

Comparison of cytotoxic and anti-angiogenic treatment responses using functional diffusion maps in FLAIR abnormal regions

B. M. Ellingson^{1,2}, M. G. Malkin^{1,3}, S. D. Rand^{1,2}, A. Hoyt⁴, J. Connelly³, D. P. Bedekar^{1,2}, S. N. Kurpad^{1,4}, and K. M. Schmainda^{1,2}

¹Translational Brain Tumor Program, Medical College of Wisconsin, Milwaukee, WI, United States, ²Department of Radiology, Medical College of Wisconsin, Milwaukee, WI, United States, ³Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, United States, ⁴Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, United States

Introduction

Diffusion-sensitive magnetic resonance imaging (MRI) sequences are valuable in assessing the relative cellularity of malignant tumors along with their response to cytotoxic treatments¹. Functional diffusion maps (fDMs) were developed to take advantage of these principles on a voxel-by-voxel basis within contrast-enhancing regions of intra-axial tumors². Although fDMs have been examined for use with cytotoxic treatments, their utility in the evaluation of anti-angiogenic treatments has not been studied. Anti-angiogenic treatments typically cause a reduction in blood-brain barrier (BBB) permeability leading to significant reduction in contrast-enhancement³; thus, the traditional fDM approach focusing on enhancing lesion volumes may be inadequate. To overcome these challenges we chose to apply the fDM technique to regions of fluid-attenuated inversion recovery (FLAIR) image abnormality, since FLAIR sequences are routinely used to visualize the extent of non-enhancing brain tumors and are sensitive to edema, demyelination, and regions of active infiltrative tumor⁴. Furthermore, recent evidence suggests that recurrence during treatment with anti-angiogenic drugs acting along the VEGF signaling pathway may result in diffuse tumors with a predominantly infiltrative phenotype⁵. Therefore, the overall purpose of the current study was to compare cellularity metrics extracted from fDMs applied to FLAIR abnormal regions between progressive, stable, or responsive patients treated with either standard therapies (chemotherapy & radiation therapy) or anti-angiogenic therapy combined with chemotherapy (bevacizumab & irinotecan). This will enable us to examine the utility of fDMs for the evaluation of anti-angiogenic treatment regimens, and determine whether these treatments result in significant increases in infiltrative tumor volume compared to standard treatment.

Methods

A total of 20 patients with intracranial tumors, scanned at least 3x, were enrolled in the current study for a total of 112 scan sessions and 92 unique fDM datasets. Eight patients were treated with bevacizumab (10mg/kg) and irinotecan (125mg/m²) for a total of 60 MRI scan sessions (52 fDMs). Twelve patients were given temozolamide (200mg/m²/day) concurrently with standard radiation therapy for a total of 52 MRI scan sessions (40 fDMs). Each scan session was classified as responsive disease (RD), stable disease (SD), or progressive disease (PD) after each scan session based on clinical MRI scans (SPGR, FLAIR, and pre-/post-contrast T1-w MRI) and neurological assessment. Functional diffusion maps (fDMs) were calculated from registered sequential diffusion weighted images and then applied to regions of FLAIR abnormality with ADC thresholds of 0.55×10^{-3} mm²/s, as per the fDM protocol². Voxels were stratified as not changing (green), increasing ADC (red), or decreasing ADC (blue) according to this threshold. The volume of hypercellularity (physical volume of blue voxels, in mL), volume of hypocalcellularity (physical volume of red voxels, in mL), and the time rate of change in hypercellular volume (in uL/day; based on the change in volume and time between each subsequent scan days), and the rate of change in hypocalcellular volume (in uL/day) were calculated from resulting fDMs.

