Exclusion of False Positive Identification of Prostate Cancer Using Diffusion Anisotropy

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Introduction

The normal prostate comprises a branching duct-acinar glandular system embedded in a dense fibromuscular stroma. The substantial decrease of mean water diffusivity due to disruption of the ductal structures by prostate cancer (PCa) provides unique contrast for tumor localization. However, it is difficult to distinguish PCa from benign prostatic hyperplasia (BPH) on the basis of changes in mean diffusivity alone because both processes affect this diffusion parameter. An alternative means of distinguishing PCa and BPH is through measures of diffusion anisotropy, which has not yet been systematically evaluated in this role. To examine the potential utility of diffusion anisotropy for PCa identification, the prostates from thirteen radical prostatectomy patients were examined by diffusion tensor imaging (DTI) *in vivo* before surgery, and *ex vivo* after surgery and formalin fixation. DTI findings were validated by co-registered histology.

Material and methods

MRI *In vivo* DTI was performed on a 1.5-tesla scanner using a phased-array body coil at 2 × 2 × 2.5 mm resolution. Diffusion sensitizing gradients were applied along six directions. Two diffusion sensitizing factors or *b* values = 0 and 500 s/mm^2 were used to calculate the apparent diffusion coefficient (ADC) and scaled relative anisotropy (sRA). Additionally, fat saturated T_2 weighted (T2W) images were acquired at 1 × 1 × 2.5 mm resolution. After surgery, prostatectomy specimens were fixed in formalin for more than 24 hours and step-sectioned at 4-mm intervals. The 4-mm sections were regrouped with a thin sheet of susceptibility matched spacer inserted between adjacent sections for MRI slice prescription. Ultra high resolution (0.125 mm^3 voxel size) *ex vivo* DTI, employing parameters reported previously [1], was performed on the regrouped slices.

Histology Individual 4-mm sections were carefully labeled to ensure correct identification of each section within the prostate. The sectioned slabs were then completely embedded in paraffin and sampled in 4 μm thick slices for hematoxylin and eosin (H & E) stains. Regions of PCa and BPH were identified and outlined in blue and red, respectively, by a urologic pathologist. The diffusion weighted (DW) images obtained *in vivo* were co-registered with the higher resolution *in vivo* T2W images, then with the even higher resolution *ex vivo* DW images, and finally with the optical microscopy images using algorithms based on 3D affine transformation and normalized mutual information.

Results and Discussions

The expanding nodules of BPH push and tighten the normal fibromuscular system around them, resulting in ordered fiber bundles with networked structure in the sRA map (Fig. 1 A). Diffusion anisotropy was higher in these ordered, compressed areas (0.34 ± 0.08, Figs. 1 B – D) compared to that of the acinar glandular tissues and PCa, for which sRA was 0.13 ± 0.05 *ex vivo* ($n = 13$, $p < 0.001$). A similar differential holds for *in vivo* diffusion anisotropy measures. sRA values were 0.13 ± 0.07 for fibromuscular tissue compared with 0.05 ± 0.02 for glandular tissue and PCa ($n = 13$, $p < 0.001$). The sRA for both types of tissues are smaller *in vivo* than *ex vivo* due to the lower image resolution and the resulting partial volume effects for the *in vivo* data. We found that diffusion anisotropy remains low both *in vivo* and *ex vivo* in the glandular tissues regardless of the presence of PCa, as also noted by Reinsberg *et al.* [2]. In light of our preliminary experimental observations and the expected tissue microstructure changes, we propose that high diffusion anisotropy can be used as an exclusion criterion for PCa diagnosis. As noted above, areas of BPH may exhibit PCa-like contrast on both the T2W images (black arrow, Fig. 2 A) and ADC maps (black arrow, Fig. 2 B), which could lead to a false positive diagnosis. In all three patients with BPH mimicking PCa, the presence of elevated diffusion anisotropy (black arrow, Fig 2 C) reliably prevents a false positive identification of PCa. The validity of this identification was confirmed by the corresponding histology (Fig. 2 D). In the representative case shown here, the area of reduced ADC (black arrow, Figs. 2 A – D) corresponds to a stromal BPH nodule (Figs. 2 E - F). Despite the much smaller diffusion anisotropy magnitude and differential *in vivo*, the presence of elevated anisotropy was sufficient to prevent misidentification of BPH as PCa.

Reference [1] Xu, *et al. Proc. Intl. Soc. Mag. Reson. Med.* **12**, 2508, 2004. [2] Reinsberg, *et al. Proc. Intl. Soc. Mag. Reson. Med.* **13**, 269, 2005.

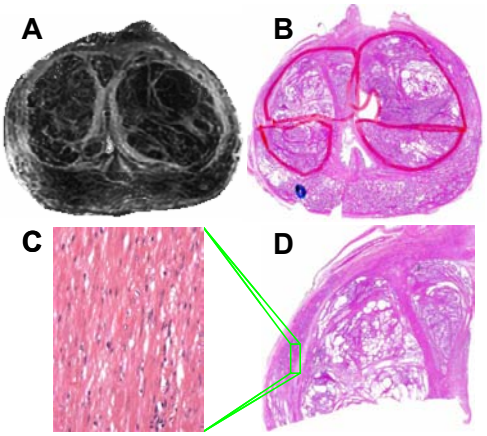

Figure 1. Corresponding *ex vivo* sRA map (A) and H & E stains (B) with PCa and BPH outlined in blue and red, respectively. The high diffusion anisotropy region in the top left quadrant of the histology slide (D) was further examined at 20 × magnification (C).

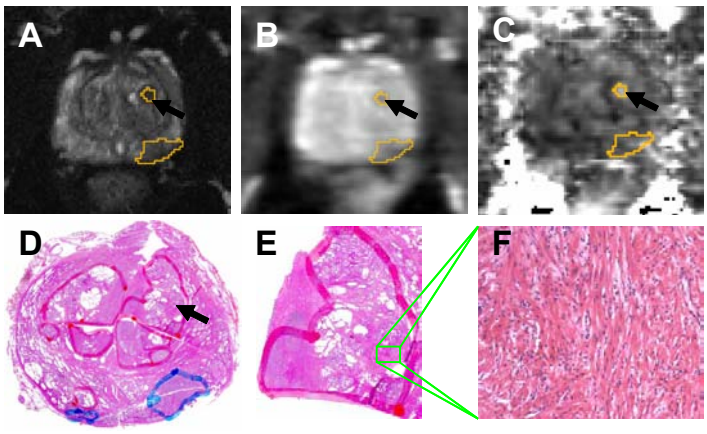

Figure 2. Corresponding *in vivo* T2W image (A), ADC map (B), sRA map (C), and H & E stains (D) with PCa and BPH outlined in blue and red, respectively. Using ADC contrast only, the suspected PCa regions were outlined in orange (B) and mapped onto the T2W image (A) and sRA map (C). The high diffusion anisotropy region (black arrow) was histologically verified as a BPH nodule (E), with its stromal structure revealed at 20 × magnification (F).