Dynamic Contrast Enhanced MRI Estimate of Tumor Interstitial Fluid Pressure in Solid Brain Tumors

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Introduction: Due to increased vessel permeability and low lymphatic drainage, many solid tumors develop a higher tumor interstitial fluid pressure (TIFP) than the surrounding normal tissue. Elevated TIFP is a central and potentially critical element for assessing therapeutic response. TIFP has most often been measured invasively using a fluid-filled wick-in-needle (WIN) method, but this is impractical in many tumor types and in repeated studies. Since a non-invasive procedure is currently unavailable for measuring TIFP, this study examined the possibility of evaluating TIFP using dynamic contrast enhanced MRI (DCE-MRI) data in a rat model of cerebral glioma.

Material and Methods: DCE-MRI studies using an MR contrast agent (Magnevist) were performed on nude rats implanted with U251 cerebral glioma. After the MRI study, TIFP was measured as a function of distance using the wick-in-needle technique. The Logan graphical plot approach was employed to measure the contrast agent distribution volume (V_D) at tumor rim[1,2]. To estimate the fluid flow velocity at the rim of the tumor, contrast-laden tumor exudate in DCE-MRI data was followed by observing the wave front of contrast enhancement as it expands over time after contrast agent injection[3]. Darcy's law[4] relates the fluid velocity (**V**) to the local pressure gradient (**∇**p) by; $\mathbf{V}=-K*\mathbf{\nabla}p$, where K is the fluid conductivity of the tissue. Since fluid conductivity is proportional to porosity, and porosity, by definition, is the volume fraction of the voids in the total volume, porosity has an inferred proportionality to the distribution volume (i.e. $K=Const.*V_D$). Thus, distribution volume and fluid velocity measured at the tumor rim, in combination with Darcy's law, can be utilized to estimate TIFP non-invasively.

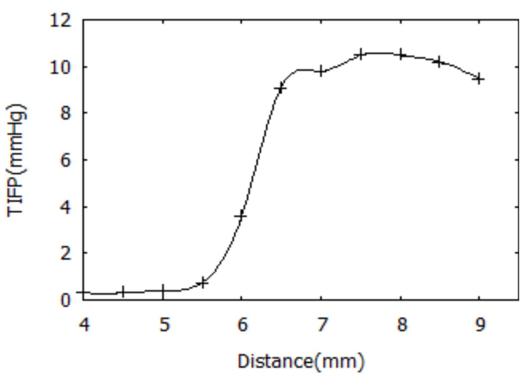

Figure 1: The plot of WIN estimates of TIFP vs. distance (depth) measured at 0.5 mm intervals.

Results: Nine animal studies having DCE-MRI and WIN estimates of TIFP were available. *In-vivo* high resolution T_2-weighted brain images, taken after MRI studies following TIFP measurements, were employed to confirm the position of the needle for TIFP measurements. The plot of TIFP values measured at different depths of the tumor is shown in Figure 1. As shown, measured TIFP increases steeply from 5.5 mm reaching to a relatively steady state at 7 mm giving a nearly constant TIFP values afterwards. The WIN estimates of TIFP ranged from 5.65 to 19.37 mmHg with a mean(±std) of 11.40(±4.46) mmHg.

Mean fluid velocity at the tumor rim measured by observing the wave front of contrast enhancement was $(3.81\pm1.03)x10^{-2}$ mm/s, and the mean distribution volume was (10.45±4.26)%. Figure 2 shows a well-correlated plot of DCE-MRI estimates of TIFPs *versus* WIN estimates ($R=0.77$, $p \leq 0.02$). Using the slope ($8.40x10^{-4}$ mm^2 $mmHg^{-1}$ s^{-1}) of the plot and mean tumor rim V_D (10.45%), the mean fluid conductivity was calculated to be $8.78x10^{-7}$ cm^{-2} $mmHg^{-1}$ s^{-1}, which is in the range of the previously reported values for different solid tumors. Interestingly, none of the distribution volumes; neither at tumor region nor at the tumor rim, showed any significant correlation to TIFP; however, the ratio of the two distribution volumes; tumor to tumor rim, showed a significant correlation with TIFP ($R=0.66$, $p\approx0.05$) indicating that the TIFP and normal tissue compression are correlated.

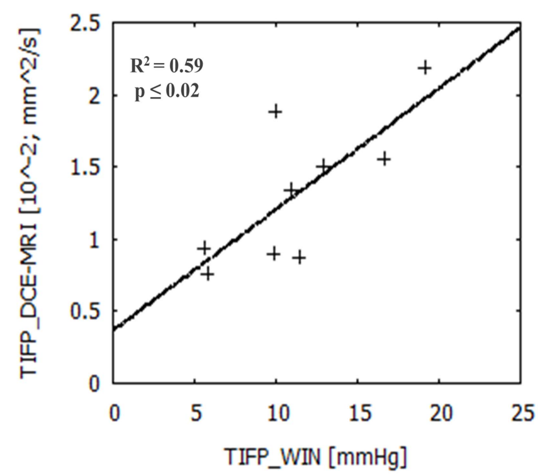

Figure 2: Scatter plot of the DCE-MRI estimates of TIFP versus TIFP measured by WIN technique. Solid line shows the linear fit of the plot

Conclusion: This study established a significant correlation between DCE-MRI derived TIFPs with those of WIN estimates in rat model of cerebral glioma, and also provided a means for estimating fluid conductivity in tumor surround. These data strongly demonstrate the possibility of employing DCE-MRI for non-invasive estimates of TIFP in solid brain tumors.

References: 1) Aryal et al; Magn Reson Med 2014, 71:2206–22
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