

Original paper

Prediction of isocitrate dehydrogenase mutation status in WHO grade II glioma by diffusion kurtosis imaging

Wenjie Wu^{1,B,C,F}, Hui Zhang^{2,A,D}

¹Shanxi Traditional Chinese Medical Hospital, Shanxi, China

²First Hospital of Shanxi Medical University, Shanxi, China

Abstract

Purpose: Isocitrate dehydrogenase (IDH) mutation status serves as a crucial prognostic indicator for glioma, typically assessed via immunohistochemical analysis post-surgery. Given the invasiveness of this approach, perhaps we can utilise convenient and noninvasive magnetic resonance imaging (MRI) methods to predict IDH mutation status. However, the current landscape lacks a standardised MRI technique for accurately predicting IDH mutations. In this study, we explore the potential of MRI diffusion kurtosis imaging (DKI) in forecasting the IDH mutation status of WHO grade II brain gliomas.

Material and methods: Twenty-five patients with WHO grade II gliomas were retrospectively included. Patients underwent routine MRI and DKI scanning before surgery, measuring tumoural solid portion, peritumoral oedema, and normal-appearing white matter (NAWM) DKI parameters, including fractional anisotropy (FA), mean diffusivity (MD), mean kurtosis (MK), axial kurtosis (Ka), and axial radial kurtosis (Kr). The DKI parameter corrections were made (tumour or oedema parameters values divided by the NAWM value) to obtain the rFA (ratio of FA), rMD (ratio of MD), rMK (ratio of MK), rKA (ratio of KA), and rKr (ratio of Kr) values. Postoperative specimens were made of wax blocks and analysed by Sanger gene sequencing. DKI parameters between the 2 groups were compared by independent sample *t*-tests. The ROC curve was used to analyse the diagnostic value of each parameter.

Results: Twenty-five patients were diagnosed with IDH-mutant (16 cases) and IDH-wild type (9 cases). The rFA and rMK values in the parenchymal region of IDH wild-type tumour were higher than those of IDH mutant, while the rMD values were lower than those of IDH mutant, and the difference between them was statistically significant ($p < 0.05$). The values of DKI parameters of peritumoral oedema in the 2 groups were not statistically significant.

Conclusions: DKI can provide microstructural changes of diseased tissues and provide more imaging information for preoperative non-invasive judgment of IDH mutation status of WHO grade II gliomas. The values of rMK, rFA, and rMD are helpful in the assessment IDH mutation status, benefiting accurate diagnoses and treatment decisions.

Key words: gliomas, IDH mutation status, diffusion kurtosis imaging, magnetic resonance imaging.

Introduction

Glioma is the most common tumour of the intracranial central nervous system (CNS). It was previously classified as grade I-IV according to the histological characteristics of tumour. Over the past 15 years of research, gliomas with the same histology type have been found to have different genetic characteristics, such as isocitrate dehydrogenase (IDH) mutation, codeletion of chromosome 1P/19q, and promoter methylation of O⁶-methylguanine-DNA-methyltransferase (MGMT) [1]. The 2016 edition of the WHO Central Nervous System Tumour Classification uses molecular characteristics to define brain tumours for the first time on the basis of traditional histology [2]. The 2021 edition of the WHO Central Nervous System Tumour Classification continues to expand the role of

drogenase (IDH) mutation, codeletion of chromosome 1P/19q, and promoter methylation of O⁶-methylguanine-DNA-methyltransferase (MGMT) [1]. The 2016 edition of the WHO Central Nervous System Tumour Classification uses molecular characteristics to define brain tumours for the first time on the basis of traditional histology [2]. The 2021 edition of the WHO Central Nervous System Tumour Classification continues to expand the role of

Correspondence address:

Dr. Hui Zhang, First Hospital of Shanxi Medical University, Shanxi, China, e-mail: huizhangmri@163.com

Authors' contribution:

A Study design · B Data collection · C Statistical analysis · D Data interpretation · E Manuscript preparation · F Literature search · G Funds collection

molecular signatures in tumour diagnosis, defining more tumour types through molecular signatures [3]; the most dominant molecular feature is IDH mutation status. At present, many scholars have shown that IDH mutation status has great significance for the prognosis of glioma patients [4], so it is of great clinical significance to predict preoperative IDH mutation status.

