Prediction of Isocitrate Dehydrogenase Genotype in Brain Gliomas with MRI: Single-Shell versus Multishell Diffusion Models

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Conflicts of interest are listed at the end of this article.

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**Purpose:** The primary aim of this prospective observational study was to assess whether diffusion MRI metrics correlate with isocitrate dehydrogenase (IDH) status in grade II and III gliomas. A secondary aim was to investigate whether multishell acquisitions with advanced models such as neurite orientation dispersion and density imaging (NODDI) and diffusion kurtosis imaging offer greater diagnostic accuracy than diffusion-tensor imaging (DTI).

**Materials and Methods:** Diffusion MRI (b = 700 and 2000 sec/mm²) was performed preoperatively in 192 consecutive participants (113 male and 79 female participants; mean age, 46.18 years; age range, 14–77 years) with grade II (n = 62), grade III (n = 58), or grade IV (n = 72) gliomas. DTI, diffusion kurtosis imaging, and NODDI metrics were measured in regions with or without hyperintensity on diffusion MR images and compared among groups defined according to IDH genotype. 1p/19q codeletion status, and tumor grade by using Mann-Whitney tests.

**Results:** In grade II and III IDH wild-type gliomas, the maximum fractional anisotropy, kurtosis anisotropy, and restriction fraction were significantly higher and the minimum mean diffusivity was significantly lower than in IDH-mutant gliomas (P = .011, P = .002, P = .044, and P = .027, respectively); areas under the receiver operating characteristic curve ranged from 0.72 to 0.76. In IDH wild-type gliomas, no difference among grades II, III, and IV was found. In IDH-mutant gliomas, no difference between those with and those without 1p/19q loss was found.

**Conclusion:** Diffusion MRI metrics showed correlation with isocitrate dehydrogenase status in grade II and III gliomas. Advanced diffusion MRI models did not add diagnostic accuracy, supporting the inclusion of a single-shell diffusion-tensor imaging acquisition in brain tumor imaging protocols.

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Recent update of the World Health Organization (WHO) classification of brain tumors introduced molecular markers that add greater prognostic accuracy than histopathologic findings alone (1,2). Isocitrate dehydrogenase (IDH) genotype and epigenetic 1p/19q codeletion are two key molecular markers. Patients with IDH wild-type gliomas have a worse prognosis than those with IDH-mutant gliomas. Patients with 1p/19q uncodeleted gliomas have a worse prognosis than those with codeleted IDH-mutant gliomas (3). The establishment of in vivo biomarkers that enable prediction of IDH and 1p/19q status would thus be relevant for patient management (4) and clinical trials.

Diffusion MRI is a potential method for providing such in vivo biomarkers. It enables assessment of the microstructure of the whole tumor at a relatively high spatial resolution and is easily accessible. Diffusion-tensor imaging (DTI) is currently the most used method (5). DTI parameters such as mean diffusivity (MD) and fractional anisotropy (FA) correlate with changes in cellular density and in extracellular matrix features induced by glioma infiltration and growth.

Several studies aimed to grade gliomas with use of DTI. Most of these have demonstrated significantly lower MD values in high-grade gliomas (6–12), but the majority failed to differentiate WHO grade II gliomas from grade III gliomas due to overlapping MD and FA values. A limitation of the above studies is that the authors did not stratify patients according to IDH
Diffusion MRI has the potential to contribute to stratifying patients with lower-grade gliomas in clinical trials.

Materials and Methods

Participants

All participants gave informed written consent for the surgical procedure and this prospective study, according to the World Medical Association Declaration of Helsinki statement for research involving human subjects. This prospective study was approved by the local institutional review board and performed between April 2012 and November 2015. Patients were included in this study if (a) MRI with multishell diffusion was performed less than 2 weeks before surgery and (b) glioma was diagnosed with histopathologic examination and molecular analysis. Patients who had previously undergone brain surgery were included. Exclusion criteria were diagnosis of WHO I gliomas, ependymomas, metastases, and other nonglial brain tumors and age younger than 12 years.

