DCE-MRI Summary and Heterogeneity Statistics Predict Response to Combined Chemo- and anti-VEGF Therapy

C. J. Rose[1], J. P. O'Connor[1], Y. Watson[1], C. Roberts[1], G. A. Buonaccorsi[1], S. Cheung[1], B. Whitcher[2], G. Jayson[3], A. Jackson[1], and G. J. Parker[1]

[1]Imaging Science and Biomedical Engineering, School of Cancer and Imaging Sciences, The University of Manchester, Manchester, United Kingdom, [2]MRI Modelling, Clinical Imaging Centre, GlaxoSmithKline, London, United Kingdom, [3]Cancer Research UK Dept. of Medical Oncology, The Christie, Manchester, United Kingdom

INTRODUCTION Clinical trials of cancer therapies increasingly use dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and tracer kinetic modelling[1]. Typically, a model is fitted to the contrast agent concentration time series of each tumour voxel; the tumour is then summarised by the average value of each parameter over the tumour voxels. There is limited evidence that DCE-MRI parameters predict response to novel or cytotoxic therapies[2]. While useful, this approach neglects intratumoural structure and spatial heterogeneity–see Fig. 1–that may carry important diagnostic and prognostic information. Recently, methods based on fractal measures have been proposed to capture this aspect of DCE-MRI data[3]. In this abstract we investigate the ability of one of these fractal measures, the *correlation dimension* (CD), to predict treatment response.

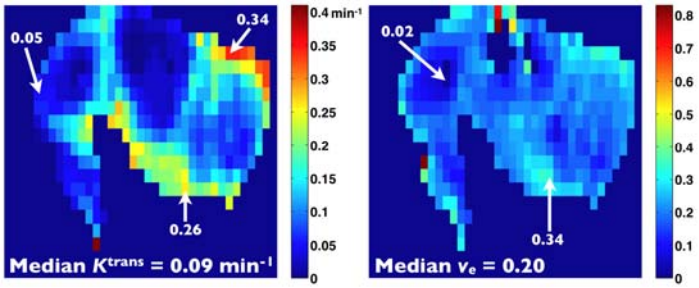

Figure 1 *K^{trans} (left) and v_e (right) maps of tumours are typically summarised by a median. Unfortunately, this practice neglects both the distribution (histogram) of parameter values and their spatial structure, which may be of prognostic value.*

THEROY We now provide a very coarse overview of CD; the interested reader is referred to Ref. 4. Given a 3-D parameter map, CD is computed by normalising the parameter values such that they sum to one. The resulting map is recursively subsampled, creating versions of the original at a number of scales; at each step the sum of squared normalised parameter values is computed. CD is calculated as follows: the log of these sums is plotted against the log of the corresponding scales; CD is equal to the slope of the line of best fit to these points. In this abstract we investigate whether CD and summary statistics of DCE-MRI parameter maps are able to predict response to treatment.

METHOD Ten patients with 26 analysable liver metastases from histologically-confirmed colorectal cancer underwent DCE-MR imaging on a 1.5T Philips Intera system following Research Ethics Committee approval and written informed consent. Scanning was performed twice at baseline to allow repeatability to be assessed. The DCE-MRI time series were modelled using the extended Tofts model[5], providing estimates of K^{trans}, v_p and v_e at each voxel. All DCE-MRI data underwent a thorough quality assurance procedure. The patients received a combination of VEGF antibody and conventional chemotherapy over five two week cycles. The patients were clinically evaluated using RECIST criteria[6], providing one-dimensional measurements of tumour size at baseline and after treatment. At each baseline visit, median K^{trans}, mean v_p, median v_e and correlation dimension for all three model parameters were computed. We assessed the repeatability of each biomarker by computing the within-subject coefficient of variation[7]. Multiple linear regression was performed to investigate the relationship between the baseline DCE-MRI biomarkers and the change in tumour size after the five treatment cycles.

