

Comparison of R₂* measurements values and reproducibility in liver metastases and normal liver

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Target audience: Radiologists and physicists with an interest in molecular oncological imaging and drug development.

Purpose: Tumour hypoxia, often found in advanced solid tumours as a result of the imbalance between oxygen supply and consumption, represents a poor prognostic factor and is associated with tumour progression and resistance to treatment¹. Intrinsic susceptibility weighted (ISW)-MRI and derived R₂* measurements have been described as potential tool for tumour hypoxia assessment in prostate and breast cancer if there is complementary information about local blood flow available². Liver metastases are one of the commonest sites for metastatic disease and knowledge about local hypoxia would prove useful for radiotherapy planning and choice of anti-cancer regimens but liver R₂* measurements have only been exploited for obtaining noninvasive estimates of hepatic iron³ with limited published data in liver metastases. The aim of this study therefore was to measure R₂* in normal liver and in liver metastases, compare these measurements and establish their reproducibility.

Methods: 10 healthy volunteers and 10 patients (12 liver metastases) enrolled in a novel anticancer AKT inhibitor phase I clinical trial were scanned twice, 1-7 days apart, on 1.5T Avanto (Siemens, Erlangen, Germany). The ISW-MRI protocol consisted of a water only excitation multiple 2D-gradient-recalled echo sequence with multiple TEs ranging from 5 to 60 ms (5, 20, 35, 45, 60 ms), all echoes acquired with positive gradient readouts, TR = 100 ms, flip angle $\alpha = 40^\circ$, field of view = 200 mm, 256 × 256 matrix, 4 slices, 5 mm thickness acquired during one breath hold (n=16s). Parallel imaging (Grappa factor= 3) and additional phased array receiver coils were used. The multiparametric MRI protocol also included Diffusion-weighted and Dynamic Contrast Enhanced sequences. An experienced radiologist drew regions of interest (ROIs) through the right lobe of the liver in normal volunteers and when possible in areas of "normal" liver in patients as determined by anatomical and DW-MRI sequences. The tumours were delineated by ROIs drawn on DW-MRI sequences, using previously described methods⁴ (Figure 1). The normal liver ROIs were

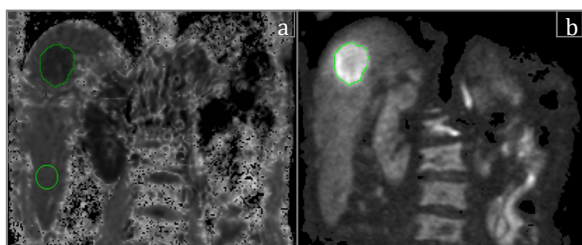


Figure 1. Matched coronal DW-MRI - b=900 s/mm² (a) and coronal R₂* maps (b) illustrating the tumour ROI drawn on the high b value images copied on the R₂* map and a normal liver ROI (smaller, inferior ROI) in a patient with metastatic liver disease.

matched between the two visits. ROIs of identical size (200pixels) were used throughout and care was taken to avoid vessels and artefacts. R₂* maps were calculated on a pixel-by-pixel basis using in-house software (Adept, IDL Research Systems). Assuming a mono-exponential decay and a linear solver a straight line was fitted to a plot of ln signal Intensity (S) against TE for each pixel; the gradient of this line is represented by R₂* (s⁻¹). Median parameter values were used to summarise the distribution. Bland-Altman analysis was performed to test reproducibility.

Results: The mean ± SD of the median R₂* value was 35.35 ± 7.6 s⁻¹ in normal liver and 22.94 ± 8.5 s⁻¹ in liver metastases. The measurement reproducibility was: r% = -42.7 + 21.6 % in normal liver and r% = -28.8 + 24.7 % in metastases (Figure 2). A Grubbs' test demonstrated no significant outliers (p > 0.05). The median R₂* values of the liver metastases were significantly lower (p = 0.002) than in the normal liver parenchyma whilst there was no significant difference between the median R₂* values in the normal liver in volunteers and patients with metastatic disease (31.2 ± 1.07 s⁻¹) (n=5, p= 0.25). Measurements performed at day 7 and day 50 post treatment showed no significant change in liver metastases median R₂* values.

Discussion: The values we found in metastatic disease and normal liver are similar to those described by Naik et al⁴ in HCC (31.72 ± 10.78 s⁻¹) and normal liver (43.54 ± 10.18 s⁻¹) respectively on same scanner but with a maximum TE of 40ms. The lower R₂* values in liver tumours compared to normal liver is multifactorial and partially explained by the presence of areas of non-perfused tissue (no enhancement on DCE-MRI) and necrosis (high T₂*). The presence of artefact, especially in the lesions situated close to the diaphragm may result in increased measurement error.

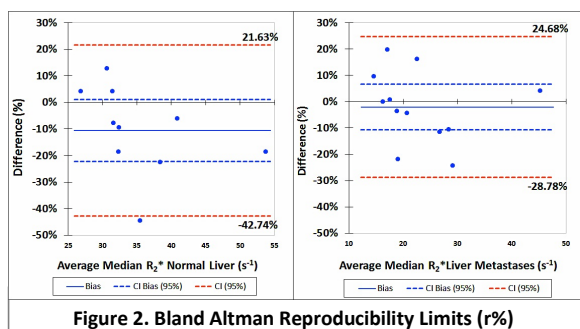


Figure 2. Bland Altman Reproducibility Limits (r%)

Conclusion: This small study showed that R₂* measurements in liver metastases are significantly different from normal liver R₂* values and can be obtained with reasonable reproducibility. Improvement in data acquisition and data post processing are essential before including ISW-MRI in a multiparametric protocol on a larger scale. Liver R₂* values also need validation with regard to their utility as a surrogate biomarker for hypoxia.

References: ¹Vaupel P. Cancer Metastasis Rev. 2007; ²Padhani AR Radiology 2010; ³Tunariu N et al ISMRM 2011; ⁴Naik M et al. ISMRM 2008.

Acknowledgements: We acknowledge the support received for CR-UK and EPSRC Cancer Imaging Centre, in association with the MRC and Department of Health (England) grant C1060/A10334, NHS funding to the NIHR Biomedical Research Centre and The Experimental Cancer Medicine Centre grant to the Institute of Cancer Research and The Royal Marsden Hospital.