Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2018

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2018.02.014

● *Original Contribution*

HIGH-FREQUENCY QUANTITATIVE ULTRASOUND FOR IMAGING PROSTATE CANCER USING A NOVEL MICRO-ULTRASOUND SCANNER

Daniel Rohrbach,* Brian Wodlinger,† Jerrold Wen,† Jonathan Mamou,* and Ernest Feleppa*

* Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY 10038, USA; and † Exact Imaging, Markham, Ontario, Canada

(*Received* 14 *August* 2017; *revised* 20 *February* 2018; *in final form* 26 *February* 2018)

Abstract—Currently, biopsies guided by transrectal ultrasound (TRUS) are the only method for definitive diagnosis of prostate cancer. Studies by our group suggest that quantitative ultrasound (QUS) could provide a more sensitive means of targeting biopsies and directing focal treatments to cancer-suspicious regions in the prostate. Previous studies have utilized ultrasound signals at typical clinical frequencies, *i.e.,* in the 6-MHz range. In the present study, a 29-MHz, TRUS, micro-ultrasound system and transducer (ExactVu micro-ultrasound, Exact Imaging, Markham, Canada) was used to acquire radio frequency data from 163 patients immediately before 12-core biopsy procedures, comprising 1956 cores. These retrospective data are a subset of data acquired in an ongoing, multisite, 2000-patient, randomized, clinical trial (clinicaltrials.gov NCT02079025). Spectrum-based QUS estimates of effective scatter diameter (ESD), effective acoustic concentration (EAC), midband (M), intercept (I) and slope (S) as well as envelope statistics employing a Nakagami distribution were used to train linear discriminant classifiers (LDCs) and support vector machines (SVMs). Classifier performance was assessed using area-under-the-curve (AUC) values obtained from receiver operating characteristic (ROC) analyses with 10-fold cross validation. A combination of ESD and EAC parameters resulted in an AUC value of 0.77 using a LDC. When Nakagami-μ or prostate-specific antigen (PSA) values were added as features, the AUC value increased to 0.79. SVM produced an AUC value of 0.77, using a combination of envelope and spectral QUS estimates. The best classification produced an AUC value of 0.81 using an LDC when combining envelope statistics, PSA, ESD and EAC. In a previous study, B-mode-based scoring and evaluation using the PRI-MUS protocol produced a maximal AUC value of 0.74 for higher Gleason-score values (GS >7) when read by an expert. Our initial results with AUC values of 0.81 are very encouraging for developing a new, predominantly user-independent, prostate-cancer, risk-assessing tool. (E-mail: drohrbach@RiversideResearch.org)

Key Words: **Prostate cancer, Quantitative micro-ultrasound, High frequency, Quantitative ultrasound, QUS.**

Prostate cancer (PCa) is the most prevalent, non-cutaneous, male malignancy in the United States, with an estimated 181,000 new diagnosed patients in 2016 and about 26,000 PCa-related deaths, which makes PCa the second leading cause of male-cancer–related death in the United States (American Cancer Society 2016). Currently, no imaging device or technology is available that reliably detects clinically significant cancerous regions in the prostate. Screening is performed using a digital rectal examination and prostate-specific antigen (PSA) assay, and definitive diagnosis is determined by a pathologist examining tissue samples obtained by transrectal-ultrasound (TRUS) guided biopsies. However, PCa is not well visualized in TRUS-based B-mode images, which has led to a systematic biopsy procedure typically employing 12 uniformly spaced tissue samples rather than by targeted sampling of suspicious regions. Thus, TRUS-guided biopsies have a high rate of false-negative outcomes (Applewhite et al. 2002; Feleppa et al. 2001b; Haas et al. 2007) and biopsy-related morbidity, hemorrhage and infection (Loeb et al. 2012). Furthermore, the current approach makes focal treatments difficult because the biopsy gives insufficient information about the extent and severity of disease.

Results from recent studies suggest a good classification performance of multi-parametric magnetic resonance imaging (mpMRI) (Barentsz et al. 2012; Felker et al. 2016; Gupta et al. 2013; Hricak et al. 2007; Qian et al. 2016; Trigui et al. 2017). The ability of mpMRI to include

Address correspondence to: Daniel Rohrbach, Lizzi Center for Biomedical Engineering, Riverside Research, 156 William Street, 9th Floor, New York, NY 10038, USA. E-mail: drohrbach@RiversideResearch.org

functional parameters in PCa MRI analysis has yielded promising results. New tools that allow co-registering mpMRI data acquired before a TRUS examination with B-mode TRUS images used to guide biopsies are rapidly emerging in clinical settings. Parameter maps derived from mpMRI overlaid on B-mode images highlight tissue areas suspicious for PCa. Nevertheless, the application of mpMRI to screening, image-directed biopsy, or treatment planning still has limitations (Sosnowski et al. 2016) and is costly (Manley et al. 2016), which motivates development of novel, patient-tolerated, ultrasound-based imaging technologies that maintain the current cost-effectiveness and streamlined workflow of conventional TRUS-guided biopsies (Palmeri et al. 2016).

