Graded functional diffusion maps (fDMs) predict survival in recurrent glioblastoma treated with bevacizumab

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Introduction

The functional diffusion map (fDM) was developed in order to examine localized ADC changes by calculating voxel-wise changes in ADC (ΔADC) measured in the same patient over time [1-5]. This technique has demonstrated utility in predicting the effect of cytotoxic chemotherapy and radiotherapy within the contrast-enhancing tumor bed[1-4] as well as within regions of abnormal fluid-attenuated inversion recovery (FLAIR) signal[5-7]. Additionally, this method has shown early promise in the evaluation of anti-angiogenic therapies[5,6]. In the current study, we use a modified fDM technique proposed by Ellingson *et al*. [6] that uses graded thresholds which are believed to reflect differing degrees of cell density change. These graded fDMs computed from pre- and post-treatment ADC maps were evaluated for their ability to serve as early predictors of bevacizumab treatment response in patients with GBM.

In contrast to the "traditional" fDM approach, the graded fDM technique allows quantification and tracking of the volume of hyper-/hypocellularity *between* different ΔADC thresholds. We hypothesize this approach will allow for isolation of specific tissue subtypes that experience only a narrow range in ΔADC. In the context of the current study, empirical evidence has shown that bevacizumab significantly reduces vasogenic edema; therefore, we hypothesized that regions of the brain containing either solid or infiltrating tumor plus edema are likely to exhibit less of a decrease in ADC following bevacizumab treatment compared to regions containing a larger proportion of edema (*Fig. 1*). By using graded fDMs, these more subtle differences in ADC can be visualized and quantified. We hypothesized the tissue subtype defined by graded fDMs that isolates only a subtle decrease in ADC would be larger in patients having a more extensive pre-treatment tumor burden.

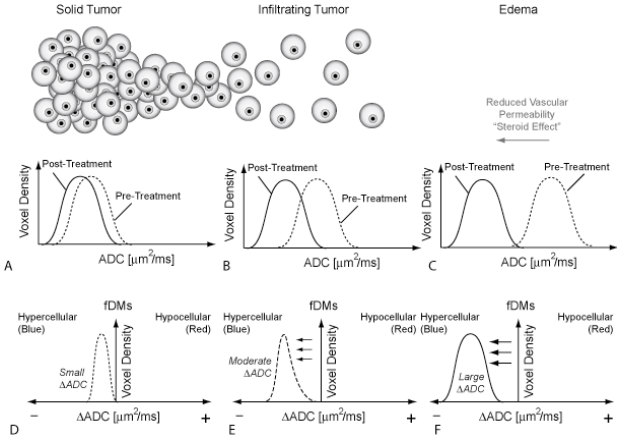

Fig.1: *fDM Hypothesis in Anti-Angiogenic Therapy. In regions of solid tumor, the change in ADC is expected to be small compared with regions of edema and infiltrating tumor. Using graded fDMs, regions of solid tumor can then be isolated by using a narrow range of ΔADC.*

Methods

All patients participating in this study signed institutional review board-approved informed consent. A total of n = 85 patients with high quality diffusion-weighted images before and after initiation of bevacizumab treatment were retrospectively examined from our Neuro-Oncology database. Baseline scans were obtained approximately 1 week pre-treatment. Follow-up scans were obtained at approximately 4-6 week intervals. 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 the 1.0mm isotropic MNI Atlas using a mutual information algorithm and a 12-degree of freedom transformation. 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 based on the change in ADC relative to the baseline ADC map (+/- 0.25 um^2/ms, +/- 0.40 um^2/ms, +/- 0.75 um^2/ms).

