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Nonlinear Registration of Diffusion-Weighted Images Improves Clinical Sensitivity of Functional Diffusion Maps in Recurrent Glioblastoma Treated With Bevacizumab

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Diffusion-weighted imaging estimates of apparent diffusion coefficient (ADC) have shown sensitivity to brain tumor cellularity as well as response to therapy. Functional diffusion maps (fDMs) exploit these principles by examining voxelwise changes in ADC within the same patient over time. Currently, the fDM technique involves linear image registration of ADC maps from subsequent follow-up times to pretreatment ADC maps; however, misregistration of ADC maps due to geometric distortions as well as mass effect from growing tumor can confound fDM measurements. In this study, we compare the use of a nonlinear registration scheme to the current linear fDM technique in 70 patients with recurrent glioblastoma multiforme treated with bevacizumab. Results suggest that nonlinear registration of pretreatment ADC maps to posttreatment ADC maps improves the clinical predictability, sensitivity, and specificity of fDMs for both progression-free and overall survival. Magn Reson Med 67:237–245, 2012. © 2011 Wiley Periodicals, Inc.

Key words: functional diffusion map; fDM; glioblastoma; bevacizumab; diffusion MRI

Glioblastoma multiforme (GBM), a particularly infiltrative and aggressive type of glioma, makes up nearly 17% of all primary brain tumors and approximately 54% of all primary brain and central nervous system gliomas (1). GBMs are trademarked by a very poor patient prognosis, with a mean survival of only around 14.6 months following standard therapy including radiation and chemotherapy (2). Because of this poor prognosis, there is a great need for early imaging biomarkers to evaluate effectiveness of new therapies and predict patient survival. Diffusion-weighted magnetic resonance imaging (DWI) techniques have shown value in evaluating regions suspected of tumor invasion and proliferation (3), as well as the efficacy of specific treatment paradigms. Through calculation of an apparent diffusion coefficient (ADC) from DWIs, multiple studies have reported an inverse relationship between ADC and tumor cell density (4–6), suggesting that DWIs can potentially be used as imaging biomarkers to evaluate growing tumor and treatment effectiveness.

The functional diffusion map (fDM) was first proposed in 2005 as a method to detect changes in ADC known to accompany successful cytotoxic therapies (7,8). In contrast to other techniques that average the ADC measurements for an entire region, fDMs do not assume homogeneity within tumors. Instead, multiple ADC maps collected on different days are coregistered with a baseline image at an initial time point, and then regional (voxelwise) changes in ADC are isolated and labeled according to the magnitude of their change. This technique has shown to be one of the most sensitive early biomarkers for tumor response to chemotherapeutics and radiotherapy and has shown to be highly specific to progression of high-grade gliomas (9,10). Additionally, investigators have shown that fDMs can be used as a tool for long-term clinical assessment of recurrent brain tumors (11), are sensitive to infiltrating tumors such as gliomatosis cerebri (12), and allow visualization and quantification of regional changes in cellularity that correlate with tumor status and response to various treatments (11,13).

Despite promising results from early fDM studies, proper image registration between DWI datasets remains a major limitation to this technique. Slight misregistration between DWI datasets due to image distortion as well as mass effect from edema or growing tumor can potentially confound the interpretation and quantification of fDM-classified tumor regions. To date, implementation of fDMs for brain tumor evaluation has consisted of only linear image registration techniques to match baseline DWIs to subsequent DWI datasets. We hypothesize that an additional step of nonlinear (elastic) registration after a linear registration step may improve the clinical sensitivity of fDMs when applied to the brain, reducing the effects of misregistration and misclassification. In this study, we explore the effects of nonlinear registration of DWIs on fDMs in patients with recurrent glioblastoma before and after treatment with the antiangiogenic agent bevacizumab.

