The 2021 WHO Classification for Gliomas and Implications on Imaging Diagnosis: Part 1—Key Points of the Fifth Edition and Summary of Imaging Findings on Adult-Type Diffuse Gliomas

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The fifth edition of the World Health Organization (WHO) classification of central nervous system tumors published in 2021 advances the role of molecular diagnostics in the classification of gliomas by emphasizing integrated diagnoses based on histopathology and molecular information and grouping tumors based on genetic alterations. Importantly, molecular biomarkers that provide important prognostic information are now a parameter for establishing tumor grades in gliomas. Understanding the 2021 WHO classification is crucial for radiologists for daily imaging interpretation as well as communication with clinicians. Although imaging features are not included in the 2021 WHO classification, imaging can serve as a powerful tool to impact the clinical practice not only prior to tissue confirmation but beyond. This review represents the first of a three-installment review series on the 2021 WHO classification for gliomas, glioneuronal tumors, and neuronal tumors and implications on imaging diagnosis. This Part 1 Review focuses on the major changes to the classification of gliomas and imaging findings on adult-type diffuse gliomas.

Evidence Level: 3.

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Gliomas are primary central nervous system (CNS) tumors characterized by the widespread infiltration of tumor cells displaying cytologic and histological features of glial differentiation (i.e. astrocytes, oligodendrocytes, etc).[1] Linking the origin of cancers from otherwise normal cells starts from Rudolf Virchow (1821–1902), the renowned German pathologist.[2] In the early World Health Organization (WHO) classification, the histopathological diagnosis of gliomas was largely made on comparing features of tumor cells with those of normal tissue; brain tumors with cells resembling astrocytes were called astrocytomas, whereas those with cells resembling oligodendrocytes were called oligodendrogliomas. Thus, until

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the 2016 WHO classification, diffuse gliomas were classified based upon their morphologic features, with molecular testing merely playing an ancillary role.

During the past decade, multiple studies have revealed molecular alterations that can classify gliomas into clinically significant subsets, leading the revised fourth edition update of WHO classification in 2016 to incorporate diagnostic entities based on the integration of morphologic features with molecular markers.[1] Further advances in the understanding of the pathogenesis and clinical behavior of specific diffuse glioma subtypes have led to the inclusion of additional molecular markers into tumor classification. As a result, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy-Not Official WHO (cIMPACT-NOW) was established to facilitate future WHO classification updates.[3–9] The subsequent 2021 WHO fifth edition reflects updates from cIMPACT-NOW and relies even more on molecular test results for classification of gliomas.[10] DNA methylation profiling continues to identify numerous tumor types with specific methylation patterns that have characteristic genetic alterations and clinical behavior.

Although imaging features are not included in the WHO classification, imaging can serve as a powerful tool to impact the clinical practice not only prior to tissue confirmation but beyond in gliomas. Before tissue confirmation and also in rare cases that tissue confirmation is impossible, imaging features are the key information that drives the clinical decision. Fully acknowledging the 2021 WHO classification is crucial for radiologists for their daily practice and communication with clinicians.

This Part 1 Review will focus on the major changes of the 2021 WHO classification of gliomas and introduce imaging findings on adult-type diffuse gliomas. The subsequent Part 2 Review will focus on the imaging findings of pediatric-type diffuse high-grade gliomas, pediatric-type diffuse low-grade gliomas, and circumscribed astrocytic gliomas, while the Part 3 Review will focus on the imaging findings of glioneuronal and neuronal tumors.

General Changes

"Type" and "Subtype" Replacing "Entity" and "Variant"

In the 2021 WHO classification, for consistency with the other fifth edition WHO Blue Books, the term "type" is used instead of "entity," and "subtype" is used instead of "variant." For example, glioblastoma, IDH-wildtype, is a type of brain tumor within the category of adult-type diffuse gliomas, with three subtypes: giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma.

Separation of Adult- and Pediatric-Type Gliomas

For the first time in the WHO classification, "adult-type" diffuse gliomas are separated from the "pediatric-type." The rationale for this separation is based on the clinical and molecular distinctions between diffuse gliomas that occur primarily in adults and those that occur primarily in children termed "adult-type" and "pediatric-type," respectively. The usage of the word "primarily" may be emphasized; pediatric-type tumors may sometimes occur in adults, particularly in younger adults, while adult-type tumors may rarely occur in children.

