The effect of heterogeneous tumour enhancement on the assessment of response to treatment

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Introduction: In order to assess the response of tumours to treatment using DCE-MRI, two approaches are typically used to characterise tumours: 1) the averaged contrast agent uptake curve from a region of interest (ROI) is fitted with a pharmacokinetic model and the resultant parameters are assumed to be representative of the whole tumour, or 2) uptake curves are fitted on a pixel-by-pixel basis and statistics such as the mean, median, standard deviation, etc. are used to characterise the tumour [1]. Both approaches are useful first approximations; however, in the presence of spatially heterogeneous enhancement, it is unclear which approach is the most sensitive to localised change caused by therapy. Figure 1 shows a breast tumour displaying this type of heterogeneous enhancement, before and after treatment with chemotherapy. The map of K^{trans} (vascular transfer constant) shows greater enhancement at the periphery of the tumour than at the centre. Following therapy, peripheral K^{trans} decreases by approximately 80%, whereas the central region K^{trans} decreases by 95%. Given this type of heterogeneous response, this study aimed to evaluate the relative sensitivity of each summary measure of response in simulations of both homogeneously and heterogeneously enhancing tumours.

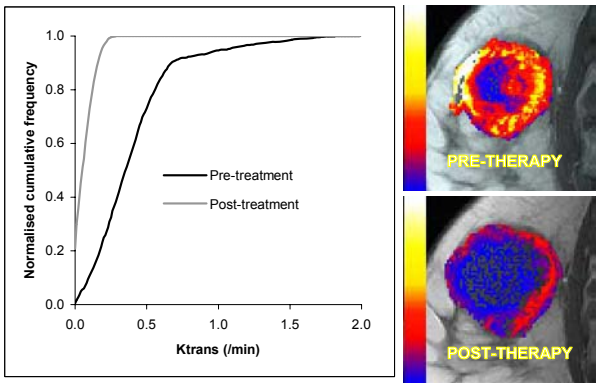

Figure 1: Cumulative frequency histograms and maps of K^{trans} in a breast tumour, pre- and post chemotherapy.

Methods and Materials: DCE-MRI data were simulated using the Tofts and Kermode model with a standard plasma curve [2], temporal resolution of 5s and total duration 250s. An idealised, homogeneously enhancing tumour was simulated by embedding a circular region, containing approximately 3100 enhancing pixels, into a 64x64 matrix, with K^{trans} and v_e equal to 0.3min^{-1} and 0.1, respectively. Therapeutic response was simulated by decreasing K^{trans} to 0.25min^{-1}. An idealised, heterogeneously enhancing tumour was simulated by inserting a central region into the homogeneous tumour simulation, with lower K^{trans} (0.08min^{-1}) (see figure 2). Both the central and peripheral regions were of equal area. A heterogeneous response to treatment was simulated by decreasing the peripheral K^{trans} to 0.25 whilst keeping the central K^{trans} constant. This type of behaviour could be expected following treatment with an anti-angiogenic compound that selectively targets the more vascular peripheral region. Gaussian noise was added to the simulated contrast agent uptake curves, with a variance based on measurements from in-vivo data (+/-0.016mMol/l) and mean value of zero. The data were fitted with the Tofts and Kermode model on a pixel-by-pixel basis. Histograms of fitted K^{trans} and v_e were produced and the mean and median values were found. Standard errors in median values were evaluated using bootstrapping. Each distribution was tested for normality and log-normality using the Kolmogorov-Smirnov statistic. Mean uptake curves from each tumour were calculated and also fitted with the Tofts and Kermode model. Parameter uncertainties were estimated using the least squares sigma uncertainty values.

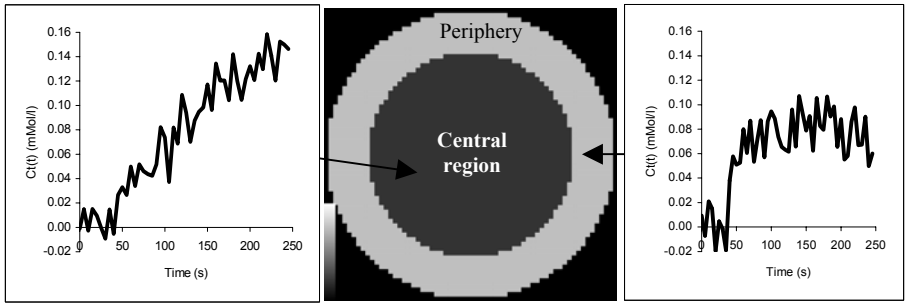

Figure 2: (centre) Simulated K^{trans} map from the pre-treatment heterogeneous simulation with (left) an example curve from the central region (K^{trans}=0.08, v_e=0.3) and (right) and an example curve from the peripheral region (K^{trans}=0.3, v_e=0.1).

