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# Noninvasive Characterization of Locally Advanced Breast Cancer Using Textural Analysis of Quantitative Ultrasound Parametric Images

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## Abstract

*PURPOSE:* The identification of tumor pathologic characteristics is an important part of breast cancer diagnosis, prognosis, and treatment planning but currently requires biopsy as its standard. Here, we investigated a noninvasive quantitative ultrasound method for the characterization of breast tumors in terms of their histologic grade, which can be used with clinical diagnostic ultrasound data. *METHODS:* Tumors of 57 locally advanced breast cancer patients were analyzed as part of this study. Seven quantitative ultrasound parameters were determined from each tumor region from the radiofrequency data, including mid-band fit, spectral slope, 0-MHz intercept, scatterer spacing, attenuation coefficient estimate, average scatterer diameter, and average acoustic concentration. Parametric maps were generated corresponding to the region of interest, from which four textural features, including contrast, energy, homogeneity, and correlation, were determined as further tumor characterization parameters. Data were examined on the basis of tumor subtypes based on histologic grade (grade I versus grade II to III). *RESULTS:* Linear discriminant analysis of the means of the parametric maps resulted in classification accuracy of 79%. On the other hand, the linear combination of the texture features of the parametric maps resulted in classification accuracy of 82%. Finally, when both the means and textures of the parametric maps were combined, the best classification accuracy was obtained (86%). *CONCLUSIONS:* Textural characteristics of quantitative ultrasound spectral parametric maps provided discriminant information about different types of breast tumors. The use of texture features significantly improved the results of ultrasonic tumor characterization compared to conventional mean values. Thus, this study suggests that texture-based quantitative ultrasound analysis of *in vivo* breast tumors can provide complementary diagnostic information about tumor histologic characteristics.

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## Introduction

Breast cancer is the most frequently diagnosed cancer in women, excluding skin cancer, and the second most common cause of cancer related death in women [1]. In the United States, breast cancer affects one in eight women over the course of their lifetime [2]. Breast cancers range from small early-stage tumors to larger locally advanced cancers. Early stage breast tumors tend to be less than 2 cm in size and low in histologic grade. Locally advanced breast cancer (LABC), on the other hand, is an aggressive subtype of breast cancer (mainly stage III) that is clinically characterized as being larger than 5 cm, often unresectable, and with chest wall, ipsilateral supraclavicular, infraclavicular, skin, or lymph node involvement. Despite treatment efforts using systemic chemotherapy, surgery, and radiation therapy,

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estimated 3- and 5-year survival rates of 70% and 55% were reported, respectively, in the United States in 2004 for women with stage III breast cancer [3]. LABC outcomes are typically worse, with 5-year survival rates less than 50% [4].

An accurate diagnosis of breast tumors plays an important role in prognosis and therapy planning, and can improve overall survival. X-ray mammography is currently the primary imaging modality for breast examinations. However, mammographic sensitivity declines significantly with increasing breast density particularly in young women [5]. Clinical ultrasound, when performed in conjunction with mammography, has been reported to increase diagnostic accuracy (area under the receiver-operator characteristic [ROC] curve) from 0.78 to 0.91 [6]. However, due to the many instrument parameters that can be chosen during an ultrasound imaging session, a comparative interpretation of conventional B-mode images becomes difficult when different imaging settings are applied or when different ultrasound machines are used. In addition, B-mode images, which are used by radiologists for breast examination, lack readily accessible information about microstructural properties of soft tissues. This information is lost when raw ultrasound data, or radiofrequency (RF) data, are converted to gray-scale pixels. Quantitative ultrasound (QUS) techniques, which examine the frequency dependence of backscatter from tissues (from analyzed RF data), have been developed to overcome these limitations. Such techniques have been applied *in vivo* in a variety of applications to reveal information about tissue microstructure, enabling the differentiation of disease from nondisease and the characterization of disease into its subtypes. Applications include the characterization of tissue abnormalities, such as those in the eye, prostate, and myocardium, and to detect and classify cancer in the lymph nodes [7–10]. Specifically, QUS parameters including average scatterer diameter (ASD) and average acoustic concentration (AAC; related to effective scatterer number density and relative acoustic impedance) have demonstrated the potential to be used to distinguish between mouse models of mammary carcinoma and rat models of fibroadenoma. These parameters can be obtained by fitting a form factor model, such as the Gaussian form factor, to the measured backscatter coefficient [11–13]. To avoid complex model fitting, basic spectral parameters extracted via a linear regression analysis of the RF power spectrum, including mid-band fit (MBF), spectral slope (SS), and spectral 0-MHz intercept (SI), have also been used for tissue characterization previously [7–10]. By modeling the ultrasonic power spectrum as an acoustic impedance autocorrelation function, Lizzi et al. demonstrated that parameters, extracted from a linear fit to the power spectrum within the usable frequency bandwidth, are related to the scattering properties of the tissue of interest. In particular, they found that SS is related to effective scatterer size and attenuation, SI is related to effective scatterer size and acoustic concentration, and MBF is related to effective scatterer size, acoustic concentration, and attenuation [14,15]. As frequency-dependent backscatter measurements are affected by the inherent frequency-dependent attenuation of intervening tissues, it is standard to compensate the tissue power spectrum for frequency-dependent attenuation before computing spectral parameters, as done in many studies [8–10].

