The effect of b-value on ADC values in a rat U87 brain tumor model

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Target Audience Brain cancer imaging researchers, radiologists and clinicians.

Purpose Diffusion weighted imaging (DWI) is an MR technique that measures the Brownian motion of water molecules. Images are collected at different diffusion weightings (b-values) and the corresponding signal decreases as b-value increases. The current standard for DWI in cancer imaging is to collect data at two b-values to calculate an apparent diffusion coefficient (ADC). Calculating ADC in this way involves the underlying assumption that the diffusion-related signal decay behaves monoexponentially as a function of b-value. However, studies have shown this is often not the case[1,2,3]. Lower b-values are affected by perfusion as the relatively fast moving blood of the microcirculation causes a quicker decrease in signal compared to pure Brownian motion[1]. The signal also deviates from monoexponential behavior at b-values > 1000 s/mm^2 due to the presence of multiple diffusion pools and restrictions to water movement[2,3]. As a result, ADC can vary substantially depending on which b-values are used in its calculation. Furthermore, ADC can be made more sensitive to different diffusion pools by cleverly selecting the b-values used to calculate it. In this study, ADC is calculated using different combinations of b-values and compared between tumor and contralateral normal gray matter (GM) in a rat U87 brain tumor model.

Methods Male Athymic nude rats were inoculated with U87 brain tumor cells and imaged on day eight post-inoculation prior to any treatment. In total, 42 rats were imaged. Five 2mm axial (rat coronal) imaging slices were collected and were centered on the tumor. Pre and post contrast T1-weighted spin-echo images were acquired (TE/TR = 11 ms/500ms; matrix = 256x256; FOV = 3.5 cm; slice 2mm). Diffusion weighted images (DWI) were also collected prior to contrast injection (TE/TR = 35/1500ms; matrix = 128x128, FOV = 3.5cm, Flip Angle = 90deg, diffusion weighting (b-values) = (0, 50, 100, 150, 200, 400, 600, 800, 1000, 2000, 3000) s/mm^2, 3 orthogonal diffusion directions). The three orthogonal DWI images were averaged to create a single trace DWI image. A tumor region of interest (ROI) was determined from the contrast-enhancing region on the post-contrast T1-weighted image. Contralateral GM ROIs were also drawn. These ROIs were then propagated to the DWI scans. Apparent diffusion coefficient (ADC) maps were computed using Equation 1, where b_1 is the smaller b-value, b_2 is the higher b-value and S_1 and S_2 are their respective images. In order to differentiate diffusion contributions from different compartments, various b-value combinations were evaluated, including: b_1,b_2 = 0,1000 s/mm^2; b_1,b_2 = 0,200 s/mm^2; b_1,b_2 = 200,1000 s/mm^2; b_1,b_2 = 1000,3000 s/mm^2; b_1,b_2 = 2000,3000 s/mm^2. These different ADC values are denoted $ADC_{b1,b2}$. The percent difference between $ADC_{0,1000}$ and $ADC_{2000,3000}$ was also computed. Voxelwise ADC and percent difference values were averaged in the tumor and GM ROIs and compared with a paired two-sample t-test. ADC was compared across tumor and GM ROIs with a repeated measures ANOVA and post hoc Tukey's multiple comparison test.

$$ADC_{b_1,b_2} = \left(\frac{1}{b_2 - b_1}\right) \cdot \ln\left(\frac{S_1}{S_2}\right) \quad (1)$$

Results Significant differences were seen between tumor and GM ROIs for ADC calculated with all b-value combinations (P < 0.001, Figure 1). Tumor ADC was *greater than* GM ADC for $ADC_{0,1000}$, $ADC_{0,200}$, and $ADC_{200,1000}$. Tumor ADC was *less than* GM ADC for $ADC_{1000,3000}$, $ADC_{2000,3000}$. The percent difference between $ADC_{0,1000}$ and $ADC_{2000,3000}$ was higher in tumor compared to GM (P < 0.0001). A one way repeated measures ANOVA of the mean ADC within tumor ROIs proved significant (P < 0.0001). The subsequent Tukey's multiple comparison test showed significant differences between all ADC combinations (P < 0.01) except for $ADC_{0\text{-}1000}$ vs. $ADC_{200\text{-}1000}$, $ADC_{0\text{-}1000}$ vs. $ADC_{0,200}$, and $ADC_{1000,3000}$ vs. $ADC_{2000,3000}$. For the GM ROIs, the ANOVA was also significant (P < 0.0001). The Tukey's multiple comparison test showed significant differences between all ADC combinations (P < 0.01) except for $ADC_{0,1000}$ vs. $ADC_{200,1000}$ and $ADC_{0,1000}$ vs. $ADC_{0,200}$. Example ADC maps are shown in Figure 2.

