Correlations between Functional Diffusion Maps and Anti-angiogenic Treatment Response in Glioblastoma

W-T. Zhang[1], P-J. Chen[1,2], M. Zhu[1], E. di Tomaso[3], D. G. Duda[3], R. K. Jain[3], T. T. Batchelor[4], and A. G. Sorensen[1]

[1]Radiology, Massachusetts General Hospital, Boston, MA, United States, [2]Nuclear Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States, [3]Radiation Oncology, Massachusetts General Hospital, Boston, MA, United States, [4]Neurology, Massachusetts General Hospital, Boston, MA, United States

Introduction: Differences in water diffusion values in lesions early after treatment can be calculated as functional diffusion maps (fDM). It has been suggested that fDM may be helpful to identify tumor responsiveness [1] to radio- and/or chemo- therapies as early as 3 weeks after initiation of therapy, and that fDM status is correlated with time to progression [2]. We sought to investigate whether fDM is correlated with treatment response to an anti-angiogenic agent, AZD2171, a pan-VGEF receptor tyrosine kinase inhibitor, as part of a phase-II clinical trial (AstraZeneca; ClinicalTrials.gov identifier: NCT00254943).

Patients and methods: Twenty-three patients (mean age 53.7, range 20-77 years) with recurrent glioblastoma multiforme (GBM) underwent two consecutive MRI with Auto-Align technique [3] in the same 3T MRI scanner (TimTrio, Siemens Medical Solutions, Malvern, PA) one day before and 26-28 days after the initiation of AZD2171 treatment (45 mg daily by mouth). Sixty slices of twice-refocused echo-planar diffusion-weighted images were acquired with TR 7500 ms, TE 84 ms and a b-value of 700 s/mm2 in 42 directions as well as 7 low b value images to allow reconstruction of the diffusion tensor at each voxel. Resolution was 2 mm isotropic, with a 128x128 matrix. Standard T2-TSE, FLAIR, pre- and post-contrast T1 images were also acquired at each visit. Apparent diffusion coefficient (ADC) maps were created from the low and high b value images using custom-written software implementing the standard algorithm. The post-treatment ADC maps were co-registered to day-1 and functional diffusion maps were created similarly as described in [1]. The percentage of voxels in tumor lesion was calculated as Vd for the total of voxels with decreased ADC values and Vi for increased ADC. Vt equals to the sum of Vd and Vi. Tumor lesions of both visits were manually outlined on the post-contrast T1 images by a blinded neuroradiologist and the total volume of contrast-enhanced voxels were calculated. Radiographic response at 4 weeks was determined as (1) partial response (PR) if the tumor volume decreased by at least 50%, (2) stable disease (SD) if the tumor volume changed within the range of -50% to +25%, and (3) progressed disease (PD) if the tumor volume increased by at least 25%. Linear regression was performed between the % change of tumor volumes and Vd, Vi, and Vt, respectively.

Results and discussion: Using only the 4 week MRI to grade response, 8 out of 23 patients responded to AZD2171 as PR, 13/23 patients as SD, and 2/23 patients as PD. **Fig. 1** shows three examples of fDM overlaid on post-contrast T1 images, each representing patients of PR, SD, and PD. As there are only two patients with PD, no significant difference in Vd, Vi, and Vt was found between three groups of patients. However, Vt significantly correlated with the % change of tumor volumes (**Fig. 2A**, r^2=0.1932, p=0.0358), i.e., the greater the change in ADC values from baseline to followup, the better response to the treatment. This is consistent with previous reports [1,2], but extends these earlier reports by applying fDM in the setting of anti-angiogenic therapy for the first time. There was a trend of correlation between Vi and % change of tumor volumes (**Fig. 2B**, r^2=0.1274, p=0.0945). The follow-up showed that 18 out of 23 patients have progressed. There was a weak correlation between Vi and time to progression (TTP) (**Fig. 2C**, r^2=0.1954, p=0.0663). The higher percentage of voxels with increased ADC, the longer the TTP. There was no correlation between Vd and the % change of tumor volumes, and between Vd or Vt and TTP.

Conclusions: Early changes of diffusion ADC maps were correlated with anti-angiogenic treatment response and time to progression. With further validation, fDM may find use as a prognostic biomarker for glioblastoma.

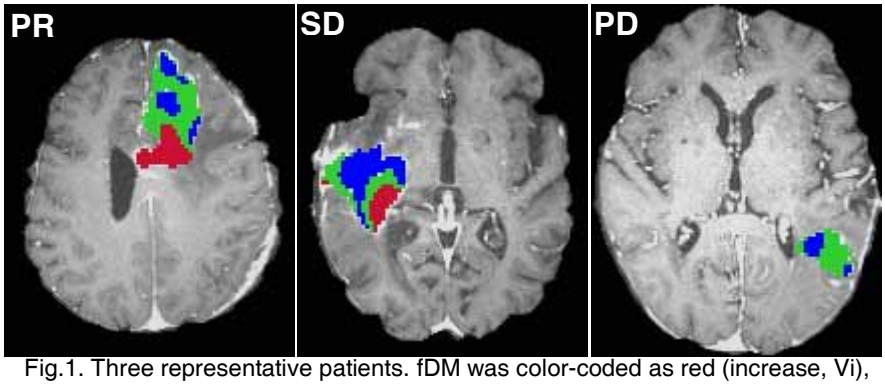

Fig.1. Three representative patients. fDM was color-coded as red (increase, Vi), blue (decrease, Vd), and green (unchanged).

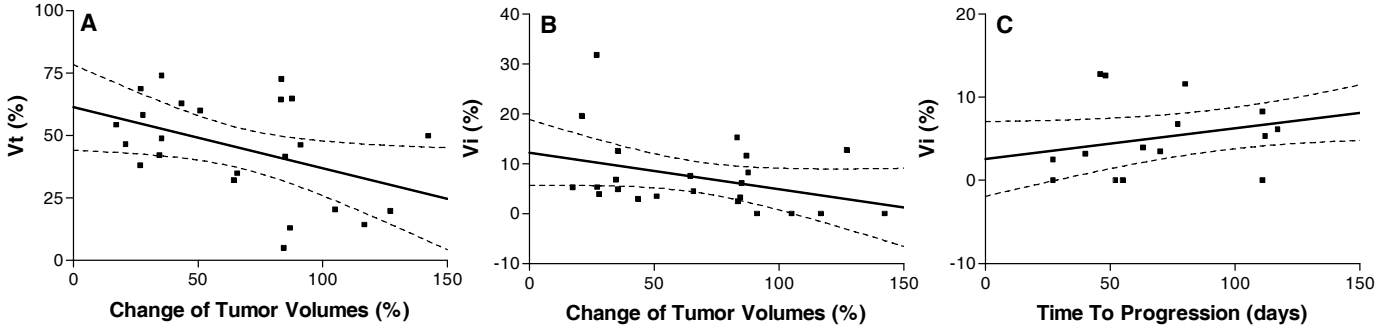

Fig. 2. Linear regression graphs showing the correlation between fDM and treatment effect by AZD2171. Vi: the percentage of voxels with increased ADC; Vt: the percentage of voxels with either increased or decreased ADC from day-1 to day28.

References:

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