Apparent Diffusion Coefficient as a predictive biomarker of prostate cancer progression: value of fast and slow diffusion components

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Introduction Prostate cancer, particularly early stage disease, often behaves in an indolent fashion, with no effect either on health or longevity (1). Since radical treatment carries risks of incontinence and impotence, patients may be offered a programme of active surveillance, which involves regular monitoring with prostate specific antigen (PSA) levels, magnetic resonance (MR) imaging and repeat biopsy at 2 yearly intervals, or sooner if there is a rise in PSA. In considering patients most suitable for surveillance, there is a need for markers of prostate cancer behaviour that can be used to distinguish those with clinically relevant cancers, who may benefit from radical treatment, from the remainder who do not need treatment (2). The aim of this study was to investigate whether the fast and slow components of the apparent diffusion coefficient (ADC) of prostate tumor obtained on diffusion-weighted imaging (DW-MRI) could be used to distinguish those that subsequently progressed on histology and to predict at the outset those prostate cancers most likely to progress.

Methods 81 patients with localized prostate cancer managed by active surveillance underwent DW-MRI in addition to their standard T2-W MRI between Aug 04 and Sep 06. (At time of scan, mean age = 67 years, mean PSA = 7.6ng/ml, mean Gleason = 6, 2 cores positive in 22%). MR studies were performed using a 1.5-T Intera (Philips Medical Systems, Netherlands) using a balloon design endorectal coil (Philips Medical Systems, Netherlands) inflated with 55ml of air. Hyoscine butyl bromide 20 mg was administered intramuscularly immediately prior to scanning to reduce peristalsis. Conventional T2-W fast spin echo images were obtained in 3 orthogonal planes (TSE 2000/90 ms [TR/effective TE], echo train length 16, 2 signal averages) with a 256x512 matrix (interpolated to 512 x 512), 3mm slice thickness, no gap and a 14cm FOV (total imaging time 12 mins). Echo-planar DW images (2500/69 [TR/TE]) with b values of 0, 100, 300, 500 and 800 s/mm^2 were obtained transverse to the prostate and parallel to the corresponding set of T2-W images. Phase-encoding gradient was left to right to minimize motion artefacts. Twelve 4mm thick slices (no gap, 20 cm FOV, matrix 128x128) covered the prostate with an image acquisition time of 1min 24s.

Axial T2-W and DW- images were transferred offline for analysis and ADC maps created. Regions of interest (ROIs) were drawn on ADC maps over tumor (identified as focal restricted diffusion in the peripheral zone on ADC maps), using T2-W images to guide placement. Mean ADC values (x10^{-6}mm^2/sec) for tumor were calculated for all b values ($ADC_{overall}$), and with only the low (0-300, ADC_{fast}) and only the high (300-800, ADC_{slow}) b values to reflect fast and slow diffusion components. ADCs in those whose repeat biopsies were upgraded at follow-up were compared with those whose biopsies were histologically stable. Cox's regression was used to predict likelihood of progression to radical treatment based on $ADC_{overall}$, ADC_{fast} and ADC_{slow}.

Results $ADC_{overall}$, ADC_{fast} and ADC_{slow} for the whole group n=81 were 1285±300, 1476±331 and 1033±254 x10^{-6}mm^2/sec respectively. 34 patients had at least one repeat biopsy and hence were included in the analysis of histological progression; 10 of these were upgraded on repeat biopsy. ADCs of those that were upgraded on repeat biopsy were significantly lower than those that were stable at repeat biopsy (Table 1). Of 81 patients, 1 patient was excluded from the time to treatment analysis because MRI was done after TURP for urinary tract symptoms. Of the remaining 80 patients, 11 progressed to radical treatment (4 radiotherapy, 1 brachytherapy, 6 hormone therapy). In this cohort, $ADC_{overall}$ and ADC_{slow} were significant predictors of progression to radical treatment (p values 0.048 and 0.013 respectively; hazard ratios 0.997 [95% CI 0.994-1.0] and 0.995 [95% CI 0.991-0.999] respectively); ADC_{fast} was not.

Table 1: Comparison of ADCs from patients with and without histological progression

	$ADC_{overall}$ X10^{-6}mm^2/s		ADC_{fast} X10^{-6}mm^2/s		ADC_{slow} X10^{-6}mm^2/s	
	mean	**sd**	**mean**	**sd**	**mean**	**sd**
Stable on repeat biopsy (n=24)	1321	339	1475	383	1096	287
Upgrade on repeat biopsy (n=10)	1047	99	1241	132	834	72
p	0.001		0.013		<0.001	

**p-values for independent sample t-test with unequal variance, for upgrade vs stable on repeat biopsy*

Figure 1 – Progressed to radical treatment, tumor indicated by arrow

Axial T2 image Axial ADC Map

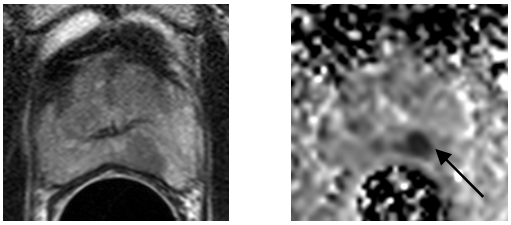
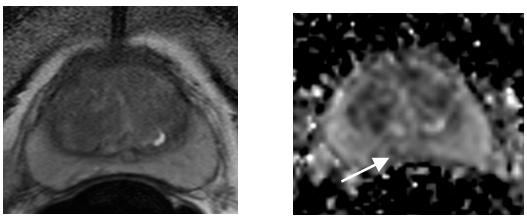


Figure 2 – Disease stable at 2 years, did not progress to radical treatment, (tumor arrowed)

Axial T2 image Axial ADC Map



Conclusion Both ADC components were significantly lower in those that were subsequently upgraded on histology indicating lower microcapillary perfusion and cellularity in this group at the outset. However, it is the true diffusion, ADC_{slow}, a surrogate biomarker of tumor cellularity that appears to be a significant predictor of progression to radical treatment.

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References

1. O'Donnell H, Parker C, World J Urol. 2008 Oct;26(5):415-22. Epub 2008 Jun 21
2. Klotz L, Urol Oncol. 2006 Jan-Feb;24(1):46-50