Molecular Diagnostics in Diffuse Gliomas

The 2021 WHO classification emphasizes the role of molecular features for classification of gliomas, glioneuronal tumors, and neuronal tumors.[10] A recent guideline from the College of American Pathologists introduces evidence-based recommendation of molecular biomarker testing in diffuse gliomas according to this updated fifth edition.[11] IDH1/2 mutational testing should be performed on all diffuse gliomas, while 1p/19q codeletion status should be assessed in all IDH-mutant gliomas unless they show ATRX loss or *TP53* mutations. In astrocytoma, IDH-mutant, *CDKN 2A/B* homozygous deletion testing should be performed to determine WHO grade 4. *MGMT* promoter methylation status, although not incorporated in the 2021 WHO classification, is a powerful predictive and prognostic marker[12] and should be performed on glioblastoma, IDH-wildtype. For histological grade 2–3 IDH-wildtype diffuse gliomas, *TERT* promoter mutation, *EGFR* amplification, and combined whole chromosome 7 gain and combined chromosome 10 loss (chromosome +7/−10) should be performed to establish the molecular diagnosis of glioblastoma, IDH-wildtype. H3 K27 alteration testing should be performed in diffuse gliomas that involve the midline in appropriate pathologic setting, whereas H3 G34 testing should be performed in pediatric and young adult patients with IDH-wildtype diffuse gliomas. MYB/MYBL1 and FGFR1 testing may be performed in pediatric and young adult patients with diffuse gliomas that are histologically grade 2–3 as well as IDH-wildtype and H3-wildtype.

DNA methylation profiling usually plays a supplementary role in establishing a diagnosis for challenging cases, but in several tumors, DNA methylation is the only method for definite diagnosis.[13] Currently, four types of tumors implement DNA methylation profiles for diagnosis. Two of these tumors, high-grade astrocytoma with piloid features and diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, are within the category of gliomas, glioneuronal tumors, and neuronal tumors, while the other two, posterior fossa ependymoma group A and posterior fossa ependymoma group B, are within the category of ependymal tumors. Some subtypes within a tumor may be diagnosed by their unique DNA methylation profiles; for example, three subtypes (RTK2, RTK1, and MYCN subtypes) within

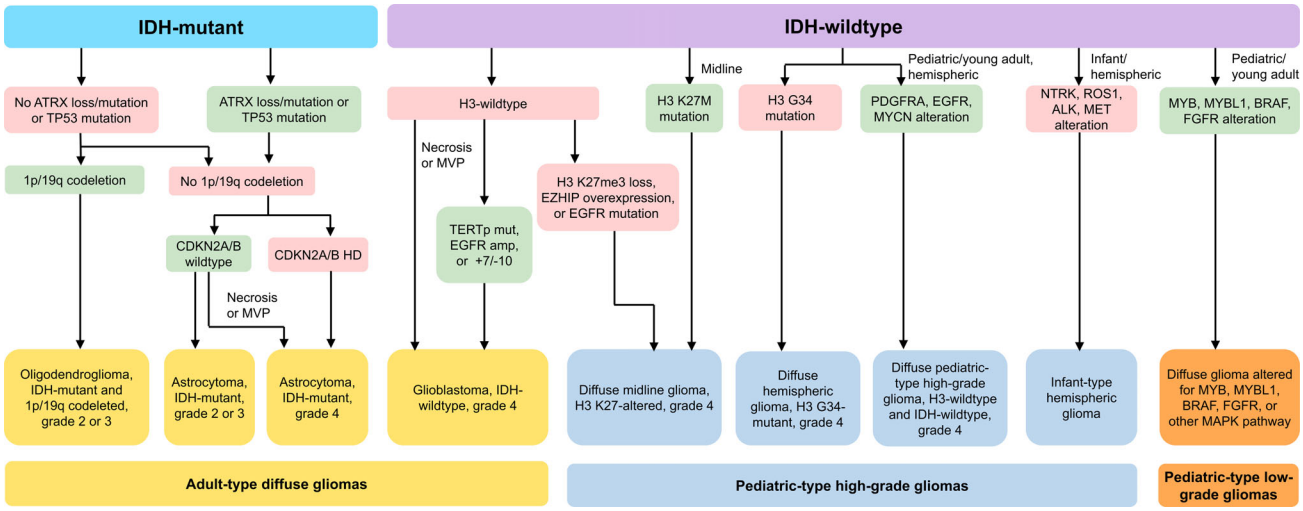

FIGURE 1: Diagnostic flowchart of diffuse gliomas in adults and pediatrics. amp = amplification; HD = homozygous deletion; mut = mutation; MVP = microvascular proliferation.

diffuse pediatric high-grade glioma, H3 wildtype and IDH-wildtype are identified by DNA methylation testing.

