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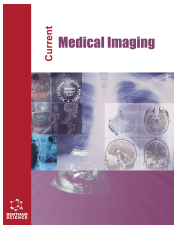

MINI-REVIEW

Latest Developments in Magnetic Resonance Imaging for Evaluating the Molecular Microenvironment of Gliomas

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Abstract:

The 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System has brought a transformative shift in the categorization of adult gliomas. Departing from traditional histological subtypes, the new classification system is guided by molecular genotypes, particularly the Isocitrate Dehydrogenase (IDH) mutation. This alteration reflects a pivotal change in understanding tumor behavior, emphasizing the importance of molecular profiles over morphological characteristics. Gliomas are now categorized into IDH-mutant and IDH wildtype, with significant prognostic implications. For IDH-mutant gliomas, the concurrent presence of Alpha-Thalassemia/mental retardation syndrome X-linked (ATRX) gene expression and co-deletion of 1p19q genes further refine classification. In the absence of 1p19q co-deletion, further categorization depends on the phenotypic expression of CDKN2A/B. Notably, IDH wildtype gliomas exhibit a poorer prognosis, particularly when associated with TERT promoter mutations, EGFR amplification, and +7/-10 co-deletion. Although not part of the new guidelines, the methylation status of the MGMT gene is crucial for guiding alkylating agent treatment. The integration of structural and functional Magnetic Resonance Imaging (MRI) techniques may play a vital role in evaluating these genetic phenotypes, offering insights into tumor microenvironment changes. This multimodal approach may enhance diagnostic precision, aid in treatment planning, and facilitate effective prognosis evaluation of glioma patients.

Keywords: Glioma, Molecular subtyping, Magnetic resonance imaging, Tumor microenvironment.

Article History	Received: October 23, 2023	Revised: December 26, 2023	Accepted: January 29, 2024

1. INTRODUCTION

Due to the 2021 World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5), the categorization of adult gliomas is now guided by the prognostic implications of diverse molecular genetic profiles. This marks a departure from the traditional histological subtypes used in the previous classification to a new system driven by molecular genotypes [1]. Research has consistently shown that molecular genotypes, in contrast to histological morphology, offer a more accurate reflection of the biological behavior of tumors, with similar molecular subtypes exhibiting analogous behavior. Considering its status as one of the top three leading causes of cancer-related mortality, this shift holds profound implications for targeted treatment, precision medicine, and survival prognosis for patients [2].

The interpretation of the patient's genetic status before surgery is essential as it significantly influences the formulation of an effective treatment plan [3, 4]. Clearly, the utilization of non-invasive functional magnetic resonance imaging enables a comprehensive assessment of gliomas, encompassing factors, such as tumor cell density, regional tumor vascularization, and metabolic status. This approach surpasses the evaluation capabilities of conventional structural Magnetic Resonance Imaging (MRI) alone [5 - 7]. Through radiomic analysis of MR images, automatic or semi-automatic segmentation of tumor images, and the high-throughput capture of nuanced imaging information beyond the visible spectrum, healthcare professionals can enhance their ability to evaluate and determine the nature and molecular status of tumors. Concurrently, the integration of structural MRI and functional multimodal MRI allows for the timely identification of relevant changes in the tumor microenvironment, both preoperatively and postoperatively. This integration provides superior guidance for formulating patient treatment plans, assessing therapeutic efficacy, and evaluating prognosis [8 - 10].

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1.1. Main Genetic Phenotypes Influencing Tumor Microenvironment

The 2021 CNS 5 classification for adult gliomas is primarily anchored in the Isocitrate Dehydrogenase (IDH) mutation. Gliomas are categorized into two main types: IDH-mutant and IDH wildtype (IDH-wt) [1, 7]. The prognosis for these two tumor categories varies significantly, with IDH-mutant gliomas demonstrating notably better outcomes than IDH-wildtype gliomas. Under the IDH-mutant status, the concurrent expression of the alpha-thalassemia/mental retardation syndrome X-linked (ATRX) gene and co-deletion of 1p19q genes lead to direct classification as oligodendroglioma or anaplastic oligodendroglioma. In IDH-mutant gliomas without 1p19q co-deletion, further classification is contingent upon the phenotypic expression of CDKN2A/B, distinguishing between wildtype and mutated, consequently leading to the classification of diffuse astrocytoma and grade 4 diffuse astrocytoma (Fig. **1**) [11].

