Prostate cancer imaging by DCE-US

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Introduction

In the United States, prostate cancer (PCa) accounts for 29% and 9% of all cancer diagnoses and deaths in males, respectively [1]. Despite the availability of efficient focal therapies, their use is hampered by a lack of reliable imaging for PCa localization and therapy targeting. Contrast-ultrasound dispersion imaging (CUDI) has been proposed as a new alternative method for PCa localization based on dynamic contrast-enhanced ultrasound (DCE-US) data [2, 3]. Different from other DCE-US methods for cancer localization, invariably based on the assessment of blood perfusion, the intravascular dispersion of ultrasound contrast agents is directly influenced by the angiogenic changes that occur in the microvascular architecture feeding PCa. Angiogenic processes and microvascular changes play a fundamental role in cancer growth [4, 5]; their detection can therefore support with the assessment of cancer aggressiveness and, therefore, with therapy decision making [5].

With the aim of characterizing the microvascular architecture and detecting those changes due to cancer angiogenic processes, the analysis of the fractal dimension (FD) of the microvascular architecture, based on DCE-US data, is also evaluated [6]. Up until now, application of this method was invasive, requiring the analysis of immunohistological data [6]. Validation of CUDI and FD is performed in mice xenograft models by comparison with immunohistological (tomato-lectin FITC binding) [7]. Validation of CUDI is also performed in humans by comparison with histology results following radical prostatectomy.

Methodology

In patients, a 2.4-mL bolus of SonoVue® (Bracco, Milan, Italy) was injected intravenously, and its passage through the prostate was imaged by transrectal DCE-US. To this end, an iU22 scanner (Philips Healthcare, Bothell, WA) was employed. Data acquisition in patients was performed at the Academic Medical Center, University of Amsterdam (the Netherlands). In mice, 0.1-mL MicroMarker® Non-Targeted Contrast Agent Kit (VisualSonics, Toronto, Canada) was injected and imaged by a Vevo 2100 scanner (VisualSonics, Toronto, Canada). Data acquisition in mice was performed at the University Hospital Schleswig-Holstein (Kiel, Germany)

All the analyses proposed in this study require a time-intensity curve (TIC) to be measured at each pixel. For the implementation of CUDI, it can be shown that analysis of the spectral coherence [3] or temporal correlation [8] of TICs measured at neighbor pixels provides an estimate of a dispersion-related parameter. Here dispersion is well represented by the dispersion coefficient in the convective dispersion equation [2, 9]. The intravascular dispersion of the injected agent reflects the effect of multipath trajectories through the microvasculature, and can therefore be employed to characterize the microvascular architecture [10]. The obtained dispersion maps were compared on a pixel basis to the results obtained from histological analysis following radical prostatectomy. Figure 1 shows an example of dispersion maps obtained by CUDI coherence and correlation analysis. The corresponding histology result is also shown.

Validation in the mice xenograft models was performed by comparison with the microvascular density (MVD) estimated by assessment of the gray-scale intensity of 5-μm tumor slices treated with tomato-lectin staining and imaged by fluorescence microscopy (Axiovert, Zeiss, Germany). Two types of PCa cell lines, DU-145 and PC-3, were used for the mice xenograft models. In total, four DU-145 models and three PC-3 models were used.

In order to evaluate the ability of the FD to distinguish between different microvascular architectures, the regions defined by MVD and CUDI in the xenograft models were also investigated for their average FD. The FD was derived from peak intensity maps extracted from the obtained DCE-US data.

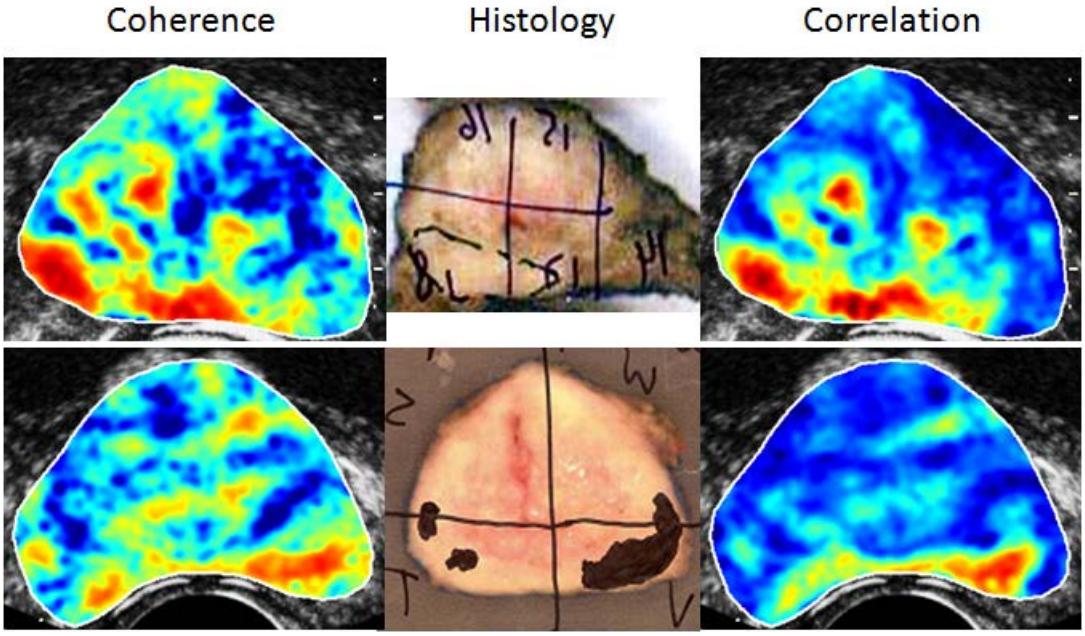

Figure 1. Dispersion maps by CUDI based on coherence (left) and correlation (right) analysis. The corresponding histology results are shown in the middle.

Results

In 10 patient datasets, the dispersion maps obtained by CUDI, both by coherence and by correlation, showed a good agreement at pixel level with the histology. In particular, CUDI outperformed all the other DCE-US maps based on perfusion assessment, such as peak intensity, wash-in rate, time to peak, area under the curve, and mean transit time.

CUDI was also the only imaging method that showed agreement with the immunohistological MVD assessment in the mice models, being able to distinguish between the different spatial distribution of the microvascular architecture in DC-145 and PC-3 ($p < 0.01$). In particular, DC-145 showed a hyper-vascular core as compared to the periphery of the tumor, while PC-3 showed a more homogenous vascularization within the tumor. The same conclusion could be drawn by estimation of the FD within the same regions ($p < 0.05$).

Conclusions

Our results, both in humans as well as in mice, are promising and motivate towards more extensive validation of CUDI for localization of PCa. The agreement between CUDI, MVD, and FD also suggest the ability of CUDI to characterize the microvascular architecture, possibly providing important opportunities for non-invasive cancer grading. In the future, once fully validated, CUDI could support targeting of biopsy and focal therapy.

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