Investigating the Repeatability of Quantitative DCE-MRI in Mice

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INTRODUCTION

With the development of MRI techniques that are sensitive to changes in the tumor microenvironment, the potential exists for imaging biomarkers of tumor response which can be identified prior to changes in tumor size. It is important to investigate the repeatability of these emerging techniques in order to ensure that observed parameter changes are due to pathophysiological changes as opposed to measurement error. To that avail, this work considers the repeatability of dynamic contrast enhanced (DCE) MRI.

METHODS

Thirteen female athymic nude mice were injected subcutaneously with trastuzumab-resistant BT474 breast cancer cells. Once the tumors reached approximately 250 mm^3 the mice were catheterized and DCE-MR images were acquired. All imaging was performed on a Varian 7.0T scanner. The imaging protocol employed a T_1-weighted, gradient echo sequence with $TR\backslash TE$ = 100 ms\3.05 ms, NEX = 2, FOV = 28 mm^2. Data was collected for acquisition matrices of 64^2 and 128^2 on separate occasions. A bolus injection of 120 µL of 0.05 mmol/kg Gd-DTPA was given after approximately 3 minutes of baseline collection, and data was collected for 20 minutes after injection; a protocol we have previously published [1]. The procedure was repeated for each animal, with three hours between scans to allow elimination of the contrast agent. Additionally, after the first imaging session, the mice were removed from the scanner and allowed to wake up, before re-anesthetizing and performing the second scan. In analyzing the data, a population AIF was employed [1]. The tumor ROI was manually outlined in each slice, and the dynamic time courses were fit using a nonlinear least squares optimization on a voxel basis to both the standard Tofts-Kety (TK) model [2] and the extended Tofts-Kety (ETK) models resulting in voxel-based values for K^{trans}, v_e, (TK and ETK) and v_p (ETK only). Repeatability analysis was performed on the center slice of the tumor, which was chosen by manual inspection and ROI voxel number. Voxels were removed from the analysis if the assigned $K^{trans} > 5$ or v_e (or v_p) > 1. The average value over the remaining voxels in the center slice was then calculated for each scan. The statistical analysis used to evaluate repeatability has been previously outlined [3]. Briefly, the distribution of differences (d) between measurements for each parameter was tested for normality and to ensure no correlation between mean parameter value and d. The mean squared difference (dsd) was then calculated as:

$$dsd = \sqrt{\frac{\sum d^2}{n}} \qquad (1)$$

where n is the number of subjects. The dsd is used to calculate the 95% confidence interval (CI) by:

$$CI = \pm \frac{1.96 * dsd}{\sqrt{n}} \qquad (2)$$

The 95% CI represents the change in parameter value between scans that would be significant at the 5% level in a group of n mice. Finally, the repeatability (r) is calculated as:

$$r = \frac{2.77 * dsd}{\sqrt{2}} \qquad (3)$$

The repeatability indicates the value below which the difference between the two measurements is expected to be in an individual subject for 95% of observations.

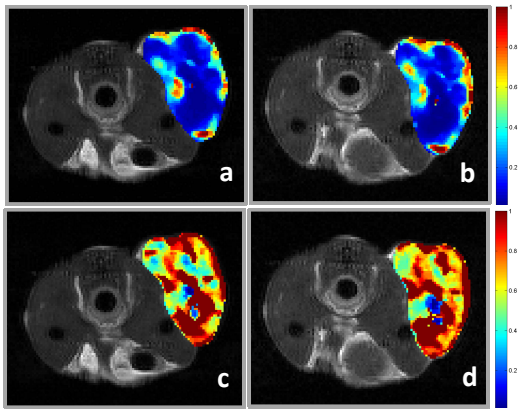

Figure 1. Representative parameter maps from scan 1 (K^{trans} (a), v_e (c)) and scan 2 (K^{trans} (b), v_e (d)) for the TK model.

Table 1. Repeatability statistics for the standard model.

		Mean	95% CI	Repeatability
128^2	K^{trans}	0.298	0.022 (7.4%)	0.080 (26.7%)
	v_e	0.490	0.027 (5.5%)	0.097 (19.9%)
64^2	K^{trans}	0.329	0.024 (7.3%)	0.084 (25.4%)
	v_e	0.508	0.020 (3.9%)	0.068 (13.4%)

Table 2. Repeatability statistics for the extended model.

		Mean	95% CI	Repeatability
128^2	K^{trans}	0.212	0.026 (12.3%)	0.094 (44.2%)
	v_e	0.526	0.026 (5.0%)	0.094 (17.9%)
	v_p	0.043	0.004 (8.3%)	0.013 (29.8%)
64^2	K^{trans}	0.235	0.026 (11.1%)	0.090 (38.4%)
	v_e	0.539	0.026 (4.8%)	0.089 (16.5%)
	v_p	0.030	0.002 (7.4%)	0.008 (25.6%)

RESULTS

A representative set of parameter maps returned from the TK model are shown in Figure 1. Thirteen data sets were used for the 128^2 acquisition analysis and 12 data sets were used for the 64^2 set. For all evaluations, it was determined that there was no correlation between average parameter value and d. The results for the TK repeatability analysis are given in Table 1, and the results for the ETK are given in Table 2. In both cases, the 64^2 acquisition matrix is more repeatable.

CONCLUSION

Using a previously established DCE-MRI protocol for mice [1], we were able to assess the repeatability of K^{trans}, v_e, and v_p to determine the changes that would have to be measured in practice for statistical significance. The results from this study indicate that a change in, e.g., K^{trans} (for a 64x64 acquisition matrix analyzed with the TK model), can be as small as 7.3% and 25.4% to see a statistically significant difference in a group of 13 animals and an individual animal, respectively.

REFERENCES [1] Loveless et al; *MRM* 2011;56:5753-69, [2] Tofts et al; *JMRI* 1999;10:223-32, [3] Galbraith et al; NMRB 2002;15:132-142.

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