Title: Short term repeatability of microstructural (VERDICT) MRI vs. ADC in prostate cancer

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Target Audience:
Biophysical modellers, diffusion MRI researchers, cancer imaging researchers, prostate cancer clinicians

Introduction:
VERDICT (Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumours) is a microstructural imaging technique that combines a detailed diffusion MRI acquisition with a mathematical model to map and measure microstructural tissue parameters. The technique has shown significant promise in the preclinical setting (1) and in a pilot study in prostate cancer (2), but to develop the technique for translational and clinical research, it must demonstrate technical validity.

This study seeks to evaluate the short-term repeatability of VERDICT MRI in normal and cancerous prostate tissue.

Materials and methods:
5 men awaiting biopsy for suspected prostate cancer were identified and recalled for VERDICT MRI, with a median of 120 days (range 43- 151) from their original multiparametric prostate MRI.

VERDICT DW-MRI was performed using a 3T scanner (Achieva, Philips Healthcare, Netherlands) using a series of pulse-gradient spin-echo sequences with various diffusion gradient strengths and timings (3). The series of scans was repeated following a 2-minute interval. The imaging parameters are shown in table 1.

Diffusion model
VERDICT is a three-compartment model that characterises diffusion in the vascular, extracellular-extravascular space (EES) and intracellular (IC) compartments in tumours. The prostate model has five parameters: f_{EES} (EES volume fraction), f_{IC} (IC volume fraction), cell radius R diffusivity D and pseudo-diffusion P. A vascular volume fraction can be determined from $f_{VASC}=1- f_{IC}- f_{EES}$. Cellularity maps are calculated by dividing f_{IC} by the cube of the cell radius (cell volume) estimate.

Image analysis
MR datasets were analysed with Osirix Version 7.0 (Bernex, Switzerland). A board certified Radiologist (EJ) manually contoured a region of interest (ROI) on each prostate lesion, using the slice at the epicentre of the tumour. ROIs were drawn on the b=2000s/mm^2 image, using the previous mpMRI for further guidance. An ROI of equal size was then drawn in a normal region of the prostate, in the same zone, on the same slice. ROIs were copied onto the subsequent

acquisition and manually refined accordingly.

We fitted the VERDICT model to the data using a similar iterative optimization procedure to Panagiotaki et al. (1,2) that accounts for local minima and Rician noise. Fitting consisted in two steps, first the model was fitted to data averaged over all voxels of the prostate (tumor and benign regions) and then the fitting was performed in each voxel. Fitting was performed using the open source Camino toolkit (http://cmic.cs.ucl.ac.uk/camino/) (4). Apparent diffusion coefficient (ADC) was also fitted for comparison.

An example of a multi-parametric (mp)MRI and the subsequent generated VERDICT maps are provided in figure 1.

Statistical analysis
Median ROI values were used for all parameters, as data was not normally distributed. Bland Altman plots were constructed and intraclass correlation coefficients (ICCs) (3,1) single measures, with absolute agreement calculated.

Results:
5 patients had a median age of 67.4 (range 58.0 – 74.6), a median prostate specific antigen (PSA) of 8.5 (range 3.3 – 18.0). Subsequent biopsy performed within a week of the scan confirmed prostate cancer in the peripheral zone (n=4) and transition zone (n=1), with Gleason scores of 3+3(n =1) and 3+4 (n=4).

Bland-Altman plots were constructed; please see in figure 2 for interpretation. Intraclass correlation coefficients (ICCs) are provided in table 2. In accordance with Landis and Koch (5), the following ICC interpretation scale was used: poor to fair (below 0.4), moderate (0.41–0.60), excellent (0.61–0.80), and almost perfect (0.81–1).

Discussion:
To be clinically useful, any quantitative imaging technique must demonstrate accurate estimates of the measured biological parameter (accuracy) and be repeatable (precision) (6).

Broadly, more complex biophysical models such as VERDICT provide a better fit to data than simpler models with fewer parameters, such as ADC, and our previous work has shown this to be the case (1,2). However, more complex models also tend to 'overfit' data, and become sensitive to noise, resulting in poor repeatability.

In this study, we were able to compare the repeatability of parametric maps generated from VERDICT MRI to those of ADC. As expected, ADC demonstrated almost perfect agreement.

Cellularity was the most reliable parameter with almost perfect agreement in both normal and cancerous prostate tissue. fIC and fEES were the next best performing, demonstrating almost perfect agreement in the normal prostate and excellent agreement in cancerous tissue.

However, cell radius and fvasc demonstrated poor to moderate repeatability, with the latter likely due to relatively low contribution to MR signal.

Conclusion
Cellularity, fEES and fIC are repeatable VERDICT parameters. Further work is required to establish the medium and long-term repeatability of VERDICT, and for biological validation to determine what constitutes a clinically useful measurement.

