Identification of Hypoxic Regions *In Vivo* in the Prostate

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Introduction: Hypoxia is an important cause of resistance to both radiotherapy and chemotherapy in solid tumors[1]. The clinical measurement of hypoxia *in vivo*, however, is unsatisfactory because current methods are based on either invasive electrode measurements or tissue immunohistochemistry and are subject to sampling error. Here, we present an approach to decipher the characteristic of signal-to-time curve pattern in Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) for hypoxia in an animal model and in patients with prostate cancer.

Methods: We use an unsupervised pattern recognition (PR) technique for the analysis of the signal-to-time curves in DCE-MRI data[2]. The strength of this approach is that it captures the pixel-enhancing behavior in its entirety – both, during the uptake and washout of the contrast agent, and thus, subtle differences in the temporal behavior of contrast enhancement related to differences in the tumor microenvironment can be detected. We analyzed two types of DCE-MRI data: 1) a preclinical prostate cancer model and 2) clinical prostate cancer data. The animal data consists of six DCE-MRI studies from Dunning R3327-AT prostate tumor model using the contrast agent Gd-DTPA, as described in detail previously[3]. Briefly, using stereotactic fiduciary markers, *in vivo* DCE-MRI data were aligned with dynamic ^{18}F-fluoromisonidazole PET and *ex vivo* studies featuring staining with hematoxylin/eosin (H&E) and pimonidazole, identifying oxygenated, hypoxic, and necrotic tumor areas[3]. The prostate cancer patient DCE-MRI data were acquired on a 3T MR scanner (Siemens Trio Tim, Erlangen, Germany): resolution 0.7×0.7× 2.5 mm^3; field of view: 360 mm × 264 mm; 72 slices (no gap); 5.1 ms repetition time/2.3 ms echo time; flip angle 10^o. Prior to contrast material injection, one set of MR images were acquired, followed by 11 post-contrast imaging datasets (37 s each).

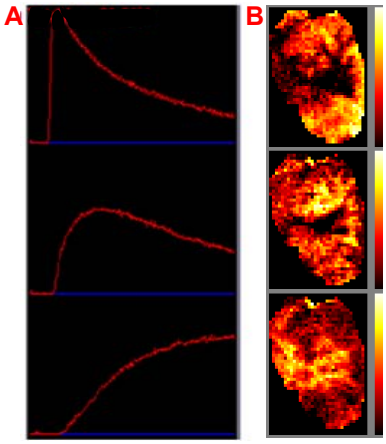

Figure 1. (A) Basic 'signal-to-time' patterns determined within the tumor in DCE-MRI studies of Dunning R3327-AT prostate tumor model. (B) The weights of the patterns together with a scale bar. Based on the *Akep* values, the pimonidazole and H&E staining, the image parts in yellow indicate high-permeability, hypoxic and necrotic areas of the tumor[3].

Results: The basic 'signal-to-time' DCE-MRI patterns and their weights, presented as heat maps, determined in the tumor of the animal data are shown in Fig. 1. This data had been analyzed previously with the Hoffman model[4] to estimate *Akep* values of individual voxels[3]. The high intensities (yellow color) in the upper image in Fig. 1B closely resembles the distribution of *Akep*[3], and thus, denotes the high-perfused areas across this slice of the tumor. Signal increases at fastest rates in the viable, oxygenated tumor area as a result of rapid Gd-DTPA uptake followed by rapid washout, which is reflected in the temporal pattern. The middle image in Fig. 1B depicts most likely hypoxic tumor areas. The temporal pattern in the Gd-DTPA uptake shows delay in signal build-up and also a delay in wash out, which is consistent with reduced vascularization, characteristic for hypoxic regions and aligns well with the hypoxic areas identified by Cho *et al.*[3] based on pimonidazole staining. And lastly, the bottom image denotes the necrotic tumor areas, based on the location identified by Cho *et al.*[3] using H&E staining. In necrotic regions of the tumor, the time-dependent increase in the MR signal was slowest, and no washout could be observed over the time course. In Fig.2, the results from a patient data set are presented. The arrows point at a hypointense area in the left peripheral zone, suspicious for tumor (Fig. 2A). The lower image indicates the tumor area automatically identified by DCE analysis of the entire prostate. The DCE-MRI curves from this region were selected for PR analysis and the corresponding three patterns and their distributions are displayed in Fig. 2B-C. The similarity in the temporal behavior between the three patterns in animal and patient data is striking. This suggests that the 2nd pattern in Fig. 2B may be related to hypoxia. The thresholded distribution of the weight of the hypoxia pattern is overlaid with the T_2-weighted MRI in Fig. 2D.

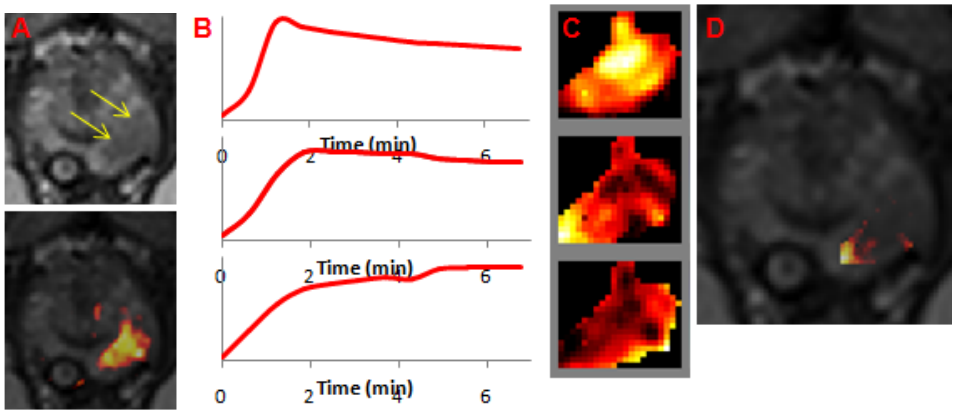

Figure 2. (A) T_2-weighted MRI of the prostate with arrows pointing at hypointense area in the left peripheral zone of the prostate (top) and overlayed with the tumor area as identified automatically via DCE analysis of the entire prostate (below). (B-C) Temporal patterns and their spatial distribution from the tumor area. Note the similarities between the 2nd patterns in Figure 1A and 2B, suggesting hypoxia. (D) Thresholded distribution of the hypoxic pattern, overlaid on the T_2-weighted MRI.

Conclusions: Characteristic patterns for hypoxic tumor regions could be identified using an unsupervised PR technique. In the animal data the pixel from high-permeability, necrotic and hypoxic areas were *manually* selected and representative DCE curves determined[3]. We recovered temporal shapes which closely resemble the published ones *directly* from the DCE-MRI data. The similarity between the temporal behavior of the curves in animal and patient data suggests that using this technique, we potentially can deconvolve the hypoxic temporal pattern in *in vivo* data from patients with prostate cancer.

References: [1]Adams GE. *Eur J Cancer* 1990;26:420–421. [2]Du S, Sajda P, Brown T, Stoyanova R. *Conf Proc IEEE Eng Med Biol Soc* 2005;2:1095-1098. [3]Cho H, Ackerstaff E, Carlin S, Lupu ME, Wang Y, Rizwan A, O'Donoghue J, Ling CC, Humm JL, Zanzonico PB, Koutcher JA. *Neoplasia* 2009;11:247-259. [4]Hoffmann U, Brix G, Knopp MV, Hess T, Lorenz WJ. *Magn Reson Med* 1995;33:506-514.