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ABSTRACT

BACKGROUND AND PURPOSE: Few studies have shown MR imaging features and ADC correlating with molecular markers and survival in patients with glioma. Our purpose was to correlate MR imaging features and ADC with molecular subtyping and survival in adult diffuse gliomas.

MATERIALS AND METHODS: Presurgical MRIs and ADC maps of 131 patients with diffuse gliomas and available molecular and survival data from The Cancer Genome Atlas were reviewed. MR imaging features, ADC (obtained by ROIs within the lowest ADC area), and mean relative ADC values were evaluated to predict *isocitrate dehydrogenase* (*IDH*) mutation, 1p/19q codeletion status, *MGMT* promoter methylation, and overall survival.

RESULTS: *IDH* wild-type gliomas tended to exhibit enhancement, necrosis, and edema; >50% enhancing area ($P < .001$); absence of a cystic area ($P = .013$); and lower mean relative ADC (median, 1.1 versus 1.6; $P < .001$) than *IDH*-mutant gliomas. By means of a cutoff value of 1.08 for mean relative ADC, *IDH*-mutant and *IDH* wild-type gliomas with lower mean relative ADC (<1.08) had poorer survival than those with higher mean relative ADC (median survival time, 24.2 months; 95% CI, 0.0–54.9 months versus 62.0 months; $P = .003$; and median survival time, 10.4 months; 95% CI, 4.4–16.4 months versus 17.7 months; 95% CI, 11.6–23.7 months; $P = .041$, respectively), regardless of World Health Organization grade. Median survival of those with *IDH*-mutant glioma with low mean relative ADC was not significantly different from that in those with *IDH* wild-type glioma. Other MR imaging features were not statistically significant predictors of survival.

CONCLUSIONS: *IDH* wild-type glioma showed lower ADC values, which also correlated with poor survival in both *IDH*-mutant and *IDH* wild-type gliomas, irrespective of histologic grade. A subgroup with *IDH*-mutant gliomas with lower ADC had dismal survival similar to that of those with *IDH* wild-type gliomas.

ABBREVIATIONS: *IDH* = *isocitrate dehydrogenase*; max = maximum; min = minimum; rADC = relative ADC; $rADC_{mean}$ = mean relative ADC; TCGA = The Cancer Genome Atlas; WHO = World Health Organization

Gliomas are a heterogeneous group of tumors, and the clinical aggressiveness and prognoses are diverse among different histopathologic grades and molecular subtypes. Previous studies have shown that histopathologic classification of diffuse gliomas has high interobserver variation and correlates imperfectly with clinical outcomes.[1,2] Nevertheless, molecular markers, particularly *isocitrate dehydrogenase* (*IDH*) mutational status, have been demonstrated to be significant and more robust prognostic markers[3] and have been incorporated into the classification of diffuse gliomas in the latest update of the World Health Organization (WHO) classification in 2016.[4] *IDH* mutation, a powerful prognostic marker of improved survival in diffuse glioma, is found mainly in lower grade gliomas (WHO grades II and III), but also in glioblastoma (WHO grade IV), though at much lower frequency.[5,6]

Preoperative and noninvasive determination of molecular subtyping is of great value in the clinical management of patients with glioma. However, studies correlating MR imaging features with *IDH*-mutation status and patient survival in diffuse gliomas are scarce. Recently, we showed that the "T2-FLAIR mismatch sign," detectable using conventional MR imaging, is a highly spe-

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cific imaging biomarker for the *IDH*-mutant, 1p/19q noncodeleted molecular subtype in lower grade gliomas.[7] Wang et al[8] demonstrated that the absence of contrast enhancement was associated with longer progression-free and overall survival in patients with *IDH1*-mutated anaplastic gliomas. MR spectroscopy could detect 2-hydroxyglutarate, a metabolite that accumulates in *IDH*-mutant gliomas but did not discover a survival difference.[9] Blood volume estimates obtained by MR perfusion have also provided potential markers for noninvasive assessment of *IDH* status.[10]

ADC can be calculated from DWI, and tumors with more freely mobile water molecules and lesser cellularity have higher ADC values.[11] ADC has been shown to be a valuable imaging marker in the diagnosis of intracranial lesions as well as in grading brain tumors.[11-15] Therefore, we hypothesized that ADC values obtained from conventional MR imaging could correlate with molecular subtype and patient survival in adult diffuse gliomas.

