Microstructural characterisation of normal and malignant human prostate tissue with VERDICT-MRI

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Target Audience Biophysical modellers, diffusion MRI researchers, cancer imaging researchers and radiologists.

Introduction Histological identification of prostate cancer remains the gold standard and the only method to provide a definitive diagnosis of the disease. Non-invasive detection has been facilitated by multi-parametric MRI, which supplements anatomical evaluation with a crude assessment of tissue cellularity and vascularity. This study utilises diffusion-weighted MRI (DW-MRI) and a three-compartment model (Vascular, Extracellular and Restricted DIffusion for Cytometry in Tumours (VERDICT) [1]) of tissue microstructure and assesses the ability of the model to differentiate between benign and cancerous prostate tissue.

Table 1 MRI acquisition parameters

b value s/mm²	*Δ/ δ ms*	*TE ms*	*G T/m*
1000	26.6 / 8.5	55	0.0902
2000	29.4 / 11.3	60	0.0924
3000	31.6 / 13.5	65	0.0921
2500	30.7 / 12.6	63	0.0911
1500	28.1 / 10.0	58	0.0912
800	25.7 / 7.6	53	0.0912
400	23.7 / 5.6	49	0.0903
200	22.2 / 4.1	46	0.0893
100	21.2 / 3.1	44	0.0849

Methods We imaged 7 patients (prior to targeted transperineal template mapping (TPM) biopsy) at 3T using conventional multi-parametric MRI[2] supplemented by additional DW-MRI sequences (as below) specifically for VERDICT modelling. The VERDICT model was then fitted to the DW-MRI signal from cancerous and benign regions of interest (ROI) to derive estimates of the underlying microstructure. Based on multiparametric MRI findings, an experienced radiologist contoured the focus most suspicious for tumour within the peripheral zone (PZ) of the prostate for subsequent targeted TPM. All 7 patients had histologically confirmed Gleason grade 3+4 and 4+3 cancer in the PZ on targeted biopsy cores patients with 3+4 median MCCL (median cancer core length) 7.5mm [range 5 to14mm] and 1 patient with 4+3 MCCL 1mm. Following review of the biopsy result the same radiologist located an ROI for each patient in a location of histologically confirmed benign prostatic tissue. The VERDICT model performance for differentiation between benign and cancerous tissue was tested by Wilcoxon matched pairs statistics and compared with the standard apparent diffusion coefficient (ADC) and intravoxel incoherent motion (IVIM) [3] models.

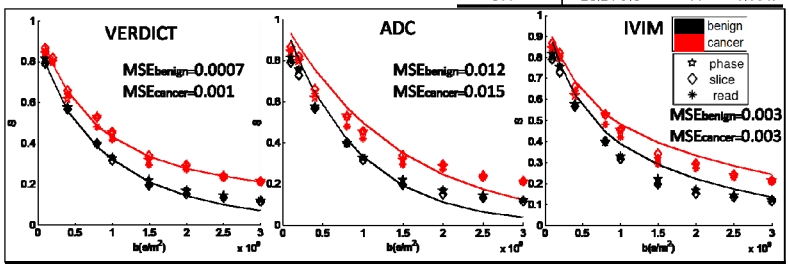

Figure 1 Fits of the ADC, IVIM and VERDICT models to the data for an example dataset. The symbols represent the measured data and the lines show the corresponding fits by the model. The normalized signal S is plotted as a function of the *b* value for all diffusion directions (x=phase direction, y=read direction, z=slice direction). The VERDICT provides a good fit, whilst the ADC and IVIM models fail to represent the whole range of the data.