RESULTS Table 1 presents the reproducibility results. Fig. 2 presents results from the linear regression analysis: change in tumour size after treatment was significantly correlated with baseline median K^{trans} (Adj. R^2=0.38, p=0.0005) and baseline CD computed for v_e (Adj. R^2=0.37, p=0.0006), with each explaining a similar proportion of the total variance in the change in tumour size. When modelled together, median K^{trans} and CD for v_e were borderline significant (p=0.07 and p=0.08, respectively) with the overall model explaining 43% of the variance in tumour size reduction ($F_{2,23}$=10.51, p=0.0006, Adj. R^2=0.43). Step-wise linear regression discards correlation dimension from the model, but at the cost of explaining 5% less variance, indicating that in this study baseline K^{trans} and baseline CD computed for v_e are providing similar prognostic information. Pre- and post-treatment tumour size were uncorrelated.

	K^{trans}	v_p	v_e
Mean or median (see text)	18.2	64.2	16.5
Correlation Dimension	5.5	19.2	49.6

Table 1 *Within-patient coeff. of variation (in %).*

CONCLUSIONS This study suggests that median K^{trans} and the spatial heterogeneity of v_e maps, assessed by CD, both appear to predict response to the combined therapy (see Fig. 2). The parameter v_e—possibly related to cellular density—should be particularly useful in cancer applications, but median v_e is rarely a useful summary statistic. Our results suggest that this parameter may be of more use in analyses of spatial heterogeneity and that its repeatability is within the range reported for summary DCE-MRI parameters. Tumours with baseline median K^{trans} greater than about 0.25 min^{-1} or with baseline CD computed for v_e greater than about 2.0 may be expected to reduce in size following combined chemo- and anti-VEGF therapy.

REFERENCES 1 O'Connor et al. Brit J Cancer, 2007;96:189–95. **2** Hahn et al. J Clin Oncol 2008:26;4572–78. **3** Rose et al. Proc ISMRM, 2007:#2821. **4** H. O. Peitgen et al. Springer, 2004. ISBN 0-387-20229-3. **5** Tofts. J Mag Reson Imag 1997:7;91–101. **6** Therasse et al. J Natl Cancer Inst 2000:92;205–16. **7** Galbraith et al. NMR Biomed 2002;15:132–42.

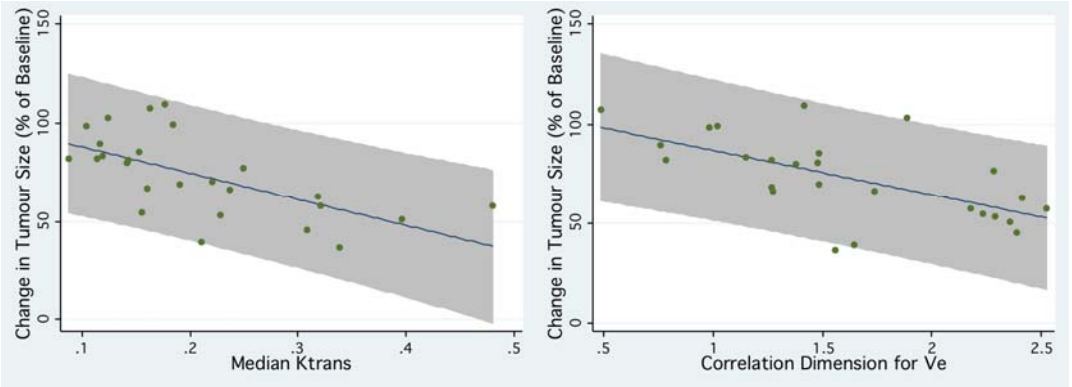

Figure 2 *Change in tumour size after combined treatment with a vascular endothelial growth factor (VEGF) antibody and chemotherapy correlated with baseline median K^{trans} (Adj. R^2=0.38, p=0.0005) and baseline correlation dimension computed for v_e (Adj. R^2=0.37, p=0.0006). The shaded regions indicate 95% confidence intervals on an individual prediction.*