Serial Changes in Diffusion Imaging Parameters Vary with Treatment Regimen for Patients with Newly Diagnosed Glioblastoma Multiforme

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Introduction: Glioblastoma multiforme (GBM) is the most common and most aggressive primary malignant brain tumor. Despite treatment with surgery, radiation therapy (RT) and the standard of care temozolomide (TMZ), the median overall survival of GBM patients remains less than 15 months [1]. Anti-angiogenic therapies have been developed to be administered concurrently with RT and TMZ to patients with GBM. These agents have been reported to eliminate the contrast-enhancing lesion (CEL), therefore making it difficult to perform an accurate imaging assessment of treatment efficacy. Diffusion-weighted imaging (DWI) is a noninvasive technique that can serve as an adjunct to the assessment of treatment efficacy in patients receiving anti-angiogenic therapies. A protein kinase C β-inhibitor (PKC-βi) believed to have anti-angiogenic properties administered to newly diagnosed patients with GBM has been shown to cause an increase in the apparent diffusion coefficient (ADC) shortly after treatment initiation [2]. An anti-VEGF monoclonal antibody (VEGF-Ab) has been reported to cause restriction on DWI. Changes in anatomic and diffusion parameters in patients with newly diagnosed GBM receiving TMZ and VEGF-Ab during RT, and the interpretation of these changes on comparison to patients receiving TMZ alone or concurrently with PKC-βi, has not been reported. The purpose of this study was to evaluate and compare anatomic and diffusion imaging parameters at pre-, mid- and post-RT scans in the CEL and non-enhancing lesions of postsurgical, patients with newly diagnosed GBM receiving a) TMZ alone, b) TMZ and PKC-βi, and c) TMZ and VEGF-Ab.

Methods: 100 patients with newly diagnosed grade IV glioma participated in this study. 31 received TMZ alone, 42 received TMZ and PKC-βi, and 27 received TMZ and VEGF-Ab. All patients were imaged prior to the beginning of therapy (post surgical resection, pre-RT), at 1 month (mid-RT), 2 months (post-RT), and every 2 months after initiation of therapy using a 3T GE MR scanner with 8-channel phased array receive coil. Patients who received TMZ alone did not receive a mid-RT scan. **TMZ only Acquisition**: T1-weighted sagittal scout (TR/TE = 54/2 ms), axial T2-weighted fluid attenuated inversion recovery (FLAIR) (TR/TE/TI = 10002/127-157/2200 ms, matrix = 256x256x48, slice thickness = 3 mm), and pre- and post- contrast T1-weighted spoiled gradient echo (SPGR) (TR/TE = 26/2-8 ms, matrix = 256x256x64, slice thickness = 3 mm) images, six-directional axial diffusion echo-planar imaging (EPI) sequences (TR/TE = 5000-10000/63-110 ms, matrix = 128x128 or 256x256, slice thickness = 3-5 mm, 21-40 slices, b = 1000 s/mm^2). **TMZ with PKC-βi** and **TMZ with VEGF-Ab Acquisition**: axial T1-weighted pre- and post-Gd 3D inversion recovery SPGR (IRSPGR) images (TR =8 ms, TE =3 ms, TI =400 ms, slice thickness =1.5 mm, matrix =256 × 256, FOV =241 × 241 mm^2, flip 158°) and axial T2-weighted FLAIR (TR/TE/TI = 9500/122/2375 ms, slice thickness =3 mm, matrix =256 × 256, FOV = 241 ×241 mm^2), six directional diffusion tensor EPI sequence (TR/TE = 7,000/63 ms, matrix size = 256 x 256, slice thickness = 3 mm, b = 1000 s/mm^2, FOV = 220 x 220 mm^2, NEX=4). Images were aligned to the corresponding post-Gd 3D SPGR images. ADC maps were calculated on a pixel-by-pixel basis using software developed in-house and were registered to anatomical imaging by rigidly aligning the T2-weighted (b=0) diffusion image to the T2-weighted FLAIR and applying the transformation to the ADC maps. Anatomical T2-weighted FLAIR images and post-Gd T1-weighted SPGR images were used to define the normal appearing white matter (NAWM), contrast-enhancing lesion (CEL), T2 hyperintense lesion (T2L), and areas of T2L that did not include CEL or cavity (NEL). Differences in imaging parameters for volumes and median values were assessed amongst scans for each cohort using signrank tests and between cohorts at pre-, mid- and post-RT using ranksum tests. For **Figure 1**, anatomic volumes were normalized to the baseline values to highlight the differences in patterns of changes.

