Clinical feasibility of time-dependent diffusion MRI for improved prostate cancer grading

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Purpose: Given reduced apparent diffusion coefficient (ADC) values in malignant prostate tissue, radiologists use ADC maps routinely to improve tumor localization. This technique exhibits strong contrast in high grade or histologically dense tumors, although shows weak contrast between normal peripheral zone (PZ) and low-grade tumors[1]. **Here we suggest that a gain or loss in ADC contrast may be tuned by acquiring ADC at different diffusion time.** Adjusting diffusion time will focus the ADC contrast based on the restrictions associated with the corresponding diffusion length, $L(t) = \sqrt{6Dt}$. In the context of tumor, shrinkage of glands results in increased restrictions and decreased relevant diffusion length $L(t)$. However, restriction is less significant in low-grade tumor, leading to marginal contrast on ADC maps. In this framework, we show feasibility of analyzing time-dependent diffusion (TDD) in a clinically acceptable time period to facilitate prostate cancer grading based on ADC. **Target Audience**: Radiologists and clinicians using MRI for prostate cancer localization and grading.

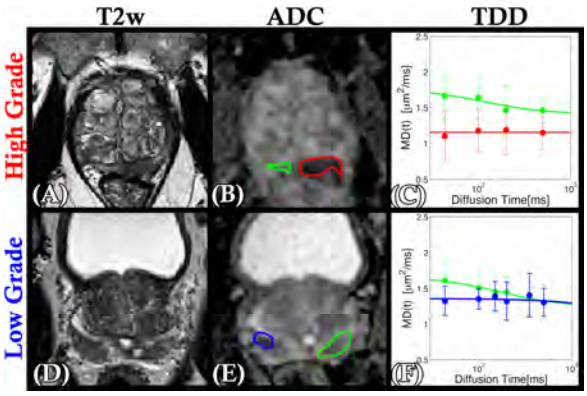

Figure 1: (**TOP**) High-grade tumor. T2WI (A), ADC (B), and TDD (C), where green ROIs and curves represent benign PZ and red represents high-grade tumor. (**BOTTOM**) Low-grade tumor. T2WI (D), ADC (E), and TDD (F), where green ROIs and curves represent benign PZ and purple represents low-grade tumor.

Methods: Patients underwent multi-parametric prostate MRI [Fig.1 (A,B,D,E)] in a MAGNETOM Trio 3T Tim system (Siemens AG, Erlangen, Germany) with a 6-channel pelvic surface array coil. DWI was acquired for b = 0, and along 12 non-collinear gradient directions for b = 500 s/mm² using a STEAM EPI diffusion preparation for 4-6 diffusion times between 43.4 ms and 500 ms. Other imaging parameters included: 1 average, TR>5 s, TE=43.2 ms, matrix=62x80x18, 3.5 mm isotropic voxels, FOV=217x280x63 mm³. Scan time ranged from 4.5-7 minutes. 4 patients with low-grade (Gleason score=3+3) tumor and 4 patients with high-grade (Gleason score≥4+3) tumors were included in this pilot study. All tumors were confirmed by biopsy, including 6 of 8 via MRI/ultrasound fusion targeted biopsy. ROIs within histologically confirmed tumors were delineated on ADC maps, using T2WI for reference. TDD images (78 diffusion volumes) were coregistered using in-house software.
The average mean diffusivity $MD(t)$ from each ROI was quantified using the effective medium theory (EMT) of diffusion in random media[3], [Fig.1 (C,F)], which assumes pockets of high ADC (glandular lumen) surrounded by low ADC background (stroma and epithelium)[4].

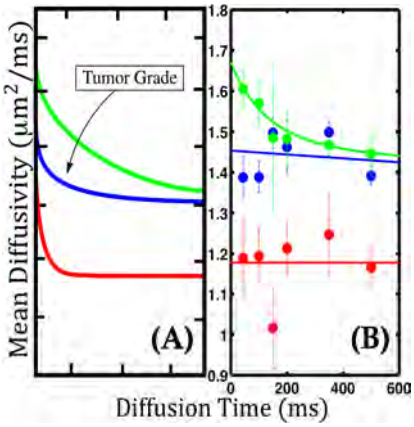

Figure 2: (A) Schematic of the proposed time dependence in benign PZ (green), low-grade tumor (blue), and high-grade tumor (red) predicting behavior at short time scales.
(B) Experimental time dependence in prostate averaged across all patients, showing the time range is enough to capture $D(t)$ in benign tissue, while shorter t are needed to capture D(t) in tumor.

Results: Absolute differences between tumor and benign PZ, averaged among patients, were: at the shortest available diffusion time (43.2 ms), 0.368 ± 0.150 μm²/ms in high grade tumor and 0.266 ± 0.075 μm²/ms in low grade tumor; for the longest available diffusion time (500 ms), 0.232 ± 0.047 μm²/ms for high grade and 0.109 ± 0.081 μm²/ms for low grade. Thus, at long diffusion times, low-grade tumor was indistinguishable from benign tissue. There was a steady loss of tumor vs. PZ contrast with increasing diffusion time due to the visible time dependence of diffusion in benign tissue. Conversely, the contrast increases when employing shorter diffusion times [Fig.2 (A,B)].

Discussion: We show strong potential to increase tumor vs. PZ contrast by using shorter diffusion times in individual images. We also demonstrated that acquiring multiple ADC maps at different diffusion times may increase specificity given different TDD behavior between low-grade tumor, high-grade tumor, and benign tissue. Within our range of diffusion times, we infer that high-grade tumor has no time dependence of diffusion for clinical t, which may facilitate non-invasive grade prediction. This low diffusivity and no time dependence down to t~50ms suggests that restrictions in high-grade tumors are smaller than L~15 μm, consistent with [3]. Low-grade tumors exhibited diffusivities closer to benign tissue and likely experienced transient time dependence at longer length scales, possibly induced by the scale of glands. In benign tissue, t-dependence persists across all time range, allowing us to use the EMT model to predict an average restriction of 50.531 ± 0.152 μm, consistent with healthy glandular lumina ~ 100 μm. Increasing the spatial resolution will likely amplify these differences by minimizing partial volume effects and subsequent mixing between benign and malignant tissue ADC[1].

Conclusion: We have provided a model for improved non-invasive differentiation of prostate cancer grade based on TDD behavior. We also provide motivation for shortening the diffusion times in clinical protocols for increased tumor-to-PZ contrast.

References: [1] Langer et al. Radiology. 249:900-908(2008); [2] Novikov et al. NMR Biomed. 23: 682–697 (2010); [3] Xu et al. Magn. Reson. Med. 61:842-850 (2009); [4]Bourne et al. Magn. Reson. Med. 66:244-247(2011);