MATERIALS AND METHODS

This was a retrospective study using data from the publicly available National Institutes of Health/National Cancer Institute–approved databases of The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov) and The Cancer Imaging Archive (http://www.cancerimagingarchive.net/),[16-18] from which all 461 cases with imaging data were reviewed, and only cases of treatment-naïve diffuse gliomas (WHO grades II–IV) with available DWI and ADC maps were included. WHO grade, the status of 3 validated molecular prognostic markers (*IDH* mutation, 1p/19q codeletion, *MGMT* promoter methylation), and survival data were retrieved from The Cancer Genome Atlas. MR images were reviewed, in consensus, by 2 board-certified neuroradiologists (with 8 and 17 years of experience) who were blinded to pathologic and molecular diagnosis. The order of cases viewed was randomized to avoid bias.

Each tumor was scored for 9 MR imaging features according to the following criteria modified from the Visually Accessible Rembrandt Images MR imaging feature set[19]: T2 signal intensities (higher than gray matter or mixed [the presence equal to or darker than that of gray matter part]); T2 homogeneity (homogeneous or heterogeneous); margin (well-defined or not well-defined [either infiltrative or irregular]); edema (none to minimal or mild to marked); enhancing pattern (non-/minimally enhancing or enhancing); portion of enhancing area (<50% or ≥50%); the presence of cystic areas (presence or absence); and the presence of necrotic areas (presence or absence). We investigated the relationship among 9 different MR imaging features and 3 molecular markers (*IDH* mutation, 1p/19q codeletion, and *MGMT* promoter methylation) as well as WHO grade and overall survival.

Diffusion-weighted images were analyzed using OsiriX Imaging Software (http://www.osirix-viewer.com). ADC measurements were generated by manually drawing 3 nonoverlapping ROIs ranging from 40 to 60 mm^2 within the region of lowest ADC values within the solid component of each tumor on ADC maps. The ADC value was also calculated from contralateral normal-appearing white matter by drawing a single ROI with a size similar to that of a tumoral ROI. We obtained mean, minimum (min), and maximum (max) ADCs of each tumor, respectively, by averaging the 3 ROIs; and relative ADC ($rADC_{mean}$, $rADC_{min}$, and $rADC_{max}$) was calculated by dividing the tumor ADC by the ADC of the contralateral normal-appearing white matter.

Statistical Analysis

The Kolmogorov-Smirnov test was used to determine whether the numeric data (age and relative ADC values) for each group were normally distributed. Independent variables (clinical parameter and MR imaging features) were compared using the χ^2 test among different molecular groups. Normally distributed continuous variables (eg, age) were compared using the independent *t* test or ANOVA test, and non-normally distributed continuous variables ($rADC_{mean}$, $rADC_{min}$, and $rADC_{max}$) were compared using the Mann-Whitney *U* test among different molecular groups. The intraobserver reliability of ADC value measuring was tested using intraclass correlation coefficients. The optimal cutoff value of each rADC was obtained from receiver operating characteristic curve analysis when the Youden index reached a maximum. Survival curves were estimated and plotted by the Kaplan-Meier method with log-rank tests to compare Kaplan-Meier curves among groups. Variables were first analyzed by the univariate model. MR imaging features and clinical and molecular parameters (including age, sex, WHO grade, *MGMT* promoter methylation status, *IDH* mutation status, and 1p/19q codeletion status) with statistical significance in univariate analysis ($P < .05$) were entered into a Cox proportional hazards ratio model for multivariate analysis. Statistical significance was defined as $P < .05$ for all tests. The statistical analyses were performed using the statistical software package SPSS 23.0 (IBM, Armonk, New York) and R statistical and computing software, Version 3.3.2 (http://www.r-project.org).