Results and Discussion: Both K^{trans} and v_e were significantly log-normally distributed and consequentially, the median, mean, whole-ROI and true K^{trans} values are similar (see table 1). The whole-ROI value is the most accurate, followed by the median, then the mean. All summary measures of the homogeneous simulation reflected the change caused by treatment equally well. The heterogeneous simulation fitted parameters were neither normally nor log-normally distributed due to the sub-populations within the distribution (see figure 3). The mean and median of K^{trans} in the heterogeneous distributions, pre- and post-treatment were similar to the average of the peripheral and central regions' K^{trans}, whereas the whole-ROI curve K^{trans} was much closer to that found in the central region (see table 1). All parameters under-estimated the true change in peripheral K^{trans} due to therapy in the heterogeneous simulation by approximately a half, which can be explained by considering that only half of the tumour K^{trans} was varied. It should be noted that this simulation does not include other sources of error found in in-vivo measurements such as those due to slice positioning or physiological motion.

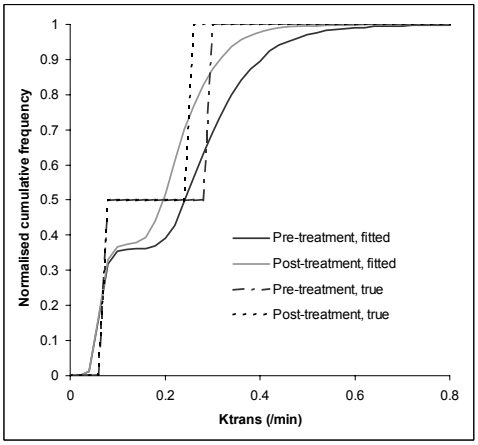

Figure 3: Cumulative frequency histogram of K^{trans} pre- and post-treatment in the heterogeneous simulation.

Conclusion: Measures such as the mean and median of pharmacokinetic parameters are useful measures of change due to therapy, but can underestimate regional variations that could be more indicative of a significant response. When changes in tumour contrast agent uptake are heterogeneous, whole-ROI analysis is the least sensitive of those investigated. This idealised simulation of tumour pharmacokinetics illustrates the difficulties associated with the application of statistical measures to heterogeneous data. However, real tumours are likely to exhibit a continuum of heterogeneous contrast agent uptake, which could further decrease the accuracy of the statistical measures investigated here. It is therefore necessary to develop methods whereby heterogeneous response to therapy can be more rigorously and sensitively assessed. Due to the increased sensitivity offered, the use of the mean or median as summary measures is recommended over whole-ROI fitting.

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References: [1] Leach MO et al, Br J Cancer, 2005:92(9);1599-1610 [2] Tofts PS & Kermode AG, Magn Reson Med 1991:17(2);357-67.

		True K^{trans}	Mean K^{trans}	Median K^{trans}	Whole-ROI K^{trans}
Homogeneous simulation	Pre-treatment	0.3000	0.336 ± 0.02	0.324 ± 0.02	0.293 ± 0.01
	Post-treatment	0.2500	0.279 ± 0.01	0.2677 ± 0.03	0.247 ± 0.01
	Difference	*0.0500*	*0.056* ± 0.01	*0.056* ± 0.02	*0.0466* ± 0.01
Heterogeneous simulation	Pre-treatment	0.3000, 0.0800 (Mean=0.1900)	0.218 ± 0.03	0.198 ± 0.02	0.087 ± 0.02
	Post-treatment	0.2500, 0.0800 (Mean = 0.1650)	0.187 ± 0.02	0.169 ± 0.02	0.085 ± 0.02
	Difference	*0.0500 (Mean = 0.025)*	*0.031* ± 0.02	*0.029* ± 0.02	*0.0016* ± 0.02

Table 1: K^{trans} values for pre- and post-treatment in both the homogeneous and heterogeneous models and the difference between pre- and post-treatment values for each statistic. All values are in min^{-1} and quoted uncertainties are the associated standard errors.