In the context of the revised classification, the most notable changes emerge in IDH-wildtype gliomas. Under the wildtype H3 gene situation, these gliomas manifest a prognosis similar to glioblastoma, demonstrating biological behavior akin to that of glioblastoma. Consequently, in the 2021 CNS5, they are all classified as Glioblastoma (GBM). Significantly, regardless of their histological grading, IDH-wildtype gliomas present a prognosis resembling that of glioblastoma (Fig. **2**). In cases featuring TERT promoter mutations, EGFR amplification, and simultaneous gains of chromosome 7 with losses of chromosome 10 (+7/-10), these molecular phenotypic changes markedly shorten Progression-free Survival (PFS) and Overall Survival (OS) times, resulting in a poorer prognosis compared to IDH-wildtype gliomas exhibiting histological necrosis or microvascular proliferation. Additionally, although not incorporated into the new guidelines, the methylation status of the MGMT gene underscores a significant distinction in the application of alkylating agents for the treatment of glioma patients [12 - 14].

2. APPLICATION OF MR IMAGING IN MAJOR GENOTYPES OF GLIOMAS

Currently, clinical imaging is the primary tool for making preliminary diagnoses based on the molecular classification outlined in the WHO CNS 5 guidelines [1]. This process involves identifying certain imaging-related manifestations. For instance, oligodendrogliomas are often associated with calcification, and low-grade astrocytomas may exhibit T2WI/Flair mismatch. Therefore, in the realm of clinical imaging, exclusive diagnostic approaches are currently employed to form initial assessments of the molecular phenotype of gliomas. However, the utilization of advanced imaging, radiomics, and other related technologies holds the potential to enhance our ability to diagnose gliomas more effectively (Fig. **3**).