RESULTS

A total of 131 (59 [45%] *IDH* wild-type and 72 [55%] *IDH*-mutant) gliomas were included in this study. Of the 72 *IDH*-mutant tumors, 26 (36%) were 1p/19q codeleted and 46 (64%) were non-1p/19q codeleted. Patients in the *IDH* wild-type group (mean, 60 ± 12.2 years) were significantly older than those in the *IDH*-mutant group (mean, 45.1 ± 13.9 years), and patients with *IDH*-mutant, 1p/19q codeleted gliomas (mean, 50.7 ± 13.9 years) were older than those with *IDH*-mutant, non-1p/19q codeleted gliomas (mean, 41.9 ± 12.9 years) ($P = .01$).

Correlation between Conventional MR Imaging Features and Molecular Subtypes

Among the conventional MR imaging characteristics, *IDH* wild-type gliomas were more likely to exhibit enhancement ($P < .001$), >50% enhancing area ($P < .001$), absence of cystic area ($P = .013$), the presence of necrosis ($P < .001$), and the presence of edema ($P < .001$). Within the *IDH*-mutant group, there were no MR imaging characteristics to differentiate 1p/19q codeletion status using the features tested (Table 1).

Correlation between rADC Values and Molecular Subtypes

Median $rADC_{mean}$, $rADC_{min}$, and $rADC_{max}$ values of *IDH* wild-type gliomas were significantly lower than those of *IDH*-mutant gliomas ($P < .001$) (Fig 1 and Table 1). Within the *IDH*-mutant

Table 1: MR imaging features and *IDH*-mutation and 1p/19q codeletion status

	IDH Wild-Type	*IDH*-Mutant	*P*	*IDH*-Mutant, Non-1p/19q Codeleted	*IDH*-Mutant, 1p/19q Codeleted	*P*
MR imaging features (No.) (%)						
T2 signal intensities[a]						
>Gray matter	13 (22.4%)	30 (43.5%)	.012[c]	21 (48.8%)	9 (34.6%)	.248
>Mixed	45 (77.6%)	39 (56.5%)		22 (51.2%)	17 (65.4%)	
T2 homogeneity[a]						
Homogeneous	6 (10.3%)	14 (20.3%)	.125	10 (23.3%)	4 (15.4%)	.544
Heterogeneous	52 (89.7%)	55 (79.7%)		33 (76.7%)	22 (84.6%)	
Margin						
Well-defined	32 (54.2%)	27 (38.0%)	.065	20 (44.4%)	7 (26.9%)	.143
Mixed	27 (45.8%)	44 (62.0%)		25 (55.6%)	19 (73.1%)	
Edema						
No-to-minimal	20 (33.9%)	57 (79.2%)	<.001[c]	38 (82.6%)	19 (73.1%)	.339
Mild-to-marked	39 (66.1%)	15 (20.8%)		8 (17.4%)	7 (26.9%)	
Enhancing pattern[b]						
None/minimally enhancing	4 (7.0%)	30 (42.3%)	<.001[c]	19 (41.3%)	11 (44.0%)	.826
Enhancing	55 (93.2%)	41 (56.9%)		27 (58.7%)	14 (56.0%)	
Proportion of enhancing area[b]						
<50%	14 (23.7%)	63 (88.7%)	<.001[c]	40 (87.0%)	23 (92.0%)	.704
≥50%	45 (76.3%)	8 (11.3%)		6 (13.0%)	2 (8.0%)	
Cystic area						
Presence	5 (8.5%)	28 (39.4%)	.013[c]	26 (56.5%)	17 (65.4%)	.461
Absence	54 (91.5%)	43 (59.7%)		20 (43.5%)	9 (34.6%)	
Necrotic area[b]						
Presence	49 (83.1%)	16 (22.5%)	<.001[c]	38 (82.6%)	17 (68.0%)	.159
Absence	10 (16.9%)	55 (77.5%)		8 (17.4%)	8 (32.0%)	
$rADC_{mean}$ (median)	1.1	1.6	<.001[c]	1.7	1.5	.071
$rADC_{min}$ (median)	0.9	1.4	<.001[c]	1.4	1.3	.178
$rADC_{max}$ (median)	1.3	1.8	<.001[c]	1.9	1.7	.106

[a] There were 4 cases lacking T2 MR images.

