A capillary input function for pharmacokinetic analysis of DCE-MRI breast cancer curves

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INTRODUCTION

Dynamic contrast-enhanced MRI (DCE-MRI) is frequently used to detect, diagnose and stage breast cancer [1]. A common method of data analysis is to fit a compartmental model to the signal change-versus-time curve and to characterise it by two parameters; K^{trans}, the surface area permeability, and v_e, the fractional volume of the extracellular compartment [2]. This approach requires an estimation of the amount of contrast agent (CA) in the compartment supplying the tumour. Current methods commonly assume either simply a perfect bolus with instant mixing, i.e. a delta input function (DIF), or estimate the width of the input bolus by measuring the signal change in a nearby artery, thereby defining an arterial input function (AIF) [3]. No method currently exists that can account for further spread of the bolus away from the artery, or any heterogeneity in tumour perfusion. Heterogeneity in blood flow about a tumour results in areas with differing levels of hypoxia and acidity and therefore areas that are less responsive to therapeutic treatment. It has been suggested that selective destruction of tumour vasculature may increase perfusion efficiency and improve therapeutic efficacy [4]. This work describes an alternative method of estimating an input function, using T2*-weighted images of the first pass of an injection of contrast agent through the tumour in order to define localised capillary input functions (CIF).

MATERIALS AND METHODS

Using a 1.5 Tesla NVi/CVi scanner (GE, Waukesha WI, USA) DCE-MRI investigations were acquired as part of a previously described protocol [5]. With a gradient echo sequence, sets of nine coronal slices were acquired at 10 second intervals so that 40 time points were available for T1 signal enhancement ratio modelling. ($\alpha=35^0$, TR/TE=8.3/4.2ms, bandwidth = 31.2 kHz, FoV = 34×17 cm, 5.0 mm slice thickness matrix size of 256×256, 1 NEX). A 0.2mmol/kg bolus of Gd-DTPA was administered coincident with the fifth temporal frame using a pump injector at a rate of 3ml/s, followed by a 20ml saline flush. The position of the slice at the estimated centre of the tumour was identified. After a delay of approximately 15 minutes, a single slice T2*-weighted fast gradient echo (TR=34.1ms, TE=30.0ms, slice thickness=5.0mm) was acquired at this location to facilitate input function estimation. 40 time points were acquired at 2 second intervals with 0.2mmol/kg of Gd-DTPA administered after ten seconds (injection rate 3ml/s followed by a 20ml saline flush).

Figure 1: Gamma variate function fit to initial uptake points on T2*-weighted first pass perfusion contrast agent curve.

Using 5 patient data sets, a pixel-by-pixel analysis of a single central slice through each tumour was performed. A tumour ROI was defined for pixels where the ratio of mean post-CA T1-weighted signal to mean pre-CA was greater than 1.5. A gamma variate function was fitted to the T2* signal-versus-time curve where parameters for curve height, width and gradient are variables. To correct for the effects of incomplete washout, only the data points that represent the initial passage of contrast agent are used in the fit (see fig. 1). The gamma function was subsequently normalised for the infinite integral equal to one, so only the width and gradient are factors of the input function, described by the parameters α and β. On a pixel by pixel basis these normalised input curves were convolved with the Tofts model of concentration versus time. Using both the CIF and DIF models values of K^{trans} and v_e were obtained, along with χ^2 statistics (goodness of fit), for each fitted pixel. All curve fitting was performed with in-house software developed in IDL (RSI, Inc) using the Levenberg-Marquardt algorithm. Fits were excluded using criteria as described by Galbraith et al.[6]. Wilcoxon Signed Ranks Test was used to assess the significance of any difference between parameter values returned by the two models.

RESULTS

The table shows the mean values for K^{trans} and v_e returned from pixels where both models provided a successful fit.

	DIF	CIF	Difference (%age change)
Mean K^{trans} (min^{-1})	0.383	0.458	0.196 (19.6%)
Mean v_e(%)	0.239	0.247	0.008 (1.9%)

The CIF model gives a significant increase in K^{trans} (p< 0.001) over the DIF model. This is expected due to the relationship between K^{trans} and the initial gradient of the uptake curve. The difference in v_e between the models is not significant (p=0.608). The mean value of α was 8.26 (std. err.=0.49) with a standard deviation of 2.53. Mean β was 1.97 (std. err.=0.09) with standard deviation of 2.53. Fig 2 shows plots of the extremes of the CIF observed.

Figure 2: Two examples of the normalised gamma variate function using α and β values of the upper and lower boundaries of the interquartile range.

DISCUSSION

The use of a CIF provides a localised input function in the estimation of pharmacokinetic parameters. This has the potential to return more meaningful K^{trans} values since the variability in delivery characteristics is a significant source of uncertainty in the method. The variation in the input function parameters may give an indication of the heterogeneity of tumour perfusion. This work demonstrates the feasibility of using a capillary measurement to estimate an input function for compartmental modelling of DCE-MRI data. Further work is required to investigate whether this modified input function increases reproducibility in pharmacokinetic modelling. This method may have clinical relevance for patients with reduced cardiac output, where the spread of contrast agent bolus may be markedly increased, and in particular, in patients with significantly heterogeneous tumours where the input function may be especially variable across the tumour.

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(1)Orel SG et al. *Rad.* 2001;**220:** 13-30. (2)Tofts et al. *J Magn Reson Imaging.* 1999; **10:** 223-232. (3)Gillies et al. *Neoplasia* 1999 ; **1 :** 197-207. (4)Fritz-Hansen T et al. *Magn Reson Med.* 1996; **36**: 225–231. (5)Semple et al. *Annals of Oncology.* 2006; **17:** 1393-1398 (6)Galbrait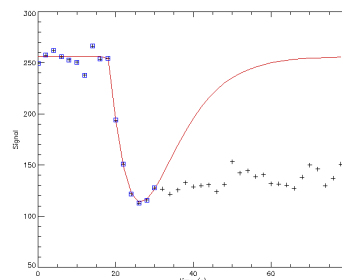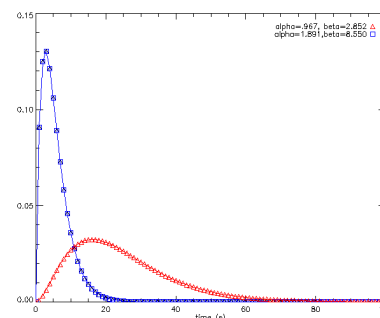h et al., NMR Biomed. 2002; **15**:132–142