

The functional diffusion map provides early prediction of recurrence in a glioma model following radiotherapy

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Introduction: The treatment of glioblastoma multiforme (GBM) remains challenging due to its response heterogeneity, which contributes to its rapid resistance to standard therapies [1]. This heterogeneity of the response can be due to spatially varying phenotypes due to genomic instability which can also lead to alterations in protein expression levels and tumor vascularity. Moreover, spatial variations in radiation dosimetry may also impact treatment. The development of new non-invasive techniques to monitor tumor response on individual patients may prove helpful for adjusting treatment schedules on a patient by patient basis. The functional diffusion map (fDM) is a voxel-based analytical approach applied to apparent diffusion coefficient (ADC) maps that have been demonstrated as a surrogate biomarker of glioma response to treatment both in clinical trials [2] and in preclinical studies [3]. The goal of this study was to evaluate fDM as a biomarker of tumor recurrence on an animal-by-animal basis in a radiation dose escalation protocol.

Methods and Materials: Twenty-four genetically engineered murine GBM model [Ink4a/Arf^{-/-} Pten^{loxP/loxP}/ Ntv-a RCAS/PDGF(+)/Cre(+)] were imaged by MRI using a 9.4T system and a quadrature mouse head coil. Tumor bearing animals were introduced to the study (D0) when the tumors reach a volume of ~20 mm³. Mice were randomized in 4 groups (n=6 per group): no therapy, 1G, 2G and 4G (treated by 1Gy, 2Gy and 4Gy every day for 5 days; respectively). Tumor volume was determined by delineating the tumor from healthy tissue by contrast-enhanced MRI. Briefly, 50µl of Gd-DTPA was administered IP and ~5 minutes post-injection a T1-weighted (T1w-Gd) image was acquired using a SE sequence with the following parameters: TR/TE=500/15ms, 128x128, and 30x30. DW-MRI was acquired using a SE sequence (TR/TE=4000/32 ms, 128x64, 30x30 and b-values of 120 and 1200 s/mm²). Images were acquired daily for a week and every two days following until the animals became moribund. Tumor volumes of interest (VOI) were manually contoured on the T1w-Gd images and reported on the diffusion map. Necrotic voxels were excluded from each tumor VOI by filtering out voxels whose signal intensity < 5 times the noise value on the high b-value images (b=1200). Time to recurrence (TTR) was defined as the time for the tumor to triple its initial volume at baseline (D0). The relative ADC (rADC) maps were computed by normalized values using a VOI defined within the contralateral striatum. fDM was performed by calculating the difference in mid-treatment from pre-treatment rADC values for each voxel in the tumor. Voxels were classified, based on a user-defined threshold set at ±337 rADC units, as significantly increasing (fDM_{rADC+}; red), significantly decreasing (fDM_{rADC-}; blue), and unchanged (fDM_{rADC0}; green) rADC values following therapy. The volume fraction of each classification was calculated by summing the class specific voxels and normalizing by the tumor volume. Finally, for each animal the maximum fDM_{rADC+} value (maxfDM_{rADC+}) was determined within the first 5 days following therapy initiation. The maxfDM_{rADC+} was correlated to TTR using a linear regression.

Results: We observed a large inter- and intra-group variability of TTR as presented in Table 1. TTR values observed within each group were determined ([min-max] = [3-5], [3-9], [13-21] and [19-25] for the control, 1G, 2G and 4G groups; respectively). We observed a peak of fDM_{rADC+} value during the treatment (at Day 2 on Fig. 1a) and this peak measured animal by animal was somewhat variable over the week of treatment administration. We observed a linear increase of maxfDM_{rADC+} value which correlated with the dose of radiation received (Fig. 1b). We also found a good correlation between TTR and the fDM_{rADC+} metric when we used the maximum value of individual animals during the week of treatment (R² = 0.85; Fig. 1c).

Discussion: This study demonstrates the efficacy of fDM as an imaging biomarker of tumor recurrence following radiotherapy. The maximum fDM_{rADC+} values measured during radiation therapy were correlated strongly with TTR. fDM_{rADC} technique may serve as a biomarker of tumor recurrence that is insensitive to the response heterogeneity typically observed in GBM.

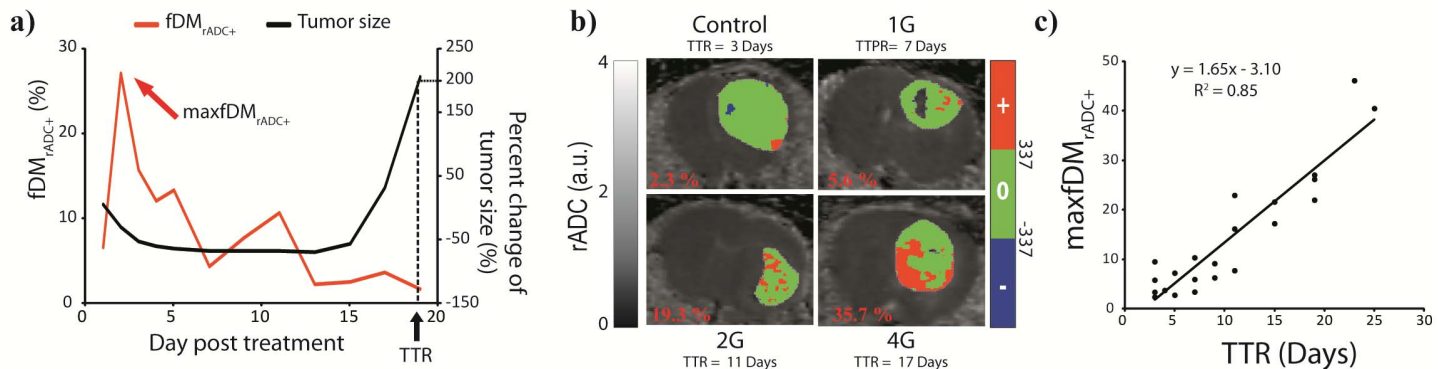


Figure 1: a) Representative time plot of the fDM_{rADC+} metric along with the percentage change of tumor volume from a 4G treated animal maxfDM_{rADC+} and TTR delineated by the red and black arrows respectively. b) fDM_{rADC} maps of a representative animal from each group (control, 1G, 2G and 4G) revealing the peak fDM_{rADC+} values observed during the first week post-treatment initiation. maxfDM_{rADC+} is represented in red in the color overlay. c) Scatter plot and linear regression of the maxfDM_{rADC+} value as function of the TTR. Each dot represents an individual animal.

References:

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