Diffusion kurtosis imaging (DKI) is a magnetic resonance technology based on a non-Gaussian distribution model, which is an extension of diffusion tensor imaging (DTI) technology. DKI can quantitatively describe the non-Gaussian distribution of water molecules inside and outside cells and quantify the microstructural changes in diseased tissue. The mean kurtosis (MK) represents the average value of the diffusion kurtosis in each gradient direction in space, reflecting the complexity of the tissue structure [5]. Therefore, DKI imaging can reflect the heterogeneity of gliomas at the functional microscopic level and provide new technical means for preoperative non-invasive evaluation of IDH mutation status [6].

Material and methods

Clinical data

The clinical and imaging data of 25 patients with WHO grade II glioma in our hospital from January 2015 to October 2019 were retrospectively analysed. There were 10 males and 15 females, with an age range of 21-71 years, and the average age was about 46.32 ± 13.19 years. Twenty-five patients underwent routine magnetic resonance imaging (MRI) and DKI scanning before the operation, and they did not receive drugs, chemotherapy, radiotherapy, or other interventions before the examination. After the operation, the tissue wax block was sent to the Medical Laboratory for Sanger (dideoxy terminal termination method) sequencing to obtain IDH mutation status.

Data acquisition

A GE 3.0T superconducting magnetic resonance scanner was used to collect information with an 8-channel head-neck combined topologically phased front coil. The conventional MRI scanning sequence included axial T1WI, T2WI, T2FLAIR, sagittal T1WI, and T1WI enhanced axial, sagittal, and coronal scanning. Conventional MR sequence parameters: axial T1WI (TR = 1677 ms, TE = 25 ms, slice thickness 6.0 mm), sagittal T1WI (TR = 1710 ms, TE = 24.5 ms, slice thickness 6.0 mm), axial T2WI (TR = 6480 ms, TE = 111 ms, slice thickness 6.0 mm), and T2WI FLAIR (TR = 8000 ms, TE = 125 ms, slice thickness 6.0 mm). Enhancement sequence (TR = 1500 ms, TE = 14 ms, slice thickness 6.0 mm), contrast medium (0.1 mmol/kg body weight of Gd-DTPA) was injected at a rate of 2 ml/s, followed by a 20 ml 0.9% saline flush using the same injection speed. DKI using echo

planar imaging (EPI) sequence, scanning parameters: TR = 23,000 ms, TE = 108 ms, spatial resolution = $0.24 \times 0.24 \times 6$ mm³, layer interval: 0 mm, 30 gradient directions, $b = 0, 500, 1000, 1500, 2000, \text{ and } 2500$ s/mm².

Image post-processing and parameter measurement

DKI parameter images were obtained by Functool software on a GE Advantage Workstation 4.4 (Figures 1 and 2). Combined with MRI conventional images, the region of interest (ROI) was set in the tumour parenchyma area, peritumoral oedema area, and contralateral normal white matter area (CNAWM) at the same level. The fractional anisotropy (FA), mean diffusion coefficient (MD), mean kurtosis (MK), axial diffusion kurtosis (Ka), and radial diffusion kurtosis (Kr) of each ROI were measured. The ROI of the parenchymal area should be selected with enhanced images. If the tumour is enhanced, the tumour enhancement area is selected, and the cystic degeneration and necrotic areas are avoided at the same time. If the tumour is not enhanced and the signal in the parenchymal area is uneven, the lowest signal area of the apparent diffusion coefficient (ADC) map of the parenchymal part of the tumour is selected as the region of interest. The ROI of the peritumoral oedema area was selected near the tumour parenchyma to remove the tumour body and normal brain tissue areas. The selected ROIs were circular or elliptical; each ROI included at least 30 pixels; and each ROI was measured repeatedly 3 times to take the average value. To exclude the influence of different regional parameters in the brain, the obtained DKI parameters were divided by the contralateral normal white matter area (NAWM) to obtain the ratio of FA (rFA), ratio of MD (rMD), ratio of MK (rMK), ratio of Ka (rKa), and ratio of Kr (rKr).

