EVIDENCE OF INTRA-PATIENT AND INTER-PATIENT HETEROGENEITY IN THE MICROVASULAR CHARACTERISTICS OF COLORECTAL CANCER LIVER METASTASES

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Purpose: To investigate the sensitivity of current DCE-MRI imaging biomarkers to detect whether summary microvascular characteristics of multiple colorectal liver metastases demonstrate significant inter-patient or intra-patient heterogeneity.

Methods: Median values of the parameters K^{trans}, v_e, vp, EF and ADC were derived from Dynamic Contrast Enhanced magnetic resonance imaging (DCE-MRI) and Diffusion Weighted Imaging (DWI). These data were acquired from patients, who had undergone 2 DCE-MRI scans, median 4 days (range 2-7 days) prior to treatment as part of clinical trial running at our institution. Twenty-five subjects were eligible with between 2 and 6 liver metastases, giving a total of 73 liver metastases. All patients had given written informed consent to participate in the study which was carried out in accordance with standards of Good Clinical practice (GCP). A multi-dimensional chi-squared analysis was constructed using these variables in order to enable comparison between liver metastases in different patients and between liver metastases in the same patient. All patients were scanned on a 1.5T Philips Intera system, the method of DCE MRI acquisition and analysis for our lab has been published elsewhere (1).

Statistical methods: In order to quantify any difference in DCE-MRI parameters between multiple liver metastases within a subject, and also the difference between subjects,; the following statistical method was developed. Repeated measurements from baseline scans were used to construct Bland-Altman plots to establish measurement reproducibility(2) These plots were then used to construct empirical models of measurement accuracy for parameters K^{trans}, v_e and v_p in the form $x \pm kx^{n/2}$ (for integer n), while the EF value was assumed to be distributed as a binomial random variable. Each error model $x \pm f(x)$ was used to derive a corresponding non-linear mapping function y(x) allowing transformation of measured median values to an approximate Gaussian function .Variances around the mean for the upper and lower data ranges were then found to be consistent within statistical error.

A chi-squared test (with 5 degrees of freedom) for the difference between tumours was defined as the sum of squares of the difference between changes in each derived DCE MRI variable divided by the reproducibility variance, A mean value of 1 could be generated for data j and k which differed only due to the presence of the modeled level of measurement error (σ_y). The statistical distance D was therefore constructed for paired differences between tumours of each subject, and also for differences between tumours from different subjects.

Results: There was evidence of significant heterogeneity in liver metastases between patients: mean value of the distribution $2.23 \pm 0.027 \pm 0.10$ (systematic and statistical components of estimation error). This was greater than the heterogeneity observed between individual metastases in the same patient: mean value of the distribution $1.39 \pm 0.099 \pm 0.06$ (systematic and statistical components of estimation error). Non-linear transformation was found to improve the statistical separation and the difference between these groups of metastases was highly significant, Chi-squared test, $p<10^{-6}$.

Discussion: This study has shown that current standard DCE- MRI techniques can detect differences between the microvascular characteristics of liver metastases in different patients and between different metastases in an individual patient. To our knowledge, this is first study which has attempted to characterize the microvascular pathology of liver metastases using DCE-MRI and demonstrated phenotypic differences between multiple liver metastases in a given patient using current standard methods of DCE MRI acquisition. We have demonstrated a statistical method which shows that combining DCE-MRI and DWI parameters gives significantly greater statistical power. This analysis approach can be used for future clinical trials involving DCE-MRI, and is particularly of relevance in the analysis of small data sets.

Conclusion: It was possible to demonstrate phenotypic differences between multiple liver metastases in a given patient using current standard methods of DCE MRI acquisition. Future work will determine whether clusters exist in this particular population of tumours and whether these have a predictive role in adaptive personalised therapy in patients potentially suitable for treatment with anti-angiogenic agents.

References:

1.   Horsley L, Cummings J, Middleton M, et al. A phase 1 trial of intravenous 4- (N- (S-glutathionylacetyl) amino) phenylarsenoxide (GSAO) in patients with advanced solid tumours. Cancer chemotherapy and pharmacology 2013.

2.   Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1: 307-10.