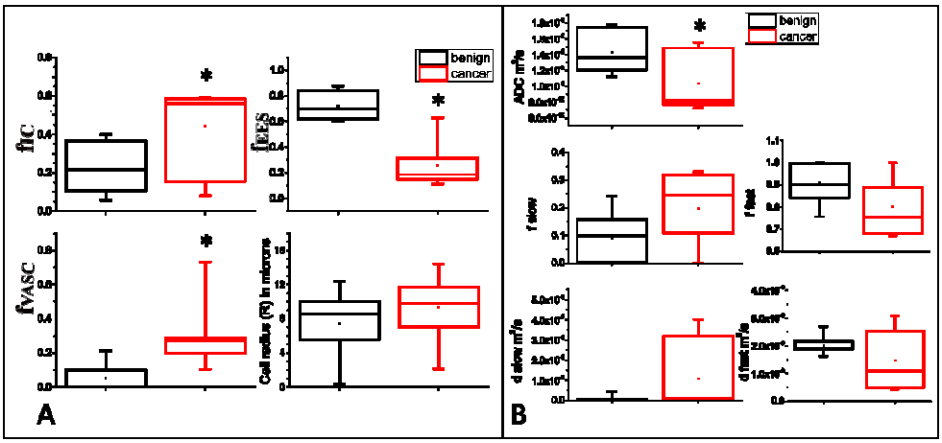

Figure 2 Microstructure parameter estimates for the benign and cancer ROIs for VERDICT (A), ADC and IVIM (B) models. Boxes define the interquartile range, whiskers the full range, the central lines the median and the dot the mean. Significant differences between groups are represented by asterisks (Wilcoxon test $p<0.05$). Only VERDICT volume fractions of the IC, EES and vascular compartments, and the ADC showed significant differences between the groups of benign and cancer tissue.

VERDICT model: VERDICT is a three-compartment model that characterises water diffusion in the vascular, extracellular-extravascular space (EES) and intracellular (IC) compartments in tumours. The total diffusion MR signal is the weighted sum of the signals from each compartment, with weights summing to 1. To model the signal for the IC compartment we assume restricted diffusion in impermeable spheres[4]. This compartment has f_{IC} (IC volume fraction), d_{IC}, (diffusivity IC) and cell radius R as parameters. The model for the EES compartment uses a diffusion tensor (DT) model[5]. Here we constrain it to be isotropic so it has f_{EES} (EES volume fraction) and d_{EES}, (diffusivity EES) as parameters. The vascular model uses an isotropically restricted model: cylinders with uniformly distributed orientations and zero diameter[5] and has f_{VASC} (vascular volume fraction) and P (pseudo-diffusion) as parameters. In total 4 parameters were estimated for this study: f_{VASC}, f_{EES}, $f_{IC=(1-}$ f_{VASC}-$f_{EES})$, R with the diffusion and pseudo-diffusion coefficients fixed to values that minimise fitting error over all voxels: $d_{IC}=d_{EES}=2\times10^{-9}m^2/s$, $P=8\times10^{-9}m^2/s$. This particular form of VERDICT resulted from preliminary work, which included a model selection similar to[6,7] that identifies a parsimonious model that fits the data.

DW-MRI for VERDICT: DW-MRI was performed with a 3T scanner using a pulse-gradient spin-echo sequence with 9 *b* values between 100 and 3000s/mm² in three orthogonal directions. For b<500 the number of averages (N_{AV}) was 6, for 500<b<1000 N_{AV}= 12 and for b>1000 N_{AV}= 18 with voxel size= 1.3x1.3x5mm, matrix size= 176x176. Table 1 shows the imaging parameters. The data was normalised to avoid T_2 dependence with a *b*=0 image for every TE. The total duration of the scan for each patient was around 35mins.

Model fitting We averaged the signal over the whole ROI and used a similar iterative optimization procedure to [6] that accounts for local minima and Rician noise.

The signal to noise ratio (SNR) was calculated as in[8] (median SNR≈13).

Results The VERDICT model captured broad trends in the data for both benign and cancer ROIs with lower mean squared error (MSE) than the ADC and IVIM model which exhibited clear departures, indicating that these simple models were unable to capture the variation in the signal (Fig.1). Results were similar for all datasets. The VERDICT IC, EES and vascular volume fraction estimates were significantly different between the benign and cancer tissue (p=0.05) (Fig.2). Only ADC was significantly different (p=0.05) between tissue types and none of the IVIM parameters (p=0.11to 0.29).

Discussion & Conclusions We examined 7 patients with biopsy proven prostate Gleason grade 3+4 PZ cancer. VERDICT parameters IC, EES and vascular volume fractions were significantly higher for cancer than benign tissue (Wilcoxon test p=0.05) in agreement with existing knowledge of increased cellularity and vascularity in prostate cancer [8]. Future work will create an economical protocol for shorter clinical acquisitions using, for example the experiment design optimization in [10], and also verify the VERDICT estimates with histology.

References & Acknowledgements 1 Panagiotaki et al ISMRM Diffusion Workshop 2013, 2 Barentsz Eur Radiol (2012) 3 Le Bihan et al, Radiology (1988) 4 Murday and Cotts, JChemPhys, (1984), 5 Basser et al, Biophys J, (1994),6 Panagiotaki et al NeuroImage (2012) 7 Panagiotaki et al, ISMRM 2013, 8Dikaios et al MRM (2013) 9 Imaging in Oncological Urology JJ de la Rosette (2009) 10Alexander MRM (2008). We acknowledge the NIHR-funded Biomedical Research Centre at UCH. This work is funded by the EPSRC grant EP/H046410X1 and EP/I018700/1.