Persistent Restricted Diffusion Abnormalities in bevacizumab-treated Glioma Patients: Relationship to Outcomesχ

Sandy Mong[1], Ben M Ellingson[2], Timothy F Cloughesy[3], Kim J Hyun[4], Albert Lai[3], Phioanh Leia Nghiemphu[3], Leili Mirsadraei[5], William H Yong[5], and Whitney B Pope[4]

[1]Radiology, UCLA, Los Angeles, CA, United States, [2]UCLA, [3]Neurology, UCLA, [4]Radiology, UCLA, [5]Pathology, UCLA

Figure A.

Figure B.

Figure C.

Figure D.

Introduction:

An emerging treatment for recurrent glioblastoma is bevacizumab, a monoclonal antibody targeted against vascular endothelial growth factor (VEGF), used either alone or in combination with other chemotherapies (1). Because anti-angiogenic treatment decreases permeability of the blood-brain barrier, its therapeutic application reduces the value of contrast enhancement as a radiographic proxy for tumor response (2). Alternative MR imaging techniques such as diffusion weighted imaging are being applied to define both tumor response and non-enhancing tumor progression in the setting of bevacizumab treatment. Apparent diffusion coefficient (ADC) is "restricted" by the presence of cell membranes such as occurs in hypercellular tumor; by high viscosity or protein content such as occurs in abscess (3) and by movement of water from the extraceullar to intracellular space as seen in ischemia (4). Though a spectrum of diffusion imaging findings in glioblastoma has been described (5), the clinical significance of diffusion abnormality in patients treated with bevacizumab is debated.

A small percentage of glioma patients treated with bevacizumab have been noted to have lesions that show persistent restricted diffusion. Possible etiologies that have been proposed include hypercellular and aggressive tumor as well as chronic hypoxia and atypical necrosis (6-8). Our aim is to characterize the evolution of diffusion restriction in these patients, correlate these lesions with advanced imaging findings, and determine the relationship of these lesions with outcomes.

Methods: This retrospective study was granted a waiver of informed consent by the institutional review board. Twenty patients with gliomas grade III-IV treated with bevacizumab developed persistent diffusion-restricted lesions near the original tumor site for at least two months. Additional inclusion criteria applied to this cohort included: age over 18 years old, diagnosis confirmed by histology and imaging; history of surgical resection, evacizumab treatment, temozolomide administration and irradiation; Karnofsky performance score (KPS) equal to or greater than 70 at diagnosis, history of surveillance imaging for at least 2 months, the absence of intracranial hemorrhage, and the absence of clinical findings or observations of acute or subacute ischemia. Change in mean ADC value and change in volume of diffusion-restricted abnormality at each time-point during follow-up was computed. An unpaired Student t-test was used to compare the mean ADC values across tumor grade. The relationships between change in mean ADC over time and change in volume of diffusion-restricted lesion over time to survival outcomes were analyzed using Kaplan Meier analysis with log-rank test and Cox hazard models. Controls matched by sex, age, bevacizumab treatment, tumor grade, and tumor diagnosis were also analyzed. Survival analysis was also performed to compare outcomes including time to progression (TTP), progression free survival (TTS), and overall survival (OS) from initial diagnosis, between the restricted diffusion cases and matched controls.

Results: Of the patients with restricted diffusion lesions, 14 (70%) had glioblastoma, and the rest were grade III gliomas. OF the patients with restricted diffusion that developed after initiation of bevacizumab (75%), lesions occurred at a mean of 232 days after bevacizumab treatment, and persisted for a mean of 404 days from lesion onset. The average of mean ADC values for these lesions was not significantly different across tumor grades (p=0.97; *unpaired T-test*) (Fig. A). Positive change in mean ADC over time trended towards longer TTP and TTS when compared with stable or decreasing temporal changes in mean ADC (p=0.15; *log-rank, p*=0.11; *log-rank,* respectively). Similarly, increasing volume of restricted diffusion over time trended with shorter TTS compared with patients demonstrating stable or decreasing volume, though this did not reach statistically significance *(*p=0.08; *log-rank*). Interestingly, compared to matched controls, patients with diffusion-restricted lesions had significantly greater median TTP (248 versus 159 days, *log-rank,* p=0.01), TTS (596 versus 348 days, *log-rank,* p=0.01) and OS (1676 versus 633 days, *log-rank,* p=0.01) compared to matched controls (TTS shown in Fig. B). For patients with advanced physiologic imaging, regions of diffusion signal abnormality were hypoperfused and showed decreased activity on PET scans (Fig C). Necrosis of the diffusion abnormality was confirmed by surgical resection in one patient (Fig D).

