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# Functional diffusion maps (fDMs) evaluated before and after radiochemotherapy predict progression-free and overall survival in newly diagnosed glioblastoma

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Functional diffusion mapping (fDM) has shown promise as a sensitive imaging biomarker for predicting survival in initial studies consisting of a small number of patients, mixed tumor grades, and before routine use of anti-angiogenic therapy. The current study tested whether fDM performed before and after radiochemotherapy could predict progression-free and overall survival in 143 patients with newly diagnosed glioblastoma from 2007 through 2010, many treated with anti-angiogenic therapy after recurrence. Diffusion and conventional MRI scans were obtained before and 4 weeks after completion of radiotherapy and concurrent temozolomide treatment. fDM was created by coregistering pre- and posttreatment apparent diffusion coefficient (ADC) maps and then performing voxel-wise subtraction. fDMs were categorized according to the degree of change in ADC in pre- and posttreatment fluid-attenuated inversion recovery (FLAIR) and contrast-enhancing regions. The volume fraction of fDM-classified increasing ADC(1), decreasing ADC(2), and change in ADC(1/2) were tested to determine whether they were predictive of survival. Both Bonferroni-corrected univariate log-rank analysis and Cox proportional hazards modeling demonstrated that patients with decreasing

with a lower volume fraction. The current study supports the hypothesis that fDM is a sensitive imaging biomarker for predicting survival in glioblastoma.

Keywords: biomarker, fDMs, functional diffusion maps, glioblastoma, MRI.

**M**alignant gliomas are the second leading cause of cancer-associated mortality among persons > 35 years of age, the fourth leading cause among persons < 54 years of age, and kill ~13 000 persons per year.<sup>1</sup> Glioblastoma is the most malignant type of glioma and has a very poor prognosis, having a mean survival of only ~14.6 months.<sup>2</sup> This dismal prognosis is largely attributed to tumor growth and infiltration sometimes difficult to detect by conventional MRI, making novel imaging biomarkers important for aiding in both tumor spatial localization and in predicting patient survival.

Diffusion-weighted imaging (DWI) using magnetic resonance is a valuable tool used to elicit insight into the microstructure of the underlying tissue of interest.<sup>3</sup> From multiple DWIs, measurements of an apparent diffusion coefficient (ADC) can be calculated, reflecting the

to other techniques that evaluate the average ADC measurements for an entire region, fDMs do not assume homogeneity in tumors. Instead, ADC maps collected on posttreatment days are coregistered with a base image at an initial pretreatment time point, and then voxel-wise changes in ADC are calculated and labeled according to the magnitude of their change. This technique has been shown to be one of the most sensitive early biomarkers for tumor response to chemotherapeutics and radiotherapy and has been shown to be highly specific to progression of high-grade gliomas;<sup>11,12</sup> however, this technique has only been tested in a limited number of patients and a mixture of tumor grades. In addition, these early studies were performed before routine use of anti-angiogenic therapies after tumor recurrence, calling for a re-evaluation of fDMs in the new therapeutic paradigm.

In the current study, we implemented fDMs in a large cohort ( $n = 143$ ) of patients with glioblastoma (World Health Organization [WHO] grade IV), examining spatially specific ADC changes before and 4 weeks after completion of radiotherapy with concurrent temozolomide (radiochemotherapy) after tissue diagnosis. The usefulness of fDMs as a predictive biomarker for response to initial radiochemotherapy was tested using progression-free (PFS) and overall survival (OS) as clinical end points.

## Materials and Methods

### Patients

All patients participating in this study signed institutional review board–approved informed consent. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act regulations. Patients were retrospectively selected from our institution's neuro-oncology database from 1 January 2007 through 15 September 2010. Initially, a total of 169 patients who met the following criteria were selected: (1) pathology-confirmed glioblastoma, (2) treatment with standard external beam radiotherapy (typically in 2 Gy fractions given once daily for 5 days over a 6-week period, totaling 60 Gy) and concomitant temozolomide (75 mg/m<sup>2</sup>/day, 7 days per week during radiotherapy, followed by a 4-week break, then 6–12 cycles of adjuvant therapy at 150 mg/m<sup>2</sup>/day to 200 mg/m<sup>2</sup>/day), and (3) baseline (postsurgical, preraiochemotherapy) and minimum of 1 follow-up MRI scan after radiochemotherapy. The mean age ( $\pm$  stand-

