Reproducibility of a single slice, single region method for monitoring the effect of treatment of metastases using Dynamic Contrast Enhanced MRI

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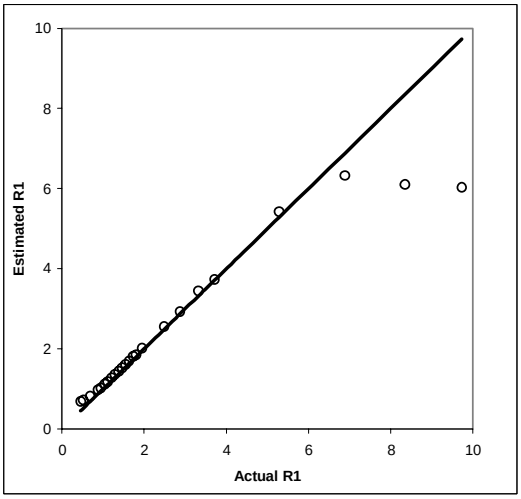
Introduction: There is an increasing interest in the use of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in the development of novel cancer therapies. A practical, reproducible and easily implementable MRI method for measuring the enhancement parameters of human tumours is likely to be of considerable value in developing these agents. We have shown that high temporal resolution DCE-MRI using a single slice, single ROI approach, through the center of a reference tumor can be performed without breath holding, and can act as a biomarker for the effect of an anti angiogenesis agent by predicting response and showing a relationship to administered dose and plasma concentrations [1]. However, in order to plan clinical trials it is important to know the inherent variability of the DCE-MRI approach.

Figure 1



Method: As most metastatic disease is in the lung and liver, we use an image acquisition time of < 500 ms to freeze motion due to respiration. As respiratory motion is largely in the cranio-caudal direction, a coronal oblique plane keeps the tumor in the same slice during the imaging sequence. To achieve rapid image acquisition an inversion recovery snapshot FLASH sequence was performed with 10 mm slice thickness, TR 3.3 ms, TE 1.4 ms, flip angle (FA) 8^0, matrix 100 x 128, an interval between inversion pulses (TR_0) of 3 s and an effective inversion time (TI) of 815 ms. The inversion pulse was not slice selective. A proton density image sequence with no inversion pulse was performed at the beginning of the dynamic run to allow estimation of R_1. Since the flip angle is small and TR_0 long relative to T_1, R_1 can be estimated from the signal with inversion pulse on ($S_{(t)}$) and with the inversion pulse off (S_0) as $R_1 = (\ln[0.5(1-S_{(t)}/S_0))/TI$. Using this sequence for phantoms with varying known R_1, gives a reasonable estimate of R_1 for values from 0.7 to $5s^{-1}$ (Figure 1). The marked error occurring at R_1 values above $5s^{-1}$ is due to almost complete relaxation occurring during the TI interval.

Clinical Method: 11 patients with advanced cancers, including 6 colorectal cancers with liver metastases, were recruited. Studied lesions ranged from 2.5 to 17cm (mean 6.5 cm). Patients had 2 DCE-MRI scans one week apart, prior to treatment. Permission of local ethics regulatory bodies was obtained. All studies used a 1.5 Tesla whole body magnet (Siemens Magnetom Vision, Erlangen, Germany). All patients underwent standard imaging sequences. The supervising radiologist then selected a representative disease site and a single coronal oblique slice was planned to bisect the midline of the tumor and the aorta. Preference was given to larger metastases and to lower T2* signal intensity, to avoid purely necrotic / cystic tumors. Low molecular weight gadolinium-chelate 0.1 mmol/kg (Omniscan, Nycomed) was injected as a rapid bolus through an arm vein in less than 5 seconds. Injection was commenced after the first 4 measurements to allow development of a steady state. Signal intensities were taken from a Region of Interest (ROI) drawn around the tumor and aorta separately. The position of the ROI was corrected on a time point by time point basis for any movement over time. In all cases the profile of the tumor remained constant throughout the imaging sequence so the region of interest did not have to be altered in shape and volume. Data were processed in two ways: firstly using the 'raw data' set of signal intensities over time and secondly, using the signal intensities converted to R_1 values as described. These data sets were used to calculate the area under the enhancement curve at 60 and 180 seconds ($AUC_{(60)}$ and $AUC_{(180)}$), and the bi-directional transfer constant (K^{trans}, ml/min) was calculated using a two compartment model. K^{trans} was calculated using the measured arterial signal for the 'raw data' analysis and a standard data set for arterial [Gd] for the 'R_1 data' analysis.

Results: One patient was excluded due to incorrect positioning of the imaging slice on the 2nd scan. Despite breathing motion, it was possible to maintain the ROI on the tumour in all cases. Although all slices included a major artery (aorta or iliac artery), ghosting from motion artifact in the phase-encoded direction was not a problem with this sequence. The minimum observed baseline R_1, averaged over the whole ROI, was $0.95s^{-1}$. The maximum R_1 after i.v. contrast injection was $3.4s^{-1}$. Table 1 shows repeatability of results for 'raw data' and 'R_1 data' scaled by conversion to R_1. For the R_1 data there is no significant difference between the 1st and 2nd result averaged over 10 patients. The standard deviation shows the variability of the study. There is less variability in the R_1 data results.

Table 1	Mean change (%)	Standard Deviation (%)		Mean change (%)	Standard Deviation (%)
Raw data			**R_1 data**		
$AUC_{(60)}$	-19.2	52.3	AUC(60)	-1.7	15.8
$AUC_{(180)}$	-19.2	51.0	AUC(180)	-0.9	16.1
K^{trans}	-4.0	40.1	Ktrans	-3.1	19.1

Sample sizes can be estimated from these data [2]. Our previous work suggests that a 40% reduction in K^{trans} is associated with clinical response [1]. The repeatability of the K^{trans} and the $AUC_{(60)}$ results, using signal intensities converted to R_1, are 36.1% and 29.5%. This is the value outside of which would indicate a significant individual result. The K^{trans} approach, with a SD of 19.1, shows that for a cohort of 10 patients, a 24% difference is required to expect a statistically significant result. For an expected difference of 40%, only four patients per cohort are required. Further using the $AUC_{(60)}$ analysis for a cohort of 10 patients, a 20% difference is required to expect a significant result. For a difference of 40 %, only three patients per cohort are required.

Discussion: This technique provides a rapid, straightforward, reproducible method of monitoring tumor enhancement during therapy. Disadvantages include insensitivity to contrast enhancement greater than R_1 of $5s^{-1}$. This was not a problem for the tumors in this series but is for the arterial input function. A potential problem with inversion recovery is potential negative polarity of the signal for long R_1. This was not a problem for the range of R_1 seen in this study.

References:

1. Morgan B, Thomas A, Drevs J, et al Dynamic Contrast Enhanced Magnetic Resonance Imaging as a Biomarker for Pharmacological Response of PTK787/ZK 222584, an Inhibitor of the Vascular Endothelial Growth Factor Receptor Tyrosine Kinases, in Patients with Advanced Colorectal Cancer and Liver Metastases. J Clin Oncol 21:3955–3964, 2003

2. Bland JM, Altman DG. Statistics Notes: Measurement error proportional to the mean. BMJ 1996;313:106.