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 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).

A. Growth curves for untreated and treated tumor mice (mean ± SEM, N=10).

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 (enhancing lesion) and non-enhancing “normal appearing” contralateral hemisphere and overlaid onto the ADC and MTR maps.

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. 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. Of critical import, and the subject herein, are the ADC and MTR values 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.

**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.