MRI Examination

MRI studies were performed with the same 3.0-T MRI unit (Magnetom Verio; Siemens, Erlangen Germany). Diffusion MRI was performed with the following parameters: repetition time, 15 seconds; echo time, 96 msec; eight volumes with $b = 0$, 20 volumes with $b = 700 \text{ sec/mm}^2$, and 40 volumes with $b = 2000 \text{ sec/mm}^2$; 64 axial sections; field of view, 256 $\times$ 256 mm; and isotropic resolution of 2.0 $\times$ 2.0 $\times$ 2.0 mm. The acquisition time for the diffusion MRI sequence was approximately 20 minutes. The conventional MRI protocol included a T2-weighted turbo spin-echo sequence (repetition time msec/echo time msec, 5420/106; 40 sections; field of view, 240 $\times$ 240 mm; voxel size, 0.47 $\times$ 0.47 $\times$ 3 mm) and a T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence (repetition time msec/echo time msec/inversion time msec, 1800/2.7/900; nominal isotropic spatial resolution of 1 mm) before and after injection of a gadolinium-based contrast agent (Gadovist, Bayer Schering Pharma, Berlin, Germany; 0.1 mL per kilogram of body weight).

Image Processing

Diffusion MR images were corrected for motion and eddy current distortions by using ExploreDTI (20), which also corrects the $b$ matrix accordingly (21). The diffusion tensor was estimated from each shell separately ($b = 700$ and 2000 sec/mm$^2$) as well as from both shells combined by using the nonlinear robust estimation of tensors by outlier rejection algorithm in ExploreDTI (22). With the same software, the diffusion kurtosis tensor was estimated from both shells by using the robust extraction of kurtosis indexes with the linear estimation approach (23); mean kurtosis and KA maps were derived. The NODDI model was fitted to both diffusion MRI metrics correlate with IDH genotype. We tested the hypothesis that IDH wild-type lower-grade gliomas have foci of significantly lower diffusivity and higher restricted fraction. In addition, we investigated whether advanced models such as NODDI and diffusion kurtosis imaging would offer greater diagnostic accuracy than DTI.

Diffusion metrics from three models correlated with isocitrate dehydrogenase genotype in grade II and III gliomas. Advanced diffusion models did not add significant diagnostic accuracy. Diffusion-tensor imaging plays a role in the identification of those who may benefit from more aggressive treatments despite lacking high-grade features at neuropathologic examination.

Implications for Patient Care

- Metrics derived from diffusion-tensor imaging, diffusion kurtosis imaging, and neurite orientation dispersion and density imaging correlated with isocitrate dehydrogenase genotype in grade II and III (ie, lower-grade) gliomas.
- The results of diffusion-tensor imaging and multishell advanced models were comparable in the identification of those patients who may require more aggressive treatment due to worse prognosis despite being classified as having a lower-grade glioma with neuropathologic examination.
- Diffusion MRI has the potential to contribute to stratifying patients with lower-grade glioma in clinical trials.

Abbreviations

DTI = diffusion-tensor imaging, FA = fractional anisotropy, IDH = isocitrate dehydrogenase, KA = kurtosis anisotropy, MD = mean diffusivity, NODDI = neurite orientation dispersion and density imaging, ROI = region of interest, WHO = World Health Organization

genotype. Only the authors of recent retrospective DTI studies have stratified lower-grade gliomas by IDH and 1p/19q status. They have reported lower apparent diffusion coefficient and higher FA values in IDH wild-type astrocytomas (13) and oligodendrogliomas (14) but no significant differences between gliomas with and gliomas without 1p/19q loss (15). If confirmed in a large prospective study, these findings would expand the use of DTI in gliomas.

Other investigators have shown that advanced models with a high $b$ value provide better performance than DTI with regard to glioma grading. Diffusion kurtosis imaging (16) parameters, most commonly mean kurtosis and kurtosis anisotropy (KA), can help characterize the non-Gaussian diffusion contribution. Higher mean kurtosis values have been reported in high-grade compared with low-grade gliomas (17,18). Alternatively, multicompartment models have been proposed to improve specificity to brain microstructure by measuring the diffusion of water molecules in different compartments. One such model is neurite orientation dispersion and density imaging (NODDI) (19). NODDI separates the contribution of three main tissue compartments where water diffusion is restricted, hindered, or free. NODDI parameters such as restriction fraction, isotropic fraction, and orientation dispersion index might be more sensitive to glioma microstructure than are conventional DTI metrics. A multishell acquisition protocol is required for application of advanced diffusion models, with the drawback that it increases imaging time. Therefore, it would be important to assess whether advanced models with high $b$ values would also be beneficial in stratifying lower-grade gliomas according to IDH status.