radiotherapy. Of all patients enrolled, 143 patients had good quality diffusion-weighted images before and after initiation of radiochemotherapy. Exclusions were based on gross geometric distortions or low signal-to-noise ratio in the raw DWI datasets. Baseline scans were obtained  $\pm$  1 week before treatment (mean  $\pm$  SEM, 8  $\pm$  1.4 days). Follow-up scans were obtained  $\pm$  10 weeks from the time of treatment initiation (mean  $\pm$  SEM, 75  $\pm$  2.6 days) or  $\pm$  4 weeks from the end of initial radiochemotherapy. At the time of last assessment (July 2011), 118 of the 143 patients had died.

### MRI

Data were collected on 1.5T MR systems (General Electric Medical Systems; Siemens Medical Solutions) using pulse sequences supplied by the scanner manufacturer. Standard anatomical MRI sequences included axial T1-weighted (TE/TR  $\frac{1}{4}$  15 ms/400 ms, slice thickness  $\frac{1}{4}$  5 mm with 1 mm interslice distance, number of excitations [NEX]  $\frac{1}{4}$  2, matrix size  $\frac{1}{4}$  256  $\times$  256, and field-of-view [FOV]  $\frac{1}{4}$  24 cm), T2-weighted fast spin-echo (TE/TR  $\frac{1}{4}$  126–130 ms/4000 ms, slice thickness  $\frac{1}{4}$  5 mm with 1 mm interslice distance, NEX  $\frac{1}{4}$  2, matrix size  $\frac{1}{4}$  256  $\times$  256, and FOV  $\frac{1}{4}$  24 cm), and fluid-attenuated inversion recovery (FLAIR) images (TI  $\frac{1}{4}$  2200 ms, TE/TR  $\frac{1}{4}$  120 ms/4000 ms, slice thickness  $\frac{1}{4}$  5 mm with 1 mm interslice distance, NEX  $\frac{1}{4}$  2, matrix size  $\frac{1}{4}$  256  $\times$  256, and FOV  $\frac{1}{4}$  24 cm). DWIs were collected with TE/TR  $\frac{1}{4}$  102.2 ms/8000 ms, NEX  $\frac{1}{4}$  1, slice thickness  $\frac{1}{4}$  5 mm with 1 mm interslice distance, matrix size  $\frac{1}{4}$  128  $\times$  128 (reconstructed images were zero-padded and interpolated to 256  $\times$  256) and a FOV  $\frac{1}{4}$  24 cm using a twice-refocused spin echo echo planar preparation.<sup>12,13</sup> ADC images were calculated from acquired DWIs with  $b = 1000$  s/mm<sup>2</sup> and  $b = 0$  s/mm<sup>2</sup> images. In addition, gadopentetate dimeglumine–enhanced (Magnevist; Berlex; 0.1 mmol/kg) axial and coronal T1-weighted images (T1 + C; coronal: TE/TR  $\frac{1}{4}$  15 ms/400 ms, slice thickness 3 mm with 1 mm interslice distance, NEX  $\frac{1}{4}$  2, a matrix size of 256  $\times$  256, and FOV  $\frac{1}{4}$  24 cm) were acquired after contrast injection.

### Image Registration

All images for each patient were registered to their own pretreatment, precontrast, T1-weighted image with use of a mutual information algorithm and a 12-degree of freedom transformation with use of FSL (EMPIRE;

significant mass effect was an issue, attempts were made to align tumor regions exclusively. Regions of obvious misregistration (eg, near ventricles or edge of the brain) were excluded from final fDM analysis.