[b] One case in the *IDH*-mutant group lacked postcontrast studies.

[c] Statistically significant ($P < .05$).

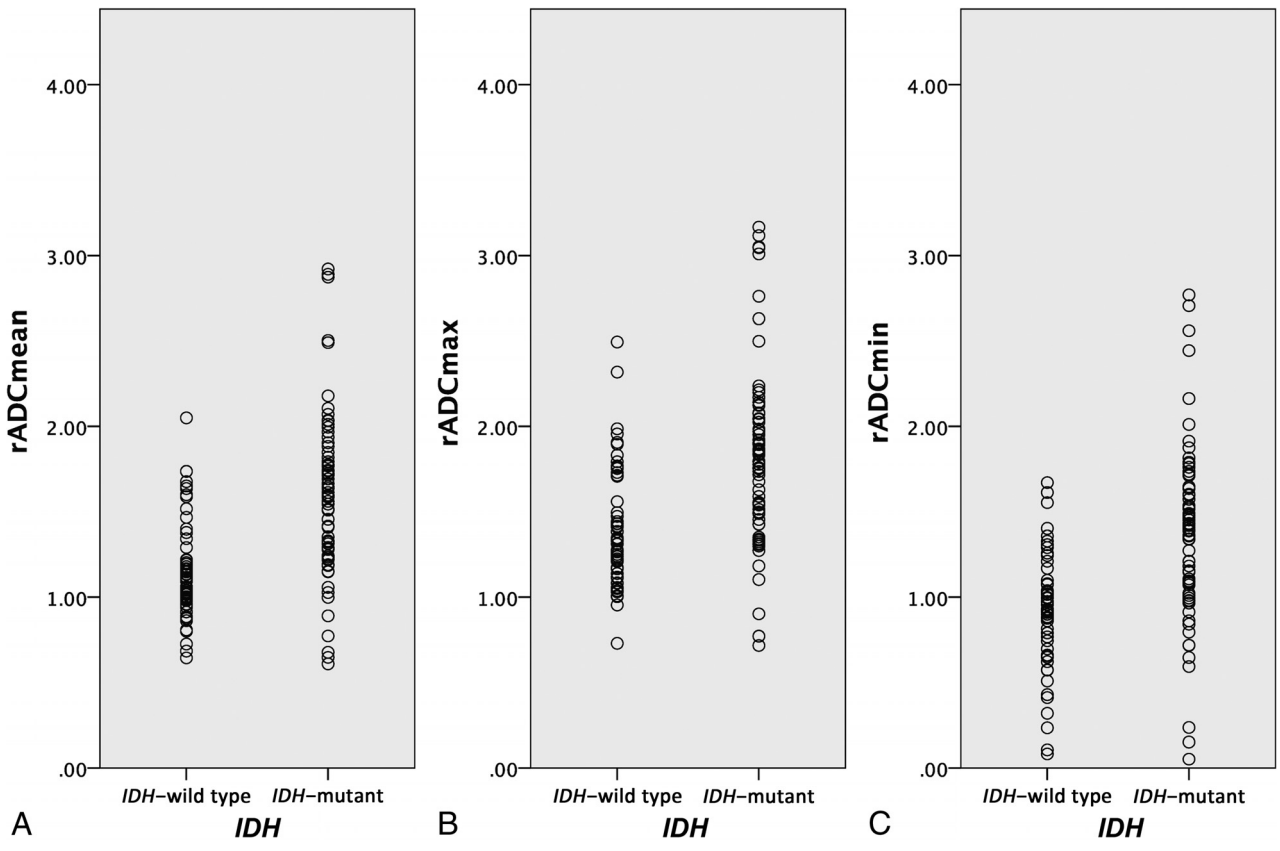

FIG 1. Boxplot representation of $rADC_{mean}$ values by glioma *IDH* genotype.