Our study of a large population of patients with gliomas was conceived with a prospective design to confirm whether
between the groups defined according to histopathologic characteristics and genetics. Because the latter are provided for a single sample per participant, one ROI mean value per diffusion parameter had to be chosen in each participant. To reflect what is routinely done in neuropathologic examination, where the most aggressive component of the tumor is taken into consideration, and on the basis of the biologic interpretation of diffusion MRI parameters, we selected the maximum values for restricted fraction, isotropic fraction, orientation dispersion index, FA, mean kurtosis, and KA and the minimum value for MD. The same approach was followed in previous DTI studies on this topic (14,15).

Neuropathologic Examination
Surgery was performed by a team of three board-certified neurosurgeons as previously described (25). Diffusion MR images were available on a neuronavigation system (Brainlab, Munich, Germany). Hyperintense foci at diffusion-weighted imaging were sampled in all patients. One board-certified neuropathologist made all histomolecular diagnoses (B.F., with 12 years of experience). Tumor grade was determined according to the 2007 WHO classification (26). An IDH-1 mutational analysis was conducted with immunohistochemistry analysis by using antibody to IDH R132H in all cases. Wild-type cases were then validated by means of pyrosequencing. The 1p/19q codeletion status was assessed with fluorescence in situ hybridization, and the cell proliferation index was measured with immunohistochemistry analysis by using the MIB-1 antibody against the Ki-67 protein.

Statistical Analysis
The $\chi^2$ test was used to compare the hyperintensity on diffusion MR images obtained with a $b$ value of 2000 sec/mm$^2$ and contrast enhancement frequencies across groups.

To address the main objective of our study, we first focused on the relationship between diffusion MRI results and groups defined according to IDH mutation genotype. Subsequently, the IDH mutation group was further divided according to 1p/19q phenotype; these two groups were compared among themselves and with IDH wild-type gliomas. Finally, we compared the diffusion metrics among the groups defined according to tumor grade and histotype to be able to relate our results to those of most previous studies.

The Mann-Whitney test was used to evaluate the statistical significance of the differences. $P < .05$ after Bonferroni correction was considered indicative of a statistically significant difference; all tests for each metric were considered as independent (11 metrics $\times$ 6 tests = 66 comparisons). A receiver operating characteristic curve analysis was also performed for all comparisons.

The McNemar test was used to compare the accuracy between multishell and single-shell models in predicting the IDH mutation genotype.
of the 58 grade III gliomas, and 11 of the 72 grade IV gliomas. A chart showing stratification according to IDH and 1p/19q status is shown in Figure 1.

**Qualitative Assessment of MR Images**

MR images in two representative participants with WHO grade II and grade III IDH wild-type gliomas are shown in Figures 2 and 3, respectively. Hyperintensity on diffusion-weighted images and low MD were present in nine of the 62 grade II gliomas, 31 of the 58 grade III gliomas, and 61 of the 72 grade IV gliomas. Enhancement on postcontrast T1-weighted images was found in five of the 62 grade II gliomas, 24 of the 58 grade III gliomas, and 70 of the 72 grade IV gliomas. Hyperintensity on diffusion-weighted images associated with enhancement occurred in two of the 62 grade II gliomas, 18 of the 58 grade III gliomas, and 60 of the 72 grade IV gliomas. The frequency of hyperintensity and enhancement increased with grade ($P < .001$); however, diffusion hyperintensity tended to be more frequent than enhancement in lower-grade gliomas (although not significantly according to the $\chi^2$ test, $P = .26$ for grade II and $P = .19$ for grade III).

**Correlation of Diffusion MRI Metrics with IDH Genotype and 1p/19q Loss**

To test our hypothesis that the occurrence of foci with hyperintensity at diffusion MRI is associated with molecular and histopathologic markers of poor prognosis, we focused on 120 lower-grade gliomas. IDH wild-type gliomas showed significantly higher maximum restricted fraction, maximum KA, and maximum FA, as well as lower minimum MD (derived from the single-shell model with $b = 2000$ sec/mm$^2$), when compared with IDH-mutant gliomas (Fig 4 and Tables 1, 2; unadjusted $P$ values are in Table E1 [online]).

