Functional diffusion maps (fDMs) applied to FLAIR abnormal regions can detect pseudoprogression from recurrent tumor in malignant glioma

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Introduction

Standard treatment for malignant gliomas consists of concurrent radiation therapy and chemotherapy[1], both of which can be considered cytotoxic in their therapeutic mechanism. Patients with malignant gliomas undergoing cytotoxic therapy have been shown to have an increase in the size of lesions containing contrast-enhancement on T1-weighted MR images due to radiation necrosis[2,3]; however, growing or progressing gliomas also are trademarked by an increase in size of contrast-enhancing lesions. This phenomenon, known as pseudoprogression, is of significant clinical interest because routine anatomical MRI techniques cannot reliably distinguish these two mechanisms of contrast enhancement during, and following, cytotoxic therapy. Alternatively, multiple studies have demonstrated that diffusion-weighted MRI (DWI) can be used to distinguish treatment effects from recurrent tumor[5-7], where a higher than average apparent diffusion coefficient (ADC) occurs within the contrast-enhancing lesions in patients with confirmed radiation necrosis and a lower than average ADC occurs within lesions containing recurrent tumor. The functional diffusion map (fDM) is a technique that involves co-registering serial DWIs from the same patient to a pre-treatment, baseline DWI scan, then examining voxel-wise changes in ADC over time[8-10]. Because measurements of ADC are sensitive to tumor cell density[11,12], fDMs can be used to spatially identify regions of increasing ADC, indicative of a decreasing cellularity, and regions of decreasing ADC, suggesting increasing tumor cell density, with a higher sensitivity and specificity than DWI alone[13]. Currently, the traditional fDM technique relies on a single threshold for stratifying voxels as having increasing or decreasing ADC relative to the baseline at a single time point within the contrast-enhancing regions exclusively, and has shown sensitivity for detecting early response to cytotoxic treatment. We hypothesize that the fDM technique, applied to FLAIR signal abnormalities and combined with the volume kinetics of the fDM-labeled regions, will be more useful for distinguishing treatment effects (pseudoprogression) from recurrent tumor than the traditional fDM technique.

Methods

A total of 30 patients with malignant gliomas were enrolled in this study approved by the Institutional Review Board at our Institution. All patients were treated with standard radiotherapy followed by adjuvant temozolomide (100-150 mg/m^2/day over 5 days per 28 day cycle, for a maximum of 12 cycles). Clinical MRI scans included 3D-SPGR anatomical, pre- and post-contrast T1-weighted, and FLAIR sequences on a 1.5-T MR scanner (GE Medical Systems, Waukesha, WI). ADC was calculated from diffusion weighted images acquired with b=0 and b=1,000 s/mm^2, using all gradients applied equally (isotropic). All images for each patient were registered to their own pre-treatment baseline SPGR anatomical images using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK). After registration, voxelwise subtraction was performed between ADC maps acquired at subsequent time points and the baseline ADC maps to create ΔADC images. Individual voxels were stratified into three categories used to quantify the degree of hyper-/hypocellularity: voxels where ADC increased beyond a ΔADC threshold of 0.4 um^2/ms ("hypocellular", red), and voxels where ADC decreased beyond the same threshold ("hypercellularity", blue). This particular thresholds was chosen based on the 95% confidence intervals for a mixture of normal-appearing white and gray matter (0.4 um^2/ms) in 69 patients evaluated from 1 week to 1 year post-baseline[14]. Kinetic profiles were constructed based on the physical volume of voxels demonstrating a change in ADC beyond 0.4 um^2/ms with respect to baseline.[15] Progressive disease was defined as a combination of confirmed neurological decline and radiographic progression as noted by board certified neuro-oncologists and radiologists, respectively.

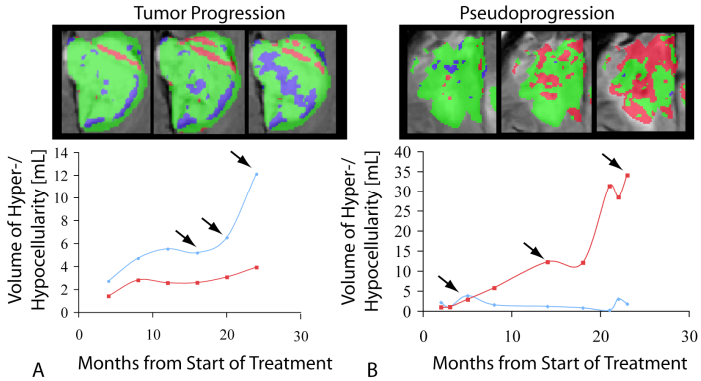

Fig. 1: fDMs and kinetic profiles for representative patients having A) tumor progression and B) pseudoprogression (treatment-changes).

Results

In general, patients with recurrent tumor demonstrated an increase in the volume of hypercellularity (blue regions), regardless of the change in hypocellualarity (Fig. 1A). Alternatively, patients with treatment-induced changes (pseudoprogression) demonstrated a steady increase in the volume of hypocellularity (red regions) within FLAIR abnormal regions with no substantial increase in the volume of hypercellularity (Fig.1B). All patients that demonstrated confirmed tumor progression within the first six months (n = *11*) illustrated at least two successive increases in the volume of hypercellularity on kinetic profiles (Fig.2A). Using "two successive increases in hypercellular volume immediately after treatment" as a criterion for distinguishing responders from non-responders to cytotoxic therapy, graded fDMs more effectively predicted time-to-progression (TTP) compared with standard prognostic factors such as tumor grade (Fig. 2B-C).

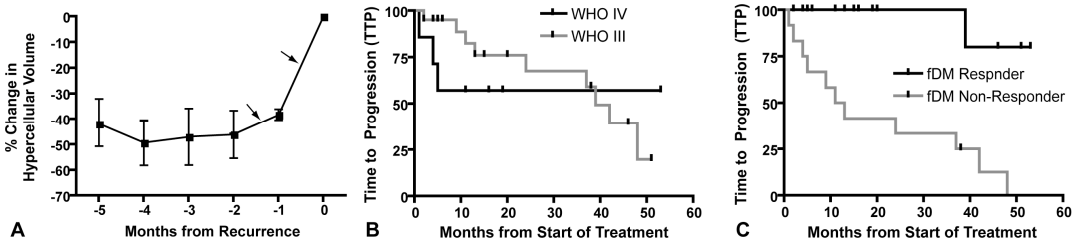

Fig. 2: A) Patients exhibiting tumor progression (n = 11 of 30 patients) demonstrated at least two sequential increases in the volume of hypercellularity (low ADC) prior to recurrence. B) Time-to-progression (TTP) based on tumor grade (WHO III – Anaplastic Astrocytoma; WHO IV – Glioblastoma Multiforme). C) TTP was significantly shorter for patients exhibiting two sequential increases in the volume of hypercellularity in the first months after treatment (Log-Rank, P = 0.0002).

Discussion

Results from the current study support the use of the fDM technique, applied to regions of FLAIR signal abnormality and combined with the kinetic profiles of hyper- and hypocellular volume, as a useful tool for long-term patient monitoring and distinguishing pseudoprogression (fDM responders) from recurrent tumor (fDM non-responders). Results also suggest fDMs applied to regions of FLAIR abnormality are better predictors of TTP than the traditional fDM technique applied to regions of contrast-enhancement, exclusively.

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