Diffusion Imaging of Prostate at 3-Tesla using High B-values and Stretched-exponential Modeling

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Introduction: Recent advances using multi-parametric magnetic resonance imaging (MRI) techniques have significantly improved the capability for diagnosis, localization, and staging of prostate cancer by providing high-resolution anatomical images as well as physiologic and metabolic information for tissue characterization[1]. In addition to T1- and T2-weighted imaging (T1 and T2WI) and dynamic contrast-enhanced (DCE) examination, diffusion-weighted imaging (DWI) with quantitative apparent diffusion coefficient (ADC) has been employed to depict differences in water molecular diffusivity between normal and cancerous tissues[2]. Diffusion prostate MRI is typically performed using a single b-value in the range of 500-2000 s/mm^2 [3,4] (in addition to a baseline image with b≈0). Recently, diffusion imaging with multiple b-values has shown benefits in not only revealing water diffusivity but also characterizing other tissue properties such as heterogeneity[5,6]. In this study, we have applied a novel "stretched-exponential" (or fractional order calculus) diffusion model[5,6] to investigate the feasibility of using multi-b-value diffusion imaging for the detection of prostate adenocarcinoma.

Methods and Materials: Over a four-month period, a total of nine patients who had transrectal ultrasound biopsy-proven prostate cancer and referral for prostate MRI at our institution were identified and enrolled in the study. All patients had subsequent radical prostatectomy. Prostate MRI examination was carried out at 3-Tesla using a 16-channel phased-array coil with the following sequences: T1WI spin echo (TR/TE = 668ms/10ms, slice thickness = 3mm, inter-space gap = 0mm, matrix size = 256x256), T2WI turbo spin echo (TR/TE = 3827ms/100ms, slice thickness = 3mm, inter-space gap = 0mm, matrix size = 256x256), DCE gradient echo with 20 mL Omniscan administered intravenously (TR/TE = 6.5ms/3.1ms, slice thickness = 6mm, inter-space gap = 3mm, flip angle = 12°), and DWI with single-shot EPI using multiple b-values (b = 50, 500, 1500, and 2000 s/mm^2, TR/TE = 1538ms/69.8ms, slice thickness = 4mm, matrix size = 128x128, FOV = 18x18cm^2, number of slices = 6, and total scan time = 3.5 minutes). A stretched-exponential diffusion model was used to fit the multi-b-value DWI images on a pixel-by-pixel basis using the following equation: $S/S_0 = \exp[-(b\times DDC)^{\beta}]$, where parameter β has been correlated to the degree of tissue heterogeity[5,6]. In this model, the initial value of DDC was estimated by a mono-exponential model using data acquired at b-values ≤ 1000 s/mm^2. In addition to this analysis, ADC values were also produced using the conventional mono-exponential model with individual b-values of 500, 1500, and 2000 s/mm^2, respectively. Image processing and analysis were performed using customized software developed in Matlab (Mathworks Inc, MA).

The MRI images were reviewed concurrently by two radiologists to evaluate for normal prostate tissue and cancer lesions. Cancer tissue was identified as areas of low signal intensity on T1WI and T2WI within the peripheral zone, and with abnormal contrast media perfusion and washout kinetics. The cancer lesions were retrospectively correlated with histopathologic results from prostatectomy specimen reviewed by two pathologists, with reconstruction of 3D map of the tumor locations to overlay onto diffusion images to define the regions of interest (ROI) for diffusion analysis. Diffusion parameters of DDC, β, and ADCs (b=500, 1500, 2000 s/mm^2, respectively) were calculated from these ROI's and from the normal prostatic tissue. Based on the measurements, ratios of the diffusion parameters of tumor relative to normal stroma in each individual patient were calculated as quantitative measurements of contrast between tumor and normal stroma.

Results: The mean age of the nine patients was 58 ± 7 with PSA of 12.9 ng/mL ± 15.8 and Gleason scores of 6.9 ± 0.6. T1WI, T2WI, DCE, DWI, and ADC maps correlated closely with each other as well as with histopathology results. Compared to conventional ADCs, the new parameters offered by the stretched-exponential model, DDC and β, demonstrated improved ability to differentiate tumor from the surrounding benign stroma (**Figure 1**). The abnormal areas also quantitatively and statistically demonstrated lower DDC and higher β values relative to the surrounding benign stroma, exhibiting greater sensitivity than conventional ADC using any of the three b-values **(Figure 2, Table 1)**. Quantitative maps showed a sharp distinction between tumor and the surrounding normal tissue, with greater statistical significance compared to the conventional ADC approach in all patients.

Conclusions: Our results demonstrate the clinical potential of the new diffusion parameters (DDC and β) provided by the stretched-exponential (or fractional order calculus) diffusion model using multiple b-values, thereby improving the detection of prostate cancer. An expanded double-blinded study would further evaluate the possibility for increased sensitivity and specificity of cancer diagnosis using the new quantitative diffusion imaging technique. The tissue heterogeneity information extracted from β may have potential for predicting cancer grade, monitoring tumor progression, and evaluating nonsurgical treatment response.

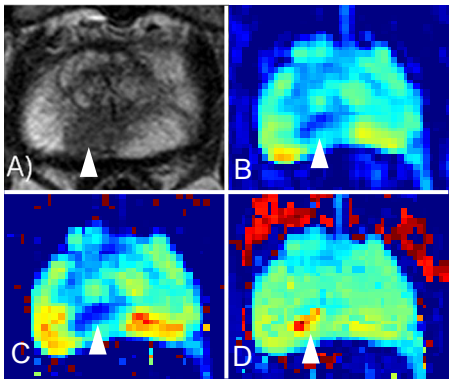

Figure 1 Appearance of right posteromedial peripheral zone cancer: hypointense on T2WI (A), decreased ADC (B), decreased DDC (C), and increased β (D). Visual appearance of (C) and (D) was improved compared to (B).

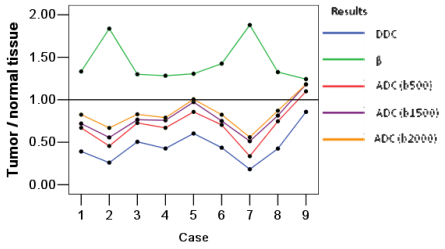

Figure 2 Ratios of calculated diffusion coefficients of tumor relative to adjacent normal stroma in individual patients. Tissue contrast depicted by ratios from DDC and β coefficients are higher in all cases than ratio from conventional ADC at any of the three b-values, as seen by greater deviation from the reference line (ratio = 1.0).

	Tumor	Normal	P
β	0.65	0.48	0.007
DDC (μm^2/ms)	1.01	2.55	0.008
$ADC_{b=1500}$ (μm^2/ms)	0.688	0.884	0.021

Table 1 Median DDC and β coefficients of tumor and normal prostate tissue as compared to median ADC (b=1500). A greater statistical significance (P <0.01) was achieved from the DDC and β coefficients.

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