All three models provided at least one significantly different parameter with an effect size larger than 1. Receiver operating characteristic curves are shown in Figure 5, and the associated area under the curve, accuracy, sensitivity, specificity, and positive and negative predictive values are reported in Table 3. The four significantly different metrics had similar areas under the curve, ranging from 0.72 to 0.76. The accuracies of the single-shell versus the multishell model in identifying the correct IDH genotype were not significantly different ($P > .05$), except for minimum MD, which had significantly lower accuracy with respect to maximum restricted fraction ($P < .001$), as reported in Table 4.

In IDH-mutant gliomas, we found no significant difference between participants with and those without 1p/19q codeletion ($P > .99$ for all after Bonferroni correction) (Tables 1, 2). In IDH wild-type gliomas, no significant
Correlation of Diffusion MRI Metrics with Glioma Grade, Histotype, and Cell Proliferation Index

DTI, diffusion kurtosis imaging, and NODDI metrics of grade IV gliomas were significantly different from those of grade II and III gliomas (Tables 1, 2). Among lower-grade gliomas, none of the metrics were significantly different between grade II and III gliomas or between astrocytomas and oligodendrogliomas (histotype) (\( P > .99 \) for all after Bonferroni correction). No correlation was found between any diffusion metric and the cell proliferation index; on the other hand, MIB-1 significantly increased with tumor grade as expected (\( P < .001 \) for all comparisons between WHO grades).

Discussion

Our results showed that minimum MD values were significantly lower and maximum restricted fraction values were significantly higher in IDH wild-type gliomas than in IDH-mutant WHO grade II and III gliomas. Maximum KA and maximum FA values were also significantly higher in IDH wild-type gliomas. These results held true with Bonferroni correction, the most conservative approach to multiple comparison correction (27). The results also showed that the benefit of upgrading the imaging protocol for advanced diffusion models is small, meaning that identification of IDH status with DTI is as good as that with multishell methods.

Recent advances in neuro-oncology have shifted the focus from histopathologic grading to molecular features that have been integrated into the WHO classification. Grading is no longer the most relevant information requested to neuroradiologists, especially in nonenhancing lower-grade gliomas. To stay relevant, imaging must adapt to this paradigm shift and its role should be redirected to identify molecular status. Noninvasive prediction of IDH wild-type lower-grade gliomas is clinically important and challenging. These tumors have a malignant clinical course despite a more indolent appearance on conventional MR images. They also have a lower-grade appearance at histopathologic examination: low cellularity, a low mitotic index, and no neoangiogenesis. Thus, DTI might help identify those patients who
advanced multishell diffusion data, which allowed us to further investigate whether more complex models offered any clinical benefit. The benefit gained with advanced models was small in our study. Our comparison of the three models demonstrated that maximum FA was comparable to maximum KA and maximum restricted fraction in the stratification of tumors according to IDH status. This has an impact on clinical applications because DTI metrics can be acquired in less time than multishell data.

An advantage of biophysical models is that they enable biologic interpretation of diffusion data. Traditionally, decreased MD in gliomas has been interpreted as an increase in tumor cellularity (6,12,31–33). This may be true in glioblastomas, which contain foci of very high cellularity. However, we also observed decreased MD in IDH wild-type lower-grade gliomas, where high cellularity is not a reported histopathologic feature. This suggests that the underlying mechanism may be different. A recent PET study with the amino acid O-(2-18F-fluorethyl)-l-tyrosine showed that radiotracer uptake (ie, high metabolic activity and cellular density) did not co-localize with foci of low diffusivity in nonenhancing lower-grade gliomas, which suggests that tumor cellularity determines a smaller portion of the diffusion MRI signal than other microstructural elements, such as the volume of extracellular space, the distribution of macromolecules in the extracellular matrix, and vessels (34). We observed increased restricted fraction in the NODDI model, which can be driven either by increased volume of the intracellular space (eg, increased cellularity) or by decreased volume of the extracellular space. Our observations indicate that changes in the volume of the extracellular space may play a role in the modulation of the diffusion signal and may drive the observed changes in restricted fraction, mean kurtosis, and MD. It has been suggested that diffusivity in gliomas may be affected at least in part by decreased hydrophilic components or the expression of hyaluronan in the extracellular matrix (35).

