Evaluation of area under curve [Gd] data derived from DCE-MRI time series in brain tumours

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Abstract
Area under the Gd concentration-time curve (a.u.c [Gd]) is used as an alternative to pharmacokinetic model based methods of dynamic contrast-enhanced (DCE) MRI data analysis [1]. DCE-MRI is widely used in the evaluation of response to therapy and the detection of malignant tumours [2]. We have investigated the relationship between data derived from a.u.c [Gd] and two pharmacokinetic model-based methods of data evaluation. The DCE-MRI data were obtained in-vivo from malignant tumours in brain. We show that a strong correlation exists between estimates of the extra-cellular extra-vascular space (Ve) derived from the standard Tofts model and the a.u.c [Gd] for specific ranges. We demonstrate there is an improved correlation between a.u.c [Gd] and transfer constants derived from the Tofts model only when arterial Gd concentration is reasonably constant after the initial first pass of Gd.

Introduction
a.u.c [Gd] is desirable for the analysis of T1w DCE-MRI due to its simplicity and signal to noise advantage making it suitable for pixel-by-pixel analysis. The a.u.c method is also reliable and reproducible. It has been argued that it is possible to normalise the a.u.c method to account for differences in cardiac output and variations in bolus delivery using an adjacent radiologically normal tissue a.u.c or using a measure of the arterial concentration [1]. A further advantage is that no kinetic model is required. The a.u.c is thought to relate to the tissue extraction fraction (Ktrans) based on an analysis of the flow limited Kety equation [1]. We have compared data derived from a.u.c estimates with parameters derived from pharmacokinetic models. The a.u.c [Gd] was evaluated at three time intervals: 0-30s, 0-90s and 50-80s, where t=0 was defined as the mean time at which contrast agent arrived in the tumour (approximately 30s after the start of the sequence). These intervals were chosen with the following rationale: from 0-30s, the first pass of Gd is dominant; at 90s exchange between vascular and extra-vascular compartments has reached near equilibrium, and from 50-80s the concentration in the arteries is reasonably constant. These values are based on the blood kinetics following the bolus, which were obtained from a T2* time series obtained simultaneously, converted to ∆R2* [3] (figure 1a).

Methods
DCE-MRI data were acquired from patients with brain tumours using a Sliding-Window dual-spooled gradient echo sequence [3]. The sequence includes the following parameters: TE=7/30ms, TR=31ms, nutation angle 5º for proton density and 30º for T1w. Single slice images were reconstructed, with a temporal resolution of 1.1s and total sequence duration of 165s. Contrast medium (Magnevist) was injected at 5ml/s starting 8s after the start of the sequence. Both T1w and T2* images are provided by the sequence for the evaluation of contrast agent kinetics. T1w time series curves were converted into [Gd] using the method of Hittmair [4]. The [Gd] time series was then evaluated using the Tofts model and Weinmann [Gd] extraction coefficients [5]. Gamma-variates were fitted to the T2*w images are provided by the sequence for the evaluation of contrast agent kinetics. T1w time series curves were converted into 

\[ P_y = \sum_{i=1}^{n} \frac{[v_i - y_i]}{[v_i]^2} \]

where x and y are vectors containing parameter values. P_y can take a value between -1 and 1, where -1 indicates strong negative correlation and +1 indicates strong positive correlation; P_y = 0 indicates no correlation. x and y were then plotted against one another and a linear regression was performed (figure 1b). The quality of this fit was given by an r² parameter.

Discussion
Parameters most significantly correlated according to P_y and r², were Ve (derived from the Tofts model) and a.u.c [Gd] for 0-90s (figure 1b.). All patients show a stronger correlation between Ktrans and a.u.c [Gd] (50-80s) than a.u.c [Gd] (0-30s) or a.u.c [Gd] (0-90s), even though in some cases r² or P_y < 0.64. This suggests that Ktrans only correlates with a.u.c [Gd] when arterial Gd concentration is reasonably constant. There was no significant correlation found between the a.u.c [Gd] and parameters derived from the fitting of gamma-variates to the T2* data. Inconsistencies between P_y and r² are likely to be due to poor SNR, which introduces scatter into plots of image vectors but does not affect the spatial correlation as significantly.

Conclusion
a.u.c [Gd] (0-30s, 0-90s) correlate well in these examples with Ve derived from the standard Tofts model in brain tumours. Ktrans is not significantly correlated with either of the initial a.u.c [Gd] (0-30s, 0-90s) intervals. The a.u.c [Gd] (50-80s) has an improved correlation with Ktrans .

Acknowledgements
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References

Table 1: Cross-correlation P_y values and r² values for Ktrans and Ve compared with a.u.c. [Gd] maps for various ranges.

<table>
<thead>
<tr>
<th>a.u.c. [Gd] (s)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td>P_y = 0.726</td>
<td>r² = 0.527</td>
<td>P_y = 0.187</td>
</tr>
<tr>
<td>0-90</td>
<td>P_y = 0.706</td>
<td>r² = 0.487</td>
<td>P_y = 0.975</td>
</tr>
<tr>
<td>50-80</td>
<td>P_y = 0.730</td>
<td>r² = 0.528</td>
<td>P_y = 0.718</td>
</tr>
</tbody>
</table>

Figure 1: a) Example of ∆R2* with time. Arrival of Gd is identified by a large peak at ~40 seconds that then drops to a constant value by 30s after arrival. From 50s to 80s after arrival, ∆R2* is constant, which indicates a constant Gd concentration. b) Relationship between a.u.c. [Gd] (0 to 90 seconds) and Ve for patient 3, with linear regression fit overlaid.