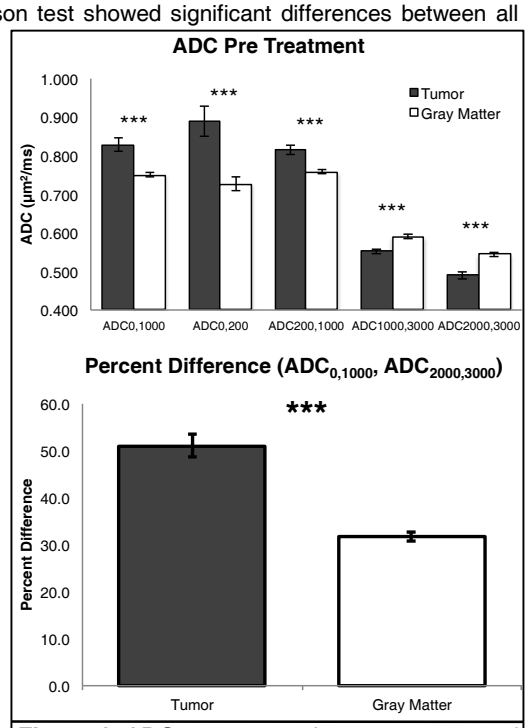

Figure 1. ADC comparison between tumor and GM (top) and the percent difference between $ADC_{0,1000}$ and $ADC_{2000,3000}$ (bottom). Error bars represent standard error.

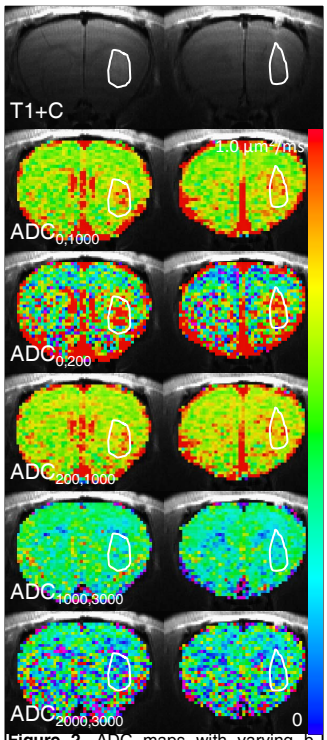

Figure 2. ADC maps with varying b-values from one rat. Note the differences in heterogeneity between the maps. The tumor is outlined in white.

Discussion Results in humans have shown low ADC in areas of high cellularity[4]. This study showed *higher* ADC in tumor vs. GM when *lower* b-values (b ≤ 1000 s/mm^2) were used in its calculation. This was despite increased cellularity in the tumor compared to GM seen on histology. One possible explanation is that increased perfusion in the tumor caused artificially increased ADC with b=0 s/mm^2 included in the calculation. However, tumor ADC was also higher for $ADC_{200,1000}$, where perfusion effects were compensated for. ADC was found to be *lower* in tumor vs. GM when *higher* b-values (b > 1000) were used in its calculation. ADC calculated with high b-values may be more sensitive to cellularity as the faster diffusing extracellular components have been suppressed.

Conclusion ADC values depend on the b-values chosen for its calculation, even reversing direction relative to GM when using the highest b-values. Therefore, care must be taken when choosing b-values and comparing ADC across studies or monitoring treatment response, as the contribution from the different pools may also be changing and can confound interpretation.

References 1. Le Bihan D et al. *Radiology*. 168:497-505, 1988. 2. Le Bihan D et al. *NeuroImage* 61:324-341, 2012. 3. Niendorf et al. *MRM*. 36:847-857, 1996. 4. Ellingson et al. *JMRI*. 31:538-548, 2010.