Monitoring prostate cancer progression with Diffusion Weighted Imaging: utility of fast and slow diffusion components of the apparent diffusion coefficient.

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Introduction Early stage prostate cancer is sometimes managed with active surveillance as the disease may be low risk and behave indolently. Active surveillance involves regular monitoring of prostate specific antigen (PSA) levels. These alone are inadequate to predict the need for radical intervention and necessitate repeat 10 core Trans Rectal Ultrasound Guided (TRUS) biopsy at 2 yearly intervals or sooner if there is a rise in PSA. TRUS biopsy is invasive, poorly tolerated, carries a morbidity and is subject to sampling error. Non-invasive biomarkers of disease progression are therefore being sought. The aim of this study was to determine whether a change in fast and slow components of apparent diffusion coefficient (ADC) in whole prostate and in tumor in patients on active surveillance is indicative of disease progression.

Methods 32 consecutive patients with localized prostate cancer at the time of the first scan (Stage 1 or 2a disease, Gleason n=23(3+3), n=7(3+4), n=1(4+3), n=1(no tumor on 1st Biopsy) Median PSA 7.6ng/ml (Min PSA 0.41ng/ml, Max 15.0ng/ml) managed with active surveillance underwent DW-MRI in addition to their standard T2-W MRI at baseline (time-point 1) and after a mean of 23months (time-point2) (min=11, max=35months). MR studies were performed using a 1.5-T Intera (Philips Medical Systems, Netherlands) and 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 in order to reduce peristalsis. Conventional T_2-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. Left-to right phase-encoding minimized motion artifacts. Twelve 4mm thick slices (no gap, 20 cm FOV, matrix 128x128) covered the prostate with an image acquisition time of 1min 24s.
Regions of interest were drawn on ADC maps around whole prostate (WP) and the low signal-intensity tumor (T) in the peripheral zone on all slices containing focal T2-W abnormality consistent with tumor in biopsy-positive octants. ADC values were obtained for all b values ($ADC_{overall}$) and for low (0-300) and high (300-800) b values to reflect ADC_{fast} (perfusion) and ADC_{slow} (true diffusion) respectively. Percentage change in ADCs of those that progressed to radical treatment (based on PSA velocity, Gleason grade and number of positive cores, (n=10) were compared to those that did not (n=22). Differences between those that progressed on histology and histologically stable patients were also compared.

Results Over the entire group, there was a significant reduction at TP2 compared to TP1 in tumor $ADC_{overall}$ (5.2%; p=0.03) and ADC_{fast} (4.3%; p=0.03) but not in ADC_{slow} nor in any ADC components of WP. This indicates a reduction in tumor microcapillary perfusion over this time. Those that progressed to radical treatment were primarily responsible for this effect (Table 1, Fig 1). In progressors, however, changes were also seen over the WP in $ADC_{overall}$ and ADC_{fast} which were significantly greater than for tumor (Table 2). Similarly, in those that progressed on histology $ADC_{overall}$ and ADC_{fast} were significantly reduced compared to those that remained histologically stable (Table 3). In addition, the ADC_{slow} in this group appeared significantly lower.

Table 1. Whole group ADC values for Whole Prostate (WP) and Tumor (T) at 2 timepoints.

	$ADC_{overall}$ mm^2/s				ADC_{fast} mm^2/s				ADC_{slow} mm^2/s			
	WP		**T**		**WP**		**T**		**WP**		**T**	
	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD
Whole GroupTimePoint 1	1739	151	1471	280	1993	180	1669	312	1351	101	1185	228
Whole Group TimePoint 2	1718	122	1373	244	1954	125	1558	236	1357	114	1133	233
Sig.	0.31		**0.03**		0.13		**0.03**		0.75		0.22	
% change TP1-TP2	-0.9	6.7	-5.2	15.7	-1.5	7.0	-4.3	16.5	0.7	7.5	-2.9	18.4
Progressors TP1	1759	105	1380	140	2029	105	1596	171	1354	109	1097	141
TP2	1674	98	1231	106	1926	104	1417	134	1290	84	1005	107
Sig.	**0.03**		**0.03**		**0.03**		**0.046**		0.07		0.18	
Non-Progressors TP1	1730	170	1512	319	1976	205	1702	357	1350	100	1224	251
TP2	1738	129	1438	263	1966	134	1622	246	1388	114	1191	252
Sig.	0.75		0.21		0.75		0.21		0.09		0.53	

Table2. Percentage change over time for those that progressed to treatment or not.

	$ADC_{overall}$				ADC_{fast}				ADC_{slow}			
	WP		**T**		**WP**		**T**		**WP**		**T**	
	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD
Progressor to radical treatment	-0.4	5.8	-10.0	11.3	-0.6	5.6	-10.2	13.5	1.6	6.6	-6.8	17.6
Non-Progressor to radical treatment	0.8	6.5	-2.9	17.1	0.0	7.1	-2.2	17.4	3.0	7.4	-1.2	18.9
Sig	**0.03**		0.17		**0.046**		0.18		**0.01**		0.42	

Table 3. Percentage Change over time for progressors on Biopsy

	$ADC_{overall}$				ADC_{fast}				ADC_{slow}			
	WP		**T**		**WP**		**T**		**WP**		**T**	
	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD	Mean	+/- SD
Progressor on histology	-6.5	5.7	-14	9.1	-6.7	5.3	-15.5	10.5	-6.0	7.15	-8.2	17.2
Non-Progressor on histology	1.0	6.0	-2.2	16.4	0.2	6.6	-1.1	16.6	2.9	6.8	-1.1	18.6
Sig	**0.01**		**0.02**		**0.01**		**0.01**		**0.01**		0.34	

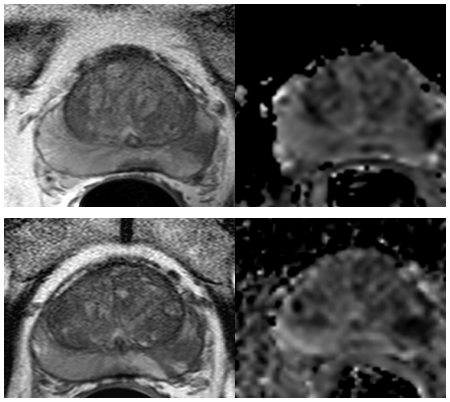

Fig 1.T2W axial (left) & DWI slice (right) at TP1 (top) & (bottom) in a patient that progressed to radical treament

Conclusion: Changes in ADC, particularly in ADC_{fast} over a 1-3yr time period show potential for monitoring disease progression in prostate cancer patients managed by active surveillance. **This work was supported by Cancer Research UK grant number C1060/A5117 and also NHS funding to the NIHR Biomedical Research Centre.**