Longitudinal Assessment of Mouse Tumor Pharmacokinetics without an Arterial Input Function

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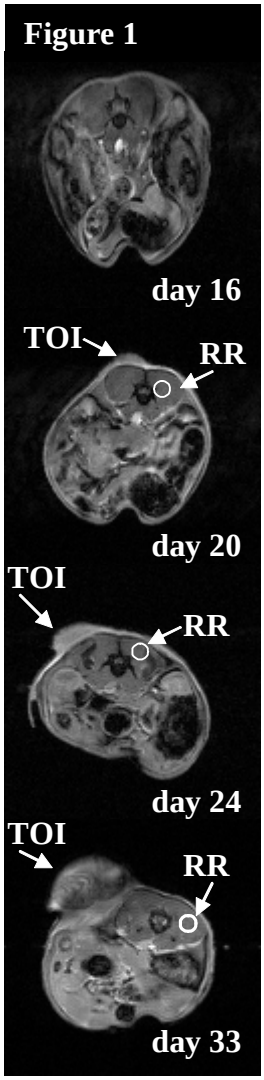
INTRODUCTION Dynamic contrast enhanced MRI (DCE-MRI) may be used to assess tumor perfusion, microvascular vessel wall permeability, and extravascular extracellular volume fraction (1). Analysis of DCE-MRI data is based on indicator dilution theory (2) and normally requires knowledge of the concentration of the contrast reagent in the blood plasma, $[CR_p]$, the so-called arterial input function (AIF). We have developed a reference region model that does not require knowledge of the AIF to compute tumor pharmacokinetics. We apply the reference region (RR) method to a Lewis Lung Carcinoma mouse model to show that longitudinal changes in a tumor locus (the tissue of interest, TOI) can be measured without an AIF.

THEORY The reference region model establishes a relationship between $[CR_{TOI}]$ and $[CR_{RR}]$ (the concentrations of CR in the TOI and RR, respectively) allowing the derivation of a model that is independent of $[CR_p]$. [CR] can then be calibrated to the measured longitudinal relaxation rate *via*, for example, the fast exchange limit approximation (3) yielding the main result of the theory:

$$R_1^{TOI}(T)-R_{10}^{TOI} = R\bullet(R_1^{RR}(T)-R_{10}^{RR}) + R\bullet[(K^{trans,RR}/v_{e,RR}) - (K^{trans,TOI}/v_{e,TOI})]\bullet \int_0^T (R_1^{RR}(t) - R_{10}^{RR}) \cdot \exp(-K^{Trans,TOI}/v_{e,TOI}) \cdot (T-t))dt \,, \quad [1]$$

where R_1^{RR} and R_1^{TOI} are the longitudinal relaxation rate constants in the RR and the TOI, respectively, $K^{trans,RR}$ and $K^{trans,TOI}$ are the CR extravasation rate constants for the RR and TOI, respectively, and $v_{e,RR}$ and $v_{e,TOI}$ are the extravascular extracellular volume fractions for the RR and TOI, respectively, R_{10} is the pre-contrast R_1, and $R = K^{trans,TOI}/K^{trans,RR}$. Eq. [1] can be employed in a curve-fitting routine to extract $K^{trans,TOI}$ and $v_{e,TOI}$ if $R_{1,TOI}$ and $R_{1,RR}$ can be measured.



EXPERIMENTAL A male mouse with 10^6 Lewis Lung Carcinoma cells injected subcutaneously in the hind limb was imaged using a Varian 7.0 T scanner equipped with a 38 mm quadrature birdcage coil and imaged on days 16, 20, 24, and 33 days post injection. A variable flip angle gradient echo approach was employed to produce a R_{10} map. The DCE-MRI protocol employed a standard T_1-weighted, GRE sequence to obtain 90 serial images for each of 12 axial oriented planes in 60 min of imaging. The parameters were: TR = 100 ms, TE = 4.1 ms, flip angle = 30°, FOV = $(30\ mm)^2$, slice thickness = 1.0 (or 1.5) mm, matrix = 128^2, NEX = 4. A bolus of 0.4 mmol/kg Magnevist was delivered within 30 s *via* a tail vein catheter. The entire tumor TOIs (**Figure 1**) were selected for analysis. In each case, twenty pixels within the perivertebral muscle were selected as the RR.

RESULTS Given R_{10}, MR signal intensity time courses were converted to R_1 time courses in the manner of (3). The RR and TOI time courses are indicated in Figure 1. Reasonable muscles values of $K^{trans,RR} = 0.08\ min^{-1}$ and $v_{e,RR} = 0.1$ were assigned (4). $K^{Trans,TOI}$ and $v_{e,TOI}$ were adjustable parameters in fitting the TOI data to Eq. [1]. Standard deviations were determined using standard Monte Carlo simulations and multiple manual counts for the kinetic values and tumor volumes, respectively. **Figure 2** depicts how tumor volume, K^{trans}, and v_e, respectively, changed as a function of time (in days) after subcutaneous injection of the tumor cells. (The dashed lines are meant only to guide the eye.) In all graphs the first data point is set at zero as there was no tumor apparent in the images (Figure 1). The results are reasonable; as the tumor grows (panel A) a smaller proportion of total tumor volume is well vascularized while an increasing proportion becomes necrotic, implying a smaller K^{trans} value (panel B) and a larger v_e value (panel C).

DISCUSSION We have presented a simple method by which tumor pharmacokinetics can be extracted from DCE-MRI data without knowledge of the arterial input function. The method could be used to analyze DCE-MRI data collected in mice over time to non-invasively measure, for example, tumor growth and response to treatment.

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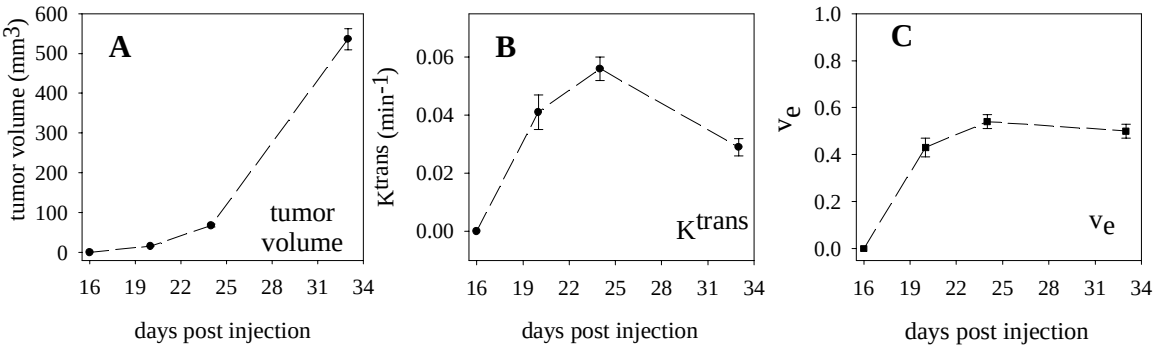

Figure 2