Changes in epithelium, stroma, and lumen space predict ADC changes with prostate cancer Gleason grade

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Target audience Researchers and clinicans interested in biophysical basis of diffusivity variations in normal and cancerous prostate

Introduction Reduced water mobility in cancer tissue is commonly attributed to "increased cellularity", however, this explanation includes many tacit assumptions about the microscopic diffusion properties of the tissue. We hypothesise that the biophysical basis of reduced apparent diffusion coefficient (ADC) with presence and increasing cancer Gleason grade may lie, at least partially, in microscopic tissue composition changes, specifically an increase in partial volume of low diffusivity epithelial cells and loss of higher diffusivity stroma and lumen space [2].

Method Six radical prostatectomy specimens were sectioned, H&E stained and scanned at 40× magnification using digital brightfield microscopy (Aperio Image Scope). Scans were divided into 2 × 2 mm sub images and processed to increase contrast. Based on colour, intensity, morphology, and background the sub-images (n = 494) were automatically segmented (Image Pro Premier) into three compartments (stroma, lumen and epithelium) previously shown to have distinct water diffusivities [2]. The measured tissue composition was used to estimate diffusion signal contribution from each component and calculate the ADC at a *b*-value of 1000 sec/mm^2. Literature reporting the diffusivities of epithelium, stroma, and lumen space [2], effects of fixation [4], temperature [5] were used to estimate ADC in vivo and ex vivo and compared with literature values[1,3,6] (ADC values used for epithelium, stroma, and lumen space were 0.3, 0.9, 2.1 μm^2/ms for fixed tissue ex vivo at 22°C, and 0.6, 1.6, 3.0 μm^2/ms for 'in vivo' at 37°C).

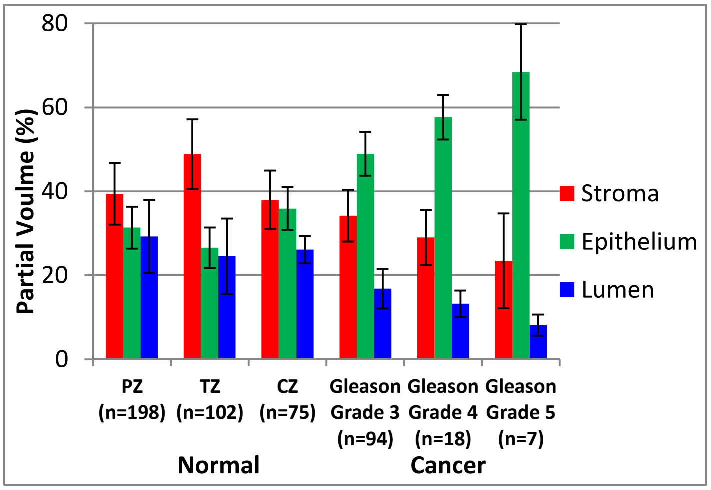

Fig. 1. Tissue composition estimated by histology

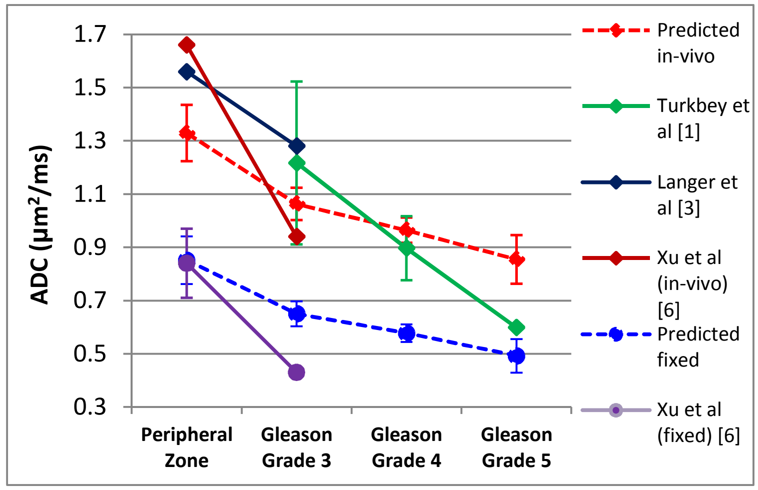

Fig. 2. Reported and predicted ADC changes

Results Fig. 1 shows the measured tissue composition of the normal prostate zones and different cancer Gleason grades, indicating a decrease in stroma and lumen, and an increase of epithelium with presence and increasing grade of cancer. There was a significant ($P<0.05$) difference in tissue composition, not only between normal tissue in the three prostate zones, but also between normal tissue and the different grades of cancer. Fig. 2 shows the calculated tissue ADC values follow the trend of reduced ADC with increasing Gleason pattern observed in vivo[1,3,6].

The predicted decrease in ADC with increasing Gleason grade is lower than that reported in the literature. These differences may relate to different different diffusion times for typical in vivo versus ex vivo ADC measurements and tissue perfusion effects in vivo.

Conclusion: This study quantifies prostate tissue composition changes associated with the presence and Gleason grade of prostate cancer and predicts consequent ADC changes. The results support an hypothesis that the clinically observed negative correlation between cancer grade and ADC can be at least partially attributed to an increasing partial volume of low diffusivity epithelial cells, and corresponding decreasing volume of stroma and lumen space.

References: [1] Turkbey, B., et al., Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? Radiology, 2011. 258(2):488-495 [2] Bourne, R.M., et al., Microscopic diffusivity compartmentation in formalin-fixed prostate tissue. Magn Reson Med, 2012. 68(2):614-20 [3] Langer, D.L., et al., Prostate tissue composition and MR measurements: investigating the relationships between ADC, T2, K(trans), v(e), and corresponding histologic features. Radiology, 2010. 255(2):485-94 [4] Bourne, R., et al., Effect of formalin fixation on biexponential modeling of diffusion decay in prostate tissue. Magn Reson Med, 2013. 70(4):1160-1166 [5] Thelwall, P.E., et al., Effects of temperature and aldehyde fixation on tissue water diffusion properties, studied in an erythrocyte ghost tissue model. Magn Reson Med, 2006. 56(2):282-9. [6] Xu, J., et al., Magnetic resonance diffusion characteristics of histologically defined prostate cancer in humans. Magnetic resonance in medicine, 2009. 61(4):842-850