MATERIALS AND METHODS

Patients

All patients participating in this study signed institutional review board-approved informed consent to have
their data collected and stored in our institution’s neuro-oncology database. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act regulations. The study spanned November 15, 2005 to August 31, 2010. Patients were retrospectively selected from our institution’s neuro-oncology database. A total of $n = 252$ patients who met the following criteria were initially selected: (1) pathology confirmed GBM with recurrence based on MRI and clinical data, (2) regularly treated every 2 weeks per cycle with bevacizumab (Avastin, Genentech, South San Francisco, CA; 5 or 10 mg/kg body weight), and (3) baseline (pre-bevacizumab treatment) and minimum of one follow-up MRI scans. Of these patients, $n = 70$ patients had good quality DWIs before and after initiation of bevacizumab treatment and had adequate image registration (linear and nonlinear) without gross misalignment. Baseline scans were obtained approximately 1.5 weeks before treatment, and follow-up scans were obtained at approximately 6 weeks after the initiation of bevacizumab. At the time of last assessment (August, 2010), 57 of the 70 patients were deceased. All patients were treated with radiation therapy (typically 6000 cGy) and maximal tumor resection at time of initial tumor presentation. Patients did not receive additional radiation or chemotherapy between pretreatment and post-treatment MRI scans.

**MRI**

Data were collected on a 1.5-T MR system (General Electric Medical Systems, Waukesha, WI) using pulse sequences supplied by the scanner manufacturer. Standard anatomical MRI sequences included axial $T_1$-weighted (echo time [TE]/repetition time [TR] = 15 ms/400 ms, slice thickness = 5 mm with 1 mm interslice distance, number of excitations (NEX) = 2, matrix size = $256 \times 256$, and field-of-view [FOV] = 24 cm), $T_2$-weighted fast spin-echo (TE/TR = 126–130 ms/4000 ms, slice thickness = 5 mm with 1 mm interslice distance, NEX = 2, matrix size = $256 \times 256$, and FOV = 24 cm), and fluid-attenuated inversion recovery (FLAIR) images (inversion time = 2200 ms, TE/TR = 120 ms/4000 ms, slice thickness = 5 mm with 1 mm interslice distance, NEX = 2, matrix size = $256 \times 256$, and FOV = 24 cm). DWIs were collected with TE/TR = 102.2 ms/8000 ms, NEX = 1, slice thickness = 5 mm with 1 mm interslice distance, matrix size = $128 \times 128$ (reconstructed images were zero-padded and interpolated to $256 \times 256$), and a FOV = 24 cm using a twice-refocused spin echo echo planar preparation (14). ADC images were calculated from acquired DWIs with $b = 1000 \text{ s/mm}^2$ and $b = 0 \text{ s/mm}^2$ images. Additionally, gadopentetate dimeglumine-enhanced (Magnevist; Berlex, Wayne, NJ; 0.1 mmol/kg) axial and coronal $T_1$-weighted images (coronal: TE/TR = 15 ms/400 ms, slice thickness 3 mm with 1 mm interslice distance, NEX = 2, a matrix size of $256 \times 256$, and FOV = 24 cm) were acquired immediately after contrast injection.

**Linear Registration**

All images for each patient were registered to baseline anatomical $T_1$-weighted images using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK; http://www.fmrrib.ox.ac.uk/fsl/). Fine registration (1–2 degrees and 1–2 voxels) was then performed using a Fourier transform-based, 6-degree of freedom, rigid body registration algorithm (15) followed by visual inspection to ensure adequate alignment. Similar registration techniques were used in previous fDM studies (5,7,12,16).

**Nonlinear Registration**

After linear registration was complete, nonlinear registration was implemented using the FMRIB non-linear registration tool (FNIRT), a free-form deformation algorithm using a B-spline basis function (17–19). FNIRT uses a Levenberg-Marquardt modification of the Gauss-Newton method for optimizing the minimum of a sum-of-squares cost function to perform the nonlinear registration. Default values for registration parameters supplied by FMRIB were used in this study (see http://www.fmrib.ox.ac.uk/fsl/fnirt/index.html for more details). Two different nonlinear registrations were performed (Fig. 1b and c). First, we performed nonlinear registration on pretreatment ADC maps to register to post-treatment ADC maps (“pre-to-post”). This registration scheme was thought to reduce the amount of mass effect and edema present in the pretreatment ADC maps by warping to the post-treatment ADC maps. Second, we performed nonlinear registration on post-treatment ADC maps to align with pretreatment ADC maps (“post-to-pre”). We expected this registration scheme to produce similar fDM measurements to the linear case, as much of the effects are likely to be due to reduction in edema.