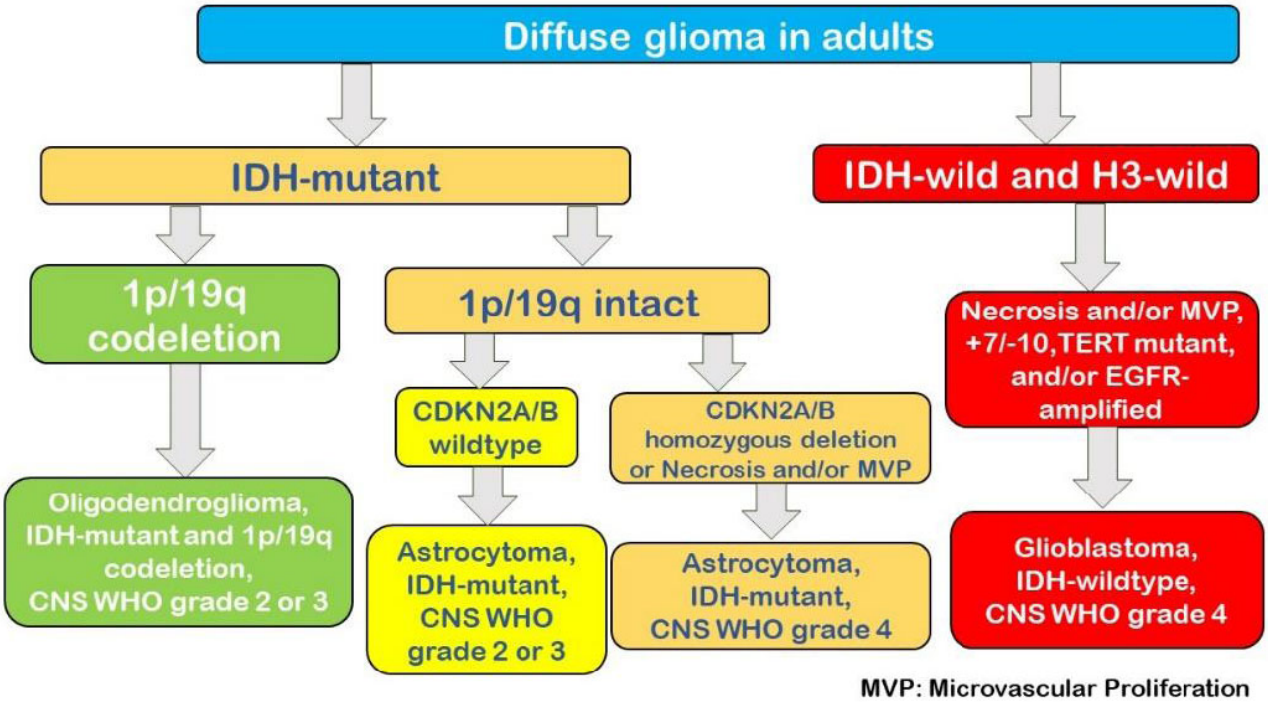

Fig. (1). Molecular subtypes of adult diffuse glioma and world health organization classification.

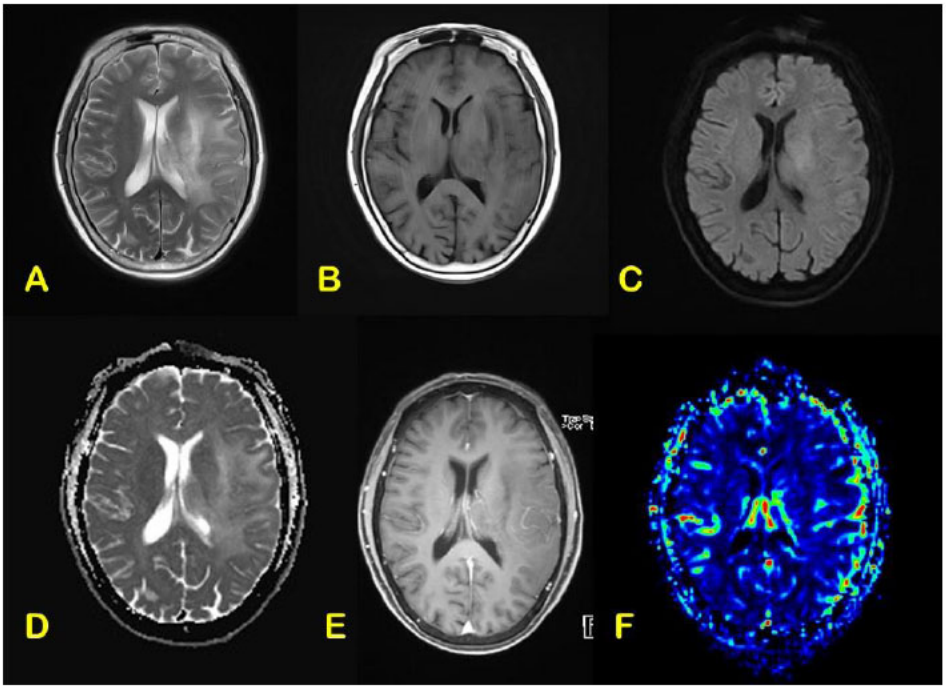

Fig. (2). 2021 WHO CNS 5-related case analysis. *Patient profile*: 76-year-old female with glioma in the left frontotemporal lobe. *Pathology*: Astrocytoma WHO grade 2; IDH wild-type, TERT unmutated, H3K27M unmutated. *Imaging:* (**A**). T2-weighted; (**B**). T1-weighted; (**C**). DWI; (**D**). ADC map; (**E**). T1-weighted with contrast; (**F**). Perfusion-weighted (CBV). *Classification*: 2016 WHO CNS4: astrocytoma grade II, 2021 WHO CNS5: glioblastoma grade 4. *Prognosis*: Recurrence at 10 months and death 12 months after the surgery.

