

New Diffusion Restriction Precedes the Development of Enhancing Tumor in Glioblastomas

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Introduction:

The prognosis of the glioblastomas (GBMs), the most malignant brain tumors, remains poor. Assessment of glioma progression vs. stability or response has traditionally relied on typical MR imaging characteristics, such as changes in tumor size and extent of contrast enhancement. Finding earlier imaging biomarkers of glioma progression can have an enormous impact on clinical treatment decision-making. Restricted diffusion at presentation has been correlated with increased glioma cellularity and increased glioma grade (1, 3, 4). The significance of restricted diffusion occurring during treatment, however, is unknown. We hypothesize that new restricted diffusion can predict the future development of new enhancing tumor.

Materials and Methods:

We retrospectively identified 122 consecutive patients with pathologically proven GBM. Patients were imaged on a 1.5 T magnet (Signa HDx and Excite, GE Medical Systems, Milwaukee, WI) using a standard quadrature head coil. Standard doses of 0.1 mmol/kg gadodiamide (Winthrop Labs, Rensselaer, NY) were used for contrast images. All studies included diffusion weighted imaging (DWI) using single shot echo planar images (high b-value images at 1000 mm²/s and low b-value images at 0 mm²/s). Apparent diffusion coefficient (ADC) maps were calculated. All patients with restricted diffusion related to the tumor were identified, with further analysis only performed on those patients with restricted diffusion extending beyond the margins of the enhancing lesion (without corresponding enhancement or hemorrhage). In these patients, ADC value measurements were obtained using region-of-interest (ROI) analysis (GE Functools, AW workstation, GE Medical Systems, Milwaukee, WI). The region of interest (approximately 0.5 cm² or 15 pixels) was placed in the same focal anatomic region on: 1) all available MRIs before the development of restricted diffusion, and 2) on all available subsequent MRIs after the development of restricted diffusion. The cases were followed to determine if new enhancing lesions developed in the same regions of new restricted diffusion. A chart review was performed to classify the patients as having progressive disease, partial response, stable disease or complete response, according to a standard clinical classification scheme (2). The means of the ADC values obtained before and after the development of restricted diffusion were compared using a Wilcoxon Signed Rank Test. A *p*-value of less than .05 was considered statistically significant. A time-to-event (enhancement) curve with a 95% confidence interval was constructed using the Kaplan-Meier method.

Results:

A total of 54 of the 122 patients (44%) displayed restricted diffusion (low ADC) related to the tumor at some point during treatment. In these patients, direct comparisons were made between the ADC maps and contrast T1-weighted images to determine the congruence of the diffusion and enhancing abnormalities. Patients with regions of diffusion restriction equal to or smaller than the regions of abnormal enhancement or in the presence of blood products (n=38) were excluded from further analysis. The remaining 16 patients (16/122=13.1%) displayed at least one study with restricted diffusion that extended beyond the margins of the enhancing lesion. All 16 patients developed clinical evidence of progressive disease at or soon after the scan that showed the focus of restricted diffusion. Nine of the 16 patients had studies before the development of restricted diffusion; these 9 patients showed a 26% decrease in ADC values from baseline (*p*=0.0078) as shown in **Table 1**. Thirteen of the 16 patients developed a new enhancing lesion at the site of the diffusion abnormality with a mean time of 4.1 months (range, 1.2-9.4 months). A representative case is illustrated in **Fig 1**. Of the other 3 patients, 2 have not developed new congruent enhancing lesions after 0.8 and 3.9 months of follow up, while the last patient showed new restricted diffusion in the left corona radiata that resolved on follow up at 4.2 months after beginning chemoradiation therapy. In 15 of 16 patients, the ADC abnormality extended along major white matter tracts from the enhancing tumor. In the 8 patients that received radiation therapy before the development of ADC abnormality, 5 patients had FDG-PET/CT imaging or dynamic susceptibility contrast perfusion MR imaging that did not show evidence of radiation necrosis to explain the new enhancing lesions. A Kaplan-Meier time-to-event (enhancement) curve combining all 16 patients regardless of treatment type is shown in **Fig 2**. For an area of restricted diffusion without abnormal enhancement, there is an 80% chance of being enhancement-free (95% confidence interval of 0.62 and 1) at 3 months. A large drop in enhancement-free survival is seen between 3-5 months, at which time a greater than 80% chance of enhancement occurs.

Table 1. Changes in ADC.

	Baseline	Event
ADC (x 10 ⁻⁵ mm ² /sec)	111	82

(*p*=0.0078)

Fig 2. Kaplan-Meier curve showing the time from a region of restricted diffusion to a new enhancing lesion, with the most rapid changes occurring at 3-5 months.

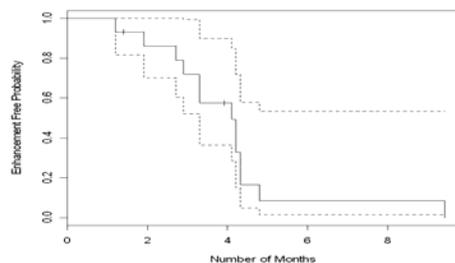
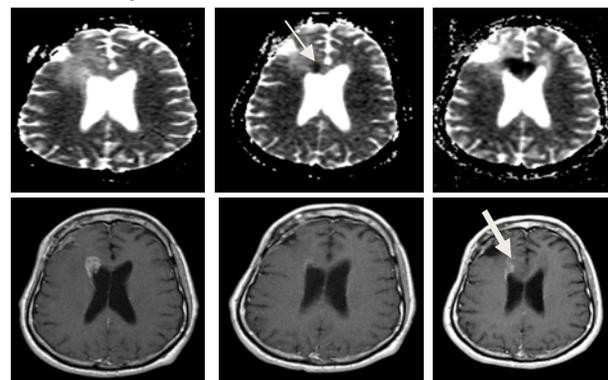


Fig 1. DWI (top row) and contrast T1 images (bottom row) in a single patient at 7, 9 and 12 months after presentation, showing a new region of restricted diffusion in the splenium of the corpus callosum (thin arrow) that precedes a new enhancing mass lesion (thick arrow).



Discussion: This study demonstrates that in a subset of patients with GBM, development of a new focus of restricted diffusion during treatment can predict the progression of new tumor enhancement. New enhancement represented tumor progression in at least 13/16 cases: half of the patients never received radiation therapy and those that did had advanced imaging which was consistent with tumor rather than radiation necrosis in 5/8 patients. Although the mechanisms underlying diffusion restriction in gliomas are not entirely understood, the proliferating tumor cells may result in increased cellularity and decreased free extracellular space, thereby reducing the diffusivity of water protons and causing a decrease in the ADC values. In conclusion, our results suggest that in this subset of patients with GBM, new nonenhancing regions of restricted diffusion can predict the future development of enhancing tumor and tumor progression.

References: 1. Guo et al. Radiology 2002; 224:177-183. 2. Levin et al. Clin Cancer Res 2003; 9:981-990. 3. Higano et al. Radiology 2006; 241:839-846. 4. Alvarez-Linera J et al. J Neuroimaging 2008. 5. Moffat et al. PNAS 2005.