As FNIRT uses a sum-of-squares cost function, which may lead to problems due to dependence on image intensities, we also tested a nonlinear registration algorithm using the image registration toolkit (IRTK), which uses cubic B-splines basis function and a normalized mutual information cost function (20,21). Default values for registration parameters supplied by IRTK were used (see http://www.doc.ic.ac.uk/~dr/software/usage.html for more details). Additionally, we explored the use of nonlinear registration between $T_1$-weighted anatomical datasets to determine whether results differed compared to registering ADC maps directly. Specifically, nonlinear registration was used to align pretreatment and post-treatment $T_1$-weighted anatomical images, and then this transformation was subsequently applied to link pretreatment and post-treatment ADC maps.

**Regions of Interest**

In this study, we chose to examine both regions of FLAIR signal abnormality on pretreatment FLAIR images as well as regions of contrast enhancement on pretreatment, post-contrast $T_1$-weighted images to provide a comprehensive comparison. FLAIR regions of interest (ROIs) (5,11–13,22) and contrast-enhancing ROIs (7–9,16) have both previously been used in interpreting fDM results. For isolating ROIs, we used a semi-automated process consisting of: (1) manually defining the relative region of tumor occurrence, then (2) thresholding either the FLAIR or postcontrast
images using an empirical threshold combined with a region-growing algorithm, and then (3) manually editing the resulting masks to exclude obvious errors.

Functional Diffusion Map Calculation

fDM calculation was performed as recommended in a previous publication (5). After proper registration was visually verified, voxelwise subtraction was performed between acquired, post-treatment ADC maps and baseline, pretreatment ADC maps. Individual voxels were stratified into three categories based on the change in ADC relative to the baseline ADC map. Voxels were defined as “significantly increasing” or “significantly decreasing” if ΔADC values were beyond 0.40 mm²/ms, which has been suggested to be the best threshold for a balance between sensitivity and specificity to progressing disease and corresponds to an estimated change in cell density of more than ±3960 nuclei/mm² in untreated gliomas (5). The percent fractional volume of increasing (%V_{ADC} > 0.4 μm²/ms; red) and decreasing (%V_{ADC} < 0.4 μm²/ms; blue) voxels within FLAIR and contrast-enhancing regions were used as biomarkers for comparing linear to nonlinear fDMs and for predicting patient outcomes.

Hypothesis Testing

We hypothesized that fDMs generated from ADC maps using nonlinear registration (“nonlinear fDMs”) would have significantly lower volume fraction of changing voxels (increasing or decreasing) compared to fDMs generated using only linear registration (“linear fDMs”). To test this hypothesis, we performed multiple repeated measures, two-way analysis of variance for each of the fDM measures (%V_{ADC} > 0.4 μm²/ms and

FIG. 1. Linear and nonlinear fDM calculations. a: Linear (traditional) fDMs consisting of using a linear registration algorithm to align post-treatment ADC maps to pretreatment ADC maps. b: Pre-to-post nonlinear fDMs consisting of nonlinear registration of pretreatment ADC maps to post-treatment ADC maps. c: Post-to-pre nonlinear fDMs consisting of nonlinear registration of post-treatment ADC maps to pretreatment ADC maps. For fDMs, blue voxels represent a significant decrease in ADC (beyond 0.4 μm²/ms), red voxels represent a significant increase in ADC (beyond 0.4 μm²/ms), and green voxels are those with no significant change in ADC.
% $V_{\text{ADC}} < 0.4$ $\mu$m²/ms), ROIs (FLAIR and contrast enhancing), and registration algorithms (FNIRT-ADC, FNIRT-Anatomy, IRTK-ADC, and IRTK-Anatomy) across the different registration schemes (linear, pre-to-post nonlinear, and post-to-pre nonlinear). Tukey’s test for multiple comparisons was used for post hoc comparisons. Additionally, we tested whether the volume fraction of tissue showing a significant decrease in ADC using either the linear or nonlinear techniques was a significant predictor of time-to-progression (TTP) or overall survival (OS) with respect to the post-treatment MRI scan date. The volume fraction of decreasing ADC (blue regions) was used as a predictor of patient outcomes because it is thought to reflect both reduction in edema as well as a change in tumor cellularity after bevacizumab treatment (13,22). Disease progression was defined by a modified Macdonald criteria (23,24), which included either a 25% increase in enhancing tumor or an increase in nonenhancing tumor evident by increased mass effect and/or architectural distortions such as the blurring of the gray–white matter interface. We hypothesized that nonlinear fDMs would be a better predictor of these outcomes compared to linear fDMs. Log-rank statistical analyses on Kaplan–Meier data were performed using GraphPad Prism® v4.0 statistical software to test this hypothesis. Additionally, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for 3-month progression-free survival (PFS), 6-month PFS, 6-month OS, and 12-month OS using each of the fDM metrics, ROIs, and registration schemes.