References:

1.   Panagiotaki E, Walker-Samuel S, Siow B, et al. Noninvasive quantification of solid tumor microstructure using VERDICT MRI. Cancer Res. 2014 Apr 1;74(7):1902-12

2.   Panagiotaki E, Chan RW, Dikaios N, et al. Microstructural Characterization of Normal and Malignant Human Prostate Tissue With Vascular , Extracellular , and Restricted Diffusion for Cytometry in Tumours *Investigative Radiology*, 50 (4), 218-227.

3.   Panagiotaki E, Ianus A, Johnston E et. al, Optimised VERDICT MRI protocol for prostate cancer characterisation. 24th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Toronto, Canada 2015.

4.   P. A. Cook, Y. Bai, S. Nedjati-Gilani, K. et. al, Camino: Open-Source Diffusion-MRI Reconstruction and Processing, 14th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Seattle, WA, USA, p. 2759, May 2006.

5.   Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;**33**:159-174.

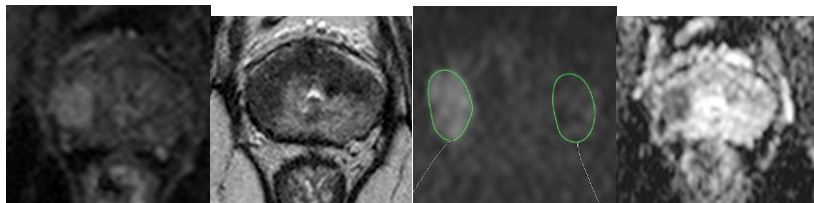6.   Tofts P. QA: quality assurance, accuracy, precision and phantoms. 2003; Available from: http://discovery.ucl.ac.uk/188427/. Accessed 8th November 2015.

Figures and tables

b value s/mm^2	Δ/δ ms	TE ms	$|G|$ T/m
3000	24.7/43.8	90	0.0439
2000	13.2/32.3	67	0.0758
1500	24.7/43.4	90	0.0311
500	12.2/31.3	65	0.0415
90	12.2/23.8	50	0.0506

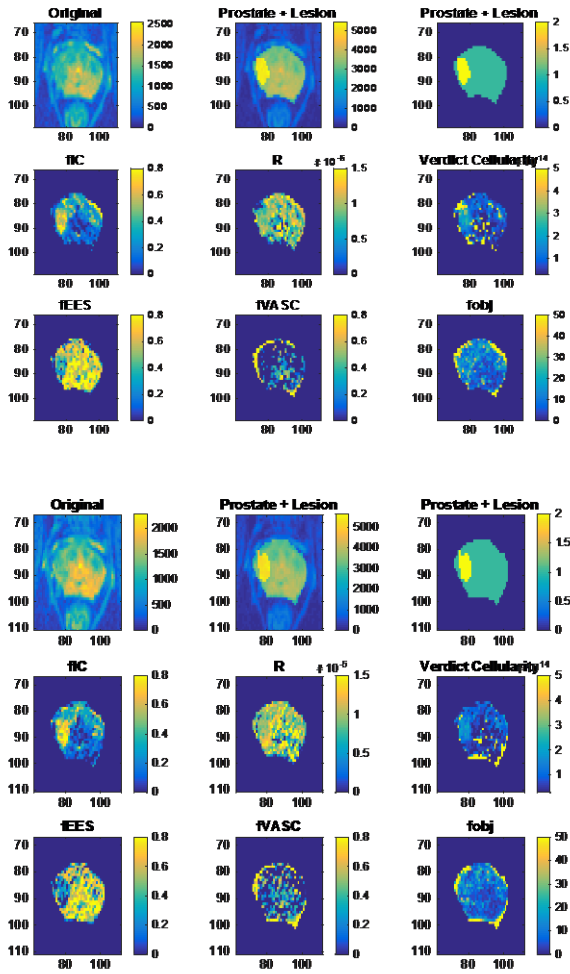Table 1: Diffusion MRI protocol details for VERDICT analysis.

