Short term measurement reproducibility of perfusion fraction (f), pseudo-diffusion coefficient (D*) and diffusion coefficient (D) in colorectal liver metastases derived by intravoxel incoherent motion analysis of respiratory-triggered diffusion-weighted MR imaging

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Introduction: Quantitative parameters derived by diffusion-weighted MR imaging (DWI) are used for lesion characterization and for assessing treatment response. There is growing interest in applying the principles of intravoxel incoherent motion (IVIM) to derive quantitative indices which reflect tissue microcapillary perfusion [perfusion fraction (f) and pseudo-diffusion coefficient (D*)] and tissue diffusivity [diffusion coefficient (D)]. The apparent diffusion coefficient (ADC) calculated using only low b-values ≤ 100 s/mm^2 [ADClow] is perfusion sensitive and has relatively poor measurement reproducibility compared with perfusion insensitive ADChigh calculated from b-value images ≥ 100 s/mm^2[1]. We hypothesize that f and D* may thus show considerable measurement variability, but the magnitude of this in the liver is not established. By applying a Bayesian statistical approach to the IVIM model fitting [2], it is possible to account for measurement uncertainties in the derivation of f, D* and D. Such an approach may improve the measurement reproducibility of IVIM model fitted parameters but has not been previously reported. Knowledge of the measurement reproducibility is critical to the confidence that can be ascribed to changes observed in f, D* and D values in sequential measurements.

Purpose: The aims of this study were to (a) determine the measurement reproducibility of f, D* and D of colorectal liver metastases and normal liver derived by IVIM model fitting and analysis; and (b) to compare the measurement reproducibility of f, D* and D derived using the widely used least squares model fitting algorithm versus a Bayesian model fitting algorithm in colorectal liver metastases and normal liver.

Materials and methods: <u>Patient population</u> In an ongoing prospective study, 10 patients with colorectal liver metastases measuring at least 2 cm in the maximum axial diameter underwent DWI of the liver twice at least one hour apart on a 1.5T MR system (Siemens' Avanto, Erlangen, Germany). Patients were fasted 4 hours prior to imaging and were asked to leave the scanner between examinations. <u>MR technique</u> DWI was performed with a phased-array body receiver coil, using a navigator-controlled respiratory-triggered (RT) single-shot echo-planar imaging technique [spin-echo, TR/TE = 5000/68, 380-450 mm field view, 128 x 128 matrix GRAPPA = 2, section thickness = 6 mm, number of sections = 14, spectral attenuated inversion recovery fat suppression, bandwidth = 1780Hz per pixel, number of excitations = 4, three-scan trace technique, scan duration = 6 minutes 35 seconds] employing 8 b-values (0, 25, 50, 75, 100, 250, 500, 900 s/mm^2). The typical image acquisition time varied between 9 to 15 minutes. <u>Image analysis</u> Images were analyzed offline using proprietary software (ADEPT, Institute of Cancer Research, UK) by a radiologist with 5 years experience. In each patient, a target metastasis > 2 cm in diameter are randomly selected, avoiding the subcardiac and subdiaphragmatic regions prone to artefacts. For each MR study, regions of interest (ROIs) were drawn just within the outer border of the selected metastasis and also over adjacent area of normal appearing liver on the b = 500 s/mm^2 image. This was repeated for every tumour-bearing image section and all ROIs of metastases and normal liver regions were saved. The ROIs and imaging data were processed by a clinical scientist with 3 years experience using a self scripted software (MATLAB®, The Mathwork Inc, USA) to generate parametric maps by least squares fitting and Bayesian fitting of ADC (using all b-values), ADChigh and IVIM modelled parameters of f, D* and D. The ROIs were overlaid on these maps and the median voxel value (of all voxels in entire segmented volume) of metastases and normal liver were derived and recorded for each MR study. <u>Statistical analysis</u> We compared the averaged median ADC, ADChigh, f, D* and D values between metastases and normal liver using the Mann-Whitney test. A p-value of < 0.05 was deemed statistically significant. We performed Bland-Altman analysis to compare the mean difference between the logarithm of the median ADC, ADChigh, f, D* and D between the two studies to determine the 95% confidence limits of the difference (in %). Results of least squares fitting and Bayesian fitting were compared by variance F-test.

