# The relationship between short and long diffusion time ADC values in rat brain tumors

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Target Audience

Brain cancer imaging researchers, radiologists and clinicians.

Purpose

Advanced imaging techniques, such as diffusion weighted imaging (DWI), have been developed to detect brain tumor progression and invasion. Biological systems are heterogeneous and contain physical boundaries that can hinder the motion of water molecules and lead to an underestimation of a material's true diffusion coefficient when the diffusion time is large. Standard clinical DWI protocols involve diffusion times (Δ) high enough for these effects to be significant (~25ms). Techniques, such as oscillating gradient spin echo (OGSE) DWI, are able to achieve diffusion times on the order of 1ms leading to more accurate diffusion measurements[1]. This study looks at the relationship between short and long diffusion time apparent diffusion coefficient (ADC) values in a rat C6 glioma brain cancer model. It was hypothesized that the difference between short and long diffusion time derived ADC would be higher in tumor compared to normal tissue. This is due to increased heterogeneity and more diffusion-hindering barriers in tumor leading to restricted diffusion in the long Δ, but not the short Δ regime . These results are then compared to parameters derived from multiple b-value DWI and the stretched exponential model. This model has been shown to give estimates of intravoxel heterogeneity[2].

Methods

***Rats*** Sprague-Dawley rats were inoculated with C6 glioma cells and imaged on day 14 post-inoculation. Tumors were localized to the right hemisphere. In total, 19 rats were imaged. One rat was excluded due to poor scan quality leaving 18 rats for further analysis. ***Imaging*** All images were acquired on a 9.4T Bruker scanner. DWI and contrast enhanced T1-weighted images (T1+C) were acquired. For the DWI imaging, short diffusion times were obtained by using a pair of balanced bipolar gradients around a 180° refocusing pulse. Five sets of spin echo (SE) DWI images were acquired.

**Table 1. Diffusion Parameters**

| Dataset | TE (ms) | Δ (ms) |
|---|---|---|
| **Set A** | 59.1 | 30 |
| **Set B** | 26 | 4 |
| **Set C** | 50 | 4 |
| **Set D** | 50 | 10 |
| **Set E** | 70 | 10 |

Set A was acquired with Stejskal-Tanner diffusion lobes and TR/TE=2000/59.1ms, Δ=30ms, and b-values of 0, 500, 1000, 2000, and 3000 s/mm$^2$. Sets B-E were acquired with bipolar SE DWI, TR=2000ms, b-values of 300 and 1500 s/mm$^2$, and Δ=4 or 10ms. Additional parameters are shown in Table 1. T1+C images were acquired with TR/TE=1500/7.5ms, FA=121.4°, Matrix=256x256, and Thickness=1mm. ***Data Analysis*** ADC was calculated using the standard two point model for the bipolar diffusion scans (Sets B-E). The heterogeneity index, alpha, was calculated by fitting the multiple b-value DWI data (Set A) with the stretched exponential model, $S(b)=S_0 \bullet \exp(-(b \bullet DDC)^{\wedge}\alpha)$, where DDC is the distributed diffusion coefficient and α is the intravoxel heterogeneity index. The intravoxel heterogeneity index ranges from 0 to 1 with lower values meaning more heterogeneity. Tumor masks were manually drawn on the T1+C images to include areas of heightened intensity. Contralateral normal tissue ROIs were then drawn in a similar location and size of the tumor. To examine the effects of TE and Δ on diffusion, ADC values were averaged in both the tumor and normal ROIs and compared between ROIs and scans using a repeated measures ANOVA and Tukey's multiple comparisons test. ADC-difference maps were computed by subtracting the ADC maps from Sets C and D. These maps had the same TE, but different Δ. They were then compared between ROIs using a two-sample t-test. Stretched exponential derived parameters including DDC and α, were also averaged in the tumor and normal ROIs and compared between ROIs using a two sample t-test. Finally, correlations between ADC-difference values and α values were assessed using Pearson's correlation coefficient.

