DCE-MRI biomarkers of microvascular structure and function predict CRC liver metastasis shrinkage induced by bevacizumab and FOLFOX6

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INTRODUCTION Current and emerging anti-VEGF and vascular disrupting agents have the potential to facilitate substantial improvements in survival (e.g., by reducing tumour burden to the point where surgical options become practical). However, such therapies are expensive and patient response is variable. The ability to predict which patients will benefit from a particular treatment could dramatically improve patient outcomes and decrease costs to healthcare providers, and the possibility has attracted much attention[1]. Dynamic contrast-enhanced (DCE-) MRI in combination with tracer kinetic modelling provides a number of potentially relevant imaging biomarkers. In addition to tracer kinetic parameters, emerging biomarkers of heterogeneity[2,3] provide information about the spatial configuration of the tumour microvasculature, and this may play an important role in understanding tumour response to therapy. In this work we show that DCE-MR imaging biomarkers are able to predict the degree to which colorectal liver metastases will shrink in response to combined first-line treatment with bevacizumab and FOLFOX6[4]. We show that post-treatment tumour volume can be predicted from pre-treatment imaging data with median error of just 12% and interpret our results to hypothesise that tumour response can be explained and predicted on the basis of drug penetration and accumulation.

METHOD Ten patients with 26 analysable liver metastases from histologically-confirmed colorectal cancer received single agent bevacizumab (10mg/kg) followed every two weeks by combined bevacizumab and FOLFOX6 (oxaliplatin/5FU/leucovorin) for 5 cycles (10 weeks)[5]. High-resolution T_1- and T_2-weighted imaging and DCE-MR imaging were performed at two pre-treatment sessions on a 1.5T Philips Intera system (allowing tumour location and volume to be determined, and biomarker reliability to be quantified). DCE-MRI time series were modelled using the extended Kety model[6], providing voxel-wise estimates of K^{trans}, v_p and v_e. All DCE-MRI data underwent a thorough quality assurance procedure. X-ray CT was performed at the end of cycle 5 (EC5) to measure clinical response in terms of change in tumour volume (an important factor in assessing suitability for resection[7]—i.e., of particular interest if our aim is to predict those patients who might become eligible for surgery). All scanning was performed according to local research ethics committee approval; written informed consent was obtained from all patients.

Pre-treatment biomarkers of tumour tumour volume, microvascular function (median K^{trans}, mean v_p, median v_e), heterogeneity (enhancing fraction, EF; standard deviation of K^{trans}, v_p, v_e) and spatial heterogeneity (box dimension of the map of enhancing voxels, d_0; and information and correlation dimensions[3] of the K^{trans}, v_p and v_e parameter maps) were computed for each of the two pre-treatment visits. In one patient (3 tumours), data were available only for one pre-treatment scan; subsequent statistical analyses used data imputation or list-wise deletion as appropriate. Tumour response was quantified as percentage change in tumour volume at EC5 relative to baseline (henceforth "shrinkage"). Preliminary analysis used mixed effects modelling to investigate potential within-patient clustering: no statistically significant evidence of such an effect was found; subsequent analyses assumed tumours to be independent. Tumour shrinkage was modelled as a linear function of the pre-treatment biomarkers at visit 1: stepwise errors-in-variables regression was used to account for differences in reliability (repeatability) between the various biomarkers and to identify biomarkers that were sufficiently reliable. The regression was repeated for the second pre-treatment imaging session to determine whether the model was stable across visits. The model's ability to predict tumour shrinkage was evaluated using two leave-one-out analyses. In the first, each *tumour* was left out in turn; the coefficients on each variable were computed—by applying errors-in-variables regression to the left-in tumours' data—and used to predict shrinkage for the left-out tumour. In the second, the data for each *patient* was left out in turn (allowing us to further investigate potential intra-patient clustering effects); the coefficients on each variable were computed—by applying errors-in-variables regression to the left-in patients' data—and used to predict shrinkage for the left-out patient's tumours. Statistical analyses were performed using Stata (StataCorp LP, College Station, TX) and Mathematica (Wolfram Research Inc., Champaign, IL).

