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Update on Breast Cancer Detection Using Comb-push Ultrasound Shear Elastography

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Abstract

In this work, tissue stiffness estimates are used to differentiate between benign and malignant breast masses in a group of pre-biopsy patients. The rationale being that breast masses are often stiffer than healthy tissue; furthermore, malignant masses are stiffer than benign masses. The comb-push ultrasound shear elastography (CUSE) method is used to noninvasively assess a tissue's mechanical properties. CUSE utilizes a simultaneous multiple laterally spaced radiation force (ARF) excitations and detection sequence to reconstruct the region of interest (ROI) shear wave speed map, from which a tissue stiffness property is quantified by Young's modulus. In this study, the tissue stiffness of 73 breast masses is interrogated. The mean shear wave speeds for malignant masses (3.42 ± 1.32 m/s) were higher than benign breast masses (6.04 ± 1.25 m/s). These speed values correspond to higher stiffness in malignant breast masses (114.9 ± 40.6 kPa) than benign masses (39.4 ± 28.1 kPa and $p < 0.001$), when tissue elasticity is quantified by Young's modulus. A Young's modulus > 83 kPa is established as a cut-off value for differentiating between malignant and benign suspicious breast masses, with receiver operating characteristic curve (ROC) of 89.19% sensitivity, 88.69% specificity, and 0.911 for the area under the curve (AUC).

Keywords

Breast Cancer; Tissue Elasticity; In vivo; Ultrasound; Shear Wave

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Introduction

Mammography and conventional B-mode ultrasound (US) are the most common diagnostic methods for the detection of breast masses. Conventional B-mode US is used as an adjunct to mammography for breast imaging to improve sensitivity [1–4]. However, B-mode US has shown low specificity in the differentiation of benign from malignant breast masses [5–9]. In order to increase specificity, breast lesions are categorized according to the Breast Imaging-Reporting and data system (BI-RADS) criteria defined by the American College of Radiology (ACR)[10, 11]. Although increasing the specificity for malignant breast masses, the BI-RADS criteria generate a number of false positive results leading to number of unnecessary biopsies of benign breast lesions [12].

Shear wave elastography is an emerging field, that assesses a tissue's pathology based on its mechanical properties [13]. The premise is that malignant tissue are usually stiffer than benign tissue [14, 15]. Sarvazyan et al., proposed Shear Wave Elasticity Imaging (SWEI) [16] as a medical imaging modality. This modality employs acoustic radiation force (ARF) beams to generate shear waves within a tissue. The tissue stiffness is quantified from the measured shear wave speed. The most common breast SWEI methods are shear wave imaging using acoustic radiation force impulse (ARFI) [17] and SuperSonic Imagine (SSI) [18, 19]. ARFI shear wave imaging method employs an impulsive acoustic radiation force (ARF) to generate shear waves. Thereafter, pulse-echo ultrasound is used to track the shear wave in tissue. The measured shear wave speed is used to calculate the tissue stiffness [20–22]. SSI utilizes multiple consecutive ultrasound pulses to exert radiation force and establishes a supersonic regime of moving-source to generate approximately planar shear waves in the tissue. The motion of the tissue is captured at a high frame rate using plane-wave imaging technique [18, 19, 23]. The SSI system then creates a two-dimensional shear wave speed map. This information is used to obtain an estimate of tissue elasticity at each location expressed in units of kiloPascals (kPa) [24–32].

Song et al. [33, 34] have recently developed an ultrasound shear elastography technique called Comb-push Ultrasound Shear Elastography (CUSE) that uses multiple simultaneous laterally spaced ARF push beams. In CUSE, one can obtain a full field of view (FOV) shear wave speed, with a single push-detect data acquisition. The relatively short acquisition time of CUSE makes it less sensitive to interfering body or physiological motions (such as cardiac and breathing motions). In CUSE, the ARF push beams are laterally spaced to produce shear wave. The entire FOV is filled with shear waves travelling in both lateral directions (left-to-right and right-to-left). Thereafter, with the use of a directional filter, shear waves traveling in opposing directions are separated and used to assess the elasticity map of the full FOV under the transducer in one single comb-push acquisition [35]. The *in vivo* shear wave elastography using CUSE has been recently presented on differentiation of thyroid nodules [36] and initial results of breast cancer detection[37].

