Magnetic Resonance Diffusion Characteristics of Histologically Defined Prostate Cancer in Humans

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Introduction

The contrast provided by diffusion sensitive magnetic resonance (MR) in organ-confined human prostate cancer (PCa) offers the promise of improved detection and localization.[1] By employing an image co-registration procedures to align "gold standard" histology slide with *ex vivo*, and, subsequently, *in vivo* diffusion sensitive MR images,[2] the MR diffusion characteristics of histologically defined human prostate cancer were studied.

Material and methods

Patients Twelve radical prostatectomy patients (mean age 62 yrs, range 46 – 76 yrs) were enrolled in this study. *MRI* *In vivo* diffusion tensor imaging (DTI) (resolution = 2×2×2.5 mm^3) and T2-weighted (T2w) imaging (resolution = 1×1×2.5 mm^3) were performed prior to prostatectomy surgery. After surgery, prostatectomy specimens were fixed in formalin and step-sectioned at 4-mm intervals using a custom-made slicer. The regrouped 4-mm tissue blocks underwent ultra high resolution (0.5×0.5×0.5 mm^3) *ex vivo* DTI measurements.[3] *Histology* Individual 4-mm sections were carefully labeled and then completely embedded in paraffin and sampled in 4-µm thick slices for hematoxylin and eosin (H & E) staining. The histology slides and MR images were mutually aligned in the coordinate space of the standard *in vivo* T2w images.[2]

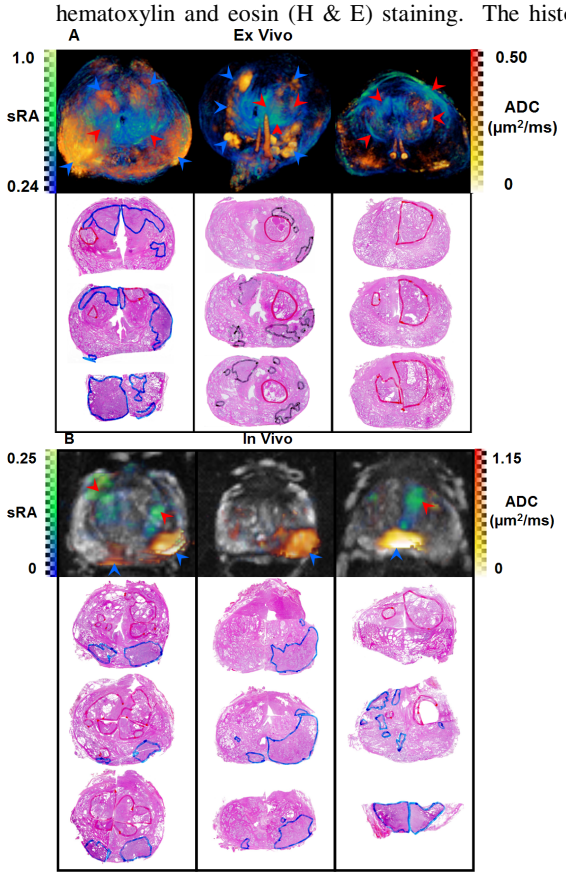

Figure 2. DTI images were co-registered with step-section histology slides from six representative specimens (each column) with different tumor sizes. PCa identified on the volume rendered DTI, *ex vivo* (panel A; projected view) and *in vivo* (panel B; projected view with a representative T2w image as background), closely correlated with those seen in histology. The histologically defined PCa extents and stages (from left to right in each panel) are 40% T3b, 16% T2c, and 4% T2c for *ex vivo*, and 15% T3a, 40% T3a, and 20% T3a for *in vivo*. The cancerous and BPH regions in the H & E slides were marked in blue/black and red, respectively, by a urologic pathologist. In the MR images, the ADC and diffusion anisotropy values were imported into the yellow-orange and green-blue channels, respectively. Bright yellow-orange regions in the MR images were identified as carcinoma determined by ADC threshold (*ex/in vivo* PCa mean ADC + standard deviation). Red and blue arrows indicate regions of fibromuscular and carcinoma tissues, respectively, as identified by histology and their co-registered diffusion contrast in the MR images. In *ex vivo* DTI images (panel A), pairs of ejaculatory ducts with high ADC value (color scale irrelevant) are segmented from the ADC map separately.