Recently, elasticity-imaging approaches using acoustic radiation force impulse (ARFI) imaging have demonstrated promising results in imaging PCa (Palmeri et al. 2015, 2016). However, application using high-frequency ultrasound (*i.e.,* >20 MHz) is difficult because of the lesser penetration depth of the ARFI *push* beam and increased risk of tissue heating at higher frequencies. Another promising ultrasound-based approach was recently published by Wildeboer et al. (2017) who employed dynamic multiparametric contrast-enhanced ultrasound for PCa imaging.

Previous studies by our group demonstrated the encouraging ability of classifiers based on quantitative ultrasound (QUS) to type prostate tissue and to identify regions in the prostate that are suspicious for cancer (Feleppa 2015; Feleppa et al. 1996). Originally, the term *QUS* was applied to spectrum analysis, seeking to derive quantitative, system and user-independent tissue properties that are related to ultrasound scattering. In the past decade, the term *QUS* is becoming more generalized to include any signal-processing approach that quantitatively exploits the information contained in the original, radio frequency (RF) echo signals, such as methods that derive estimates from the statistics of envelope signals computed from linearly processed RF data (Mamou and Oelze 2013; Porter and Wolff 2015). A QUS-based tool that reliably detects cancerous regions in the prostate would reduce the currently high numbers of false-negative diagnoses and excessive truly negative, and therefore unnecessary, biopsies. Our previous studies reported a value of 0.84 for the receiver operating characteristic (ROC) area under the curve (AUC) (Feleppa 2015) if a multi-layer perceptron (MLP) was trained, using PSA and two QUS parameters, intercept and midband, as classification features.

Recently, Exact Imaging ([EI] Markham, Ontario, Canada) developed a 29-MHz micro-ultrasound device (ExactVu micro-ultrasound) for TRUS-guided prostate biopsies. Because of the finer resolution, imaging features associated with cancer were found to be significantly different from those commonly used in conventional ultrasound (*e.g.,* hypoechoic areas or gross deviations in prostate capsule). To interpret these new fine-resolution images correctly, Ghai et al. (2016) established the prostate-risk-identification-using-micro-ultrasound (PRI-MUS) protocol for PCa-risk identification in the peripheral zone of the prostate, based on the initial data from about 400 patients. The PRI-MUS protocol provides a subjective, user-dependent, B-mode–based scoring system for estimating PCa likelihood. This method demonstrated an encouraging maximal AUC value of 0.74 for higher Gleason-score values (GS >7) when read by an expert (Ghai et al. 2016).

The aim of the current research was to investigate the potential of higher frequencies and broader bandwidths available in the EI ultrasound scanner to improve the ability to detect PCa by means of QUS. Several other studies demonstrate the potential of QUS at high frequencies. For example, in another project involving high-frequency ultrasound scanners (*i.e.,* 25.6 MHz), our group showed that metastases in excised, human lymph nodes can be detected reliably with AUC values of up to 0.98 by using only a QUS-based, scatterer-size estimate as a single feature with a linear discriminant classifier (Mamou et al. 2011a, 2011b).

MATERIALS AND METHODS

Data acquisition

A transrectal, ExactVu micro-ultrasound system was used with a 29-MHz transducer to acquire RF echo-signal data in the prostate during TRUS-guided core-needle biopsy examinations. The 29-MHz center-frequency, side-fire probe consisted of 512 elements and acquired a single sagittal image (*i.e.,* 512 RF lines) of the prostate for each biopsied region. Two identical probes (*i.e.,* same model number) were used with the system. The probes were alternated between patients to maintain the clinical workflow.

Using the ExactVu device immediately before obtaining each of the 12-core needle biopsies to provide ultrasound RF data for 1968 cores in this retrospective study, we acquired ultrasound RF echo-signal data acquired from 163 patients. These data are a subset of data acquired in an ongoing, multisite, 2000-patient, randomized, clinical trial entitled "Multi-Center Trial of High-resolution Transrectal Ultrasound Versus Standard Low-resolution Transrectal Ultrasound for the Identification of Clinically Significant Prostate Cancer" (clinicaltrials.gov NCT02079025). This clinical trial was designed to compare the new micro-ultrasound imaging modality against conventional ultrasound by examining overall PCa-detection rate on prostate biopsy with each modality. Details about the patient data set can be found in previous publications (Ghai et al. 2016; Pavlovich et al. 2014). The data set used in this study was obtained solely