Changes in tissue components with distinct diffusivities rather than 'cellularity' is the major contributor to clinically observed variations of ADC in prostate tissue

Aritrick Chatterjee[1], Geoff Watson[2], Esther Myint[3], Paul Sved[2], Mark McEntee[1], and Roger Bourne[1]
[1]*Faculty of Health Sciences, University of Sydney, Sydney, New South Wales, Australia,* [2]*Royal Prince Alfred Hospital, Sydney, New South Wales, Australia,* [3]*Douglass Hanly Moir Pathology, Sydney, New South Wales, Australia*

Target audience: Biophysical modelers, diffusion MRI researchers, cancer imaging researchers, radiologists.

Purpose: Reduced ADC in cancer tissue is commonly attributed to increased 'cellularity'. However, this explanation lacks a sound biophysical foundation [1]. While a negative correlation between ADC and cellularity is reported from a range of organs, a higher cell number per unit volume will result in a lower ADC only under specific conditions. The tacit assumption that cells have fixed diffusion properties and simply swell or multiply to displace freely diffusing extracellular water has limited observational foundation. Partial volumes of tissue compartments with distinct diffusivities [2] - epithelium, stroma, and lumen space were found to have a stronger correlations with Gleason grade than either of the cellularity metrics [3]. This study investigates whether a measured decrease in ADC can be explained by an increase in partial volume of low diffusivity epithelial cells and loss of higher diffusivity stroma and lumen space.

Method: Six whole prostates were imaged ex-vivo immediatelly after surgery and again after 24hr formalin fixation on a 9.4T Bruker Biospec system with a voxel size of 0.78×0.78×2 mm using a DWI method and apparatus similar to that described in [4]. Effective diffusion time was 18 ms (δ/Δ = 5/20 ms), b = 17, 1000, 2000 s/mm^2, at 22°C. Diffusion-weighted images, transaxial to the prostatic urethra, were matched with histology slices from approximately the same planes (Fig. 1). ROIs (≥ 20 voxels) were defined inside extensive well-defined normal and cancerous regions mapped on the corresponding histological sections (40 normal ROIs from six prostates, 12 Gleason pattern 3 from five prostates, and five Gleason pattern 4 from two prostates). ADC was calculated with a monoexponential model for b-values of 1000 and 2000 s/mm^2 using the reference of b=17 s/mm^2. Post-MRI, tissue was sectioned, H&E stained, and scanned at 40× using digital microscopy. Histology images were semiautomatically segmented (Image Pro Premier) to measure nuclear count, nuclear area, and partial volume of the gland components: stroma, lumen, and epithelium. These gland components have previously been shown to have distinct water diffusivities [2]. The measured tissue composition was used to estimate diffusion signal contribution from each component and predict ADC.

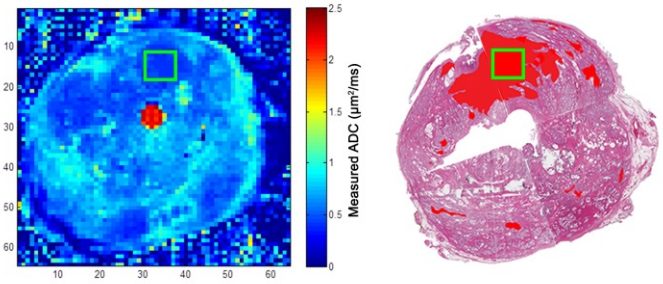

Fig. 1. Representative example of ADC map (left) and cancer mapped on corresponding H&E sections (right). A typical ROI is defined in a region of Gleason pattern 4 cancer. For MRI the prostate was suspended via the urethra on a 5-mm diameter tube containing saline (ADC = 2.1 µm^2/ms at 22°C).

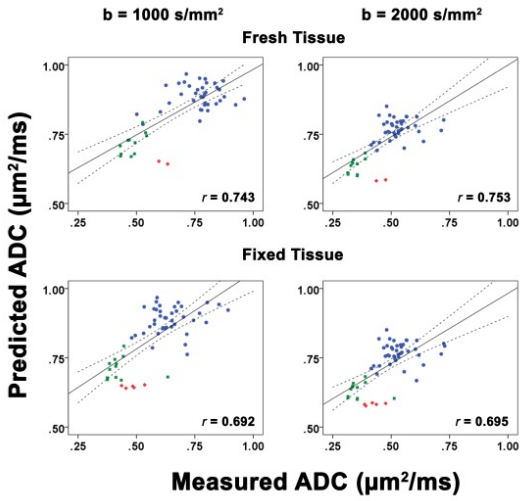

Fig. 2. Correlation of measured ADC and predicted ADC for ex vivo fresh and fixed prostate tissue at b-values of 1000 and 2000 s/mm^2. Dotted lines indicate 95% confidence interval. r = Pearson's correlation coefficient.

Results and Discussion: ADC predicted from gland component partial volumes correlated strongly (r > 0.69) with measured ADC in both fresh and fixed tissue at both b-values of 1000 and 2000 s/mm^2 (Fig.2). Epithelium (r = -0.647) and lumen (r = 0.688) partial volumes each correlated more strongly with measured ADC (fresh or fixed tissue) than did nuclear count (r = -0.598) or nuclear area (r = -0.569). Predicted ADC was generally higher than measured ADC in both normal and cancer ROIs. Due to the relatively small number of cancer ROIs (Twelve Gleason pattern 3, five Gleason pattern 4), and the absence of Gleason pattern 5 ROIs, we did not assess correlations with Gleason pattern in the ROI analysis but instead pooled the cancer ROIs. Epithelium and lumen space partial volume each showed larger differences between normal and cancer tissue (+61.2% and -44.0% respectively) than the cellularity metrics (+32.5% and +29.8%). When comparing normal and cancer ROIs there were strong Spearman correlations for measured and predicted ADC, nuclear count, epithelial partial volume, and lumen partial volume. Again, the predicted ADC and the epithelium and lumen space partial volumes showed stronger correlations with malignancy (cancer v. normal) than the cellularity metrics.

Conclusion: Differences in the partial volume of prostate gland components having distinct diffusivities, rather than changes in the conventionally cited 'cellularity' metrics, are likely to be the major contributor to clinically observed variations of ADC in prostate tissue.

References: [1] Jelescu et al. NMR Biomed (2014) 27(3): 280-290. [2] Bourne et al. Magn Reson Med (2011) 66: 244-7 [3] Chatterjee et al., *Changes in epithelium, stroma, and lumen space predict ADC changes with prostate cancer Gleason grade*. ISMRM 2014: 4422 [4] Bourne et al. Magn Reson Med (2013) 70: 1160-6.