Is there any advantage in looking at more than just IAUC for characterising tumour microvasculature?

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Introduction Dynamic contrast-enhanced MRI (DCE-MRI) has an increasing application as a tool for monitoring anti-angiogenic treatment and can provide information directly related to the condition of neovasculature associated with tumour growth. There is a range of methods that are currently used to characterise contrast agent uptake and distribution by the neovasculature. Due to its easy implementation it is common practice to apply a model-free approach, IAUC[1] (initial area under the time-concentration curve), to characterise tumour microvasculature. However, compartmental modelling allows greater insight into the true underlying physiology. To assess effects related to treatment it is vital to have knowledge of the reproducibility of a technique under conditions identical to those expected in a clinical trial, and to have as much insight into pathophysiology as possible. To this aim we assessed the reproducibility of the IAUC method and a common kinetic modelling approach in a cohort of tumour patients representative of clinical drug trials[2,3] to determine whether the additional information provided by the modelling approach affects reproducibility such that its utility in a treatment setting was reduced.

Methods 13 patients were studied. 4 patients with intracranial neoplasms were scanned twice (mean inter-scan interval of 1.5 days) using a Philips system at 1.5 Tesla. 9 patients with either renal or liver tumours were scanned twice on a Siemens Vision 1.5 T system, at a separate site. Both scanning protocols consisted of a baseline T_1 calculation acquisition, followed by a T_1-weighted dynamic time series. At both sites the T_1 calculation acquisition consisted of 3 separate 3-D spoiled gradient echo acquisitions. T_1 was calculated using the standard relationship between gradient echo signal intensity and T_1[4]. The dynamic series consisted of several volumes (17 for abdominal protocol, 40 for brain protocol) acquired over a period of approximately 5 minutes, with a temporal resolution of 7.8 s (extended to 75 s to cover the later time points) for the abdomen and 5.1s for the brain data. Contrast agent was administered as an i.v. bolus administration of 0.1 mmol/kg.

The kinetic model introduced by Tofts[5,6], allowing K^{trans} (transfer coefficient) and v_e (extracellular extravascular space) to be defined, an extended variant allowing an additional estimate of v_p (blood plasma space), and the IAUC method, defined over 60 seconds post contrast agent arrival in the tissue, were implemented. The modelling approaches were applied on a voxel-by-voxel basis, used an assumed arterial input function[5] and fitted for onset time. Parameter maps were generated of K^{trans}, v_e, v_p, $IAUC_{60}$ and baseline T_1. Volumes of interests were defined by a qualified radiologist allowing mean and median parameter values and tumour volumes to be derived. The median values were used to calculate the absolute mean changes between visit 1 and visit 2 across both study groups. The root-mean-squared CoV over the group of patients was calculated to test the reproducibility of the technique. The 95% confidence intervals were also determined for each parameter of interest.

Results The parameters K^{trans} and $IAUC_{60}$ have similar reproducibility. However, K^{trans} (in particular as determined by the standard model) shows to be a more robust parameter. With a confidence limit of 95%, a change in K^{trans} above 33.2% following treatment in any patient would be significant, whereas a higher change of 46.8% would be required for $IAUC_{60}$ (table 1). Figure 1 shows differences between visits are in the order of 20% for most parameters, except v_p, which has higher intra-patient variability. The more sophisticated model, the extended Tofts model, produces estimates that in general are less reproducible.

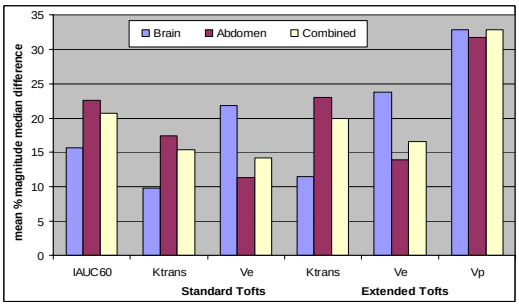

Figure 1: Mean % absolute difference of median parameter values.

	Parameter	Brain	Abdomen	Combined
RMS CoV	**$IAUC_{60}$**	0.11	0.18	0.17
	K^{trans} (standard Tofts)	0.08	0.13	0.12
95% confidence interval (%)	**$IAUC_{60}$**	31.1	51.3	46.8
	K^{trans} (standard Tofts)	21.7	36.4	33.2

Table 1

Conclusions In any clinical trial setting it is essential to know the reproducibility of the technique used to produce endpoints, and it is important to know this for a range of tumour locations. Compartmental modelling of contrast agent distribution in tumours provides us with a range of physiological variables which can be monitored during a course of anti-cancer treatment. These modelling approaches produce robust and reproducible output that provides us with valuable information regarding the underlying tumour pathophysiology. Model-free approaches, such as IAUC, provide us with a heuristic description only, without elucidating underlying physiology. Our analysis suggests that the standard Tofts approach is at least as robust as the $IAUC_{60}$, implying no penalty for this potentially more informative approach. This is likely to be due to the fact that the modelling approaches utilise all available data, whilst the $IAUC_{60}$ method uses only the first 60 s of the time series. The extended Tofts model is the least reliable method investigated, as expected, due to the larger number of fit parameters.

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References 1. J.L. Evelhoch. *J Magn Reson Imaging.* **10**(3):254-9, 1999; 2. J.L. Evelhoch *et al. Proc. ISMRM*, 1095, 2002; 3. J.L. Evelhoch *et al. Proc. ASCO*, 399, 2001;.4. A. Hasse. *Magn. Reson. Med.* **13**, 77-89, 1990; 5. P.S. Tofts & A.G. Kermode. *Magn. Reson. Med.* **17**, 357-367, 1991; 6. P.S. Tofts *et al. J. Magn. Reson. Imag.* **10**, 223-232, 1999.