filtering Technique

One additional focus of this clinical study is to apply tissue characterization algorithms to the captured ultrasound B-mode images to provide feature recognition for microcalcifications with the breast biopsy samples. This tissue characterization works by calculating the Nakagami parameter, which is generated from the ultrasound backscatter envelope of the B-mode image. The probability density function (pdf) of the ultrasonic backscatter envelope R is given by¹²

$$f(r) = \frac{2m^m r^{2m-1}}{\Gamma(m)\Omega^m} \exp\left(-\frac{m}{\Omega} r^2\right) U(r), \quad (1)$$

where $\Gamma(\cdot)$ and $U(\cdot)$ are the gamma function and the unit step function, respectively. $E(\cdot)$ denotes the statistical mean, the scaling parameter Ω , and the Nakagami parameter m , which corresponds to the Nakagami distribution. The scaling parameter can be obtained from $\Omega = E(R^2)$ and the Nakagami parameter is given by

$$m = \frac{[E(R^2)]^2}{E[R^2 - E(R^2)]^2}. \quad (2)$$

The scaling parameter Ω provides structural information of the tissue and the Nakagami parameter m is useful in

characterizing tissue type and is a shape parameter determined by the pdf of the backscatter envelope.¹²

3 Results

Ultrasound and pathology image sets were recorded and compared with each other. Ultrasound and pathology image sets were matched using microcalcifications as landmarks according to the method described previously. At least two separate ultrasound–pathology image pairs where microcalcifications were matched served as the bases of matching the ultrasound and pathology image sets. In each of these ultrasound–pathology image pairs at least one microcalcification match was observed. In ultrasound images, microcalcifications appeared as bright specular reflectors with acoustic shadowing. In pathology slides and their corresponding digital images, calcium phosphate microcalcifications appeared as dark purple refractile structures. Calcium oxalate crystals were not identified. Image sets were successfully aligned by indexing both image sets separately (i.e., 1, 2, 3, ...) then identifying these structures in both image sets.

3.1 Ultrasound and Pathology Imaging Results

By finding at least two matching image sets, all other image indices were able to be mapped to each other as the images were captured with fixed separation intervals. These matching image sets were comprised of individual image slices adjacent to each other. The microcalcifications imaged in this study were sufficiently wide that they spanned several image slices, therefore, adjacent image slices depicted the single microcalcification at its varying cross-sections. Figure 2 shows three adjacent

Fig. 6 (a) Pathology image with (b) Ω -parameter and m -parameter maps of ultrasound image as well as the (c) original B-mode image.

ultrasound B-mode image slices captured at 100 μm intervals from one biopsy specimen.

The presence of microcalcifications indicated by the white dashed circles in Fig. 2 was confirmed by matching these images with the corresponding pathology images shown in Fig. 3. Figure 3 shows three successive pathology slices captured at 50 μm intervals. Intervals for pathology image sets were chosen to be shorter than that for ultrasound image acquisition as biopsy specimens shrink when submerged in formalin, and we required an equal number of pathology and ultrasound images to compare the image sets.

After generating image sets using larger microcalcifications as landmarks, additional smaller microcalcifications were identified as shown in Fig. 4. Dashed circles in Fig. 4(b) highlight microcalcifications visualized with a single element ultrasound imaging system, and the dashed circles and arrows in Fig. 4(a)

show the matching features visualized with digital histology images.

3.2 Tissue Characterization Processing

Figure 5 shows the ultrasound B-mode image and the corresponding algorithmic display using the Nakagami filter technique. Rectangular regions A and B and the m -parameter display a plot of magnitude distribution versus normalized magnitude for the speckle pattern contained within these regions. The pathological images confirmed the presence of two distinct tissue types within the specimen, namely fat, highlighted in region A, and adenocarcinoma tumor, highlighted in region B.

The Nakagami filtering technique was applied to image sets from a different biopsy specimen with more microcalcifications identified during pathological analysis. Figure 6 demonstrates

Fig. 7 (a) Pathology image with regions highlighted by pathologists to indicate microcalcifications (red) and necrotic tissue (green). These region outlines were then matched to (b) the original B-mode image, (c) Ω -parameter, and (d) m -parameter maps of ultrasound image plotted over original ultrasound image. These parameter maps had a threshold applied to them so only regions of the highest parameter magnitude were displayed.

how both the Ω -parameter and m -parameter maps were plotted separately along with the corresponding pathology image.

The Ω -parameter maps seemed to show the microcalcifications especially when an amplitude threshold was applied as shown in Fig. 7. The absolute intensity level was adjusted until the parameter maps matched with the region identification maps created by the pathologists. This is likely due to the fact that the microcalcifications have very bright, homogenous speckle patterns that contrast greatly to the surrounding soft-tissue, which has more diffuse and lower intensity speckle patterns. These preliminary clinical imaging results and tissue characterization maps show promising useful clinical feature identification in breast tissue during high-frequency ultrasound imaging. Further investigation is underway to substantiate this approach.

4 Discussion

Initial results, based on radiologists reviewing both image sets simultaneously, suggest that high-frequency ultrasound imaging can identify microstructures such as microcalcifications that were previously seen only on mammography. This will allow biopsy of microcalcifications under ultrasound guidance with increased yield for accurate diagnoses of DCIS and decreased incidence of false negative results. We have preliminary confirmation that microcalcifications in the breast $<100\ \mu\text{m}$ in size can be clearly visualized with high-frequency ultrasound imaging. Additionally, Nakagami filtering techniques have been investigated to provide improved feature identification for biopsy specimens. Future work will include testing of transducer array performance within a biopsy needle and collection of tissue images to investigate how well microstructures such as microcalcifications can be identified in real-time.

Acknowledgments

This work was supported by the National Institutes of Health (NIH) through the Grant: P41-EB002182. This project was also supported in part by award number P30CA014089 from the NIH through the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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