Figure 1:
Top - multiparametric prostate MRI showing a tumour in the right peripheral zone, between 7 and 10 o'clock. L >R: The tumour is low signal on T2, of low ADC value and high signal on B2000 and early DCE.
Bottom images: Subsequent multiparametric VERDICT maps (acquisitions 1 and 2) demonstrating similar qualitative repeatability.
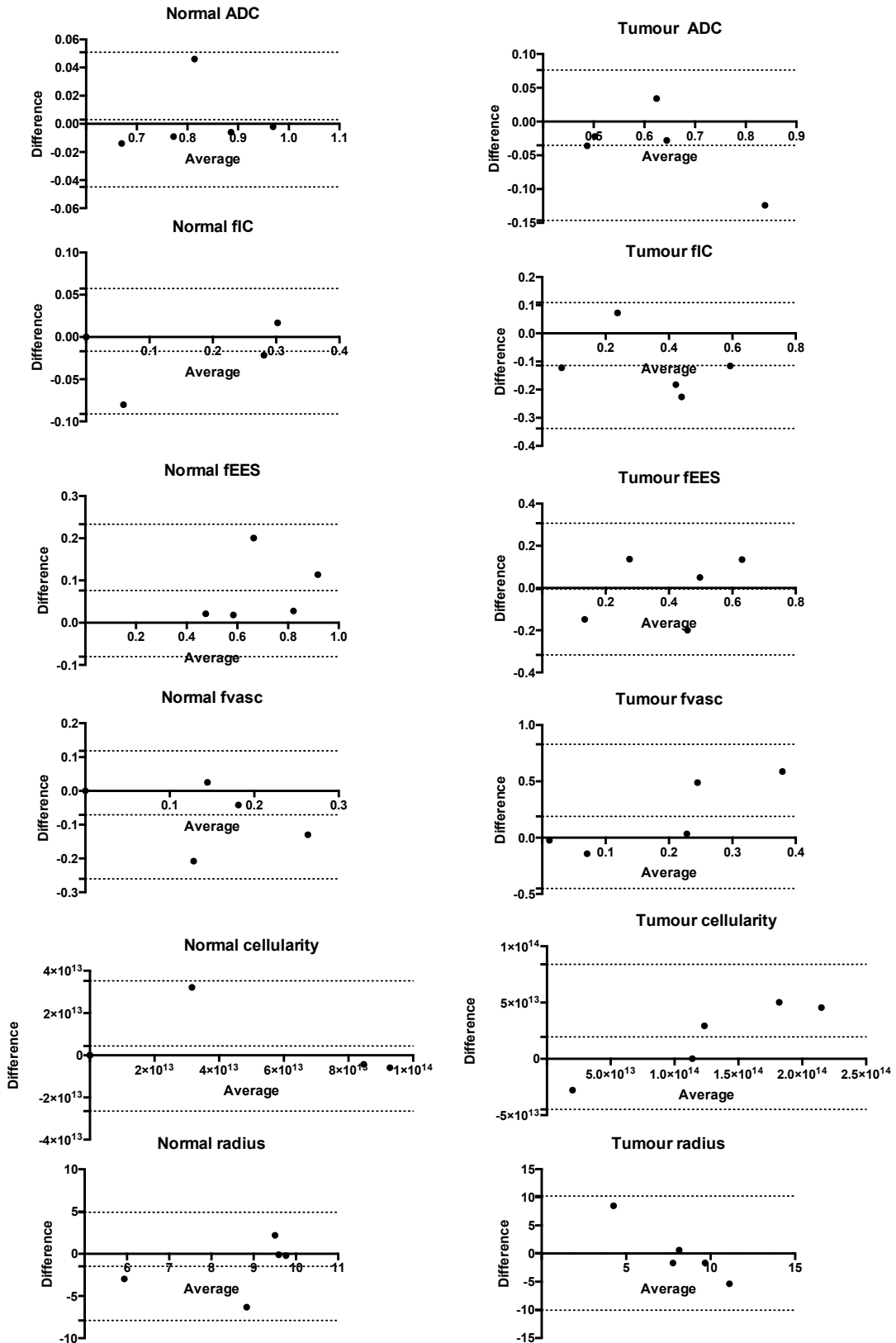
Figure 2: Bland-Altman plots, which show similar repeatability for tumour (right column) and non-tumour (left column) regions. ADC, fIC, fEES and cellularity maps demonstrate acceptable levels of agreement whereby the intersubject variation is greater than intrasubject (test-retest) variation. Units are: ADC

$\mu m^2/ms$, fIC, fEES and fvasc are fractions, cellularity is number of cells/cm^2 and radius x10-6 cm

Parameter	Normal	Tumour
ADC	0.98 (0.84, 0.99)	0.90 (0.46, 0.99)
fIC	0.97 (0.79, 0.99)	0.77 (-0.02, 0.97)
fEES	0.87 (-0.12, 0.94)	0.76 (-0.30, 0.97)
fvasc	0.52 (-0.23, 0.93)	-0.09 (-0.70, 0.80)
Radius	-0.22 (-0.81, 0.80)	-0.07 (-1.27, 0.84)
Cellularity	0.95 (0.63, 0.99)	0.90 (0.42, 0.99)

Table 2 ICCs (3,1) of VERDICT parameters. 95% CI (lower, upper) are provided