

## In Vivo Assessment of the Tissue Cellularity Index (TCI) in Brain Tumors using Multi-Echo DSC-MRI

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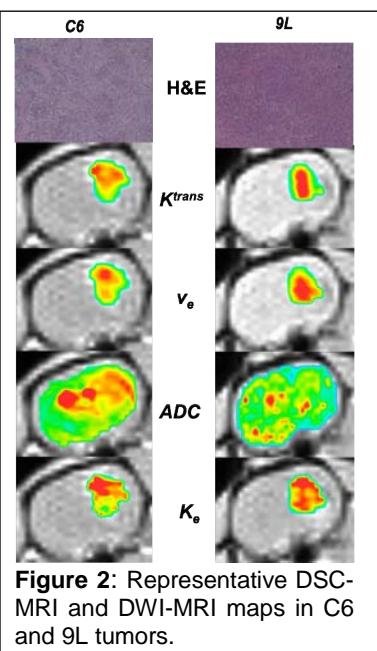
**Target Audience:** Clinicians and basic scientists who apply and investigate DSC-MRI methods in patients with brain tumors.

**Purpose:** Multi-echo DSC-MRI data in brain tumors contains a wealth of information since the  $T_1$  and  $T_2^*$  effects can be separated and quantified. When small-molecular weight Gd-based contrast agents (CA) are used, such studies are influenced by the extravascular compartmentalization of CA and could potentially be used to extract information about the underlying cellular properties within tissue [1,2]. Recently, we described how the  $T_1$  and  $T_2^*$  leakage effects can be leveraged to derive a cellularity metric, which we termed the tissue cellularity index (TCI) [2]. The goal of this study was to evaluate and characterize the TCI using simulations, brain tumor animal models and in a glioma patient.

**Methods:** The TCI parameter can be derived from the approach described in [1]. Briefly, at time points well past the first pass of CA, when the intra- and extravascular CA concentration ([CA]) is equivalent, the  $\Delta R_2^*$  is equal to the product of the effective tissue relaxivity and the tissue [CA]. We

proposed that the effective tissue relaxivity, which we term the TCI, is related to tissue cellularity and can be computed as  $TCI = \Delta R_2^*/(\Delta R_1/r_1)$ , where  $r_1$  is the CA  $T_1$  relaxivity. To simulate the dependence of TCI on cellular features, we created 3D tissue structures using fractal tree based vascular networks and randomly distributed ellipsoids and computed the associated gradient echo transverse relaxation rates as previously described [3]. For preclinical and clinical studies, multi-echo DSC-MRI data was acquired for 15 and 7 minutes, respectively. The last two minutes of the DSC-MRI data were used to compute TCI maps. The TCI maps were compared to H&E staining, ADC,  $K^{trans}$  and  $v_e$ .

**Results:** Simulations reveal that TCI increases with increasing cell density (**Fig. 1**). The H&E stains indicate that the 9L tumor cell density is greater than that found in the C6 tumors (**Fig. 2**). Within the tumor tissue, the TCI values were spatially heterogeneous in both tumor types and visually not correlated to the other parameters. Consistent with the histological results, 9L tumors had significantly lower ADC values as compared to the C6 tumors ( $p=0.004$ ). The TCI values in 9L tumors, across all animals, were twice as high as those found in C6 tumors ( $p = 0.0003$ ) as shown in **Fig. 3**. Interestingly, there was no spatial correlation between TCI and the other parameters in either the animals or the one patient. **Figure 4** shows the types of information afforded by multi-echo DSC-MRI, including DSC- and DCE-MRI kinetic parameter maps along with the newly proposed TCI maps.

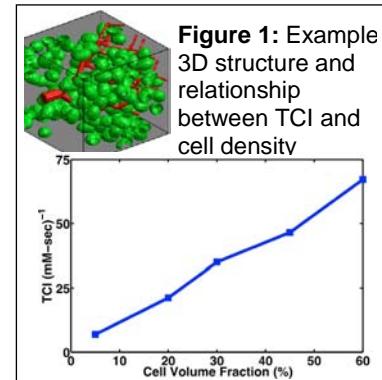


**Figure 2:** Representative DSC-MRI and DWI-MRI maps in C6 and 9L tumors.

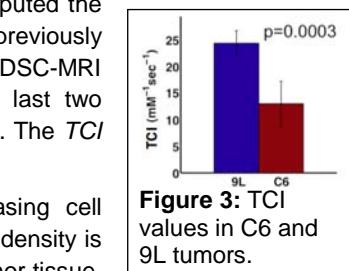
**Discussion/Conclusions:** The results support the hypothesis that DSC-MRI brain tumor data are highly sensitive to variations in tumor cellular features. The higher cell density found in the 9L tumors likely created a more heterogeneous compartmentalization of the CA in the extravascular space and therefore more heterogeneous field perturbations and larger  $\Delta R_2^*$  changes. In addition to the dissimilar TCI values between the tumor types, the lack of correlation between TCI and ADC,  $K^{trans}$  or  $v_e$  indicate that these maps could potentially serve as a new metric with which to evaluate tumor cellularity. The approach used herein enables the simultaneous acquisition of TCI, along with traditional DSC- and DCE-MRI derived parameters and could serve as a valuable tool for evaluating the brain tumor microenvironment and treatment response.

**References:** [1] Quarles CC, et al, Phys Med Biol, 2009. [2] Semmineh N., et al. ISMRM 2011 and 2012.

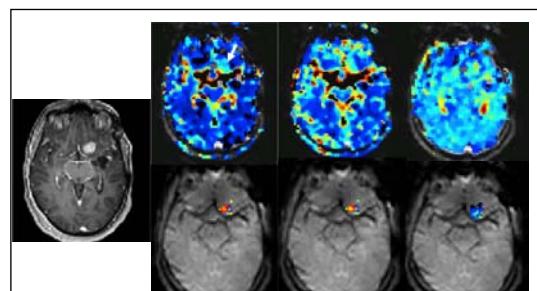
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**Figure 1:** Example 3D structure and relationship between TCI and cell density



**Figure 3:** TCI values in C6 and 9L tumors.



**Figure 4:** Example CBF, CBV, MTT,  $K^{trans}$ , TCI and  $v_e$  maps in a glioma patient.