Table 2: Comparison of overall survival by relative ADC and glioma *IDH*-mutation status

Variable[a]	Case No.	Survival Time[b]	Coefficient (β)	*P* Value
IDH mutant, high $rADC_{mean}$	63	62.0		
vs *IDH* mutant, low $rADC_{mean}$			.141	.003
vs *IDH* wild-type, high $rADC_{mean}$			.06	<.001
vs *IDH* wild-type, low $rADC_{mean}$			.24	<.001
IDH mutant, low $rADC_{mean}$	9	24.2 (0.0–55.0)		
vs *IDH* wild-type, high $rADC_{mean}$			.45	.614
IDH wild-type, high $rADC_{mean}$	30	17.7 (11.6–23.7)		
vs *IDH* wild-type, low $rADC_{mean}$			.25	.041
IDH wild-type, low $rADC_{mean}$	29	10.4 (4.4–16.4)		
vs *IDH* mutant, low $rADC_{mean}$			.51	.179

[a] High $rADC_{mean}$: $rADC_{mean}$ values ≥ 1.08; low $rADC_{mean}$: $rADC_{mean}$ values < 1.08.
[b] Survival time is expressed as median (95% CI) (months).

glioma cohort, rADC values trended lower in 1p/19q codeleted gliomas than in noncodeleted gliomas; however, this trend did not reach statistical significance. Receiver operating characteristic analysis identified an $rADC_{mean}$ of 1.2 as the optimal cutoff value to differentiate *IDH* wild-type and *IDH*-mutant gliomas irrespective of WHO grade, with the best combination of sensitivity (81.9%) and specificity (74.6%) and area under the curve (0.790; 95% CI, 0.707–0.869; $P < .001$). In the analysis of intraobserver reliability, the intraclass correlation coefficients indicated a good correlation of the first evaluator (intraclass correlation coefficient, 0.951; 95% CI, 0.829–0.987; $P < .001$) and the second evaluator (intraclass correlation coefficient, 0.926; 95% CI, 0.785–0.975; $P < .001$).

Correlation between rADC and Overall Survival

Median overall survival was 25.4 months (95% CI, 19.0–31.7 months), and overall cumulative survival rates were 79% at 1 year, 59% at 2 years, 42% at 3 years, and 36% at 5 years in all 131 cases. Univariate survival analysis found survival to be significantly related to 6 MR imaging features, including T2 homogeneity, enhancing pattern, enhancing areas, presence of necrosis, $rADC_{mean}$, and $rADC_{min}$ values, in addition to age, WHO grade, *MGMT* promoter methylation status, *IDH*-mutation status, and 1p/19q codeletion status.

Multivariate analysis identified *IDH* status and $rADC_{mean}$ as the only prognostic factors that independently impacted overall survival after considering the WHO grade, *MGMT* promoter methylation, and 1p/19q codeletion status and adjusting for patient age. Specifically, *IDH*-mutant gliomas had significantly longer overall survival (median, 62.0 months) than *IDH* wild-type gliomas (median, 14.7 months) ($P < .001$ by log-rank test; age-adjusted hazard ratio, 13.5; 95% CI, 4.8–38.4; $P < .001$ by multivariate Cox analysis). Overall cumulative survival rates were 97% at 1 year, 71% at 3 years, and 61% at 5 years in *IDH*-mutant gliomas, and 76% at 1 year and 13% at 3 years in *IDH* wild-type gliomas. Gliomas with higher $rADC_{mean}$ had longer overall survival compared with those with lower $rADC_{mean}$ ($P = .001$ by univariate regression; age-adjusted hazard ratio, 0.17; 95% CI, 0.1–0.6; $P = .004$ by multivariate Cox analysis). No statistically significant differences were noted for the remaining MR imaging features, WHO grade, *MGMT* promoter methylation status, and 1p/19q codeletion status in multivariate analysis.