Statistical analysis

The obtained data were statistically analysed using SPSS 25.0. The measurement data were expressed as mean \pm standard deviation ($\bar{X} \pm S$), and the normality of all the data was tested by a single-sample K-S test. After confirming that the data were normally distributed, 2 independent sample *t*-test were used to analyse the age, tumour parenchyma, and peritumoral oedema parameter values of the 2 groups of patients. If there were statistical differences, receiver operating characteristic curves (ROC curves) were drawn and the sensitivity and specificity were calculated. The difference was statistically significant at $p < 0.05$.

Results

Comparison of clinical data of patients

Among the 25 patients with glioma (23 diffuse astrocytomas and 2 oligodendrogliomas), there were 9 wild-type IDH (4 males and 5 females) and 16 mutant IDH

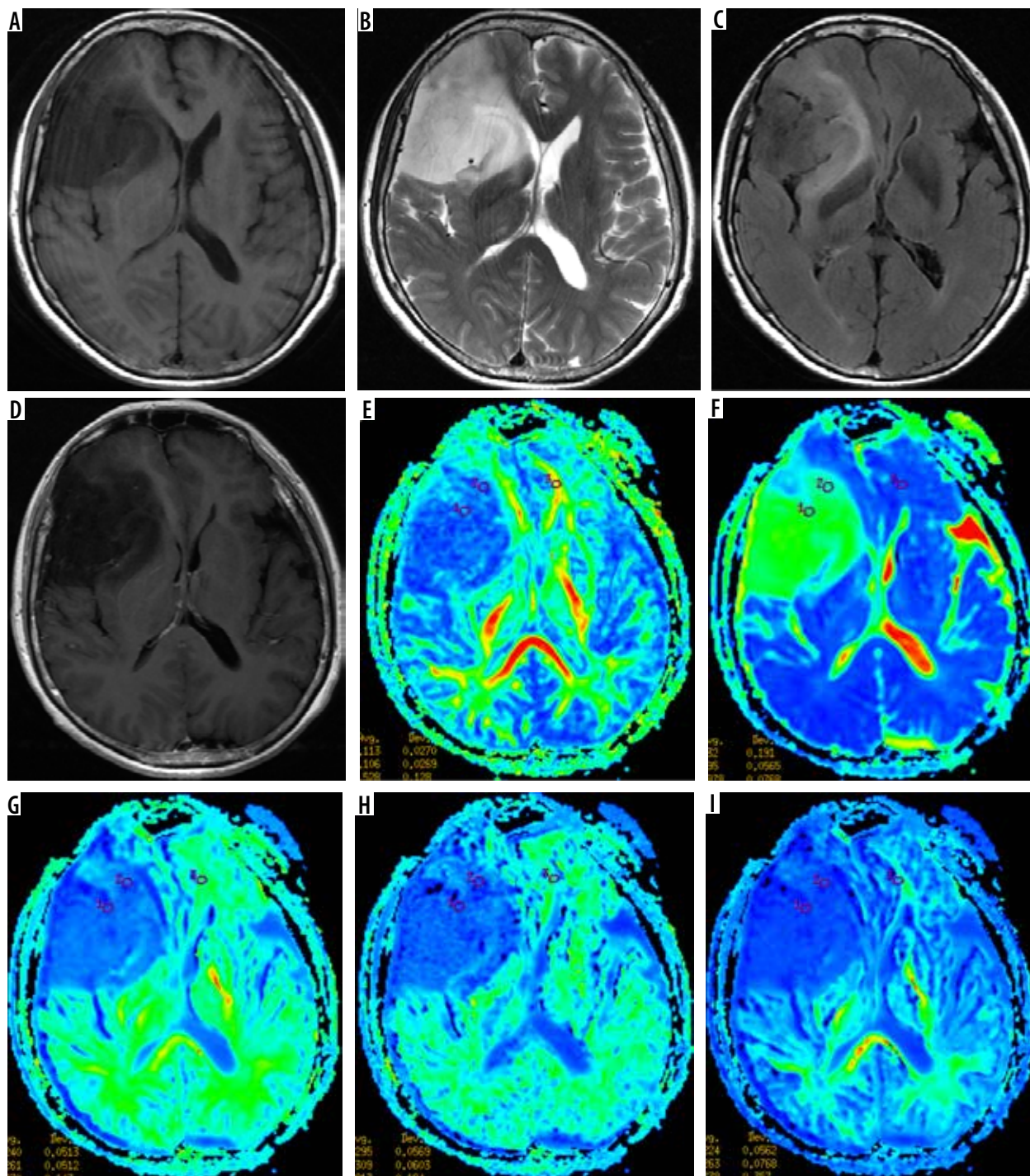


Figure 1. Female, 59 years old, WHO II grade astrocytoma, isocitrate dehydrogenase (IDH)-mutant type, and abnormal unreinforced signal in the right frontotemporal island lobe, multiparametric magnetic resonance (MR) images include T1WI (A), T2WI (B), T2-FLAIR (C), Gd-enhanced T1WI (D), and maps of fractional anisotropy (E), mean diffusivity (F), mean kurtosis (G), axial kurtosis (H), and radial kurtosis (I). Multiparametric MR indices were measured in regions of the tumour (1), oedema (2), and contralateral normal white matter area (3)

(6 males and 10 females). There was no statistically significant gender difference between the 2 groups of cases ($p = 0.53$). The average age of IDH wild-type patients was 55.33 ± 12.09 years, and the average age of IDH mutant patients was 41.25 ± 11.15 years (Table 1). The age difference between the 2 was statistically significant ($p = 0.007$). The area under the ROC curve (AUC) was 0.82. When

the cut-off point was 57.5, its sensitivity was 66.7% and its specificity was 93.7% (Table 2).

Comparison of DKI parameters

The rFA and rMK values in the parenchymal region of IDH wild-type tumors were higher than those of IDH