Frequency-dependent attenuation has also been shown to be a useful parameter in characterizing tissues, especially tumors and normal tissues of the breast [16]. Furthermore, a previous clinical study found large variations in the attenuation coefficient estimates (ACEs) among breast carcinoma tumors (1.16±0.8 dB/cm per MHz), which included invasive ductal carcinoma, invasive lobular carcinoma, intracystic papillary carcinoma, and adenocarcinoma [17]. Another parameter, scatterer spacing, also known as spacing among scatterers (SAS), has been investigated as a tissue characterization parameter when the tissue of interest contains detectable periodicity in its structural organization. Previous studies have investigated the potential of SAS mainly for characterizing diffuse diseases of the liver [18,19]. For instance, in [20], the interscatterer distribution and the mean scatterer spacing (MSS) were examined in focal diseases of the liver using wavelet transform–based methods, whereas in [21], the MSS was considered for characterization of pathologic human liver using Fourier transform–based methods. The terms *SAS* and *MSS* are used interchangeably in the literature to refer to the mean scatterer spacing in a scattering volume. More recently, SAS was used to characterize human breast tumors in terms of normal breast tissue, fibroadenoma, simple carcinoma, and infiltrating papillary carcinoma [22]. SAS was determined to be 1.25 ± 0.21 μm for normal breast tissue, 0.82 ± 0.10 μm for simple carcinoma, 0.92 ± 0.09 μm for infiltrating apillary carcinoma, and 1.09 ± 0.07 μm for breast adenoma; however, no statistical significance tests comparing these tissue abnormalities were reported.

Whereas the conventional quantitative ultrasound spectral parameters discussed above describe the frequency-dependent properties of tissue microstructure, an analysis of textural characteristics of QUS-based parametric maps can potentially provide second-order statistics by quantifying the patterns of gray-level transitions. In 1983, Wagner et al. demonstrated that the second-order statistical properties (based on the Rayleigh distribution) of B-mode images carry subresolution information about the medium's microstructure [23]. Following this work, various statistical models were developed to further characterize the textural properties of B-mode images [24,25]. Alternatively, second-order textural properties of images, including but not limited to ultrasound, can be quantified using the gray-level co-occurrence matrix (GLCM). Initially developed as an image classification tool for landmark aerial photographs and sandstone photomicrographs [26], the application of the GLCM was later extended to ultrasound tissue characterization, such as discriminating between benign and malignant breast tumors [27,28]. The principle behind this tissue classification technique is that malignant tumors tend to present as heterogeneous internal echoes, whereas benign masses often demonstrate homogeneous internal echoes. Textural analysis techniques aim at extracting the tissue internal echo properties or "texture," based on the ultrasonic gray-level transitions, and hence can define differentiable characteristics in this application. However, previous studies [27,28] have used conventional B-mode images for textural analysis, which may present undesirable variations in textural estimates due to variations in instruments settings, ultrasound beam diffraction, and attenuation effects. Such limitations can be addressed by performing texture analysis on quantitative ultrasound parametric images for which these artifacts have been compensated. In a study by Sadeghi-Naini et al. [29], texture analysis based on a GLCM was applied to ultrasonic parametric maps (i.e., MBF, SS, and SI) to characterize tumor cell death responses to chemotherapy *in vivo*. Extracted GLCM features were contrast, energy, and homogeneity. In a study by Tadayyon et al. [30], a similar texture analysis was applied to ASD, AAC, and SAS images of LABC tumors in addition to MBF, SS, and SI images for purposes of tumor grade discrimination. Here, we examined the means and four GLCM features (contrast, correlation, energy, and homogeneity) of six QUS parameters, as done in [30], for