CONTRAST DISPERSION MAPPING IN DCE MRI: A NEW OPTION FOR PROSTATE CANCER DETECTION

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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 timely and efficient use is hampered by a lack of reliable imaging methods for timely localization of prostate cancer. As a result, current clinical diagnosis is still based on repeated systematic biopsies.

Based on the established link between cancer growth and angiogenesis [2,3], several contrast imaging methods have been proposed in the past years with the aim of detecting those microvascular changes associated with PCa [2]. These mainly relate to an increase in microvascular permeability and density [2].

The increased permeability can be investigated by dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI). The adopted contrast agents, based on gadolinium chelates, leak across the vascular wall into the extravascular space. Assessment of this transport process can be obtained by fitting measured time-concentration curves (TCCs) by the compartmental model introduced by Tofts *et al* [4], provided that an estimate of the arterial input function (AIF) is available. This procedure results in an estimate of the volume transfer coefficient between the intravascular and extravascular space, k_{trans}, and, in particular, its normalized value $k_{ep}=k_{trans}/v_e$, with v_e being the extravascular volume fraction.

More challenging is the assessment of changes in the microvascular architecture, leading e.g. to increased microvascular density [2,3]. By means of intravascular agents, such as those available for DCE ultrasound (US), many authors have investigated the link between angiogenesis and increased blood perfusion. However, while a lack of vasomotor control and the presence of arteriovenous shunts reduce flow resistance, this can be counterbalanced by a small microvessel diameter and an increase in interstitial pressure due to extravascular leakage [5]. As a result, characterization of the microvascular architecture by perfusion quantification may be unreliable. Recently, a new DCE-US method has been introduced that characterizes the microvascular architecture by assessment of the dispersion kinetics of an intravascular contrast agent [6]. The results are promising and seem to overcome the limitations of previous methods based on perfusion quantification. In this work, the feasibility of dispersion imaging by DCE MRI is investigated for the first time, and a preliminary validation proposed.

Methods

Intravascular dispersion is assessed by fitting the modified Local Density Random Walk (mLDRW) model to the measured TCCs. This model is a solution of the convective dispersion equation assuming a Gaussian distribution of the contrast bolus in space prior to the bolus passage through each detection pixel [6]. More precisely, the estimated intravascular dispersion parameter, $\kappa = v^2/D$, represents the local ratio between contrast convection (squared velocity v^2) and dispersion (D). Dispersion, represented by the dispersion coefficient D of the convective dispersion equation, is affected by concurrent processes, comprising molecular diffusion, flow profile, and transit time distribution due to the multipath trajectories defined by the microvascular network. In the microvasculature, the latter term is dominant, and dispersion may represent a valuable option to characterize the microvascular architecture.

While the mLDRW model can directly be applied when blood pool agents are used, the presence of extravascular leakage requires separating the intravascular from the extravascular phase. To this end, the intravascular concentration in the Tofts model is represented by the mLDRW model. Under the assumption of $v_p \ll v_e$, with v_p being the intravascular volume fraction, the measured TCC, $C(t)$, can be modeled as

$$C(t) = \alpha \int_{t_0}^{t-t_0} \sqrt{\frac{\kappa}{2\pi(\tau-t_0)}} \exp\left[\frac{-\kappa}{2(\tau-t_0)}(\tau-t_0-\mu)^2\right] \exp\left[-k_{ep}\left(t-(\tau-t_0)\right)\right] d\tau, \tag{1}$$

with $\kappa = v^2/D$ being the dispersion-related parameter, t_0 the theoretical injection time, μ the contrast mean transit time, and $\alpha = k_{trans}A$, with A being the time integral of the intravascular TCC. The theoretical injection time t_0 is the injection time under the assumption of constant hemodynamic conditions along the full path from the injection to the detection site. Estimation of the five model parameters in Eq. (1) provides the simultaneous assessment of dispersion (κ) and leakage (k_{ep}), characterizing vascular architecture and permeability, respectively. The estimation of an AIF is not necessary for application of the model in Eq. (1).

DCE MRI was performed at the Academic Medical Center, University of Amsterdam (the Netherlands) by intravenous injection of a 0,1 mmol/Kg bolus of gadolinium-DPTA. Imaging was performed with a 1.5 T system (Magnetom Avanto, Siemens) equipped with an endorectal coil, and using a spoiled gradient recalled sequence and phase oversampling. The adopted sequence parameters were repetition time of 50 ms, echo time of 3.9 ms, flip angle of 70 degrees, slice thickness of 4 mm, and pixel size of 1.67x1.67 mm^2. A preliminary validation was performed by comparison with the histological results in 7 patients referred for radical prostatectomy. An example is provided in Fig. 1. Histological analysis was performed on 4-mm slices. Tissue classification was evaluated on a pixel level on 3 to 5 MRI slices per patient.

Results

Classification (pixel level) by the dispersion parameter κ was accurate, providing sensitivity=82.6, specificity=89.5, and ROC area=0.91. The simultaneously derived k_{ep} parametric map provided sensitivity=58.0, specificity=80.9, and ROC area=0.72.

Discussion

The proposed dispersion maps show accurate classification of cancer tissue as compared to histology. Classification by the simultaneously estimated k_{ep} parameter is less accurate. The reason can possibly reside in a dependency between the model parameters. In future work, model sensitivity analysis will be carried out to investigate this issue. Histology was considered as the ground truth for validation. However, while histology grading is based on the degree of cell differentiation (Gleason score), dispersion characterizes the microvascular architecture. In the future, comparison with immunohistological microvascular-density maps will therefore be considered.

Conclusions

A new DCE-MRI method is proposed for the characterization of microvascular architectures by assessment of contrast intravascular dispersion, without need for separate AIF estimation. The results are promising and motivate further research on this new option for PCa localization. More in general, this new method can provide a valuable contribution to MRI multimodal diagnosis of any form of cancer where angiogenesis plays an important role.

References

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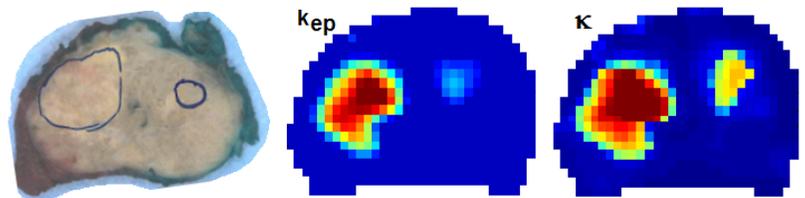[6] M.P.J. Kuenen et al, *IEEE Trans Med Im*, 30(8):1493-1502, 2011.

Fig. 1: Histology results with corresponding parametric maps of k_{ep} and dispersion κ.