A subset of molecular findings in the 2021 WHO classification that involve the classification and grading of IDH-mutant and IDH-wildtype diffuse gliomas in adults and pediatrics are summarized in Fig. 1. The increasing complexity in the molecular markers, particularly in pediatric-type diffuse gliomas, is reflected.

Tumor Grading

Three specific aspects of tumor grading have changed for the 2021 WHO classification: tumors are graded within tumor types (rather than across different types); combined histopathology and molecular features are used for grading; and Arabic numerals are used (rather than Roman numerals).

GRADING WITHIN TYPES. In the previous 2016 WHO classification, if a tumor had been classified as an anaplastic astrocytoma, it was automatically assigned a CNS WHO grade of III; there was no option to grade an anaplastic astrocytoma as grade I, II, or IV. In the 2021 WHO classification, tumors are graded within tumor types (rather than across different types) and the terms such as "anaplastic astrocytoma" is obsolete. For example, astrocytoma, IDH-mutant, is a single type, and can be graded as WHO grade 2, 3, or 4 within the type. This change was made for a few reasons: 1) to provide more flexibility in using grade relative to the tumor type, 2) to emphasize biological similarities within tumor types, and 3) to conform with WHO grading of non-CNS tumor types.

The flexibility in grading within tumor type is due to the fact that there are no strict threshold for grading; for example, CNS WHO grade 2 and 3 astrocytomas, IDH-mutant are distinguished based on increased mitotic activity and cytological anaplasia, but there is no absolute cutoff value defined for designation of grade 3.[14]

It should be kept in mind that the clinical behaviors of different tumor types with the same WHO grades may be completely different; for example, astrocytoma, IDH-mutant, WHO grade 3 should not necessarily demonstrate similar survival times to meningioma, WHO grade 3.

COMBINED HISTOLOGICAL AND MOLECULAR GRADING. In the 2021 WHO classification, molecular parameters have now been added for grading and estimating prognosis in multiple tumor types. For example, astrocytomas, IDH-mutant, WHO grade 4 tumors must manifest necrosis and/or microvascular proliferation in addition to the features of CNS WHO grade 3 lesions, but if the tumor shows homozygous deletion of *CDKN2A/B*, the designation of grade 4 is warranted even in the absence of necrosis or microvascular proliferation. In addition, for histological grade 2–3 IDH-wildtype diffuse gliomas without necrosis or microvascular proliferation, *TERT* promoter mutation, *EGFR* amplification, and chromosome +7/−10 leads to diagnosis of glioblastoma, IDH-wildtype, WHO grade 4. In

TABLE 1. Example of Integrated, Layered Diagnosis

Cerebrum	
Integrated diagnosis	**Diffuse astrocytoma, *MYB*- or *MYBL1*-altered**
Histopathological classification	Diffuse astrocytoma without anaplasia
CNS WHO grade	1
Molecular information	Fusion between *MYB::PCDHGA1* on next-generation sequencing (NGS)

these situations, molecular parameters are preferred to be used over histological findings in assigning a grade.

ARABIC VS. ROMAN NUMERALS. To decrease the possibility of errors in Roman numerals used previously in grading, all CNS WHO grades have been changed to Arabic numerals in the 2021 WHO classification.

Integrated and Layered Diagnoses

To display the full amount of diagnostic information available, the use of layered (or tiered) diagnostic reports is strongly encouraged. Such reports feature an integrated diagnosis at the top, followed by layers that display histological, molecular, and other key types of information (example in Table 1).

NOS and NEC

The designations "not otherwise specified (NOS)" and "not elsewhere classified (NEC)" allow the separation of standard, well-characterized WHO diagnoses from those diagnoses that result from either 1) insufficient diagnostic information or 2) non-diagnostic or negative results. The NOS designation indicates that the diagnostic information necessary to assign a specific WHO diagnosis is not available, alerting the oncologist that a full molecular workup has not been undertaken or was not successful. In contrast, the NEC designation indicates that the necessary diagnostic testing has been successfully performed but that the results do not readily allow for a WHO diagnosis despite the adequate diagnostic testing. Examples of NOS and NEC, as well as a specific diagnosis based on sufficient diagnostic testing, are shown in Fig. 2.

