

## Apparent diffusion coefficient as an early quantitative biomarker of radiation response in prostate cancer

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**Introduction:** An image-based early response assessment tool for prostate cancer may allow radiation delivery to be adapted during a course of treatment in order to improve patient-specific outcomes. Studies in malignant glioma have demonstrated the predictive value of a 'functional Diffusion Map' (fDM), defined as per voxel mapping of ADC changes during radiotherapy (1). ADC is known to correlate with cellular density, which helps to provide a biologic basis for clinical significance of the metric (2). This study investigates ADC as a quantitative biomarker of early radiation response in patients with localized prostate cancer. It was hypothesized that tumor-dense versus microscopically or uninvolved prostate regions would present with differential responses. Evaluation tracked mean signal changes to obviate concerns to fDM analysis of prostate motion, deformation, and prostate and tumor volume changes during an 8-week radiotherapy time-course.

**Methods:** 15 patients with low or intermediate risk localized prostate cancer were enrolled for MRI evaluation throughout their 8-week treatment regimen. Patients were positioned supine within a 1.5T GE Signa, using a torso-phased array (MEDRAD ATD) for signal reception. The MRI examination included serial axial FSE (TE/TR=98/5000ms, 320x256 over 20cm), 3mm slices) and DWI acquisitions (TE/TR=64/5575ms; 128x128 over 20cm, 6mm slices). DWI acquisitions were repeated at b-values of 0 and 600, and 0 and 1200 s/mm<sup>2</sup>. The clinically high b-value was included to investigate SNR and b-value limits for clinical prostate ADC quantification at 1.5T, and as an exploratory test for a b-value dependence of ADC radiation response.

Analysis used manually delineated regions of interest (ROIs) on FSE images by a radiation oncologist (MIPAV, NIH), based on imaging features and histopathology. ROIs included the central gland (CG), tumor-dense regions (T), and uninvolved regions of the peripheral zone (PZ). Contours were then applied to DWI and ADC maps, and adjusted manually to correct for evident mis-registration and DW-EPI susceptibility artifacts. Histogram analysis (MIPAV, NIH) provided measurements of mean and standard deviation of ADC at each time-point, and DWI SNR. Significance in ADC response was tested using Student's paired t-test using each patient as his own control. SNR impact on ADC precision was tested via comparison to Monte Carlo simulation predictions (Matlab, The Mathworks).

**Results:** Tumor-dense regions were visualized in 11 of 15 patients. As per literature values (2), baseline ADCs were highly significantly different between CG, PZ, and tumor regions (at b=600s/mm<sup>2</sup>, CG: 1375±117; PZ: 1663±150; T: 1144±179; in 10<sup>6</sup> mm<sup>2</sup>/s). The same trends were denoted at b=1200s/mm<sup>2</sup> but ADC values were reduced (CG: 976±104; PZ: 1239±140; T: 838±133; in 10<sup>6</sup> mm<sup>2</sup>/s). ADC values were uncorrelated with tumor volumes (r of 0.036 and 0.10 at b=600 and 1200s/mm<sup>2</sup>). ADC values displayed similar trends in response to radiation at both b-values (Figure A). CG ADC increased significantly at Wk2 by 7% (p<0.0001) and remained elevated by at least 5% (p=0.003, 0.0019, and 0.0272, through Wks 4 to 8 respectively). PZ ADC trended towards equivalence with baseline at Wk2 and 4 (p=0.54 and 0.50), and declined towards significant 5-7% reductions at Wk6 and 8 (p=0.053 and 0.075). Tumor ADC trended upwards, nearing 10% mean elevations at Wk 2s and 4 (p = 0.055, 0.079) towards significant 12% and 15% elevations at Wk 6 (p=0.0272) and Wk8 (p=0.0123).

DW images displayed whole-gland SNR of 28±5 at b=0s/mm<sup>2</sup>. At experimental ADC of 1200mm<sup>2</sup>/s, Monte Carlo simulation predicts a noise contribution to  $\sigma_{ADC}$  of 10% in voxel-based analysis. At b=600 and 100s/mm<sup>2</sup>, SNR reduced to 12±2 and 8±2, so that per voxel ADC calculation was not significantly biased by the noise baseline in magnitude images. However, b=1200mm<sup>2</sup>/s is approaching a SNR limit for usefulness, given the field strength, DWI parameter set, and RF coil configuration of the acquisition.

**Summary and Conclusions:** ADC is a promising biomarker which is sensitive to early radiation effects in patients with low and intermediate risk localized prostate cancer, showing distinctive responses in CG, PZ, and tumor-dense regions. Selection of clinically-high b-values did not further potentiate ADC response evaluation. Limited SNR at 1.5 Tesla necessitates a transition to stronger magnets and more sensitive RF components to potentiate voxel-based tracking of ADC changes.

**References:** (1) D. Hamstra et al, PNAS, 2005; (2) B. Zelhof et al. BJUI, 2008.

**Figures:** (A) ADC time-courses for PZ (circle), CG (square), and T (triangle) for b=600s/mm<sup>2</sup>; (B) Representative FSE and ADC images at baseline and at 2-week intervals through to week 8 (from left to right). An arrow in the Wk0 FSE demarcates a PZ tumor.