RESULTS

In general, linear fDMs showed a substantial volume of tissue with decreased ADC after treatment with bevacizumab, presumably due to reduction in edema or growing tumor, both of which are thought to reduce ADC within FLAIR abnormal regions (Fig. 1a). When examining pre-to-post nonlinear fDMs, the quantity of tissue with high ADC was typically lower as the pretreatment ADC maps were warped to the post-treatment, edema-reduced, ADC maps (Fig. 1b). This resulted in a general decrease in the number of fDM-classified voxels. Qualitatively, post-to-pre nonlinear fDMs appeared similar to linear fDMs, showing a large volume of tissue with a significant reduction in ADC (Fig. 1c) likely due to either reduction in edema or increased tumor cellularity.

Quantitative analysis confirmed these observations, suggesting a significant difference in all fDM metrics and all ROIs due to the different registration schemes (Fig. 2; repeated measures, two-way analysis of variance, $P < 0.001$ for all fDM metrics and ROIs); however, no differences were observed between nonlinear registration algorithms or due to registration of ADC versus anatomical images (repeated measures, two-way analysis of variance, $P > 0.8$ for all combinations and interactions). Within contrast-enhancing regions, the fractional volume of tissue having a significantly lower ADC (blue regions) was reduced in pre-to-post nonlinear fDMs compared to both linear fDMs in Fig. 2a (Tukey, $P < 0.05$ for all registration algorithms) and post-to-pre nonlinear fDMs (Tukey, $P < 0.05$ for all registration algorithms). The fractional volume of tissue having a significantly higher ADC (red regions) within pretreatment contrast-enhancing regions was significantly different between linear fDMs and post-to-pre nonlinear fDMs (Fig. 2b; Tukey, $P < 0.01$ for all registration algorithms). Similar to contrast-enhancing ROIs, the fractional volume of tissue having significantly lower ADC within FLAIR ROI was significantly lower in pre-to-post nonlinear fDMs compared to linear fDMs (Fig. 2c; Tukey, $P < 0.01$ for all registration algorithms). The volume fraction of tissue having significantly increasing ADC within FLAIR ROIs was significantly different between linear fDMs and nonlinear fDMs (Fig. 2d; Tukey, $P < 0.001$ for linear fDMs vs. both pre-to-post and post-to-pre nonlinear fDMs).

Next, we tested the hypothesis that a fractional volume of tissue having a decrease in ADC larger than the median change in all patients results in a shorter TTP and shorter OS, and that nonlinear fDMs provide better stratification of survival compared to linear fDMs. As no statistical difference was observed between volume fractions calculated with FNIRT versus IRTK, or between ADC registration and registration performed between $T_1$-weighted anatomical datasets (Fig. 2), we chose to test survival differences using FNIRT applied to ADC maps. Within contrast-enhancing ROIs, the median percentage of tumor volume exhibiting a significant decrease in ADC for linear and pre-to-post nonlinear fDMs was not able to stratify TTP (Fig. 3a; log-rank, linear fDMs, $P = 0.1060$, pre-to-post nonlinear fDMs, $P = 0.0666$) or OS (Fig. 3b; log-rank, linear fDMs, $P = 0.1229$, pre-to-post nonlinear fDMs, $P = 0.0539$). Interestingly, the fractional volume of tissue with decreasing ADC within contrast-enhancing ROIs in post-to-pre nonlinear fDMs were able to stratify long- and short-term TTP (log-rank, $P = 0.0167$) and OS (log-rank, $P = 0.0260$), despite not having statistically different fractional volumes to linear fDMs after pairing (Fig. 2a; linear fDMs vs. nonlinear fDMs, $P > 0.05$). Within FLAIR ROIs, however, both linear and nonlinear fDMs were able to significantly stratify short- and long-term TTP and OS (Fig. 3c and d). Specifically, a volume fraction of tissue having a significant decrease in ADC within FLAIR ROIs larger than the median using linear fDMs resulted in a statistically shorter TTP (Fig. 3c; Log-rank, $P = 0.0016$) and OS (Fig. 3d; Log-rank, $P = 0.0385$). Post-to-pre nonlinear fDMs showed similar trends to linear fDMs with respect to TTP (Log-rank, $P = 0.0171$) and OS (Log-rank, $P = 0.0137$); however, pre-to-post nonlinear fDMs showed a substantial reduction in the level of significance ($P$ value) compared to both linear and post-to-pre nonlinear fDMs for TTP (Log-rank, $P = 0.0009$) and OS (Log-rank, $P = 0.0004$). Pre-to-post nonlinear registration applied to FLAIR regions appeared to provide the best stratification between short- and long-term PFS and OS, as well as had the highest hazard ratio; however, statistical comparison of hazard ratios suggests that only linear fDMs applied to contrast-enhancing regions had a significantly different hazard ratio for both PFS and OS compared to other biomarkers. Results further suggest pre-to-post nonlinear fDMs evaluated in FLAIR abnormal regions had a higher sensitivity and specificity to 3-month and 6-month PFS compared to other measures.
Similarly, results also suggest that pre-to-post nonlinear fDMs had a higher sensitivity and specificity to 6-month and 12-month OS compared to other measures (Table 2). Together, these results indicate that pre-to-post nonlinear fDMs applied to FLAIR abnormal regions provides the best clinical predictability, sensitivity, and specificity to both TTP and OS compared to linear fDMs or post-to-pre nonlinear fDMs applied to FLAIR or contrast-enhancing regions.