RESULTS Median v_e, EF and d_0 explain 86% of the variance in tumour shrinkage ($P \leq 0.00005$). The biomarkers that were reliable, statistically significant predictors of tumour shrinkage, and stable across the two pre-treatment visits are shown in Table 1 (median v_e was not quite significant at pre-treatment visit 2: P=0.07). Fig. 1 shows Bland-Altman plots and cumulative distribution functions (CDFs) of prediction error for the two leave-one-out analyses. Fifty percent of predictions have error ≤12%; 80% of predictions have error ≤31%. The results for the two leave-one-out analyses are very similar, revealing no evidence of intra-patient clustering.

Table 1 *Errors in variables regression results showing the estimated coefficients on each variable, their P-values & 95% confidence intervals.*

$F_{3,22}$	25.86
P-value for Model	≤ 0.00005
R^2	0.86

Variable	Coefficient	*P*-value	95% CI on Coefficient	
Median v_e	-147.08	0.003	-237.49	-56.67
EF	-2.35	≤0.0005	-2.93	-1.78
d_0	156.10	0.001	75.91	236.30
Constant Term	-47.19	0.506	-191.83	97.45

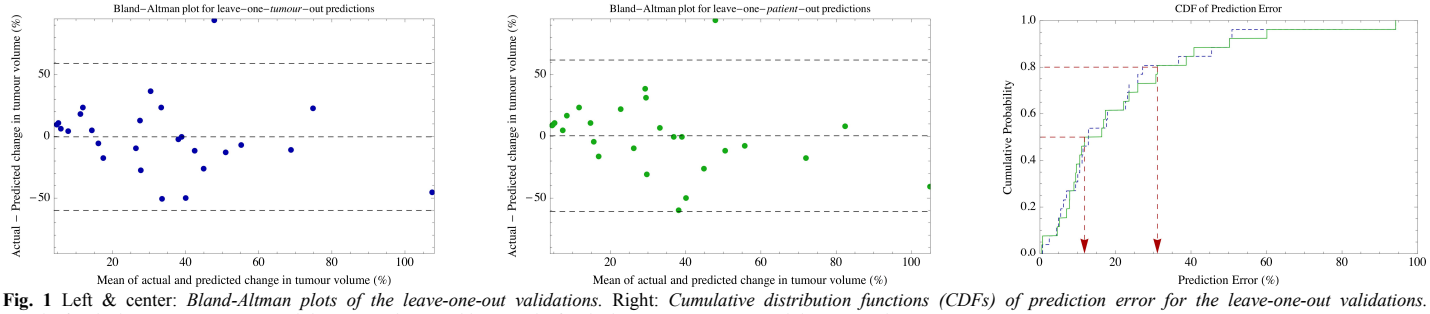

Fig. 1 Left & center: *Bland-Altman plots of the leave-one-out validations.* Right: *Cumulative distribution functions (CDFs) of prediction error for the leave-one-out validations. Results for the leave-one-*tumour*-out validation are shown in blue; results for the leave-one-*patient*-out validation are shown in green.*

CONCLUSIONS This retrospective analysis suggests that tumour shrinkage can be predicted with high accuracy. We hypothesise that the biomarkers identified as being reliable, predictive and stable across pre-treatment visits can be explained in terms of drug penetration and accumulation: median v_e reflects the extravascular extracellular volume into which contrast agent (and by extension therapeutic agents) can accumulate; enhancing fraction reflects the proportion of tumour to which contrast or a therapeutic agent can be delivered; box dimension (d_0) characterises the spatial uniformity of the enhancing portion of the tumour (and by implication, the uniformity with which a therapeutic agent can be delivered throughout a tumour). These results encourage prospective evaluation of the model identified, and the application of similar analyses to other patient groups and therapies. Ultimately, such an approach may allow us to select patients that will benefit from a given therapy, in turn improving patient outcomes and the cost effectiveness of expensive treatment strategies, and facilitating imaging-based personalised medicine.

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