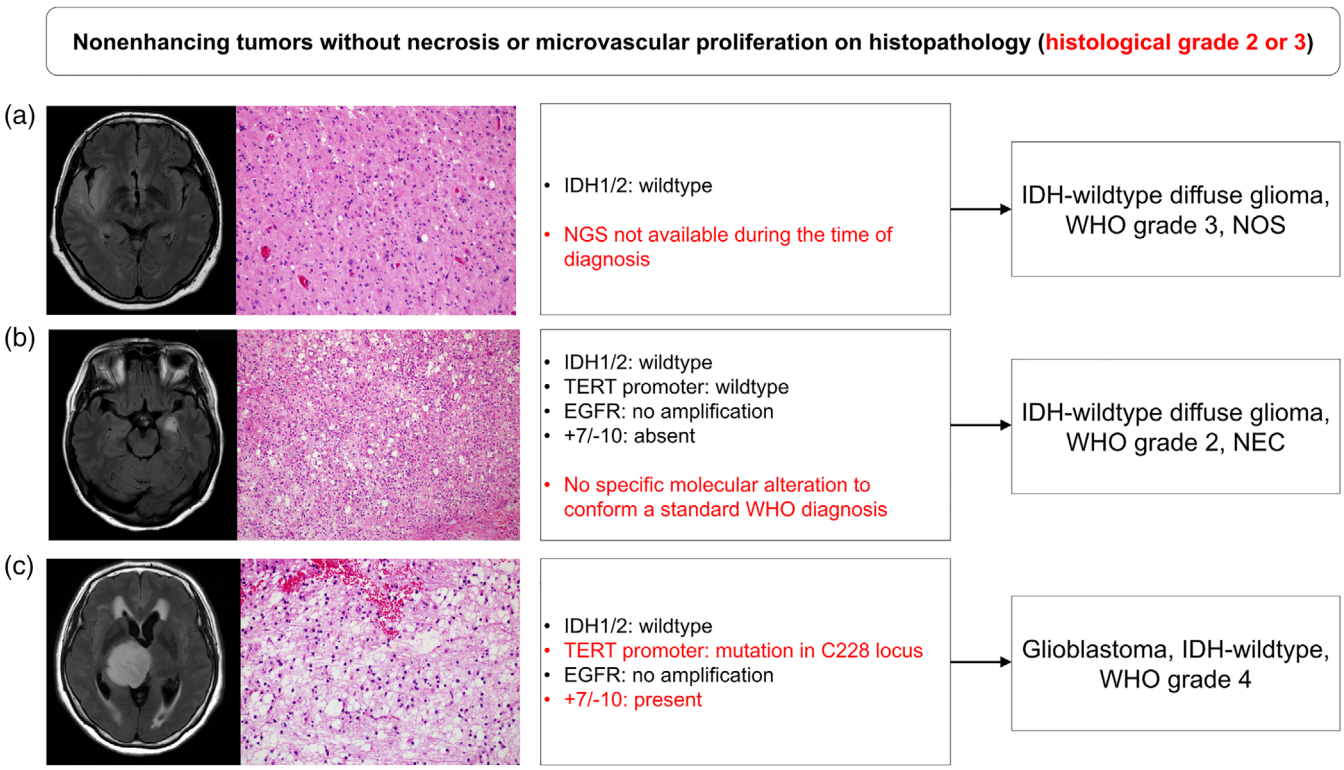

FIGURE 2: Examples of not otherwise specified (NOS), not elsewhere classified (NEC), and a specific diagnosis based on sufficient diagnostic testing in three different patients with IDH-wildtype diffuse glioma. All patients had nonenhancing tumor on FLAIR imaging and were negative on IDH1/2 mutation. Histopathology slides of all patients show well-differentiated fibrillary glial cells that diffusely infiltrate the brain parenchyma. Mitotic activity and cytological atypia were increased in the first patient with a histological grade 3 while the other two patients showed a histological grade 2. There was no necrosis or microvascular proliferation on histopathology. (a) A 54-year-old female with a nonenhancing tumor centered at the insula. At the time of diagnosis, next-generation sequencing (NGS) was not available. This patient was previously diagnosed as IDH-wildtype anaplastic astrocytoma, WHO grade III in the prior 2016 classification, but now should be termed as "IDH-wildtype diffuse glioma, WHO grade 3, NOS" according to the 2021 WHO classification. (b) A 53–year-old female with a nonenhancing tumor at the left temporal lobe. Despite an adequate pathologic work-up including NGS, there was no specific molecular alterations to conform to a standard WHO diagnosis. Thus, this patient was diagnosed as "IDH-wildtype diffuse glioma, WHO grade 2, NEC". (c) A 57–year-old female with a nonenhancing tumor at right thalamus. There was no mutation in histone H3, excluding the possibility of diffuse midline glioma, H3 K27-altered. This patient did not show necrosis or microvascular proliferation, but *TERT* promoter mutation and combined chromosome 7 gain and chromosome 10 loss were noted. Thus, this patient was diagnosed as "Glioblastoma, IDH-wildtype, WHO grade 4."