**DISCUSSION**

Voxelwise analysis of imaging parameters is a novel approach for both quantifying and visualizing potentially heterogeneous tumor response to various cancer treatments. By examining voxelwise changes in ADC, the fDM technique has shown promising sensitivity to both cytotoxic (7,8) and antiangiogenic therapies (22). Despite these initial results, no significant improvements to the fDM technique have been made since the application of fDMs in regions of FLAIR abnormality (compared to region of contrast enhancement, exclusively). Since the development of fDMs in 2005, a linear registration scheme has been used for aligning ADC maps within the same patient over time. This technique poses several challenges when geometric distortions arise in ADC maps, or when misalignment of ADC maps occurs due to mass effect from growing tumor. These limitations to
linear fDMs have been identified for some time; however, it has not been clear how best to implement an alternative registration scheme. For example, should baseline ADC maps be nonlinearly registered to each subsequent ADC map during follow-up (the “pre-to-post” scheme), or should each follow-up ADC map be nonlinearly registered to the baseline ADC map (the “post-to-pre” scheme). Alternatively, one might propose registering all ADC maps to a template space for subsequent analysis. As a first attempt to improve the fDM technique, we have implemented a simple nonlinear, elastic registration scheme. Results from this study suggest that nonlinear registration of ADC maps significantly changes the calculated fDMs and measured parameters, and these changes in fDM parameters tend to improve clinical predictability of fDMs with respect to bevacizumab treatment.

Although our results suggest that nonlinear registration improves the ability for fDMs to predict survival, it is still not clear whether voxels classified as significantly increasing or decreasing in ADC accurately depict physical changes in tumor microstructure or whether this is an artifact of image registration. To address this concern, the authors of a previous study have proposed using a similarity-guided correspondence correction algorithm for improving alignment of ADC maps for fDM analysis (25). Results from this pilot study suggested that fDM analysis was more accurate after application of this correction algorithm; however, no validation with respect to tissue or patient outcomes was presented. Therefore, tissue validation of nonlinear fDM-classified voxels is still required.

Comparison to Other Biomarkers

This study demonstrates a significant improvement in biomarker technology for use in predicting response of GBM to antiangiogenic therapies. Many imaging biomarkers have been explored for use in assessing the response to antiangiogenic therapies (26), including...
### Table 1
Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for Linear and Nonlinear fDM Metrics With Respect to 3-Month and 6-Month Progression-Free Survival