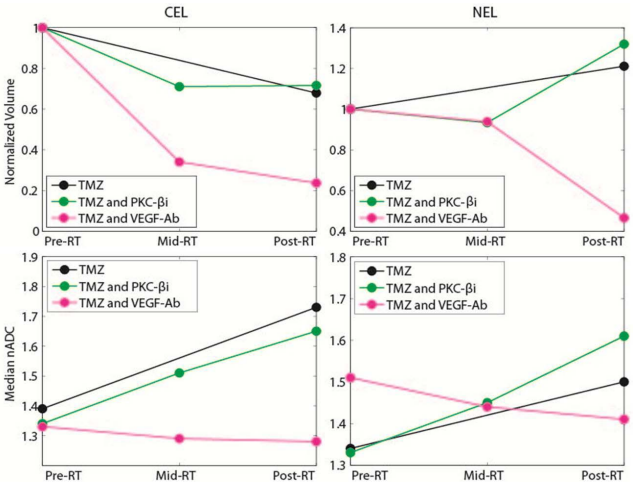

Figure 1. From top left clockwise- plots of CEL median normalized volume, NEL median normalized volume, NEL median nADC, and CEL median nADC at pre-, mid- and post-RT.

Results: Median normalized anatomic volumes and median nADC in CEL and NEL during the course of RT in the three study groups are illustrated in **Figure 1**. **TMZ** - CEL, T2L, and NEL volumes did not change significantly from pre- to post-RT scans but the median ADC in the CEL, T2L, and NEL regions significantly increased from pre- to post-RT scans ($p < 0.0004$, $p < 0.0012$, and $p < 0.0014$). **TMZ and PKC-βi –** the CEL volume decreased significantly from pre- to mid-RT ($p < 0.0013$) but not from mid- to post-RT. The T2L and NEL volumes did not change from pre- to mid-RT but increased from mid- to post-RT ($p < 0.0301$ and $p < 0.0401$). CEL median nADC increased significantly between pre-and mid-RT and mid- and post-RT ($p < 0.0029$ and $p < 0.0001$). The T2L and NEL median nADC increased significantly between mid- and post-RT ($p < 0.0048$ and $p < 0.0058$). **TMZ and VEGF-Ab** – the CEL volume significantly decreased from pre- to mid-RT ($p < 0.0074$) and the T2L and NEL volume significantly decreased from mid-to post-RT ($p < 0.0005$ and $p < 0.0006$), while the CEL, T2L, and NEL median nADC values were stable at all three time points.

Conclusion: Previous studies have suggested that brain tumors responding favorably to RT or chemotherapy show an increase in the ADC values shortly after treatment [3]. In the present study, an increase in ADC values in the CEL, T2L, and NEL was observed in the patients receiving TMZ alone and TMZ with PKC-βi but not in patients receiving TMZ and VEGF-Ab. There were differences in the pattern of changes for T2L and NEL volumes for patient cohorts receiving TMZ alone and TMZ with PKC-βi versus TMZ and VEGF-Ab. For the latter cohort, the decrease in T2L and NEL volume with stable ADC values suggests that the VEGF-Ab is protective against the formation of edema and damage to normal tissue. Overall, the results from this study suggest that imaging biomarkers used to predict response and prognosis to therapy need to be tailored to take into account the specific treatment regimen being considered. Further studies will compare the long term serial effects of TMZ and VEGF-Ab on anatomic and diffusion parameters with those of patients receiving TMZ alone and patients receiving TMZ and PKC-βi to see which biomarkers are predictive of clinical outcomes such as 1-year progression free and overall survival.

References: [1] Stupp et al. N Engl J Med. 2005: 352:987-96. [2] Khayal et al. Neuro Oncol. 2010 Sep;12(9):908-16. [3] Mardor et al. J Clin Oncol. 2003;21:1094–1100. This study was supported by the NIH Grant RO1CA127612 and NIH P01 CA118816.