NODDI also helped explain the DTI and diffusion kurtosis imaging anisotropy results: FA and KA were higher in IDH wild-type gliomas than in IDH-mutant lower-grade tumors, which suggests that the integrity of fibers was preserved. On the contrary, the higher orientation dispersion index values suggest that fibers are actually more dispersed in IDH wild-type gliomas.

Figure 4: Box plots of diffusion-tensor imaging (left), diffusion-kurtosis imaging (middle), and neurite orientation dispersion and density imaging (NODDI) (right) metrics in lower-grade gliomas stratified according to isocitrate dehydrogenase (IDH) status (IDH mutant and IDH wild type). Horizontal red line indicates median, and bottom and top edges of box indicate 25th and 75th percentiles, respectively. Whiskers extend to the most extreme data points not considered outliers. Outliers are plotted individually by using red crosses. FA = fractional anisotropy, fR-max = maximum restricted fraction (volumetric fraction of compartment with restricted diffusion in NODDI model), KA-max = maximum kurtosis anisotropy, MD-min = minimum mean diffusivity, MK-max = maximum mean kurtosis, ODI-max = maximum orientation dispersion index. * = statistically significant difference ($p < .05$).
Table 1: Bonferroni-corrected P Values for All Comparisons and All Considered Diffusion MRI Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IDH-Mutant ((n = 96)) vs IDH WT ((n = 24)) Glioma (WHO II and III)</th>
<th>IDH-Mutant 1p/19q Codeleted ((n = 59)) vs IDH-Mutant 1p/19q Uncodeleted ((n = 60)) Glioma (WHO II and III)</th>
<th>IDH-Mutant ((n = 11)) vs IDH WT ((n = 60)) Glioma (WHO IV)</th>
<th>WHO II vs WHO III</th>
<th>WHO II vs WHO IV</th>
<th>WHO III vs WHO IV</th>
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<tbody>
<tr>
<td>(fR)-max</td>
<td>.044*</td>
<td>.99</td>
<td>.99</td>
<td>&lt;.001*</td>
<td>&lt;.001*</td>
<td></td>
</tr>
<tr>
<td>KA-max</td>
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<td>.99</td>
<td>.99</td>
<td>.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA-max (both shells)</td>
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<td>.99</td>
<td>.99</td>
<td>.133</td>
<td>.018*</td>
<td></td>
</tr>
<tr>
<td>FA-max ((b = 700 \text{ sec/mm}^2))</td>
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<td>.99</td>
<td>.99</td>
<td>.008*</td>
<td>.003*</td>
<td></td>
</tr>
<tr>
<td>FA-max ((b = 2000 \text{ sec/mm}^2))</td>
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<td>.99</td>
<td>.99</td>
<td>.303</td>
<td>.111*</td>
<td></td>
</tr>
<tr>
<td>MD-min (both shells)</td>
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<td>.99</td>
<td>&lt;.001*</td>
<td>&lt;.001*</td>
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</tr>
<tr>
<td>MD-min ((b = 700 \text{ sec/mm}^2))</td>
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<td>.99</td>
<td>.99</td>
<td>&lt;.001*</td>
<td>&lt;.001*</td>
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</tr>
<tr>
<td>MD-min ((b = 2000 \text{ sec/mm}^2))</td>
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<td>.99</td>
<td>.99</td>
<td>&lt;.001*</td>
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<tr>
<td>MK-max</td>
<td>.122</td>
<td>.99</td>
<td>.99</td>
<td>&lt;.001*</td>
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<tr>
<td>ODI-max</td>
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<td>.99</td>
<td>&lt;.001*</td>
<td>.469</td>
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<td>fiso-max</td>
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<td>.99</td>
<td>.99</td>
<td>.99</td>
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</tr>
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</table>

Note.—OA-max = maximum fractional anisotropy, fiso-max = maximum isotropic fraction, \(fR\)-max = maximum restricted fraction, IDH = isocitrate dehydrogenase, KA-max = maximum kurtosis anisotropy, MD-min = minimum mean diffusivity, MK-max = maximum mean kurtosis, ODI-max = maximum orientation dispersion index, WHO = World Health Organization, WT = wild type.
* Significant difference.