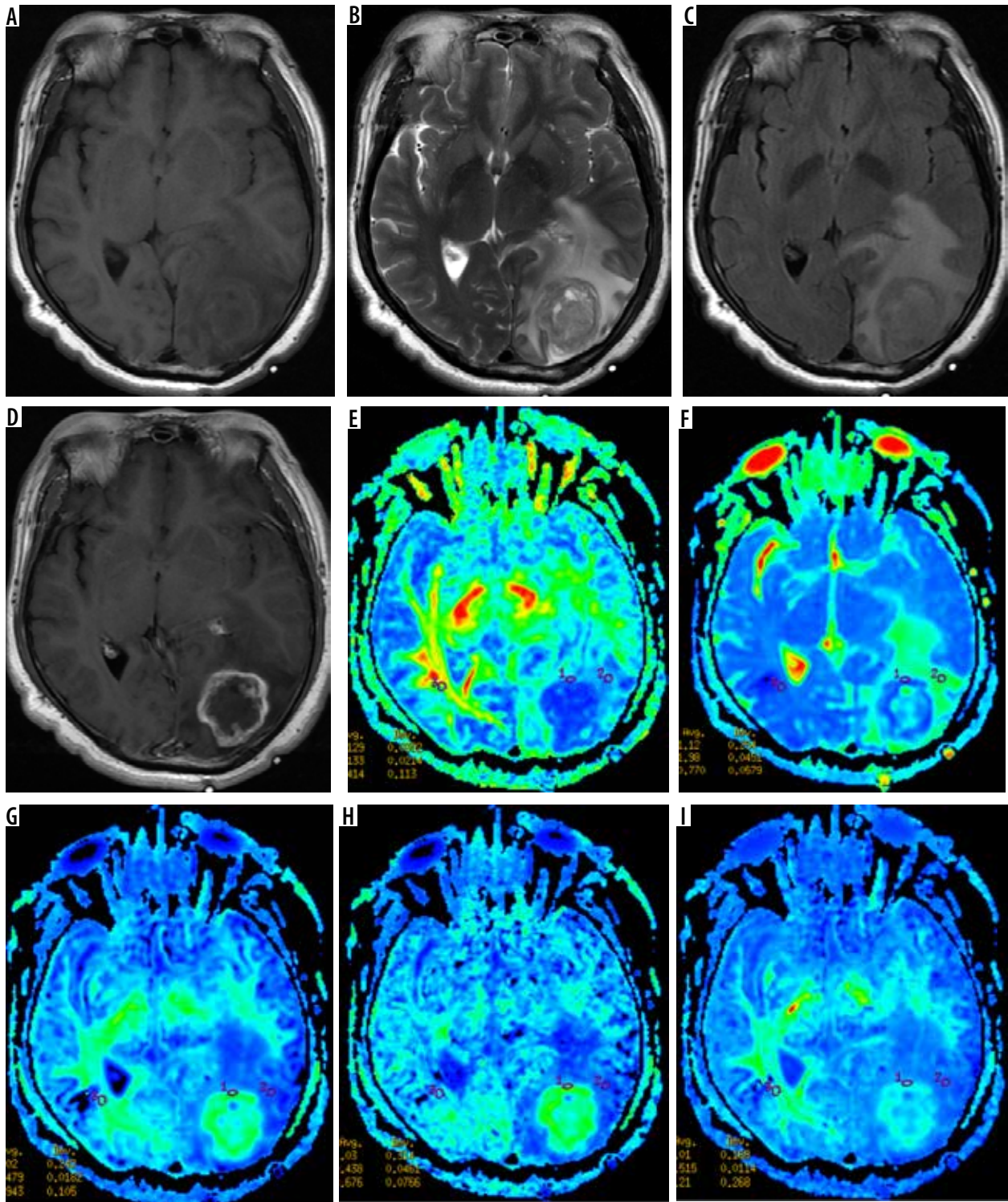


Figure 2. Female, 63 years old, WHO II grade astrocytoma, isocitrate dehydrogenase (IDH)-wild type, abnormal strengthening signal in the left temporal occipital lobe, multiparametric magnetic resonance (MR) images include T1WI (A), T2WI (B), T2-FLAIR (C), Gd-enhanced T1WI (D), and maps of fractional anisotropy (E), mean diffusivity (F), mean kurtosis (G), axial kurtosis (H), and radial kurtosis (I). Multiparametric MR indices were measured in regions of the tumour (1), oedema (2), and contralateral normal white matter area (3)

mutants, and the rMD value was lower than that of IDH mutants, and the difference between the two was statistically significant ($p < 0.05$); the values of each parameter of peritumoral oedema in the 2 groups were not statistically significant. The detailed results are listed in Table 3.

The area under the ROC curve of the tumour parenchymal rMK value was 75.7%; when the cut-off point was 0.515, the sensitivity was 77.8% and the specificity was 68.7%. The area under the ROC curve of tumour parenchymal rFA value was 72.9%; when the cut-off point was

Table 1. Clinical information

Characteristics	All patients	IDH wild-type	IDH mutant-type
No. of patients	25	9	16
Age (years)			
Mean	46.32 ± 13.19	41.25 ± 11.15	55.33 ± 12.09
Range	21-71	37-71	21-59
Sex, <i>n</i>			
Male	10	4	6
Female	15	5	10
Histopathology, <i>n</i>			
Astrocytoma	23	8	15
Oligodendroglioma	2	1	1

IDH – isocitrate dehydrogenase

Table 2. ROC curve analyses of rMD (ratio of mean diffusivity), rMK (ratio of mean kurtosis), rFA (ratio of fractional anisotropy), and age in isocitrate dehydrogenase (IDH) mutation status discrimination

IDH-mutant vs. IDH wild-type	MR index	Optimal threshold	AUC	Sensitivity (%)	Specificity (%)
	Age	57.5	0.82	66.70	93.70
	rMK	0.515	0.757	77.80	68.70
	rMD	0.527	0.757	87.50	66.70
	rFA	1.261	0.729	66.70	93.70

IDH – isocitrate dehydrogenase, rFA – ratio of fractional anisotropy, rMD – ratio of mean diffusivity, rMK – ratio of mean kurtosis.

