Applying MAP-MRI to Identify the WHO Grade and Main Genetic Features of Adult-type Diffuse Gliomas: A Comparison of Three Diffusion-weighted MRI Models

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Rationale and Objectives: Currently, there is no noninvasive method to effectively judge the genotype of diffuse gliomas. We explored the association between mean apparent propagator-MRI (MAP-MRI) and WHO grade 2/3, IDH 1/2 mutations, and chromosome 1p/19q combined deletion genotypes in adult-type diffuse gliomas and compared it with the diagnostic efficiency of diffusion tensor imaging (DTI) and diffusional kurtosis imaging (DKI).

Materials and Methods: We prospectively recruited 67 participants histopathologically diagnosed with adult-type diffuse gliomas. Routine MRI, DKI, and DSI were performed before surgery. The extreme and average partial diffusion indexes of solid tumors were measured. A comprehensive assessment of statistically significant diffusion parameters was performed after Bonferroni correction, including ROC curves, correct classification percentage (CCP), integrated discrimination improvement (IDI), net reclassification improvement (NRI), and k-fold cross validation.

Results: For differentiating WHO grade 2/3, q-space inverse variance (QIV), mean kurtosis (MK), non-Gaussianity (NG), and return to the origin probability (RTOP) were different ($p' < .05$), with the mean QIV exhibiting the best diagnostic efficacy and stability (AUC = 0.973, CCP = 0.906). We observed significant differences in mean diffusivity (MD), mean square displacement, QIV, MK, and RTOP between the IDH wild-type and IDH mutant groups ($p' < .001$) (AUC, 0.806 – 0.978) and MAP-MRI showed a higher IDI than DTI and DKI (0.094 – 0.435, NRI > 0, respectively). For the chromosome 1p/19q combined deletion, the minimum QIV was different between the overall ($p' < .05$) and no significant differences in MD and MK was observed.

Conclusion: MAP-MRI effectively predicts the WHO grade 2/3, IDH 1/2 mutations, and chromosome 1p/19q combined deletion in adult-type diffuse gliomas, and it may perform better than DTI and DKT.

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Abbreviations: 1p/19q synchronous deletion of the short arm of chromosome 1 and long arm of chromosome 19, CCP correct classification percentage, DKI diffusion kurtosis imaging, DSI diffusion spectrum magnetic resonance imaging, FA fractional anisotropy, IDH isocitrate dehydrogenase, IDHmut/1p19qdel IDH mutant and chromosome 1p19q synchronous deletion, IDHmut/1p19qint IDH mutant and chromosome 1p19q intact, IDHwt IDH wild-type, IDI integrated discrimination improvement, MAP-MRI mean apparent propagation diffusion MRI, MD mean diffusivity, MK mean kurtosis, MSD mean square displacement, NG non-Gaussianity, NRI net reclassification improvement, QIV q-space inverse variance, ROI region of interest, RTOP return to the origin probability

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INTRODUCTION

Gliomas account for 80% of all primary central nervous system malignancies (1). Even when surgery, radiotherapy and chemotherapy are actively used, patients usually have a poor prognosis (2). Previous studies have clarified part of the genetic basis of gliomas, information that has helped classify gliomas and has provided prognostic and predictive data for patients (3-5). The 2021 edition of the World Health Organization (WHO) classification of central nervous system tumors increases the importance of the genetic features of diffuse gliomas, compared to the 2016 edition, and may enable reclassification of the histologic grading in certain characteristic cases (6). Advanced knowledge of the histological and genetic characteristics of the tumor is a fundamental and necessary step to optimize the treatment process, because the scope of surgical resection and subsequent concurrent radiotherapy and chemotherapy are usually based on this information (7). Currently, histopathological analysis and genetic testing of tumor specimens are regarded as the gold standards for glioma analysis. However, in some cases, tumor tissues may not be effectively obtained, or genetic testing may not be possible. Because of the heterogeneity of these tumors, a small amount of pathological material may lead to a misdiagnosis in the classification, grading and genetic feature detection of gliomas (8) or incorrect results caused by the detection technology itself (9). These factors affect the diagnosis, treatment and prognosis of this disease. Therefore, a feasible technology or imaging method is required that can effectively provide genotype information.