<table>
<thead>
<tr>
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<th>3-month progression-free survival</th>
<th>6-month progression-free survival</th>
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<tbody>
<tr>
<td></td>
<td>Median % volume</td>
<td>Sensitivity (%)</td>
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<td>Contrast-enhancing</td>
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<td>regions</td>
<td>$V_{ADC} &lt; 0.4 \mu m^2/ms$</td>
<td>Linear fDMs</td>
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<td></td>
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<td>Pre-to-post nonlinear fDMs</td>
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<td>Post-to-pre nonlinear fDMs</td>
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<tr>
<td>FLAIR abnormal</td>
<td>$V_{ADC} &gt; 0.4 \mu m^2/ms$</td>
<td>Linear fDMs</td>
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<tr>
<td>regions</td>
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<td>Pre-to-post nonlinear fDMs</td>
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<td>$V_{ADC} &gt; 0.4 \mu m^2/ms$</td>
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<td>Post-to-pre nonlinear fDMs</td>
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### Table 2
Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for Linear and Nonlinear fDM Metrics With Respect to 6-Month and 12-Month Overall Survival

<table>
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<th>6-month Overall survival</th>
<th>12-month Overall survival</th>
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<td></td>
<td>Median % volume</td>
<td>Sensitivity (%)</td>
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<td>Contrast-enhancing</td>
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<td>Linear fDMs</td>
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<td></td>
<td>Post-to-pre nonlinear fDMs</td>
<td>17.28%</td>
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<tr>
<td></td>
<td>$V_{ADC} &gt; 0.4 \mu m^2/ms$</td>
<td>Linear fDMs</td>
</tr>
<tr>
<td>FLAIR abnormal</td>
<td>$V_{ADC} &lt; 0.4 \mu m^2/ms$</td>
<td>Post-to-pre nonlinear fDMs</td>
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<tr>
<td>regions</td>
<td>$V_{ADC} &gt; 0.4 \mu m^2/ms$</td>
<td>Linear fDMs</td>
</tr>
<tr>
<td></td>
<td>Pre-to-post nonlinear fDMs</td>
<td>11.38%</td>
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<td>Post-to-pre nonlinear fDMs</td>
<td>17.14%</td>
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<tr>
<td></td>
<td>$V_{ADC} &gt; 0.4 \mu m^2/ms$</td>
<td>Linear fDMs</td>
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<td>Pre-to-post nonlinear fDMs</td>
<td>5.20%</td>
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<tr>
<td></td>
<td>Post-to-pre nonlinear fDMs</td>
<td>2.54%</td>
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positron emission tomography tracers (27), perfusion MRI (28), and other diffusion MR analyses (29); however, this is the first study to demonstrate the ability to predict both TTP and OS in recurrent GBM patients treated with bevacizumab. Additionally, linear fDM analyses have been successfully performed on patients treated with bevacizumab (22) by focusing on temporal changes in fDM-classified tissue volumes over time. Unlike this previous study, this study focused on using the initial changes after treatment to predict patient outcomes. Consistent with previous results, however, we found that patients having a larger volume of tissue with a lower ADC after treatment were more likely to progress sooner and have a shorter survival than patients having a lower volume of tissue with significantly lower ADC after treatment.

Technical Limitations and Considerations

In the current retrospective study, we have chosen to use ADC maps calculated from diffusion MR data that were collected with only $b = 0$ s/mm$^2$ and $b = 1000$ s/mm$^2$. By performing ADC calculations on only these DWIs, we ensure that our techniques can be retroactively applied across multicenter clinical trials. Despite this potential advantage, the use of a standard, clinical diffusion MR sequence parameters with only two $b$ values poses potential limitations as to the accuracy of ADC measurements. The National Cancer Institute has recommended that ADC calculations should be performed using three or more DWIs at different $b$ values ($0, >100$, and $>500$ s/mm$^2$) for perfusion-insensitive estimates of ADC. Additionally, the use of only two $b$ values for calculation of ADC maps in fDM analyses can be confounded by other pathologies that may have been present, including cerebral ischemia.

Another potential limitation is the nonlinear algorithm used for image registration. Many nonlinear image registration algorithms have been proposed and compared (30), and each has advantages and disadvantages. We chose to use FNIRT as part of the FSL software package for ease of use in our fDM postprocessing pipeline, as well as previous studies suggesting adequate performance (30).

CONCLUSIONS

In summary, nonlinear fDMs appear to provide a significant improvement in clinical predictability, sensitivity, and specificity of fDMs compared to the traditional, linear fDM approach. Additionally, pre-to-post nonlinear fDMs applied in FLAIR abnormal regions may provide the best sensitivity and specificity for progressing disease and survival compared to post-to-pre nonlinear fDMs.

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