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Commentary

Non-Invasive Quantitative Ultrasound Imaging for the Assessment of Therapy Response

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DESCRIPTION

Over the years, multiple imaging technologies have facilitated improvements in the treatment of cancers. Currently, technologies such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), ultrasound, and X-ray have revolutionized the way cancers are diagnosed and treated [1,2]. Quantitative Ultrasound (QUS) is one method that has gained a recent resurgence in interest by offering many advantages over other modalities. Such instruments are cost-effective, portable, and ionizing radiation-free [3]. Several studies have extensively explored the use of QUS in diagnostic as well as therapeutic imaging.

Prior to the work here, QUS has been implemented in several preclinical and clinical studies to monitor and predict cancer treatment responses [4-9]. Different parameters determined from QUS-digital RF data can be applied to assess treatment responses. These parameters include Mid-Band Fit (MBF), Spectral Slope (SS), 0-MHz Intercept (SI), and parameters determined through fitting of scattering models such as the Average Acoustic Concentration (AAC), Average Scatterer Diameter (ASD), and SAS (Spacing Among Scatterers). Parameters such as MBF, SS, and SI are determined by linear regression analysis using the normalized power spectra of RF ultrasound data, methodology described in [5-7]. The MBF is associated with scatterer size, acoustic concentration, and attenuation of the scatterer. The SI is related to scatterer size and acoustic concentration, whereas SS is related to scatterer size and attenuation [8,9]. The AAC, ASD, and SAS parameters can be estimated using a Spherical Gaussian Scattering Model (SGM) and a Fluid-Filled-Sphere Model (FFSM) form factor models to the ultrasonic Backscatter Coefficient (BSC) (methodology described in [10]. That study revealed 45% apoptotic cell death indicating at 24 hours after treatment corresponding to a maximum increase in SS with a value of 0.435 ± 0.07 dB/MHz. A similar increase in MBF was reported between 12 to 24 hours. At 48 hours with identical treatment conditions, approximately 50% of the cells had their nuclei compacted and-or fragmented as a result of late apoptosis. The disintegration of cell nuclei at 48 hours in that work resulted in a decrease in MBF and SS variables [11]. Thus, the study confirmed that there exists a direct link between cell death and ultrasound parameters. A clinical study conducted by Sadeghi-Naini, et al. with Locally Advanced Breast Cancer (LABC) patients receiving chemotherapy, reported similar outcomes. At week 4 of treatment, an increase in MBF, and SI was observed. The MBF value from non-responder to responder patients differed from 1.9 ± 1.1 dBr to 9.1 ± 1.2 dBr. Similarly, the SI variable differed from 1.6 ± 0.9 dBr to 8.9 ± 1.9 dBr from non-responder to responder patients. In addition, histopathology data from responding patients demonstrated minimal or no residual masses in mastectomy specimens however large residual masses were typically observed in the specimens of non-responder patients. The results demonstrated that patients responding to treatment showed significant changes in QUS parameters while in non-responders the parameters remained invariant [12]. Furthermore, parameters such as AAC and ASD have also been shown to strongly correlate with cell death. Evidence from previous clinical studies demonstrated substantial changes in AAC and ASD at weeks 1, 4, and 8 in LABC patients that responded to chemotherapy with a maximum increase in AAC observed at week 8. However, no such increase was observed in non-responding patients [6]. Similarly, a study with breast cancer xenografts upon exposure to chemotherapy revealed higher AAC associated with cell death levels nearing 60% at 24 hours after treatment. A strong correlation between AAC and cell death with (R^2 SGM=0.40) was reported in that work [7].

In our study, QUS was explored for the treatment of prostate cancer in vivo following treatment with Ultrasound-Stimulated Microbubbles (USMB) and Hyperthermia (HT) [13]. The study incorporated several treatment permutations including, varying ultrasound pressures (0, 246, and 570 kPa) and HT duration (0, 10, 40, and 50 min). A preclinical ultrasound system operating with a central frequency of 25 MHz was used for collecting the RF data. In order to evaluate the treatment response two scattering properties, namely AAC and ASD were estimated using SGM

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and FFSM form factor models. Results indicated that changes in AAC reflected changes in histological findings. AAC parameters using the SGM model significantly increased in combined treated groups of 246 kPa + 40 min, 246 kPa + 50 min, 570 kPa + 40 min, 570 kPa + 50 min depicting (mean ± sem) to 1.67 ± 0.22 dB/cm^3, 1.64 ± 0.40 dB/cm^3, 1.38 ± 0.32 dB/cm^3 and 1.75 ± 0.23 dB/cm^3, respectively compared to the control group of 0 kPa + 0 min (-0.56 ± 0.5). Similarly, an increase in AAC using the FFSM model was observed indicating values of 1.55 ± 0.25 dB/cm^3 at 246 kPa + 40 min, 1.48 ± 0.24 dB/cm^3 at 246 kPa + 50 min, 1.28 ± 0.23 dB/cm^3 at 570 kPa + 40 min and 1.53 ± 0.33 dB/cm^3 at 570 kPa + 50 min compared to the control group 0 kPa + 0 min (-0.21 ± 0.3 dB/cm^3). In contrast, the changes in ASD indicated a decreasing trend in the combined treated group. The results of this study further indicated an increase in BSC in the combined treated group likely due to the alteration of nuclear materials as a result of cell death. Lastly, a strong correlation between changes in AAC from SGM and cell death (R^2 =0.62) was illustrated using a graphical representation of a scatterplot that suggested higher changes in AAC coincident with cell death [13].

A study by Sadeghi-Naini, et al. explored different texture features to discriminate between benign versus malignant lesions in LABC patients. Based on the size, density, and distribution of acoustic scatterers, QUS texture parameters can be utilized to quantify intra-lesional heterogeneity providing a characterization of tissue microstructure. In their study, several texture features including Contrast (CON), Correlation (COR), Homogeneity (HOM), and Energy (ENE) were generated using parametric maps of MBF, SS, SI, SAS, AAC, and ASD. These texture features were then used as biomarkers to classify breast lesions. The results revealed significant differences in benign versus malignant lesions with ($p<0.05$) in most of the textural features [14].

CONFLICT OF INTEREST

There are no conflicts of interest.

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