# MRI T2* and T1 Ratio for Assessment of Transport of Macromolecular Contrast Agent in Tumor Interstitium

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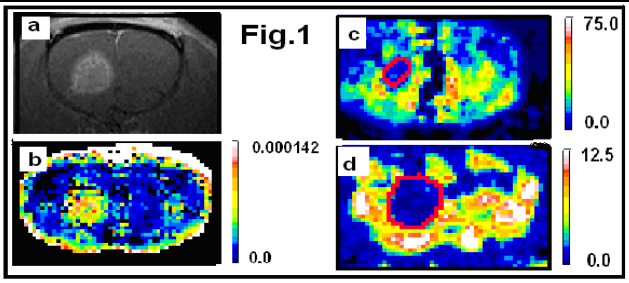
**Introduction**: Contrast enhanced-MRI (CE-MRI) utilizes paramagnetic contrast agents (CAs) and $T_1$ and/or $T_2$* contrast mechanisms to characterize cerebral tumors' microvascular function *via* tracer kinetic analysis (1, 2). Generally, $R_1$ ($R_1 = 1/T_1$) and $R_2$* ($R_2^* = 1/T_2^*$) are used as measures of CA concentration, with the assumption that the $R_1$ and $R_2$* relaxivities are constant for the duration of the measurement. These relaxivities are probably constant if the CA is localized in the blood pool, but are not constant if the CA extravasates, since the $R_2$* contrast mechanism depends strongly on the gradients created around microvessels when the CA resides entirely within them. In this study, maps of the ratio of $T_2$* to $T_1$ relaxivities (which we characterize as $\Gamma_2$, $\Gamma_2 = \frac{\Re_2^*}{\Re_1}$, where $\Re_2^*$ and $\Re_1$ are the $R_2$* and $R_1$ relaxivities) was constructed in 6 animals implanted with experimental 9L cerebral tumors. The transport of the extravasated CA radially outward from the tumor periphery allows the velocity of its wave front, which may a function of the interstitial fluid pressure (IFP) to be determined. Because IFP relates strongly to the efficiency of transfer of chemotherapeutic agents to the tissue in solid tumors, its estimation may be clinically very significant. In this study, we have utilized $\Gamma_2$ maps to track the wave fronts velocity of the paramagnetic macromolecular CA i.e., Gadomer in the interstitium of cerebral tumors.

**Materials and Methods**: TOMROP (3), an imaging variant of a Look Locker sequence, was utilized to construct maps of $\Gamma_2$. TOMROP uses a gradient-echo readout of an inverted magnetization vector, and is thus affected by both $R_1$ and $R_2$* relaxivities. In the process of studying permeability in experimental cerebral tumors, six Male Fischer 344 rats (250 - 300 g) were implanted with 10,000 9L cells and studied about 14 days post-implantation in a 7 Tesla, 12 cm (clear bore) magnet (gradients of 25 g/cm, 100 µs rise times), interfaced to a Bruker Avance console running Paravision V2.6 (Bruker Inc., Billerica MA) imaging system. Matrix size was 128X64, FOV 32 mm, three 2 mm slices. Prior to the administration of Gadomer, two baseline TOMROP images were acquired. After the acquisition of baseline images, 10 iterations of TOMROP were run to produce $T_1$ maps at 145 s intervals following injection of Gadomer (250 µmol/kg in a 1 ml dose over 1 minute). $\Delta R_1$ maps were generated utilizing both base line and CE TOMROP images and utilized to construct maps of vascular permeability (1). Regions of interests (ROIs) were manually drawn on the $\Gamma_2$ maps to analyze the outward movement of the Gadomer wave front.

**Results and Discussions:** Fig 1 shows typical MR images of (a) post contrast $T_1$ weighted image, (b) a map of influx rate constant ($K_i$) as well as the temporal evolution of $\Gamma_2$ maps generated from (c) the first and (d) seventh TOMROP images after administration of Gadomer, with a red line showing the ROIs selected. Fig 2 plots curves of the mean diameters of ROIs obtained from temporal evolution of the $\Gamma_2$ maps. In all cases, the ROIs enlarge. Since these tumors have well-defined boundaries, the enlargement of these ROIs is not due to extravasation in the boundaries, but must be due to redistribution of CA to the adjacent regions via convection and diffusion mechanisms. A linear fit to the data shows that the slopes these lines vary over the range of 0.89 - 2.1 mm/ms, respectively. These values represent the typical wave front velocity of the macromolecular CA in the tumor interstitium.

In cerebral tumors, the pressure gradient developed between the tumor's center and its periphery forces the movement of macromolecular CA across the tumor interstitium. As Jain has noted (4), the velocity of fluid flow, i.e., Darcy's velocity, at the tumor boundary must be proportional to the interstitial fluid pressure (IFP) gradient at the tumor center to the periphery. Thus, since IFP plays a central role in restricting the administration of therapeutic agents, wave front velocity of interstitial fluid as measured by $\Gamma_2$ may have profound clinical significance in the treatment of solid tumors.



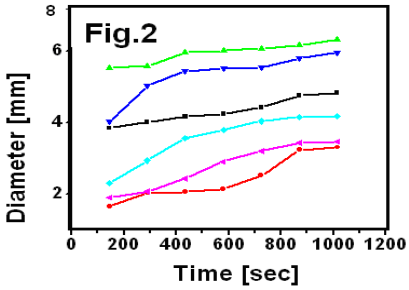




Fig.1. (a) $T_1$ weighted image, (b) a map of influx rate constant ($K_i$) $min^{-1}$. Representative $\Gamma_2$ maps profile from the first (c) and seventh (d) TOMROP images after administration of Gadomer. The red line represents ROIs for temporal evolution of $\Gamma_2$ profile.

Fig.2. A plot of the ROIS diameter versus time of the temporal $\Gamma_2$ map

**References:**

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