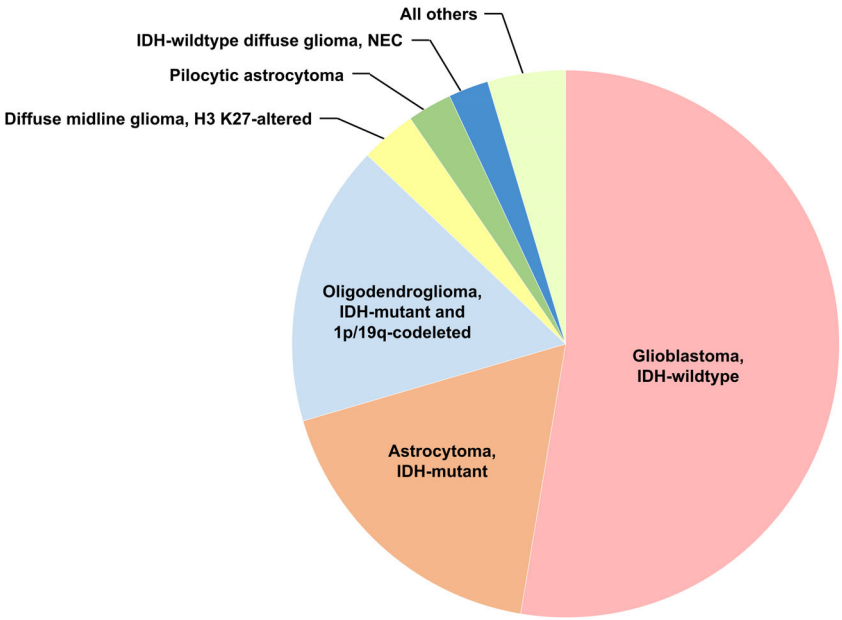

FIGURE 3: Graphic depicting the relative prevalence of gliomas, glioneuronal tumors, and neuronal tumors in adults. Data were derived from 1480 molecularly classified gliomas, glioneuronal tumors, and neuronal tumors from Severance Hospital. This pie chart aims to serve as a schematic rather than an accurate depiction of prevalence due to the different proportion of tumor types according to ethnicity and institutions. NEC = not elsewhere classified.

Before Starting: Always Keep the "Big Picture' In Mind

As radiologists, we recommend to refrain from being focused on a particular imaging finding to make a specific diagnosis; we should rather be aware of the "big picture" of the patient such as the age, location, and relative prevalence of diseases. The relative prevalence of gliomas, glioneuronal tumors, and neuronal tumors in adults should be kept in mind (a schematic is shown in Fig. 3). As expected, adult-type diffuse gliomas are most common in adults, among which glioblastoma, IDH-wildtype is most prevalent. Among adult-type diffuse gliomas of all grades, the incidence of IDH mutation is reported around 40%–50%.[15] However, in our experience, East Asians are underrepresented in the literature due to their low proportion in reports from Western Population, and East Asians show a lower incidence of IDH mutation around 33%.[16,17] Diffuse midline glioma, H3 K27-altered, and pilocytic astrocytoma, which are tumor types from pediatric diffuse high-grade glioma and circumscribed glioma, respectively, are also relatively prevalent in adults, especially in young adults.[18]

Table 2 shows a summary of key molecular alterations, WHO grade, age, location, and imaging features in each type of tumor in adult-type diffuse gliomas.