By means of the area under a time-dependent receiver operating characteristic curve for prediction of survival at 12 months, the optimal cutoff value of 1.08 for $rADC_{mean}$ could differentiate survival differences within both *IDH*-mutant and *IDH* wild-type gliomas. Patients having *IDH*-mutant gliomas with an $rADC_{mean}$ below the cutoff value of 1.08 had poorer survival than those with an $rADC_{mean}$ above 1.08 ($P < .001$). In addition, median survival associated with *IDH*-mutant gliomas with a low $rADC_{mean}$ was very poor. Survival time for this group was similar to that of those with *IDH* wild-type gliomas with either high or low $rADC_{mean}$ (Table 2 and Fig 2). Finally, the $rADC_{mean}$ cutoff value of 1.08 could also distinguish a survival difference within *IDH* wild-type gliomas ($P < .041$).

DISCUSSION

Mutations in the *IDH* genes are among the most important diagnostic and prognostic markers of diffuse gliomas.[20] Patients with *IDH*-mutant gliomas have significantly longer survival compared with those with *IDH* wild-type gliomas, and management of these 2 molecular subgroups differs significantly. Previous studies have investigated the potential of various conventional and advanced MR imaging characteristics, including perfusion, diffusion tensor, and MR spectroscopy, in identifying genetic subtypes of diffuse gliomas.[10,21,22] Here, our results indicate that rADC values correlate with *IDH* mutation status as well as survival in both *IDH*-mutant and *IDH* wild-type diffuse gliomas, independent of their WHO grade. Additionally, using rADC, we could identify a particularly poor prognosis subset of *IDH*-mutant gliomas, with outcomes similar to those in patients *IDH* wild-type disease. Most important, determining the rADC value is a simple approach that requires no specialized software; hence, our findings potentially have immediate clinical impact.

The mechanism by which *IDH*-mutant and *IDH* wild-type gliomas differ in terms of the rADC is not clear; however, it may be related to tumor cellularity. In many previous studies, DWI has shown utility for preoperative grading and outcome of gliomas and for evaluating the response to therapy in patients with glioblastoma.[13,23-27] ADC values provide quantitative information that reflects Brownian motion of water molecules within a scanned area and are determined by many factors. Mainly, differences in ADC have been attributed to tumor cellularity but also to the presence of necrosis or cysts and water content in interstitial space.[11,13,28] ADC has been shown to correlate inversely with tumor cellularity on histologic examination, one of the main features of the WHO classification of brain tumors. Our results demonstrate that most *IDH*-mutant gliomas exhibit higher $rADC_{mean}$ values and MR imaging features accordant with their low-grade features, while most *IDH* wild-type gliomas show necrosis and a lower $rADC_{mean}$ in solid portions, likely representing higher cellularity, which is associated with higher grade features.

Previous studies have observed an association between ADC and *IDH* status in gliomas. One study of 37 anaplastic astrocytomas showed that the minimum ADC (cutoff point, 0.95×10^{-3} mm^2/s) had acceptable discrimination (area under the curve,

