Prostate cancer localization based on multiparametric quantification of three-dimensional transrectal contrast-enhanced ultrasound

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Introduction
Despite being a prominent field of biomedical research, imaging of prostate cancer (PCa) has not yet been demonstrated to enable replacing systematic biopsy (SBx) [1]. The latter procedure relies on a standard 10 to 12-core biopsy template to sample the prostate tissue for subsequent histopathological examination [2]. Reliable imaging does not only have the potential to reduce procedure time and patient discomfort, but it could potentially also reduce the incidence of SBx-related complications [3] and improve diagnostic accuracy by providing means for a targeted biopsy procedure.

Dynamic contrast-enhanced ultrasound (DCE-US) has been considered as one of the candidates for robust PCa diagnosis [4]. Especially three-dimensional (3D) DCE-US, alleviating the limitation of being bound to a 2D plane, might be used to characterize prostate tissue prior to biopsy [5]. The underlying principle is that the visualization of vascularity through the use of tiny microbubble contrast agents [6] could highlight changes in the microvascular network associated with cancer angiogenesis [7].

Over the years, several quantification algorithms have been developed to extract features from the dynamic DCE-US recordings that reflect those changes. For this, we analyse the contrast intensity over time (i.e., the time-intensity curve, TIC) as the contrast bolus spreads through the prostate vasculature. In 2D, TIC features ranging from the simple heuristic wash-in time to more sophisticated parameters representing contrast-agent velocity and dispersion were proven useful in the diagnosis of prostate cancer [8]–[10]. Especially in 3D, where the sizable volume videos are not readily interpreted, these parameters can considerably elevate the diagnostic potential [5], [11], [12].

The aim of this work is therefore to expand the former 2D-only analyses to three dimensions and investigate their joint potential for the localization of PCa. As shown in 2D, multiparametric combination by means of machine learning is capable of capturing complementary information of different parameters [13]. Therefore, we also compare the results of combined 3D quantification in volumetric regions of interest against the histopathological findings of SBx in those regions.

Methods
For this study, 43 patients with a suspicion of prostate cancer underwent a 12-core SBx procedure. Prior to the procedure, they received a 3D DCE-US recording using a 2.4-mL bolus injection of SonoVue® (Bracco, Milan, Italy), administered intravenously. The recording was carried out using GE’s LOGIQ E9 ultrasound scanner equipped with a RIC5-9 probe at the Second Affiliated Hospital of Zhejiang University. The SBx cores were histopathologically examined [14], marking the corresponding tissue either benign (B), Gleason 3+3=6 insignificantly malignant (iPCa), or significantly malignant (sPCa).
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Fig. 1 Schematic representation of the CUDI framework, highlighting the (1) physiology, (2) imaging, (3) data extraction, and (4) CUDI analysis.

The volumetric contrast videos were subsequently extracted from the device and subjected to several quantification analyses. More specifically, all four Contrast Ultrasound Dispersion Imaging (CUDI) algorithms were expanded to 3D and used to generate parametric maps corresponding to the 3D DCE-US data (see Fig. 1). CUDI analysis is based on modelling of contrast bolus spreading through the prostate as a convective-dispersion process. Here, (1) **model-fit analysis** (i.e., fitting each voxel’s TIC by a local-density random walk model) allows the estimation of several parameters related to dispersion and perfusion [8], whereas (2) **similarity analysis** compares the shape of the TICs in a small ring-shaped kernel to quantify the local degree of dispersion [9], [11]. In addition, the underlying convection and dispersion coefficients can be estimated by (3) **system identification** among voxels [10], or by solving the (4) **full convective-dispersion** equation in a small 3D kernel [12]. We refer to earlier publications for a more elaborate explanation of the individual quantification techniques.

The parametric maps resulting from the 3D CUDI analyses were appended with heuristic parameters and fractal dimension analysis [15] to create a dataset comprising 16 CEUS parameters that could be correlated to SBx-histopathology. To this end, we divided the volumetric maps into 12 regions of interest corresponding to the SBx locations [16], and computed the median parameter values per region. Their diagnostic potential was subsequently assessed using Receiver Operating Characteristics (ROC) analysis, more specifically, the area under the ROC curve. To combine the parameters, we employed machine learning through a Gaussian Mixture Model (GMM) which was trained in a leave-one-prostate-out cross-validation fashion. Features were selected within the training loop following the backward feature elimination scheme based on the ROC curve areas.

**Results**
The individual parameters had an appreciable classification performance for both PCa and sPCa versus the benign SBx-cores. The best-performing parameters in terms of PCa classification were convective-dispersion velocity (ROC = 0.71) and the wash-in time (ROC = 0.71). Best suited for classification of sPCa were the convective-dispersion velocity (ROC = 0.80) and the model-fitted mean transit time (ROC
Conclusions

This work reports on the use of 3D DCE-US quantification for the localization of prostate cancer, showing appreciable results when correlating the median parameter values in volumetric regions of interest with the outcomes of SBx-histopathology. Moreover, we showed that a multiparametric 3D DCE-US approach could potentially add to the diagnostic accuracy of the technique.

We recognize that biopsy-core histopathology is limited by its tendency to undersample the tissue; therefore, tumour hotspots could have been missed or biopsy positions might have deviated from the centre of the corresponding region of interest. In future studies, this limitation will be alleviated through comparison of the parametric maps with whole-prostate pathology after radical prostatectomy, allowing us to assess the PCa localization performance on a smaller scale. Moreover, further assessment of the possible benign disease in false-positive regions of interest might elucidate on the relation between 3D DCE-US parameters and underlying physiology and spur the development of more specific imaging.

In the future, we hope to confirm the results of this preliminary study in an extended patient group, enabling also comparison with radical prostatectomy specimens. Extension of the dataset will also allow more extensive machine-learning strategies, which we deem a very promising approach given the feasibility shown in this work.

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References


