ADC Decrease in Histology Identified Prostate Cancer

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Introduction

The ability to accurately localize prostate carcinoma (PCa) within prostate gland non-invasively can dramatically improve PCa diagnosis and treatment. However, conventional T2 weighted (T2W) imaging has not proven sensitive or specific enough to localize gland-confined PCa. Recently substantial decrease of mean water apparent diffusion coefficient (ADC), due to disruption of the prostate ductal structures by PCa, provides a unique contrast for tumor localization. This promising ADC contrast has been explored *in vivo*, as recently summarized by Pickles *et al.* [1]. Nevertheless, none of the reports to date validated the suspected PCa region, either diagnosed by T2W, ADC contrast, or biopsy, with the "gold standard" histology. Herein, we propose a co-registration strategy to determine the *in vivo* ADC of histology identified PCa.

Material and methods

Patients Twelve radical prostatectomy patients (mean age 62 yrs, range 46 – 76 yrs) without any preoperative treatment were enrolled in this study.

MRI *In vivo* diffusion tensor imaging (DTI) measurement (resolution = 2×2×2.5 mm) and T2W imaging (resolution = 1×1×2.5 mm) were performed prior to scheduled prostatectomy surgery [2]. After surgery, prostatectomy specimens were fixed in formalin for more than 24 hours 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) *ex vivo* DTI measurement [3].

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) staining. Regions of PCa and BPH were identified and outlined in blue and red, respectively, by a urologic pathologist.

Image registration A two-dimensional (2D) thin plate spline (TPS) warping was performed using 10 – 20 control points (Fig 2, A and B) to transform histology to the coordinate of *ex vivo* ADC map (Fig. 1, T1). By u**sing a rigid body 3D affine transformation** (Fig. 1, T2), the *ex vivo* ADC maps were further manually co-registered with the *in vivo* T2W images through **intra-glandular structure alignment. The** *in vivo* ADC maps were also co-registered with the *in vivo* T2W images using a 3D affine transformation (Fig. 1, T3). In this manner, all the images were mutually aligned in the coordinate space of the standard *in vivo* T2W images.

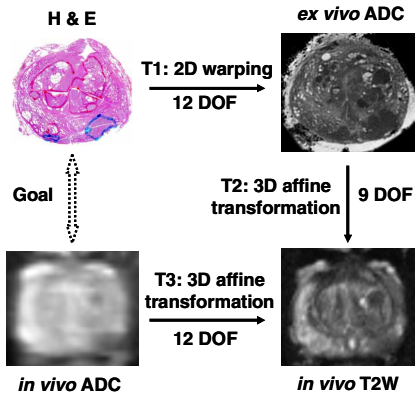

Figure 1. Overview of histology and *in vivo* ADC co-registration.

Results and Discussions

The ultra high resolution *ex vivo* diffusion anisotropy map (Fig. 2B), revealing exquisite intra-glandular structure, affords accurate placement of the control points in the corresponding histology slide (Fig. 2A). The *ex vivo* ADC map, exhibiting similar tissue contrast as the *in vivo* T2W images, provides a critical link to the *in vivo* ADC map. Excellent co-registration results were achieved despite some manual procedures involved (Fig. 3). The registration results may be further improved by utilizing mutual information based automatic procedures [4]. After image registration, cancerous (Fig. 2D) and normal (Fig. 2C) tissues in the PZ were mapped from the histology slides onto the *in vivo* and *ex vivo* ADC maps to determine the ADC values in each tissue category. The ADC values in PCa is consistently much lower than that in normal tissues (Fig. 4) in *in vivo* patients, *ex vivo* prostatectomy specimens, and an *in vivo* mouse model of PCa [5].

Reference [1] Pickles, *et al. J. Magn. Reson. Imaging* **23**, 130, 2006. [2] Xu, *et al. Proc. Intl. Soc. Magn. Reson. Med.* **13**, 2125, 2005. [3] Xu, *et al. Proc. Intl. Soc. Magn. Reson. Med.* **12**, 2508, 2004. [4] Meyer, *et al. Mol. Imaging* **13**, 16, 2006. [5] Song, *et al. Cancer Res.* **62**, 1555, 2002.

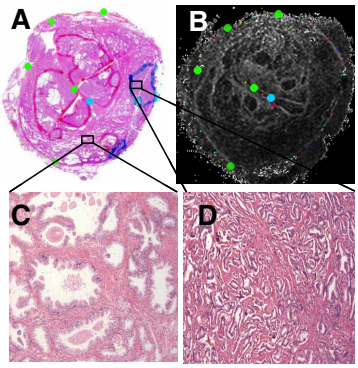

Figure 2. Representative control points that drive the 2D TPS warping in the T1 transformation are enlarged in both the H&E slide (A) and the *ex vivo* diffusion anisotropy map (B). Cancerous (marked blue in A) and non-cancerous PZ, identified by pathologist, are magnified to show the more cellular PCa (D) comparing to the normal ductal tissues (C).

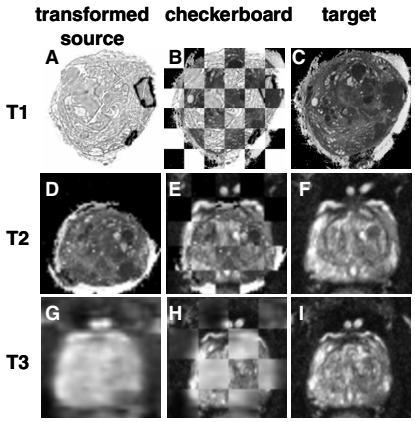

Figure 3. Registration results at three transformation stages (rows, T1 - T3). The transformed source images (left column) were overlaid onto the target images (right column) to highlight alignment results in checkerboards (center column). The transformation pairs are A) TPS warped H&E and C) *ex vivo* ADC; D) transformed *ex vivo* ADC and F) *in vivo* T2W; and G) transformed *in vivo* ADC and I) *in vivo* T2W.

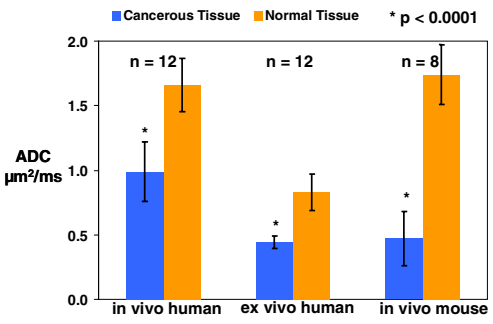

Figure 4. Decreased ADC values were observed in *in vivo* patients, *ex vivo* human prostatectomy specimens, and an *in vivo* mouse model of PCa. All results were determined by histopathology identified tissue categories. Error bars represent mean standard deviation. Statistical significance was accepted for $p < 0.0001$.