Reproducibility of quantitative and semi-quantitative dynamic and intrinsic susceptibility-weighted parameters of the cancerous human prostate gland

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Aim: To determine the reproducibility of T_1-weighted dynamic contrast enhanced (DCE) MRI, T_2*-weighted dynamic susceptibility contrast (DSC) MRI and Blood Oxygen Level Dependent (BOLD) MRI in the benign and malignant prostate gland both before and after androgen deprivation therapy.

Introduction: All quantitative biological measurements exhibit variability. These are caused by intrinsic biological variations and by measurement and analysis errors. For any measurement to be useful in the determination of whether a change has occurred, for example as a result of treatment, knowledge of its reproducibility is required. An estimate of measurement error enables interpretation of whether a change in an observation has occurred as a result of parameter variability or whether the difference is real. This estimate of error can be calculated for the study group as a whole or for individuals within a group. Quantitative functional MRI techniques are increasingly being used in the assessment of the malignant prostate gland (for tumour localisation, staging, radiotherapy planning, measurement of treatment response, detection of tumour recurrence and the evaluation of biological processes such as angiogenesis and hypoxia). For these techniques to have clinical application, their reproducibility needs to be established.

Methods: 20 patients with prostate cancer (age 57-78, Gleason 6-9, PSA 3.7-34.0 ng/ml) that were due to be treated with neo-adjuvant androgen deprivation (AD) prior to radical radiotherapy underwent 2 paired MRI investigations; two prior to the commencement of and two scans after three months of AD. Patients were imaged in a Symphony 1.5T MRI scanner (Siemens, Germany) using phased array pelvic coils. T_2-weighted images perpendicular to the urethra were used to identify tumour slice locations. Multiple gradient echo images were acquired with varying TE (5-60ms), TR=100ms, α=40^o, FOV=200mm, 256^2 matrix, & 3 slices from which R_2* (s^{-1}) maps were calculated. T_1W spoiled 2D GRE [FLASH] sequences (TE 5ms, TR 74ms, flip angle=70^o, 3 slices) were acquired before and after the bolus administration of 0.1 mmol/kg b.w. of Gd-DTPA with 40 time points over 8 min, through the prostate. ROI were placed on normal peripheral zone and tumour to calculate pixel-by-pixel values of K^{trans} (min^{-1}), v_e (%) and k_{ep} (min^{-1}) using the methods of Tofts [1] on MRIW software [2] using the modified Fritz-Hansen arterial input function [3]. Initial area under the Gd-DTPA curve ($IAUGC_{60}$; mmol/s)) was also calculated. To acquire relative blood volume (rBV (AU)) and relative blood flow (rBF(AU)) data, a T_2*-weighted sequence was used. For this the prostate was imaged every 2 seconds over 2 minutes (TE 20ms, TR 30ms, flip angle = 40 ^{o}, one slice of eight millimetre thickness). A bolus of 0.2 mmol/kg b.w. of Gd-DTPA was administered at 4ml/s after 20 seconds.

For each patient, the difference between the measurements of a parameter at each reproducibility scan, *d*, was calculated. The distribution of *d* was tested for normality using the Shapiro-Wilk test. The following statistical measures of reproducibility were then obtained from a one way analysis of variance (ANOVA) on the original or transformed data: (1) The within patient coefficient of variance (wCV). (2) The repeatability parameter (r) for n=1. (3) The variance ratio (F). (4) The Interclass correlation coefficient (ICC).

Results:

		T_1-weighted DCE-MRI				T_2*-weighted DSC-MRI		BOLD
		K^{trans}	v_e	k_{ep}	$IAUGC_{60}$	rBV	rBF	R_2*
Tumour **Baseline**	Repeatability (%)	-39.8 to 66.2	-34.6 to 34.6	-44.8 to 81.3	-36.3 to 57.1	-81.1 to 427	-77.9 to 351	-64.6 to 64.6
	Variance ratio (F)	11.2	11.0	4.9	23.0	2.5	2.2	2.3
	ICC	0.83	0.82	0.65	0.91	0.40	0.35	0.37
	WCV (%)	20.1	12.5	24.0	17.7	82.3	72.3	23.3
Tumour **After AD**	Repeatability (%)	-38.6 to 62.8	-48.6 to 48.6	-60.6 to 153.7	-49.4 to 97.7	-81.2 to 431	-78.8 to 372	-32.8 to 32.8
	Variance ratio (F)	23.2	5.9	2.6	15.7	4.6	4.2	3.6
	ICC	0.91	0.70	0.42	0.87	0.63	0.60	0.55
	WCV (%)	19.2	17.5	39.9	27.9	82.7	75.1	11.8
Benign Peripheral Zone **Baseline**	Repeatability (%)	-62.1 to 163	-41.1 to 41.1	-66.8 to 201	-58.5 to 141	-88.2 to 747	-83.8 to 516	-115 to 115
	Variance ratio (F)	3.3	11.7	2.0	4.5	5.5	2.9	2.1
	ICC	0.51	0.83	0.30	0.62	0.67	0.47	0.34
	WCV (%)	41.9	14.8	48.9	37.3	116.3	92.8	41.8
Benign Peripheral Zone **After AD**	Repeatability (%)	-41.0 to 69.4	-76.7 to 76.7	-58.4 to 140.4	-45.0 to 81.9	-80 to 399.7	-80.1 to 401	-81.4 to 81.4
	Variance ratio (F)	13.5	4.5	1.5	6.0	1.6	0.9	3.3
	ICC	0.85	0.62	0.18	0.70	0.21	-0.09	0.51
	WCV (%)	21.0	27.7	37.2	24.1	78.7	79.0	29.4

Tumour kinetic parameters were generally more reproducible than normal peripheral zone tissue. For tumours there was some deterioration in reproducibility in some T_1-weighted parameters following AD but not for K^{trans} (the most important variable for response assessments) or for T_2*-weighted parameters [4]. R_2* become less variable after AD. Consistent with the findings of Lankester [5], Galbraith 6] and Padhani [7], v_e was the most reproducible T_1-weighted DCE-MRI parameter. $IAUGC_{60}$ was almost as reproducible as v_e, with slightly more variability in terms of wCV and variance ratio for most ROIs. K^{trans} also demonstrated good reproducibility, with wCV values for whole prostate and tumour being slightly superior to that previously described in the literature for pelvic tumours (20.1% for prostate tumour, compared with 20.3% reported by Lankester and 24% reported by Galbraith). The T_2*-weighted parameters demonstrated poor reproducibility, with small variance ratios compared to T_1-weighted indices indicating larger variations within patients compared to the variation between patients.

Conclusion: This study is the first to document the variability and reproducibility of T_1-and T_2*-weighted DCE-MRI and R_2* for the benign and malignant human prostate gland. We were surprised to find that measurement error was greater for normal tissues than for malignant disease. These new data show that measurement errors do change as a result of therapy, which needs to be taken into consideration in therapy response evaluations.

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