Toward Distinguishing Radiation Effects from Tumor Regrowth in an Irradiated Glioma Model

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Target audience: Clinicians, biologists, and imaging scientists interested in cancer and its treatment with radiation.

Purpose: Accurate diagnosis is essential for proper treatment decisions. Standard anatomical MRI is incapable of differentiating recurring tumor from delayed radiation injury. Further studies are therefore necessary to accurately identify a robust imaging paradigm that can differentiate these pathologies. We investigated two MRI approaches that probe cellularity through complementary properties: Diffusion Weighted Imaging (DWI), from which we calculated the apparent diffusion coefficient (ADC), and Magnetization Transfer Contrast (MTC), from which we calculated the magnetization transfer ratio (MTR). Our approach was to test these metrics longitudinally, first in tumor and radiation injury alone[1] and then, the subject of this report, in an irradiated glioma model.

Methods: All experiments were approved by the Washington University Division of Comparative Medicine and were performed on 8-9 week old female BALB/c mice. DBT glioma cells (~10,000 in 10 µl) were injected (day 0) below the cortical layers in the left hemisphere. Tumor-bearing mice then received three radiation treatments of 7.5 Gy (50% isodose) each on days 10, 12, and 14, for a total tumor-targeted dose of 22.5 Gy, *via* the Leksell Gamma Knife Perfexion (Elekta; Stockholm, Sweden). This irradiation dose resulted in a significant tumor growth delay (**Figure 1A**). Images were acquired with a 4.7-T small-animal Agilent/Varian DirectDrive™ scanner using an actively decoupled volume coil (transmit) and 1.5-cm surface coil (receive). MTC, DWI, and post-contrast T1-weighted images were acquired for each animal. For MTC analysis, proton-density-weighted images were acquired with and without the application of a 10 ms, 500º saturation pulse applied at a frequency offset +10 ppm from the water resonance. The MTR was calculated as the percent signal lost due to the saturation pulse. For DWI analysis, the ADC was calculated as the average of three separate diffusion datasets, acquired with diffusion encoding along three orthogonal directions, with a b-value of 1000 s/mm^2. ROIs were drawn on the post-contrast T1-weighted images of the tumor (enhancing lesion) and non-enhancing "normal appearing" contralateral hemisphere and overlaid onto the ADC and MTR maps.

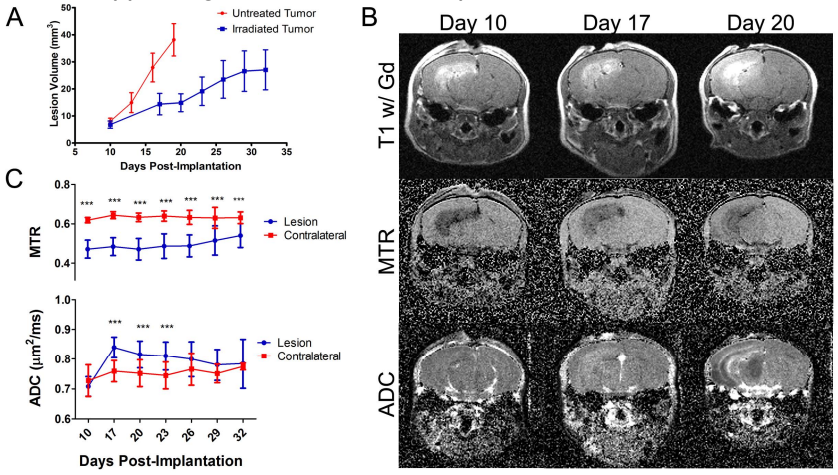

Figure 1. *Panel A.* Growth curves for untreated and treated tumor mice (mean ± SEM, N=10). Survival analysis confirms that treatment of tumors with this irradiation dose is indeed therapeutic (P<0.01 by Mantel-Cox test). *Panel B.* Post-contrast T1 (top), MTR map (middle), and ADC map (bottom) of a representative mouse at 10 (left), 17 (center), and final (right) days post-tumor-implantation. The lesion is bright on post-contrast T1. *Panel C.* Time course of group average MTR (top) and ADC (bottom) for the lesion and contralateral ROIs (mean ± SD, N=10). *** indicates P<0.001 as measured by Two-Way Repeated-Measures ANOVA with a Bonferroni post-test.

Results: Previously we showed that MTR values are consistently lower in both radiation injury (becoming significantly lower in late radiation injury) and in non-irradiated tumor when compared to contralateral brain tissue.[1] In contrast, the ADC increased with progression of radiation injury and decreased with non-irradiated tumor growth, making it a better metric than MTR for discriminating between these pathologies[1]. Of critical import, and the subject herein, are the comparative MTR and ADC changes observed when growing tumor is irradiated. **Figure 1B** shows the post-contrast T1-weighted image identifying the tumor and corresponding MTR and ADC maps in a representative mouse. MTR was consistently lower in irradiated tumor (as it was in non-irradiated tumor[1]) compared to contralateral brain tissue (**Figure 1C**). The ADC in irradiated tumor increased soon after the full course of irradiation (**Figure 1C**), then decreased as the tumor regrew.

Discussion: Our results suggest that ADC may provide a better metric than MTR for differentiating the changes that occur in growing tumor (ADC decrease) *vs.* irradiated brain tissue (ADC increase). While the ADC increased following irradiation of tumor, that increase was short lived as tumor regrew. Ideally, considering the irradiated mouse glioma model as a test bed, the goal would be to classify each voxel that is hyperintense in post-contrast T1-weighted images as either tumor or radiation injury. The work described herein suggests that another metric, complementary to ADC and MTR, will likely be needed to accomplish that goal in robust fashion.

Conclusion: MTR and ADC have been explored as possible metrics for distinguishing tumor *vs.* radiation necrosis. ADC is better at differentiating between the lesion types, while MTR has better sensitivity to the presence of either lesion. Neither contrast is definitive. It will require an additional complementary contrast to differentiate these pathologies.

References: 1. Perez-Torres CJ, *et al.* Proc. Intl. Soc. Mag. Reson. Med. (2013);21:1720.