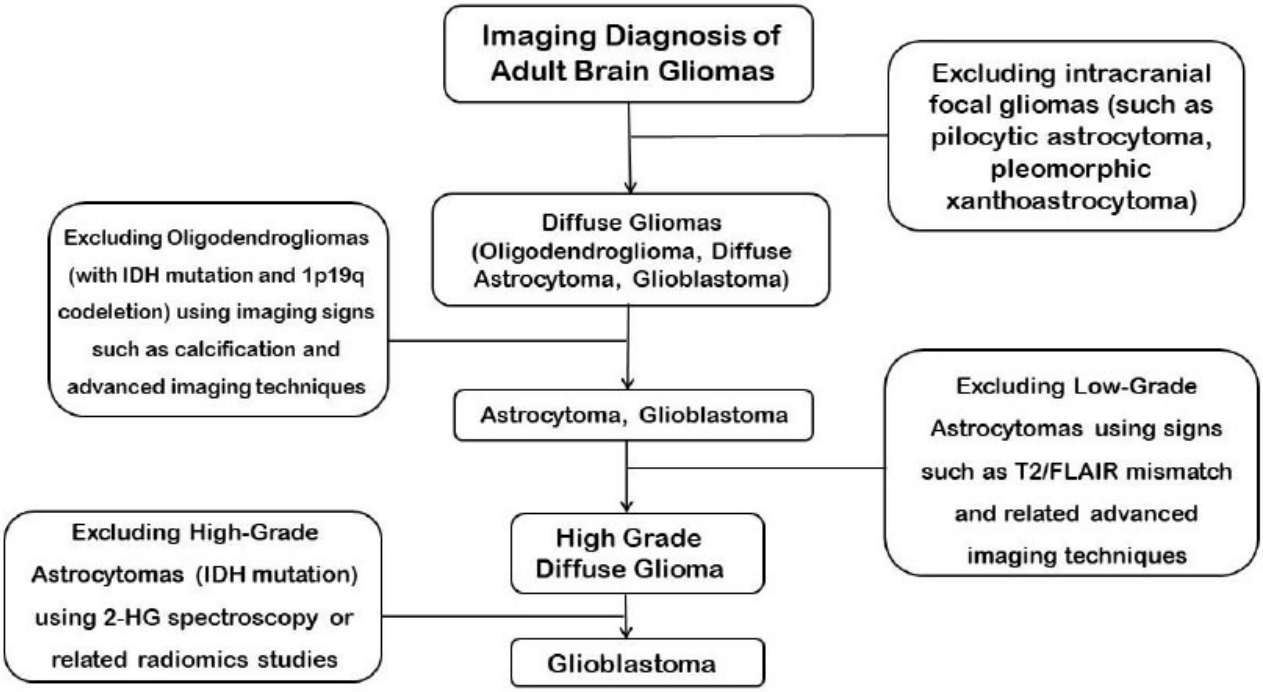

Fig. (3). Flowchart for the clinical diagnosis of glioma.