**Table 2. Statistical Results**

| | Tumor | Normal | |
|---|---|---|---|
| **ADC Difference** | $3.84 \bullet 10^{-5}$ | $-1.36 \bullet 10^{-5}$ | p<0.001 |
| **Alpha** | 0.73 | 0.83 | p<0.001 |
| | | | |
| **ADC Δ=4,TE=26ms** | $9.33 \bullet 10^{-4}$ | $7.55 \bullet 10^{-4}$ | p<0.001 |
| **ADC Δ=4,TE=50ms** | $9.13 \bullet 10^{-4}$ | $7.38 \bullet 10^{-4}$ | p<0.001 |
| **ADC Δ=10,TE=50ms** | $8.74 \bullet 10^{-4}$ | $7.52 \bullet 10^{-4}$ | p<0.001 |
| **ADC Δ=10,TE=70ms** | $8.54 \bullet 10^{-4}$ | $7.31 \bullet 10^{-4}$ | p<0.001 |
| | p<0.0001 | p=0.003 | |

Note: ADC values are given in units of mm$^2$/s

Results

Significant differences in ADC were found with both the tumor and normal cortex ROI (repeated measures ANOVA, p<0.0001 and p=0.003 respectively). Specifically, for the tumor ROI, ADC was significantly higher in sets B and C compared to sets D and E (Tukey's multiple comparisons test, p<0.01). For the normal cortex ROI, significant differences in ADC were seen between both sets B and C and set E (Tukey's multiple comparisons test, p<0.01 and p<0.05 respectively). The ADC-difference (Set B – Set C) was significantly higher in tumor vs. normal cortex (paired two sample t-test, p<0.001). The intravoxel heterogeneity index was significantly lower in tumor vs. normal cortex (paired two sample t-test, p<0.001). In addition, the ADC-difference was significantly negatively correlated with the intravoxel heterogeneity index (α) (p< 0.001). These results are summarized in Table 2 and Figure 1. Example parametric maps are shown in Figure 2.

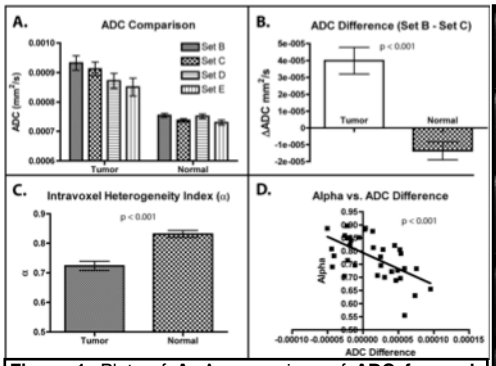


**Figure 1.** Plots of **A.** A comparison of **ADC for each scan type in tumor and normal tissue, B**. The ADC Difference of Set B – Set C, **C.** The intravoxel heterogeneity index, α, and **D.** The relationship between α and the ADC difference of Set B – Set C.

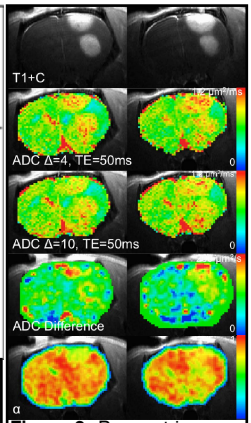


**Figure 2.** Parametric maps from one representative rat

Discussion

There were no significant differences in ADC between sequences with the same Δ, but different TE. This lends to the idea that tissue did not have compartments with different T2 relaxation times. The significant correlation between ADC-difference and α indicates ADC-difference is related to intravoxel heterogeneity. Histological studies are needed to confirm these results. These results also indicate the importance of choosing the optimal diffusion time, as optimal choice of delta may improve tumor detectability and/or tumor to brain contrast.

Conclusion

Short diffusion time DWI provides a more accurate measure of ADC and allows probing smaller tissue microenvironments. The difference between short Δ ADC and long Δ ADC is related to intravoxel heterogeneity and may be useful as a tumor biomarker.

References

**1.** Colvin DC et al. Cancer Res. 68(14):5941-7, 2008 **2.** Bennett KM et al. Magn Reson Med. 50:727–734, 2003.