Results: Comparing colorectal liver metastases with normal liver, there was no significant difference in the median ADC (1.04 vs 1.17 x 10^{-3} mm^2/s, p = 0.10) or ADChigh (1.20 vs 1.22 x 10^{-3} mm^2/s, p = 0.36). By IVIM analysis, liver metastases showed significantly lower median f (0.15 versus 0.19, p = 0.04) and D* (18.25 vs 31.33 x 10^{-3} mm^2/s, p = 0.001) but no difference in D (0.94 vs 1.05 x 10^{-3} mm^2/s, p = 0.19) compared to normal liver. *Fig 1* illustrates IVIM curves fitted with the Bayesian method showing typical signal attenuation in a liver metastasis and normal liver. Measurement reproducibility of ADC, ADChigh, f, D* and D by least squares and Bayesian analysis is summarized in *Table 1*. The 95% confidence limits for agreement of short term measurement reproducibility for ADC, ADChigh and D were smaller in the liver (- 5% to + 8%) than in liver metastases (-22% to +32%). However, a wide 95% confidence limit was observed for f and D* values, especially in metastases using least squares analysis (*Table 1*). Using the Bayesian method of model fitting to the data significantly improved the reproducibility of perfusion sensitive parameters f and D* in metastases (*Fig 2*) and D* in normal liver compared with the least squares method (p < 0.05, F-test).
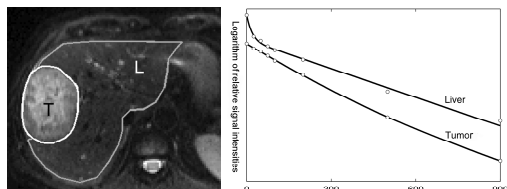

Figure 1. (Left) A b =500 s/mm2 image showing a metastasis in right lobe of liver (T) and normal liver (L). (Right) DWI signal attenuation curves by Bayesian method of model fitting of data averaged over the all segmented volumes.

	Liver Metastases		Normal Liver	
	Least squares	Bayesian	Least squares	Bayesian
ADC	-15.6, 13.2	-13.9, 9.3	-2.9, 4.6	-2.8, 4.1
ADChigh	-15.8, 9.25	-16.4, 9.7	-5.1, 6.9	-5.5, 7.1
f	-77.2, 208	-40.3, 73.2	-27.9, 32.7	-23.9, 31.2
D*	-86.7, 1690	-33.1, 68.3	-29.7, 63.5	-19.3, 22.9
D	-21.5, 32.2	-18.7, 18.2	-3.9, 7.2	-5.6, 8.2

Table 1. 95% confidence intervals of percentage difference between the two measurements. Wider intervals indicate poorer measurement reproducibility. Shaded boxes highlight where use of Bayesian analysis improved measurement reproducibility (F-test, p<0.05)

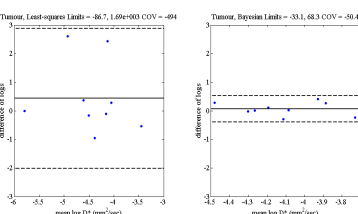

Figure 2. Bland-Altman plots of D* in metastases measured by (left) least squares method and (right) Bayesian method

Discussion: To perform quantitative DWI by IVIM based analysis requires imaging with multiple b-values. However, in clinical practice, a balance has to be achieved between a long acquisition for optimum data quality and a relatively short examination for patient acceptability and throughput. Using a respiratory triggered technique, we could evaluate a selected liver volume using 8 b-values (5 b-values ≤ 100 s/mm^2) and 4 signal averages over about 9 to 15 minutes. However, accurate characterization of signal attenuation at low b-values in DWI remains challenging. To minimize variability related to noise, we evaluated our data averaged over all ROIs drawn around a tumour or liver volume. Even then, applying the widely used least squares model fitting resulted in unacceptably poor measurement reproducibility of f and D* in liver metastases. This may in part reflect the intrinsically low f in metastases and the statistical correlations between f and D* errors, making them more susceptible to measurement and noise variations. By applying a Bayesian method of IVIM model fitting to the data [2], the measurement reproducibility of f and D* in metastases and the D* in normal liver was significantly improved compared with the least square method. By contrast, moderate to good measurement reproducibility was observed for D (and also for ADC and ADChigh). Interestingly, we have not so far observed a significant difference in the median D, ADC or ADChigh values between metastases and normal liver in this cohort, which may reflect the variegated nature of these lesions with solid areas and necrosis.

Conclusions: RT DWI in patients with colorectal liver metastases using 8 b-values showed good to moderate measurement reproducibility of D in liver and metastases. The f and D* showed relatively poor reproducibility but using Bayesian analysis significantly improved the reproducibility of f and D* in metastases and D* in the liver.

Clinical implications: When performing clinical studies for quantitative IVIM evaluation of liver diseases, it is advantageous to perform data analysis averaged over a volume and apply Bayesian method of model fitting to minimize measurement variability of perfusion sensitive parameters. This could improve the utility of the perfusion sensitive parameters.

References: [1] Koh DM et al. Eur Radiol 2009, [2] Neil JJ et al. MRM 1993.