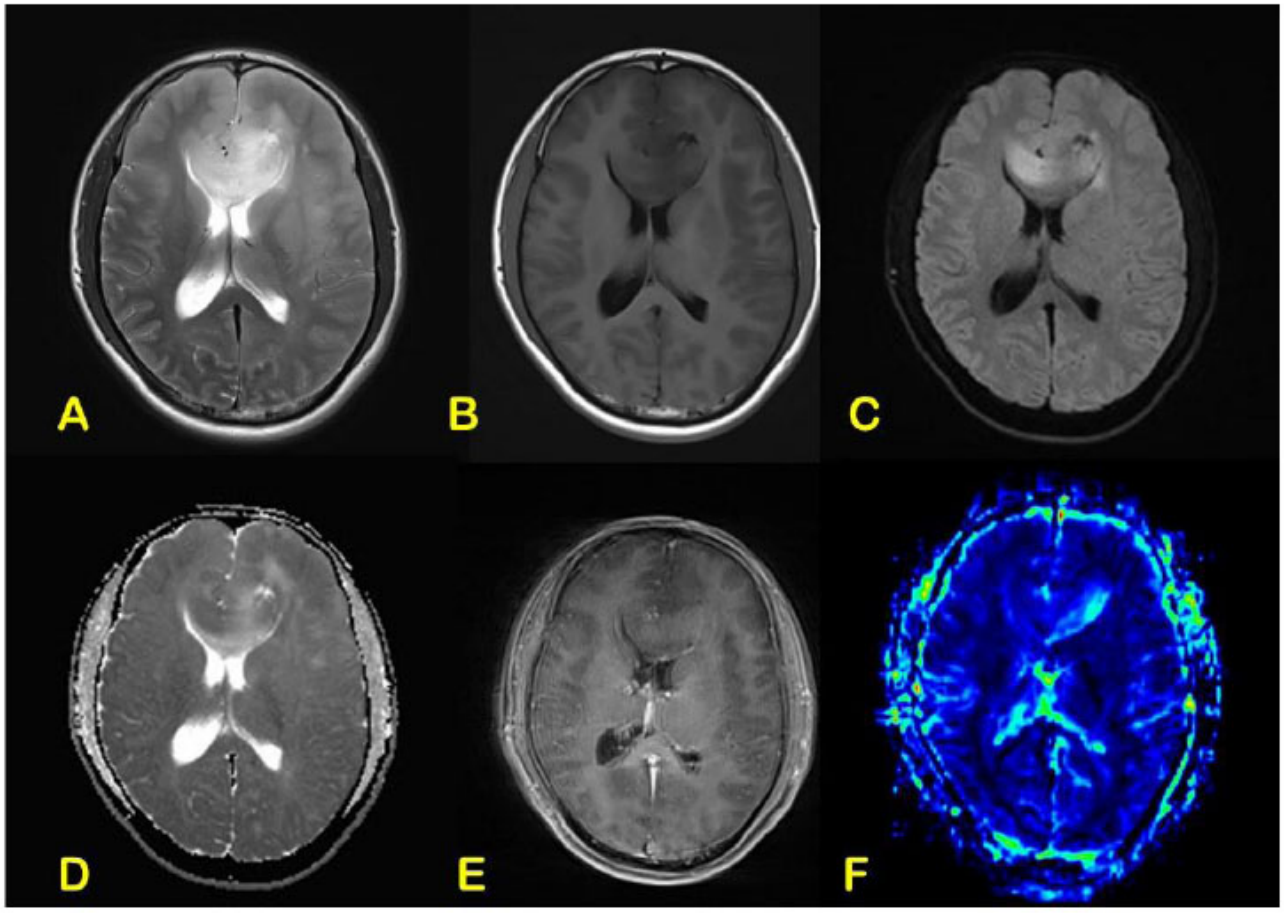

Fig. (4). 2021 WHO CNS 5-related case analysis. *Patient profile*: 40-year-old female with glioma crossing the corpus callosum. *Pathology*: Glioblastoma WHO grade 4; IDH mutation, 1p19q intact, H3K27M non-mutated. *Imaging:* (**A**). T2-weighted; (**B**). T1-weighted; (**C**). DWI; (**D**). ADC map; (**E**). T1-weighted with contrast; (**F**). Perfusion-weighted (CBV). *Classification*: 2016 WHO CNS4: glioblastoma grade IV, 2021 WHO CNS5: astrocytoma grade 4. *Prognosis*: Recurrence 16 months after the surgery and death 20 months after the surgery.

2.1. Application of MR Imaging in IDH

The significance of the IDH gene phenotype as the fundamental genetic basis for the 2021 CNS glioma classification is evident. IDH gene mutations primarily result in heightened DNA/histone methylation, activation of Hypoxia-inducible Factors (HIF), and involvement in oxidative stress mechanisms, all closely associated with the formation and occurrence of gliomas [1]. Moreover, in comparison to IDH-wildtype gliomas, IDH-mutant gliomas display significantly increased sensitivity to temozolomide, leading to a substantial improvement in the prognosis of glioma patients in the context of combined radio-chemotherapy with temozolomide [15]. IDH mutation contributes to an increase in the cell density of gliomas and the formation of neovascularization. These changes can be observed and evaluated through existing imaging techniques during preoperative examinations, such as Perfusion Weighted Imaging (PWI) for assessing tumor blood supply and Diffusion Weighted Imaging (DWI) for evaluating cell density (Fig. **4**).

Generally, tumors with a higher degree of malignancy tend to exhibit a higher density of tumor cells internally. Halefoglu *et al*., in their analysis of 170 glioma patients combining Diffusion Weighted Imaging (DWI) and its parameter, the Apparent Diffusion Coefficient (ADC), with structural Magnetic Resonance (MR) imaging, confirmed that IDH-wildtype tumors, compared to IDH-mutant tumors, demonstrate higher tumor cell density and lower ADC values [16]. During the growth and proliferation of gliomas, continuous neovascularization formation and the highly invasive nature of these tumors can lead to significant disruption of the Blood Brain Barrier (BBB). Perfusion Weighted Imaging (PWI) can effectively quantitatively evaluate this aspect. Professor Cheng Jingliang's team from the First Affiliated Hospital of Zhengzhou University utilized structural MR combined with PWI radiomics to extract 19 radiomic features, constructing a diagnostic model. Their molecular subgroup analysis of 272 grade 2-4 glioma patients revealed the model's effectiveness in distinguishing between IDH-wildtype and IDH-mutant status, with or without 1p19q co-deletion [17]. The combined application of DWI, PWI, Susceptibility Weighted Imaging (SWI), and various functional imaging techniques can better predict the status of the IDH gene and can be further applied to determine various genes [18, 19]. The Department of Radiology at Huashan Hospital, Fudan University, has successfully evaluated the IDH and ATRX

gene status of low-grade gliomas in tissue morphology by employing a combined longitudinal image created from the application of Arterial Spin Labeling (ASL) and DWI [20].