In this study, updates in the differentiation between benign and malignant breast masses using CUSE from our previous study [37] are presented. In comparison to the previous study, our cohort has increased from 54 to 73 patients with an additional 13 benign breast masses. A receiver operating characteristic curve analysis of our previous study established

an optimal Young's modulus cut-off value > 83 kPa with 87.10% sensitivity, 82.61% specificity and 0.88 area under the curve (AUC). The cohort of our study is described, as well as the statistical results of the CUSE performance are presented. Also, initial findings correlating stiffness with the histopathological characteristics of benign and malignant breast masses are discussed.

Methods and Materials

A. CUSE Imaging Method and System

CUSE is implemented on the V-1 system (Verasonics Inc., Kirkland, WA), a fully programmable ultrasound platform equipped with a linear array transducer. The ARF beams can be either unfocused (UCUSE) or focused (FCUSE)[33], depending on the depth of the mass. The FCUSE is used for deeper breast masses (>1cm).

Upon excitation of the tissue, the Verasonics system immediately switches to plane wave imaging mode to track the resulting shear wave propagation. The shear wave particle velocity is tracked by the compounding plane wave imaging method and calculated by the 1-D autocorrelation method using the in-phase/quadrature (IQ) data [29, 34, 38]. The push beams generate shear waves in the tissue, with some waves interfering with each other constructively and destructively. In order to construct a robust shear wave speed map, a directional filter is used to extract the left-to-right (LR) and the right-to-left (RL) propagating shear waves from the interfering waves at each pixel. Thereafter, a time-of-flight algorithm based on cross-correlating shear wave motion profiles along the lateral direction was used to calculate shear wave propagation speed [38]. As a shear wave quality control factor, a threshold is imposed on the normalized cross-correlation coefficient used during the shear wave speed calculation. Shear wave speeds with cross-correlation coefficients below this threshold were rejected. Thereafter, the final shear wave speed map is obtained by averaging LR and RL speed maps. The threshold is based on the quality of the final shear wave speed map. Quantitative measurements of tissue elasticity are obtained as the Young's modulus calculated from the mean shear wave speed of the tissue ROI. Assuming a linear, isotropic, incompressible and elastic soft-tissue the Young's modulus is obtained from the expression

$$E=3\rho c_s^2 \quad (1)$$

where $\rho = 1000 \text{ kg/m}^3$ is the density of the tissue and c_s is the shear wave velocity.

To demonstrate the ability of CUSE to differentiate stiff masses from soft materials, a phantom experiment was conducted. A CIRS spherical inclusion phantom (Model 059, CIRS Inc., Norfolk, VA) was used for our phantom experiment. This phantom is a breast elastography phantom (sound speed of 1540 m/s, ultrasound attenuation of 0.5 dB/cm/MHz, and density of 1030 kg m) with an inclusion shear wave speed about 1.73 times greater than that of the background. In Figure 2a, an inclusion situated in a homogeneous phantom, is excited by FCUSE ARF beams at a 4.09 MHz center frequency with 600 μs pulse duration. To track the resulting shear wave propagation, a three-angle compounding plane wave imaging at a 5 MHz center frequency is utilized. Directional filters are then used to separate

LR and RL shear waves. The directionally filtered shear waves with their corresponding speed maps are shown for the LR waves (Figures 2b and 2c) and the RL waves (Figure 2d and 2e). The color bar indicates the range of speeds on the shear wave speed maps. The final reconstructed shear wave speed map, in Figure 2d, demonstrates good contrast between the high shear wave region and the background material.

B. In vivo Human Study

Under an approved protocol by the Mayo Clinic Institutional Review Board (IRB), a total of 73 female patients with suspicious breast masses on their clinical evaluation were selected for this study. All of our patients have received a clinical ultrasound and mammography prior to participating in the study. CUSE was performed prior to biopsy in all cases. A written signed informed consent, approved by IRB, was obtained from enrolled patients. We excluded patients with a history of breast implants and mastectomies. The histology of the breast masses were established only from the core biopsy results. The lesions were categorized as benign and malignant.