The application of diffusion models in neuro-oncology is extensive (10). Several studies have used various diffusion models to genotype gliomas (11-15). Some conventional imaging features are thought to be helpful in predicting the hereditary features of gliomas, such as MRI anatomical imaging (11). However, the accurate manual extraction of imaging features relies on radiologists, which may lead to errors in prediction due to subjective bias, particularly for some patients whose imaging features are not prominent. Thus, an imaging method with high robustness and accuracy is needed to predict the molecular genotype of diffuse gliomas. Diffusion tensor imaging (DTI) is a technique based on DWI that expresses the approximate Gaussian distribution of water molecules in tissues. Tan et al. (12) reported that DTI distinguishes the IDH genotype of gliomas. However, of particular concern is that the movement of water molecules in the actual tissue is affected by various factors, and the distribution is non-Gaussian. Diffusion kurtosis imaging (DKI) is believed to describe the non-Gaussian distribution of water protons in the brain (16). However, to date, there has been little agreement on whether DKI can distinguish between the IDH 1/2 mutation and chromosome 1p/19q combined deletion genotypes in diffuse gliomas (13,14).

Mean apparent propagator-MRI (MAP-MRI) is a newer computational framework based on the acquisition of q-space data for diffusion spectrum magnetic resonance imaging (DSI) (17-19). The technology includes DTI, which may be used to not only evaluate the non-Gaussian distribution of water molecules in brain tissue but also effectively measure the probability density function of spin displacement and quantify useful indicators of the probability density function. These indexes reflect the diffusion of protons in complex microstructures (such as diffusion confinement and multiple chambers). MAP-MRI has been reported to be superior to DTI (20) and has been used to detect changes in diffusion parameters caused by different grades or different genetic features of diffuse gliomas (21,22), but the old grouping method may lead to incorrect clinical practical applications. The aim of this study was to describe the association between MAP-MRI and the histological and main genetic features of diffuse gliomas by applying the latest WHO classification criteria method, including WHO grade 2/3, IDH1/2 mutations and 1p/19q combined deletion genotypes, and to further compare its diagnostic efficacy with DTI and DKI.

MATERIALS AND METHODS

Participants and Clinical Data

We conducted a prospective study and recruited participants who visited our hospital between June 2018 and September 2021. The study was conducted in accordance with the Declaration of Helsinki. The ethics committee of our hospital approved the research protocol (Number: WZ 2022019), and all participants signed an informed consent form before the examination. The inclusion criteria for this study were as follows: (1) adult-type diffuse gliomas were pathologically diagnosed according to the 2021 WHO standards, (2) scan sequences included conventional MRI and diffusion scans (the diffusion imaging scans included at least one DKI or DSI sequence due to long scan times or a poor participant status; when the participant’s cooperation was low, the principle of randomness was adopted) with ideal image quality, (3) surgery was performed within 3 months after the scan, and (4) genotyping tests for tumor correlation were performed. The exclusion criteria were participants with glioma who had received preoperative treatment (including steroids, radiotherapy, chemotherapy, or concurrent radiotherapy and chemotherapy) and gliomas in which it was difficult to draw the region of interest (ROI). An overview of the participants selection process is shown in Figure 1.

In a previous study, 36 participants with diffuse glioma were included, and the study compared the differences in MAP-MRI parameters between groups of participants with different grades of diffuse glioma (21). In the present study, 27 participants from this previous study were included. We classified IDH wild-type participants with histologic grade 2/3 and TERT promoter mutation as the grade 4 group according to the 2021 WHO criteria. Finally, three such participants were included in the study, and the remaining hereditary features that might increase the histologic grade will be examined in future studies. According to the IDH
1/2 mutation and 1p/19q combined deletion genotypes, the participants were divided into three groups: participants were first divided into the IDH wild type (IDHwt) group and IDH mutant type (IDHmut) group, and then the IDHmut group was divided into IDH mutant and 1p19q intact (IDHmut/1p19qint) group and IDH mutant and 1p19q synchronous deletion (IDHmut/1p19qdel) group.

