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Non-invasive evaluation of breast cancer response to chemotherapy using quantitative ultrasonic backscatter parameters

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ABSTRACT

Tumor response to neoadjuvant chemotherapy in patients ($n = 30$) with locally advanced breast cancer (LABC) was examined using quantitative ultrasound. Three ultrasound backscatter parameters, the integrated backscatter coefficient (IBC), average scatterer diameter (ASD), and average acoustic concentration (AAC), were estimated from tumors prior to treatment and at four times during neoadjuvant chemotherapy treatment (weeks 0, 1, 4, 8, and prior to surgery) and compared to ultimate clinical and pathological tumor responses. Results demonstrated that among all parameters, AAC was the best indicator of tumor response early after starting treatment. The AAC parameter increased substantially in treatment-responding patients as early as one week after treatment initiation, further increased at week 4, and attained a maximum at week 8. In contrast, the backscatter parameters from non-responders did not show any changes after treatment initiation. The two patient populations exhibited a statistically significant difference in changes of AAC ($p < 0.001$) and ASD ($p = 0.023$) over all treatment times examined. The best prediction of treatment response was achieved with the combination of AAC and ASD at week 4 (82% sensitivity, 100% specificity, and 86% accuracy) of 12–18 weeks of treatment. The survival of patients with responsive ultrasound parameters was higher than patients with non-responsive ultrasound parameters (35 ± 11 versus 27 ± 11 months, respectively, $p = 0.043$). This study demonstrates that ultrasound parameters derived from the ultrasound backscattered power spectrum can potentially serve as non-invasive early measures of clinical tumor response to chemotherapy treatments.

1. Introduction

1.1. Locally-advanced breast cancer

One of the most common types of cancer diagnosed in women is breast cancer (American Cancer Society, 2013). Women with locally-advanced breast cancer (LABC) have poor long-term survival rates compared to early stage patients (5 year survival rate of ~55%) (Giordano, 2003). LABC comprises a wide range of clinical scenarios including T3/T4 disease tumor, includes tumor sized greater than 5 cm, and disease often involving the skin and chest wall with extensive axillary lymph node involvement. Standard therapy for LABC is multimodality treatment. This often starts with neoadjuvant chemotherapy to permit tumor shrinkage and metastatic control (typically mastectomy, sometime lumpectomy), and followed by surgery and then radiation therapy. However, LABC treatment remains controversial due to uncertainties in the optimization of treatment methodology (Esteva and Hortobagyi, 2008). Complete pathological response to chemotherapy treatment predicts good patient survival. Several studies demonstrated the importance of clinical and pathologic complete response to neoadjuvant chemotherapy as an indicator of a better outcome (Chollet et al., 1997; Smith et al., 2002). The early detection of treatment response of breast tumors is very important in order to be able to guide cancer therapy decisions based on individual patient responses (Esteva and Hortobagyi, 2008).

Clinical imaging techniques including mammography, CT, and magnetic resonance imaging (MRI) have been typically used for

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assessments of patient responses to cancer therapy based on anatomical tumor size measurements, typically months after treatment. However, changes in tumor size with cancer treatment are often the late cumulative result of early micro-structural changes in tumor cell morphology due to cell death, which start to take place within hours to days after treatment initiation. An imaging modality which can assess significant changes in cell-death related tumor micro-structure would be advantageous for the early assessment of treatment response and could facilitate the change of ineffective treatments early (within days), rather than having a patient subjected to months of an ineffective treatment.

1.2. Ultrasound imaging of biological tissues

Ultrasonic imaging has seen an increase in its utilization for diagnostic and therapeutic purposes over the last 50 years. It is highly sensitive to variations in micro-structural properties of tissues at many size scales. Ultrasound scattering is caused by differences in density and/or compressibility relative to the surrounding tissue across the ultrasound wave's propagation region. Backscattered acoustic signals from biological tissues contain information about the size, shape, number, and relative acoustic impedance of scattering regions within the tissues (Feleppa et al., 1997). The most popular way of displaying backscatter information is B-mode imaging. This technique uses the envelope of detected ultrasound echoes from a region of interest to typically create gray-scale images which display a cross-sectional map of the echo intensity. However, these images only use a fraction of the information contained in the signal. Several investigators have suggested that the frequency dependent information in ultrasonic echo signals can be related to acoustical and structural properties of tissue microstructure (Feleppa et al., 1986; Lizzi et al., 1988; Lizzi et al., 1997a, 1997b). The radio frequency (RF) spectrum of ultrasound backscatter signals has since been used in various tissue characterization applications such as the diagnosis of ocular tumors, examinations of liver and renal tissues, prostate cancer, and studies of cardiac and vascular abnormalities (Feleppa et al., 1997; Guimond et al., 2007; Lizzi et al., 1997a, 1997b; Yang et al., 2007). In most of these studies, spectral parameters were extracted from ultrasonic backscatter signals and related to specific pathological alternations of the investigated specimens. Those spectral parameters are mid-band fit, spectral slope, and 0-MHz intercept which are related to scatterer shape, size and acoustic concentration (product of number concentration of scatterer and the relative impedance difference between the scatterer and surrounding tissues) (Lizzi et al., 1988, 1997a, 1997b). These parameters are calculated from the linear regression analysis of backscatter power spectrum. More complex parameters are described below.