In accordance with the Warburg effect principle, the proliferation of tumor cells results in the production of metabolic byproducts, such as lactate, through anaerobic glycolysis. The gradual formation of neovascularization within the tumor is a dynamic process occurring concomitantly with the tumor's proliferation and growth [21]. Chemical Exchange Saturation Transfer (CEST) imaging, along with its derivative Magnetic Resonance Spectroscopy (MRS) and Amide Proton Transfer imaging (APT), has been proven effective in detecting this biological behavior and plays a crucial role in delineating glioma boundaries [22]. 2-Hydroxyglutarate (2-HG) is a characteristic metabolic product produced in gliomas with mutated IDH genes. Recently, Magnetic Resonance Spectroscopy (MRS) has been widely and maturely applied in detecting this substance [23]. Beyond mere metabolite analysis through MRS, Bumes *et al*. applied machine learning techniques to analyze metabolite curves from MRS, aiding in the determination of the IDH gene in gliomas [24]. In the prognostic follow-up of gliomas, Stefano *et al*. used MRS to continuously observe dynamic changes in 2-HG levels in glioma patients, facilitating the determination of tumor recurrence and pseudo-progression [25]. Hu Guo *et al*. compared Amide Proton Transfer (APT) with four diffusion-weighted models derived from Diffusion Weighted Imaging (DWI), including DTI, Diffusion Kurtosis Imaging (DKI), and Neurite Orientation Dispersion and Density Imaging (NODDI). They found that APT, reflecting metabolites, exhibited significantly better diagnostic performance for IDH compared to the four mentioned models [26]. Professor Wen Zhibo's team at Southern Medical University constructed a glioma IDH gene diagnostic model based on the deep learning dual-aware framework for the APT sequence [26].

2.2. The Application of MR Imaging to 1p19q Deletion

1p19q co-deletion refers to the simultaneous loss of the short arm of chromosome 1 and the long arm of chromosome 19, resulting in direct changes to tumor cell proliferation and differentiation. In the 2016 CNS 4, the diagnosis of oligodendroglioma primarily relied on histological features, with the status of 1p19q serving as one of the assisting genes for diagnosis. In the 2021 CNS 5, this gene has been considered a necessary criterion for diagnosing oligodendroglioma, requiring the combination of IDH mutation and 1p19q co-deletion [1].

Traditionally, calcification was considered a reflection of the relatively benign biological behavior of oligodendrogliomas, but not all oligodendrogliomas exhibit calcifications. Therefore, while there are some typical imaging features in traditional radiology for oligodendrogliomas, the use of imaging techniques that react to tumor function in conjunction with radiomics can further enhance the diagnostic capabilities for this type of tumor. Generally, the tumor cell density and vascularization in oligodendrogliomas are lower than those in malignant gliomas. Consequently, the ADC values in DWI are usually high, and in PWI, the perfusion is moderate or low. Simultaneously, the application of multimodal assessment significantly improves the diagnostic capability of gliomas with IDH mutations combined with 1p19q loss compared to a single modality approach.

In a study at Fujian Medical University on the 1p19q status of low-grade gliomas, structural MRI alone achieved an efficacy of approximately 66% for the diagnosis of oligodendrogliomas [27]. However, using DWI, SWI, and PWI alone yielded diagnostic efficacies of approximately 71%, 73%, and 73%, respectively. Nevertheless, diagnostic efficacy significantly increased to 88% when multimodal imaging was comprehensively utilized [28]. Another multimodal histogram study at West China Medical University yielded similar results [29]. Another study that combined PET with PWI for diagnosis has also confirmed that multimodal approaches can enhance the diagnostic efficiency of the 1p19q status in gliomas [30]. A study using CEST-related sequences also found that APT, compared to other CEST sequences, can better reflect the metabolic changes in the interior and periphery of IDH-mutant gliomas with 1p19q co-deletion, thereby facilitating the diagnosis of such gliomas [31]. On the contrary, in radiomics, whether applying structural imaging alone or combining a single functional modality or multiple functional modalities, it is possible to effectively detect the required molecular gene status of oligodendrogliomas in the new classification [32, 33].