**Pathology**

All the tissue samples were prepared as paraffin blocks and analyzed at our institution’s pathology department using the latest methodology consistent with the WHO 2021 guideline on histopathology and immunohistochemistry (6). The pathologist (Lixin Weng) who analyzed the images had 23 years of work experience and was blinded to the clinical information and imaging results. A one-step method (multiplex PCR amplification combined with next-generation sequencing [NGS]) was used to detect the IDH1/2 mutation, 1p/19q combined deletion genotypes and TERT promoter mutation (27,28). See the supporting materials for specific steps.
Statistical Analysis

The statistical software packages SPSS 24.0 (SPSS, Inc., Chicago, IL, USA), Medcalc Version 19.7.4 (MedCalc Software Ltd, Ostend, Belgium) and R version 4.1.2 were used to analyze the data. For the data that conformed to a normal distribution and equal variances (determined by Levene’s test for the homogeneity of variance), an independent-samples $T$ test was used for comparison. If the aforementioned conditions were not met, the Mann–Whitney $U$ test was used for analysis. The Bonferroni correction was used to correct for multiple comparisons, using $P'$ instead of $P$, and receiver operating characteristic (ROC) curves and the correct classification percentage (CCP) (29) were determined for the parameters that were statistically significant ($p' < .05$). Previous studies have suggested a correlation between the three models (14,18,30,31), and thus we compared them by performing Spearman’s rank correlation analysis (Supplementary Table E6). Differences in efficacy between the parameters were assessed using the DeLong test, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) (29). We aimed to more robustly evaluate the diagnostic efficacy, stability, and generalizability of diffusion parameters by performing $k$-fold cross validation ($K = 5$).

RESULTS

Participant Distribution

During the study period, 291 participants with suspected glioma were evaluated. Finally, 224 participants were excluded, and 67 participants with diffuse glioma (mean age, 50 ± 12 years [standard deviation]; 35 men) were included from June 2018 to September 2021. Twenty-four of these participants had undergone only one DKI or DSI scan, and thus the final test set included 55 sets of images. The characteristics of the participants are shown in Table 1.

Diffusion Parameters Quantify the Molecular Type of Diffuse Glioma

Twenty-five enhancements in 25 IDHwt tumors, nine enhancements in 17 IDHmut/1p19qint tumors, and 18 enhancements in 25 IDHmut/1p19qdel tumors were identified. The interobserver reproducibility of all the diffusion parameters was good (ICC, 0.857–0.993) (Online Supplemental Data).

In the correlation comparison of the three diffusion model parameters, a positive correlation was found between MD, MSD, and QIV with correlation coefficients ranging from 0.485 to 0.902. A positive correlation was found between MK, NG, and RTOP with correlation coefficients ranging from 0.522 to 0.863. A negative correlation was found between MD, MSD, and QIV and MK, NG, and RTOP with correlation coefficients ranging from −0.362 to −0.987. No significant correlation was found between FA and the other parameters ($p < .05$) (Online Supplemental Data).

WHO 2 and WHO 3

In grade 2/3 adult-type diffuse gliomas, the average and minimum QIV values of the grade 3 group were
significantly lower than those of the grade 2 group ($p < .01$), and the average and maximum MK, NG, and RTOP values were significantly higher than those in the grade 2 group ($p < .05$). The MD, MSD and FA values showed nonsignificant results ($p > .05$) (Online Supplemental Data and Fig. 3 and 4). Cohen’s $d$ values ranged from 1.835–2.548. The average QIV had both the highest AUC and CCP (0.973 and 0.906, respectively), and was very stable. NG may be superior to MK in predicting the tumor grade ($IDI = 0.408$ and 0.266, respectively; $NRI = 0.063$ and 0.031, respectively), but the instability of diagnostic efficacy is a concern.