1.3. Cancer response monitoring using ultrasound

Treatments such as neoadjuvant chemotherapy for LABC patients can alter the structural and mechanical properties of tumor tissues. Tumor cell death is characterized often by nuclear condensation and fragmentation, and also features significant changes in cell structure and cellular organization. Tumor degeneration in response to treatment also exhibits considerable interactions with stromal cells (Schedin et al., 2007). All of these are expected to alter ultrasonic backscatter. In an *in vitro* ultrasound based non-invasive monitoring of epithelial cell death study, results demonstrated a reasonable correlation of spectral slope and integrated backscatter coefficient, which were extracted from ultrasound power spectra, to apoptotic cell death (Brand et al., 2009). In different cancer therapy response monitoring studies, high frequency quantitative ultrasound (20–50 MHz) was initially used to detect changes in tissue microstructure due to a variety of cancer therapies *in vitro*, in situ and *in vivo* (Banihashemi et al., 2008; Czarnota et al., 1999, 2012; Lee et al., 2012; Vlad et al., 2009, 2008). Other studies used high frequency quantitative ultrasound to detect apoptotic cell death in tumors treated with photodynamic therapy, X-ray radiation, and ultrasonically activated anti-vascular microbubble treatments in a variety of *in vivo* mouse models. Those studies demonstrated up to 16-fold maximal increases in observed backscatter signal intensity accompanied by changes in spectral parameters. Recently, in studies of treatment response monitoring in breast cancer xenograft tumors (Sadeghi-Naini et al., 2013a) and clinical breast tumors treated with chemotherapy (Sadeghi-Naini et al., 2013b) using low-frequency clinical range (7 MHz) quantitative ultrasound spectral parameters, responding tumors demonstrated approximately up to a 7 to 12 – fold maximal increase in mid-band fit and 0-MHz intercept and 8 to 9 – fold maximal increases in mid-band fit and 0-MHz intercept after cancer therapy initiation.

1.4. Backscatter parameter estimation for tissue characterization

Acoustic scattering theories for biological tissues assume that tissues can be modeled as low density of random scatterers (Oelze and Zachary, 2006; Oelze et al., 2004, 2002). Since there are a large number of interdependent properties embedded in backscatter signals, it is difficult to extract estimates of individual properties accurately without simplifying assumptions. The average scatterer size and average acoustic concentration which reflect tissue microstructure observed from microscopic optical histological evaluation can be estimated from backscatter signals by assuming their shape, organization and elastic properties of scatterers in the medium (Oelze et al., 2002, 2004). This ultrasonic backscatter parameter estimation technique has been used to classify tissue abnormalities compared to normal tissues and to differentiate one tumor type from another. In those studies, several types of nonlinear frequency-dependent scattering models have been utilized to describe tissue micro-structure including the Gaussian, fluid-filled sphere, and spherical-shell models (Feleppa et al., 1997; Insana and Hall, 1990; Oelze and O'Brien, 2006). Among them, backscatter parameters estimated using the fluid-filled sphere model (FFSM) have demonstrated reasonable correlations with tissue micro-structure (Oelze and O'Brien, 2006). The quantitative ultrasound parameters used in the previous studies for tissue characterization are listed below in Table 1 with their proper definition and tissue features which determine the value of each parameter.

Previously, observational tumor response monitoring studies have been conducted with retrospective analyses of patient outcomes in breast cancer patients receiving chemotherapy treatment, using elastography and quantitative ultrasound imaging techniques (Falou et al., 2013; Sadeghi-Naini et al., 2013b). Specifically, strain ratios and strain differences in elastography, and spectral parameters in quantitative ultrasound have been correlated to treatment response. In the study here, the integrated backscatter coefficient and two individual structural properties such as average scatterer size and average acoustic concentration were determined from ultrasonic backscatter signals. These are used here for the first time to monitor micro-structural alternations within tumors in 30 LABC patients after chemotherapy treatment and to evaluate whether the patients have been responsive or not to their treatments. The FFSM was used to extract backscatter properties from breast tumors over a frequency bandwidth of 4.5–9 MHz. The clinical-response –based survival curve, which is determined months later at the time of surgery has been presented in this study in order to highlight the importance of treatment with tumor response in comparison therapy without response, since the lack of such response can significantly impact patient survival.