2.3. Application of MR Imaging to the CDKN2A/B

Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) as a biomarker for the prognosis of meningiomas has become a widespread consensus in the field of central nervous tumor studies. In the 2021 edition, the status of this genotype has also become one of the classification biomarkers for gliomas [1]. Homozygous deletion of CDKN2A/B leads to an uncontrolled transition from the G1 phase to the S phase, resulting in increased tumor cell proliferation and poorer prognosis in gliomas. Therefore, in IDH-mutant gliomas, homozygous deletion of CDKN2A/B, along with histological necrosis or microvascular proliferation, serves as a distinguishing factor between grade 2 and 3 diffuse astrocytomas and grade 4 diffuse astrocytomas. That is, the combination of IDH mutation without 1p19q co-deletion with homozygous deletion of CDKN2A/B or histological necrosis or microvascular proliferation can lead to the diagnosis of grade 4 diffuse astrocytoma.

As a newly introduced genetic classification in the 2021 edition of gliomas, there has been relatively little research on this topic, gradually gaining attention from researchers in recent years. CDKN2A/B serves as a molecular marker to differentiate between low-grade (grades 2 and 3) and high-grade (grade 4) diffuse astrocytomas with IDH mutations. However, in some cases of IDH-mutant diffuse astrocytomas, histological morphological features of necrosis or microvascular proliferation can directly lead to a diagnosis of high-grade diffuse astrocytoma. Therefore, there is almost no diagnostic research published in the field of traditional radiology, and the results are predominantly negative [34]. A study conducted in South Korea using PWI found that homozygous deletion of CDKN2A/B leads to greater

invasiveness of the tumor into the surrounding tissue, along with higher levels of perfusion within the tumor [35]. The use of radiomics may enhance the diagnostic level for this subtype of genes. A research team at Chongqing Medical University developed a novel deep learning network (FN-Net) based on preoperative MRI to predict the homozygous deletion status of CDKN2A/B. This network has the potential to become a practical tool for the non-invasive characterization of CDKN2A/B in gliomas, supporting personalized classification and treatment plans [36]. A team at the University of California has conducted similar research and found that the combination of radiomics from preoperative MRI and CNN features can improve the predictive performance of CDKN2A/B in patients with WHO grade 4 diffuse astrocytoma [4].

2.4. Application of MR Imaging to TERT

Telomerase Reverse Transcriptase (TERT) is a relatively unique gene that maintains the stability of cells after division. Mutations in this gene lead to continuous proliferation and division of cells, contributing to tumor progression. TERT mutations are almost always present in oligodendrogliomas, and in IDH-mutant gliomas, this mutation represents a better prognosis. In IDH-wildtype gliomas, TERT mutation, EGFR amplification, and +7/-10 co-deletion collectively constitute the three major poor prognostic factors for Glioblastoma (GBM), with TERT mutation being the most common genetic alteration [1]. Currently, structural imaging radiomics can accurately diagnose the TERT gene in IDH-wildtype gliomas, *i.e.*, GBM. Professor Huang Biao's team has used deep learning radiomics to analyze structural images and construct a model that can effectively interpret this genetic phenotype and provide patients with valuable radiological information [37, 38].

The phenotype of TERT has markedly different impacts on patients with high and low-grade gliomas (*i.e.*, IDH-wildtype/IDH-mutant status). Without distinguishing the IDH subtype of gliomas, direct analysis of the TERT status using functional imaging would be ineffective in providing accurate survival predictions and analyzing the microenvironment for patients [39]. Sung Hee Ahn *et al*. conducted PWI imaging analysis of TERT after IDH subtyping in gliomas and found that in low-grade gliomas, TERT mutation significantly reduces blood perfusion compared to the wildtype [40]. Koji Yamashita and colleagues found that Magnetic Resonance Spectroscopy (MRS) can reflect the status of Telomerase Reverse Transcriptase (TERT) in Glioblastoma (GBM) through the levels of N-acetylaspartate (NAA)/Creatine (Cr) and Choline (Cho)/Cr ratios, with TERT-wildtype levels typically higher than those of TERT-mutant GBM [41]. MRS for the detection of metabolites can be effectively applied to the targeted treatment of TERT-mutant cases [42]. In a recent article published in Nature Communications, advanced techniques in 1H MRS have been utilized, suggesting the flux of hyperpolarized [1-13C]-pyruvate to lactate as a biomarker for TERT [43].