Table 3. Comparison of the DKI parameters in WHO II brain gliomas with different IDH mutation status

Group	Case	Tumour parenchymal area					Periooma oedema area				
		rFA	rMD	rMK	rKa	rKr	rFA	rMD	rMK	rKa	rKr
IDH mutant type	16	0.37 ± 0.12	1.65 ± 0.38	0.48 ± 0.15	0.64 ± 0.23	0.40 ± 0.13	0.45 ± 0.16	1.95 ± 0.27	0.52 ± 0.08	0.60 ± 0.13	0.46 ± 0.11
IDH wild type	9	0.55 ± 0.23	1.28 ± 0.34	0.62 ± 0.15	0.83 ± 0.25	0.48 ± 0.19	0.38 ± 0.12	1.95 ± 0.47	0.46 ± 0.04	0.59 ± 0.07	0.40 ± 0.07
t		-2.567	2.397	-2.348	-1.967	-1.251	1.142	0.002	1.994	0.266	1.607
p		0.017	0.025	0.028	0.061	0.224	0.265	0.998	0.058	0.793	0.122

IDH – isocitrate dehydrogenase, rFA – ratio of fractional anisotropy, rMD – ratio of mean diffusivity, rMK – ratio of mean kurtosis, rKa – ratio of axial kurtosis, rKr – ratio of radial kurtosis

0.527, the sensitivity was 66.7% and the specificity was 93.7%; and the area under the ROC curve of tumour parenchymal rMD value was 75.7%; when the cut-off point was 1.261, the sensitivity was 87.5% and the specificity was 66.7% (Figure 3, Table 2).

Discussion

Analysis of clinical data

In our study, we observed that the average age of patients with IDH mutant-type in WHO II glioma was greater than that of patients with IDH wild-type in WHO II glioma (mean age 41.25 ± 11.15 years compared to 55.33 ± 12.09 years, respectively), and notably, IDH

gene mutation occurred more frequently in WHO II glioma, with a mutation rate surpassing 64%. Our results were partially consistent with the findings of Aibaidula *et al.* [7].

Analysis of DKI parameters of glioma

Isocitrate dehydrogenase mutation status is an important factor in judging the survival and prognosis of patients with glioma [8]. Although experts have shown that conventional MRI is related to the IDH gene [9], the application value of conventional MRI is limited because various imaging signs are difficult to quantify and are easily influenced by the experience and judgment of diagnosticians and other factors [10]. In the microenvironment of

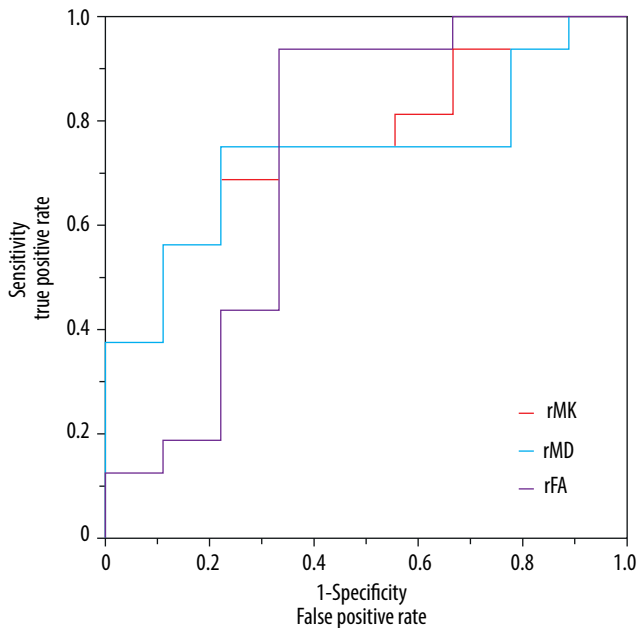


Figure 3. ROC curve of the tumour parenchymal area rFA (ratio of fractional anisotropy), rMK (ratio of mean kurtosis), and rMD (ratio of mean diffusivity)

human glioma, the diffusion and movement of water are not only affected by factors such as cell membrane barrier and inner and extracellular space, but also by pathological changes of tumour tissue, such as tumour cell density, cell atypia, nuclear polymorphism, neovascularisation, etc., which makes the movement of water molecules show a non-Gaussian distribution [11]. DKI is based on the non-Gaussian distribution and diffusion of water molecules in biological tissues, and it shows the microstructural changes of tissues and organs through the non-Gaussian distribution model [12]. Therefore, DKI can reflect changes in tissue microstructure better than traditional conventional MRI imaging.

