

Contrast leakage in high grade glioma measured with independent component analysis of dynamic susceptibility contrast MRI

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INTRODUCTION Contrast agent leakage confounds the measurement of relative cerebral blood volume (rCBV) in brain tumors due to T1 effects causing the MR signal to rise above baseline. It has been shown that a second bolus of contrast agent alleviates this effect, yet some debate still remains as to the need for two doses¹. This study measures the difference between the two separate contrast agent boluses in patients with high-grade glioma using regions of interest (ROIs) defined by a novel unbiased independent component analysis (ICA) approach. We measure and compare the signal in tumor, arteries and veins to determine the leakage effects in each tissue type. **METHODS** *Patient Population* Ten patients with high-grade glioma were enrolled in this study. *Imaging* All images were acquired on a 1.5T MRI scanner (GE, Waukesha, WI). The first dose of 0.05 to 0.1 mmol/kg (pre-load) dose of gadolinium (Gd) contrast agent was administered as single shot gradient-echo (GE) echo-planar imaging was collected²⁻⁴. Clinical post-contrast T1-weighted imaging was then obtained followed by a second bolus, during which DSC data was again gathered with the same acquisition settings. Typically, 13 slices of DSC data were acquired with the following parameters: 5mm, skip 1.5mm slice prescription, fat suppression, TE: 30ms, TR: 1s, field of view: 220 x 220mm, matrix size: 128 x 128, and voxel size: 1.72x1.72x5mm. *Independent Component Analysis* Pre-processing of the DSC data consisted of the removal of the first 4 time points and motion correction using MCFLIRT (FMRIB tool library). Data was then processed using probabilistic independent component analysis⁵ as implemented in MELODIC (FMRIB tool library). Three components were extracted from each patient's 1st-dose DSC acquisition. This separated the arterial, venous, and tumor components based on tissue perfusion characteristics similar to how ICA separates regions of functional MRI activation responding to different aspects of a cognitive task. *Region of Interest (ROI) Generation* The statistically thresholded z-values (mixture model, alternative hypothesis testing $p>0.5$ vs. null⁴) for tumor, arterial, and venous maps were binarized to create 1st-dose ROIs. Average signal from each patient/dose was then extracted.

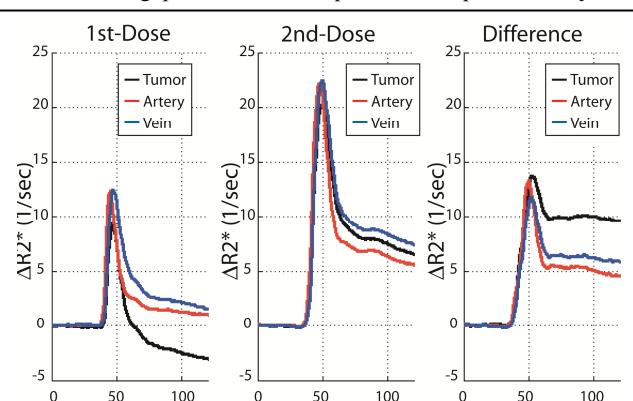


Figure 2. Concentration time curves for the 1st and 2nd dose within the ICA derived ROIs (Left and Middle). Clear Leakage effect is seen in the tumor during the 1st dose, that is not apparent in the 2nd. The difference (Right) is calculated by subtracting the 1st from the 2nd, and the tumor shows the largest difference due to leakage.

The initial drop in arterial MR signal was used to temporally align the data from all patients. The concentration time curve was then calculated as $\Delta R2^* = -\ln(S(t)/S_{bl})/TE$ where $S(t)$ is the raw MR signal, and S_{bl} is the mean baseline signal prior to the contrast bolus. For each dose the mean $\Delta R2^*$ was then plotted along with the difference in signals (2nd dose – 1st dose) shown in Figure 2. The mean residual difference in signal recovery⁶ from the tumor ROI was then calculated for each patient and compared to the arterial and venous components using an ANOVA. Differences of $p<0.005$ were considered significant. **RESULTS** Figure 1 shows the ICA components from a representative patient. The 1st-dose data produced reliable tumor, arterial, and venous components for all ten patients. Due to the contrast leakage, ICA clearly and automatically delineates enhancing tumor. The signal extracted from both boluses is shown in Figure 2. While the drop below baseline is clearly visible in the 1st-dose tumor component, it is nonexistent in the 2nd-dose. In addition the difference between tumor and normal vasculature is most apparent in the residual difference in signal recovery following the bolus peak. This measure is significantly greater in the tumor component compared to both arterial and venous components (Figure 3). **DISCUSSION** ICA represents an automatic and non-subjective approach for delineating tumor ROIs. This represents an advance over current manual methods to delineate tumor that have been time-consuming and subjective and thus prone to error. This analysis also demonstrates the efficacy of the pre-dose to diminish T1 leakage effects. Further research is needed to determine the reliability of this analysis technique applied to DSC data using different acquisition methods and for different tumor types and grades.

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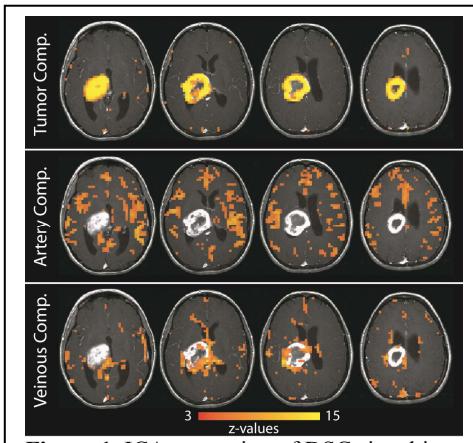


Figure 1. ICA separation of DSC signal in a patient with glioblastoma. Three components are modeled including the tumor, arteries and veins.

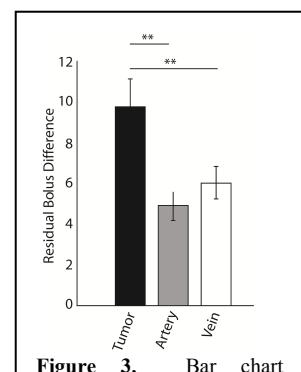


Figure 3. Bar chart demonstrating tumor residual bolus difference is greater than both arterial and venous equivalents (** $p<0.005$, ANOVA)