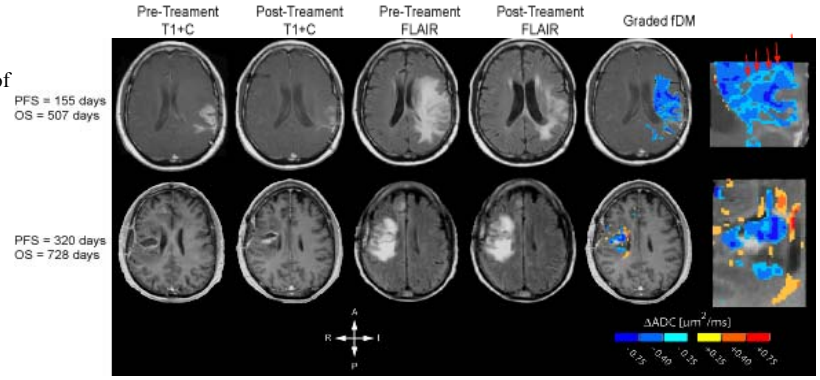

Fig.2: *Pre- and post-treatment contrast-enhanced T1w and FLAIR images along with graded fDM for two patients. Regions of light blue represent regions of suspected tumor burden having 0.25 um^2/ms < ΔADC < 0.40 um^2/ms.*

Results

In general, patients exhibiting a higher volume of hypercellularity appeared to have a shorter period of PFS and OS. When applying a threshold of 0.40 μm^2/ms, which is recommended for the best balance of sensitivity and specificity[6], we observed a significant difference in PFS, but not OS, in patients on having a volume of hypercellularity higher or lower than 40cc (*Fig. 3A,B*; PFS:*Log-rank, P=0.0134*; OS:*Log-rank, P=0.0541*). Results suggest patients having a volume of tissue exhibiting a decrease in ADC between 0.25 and 0.4 μm^2/ms more than 20cc were more likely to progress and expire earlier than patients having a lower volume (*Fig. 3C,D*; PFS: *Log-rank, P=0.0033*; OS:*Log-rank, P=0.0118*). These results suggest the physical volume of tissue exhibiting a decrease in ADC between 0.25 and 0.4 μm^2/ms is a sensitive and early biomarker for PFS as well as OS in patients treated with bevacizumab.

Discussion

Significant reduction in vascular permeability, or a "steroid effect", is commonly observed following administration of anti-angiogenic therapies [8,9]. This reduction in vascular permeability results in a decrease in ADC within areas containing edema. In regions containing solid tumor before administration of anti-angiogenic drugs, however, the change in ADC due to changes in vascular permeability are likely much smaller[10]. Consistent with this hypothesis (*Fig. 1*), we found that patients having a high volume of hypercellularity exhibiting a decrease in ADC between 0.25 μm^2/ms and 0.40 μm^2/ms immediately after treatment had a significantly shorter period of progression-free and overall survival compared with patients having a lower volume.

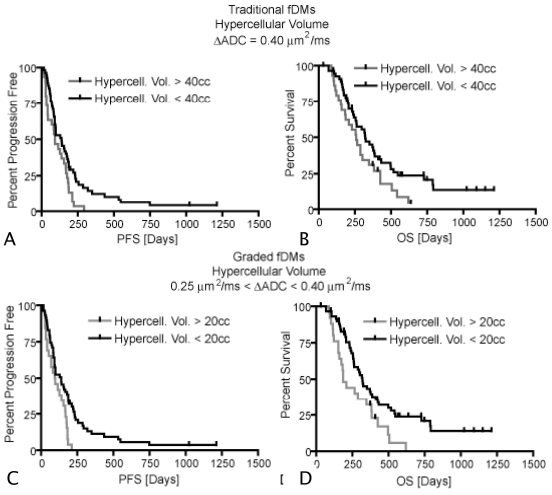

Fig.3: *A) PFS and B) OS for traditional (ΔADC=0.4 um^2/ms) fDM-classified hypercellular volumes >40cc and <40cc. C) PFS and D) OS for graded fDM (0.25<ΔADC<0.4um^2/ms) volumes >20cc and <20cc.*

References [1]Moffat, *Proc Nat Acad Sci*, 2005. [2]Moffat, *Neoplasia*, 2006. [3]Hamstra, *Proc Nat Acad Sci*, 2005. [4]Hamstra, *JCO*, 2008. [5]Ellingson, *J Neurooncl*, 2010. [6]Ellingson, *Proc Intl Soc Mag Reson Med*, 2009-2010. [7]Ellingson, *JMRI*, 2010. [8]Iwamoto, *Neurology*, 2009. [9]Nghiemphu, *Neurology,* 2009. [10]Pope, *Radiology*, 2009.