Discussion: Previous studies have attributed atypical diffusion restriction abnormalities to growing tumor, or hypoxia induced by bevacizumab treatment (6.7). In this case series, we have shown that the low ADC signal associated with diffusion restriction abnormalities remains stable over time during bevacizumab treatment, independent of tumor grade. The localized persistently decreased ADC signal across tumor grades suggests that the effect may be potentiated by treatment, sustained by the subsequent changes in vascular remodeling induced by bevacizumab, and is not specifically associated with tumor type. We hypothesized that diffusion restricted lesions reflecting growing and viable tumor would be associated with increasing volume of diffusion restriction in the setting of stable or decreasing ADC, but found no significant correlation of these factors with measures of decreased survival. In fact, our data demonstrated that the presence of diffusion restricted lesions predicted prolonged progression-free survival, time to survival, and overall survival compared to matched controls. Consistent with the idea that these lesions represents pathology other than growing tumor, we have demonstrated that these lesions spatially co-localize with areas of hypoperfusion and decreased radiotracer uptake on advanced imaging studies, and atypical necrosis on selected histologic specimens. These converging lines of evidence support the hypothesis that the development of persistent diffusion-restricted lesions after bevacizumab treatment is associated with treatment effect rather than development of aggressive tumor.

References 1) Friedman, *J Clin Onc, 2009.* 2) Pope, *AJNR,* 2011. 3) Chiang, *Br J Rad* 2009 4) Ni, *Eur J Rad,* 2010. 5) Hakyemez, *Br J Rad,* 2005. 6) Gerstner, *J Clin Onc*, 2009. 7) Rieger, *J Neurooncol,* 2010. 8) Gupta, *AJNR,* 2011.
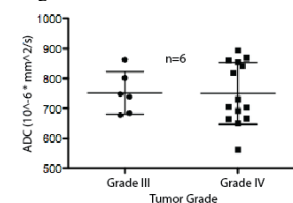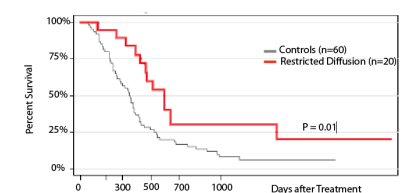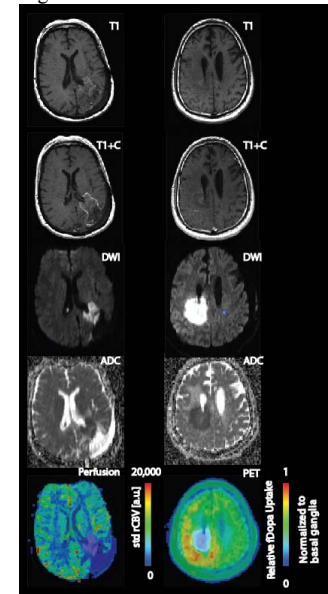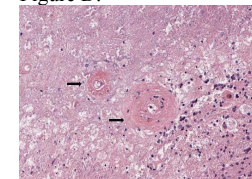
Figures: A). Mean ADC from diffusion-restri... Abnormality Stratified by Tumor Grade ,with ... median ADC and standard deviation shown. ... Kaplan Meier curves comparing time to surv... in cases versus controls. C). Representative l... that is faintly rim-enhancing on T1 with contr... DWI hyperintense, ADC hypointense, and 18-... FluoroDopa PET hyperintense. Another representative lesion that is DWI hyperintens... ADC hypointense, and hypoperfused. D). A Hematoxylin and Eosin-stained biopsy specim... from the region of diffusion restriction demonstrates necrosis and fibrotic vascular changes. Magnification: 200X.