**IDH**mut and **IDH**wt

In all the adult-type diffuse gliomas, the average and minimum MD, MSD, and QIV values of the IDH**wt** group were significantly lower than those of the IDH**mut** group ($p < .001$), and the average and maximum MK, NG, and RTOP values were significantly higher than those in the IDH**mut** group ($p < .001$). The FA values showed nonsignificant results ($p > .05$) (Online Supplemental Data and Fig 3). Cohen’s $d$ values ranged from 1.348–2.236. The ROC curve and its characteristics are shown in Figure 4 and Supplementary Table E5, with values ranging from 0.834 to 0.978, where QIV had the highest CCP. MSD, QIV and RTOP showed a higher IDI than MD (0.189–0.435 and NRI > 0, respectively), but seemed to produce the mean and extreme values with the same effect (Online Supplemental Data). The fivefold cross validation results are shown in Supplementary Table E7. The maximum RTOP value had the highest AUC (0.911 ± 0.071). The maximum NG value had the lowest accuracy (0.653 ± 0.364).

**IDH**mut/1p19q**int** and **IDH**mut/1p19q**del**

In all the adult-type diffuse gliomas, only the minimum QIV value of the IDH**mut/1p19q**int group was lower than that of the IDH**mut/1p19q**del group ($p < .05$), and none of the remaining diffusion parameters showed differences between groups ($p > .05$). Cohen’s $d$ was 1.181. However, after excluding the effect of grade, the average QIV and RTOP appeared able to identify the 1p/19q combined deletion genotype ($p < .05$). The AUC and CCP of the minimum QIV were not as high as expected (0.806 and 0.563, respectively), but high robustness (0.870 ± 0.105) was observed after fivefold cross validation.

**DISCUSSION**

In this study, the average and extreme values of the diffusion parameters of solid tumors were measured simultaneously, and the diagnostic performance of three diffusion-weighted models (including MAP-MRI, DTI, and DKI) was compared for adult-type diffuse gliomas (AUC, 0.806–0.978; CCP, 0.563–0.909) with histological grade 2/3, IDH 1/2 mutation, and 1p/19q combined deletion genotypes. Our results show that the multishell MAP-MRI model effectively distinguishes the histological and main genetic features of adult-type diffuse gliomas based on the latest WHO classification criteria, especially QIV. MD and FA are not able to be used to discriminate histological grade 2/3, while the stability of MK is poor. According to the present study, MD and MK do not effectively predict the 1p/19q combined deletion genotype. These results may be facilitated by the assumption that MAP-MRI does not rely on a priori models, unlike the Gaussian and non-Gaussian distribution models of DTI and DKI.
In most studies, the rationale for standardization is to eliminate individual differences (11, 13, 22). We believe that the parameters corresponding to the solid part of the tumor depend mainly on the tumor itself rather than the damaged white matter of the brain. In our study, no difference was observed in the FA values among the groups, which demonstrated this hypothesis. However, some researchers have revealed residual fiber bundles within tumors (32). Standardization still needs to be discussed. In addition, we do not know whether the white matter of the contralateral hemisphere is infiltrated by tumor cells (33, 34), or whether diffuse imaging is affected by the spatial resolution and cannot be used to effectively describe small changes in the solid part of a tumor (35). Therefore, we did not correct for these parameters. Shortening the scanning time is necessary. However, simultaneous multislice inspection may bias the extraction of diffusion features (36), and singleshell diffusion scanning may be less affected than multishell model. The selection of rationalized scanning parameters requires further investigation.

Our study revealed that water molecules in IDH wild-type adult-type diffuse gliomas are more restricted than those in IDH mutants, consistent with previous studies (11-14, 22). Combined with the findings reported by Wang et al. (21), we postulate that MSD effectively assesses the IDH status irrespective of rank because it explicitly calculates second-order moment tensors of the mean apparent propagator (30, 31). This same conclusion is maintained under the new classification and may be related to the epigenetics, metabolism, and redox homeostasis of tumor cells, which change the tumor extracellular volume (14, 22). IDHwt glioma has the worst prognosis (3-5), which indirectly shows the reliability of our conjecture. We propose that this finding might represent a breakthrough, as previous diffusion parameters have been influenced by the glioma grade (12-14, 21), resulting in conflicting clinical applications.