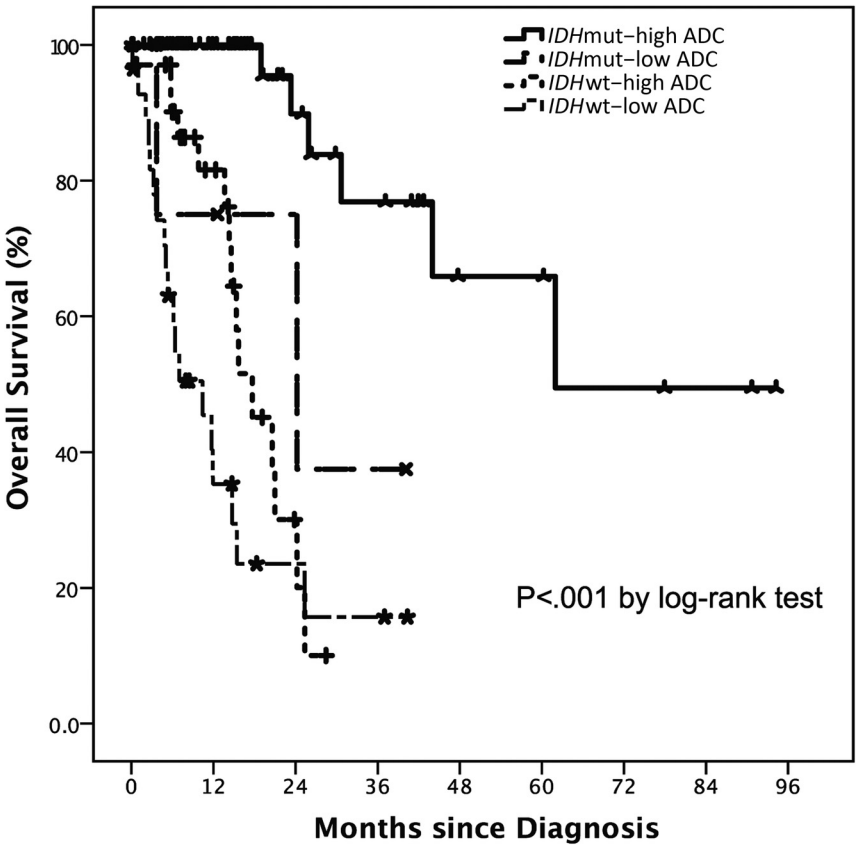

FIG 2. Kaplan-Meier survival curve subclassification for the present study by relative ADC and *IDH* genotype. Censored patients are annotated by a asterisks or plus signs. Results of the analysis are provided in Table 2. *IDH*mut indicates *IDH*-mutant; *IDH*wt, *IDH* wild-type.

0.711; 95% CI, 0.534–0.887) to predict the *IDH* status.[29] Another retrospective study of 112 cases by Tan et al[30] demonstrated that fractional anisotropy and ADC from diffusion tensor imaging can detect *IDH1* mutation in astrocytomas, with the ratio of ADC_{min} being the best metric for detecting *IDH* mutation, regardless of the WHO grade. We found that $rADC_{mean}$ can differentiate *IDH* wild-type from *IDH*-mutant gliomas with excellent discrimination, regardless of WHO grade. Our study also emphasizes MR imaging and ADC values correlating well with molecular subtype.

The main novel finding of our study is that preoperative rADC values can distinguish favorable and unfavorable prognosis within both *IDH*-mutant and *IDH* wild-type glioma subgroups. While *IDH*-mutant gliomas generally behave less aggressively and have a better prognosis compared with their *IDH* wild-type counterparts, we identified a small subset (12.5%) of *IDH*-mutant gliomas with low $rADC_{mean}$ values and poor overall survival, which was only slightly better (24 months) than that of *IDH* wild-type gliomas but was not statistically significant. Concordantly, a study by Jiao et al[31] revealed that a small subgroup (11.7%) of patients with *IDH*-mutant gliomas across all grades had a dismal prognosis (median survival of 22 months), more similar to *IDH* wild-type gliomas and glioblastomas in their cohort. These tumors had distinct genetic characteristics, lacking the typical concurrent genetic alterations observed in *IDH*-mutant gliomas. In addition, a recent study of The Cancer Genome Atlas identified a small subset (5.5%) of *IDH*-mutant gliomas with markedly worse survival than other *IDH*-mutant gliomas, and these tumors were associated with relatively decreased global DNA methylation.[32] Together, these data clearly indicate that a subgroup of *IDH*-mutant gliomas behaves as aggressively as their *IDH* wild-type counterparts. Although whether the malignant subgroups across these datasets represent the same biology is unknown, our results suggest that rADC values can potentially identify this aggressively behaving *IDH*-mutant subgroup.