CUSE evaluations were performed while the patient was in a supine or lateral oblique position. Conventional B-mode US was first performed to identify the area of the mass by an experienced sonographer. Thereafter, the probe was fixed in place by a lockable articulated arm. This breast mass area was marked on the image by freehand drawing, to identify the ROI. In order to reduce possible breathing motion artifacts, the patients were asked to momentarily suspend their respiration for each CUSE measurement. The histology of the masses was established only from core biopsy results. The lesions were categorized as benign and malignant.

Results and Discussions

The pathological diagnoses were 36 benign and 37 malignant masses. Benign and malignant breast masses showed a mean shear wave speed of 3.42 ± 1.32 m/s and 6.04 ± 1.25 m/s, respectively. The corresponding Young's modulus values are 39.4 ± 28.1 kPa and 114.9 ± 40.6 kPa for benign and malignant breast masses ($p < 0.001$), respectively. Note, the average normal breast tissue stiffness for our cohort is 14.1 ± 11.8 kPa Young's modulus. Applying the Young's modulus cut-off value > 83 kPa yields a receiver operating characteristic (ROC) curve analysis of 89.19% sensitivity, 88.89% specificity and 0.911 area under the curve (AUC). This is an improvement to the 87.10% sensitivity, 82.61% specificity and 0.88 AUC obtained from our previous study [37]. The cut-off elasticity value (> 83 kPa) is concordant with the > 80 kPa in previous studies [25, 37, 39] for suspicious breast mass. In Table 1, the sensitivity and specificity values for our study and previous studies are shown, along with the AUC for a ROC analysis.

Although, shear wave cut-off of > 50 kPa [9] (Evans et.al [28]) and > 60 kPa. (Barr [40]) have been reported, it should be noted that their patient cohort is vastly different from our patient population. Evans et al. had 4% and 38% of their benign breast masses from BIRADS 2 and 3. We recruited patients with suspicious lesions mainly composed of BIRADS 4 and 5.

In Figures 3, a few selected cases are reviewed. In Figures 3a and 3b, the US B-mode image and CUSE shear wave speed map of a 6mm (in the greatest dimension) benign intramammary lymph node are shown. The breast mass region (marked in red) has a Young's modulus of 30.9 kPa. In Figures 3c and 3d, an 8 mm benign fibroadenoma mass with myxoid change and apocrine metaplasia has a Young's modulus of 6.22 kPa. In Figures 3e and 3f, a 14 mm malignant mass with grade II invasive ductal carcinoma (IDC) has a Young's modulus of 111.9 kPa. In Figures 3g and 3h, a 16 mm malignant mass with grade I IDC has a Young's modulus of 83.3 kPa.

The pathology of the 36 benign lesions are shown in Table 2. It should be noted that some benign lesions have mixed pathologies. These lesions are classified by the pathology likeliest to result in the higher elasticity or placed in the other category. CUSE correctly identified 9 fibroadenomas for an elasticity cut-off value > 83 kPa. The mean stiffness of fibroadenomas were 24.79 ± 20.42 kPa. Breast masses with fibrocystic change ($n=5$) and papilloma ($n=6$) have a mean elasticity value of 37.69 ± 2.47 kPa and 32.44 ± 24.31 kPa, respectively. Of the 16 benign masses classified with other histology, four were classified as false positives by CUSE with a stiffness values higher than 100 kPa. Three of these benign masses had calcifications ($n=2$) and complex sclerosing ($n=1$). Calcifications have been shown to increase stiffness estimates in elastography evaluations [41]. Meanwhile, due to its fibrous structure complex sclerosing can induce false positives. The other false positives, were atypical ductal hyperplasia ($n=1$) and granulomatous inflammation ($n=1$) composition. Atypical ductal hyperplasia is known to be a possible precursor to malignancy.

In Table 3, the histopathology of the malignant breast masses are presented. Mixed pathology lesions are classified by the type likeliest to result in higher elasticity. The invasive status of the breast masses were ductal carcinoma *in situ* (DCIS) ($n=1$) and invasive carcinoma ($n=36$). The two DCIS masses were correctly classified by CUSE for >83 kPa elasticity cut-off value. The size of the DCIS masses was 66 mm with a 175 kPa elasticity value. The 36 invasive cancers had a mean size of 19 mm, with the greatest elasticity values occurring for 11 histological grade III (118.96 ± 10.36 kPa) and 9 lobular cancer (115.7 ± 29.11 kPa) histological types. It should be noted that one patient with an invasive cancer was not given a grade. In all, 32 invasive cancers were correctly classified as positive by CUSE for an elasticity cut-off value of > 83 kPa. The four false negatives were attributed to breast masses with small ROI cross-sections less than 0.49 cm^2 ($n=2$) and a small ratio of stiffness area to ROI cross-section ($n=2$).

