Characterising the Contribution of Hypoxia to R2* Differences between Prostate Tumours and Normal Tissue

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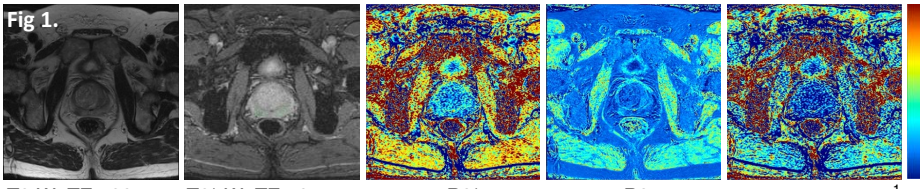
Purpose: Hypoxia is found in many tumours and is an emerging biomarker for poor prognosis in prostate cancer [**1,2**]. The R2* relaxation rate has been proposed to map hypoxia in prostate cancer [**3-5**], with R2* being found to have a strong positive correlation with needle oxygen electrode measurements of hypoxic fraction [**3**]; and a high sensitivity in predicting tumour hypoxia assessed by immunohistochemistry [**4**]. However, R2* (= R2 + R2') has a complex relationship with tissue oxygenation [**6**], with R2 thought to primarily reflect tissue macromolecular structure and R2' expected to be highly sensitive to magnetic field inhomogeneities e.g. due to paramagnetic deoxyhaemoglobin, as exploited in blood-oxygenation-level-dependent (BOLD) functional MRI. The relative contribution of R2 and R2' to R2* remains unexplored in prostate cancer. This study aimed to characterise the nature of R2* change in prostate cancer, by quantifying and comparing R2* and its components (R2 and R2') for cancerous and normal prostate tissue. We hypothesise that R2* is greater in prostate tumours than in healthy tissue and that this is driven primarily by an increase in R2' in tumours.

Methods: A retrospective study was conducted on 50 prostate cancer patients who underwent clinical 1.5 T multi-parametric (mp) (T2- and T2*-weighted (W), Diffusion Weighted and Dynamic Contrast Enhanced) prostate MRI, followed by biopsy during 2008-2009. Patients were selected according to the following criteria: (i) MRI prior to therapy and before biopsy (or ≥3 months after biopsy) to avoid haemorrhage artefacts, (ii) biopsy positive for tumour and maximum cancer core length > 4 mm, (iii) patients treated with HIFU or radiotherapy, and (iv) 18 months of clinical follow-up available. Studies with susceptibility or movement artefacts were excluded. The clinical mp-MRI protocol included T2- and T2*-W images acquired using a pelvic phased array RF coil following administration of 20 mg Buscopan to reduce bowel motion. Two T2-W images were acquired using a fast SE sequence (TE = 46, 92 ms, TR = 5170 ms, echo train length = 17, pixel BW = 190 Hz, 256 x 256 matrix) with 2 averages and two T2*-W images were acquired using a fast spoiled GRE sequence (TE = 12, 25.5 ms, $\alpha = 20°$, TR = 796 ms, pixel BW = 80 Hz, 256 x 192 matrix). Both sequences had 24 slices acquired with 3 mm thickness and a 0.3 mm gap, 200 x 200 mm field of view and were reconstructed to a final matrix size of 512 x 512. Tumour and healthy tissue regions of interest (ROI) (identified on mp-MRI and confirmed by biopsy) were contoured on a single slice with the widest tumour diameter in consensus by two experienced radiologists on matched T2- and T2*-W images. Mean R2*, R2 and R2' values for each tumour and healthy tissue ROI were calculated from the ROI mean T2-W and T2*-W signal intensities (I) and echo time difference (ΔTE) using $R2^{(*)} = \ln(I1/I2)/\Delta TE$ and R2' = R2*- R2. ROI mean relaxation rates were compared between tumour and normal prostate tissue using Student's t-test.

Results: ROI results are shown in the table. ROI R2* values agree with previous measurements [**3**]. R2* and R2 were significantly greater for cancer than normal tissue. No significant difference was found in R2' between tumours and healthy tissue. Representative images and maps from one patient are shown in **Figure 1**. Tumour (L) and healthy tissue (R) ROIs are shown on the T2*-W image.

ROI:	Tumour		Healthy Tissue		t-test
(s^{-1})	Mean	SD	Mean	SD	p-value
R2*	17.0	4.0	12.3	5.9	< 0.0001
R2	10.6	1.8	6.1	2.0	< 0.0001
R2'	6.4	3.9	6.2	5.8	0.3077



T2-W, TE= 92 ms | T2*-W, TE= 25.5 ms | R2* | R2 | R2' (All 0-50 s^{-1})

Discussion and Conclusions: Prostate tumour R2* values seem to predominantly reflect differences in R2 and not R2'. However, there are several confounding factors which are likely to have affected these results. First, the separate acquisitions for each echo time for T2 and T2* measurement could have contributed to inaccuracies in R2 and R2* due to patient motion and scanner instabilities. Second, the R2 differences observed here are likely to be dominated by the contribution of irreversible dephasing as spins diffuse through field inhomogeneities ($R2_{diff}$) potentially arising from hypoxia. The reason that the expected R2' difference due to these field inhomogeneities is not observed may be because R2' was calculated as (R2* – R2) and the measured R2 captures most of the effect of the field inhomogeneities on the signal. The field inhomogeneities may have affected R2 more than R2' because R2 was measured using relatively long TEs and ΔTE, causing significant irreversible signal loss via diffusion, whilst R2* was measured at short TEs and ΔTE, allowing relatively little signal decrease via static dephasing. These results agree with Chopra et al.'s finding [**3**] of a very strong and highly significant correlation between R2* values and a T2 signal metric, suggesting that their R2* values were also dominated by measured T2. The effect of diffusive dephasing ($R2_{diff}$) on R2 may dominate here, particularly if there are high capillary densities in the tumours. This work highlights the difficulty of relating MRI measures directly to tissue hypoxia. The results underscore the need for future prospective studies to separate and assess the contributions of R2 and R2' to R2* changes. These studies will incorporate multi-echo SE and GRE acquisitions together with image registration, or hybrid techniques [**7**], to allow voxel-based analysis.

References: 1. Jordan et al. *Front Pharmacol.* **2012** 3:94. **2.** Milosevic et al. *Clin Cancer Res.* **2012** 18:7:2108-14 **3.** Chopra et al. *Int J Radiat Biol.* **2009** 85:9:805-13 **4.** Hoskin et al. *Int J Radiat Oncol Biol Phys.* **2007** 68:4:1065-71 **5.** Baudelet et al. *MRM* **2002** 48:980-986 **6.** Baudelet et al. *Current Medical Imaging Reviews* **2005** 1:229-243 **7.** Thomas et al. *Neuroimage* **2002** 15:4:992-1002