2.5. The Application of MR Imaging to MGMT

The methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter, while not explicitly considered in the criteria for glioma classification outlined in the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5), is intricately linked to tumor resistance to chemotherapy and sensitivity to alkylating agents in gliomas [1]. As the most proficient DNA repair protein identified to date, MGMT significantly repairs tumor DNA damage caused by alkylating agents when unmethylated, leading to a poorer prognosis. Therefore, the methylation status of MGMT remains pivotal in both preoperative diagnosis and postoperative treatment strategies for gliomas [14, 15].

The correlation between MGMT and patients' postoperative prognosis is significant. Functional imaging, particularly Perfusion Weighted Imaging (PWI), along with its derived techniques, such as Dynamic Susceptibility Contrast (DSC) and Dynamic Contrast Enhanced (DCE), has been proven to be an effective approach for detecting the methylation status of MGMT [44 - 47]. Individual applications of PWI or its combination with Diffusion Weighted Imaging (DWI), Magnetic Resonance Spectroscopy (MRS), or other techniques have exhibited excellent effectiveness in determining the methylation status of MGMT [48, 49]. Studies have revealed that patients with unmethylated MGMT display higher levels of perfusion on PWI, indicating a higher likelihood of recurrence and significantly shorter Progression Free Survival (PFS) and Overall Survival (OS). In a clinical trial conducted by Michelle M. Kim, published in Neuro-Oncology, increasing the radiation dose in regions of signal enhancement on PWI and DWI images effectively extended OS and PFS for patients [16].

3. GLIOMA SURVIVAL DAY PREDICTION

Predicting the survival days of glioma patients is essential for diagnosis and patient management, considering it a prevalent malignant brain tumor with high mortality rates. However, accurately predicting survival days remains a challenge in glioma diagnosis. Currently, structural imaging is primarily employed in radiomics to address this issue.

Currently, research on survival prediction in gliomas is primarily based on the extraction of features from tumor subregion segmentation results to predict patient survival days. Baid *et al*. utilized a modified 3D UNet model for glioma segmentation, extracting radiomic features from different subregions, and then inputting these features into models, such as random forest and multilayer perceptrons, to predict patient survival days [50]. Gate *et al*., on the other hand, employed the DeepMedic model for tumor segmentation, extracting radiomic features and volume from each subregion. They subsequently utilized the Cox model to predict survival days [51]. The aforementioned studies all involve the extraction of radiomic features from the regions of interest, without specific feature design tailored to tumor survival prediction. Kao *et al*., for instance, utilized models, such as 3D UNet and DeepMedic, for tumor subregion segmentation. They combined the features extracted from tumor subregions and brain segmentation to predict patient survival [52]. This approach considers the issue of feature redundancy, utilizing feature selection methods to automatically filter out irrelevant features, thereby improving model performance. Feng *et al*. proposed a linear regression model that leverages morphological features extracted from

brain segmentation images, such as volumes and surface areas of different subregions, to predict survival days [53].

CONCLUSION

Combining structural images with functional images that can evaluate the glioma microenvironment and applying deep learning for radiomic analysis cannot only improve diagnostic efficiency and accuracy but also further reflect the pathological and physiological behaviors of gliomas in imaging. This approach can aid in precise diagnosis, the formulation of reasonable treatment plans, and effective postoperative prognosis assessment, and thus better serve glioma patients.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study has been supported by a grant from the National Natural Science Foundation of China (grant number: 82071871), Guangdong Basic and Applied Basic Research Foundation (No. 2021A1515220131), Guangdong Medical Science and Technology Research Fund Project (No. 2022111520491834), and Clinical Research Project of Shenzhen Second People's Hospital, China (No. 20223357022).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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