Table 2: Effect Size for All Comparisons and All Considered Diffusion MRI Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IDH-Mutant ((n = 96)) vs IDH WT ((n = 24)) Glioma (WHO II and III)</th>
<th>IDH-Mutant 1p/19q Codeleted ((n = 59)) vs IDH-Mutant 1p/19q Uncodeleted ((n = 35)) Glioma (WHO II and III)</th>
<th>IDH-Mutant ((n = 11)) vs IDH WT ((n = 60)) Glioma (WHO IV)</th>
<th>WHO II ((n = 62)) vs WHO III ((n = 58))</th>
<th>WHO II ((n = 62)) vs WHO IV ((n = 72))</th>
<th>WHO III ((n = 58)) vs WHO IV ((n = 72))</th>
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<tr>
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<td>0.78†</td>
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<td>0.62†</td>
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<td>0.64†</td>
<td>-0.14</td>
<td>0.45</td>
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<td>-0.55†</td>
<td>-0.29</td>
<td>-1.29*</td>
<td>-0.90†</td>
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<tr>
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<td>-0.62†</td>
<td>-0.23</td>
<td>-1.18*</td>
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<td>MD-min ((b = 2000 \text{ sec/mm}^2))</td>
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<td>-0.93†</td>
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<tr>
<td>MK-max</td>
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<td>0.20</td>
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<tr>
<td>ODI-max</td>
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<td>0.53</td>
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<td>0.17</td>
<td>-0.28</td>
<td>-0.50†</td>
</tr>
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</table>

Note.—OA-max = maximum fractional anisotropy, fiso-max = maximum isotropic fraction, \(fR\)-max = maximum restricted fraction, IDH = isocitrate dehydrogenase, KA-max = maximum kurtosis anisotropy, MD-min = minimum mean diffusivity, MK-max = maximum mean kurtosis, ODI-max = maximum orientation dispersion index, WHO = World Health Organization, WT = wild type.
* Effect size greater than 1 in absolute value.
† Effect size greater than 0.5 in absolute value.
and that, in IDH-mutant gliomas, the higher extracellular water content may be responsible for the decrease in FA and KA. The orientation dispersion index is indeed less affected by excess water content.

We observed no significant differences in diffusion MRI metrics between IDH-mutant gliomas with and without 1p/19q loss. This result also confirmed previous findings by Xiong et al (15). It may indicate either that epigenetic phenotypes do not induce microstructural changes or that diffusion is not sensitive enough to detect these. No significant correlation was found between diffusion MRI metrics and the cell proliferation index. This finding is additional indirect evidence that tumor cellularity may not be the major factor driving increased restricted fraction in lower-grade gliomas. Our findings do not support the results reported by Xiong et al (14), who found significantly lower Ki-67 levels in mutant rather than IDH wild-type oligodendrogliomas.

In the near future, machine learning classifiers using multidimensional datasets may show advantages to univariate methods used in this study. The authors of a recent study with machine learning analysis (36) showed a prediction accuracy of 92% (54 of 59 cases; area under the receiver operating characteristic curve = 0.921), relying on tumor volume and texture information from DTI data of 59 patients with grade II and III glioma.

Limitations of our study must be acknowledged. The ROI-based approach, which was based on tumor characterization with conventional and diffusion MRI, could have introduced operator-dependent variability; however, it allows more flexibility than automated methods. NODDI uses a multicompartment model that has been optimized for normal white matter. In future studies, we observed no significant differences in diffusion MRI metrics between IDH-mutant gliomas with and without 1p/19q loss. This result also confirmed previous findings by Xiong et al (15). It may indicate either that epigenetic phenotypes do not induce microstructural changes or that diffusion is not sensitive enough to detect these. No significant correlation was found between diffusion MRI metrics and the cell proliferation index. This finding is additional indirect evidence that tumor cellularity may not be the major factor driving increased restricted fraction in lower-grade gliomas. Our findings do not support the results reported by Xiong et al (14), who found significantly lower Ki-67 levels in mutant rather than IDH wild-type oligodendrogliomas.

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assumptions must be optimized for pathologic tissues with glioma cells infiltrating and modulating the extracellular matrix.

In conclusion, diffusion metrics from the three models correlated with IDH wild-type in lower-grades gliomas. No significant differences were found among IDH wild-type grade II, III, and IV gliomas. Advanced diffusion MRI models did not add diagnostic accuracy. IDH wild-type lower-grades gliomas tend to be heterogeneous and have foci with reduced diffusivity and higher anisotropy values. These patients may benefit from more aggressive treatments, despite having nonenhancing gliomas on conventional MR images and lacking high-grade features at neuropathologic examination.

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