Graded functional diffusion maps (fDMs) applied to the whole brain: A sensitive imaging biomarker for monitoring brain tumor growth and invasion

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Introduction

Diffusion-weighted MRI (DWI) measures of apparent diffusion coefficient (ADC) is believed to reflect the level of tumor cell density in malignant gliomas, where an increase in ADC is thought to reflect necrosis or a decrease in cell density as a result of successful chemotherapy or radiotherapy[2,7], and a decrease in ADC is believed to reflect an increase in tumor cell density during tumor cell proliferation[1-6]. By examining voxel-wise changes in ADC over time with respect to a baseline ADC map, functional diffusion maps (fDMs) have demonstrated the ability to detect the early effects of chemotherapy, radiotherapy, and anti-angiogenic treatment[8-13]. Currently, the traditional fDM technique relies on a *single* threshold for stratifying voxels as having increasing or decreasing ADC relative to the baseline, and is typically examined only in contrast-enhancing regions at a single time-point[8-11]. Because the particular threshold used for voxel classification dictates the sensitivity and specificity to changes in tumor cell density, we hypothesize that a *graded* fDM technique that stratifies voxels into varying degrees of change, applied to the *whole brain* (compared to in regions of contrast-enhancement or FLAIR signal abnormality) may be useful for visualizing invading and proliferating tumor with both high sensitivity and high specificity.

Methods

To date, a total of 120 patients with gliomas have been enrolled in this study approved by the Institutional Review Board at our Institution. 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 six categories used to quantify the degree of hyper-/hypocellularity: voxels where ADC increased beyond a ΔADC threshold of 0.25 um^2/ms, 0.4 um^2/ms, or 0.75 um^2/ms ("hypocellular", shades of red/yellow), and voxels where ADC decreased beyond the same thresholds ("hypercellularity", shades of blue). These particular thresholds were chosen based on the 95% confidence intervals for normal-appearing white matter (0.25 um^2/ms), a mixture of normal appearing white and gray matter (0.4 um^2/ms), and a mixture of normal-appearing white matter, gray matter, and cerebrospinal fluid (0.75 um^2/ms) in 69 patients evaluated from 1 week to 1 year post-baseline[14]. After voxel stratification, regions of obvious misregistration artifact around the ventricles and gyri/sulci were eliminated manually from whole brain graded fDMs.

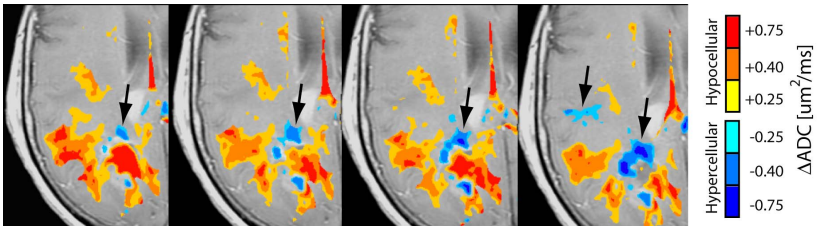

Fig. 1: Graded fDMs in a patient with progressing tumor. Arrows show regions of hypercellularity (decreasing ADC). Scans are 6 weeks apart.

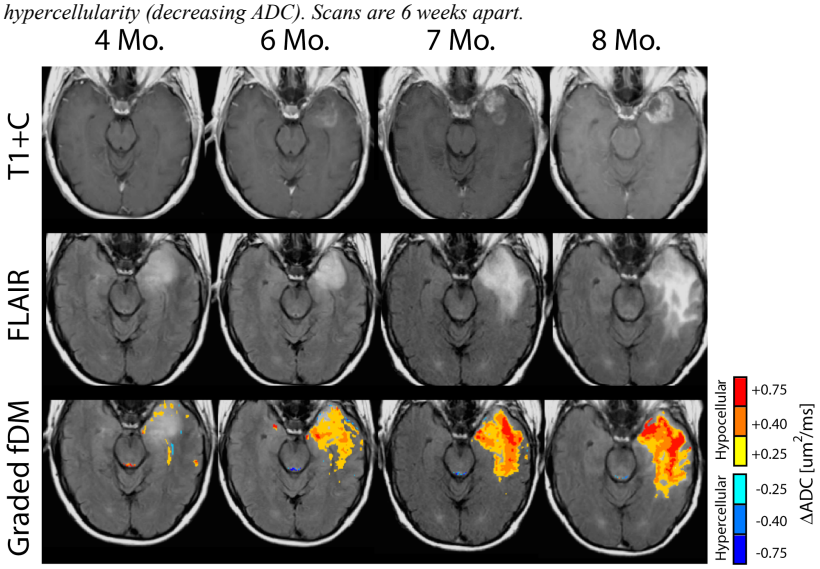

Fig. 2: Patient showing increase in volume of contrast-enhancement and FLAIR signal abnormality following radiotherapy. Graded fDMs suggest pseudoprogression (treatment effects) as illustrated by the increase in hypocellularity within suspected region. T1+C = Post-contrast T1-weighted MRI; FLAIR = Fluid-attenuated inversion recovery.

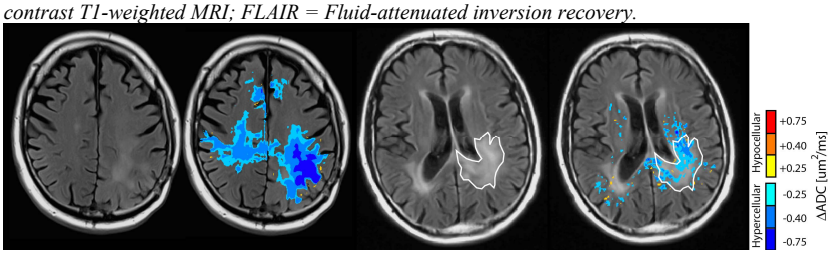

Fig. 3: Graded fDMs applied to the whole brain aids in visualization of tumor invasion beyond FLAIR signal abnormality, as demonstrated in two patients. Left: FLAIR images in a patient with recurrent GBM. Second from Left: Graded fDM shows invading tumor. Second from Right: FLAIR image in an anaplastic astrocytoma patient. Right: Graded fDMs.

Results

During tumor progression (*Fig.1*), regions of hypercellularity (decreasing ADC) grew in both volume and the degree of hypercellularity (shades of blue). Alternatively, patients with pseudoprogression (*Fig.2*) exhibited an increase in both the volume and degree of hypocellularity (shades of red/yellow). In many cases, regions containing suspected hypercellular tumor extended beyond FLAIR abnormal regions (*Fig.3*), suggesting graded fDMs may detect invading tumor beyond the traditional malignant tumor boundary (T2-hyperintensity).

Discussion

Results from the current study support the use of a graded fDM technique in visualizing both the degree and extent of hyper-/hypocellular changes within the tumor following treatment. Further, the graded fDM technique applied to the whole brain may be useful for visualizing invading tumor.

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