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● *Original Contribution*

3-D QUANTITATIVE DYNAMIC CONTRAST ULTRASOUND FOR PROSTATE CANCER LOCALIZATION

Stefan G. Schalk,*,† Jing Huang,‡ Jia Li,‡ Libertario Demi,* Hessel Wijkstra,*,† Pintong Huang,‡ and Massimo Mischi*

* Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; † Department of Urology, Academic Medical Center, Amsterdam, The Netherlands; and ‡ Department of Ultrasound, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

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Abstract—To investigate quantitative 3-D dynamic contrast-enhanced ultrasound (DCE-US) and, in particular 3-D contrast-ultrasound dispersion imaging (CUDI), for prostate cancer detection and localization, 43 patients referred for 10–12-core systematic biopsy underwent 3-D DCE-US. For each 3-D DCE-US recording, parametric maps of CUDI-based and perfusion-based parameters were computed. The parametric maps were divided in regions, each corresponding to a biopsy core. The obtained parameters were validated per biopsy location and after combining two or more adjacent regions. For CUDI by correlation (r) and for the wash-in time (WIT), a significant difference in parameter values between benign and malignant biopsy cores was found ($p < 0.001$). In a per-prostate analysis, sensitivity and specificity were 94% and 50% for r, and 53% and 81% for WIT. Based on these results, it can be concluded that quantitative 3-D DCE-US could aid in localizing prostate cancer. Therefore, we recommend follow-up studies to investigate its value for targeting biopsies. **(E-mail: stefan.schalk@gmail.com)**

Key Words: **Contrast ultrasound, Dynamic contrast-enhanced ultrasound, 3-D ultrasound, Prostate cancer imaging, Dispersion imaging, Quantitative, Core needle biopsy, Systematic biopsy.**

INTRODUCTION

The current standard method for prostate cancer (PCa) diagnosis is transrectal ultrasound (TRUS)-guided systematic biopsy, usually after suspicion has been raised by digital rectal examination (DRE) or an elevated serum prostate-specific antigen (PSA) level (Heidenreich et al. 2014). However, systematic biopsies frequently miss or undergrade tumors (Bjurlin et al. 2013; Kvåle et al. 2009). In the latest international guidelines, multiparametric magnetic resonance imaging (mpMRI) is recommended for patients with persistently elevated PSA level and a prior negative biopsy session (Barentsz et al. 2012; Heidenreich et al. 2014). However, MRI investigations cannot be performed at the bedside and are relatively costly. Several alternative TRUS-based techniques, such as (shear-wave) elastography, computer-aided TRUS and dynamic contrast-enhancedultrasound (DCE-US), have been developed and they show promise for PCa detection (Sarkar and Das 2016).

In DCE-US, intravenously injected microbubbles with a size comparable to red blood cells are used as contrast agents. Although the resolution of DCE-US imaging is not in the range of the size of the microvasculature, the kinetics of the microbubbles through the microvasculature can be captured by recording their concentration over time. PCa growth requires angiogenic microvasculature, which has different structural properties (*e.g.,* increased tortuosity, presence of arteriovenous shunts, increased permeability) resulting in different microbubble kinetics (Russo et al. 2012). Therefore, several studies have been carried out using DCE-US imaging qualitatively to detect PCa (Halpern et al. 2012; Pallwein et al. 2008; Xie et al. 2012). DCE-US features related to PCa are rapid contrast enhancement, increased contrast enhancement and asymmetric flow patterns (Aigner et al. 2009; Seitz et al. 2011); however, their effects are usually very subtle and vanish within seconds. Consequently, interpretation of DCE-US recordings is rather subjective without technical aid. To increase objectivity and improve accuracy, the possibility

Address correspondence to: Stefan Schalk, Department of Electrical Engineering, Eindhoven University of Technology, Postbus 513, Flux 7.074, 5600 MB, Eindhoven, The Netherlands. E-mail: stefan.schalk@gmail.com

of using quantitative methods by extracting perfusion-based parameters from DCE-US recordings have been investigated (Cosgrove and Lassau 2010; Frinking et al. 2010; Smeenge et al. 2011). More recently, contrast-ultrasound dispersion imaging (CUDI) has been proposed as a novel approach to distinguish between angiogenic and healthy vasculature by focusing on contrast dispersion rather than on perfusion (Kuenen et al. 2011, 2013a, 2013b; Schalk et al. 2017). In fact, it was hypothesized that dispersion better reflects the underlying micro-vascular differences. At the origin of this technique, a model was fitted to acoustic time-intensity curves (TICs) in each pixel of a DCE-US recording (Kuenen et al. 2011). From the fit, a dispersion-related parameter could be extracted. Later it was shown that the similarity between neighboring TICs could be used as an indirect measure of local dispersion, which lead to better classification results (Kuenen et al. 2013a, 2013b; Schalk et al. 2017). Three similarity measures were investigated: temporal correlation (r), spectral coherence (ρ) and mutual information (I). However, the method was still limited by the 2-D nature of the recordings. Each plane required a separate injection of microbubbles, tumors between imaging planes were missed and out-of-plane flow could not be observed.