The study of the parenchymal region of IDH wild-type and IDH mutant-type tumours showed that the values of rMD in the parenchymal region of IDH wild-type tumours were lower than those of IDH mutant-type tumours, but the rMK and rFA were greater than those of IDH mutant-type tumours, and the value of the difference was statistically significant. Among the above indicators, the value of rMK and rMD had the largest area under the ROC curve. Our results were partially consistent with the findings of Xu *et al.*'s study [13].

DKI can obtain multiple parameter values, in which the MK value represents the average value of diffusion kurtosis in each gradient direction in space, which quantitatively describes the non-Gaussian distribution of water molecule diffusion inside and outside the cell, and its size depends on the complexity of tissue structure in ROI. The more complex the structure, the greater the MK value [14]. The current study showed that the microstructure of IDH-wild type glioma is relatively more complex, with high cell density, more heterogeneous tumour populations,

and abundant tumour microvascular proliferation etc. [13,15]. These microstructural changes lead to a greater displacement of Gaussian distribution of water molecule movement [12].

The MD value reflected the speed of diffusion movement, representing the overall diffusion level of molecules and all existing obstacles. Previous studies have shown that the MD value can be used to assess the grading of gliomas [16]. The decrease in MD value with increasing tumour grade was thought to be associated with increased cellularity, i.e. the lower the MD value, the slower the diffusion movement and the greater the obstacles [17]. Thus, we hypothesised that the molecular diffusion movement of IDH wild-type tumours was slow, the obstacles were large, the microstructure of tumour tissue was more complex, the cell density was small, and the gap was small.

In this study the rFA value of WHO grade II IDH wild-type tumour is higher than that of IDH mutant tumour. Some studies reported greater FA values in higher grade gliomas, which was postulated to be associated with abundant blood vessels, vascular endothelial hyperplasia, and more organised tumour cells in more malignant tumours [18]. Through dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI) studies, Xing *et al.* [19] found that the maximum relative cerebral blood volume (rCBV) of IDH mutant WHO II and III astrocytoma tumours was significantly lower than that of IDH wild-type. Based on the results of these 2 studies, we can infer that grade WHO II IDH wild-type has more vascular distribution than IDH mutant type which may be related to the accumulation of 2-hydroxyglutaric acid (2-HG) caused by IDH mutation; the role of IDH gene mutations in glioma is still under study [4].

The results of this study showed that there was no statistically significant difference in rFA, rMD, rMK, rKa, and rKr values between WHO grade II IDH wild-type and IDH mutant-type peritumoral oedema, consistent with previous findings [20]. We think that glioma-induced blood brain barrier damage facilitates plasma water molecules and proteins to the brain parenchyma, ultimately leading to peritumoral brain oedema [21], so there is no significant difference in pathological changes of surrounding normal brain tissue between WHO grade II glioma whether IDH is wild-type or mutant-type.

There are still some shortcomings in this study. First, the number of study cases is relatively small, and we analysed WHO grade II gliomas alone but did not include other grade gliomas in this study. Secondly, the measurement of many parameters involved in the research process is easily influenced by the empirical judgment of the measurer. Perhaps it is insufficient to explore IDH genotyping through DKI imaging alone, and it is necessary to further comprehensively utilise other MRI techniques and even imaging omics analysis to explore IDH mutation status for preoperative non-invasive prediction of glioma.