Results and Discussions

After MR and histology image co-registration for each slice, the PCa region and the benign tissue region in the peripheral zone (PZ) were translated from the histology slide (Fig. 1E) to both the *ex vivo* (Fig. 1D) and *in vivo* apparent diffusion coefficient (ADC) maps (Fig. 1A). The ADC value of PCa tissue (0.43 ± 0.06 μm^2/ms *ex vivo*, Fig. 1D blue arrow, and 0.90 ± 0.13 μm^2/ms *in vivo*, Fig. 1A blue arrow) was significantly lower than that of the non-cancerous PZ tissues (0.99 ± 0.16 μm^2/ms *ex vivo*, and 1.66 ± 0.21 μm^2/ms *in vivo*). Microscopically, normal prostate has a branching duct-acinar glandular architecture embedded in a dense fibromuscular stroma (Fig. 1G). This duct-acinar structure underlies the diffusion MR characteristics of the prostate gland in human. In prostate carcinoma, tightly packed tumor cells disrupt the duct-acinar structure leading to the decreased ADC in tumor due to the cellularity induced diffusion restriction (Fig. 1H). A relatively low diffusion anisotropy was observed in the PZ (scaled relative anisotropy or sRA = 0.13 ± 0.05 and 0.06 ± 0.03 for *ex vivo* and *in vivo*, respectively). The low diffusion anisotropy in the PZ likely reflects the random orientation of fibromuscular cells in the PZ (Figs. 1G and H). Importantly, no significant diffusion anisotropy differential was observed between the cancerous and non-cancerous PZ tissues (Figs. 1C and F, sRA = 0.13 ± 0.04 *vs.* 0.13 ± 0.03, p = 0.89 for *ex vivo*; and sRA = 0.08 ± 0.02 *vs.* 0.05 ± 0.02, p= 0.012 for *in vivo*). However, when the fibromuscular cells are bundled together at a length scale comparable to MRI voxel dimensions (Fig. 1I), higher diffusion anisotropy (sRA = 0.34 ± 0.08 *ex vivo* and 0.13 ± 0.06 *in vivo*) in those regions becomes distinctive and distinguishable (red arrows, Figs. 1C and F) from that in the glandular region. The appearance of BPH in ADC map or T2w image is very heterogeneous, reflecting the complicated BPH tissue composition. BPH regions with both ADC and T2w hypointensity could mimic PCa in the CG (Figs. 1A and B, red arrows), leading to false positive PCa identification. The high diffusion anisotropy in the bundled fibromuscular cells provides a unique contrast for differentiating these BPH nodules from PCa (Figs. 1C and F). Notably, the high diffusion anisotropy appears not only in the stromal components within BPH, but also in the fibrous tissues surrounding the BPH (Fig. 2A), as the expanding BPH nodule pushes and compacts the fibromuscular tissue network around it. This high diffusion anisotropy pattern surrounding the BPH was best visualized in the volume rendered DTI images (Fig. 2A, middle column, red arrows).

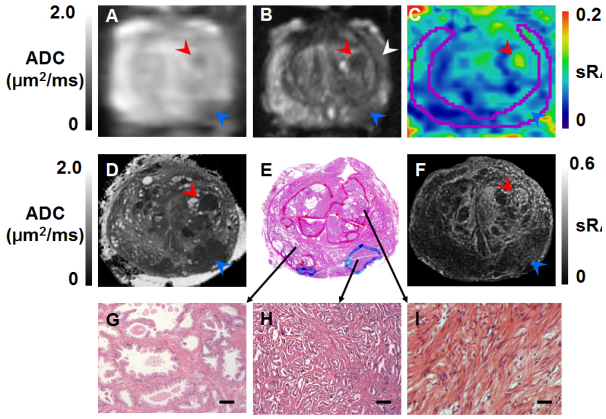

Figure 1. Co-registered images illustrate the tissue microstructure underpinning the MR diffusion characteristics. A) *in vivo* ADC, B) *in vivo* T2w, C) *in vivo* color coded sRA, D) *ex vivo* ADC, E) H & E slide, and F) *ex vivo* sRA. The cancerous and BPH regions in the H & E slide were marked in blue and red, respectively, by a urologic pathologist. Blue and red arrows indicate regions of PCa and stromal BPH, respectively, as diagnosed by histology. The white arrow in panel B indicates a T2 hypointense region that could be mistaken for PCa without the additional co-registered diffusion data. The peripheral zone region was delineated in panel B and mapped onto panel C in magenta. High resolution H & E examinations reveal the micro-structures of different types of tissues in G) benign peripheral zone, H) PCa, and I) stromal BPH (10× magnification, scale bar = 100 µm).

References [1] Pickles, *et al. JMRI* **23**, 130, 2006. [2] Xu, *et al. Proc. ISMRM.* **15**, 3666, 2007. [3] Xu, *et al. Proc. ISMRM.* **14**, 174, 2006.