In shear wave elastography studies using both commercially available breast SW systems (S3000, Siemens Ultrasound or SuperSonic Imagine, Aux en Provence, France), some breast cancers have shown low V_s that can be due a poor quality shear wave within the tumor [42] In a recent published study, Barr and Zheng [43] have shown that addition of quality measure (QM) of shear-wave (SW) velocity (V_s) estimation can increase SW elastography sensitivity for breast cancer [43] In our study, we did not intend to compare our technique using a research ultrasound machine to other available shear wave technologies, yet we did not experience cancers with low quality shear wave. In our study, as a measure of quality control, a threshold was imposed on the normalized cross-correlation coefficients were

generated during the local shear wave speed calculation. Shear wave speeds calculated at pixels below this threshold were rejected.

Although we did not assess the reproducibility, Cosgrove et al. [26] have shown shear wave elastography to be highly reproducible. One of the advantages of CUSE is that artifacts from body motion are reduced by fast acquisition (25 ms single push-detect cycle). Also, artifacts from pre-compression are reduced by applying minimal pressure on the ultrasound probe to the skin.

Several aspects of this study will require further investigation. First, the assessment of inter-observer variability, although, shear wave elastography techniques has been shown to be highly reproducible [26]. Second, correction for the effects of pre-compression on the over estimation for the elasticity values of breast masses [44]. Currently, we apply minimal pressure on the ultrasound probe to the skin.

Conclusions

In conclusion, the Young's modulus > 83 kPa is an optimal cut-off value for the ROC sensitivity and specificity for our study cohort. This is concordant with previous studies [25, 37, 39]. An improvement in the sensitivity and specificity in differentiating benign and malignant breast masses was observed with the additional number of benign cases from our previous study. These results demonstrate that CUSE may be used as a complimentary diagnostic tool to standard breast cancer modalities and could potentially aid in reducing the number of unnecessary biopsies.

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Figure 1.
(a) Unfocused and (b) focused acoustic radiation force beams

Figure 2. CUSE phantom experiment. (a) FCUSE excitation in the FOV. (b) RL shear wave propagation and (c) the corresponding speed map. (d) LR shear wave propagation and (e) its corresponding speed map. (f) Final shear wave speed map.

Figure 3.

US B-mode image and CUSE shear wave speed map for (a, b) benign intramammary lymph node, (c, d) benign fibroadenoma, (e, f) malignant mass with grade II IDC, and (g, h) malignant mass with grade I IDC.

Table 1

Statistical results

	CUSE Cut-off > 83 (kPa)	Chang et al. [25] Cut-off >80.17 (kPa)	Berg et al. [39] Cut-off > 80 (kPa)	Barr [40] Cut-off > 60 (kPa)	Evans et al. [28] Cut-off > 50 (kPa)
Sensitivity	89.19%	88.8%	97.2%	93%	97%–87%
Specificity	88.89%	84.9%	77.4%	89%	83%–78%
AUC	0.911	0.932	0.959	-	-

Table 2

Benign histopathology

Benign Lesion	Number of Patients	Average Young's Modulus (kPa)
Fibroadenoma	9	24.79 ± 20.42
Fibrocystic change	5	37.69 ± 2.47
Papilloma	6	32.44 ± 24.31
Other	16	43.99 ± 30.45

Table 3

Malignant histopathology

Malignant Histology		Number of Patients	Average Young's Modulus (kPa)
Invasive status	DCIS	1	175.10
	Invasive	36	113.19 $\pm$ 39.88
Histological grade	I	7	112.8 $\pm$ 18.05
	II	17	109.66 $\pm$ 51.33
	III	11	118.96 $\pm$ 10.36
Histological type	Ductal	27	112.33 $\pm$ 43.33
	Lobular	9	115.7 $\pm$ 29.11