Conclusions

As a new type of magnetic resonance functional imaging, DKI can reveal microstructural changes of diseased tissues and provide more imaging information for preoperative non-invasive judgment of IDH mutation status of WHO grade II glioma.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Parson DW, Jones S, Zhang X, Cheng-Ho Lin J, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiform. *Science* 2008; 321: 1807-1812.
2. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; 131: 803-820.
3. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 2021; 23: 1231-1251.
4. Miller JJ, Gonzalez Castro LN, McBrayer S, Weller M, Cloughesy T, Portnow J, et al. Isocitrate dehydrogenase (IDH) mutant gliomas: a Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. *Neuro Oncol* 2023; 25: 4-25.
5. Raab P, Hattingen E, Franz K, Zanella FE, Lanfermann H. Cerebral gliomas: diffusional kurtosis imaging analysis of microstructural differences. *Radiology* 2010; 254: 876-881.
6. Tan Y, Zhang H, Wang X, Qin J, Wang L, Yang G, et al. Comparing the value of DKI and DTI in detecting isocitrate dehydrogenase genotype of astrocytomas. *Clin Radiol* 2019; 74: 314-320.
7. Aibaidula A, Ka-Yin Chan A, Shi Z, Li Y, Zhang R, Yang R, et al. Adult IDH wild-type lower-grade gliomas should be further stratified. *Neuro Oncol* 2017; 19: 1327-1337.
8. Weller M, Wen PY, Chang SM, Dirven L, Lim M, Monje M, et al. Glioma. *Nat Rev Dis Primers* 2024; 10: 33. DOI: 10.1038/s41572-024-00516-y.
9. Hyare H, Rice L, Thuse S, Nachev P, Jha A, Milic M, et al. Modelling MR and clinical features in grade II/III astrocytomas to predict IDH mutation status. *Eur J Radiol* 2019; 114: 120-127.
10. Li Y, Qin Q, Zhang Y, Cao Y. Noninvasive determination of the IDH status of gliomas using MRI and MRI-based radiomics: impact on diagnosis and prognosis. *Curr Oncol* 2022; 29: 6893-6907.
11. Mendez AM, Fang LK, Meriwether CH, Batasin SJ, Loubrie S, Rodríguez-Soto AE, et al. Diffusion breast MRI: current standard and emerging techniques. *Front Oncol* 2022; 12: 844790. DOI: 10.3389/fonc.2022.844790.
12. Wu EX, Cheung MM. MR diffusion kurtosis imaging for neural tissue characterization. *NMR Biomed* 2010; 23: 836-848.
13. Xu Z, Ke C, Liu J, Xu S, Han L, Yang Y, et al. Diagnostic performance between MR amide proton transfer (APT) and diffusion kurtosis imaging (DKI) in glioma grading and IDH mutation status prediction at 3 T. *Eur J Radiol* 2021; 134: 109466. DOI: 10.1016/j.ejrad.2020.109466.
14. Haopeng P, Xuefei D, Yan R, Zhenwei Y, Wei H, Ziyin W, et al. Diffusion kurtosis imaging differs between primary central nervous system lymphoma and high-grade glioma and is correlated with the diverse nuclear-to-cytoplasmic ratio: a histopathologic, biopsy-based study. *Eur Radiol* 2020; 30: 2125-2137.
15. Zhao J, Wang YL, Li XB, Hu MS, Li ZH, Song YK, et al. Comparative analysis of the diffusion kurtosis imaging and diffusion tensor imaging in grading gliomas, predicting tumour cell proliferation and IDH-1 gene mutation status. *J Neurooncol* 2019; 141: 195-203.
16. Raja R, Sinha N, Saini J, Mahadevan A, Rao KN, Swaminathan A. Assessment of tissue heterogeneity using diffusion tensor and diffusion kurtosis imaging for grading gliomas. *Neuroradiology* 2016; 58: 1217-1231.
17. Van Cauter S, Veraart J, Sijbers J, Peeters RR, Himmelreich U, De Keyser F, et al. Gliomas: diffusion kurtosis MR imaging in grading. *Radiology* 2012; 263: 492-501.
18. Beppu T, Inoue T, Shibata Y, Kurose A, Arai H, Ogasawara K, et al. Measurement of fractional anisotropy using diffusion tensor MRI in supratentorial astrocytic tumors. *J Neurooncol* 2003; 63: 109-116.
19. Xing Z, Yang X, She D, Lin Y, Zhang Y, Cao D. Noninvasive assessment of IDH mutational status in World Health Organization grade II and III astrocytomas using DWI and DSC-PWI combined with conventional MR imaging. *Am J Neuroradiol* 2017; 38: 1138-1144.
20. Zhu H, Xie Y, Li L, Liu Y, Li S, Shen N, et al. Diffusion along the perivascular space as a potential biomarker for glioma grading and isocitrate dehydrogenase 1 mutation status prediction. *Quant Imaging Med Surg* 2023; 13: 8259-8273.
21. Solar P, Hendrych M, Barak M, Valekova H, Hermanova M, Jancalek R. Blood-brain barrier alterations and edema formation in different brain mass lesions. *Front Cell Neurosci* 2022; 16: 922181. DOI: 10.3389/fncel.2022.922181.