Our study did not find that MD is useful to identify WHO grade 2/3 tumors, possibly because typically IDH mutant gliomas show a larger extracellular volume as a percentage of the tumor volume than IDH wild-type gliomas (14, 22), thereby reducing the extent to which MD captures this part of the microstructure as a quantitative parameter in the Gaussian model. This characteristic allows the remaining tumor biomorphology within the group to be classified as relatively uniform after the exclusion of IDH wild-type gliomas. Numerical overlap has been described in previous studies; thus, complete reliance on diffusion parameters for classification or molecular type identification is impossible (11-14, 21). We also encountered this problem in our study. However, we found that QIV did not show obvious numerical overlap in some of the groups. As a surrogate indicator of MSD, QIV has a similar contrast to MSD in different tissue types (31), and QIV is significant and stable in predicting the 1p/19q
combined deletion. Reductions in RTOP are associated with axonal damage to fiber bundles, accompanied by an increase in isotropic tissue (18). After comparing the white matter of the contralateral side (21), we surmise that this change reflects diffuse tumor infiltration with an increased cell density in the extracellular matrix, which has a certain correlation with tumor heterogeneity. After eliminating the effect of the grade, RTOP also identifies the 1p/19q combined deletion, probably because RTOP appears to reflect cellularity and restrictions better than MD (18). The accuracy of the minimum QIV or maximum RTOP alone for predicting the IDH mutation status of adult-type diffuse gliomas (AUC = 0.97) surpassed that of ADC (DWI; AUC maximum, 0.83) (11), MD (DTI; AUC maximum, 0.93) (12) and KA (neurite orientation dispersion and density imaging; AUC maximum, 0.76) (14). Based on these results, QIV and RTOP may strongly correlate with the IDH1/2 mutation and 1p/19q combined deletion.

Oligodendrogial tumors with the 1p/19q combined deletion often show calcification on conventional images, but we found that MK does not identify the 1p/19q combined deletion, similar to the conclusion reported by Figini (14). However, Hempel et al. (13), Chu et al. (15), and Gao et al. (37) documented the opposite results, which may be caused by the difference in b value and ROI selection. The scan time is usually also reduced because the NG may be more sensitive to local reference frame estimates, which may be influenced by differences in the subject’s head orientation and motion (18).

However, in a similar study where the scan time was reduced, NG still did not seem to perform very well (37).

Our research has some limitations. First, participants with grade 4 IDH\textsuperscript{mut} glioma were not included in this study due to the insufficient sample size, which may have resulted in some erroneous results. However, the proportion of all our participants with glioma was approximately the same as their natural epidemiological rate. Therefore, we will continue to collect relevant samples or overcome this limitation by conducting multicenter research. In addition, in future studies, we will evaluate the direct acquisition of DTI and DKI parameter maps through the postprocessing and analysis of DSI. When the scan parameters are the same, the differences between DTI, DKI and MAP-MRI can be evaluated. This approach may effectively avoid the difference in results caused by the use of different scanning parameters. Finally, an
integrated diagnostic model should be built in the future that includes information such as conventional clinical information and conventional image features.

In conclusion, mean apparent propagation diffusion-MRI is useful to identify adult-type diffuse gliomas with WHO grade 2/3, IDH 1/2 mutation, and 1p/19q combined deletion genotypes with higher diagnostic efficacy and robustness than DTI and DKI. Although it may not currently exhibit a detection performance that exceeds that of pathology, the noninvasiveness of imaging-based detection is still beneficial for the diagnosis and treatment of patients with glioma.

COMPLIANCE WITH ETHICAL STANDARDS

Guarantor
The scientific guarantor of this publication is Yang Gao.

Statistics and Biometry
One of the authors has significant statistical expertise. No complex statistical methods were necessary for this paper.

Informed Consent
Only if the study is on human subjects:
Written informed consent was obtained from all subjects (participants) in this study.

Ethical Approval
Institutional Review Board approval was obtained.

Study Subjects or Cohorts Overlap
Some study subjects or cohorts have been previously reported in “Wang P, Weng L, Xie S, et al. Primary application of mean apparent propagator-MRI diffusion model in the grading of diffuse glioma. Eur J Radiol 2021;138:109622.”

Methodology
Methodology:

• prospective
• diagnostic or prognostic study
• performed at one institution

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.acra.2022.10.009.