Results

Representative fDMs are shown in Figure 1 for both treatment groups and response categories. Overall, trends in the physical volume of hypercellularity suggest that patients treated with bevacizumab/irinotecan had a significantly higher volume of hypercellularity compared with patients treated with temozolamide (Mann-Whitney, $P<0.0001$) despite comparable FLAIR volumes (ANOVA, $P=0.059$). Results further suggest that treatment and tumor status both have significant influence on the volume of hypercellularity (Fig. 2A; ANOVA, $P<0.0002$), and that PD has a higher volume of hypercellularity than both SD and RD (Tukey, $P<0.001$). Tumor status and the interaction between treatment and status were significant factors affecting the time rate of change in hypercellularity (Fig. 2B; ANOVA, $P<0.0002$). In particular, the rate of hypercellular volume was significantly higher during PD compared with either SD or RD (Tukey, $P<0.0001$), suggesting the rate of hypercellular volume change may be a good predictor of progression. Also, the rate of hypercellular volume change during a positive response to treatment was significantly different between the treatment groups (Tukey, $P<0.0001$). Hypocalcellular volume changes were not significantly different between treatments or tumor status (Fig. 2C; ANOVA, $P>0.1$). The time rate of change in hypocalcellular volume, however, was significantly different between treatments, tumor status, and the interaction between treatment and tumor status (Fig. 2D; ANOVA, $P<0.05$). Specifically, the rate of hypercellular volume change was higher in RD compared to SD (Tukey, $P=0.025$), and PD during temozolamide treatment resulted in a significantly faster decrease in hypocalcellular volume compared with bevacizumab and irinotecan treatment (Tukey, $P<0.001$).

Discussion

The results of the current study support the hypothesis that recurrence after treatment with bevacizumab results in growth of an infiltrative (i.e. non-enhancing) tumor type, since the overall volume of hypercellularity was significantly higher in patients treated with bevacizumab compared with temozolamide. However, it must also be noted that patients on the anti-angiogenic therapy regimen had recurrent tumors and failed the standard regimen of chemotherapy plus radiation therapy. Consequently, future studies are needed to determine if increased cellularity remote from the primary tumor is due to an infiltrating tumor phenotype promoted by anti-angiogenic therapies or if it is a late response to standard therapies. Still, in general, this study suggests the volume of hypercellularity and the time rate of change in hypercellular volume are sensitive metrics for detection of tumor progression in both cytotoxic and anti-angiogenic treatment paradigms.

Acknowledgements NIH/NCI R21-CA109820; MCW Advancing Healthier Wisconsin/Translational Brain Tumor Program

References

1. Sugahara T, Korogi Y, Kochi M, et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging* 1999;9:53-60.
2. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: A noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc Nat Acad Sci* 2005;102(15):5524-5529.
3. Jain RK, Tong RT, Munn LL. Effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis: insights from a mathematical model. *Cancer Res* 2007;67(6):2729-2734.
4. Husstedt HW, Sickert M, Köstler H, Haubitz B, Becker H. Diagnostic value of the fast-FLAIR sequence in MR imaging of intracranial tumors. *Eur Radiol* 2000;10(5):745-752.
5. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas. *Neurology* 2008;70:779-787.

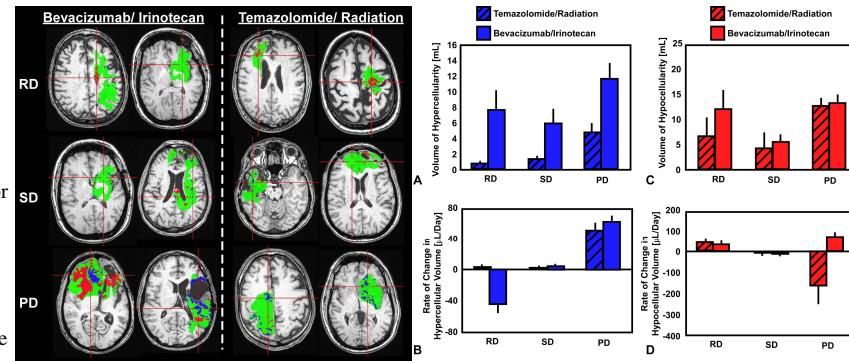


Figure 1: fDMs in representative patients showing responding disease (RD), stable disease (SD), and progressing disease (PD) for both treatment groups.

Figure 2: A) Volume of hypercellularity, B) rate of change in hypercellular volume, C) volume of hypocalcellularity, and D) rate of change in hypocalcellular volume for RD, SD, and PD in both treatment groups.