Using 3-D DCE-US enables imaging the vasculature in the entire prostate with a single injection of contrast agent and the inherently three-dimensional transport kinetics can be observed. In a recent study, the technical feasibility of 3-D CUDI as the first quantitative method using 3-D DCE-US for PCa was tested *in vivo* in two patients (Schalk et al. 2015b). Although the temporal resolution of 3-D DCE-US recordings was too low for model fitting, 3-D CUDI by similarity analysis was shown to be possible.

Because of the limitations discussed earlier, standard DCE-US is currently not recommended in the international guidelines as a routine PCa imaging technique (Heidenreich et al. 2014). However, advanced DCE-US methods may detect PCa more accurately and eventually play a role in PCa diagnosis. With its improved applicability, 3-D DCE-US may become a valuable diagnostic option, providing complementary information to DCE-MRI, which detects contrast extravascular leakage, or even represent a cost-effective alternative to mpMRI.

In this work, we tested the ability of quantitative 3-D DCE-US and, in particular 3-D CUDI by similarity analysis, for PCa detection by comparison with systematic biopsies in 43 patients. Three similarity and four perfusion parameters were extracted from the 3-D DCE-US recordings. We investigated which parameters could discriminate between benign and malignant tissue and made a preliminary estimation of their classification performance.

MATERIALS AND METHODS

Data collection

Between January 2015 and March 2016, 58 patients referred for systematic biopsy underwent 3-D DCE-US at the Second Affiliated Hospital of Zhejiang University (Hangzhou, Zhejiang, PR China). Inclusion criteria were age >18 y and referral for systematic biopsy and DCE-US based on elevated PSA level, abnormal DRE or lesions visible in MRI. This study was approved by the local institutional review board of the Second Affiliated Hospital of Zhejiang University. Written informed consent was obtained from all participants in the study in accordance with the World Medical Association Declaration of Helsinki.

After intravenous injection of 2.4 mL Sonovue (Bracco, Milan, Italy) microbubbles, 3-D DCE-US imaging was performed using a LOGIQ E9 ultrasound scanner (GE Healthcare, Wauwatosa, WI, USA) equipped with an RIC9-5 transducer. To maximize the volume rate, the imaging quality setting "BQ" was set to "low". The acoustic output power setting "AO%" was limited to "10" to prevent bubble disruption. More details on the data characteristics are reported in our technical feasibility study on 3-D CUDI (Schalk et al. 2015b). Each DCE-US recording lasted 2 min and was stored in raw Digital Imaging and Communications in Medicine format.

After technical evaluation of the DCE-US recordings, 13 patients were excluded (Fig. 1). In 7 of the 13 exclusions, the protocol was violated (wrong scanner

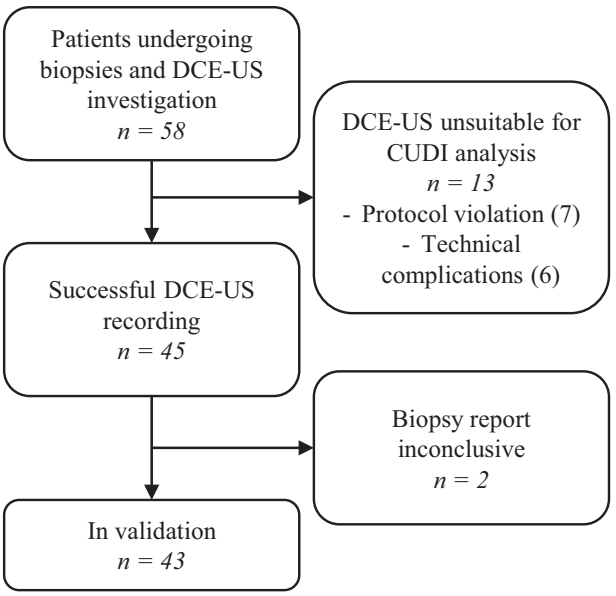

Fig. 1. Inclusion flowchart. Protocol violations included excessive probe movement, wrong scanner settings and untimely start of the recording. Technical complications encountered were low and inconsistent sample rate and lack of contrast signal. DCE-US = dynamic contrast-enhanced ultrasound; CUDI = contrast-ultrasound dispersion imaging.