Functional diffusion maps applied to FLAIR abnormal areas are valuable for the clinical monitoring of recurrent brain tumors

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Introduction

Diffusion-weighted magnetic resonance imaging (DWI) is a sensitive biomarker for tumor cellularity and response to cytotoxic treatment [1]. The recent development of functional diffusion maps (fDMs) exploits this sensitivity by examining voxel-by-voxel changes in the apparent diffusion coefficient (ADC) over time [2,3]. Currently, fDMs are only applied to contrast-enhanced regions on T1-weighted images, which represent regions of blood-brain barrier (BBB) breakdown and not necessarily the boundary of malignant tumor. In addition, the use of anti-angiogenic drugs, along with corticosteroids, decreases BBB permeability and significantly decreases the volume of contrast-enhancement. Therefore, the utility of fDMs as biomarkers for early tumor invasion and monitoring tumor progression in glioma patients exhibiting little or no enhancing lesions is of significant clinical interest. Fluid-attenuated inversion recovery (FLAIR) MRI is sensitive to vasogenic edema and infiltrating tumor cells, thus it remains the best sequence for visualizing malignant tumor extent [4]. In the current study we demonstrate the utility of performing fDM analysis in regions with abnormal FLAIR signal.
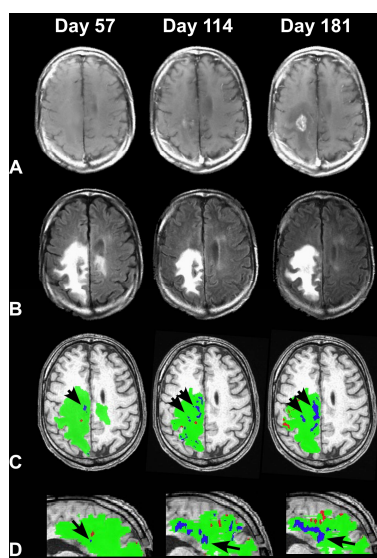
Methods

Twenty patients with recurrent intracranial tumors, who underwent at least 4 scan sessions, with total observation periods ranging from 168 to 624 days, were enrolled in the current study. Clinical MRI consisted of SPGR, FLAIR, along with pre- and post-contrast T1-weighted MRI scans. Functional diffusion maps (fDMs) were calculated by first registering sequential apparent diffusion coefficient (ADC) maps, using a mutual information algorithm and a 9-degree of freedom transformation, and then applied to regions of FLAIR abnormality (including the enhancing tumor) with ADC thresholds of 0.55×10^{-3} mm^2/s, as per the recommended fDM protocol [2,3]. Voxels were stratified as not changing (green), increasing ADC (red), or decreasing ADC (blue) according to this threshold. Voxels with decreasing ADC have been shown to correlate with an increase in cellularity; thus, the volume of hypercellularity (blue voxels) in FLAIR abnormal regions was used to track the tumor status and for comparison to neurological impairment using the Karnofsky Performance Status (KPS). Subjects were classified as progressive, stable, or responsive based on radiographic evidence (MacDonald Criteria) and neurological reports retrospectively prepared by board certified radiologists and neurologists.
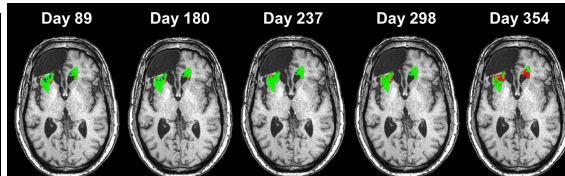
Results

Functional Diffusion Maps in Progressive Disease. The utility of fDMs for spatial localization and quantitative tracking of brain tumor progression is demonstrated in two representative patients in *Fig. 1* and *3A*, respectively. The patient in *Fig.1* had no contrast-enhancement and appeared clinically stable until 114 days after the baseline DWI scans. During the time to recurrence, fDMs showed a small grouping of hypercellular voxels within the FLAIR abnormal regions as early as day 57, or 124 days before radiographic recurrence. Similarly, *Fig. 3A* illustrates a temporal plot of hypercellular volume contrasted with KPS scores for a single patient who had a largely non-enhancing lesion. A high volume of hypercellularity was noted at day 242, or 78 days before recurrence, which continued to increase during progression. Approximately 7 of the 20 patients showed early changes in hypercellularity, ranging 55 to 120 days prior to recurrence, with an average rate of change of hypercellularity of 52 μL/day indicating this early recurrence.

Functional Diffusion Maps in Responsive Disease. fDMs applied to FLAIR abnormal regions can also provide early cues regarding successful therapy. The examples in *Fig. 2* and *3C* demonstrate the ability for fDMs to monitor successful response to chemotherapeutics and concurrent radiation therapy. *Fig. 2* demonstrates a decrease in the volume of hypercellularity, which is eventually replaced by hypocellular volumes (red voxels). This is consistent with previous findings applied to contrast-enhanced regions exclusively [2,3]. Similarly, *Fig. 3C* illustrates a temporal plot of hypercellular volume contrasted with KPS scores for the same patient. Similar patterns of decreasing hypercellularity were observed in 3 of the 20 "responding" patients; however, 2 of the 20 cases suggested a decrease in hypercellular volume with no change in KPS, which may be reflecting deficits from either treatment or surgery.

Figure 1: Representative images from a patient showing growth of hypercellular regions before recurrence. A) Post-contrast T1-weighted images. B) FLAIR T2-weighted images. C) axial fDMs D) fDMs in the sagittal plane showing growth of hypercellular tumor.

Figure 2: fDMs for a representative patient showing a positive treatment response. Regions of hypercellularity (blue) at day 89 show continual decreases in volume during observation and appear to be replaced by regions of hypocellularity (red). This is consistent with cytotoxic changes that occur during standard chemotherapy and radiation treatment.

Figure 3: Temporal change in hypercellular volume (solid line) and Karnofsky Performance Status (KPS; dashed line) for A) progressing, B) stable, or C) responding brain tumors. The solid black arrow in A) indicates a significant increase in hypercellular volume prior to changes in neurological status (blue arrow heads).
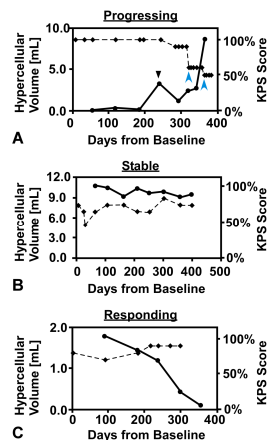
Discussion

Functional diffusion maps applied to FLAIR abnormal regions provides additional insight into the growth and treatment response of high-grade brain tumors. Trends in hypercellular volume, measured using the fDM technique, appear to follow trends in neurological and radiological status, although in some cases hypercellular volume changes preceded changes in neurological changes by as much as 120 days. The minimum cluster size necessary before tumor recurrence is detected, however, is still an area of active discussion. This study further supports the use of fDMs as an early imaging biomarker and expands its use to clinical monitoring of individual patients, with a focus on changes with FLAIR abnormalities. This demonstrates that it is a technique that can be useful independent of whether or not the primary tumor mass is enhancing or nonenhancing.

References

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