Analysis of High b-value Diffusion Data May Highlight in vivo Cellular Changes

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Diffusion properties of tissue reveal structural information. An ongoing impediment to MR-based diffusion measurements is the lack of a model that accurately represents tissue physiology without exceeding the resolution-limited modeling capabilities of diffusion-weighted MRI. Two models have typically been used to characterize water diffusion in tissue: a single-compartment model, where a constant rate of diffusion is assumed in the image voxel, and a two-compartment model. While the two-compartment model can be accurately fit to MR diffusion data, the correlation of two compartments with tissue structure has been more obfuscated. Thus, the single-compartment model is most commonly used for both research and clinical pursuits. Specifically, diffusion-weighted MRI has been explored as a method for looking at tissue response to cancer treatment [1] and in diagnosing acute cerebral infarct [2]. However, the physical significance of single-compartment diffusion measurements is also not clear. Here, we hope to further elucidate the origin of radiation-induced changes in diffusion properties in a murine model of mammary carcinoma by looking at only the slow-diffusing signal component. We compare a single-compartment analysis of an entire diffusion data set with an analysis of the high b-value data points ($b \geq 3000$ s/mm^2).

Introduction.

Investigators have shown that the rate of diffusion in many cells is highly restricted and thus approximately ten times slower than the rate of diffusion in extracellular space. Specifically, intracellular diffusion is approximately 10^{-4} mm^2/s and extracellular diffusion is approximately 10^{-3} mm^2/s [4]. Approximately 95% of the fast-diffusing component of the MR signal has decayed when the b-value is 3000 s/mm^2. Consequently, when $b \geq 3000$ s/mm^2 most of the remaining MR signal should be from the slow-diffusing component.

Materials and Methods.

Subcutaneous mammary carcinoma (MCa-29) was grown on the hind leg of C_3Hf/kam mice (N=15). When tumors were approximately 8 mm in diameter, the tumors were irradiated with 20Gy of ^{137}Cs gamma-rays (mean energy = 662 keV). Axial MR images were acquired on a 4.7T Bruker Biospec scanner (Billerica, MA) using a 4-shot EPI-based diffusion-weighted sequence with b-values up to 4000 s/mm^2. After the first imaging session (Day 0), half of the mice were sacrificed for hematoxylin and eosin (H&E) histologic analysis. The remaining mice were re-imaged three days after irradiation (Day 3) and then sacrificed for histologic analysis.

Diffusion data were analyzed using a single-compartment model, A*exp(-bD), where A is a normalization constant and D is the rate of diffusion. A pixel-by-pixel analysis was done using: 1) the entire diffusion data and 2) only data where $b \geq 3000$ s/mm^2.

Results.

Table 1 shows the mean rates of diffusion on Day 0 and Day 3 from both analysis methods. The mean values are calculated from all animals in the study. The full data set and high b-value analyses show an increased rate of diffusion from Day 0 to Day 3 ($p=0.03$, $p=0.04$, respectively). These results were compared to the diffusion maps and histology data shown in Figure 1. The diffusion maps show the difference between the two analysis methods. The histology shows that on Day 0 (Figure 1C) the cellular space is much more organized than on Day 3 (Figure 1D).

	Day 0 (x10^{-4} mm^2/s)	**Day 3** (x10^{-4} mm^2/s)
full data set	3.56 (0.23)	4.38 (1.89)
high b-value	2.35 (0.10)	2.89 (0.25)

Table 1. Diffusion values from analysis done with the full diffusion data set and with only the high b-value data. The weighted mean is shown with the error in the mean shown in parentheses. Data shown are from all animals in the study.

Discussion.

The rate of diffusion calculated over a wide range of b-values will be dominated by the fast-diffusing component. It may be possible to separate the contribution of the slow-diffusing, or highly restricted, compartment by using a high b-value analysis. The slow-diffusing compartment is often associated with cellular space, so increases in the high b-value data suggest cellular changes such as cell swelling and intracellular disorganization, both of which are precursors to necrotic cell death [5]. The histology shows a breakdown of intracellular organization, which is consistent with the results from the high b-value analysis. Thus, a separate analysis of the high-b-value data may provide more direct information about cellular changes than provided by examination of the full range of b-values.

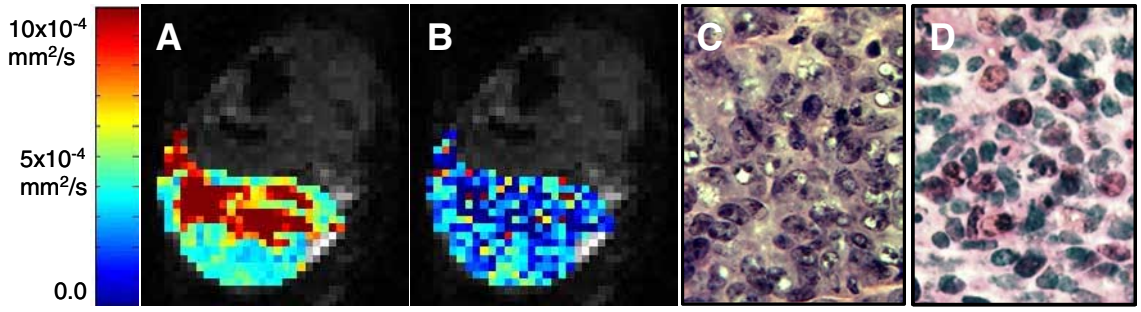

Figure 1. Diffusion maps overlaid on T_2-weighted MR images using (A) the full data set and (B) only the high b-value data. These data were obtained 3 days post-irradiation. (C) H&E-stained histology obtained on Day 0, and (D) histology obtained on Day 3.

References.

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