Furthermore, our study highlights how detection of robust imaging-phenotype correlations can be significantly improved by analyzing glioma datasets by molecular subtype rather than by histopathologic classification. We evaluated MR imaging features and prognosis in diffuse gliomas across lower and higher grades in the current study and demonstrated the power of $rADC_{mean}$ to differentiate *IDH*-mutation status and discrete survival subgroups beyond WHO grade. While many previous studies have demonstrated an inverse relationship between ADC and astrocytoma grade,[12,13,28] other studies have shown substantial overlap of ADC values between high-versus-low-grade gliomas[3,24,33,34] and no significant differences between grade II versus III[35] or grade III versus IV.[36,37] These observed variations of ADC in predicting tumor grade are likely due to limitations that make the exact histopathologic classification challenging, with high interobserver variability[2] and molecular constituent and clinical behavior being likely different in tumors with the same histopathologic grade.[3,4,38,39] Similar to a recent meta-analysis by Zulfiqar et al,[27] which showed that low ADC values correlate independently with poor survival in malignant astrocytomas (grades III and IV),

we found an inverse relationship between $rADC_{mean}$ values and prognosis for both *IDH*-mutant and *IDH* wild-type tumors independent of WHO grade.

One limitation of our study is its retrospective design, which was necessary to include a relatively large number of patients and to correlate with survival, which is relatively long in patients with *IDH* mutation. A second limitation is that the studied patients had been scanned on different MR imaging magnet types, and ADC maps were generated by diffusion-weighted imaging or diffusion tensor imaging of all collected data. However, a previous study has verified that ADC datasets from 3-directional DWI and 6-directional diffusion tensor imaging could be analyzed together.[40] We calculated the rADC to minimize the differences among absolute ADC values across platforms. Third, the treatment regimen applied to each patient was not available to us in many cases. This issue might have potentially impacted the outcome and survival in each case. However, *IDH* status has been repeatedly shown to be an independent marker of prognosis in independent datasets.[4] Finally, the ADC value has previously been reported to predict 1p/19q codeletion status, a marker of oligodendroglioma, in lower grade gliomas.[35,41] In the study by Johnson et al,[41] the ADC values were calculated from sampling both the highest and lowest ADC areas. However, we did not detect a significant correlation between rADC values and 1p/19q codeletion status. Further investigation of the optimal methods of measuring ADC and physiology correlates of ADC values in genetically defined oligodendroglioma is needed.

Our results require independent confirmation, incorporating emerging molecular markers and accounting for different treatment strategies. However, our results expand on and refine the existing correlation between DWI and tumor genetic markers and highlight its potential role as an independent imaging biomarker that can aid in substratification of patients with gliomas, both *IDH*-mutant and *IDH* wild-type. Here, we were able to identify a subset of aggressive *IDH*-mutant gliomas using ADC values easily obtained from common clinical MR images. Ongoing accumulation of tumorigenesis knowledge, together with imaging studies stratified by molecular subgroup rather than histopathologic features, will likely identify additional robust genetic-imaging-clinical phenotype correlations that will improve early detection of clinically meaningful glioma molecular subtypes.

CONCLUSIONS

We demonstrate that ADC values obtained from DWI correlate with *IDH*-mutation status and overall survival in adult diffuse gliomas. *IDH* wild-type gliomas showed low ADC values and poor survival compared with *IDH*-mutant gliomas. Within *IDH*-mutant gliomas, a small subgroup with lower ADC values had dismal survival, similar to that in *IDH* wild-type gliomas. ADC values correlated with survival in patients with *IDH*-mutant and *IDH* wild-type gliomas regardless of WHO grade. Preoperative ADC estimates may corroborate with molecular subtypes as a prognostic marker and potentially enhance risk stratification, especially within *IDH*-mutant gliomas.

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