### fDM Calculation

After proper registration was visually verified, voxel-wise subtraction was performed between ADC maps acquired posttreatment and baseline, pretreatment ADC maps. Individual voxels were stratified into 3 categories based on the change in ADC relative to the baseline ADC map. Red voxels represented areas where ADC increased beyond a DADC threshold of  $0.4 \text{ mm}^2/\text{ms}$ , or ADC(+), and blue voxels represented areas where ADC decreased beyond a DADC threshold of  $0.4 \text{ mm}^2/\text{ms}$ , or ADC(2). These DADC thresholds ( $\pm 0.40 \text{ mm}^2/\text{ms}$ ) represent the 95% confidence interval for a mixture of normal-appearing gray and white matter in 69 patients with various tumor grades and follow-up time intervals ranging from 1 week to 1 year postbaseline.<sup>6</sup> These thresholds have been calibrated with respect to change in cell density in treatment-naïve gliomas ( $+ 3960 \text{ nuclei}/\text{mm}^2$ ) in a previous publication.<sup>6</sup> In addition, the volume fraction of total changing voxels, defined as  $\text{ADC}(+ / 2) \frac{1}{4} \text{ADC}(+) + \text{ADC}(2)$ , was quantified.

### Region of Interest (ROI) Determination

In the current study, we chose to apply fDMs to regions of FLAIR signal abnormality and contrast-enhancement (T1 + C) on both pre- and posttreatment images. FLAIR ROIs have previously been used in interpreting fDM results in nonenhancing and enhancing tumors,<sup>6,15–18</sup> because tumor infiltration into normal brain parenchyma typically results in an increase in T2-weighted or FLAIR abnormal signal.<sup>19–22</sup> Furthermore, multiple investigations have suggested that T2 signal abnormalities should be routinely used to visualize the extent of malignant infiltrating tumor.<sup>23–27</sup> In addition, regions of contrast-enhancement (T1 + C) have also been used in fDM analyses.<sup>9–12</sup> fDM analysis was performed in all 143 patients, along with a subgroup fDM analysis in patients who had significant residual tumor burden. Specifically, patients with STR (defined as having a significant volume of residual contrast-enhancing tumor burden) or a diagnostic biopsy were examined separately. The mean volume of contrast-enhancement, which included postsurgical changes along the resection

### Definition of Disease Progression

Progression was defined prospectively by the treating neuro-oncologists (T.F.C., A.L., and P.L.N.). To decrease the likelihood of declaring progression in the context of pseudoprogression, the postradiation scan was considered to be the baseline scan for evaluating tumor progression. If subsequent scans showed a definite increase in imaging evaluable tumor ( $\geq 25\%$  increase in the sum of enhancing lesions, new enhancing lesion  $> 1 \text{ cm}^2$ , an unequivocal qualitative increase in noncontrast-enhancing tumor, or unequivocal new area of noncontrast-enhancing tumor), progression was declared at that time. Progression was determined using the first postradiation therapy scan only if a new lesion  $> 1 \text{ cm}^2$  was identified outside the radiation field. Change in steroid dosage was taken into consideration before defining progression. Patients who did not meet these imaging criteria for progression but had significant neurologic decline were declared to be progressed at the time of irreversible decline. Patients who died before evidence of imaging progression were defined as progressed on the date of death.

### Hypothesis Testing

To determine whether fDMs calculated before and after radiochemotherapy are valuable biomarkers for stratifying PFS and OS in patients with newly diagnosed glioblastoma, we performed a series of univariate log-rank statistical analyses on Kaplan-Meier data. Specifically, we tested whether stratifying patients by median fractional fDM change, using a single DADC threshold of  $0.40 \text{ mm}^2/\text{ms}$ , was a significant predictor of PFS and OS from the time of diagnosis. We hypothesized that the median volume fraction of tissue showing a decrease in ADC, or relatively hypercellular tissue, would result in a significantly shorter PFS and OS in patients with glioblastoma. On the basis of previous fDM studies, we also hypothesized that the median volume fraction of tissue showing an increase in ADC, or relatively hypocellular tissue, would result in a significantly longer PFS and OS in patients with glioblastoma. fDM analysis was performed independently by 2 investigators (T.Z. and R.H.) blinded from the survival data.

**Multiple Comparisons Correction.**—Bonferroni correction to the level of significance ( $\alpha \frac{1}{4} 0.05$ ) was performed to account for the multiple testing between potential imaging biomarkers. Examining a total of 3 fDM metrics (ADC[+], ADC[2], and ADC[+ / 2]) in 4