Recommended Imaging Protocol

The recommended imaging protocol of adult gliomas includes 3D precontrast and postcontrast T1-weighted imaging, 2D postcontrast T2-weighted and precontrast fluid-attenuation inversion recovery (FLAIR) imaging, and 2D diffusion-weighted imaging.[19] Postcontrast FLAIR is not a routinely recommended sequence in glioma, but from our personal experience, we strongly believe that this sequence is useful in detection of leptomeningeal metastases.[20]

Specific Molecular and Imaging Features

Adult-Type Diffuse Gliomas

Adult-type diffuse gliomas are the most common primary brain tumor, and mostly occur in the supratentorial brain.[18,21,22] IDH-mutant gliomas occur in younger adults than glioblastoma, IDH-wildtype, whereas glioblastoma, IDH-wildtype are more common in men.[18,21] Mutations in IDH1 and IDH2 genes have been postulated to be the initiating event in tumorigenesis of IDH-mutant gliomas,[23] and their presence dictates a particular path for oncogenic progression—and paradoxically, a favorable clinical behavior than IDH-wildtype gliomas—in these tumors.[24] Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, shows the most favorable prognosis, followed by astrocytoma, IDH-mutant and glioblastoma, IDH-wildtype (Fig. 4). IDH-mutant adult-type diffuse gliomas harbor distinct and generally less aggressive imaging features compared with glioblastoma, IDH-wildtype, such as frontal lobe predominance, less contrast enhancement, well-defined border, high apparent diffusion coefficient (ADC) value and low relative cerebral blood volume (rCBV) value.[15] IDH-mutant adult-type diffuse gliomas also show increased level of oncometabolite 2-hydroxyglutarate (2HG) on 2HG magnetic resonance spectroscopy.[25] The imaging landscape of adult-type diffuse gliomas is presented in Fig. 5 and will be discussed in detail afterwards.

TABLE 2. Summary of Key Molecular Alterations, WHO Grade, Age, Location, and Imaging Features in Each Type of Adult-Type Diffuse Gliomas

Tumor type	Key Molecular Alteration	WHO Grade	Age	Location	Imaging Features
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	IDH1/2, 1p/19q	2, 3	Younger adults (fourth and fifth decade)	Frontal	Cortical involvement, heterogeneous signal, calcification, and cystic change Variable enhancement (more frequent in grade 3)
Astrocytoma, IDH-mutant	IDH1/2	2, 3, 4	Younger adults (fourth and fifth decade)	Frontal	Well-defined border, less contrast enhancement T2-FLAIR mismatch sign Variable enhancement (more frequent in higher grade) *CDKN 2A/B* HD: infiltrative pattern, larger tumor size, and higher rCBV
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT*, *EGFR*, chromosome +7/−10	4	Older adults (sixth and seventh decade) (male predominance)	Supratentorial	Histological grade 4: infiltrative appearance, heterogeneous signal intensity, larger tumor size, peripheral rim enhancement with central necrosis, hemorrhage, low ADC and high rCBV, multifocal and nonlobar location Histological grade 2/3 with molecular features: nonenhancing or small proportion of enhancement, cortical involvement, infiltrative appearance, lower ADC and higher rCBV

ADC = apparent diffusion coefficient; rCBV = relative cerebral blood volume; HD = homozygous deletion; WHO = World Health Organization.

OLIGODENDROGLIOMA, IDH-MUTANT, AND 1P/19Q-CODELETED. Oligodendrogliomas are defined by IDH mutation and 1p/19q codeletion, which is not markedly changed compared to the previous 2016 WHO classification. Nearly all tumors have *TERT* promoter mutation, lack *ATRX* mutation, and show preserved nuclear ATRX expression. *CDKN2A* homozygous deletion may serve as a molecular marker of CNS WHO grade 3 in oligodendrogliomas with borderline histological features for grading (i.e. when present, a *CDKN2A* homozygous deletion indicates a CNS WHO grade 3).

Typical imaging findings include frontal location (53%–67%),[16,26] cortical involvement, heterogeneous signal on T2-weighted or FLAIR images, calcification, and presence of cystic changes.[14,27–31] Oligodendrogliomas do demonstrate contrast enhancement, but in only part of the tumor. Specifically, approximately 40%–50% of oligodendrogliomas demonstrate contrast enhancement and it is more common in

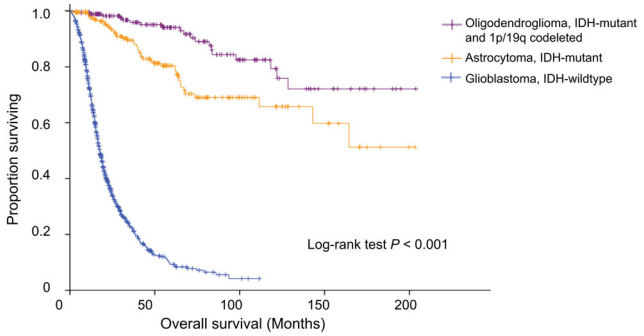

FIGURE 4: Kaplan–Meier Curve showing significantly different survival curves according to different types in adult-type diffuse gliomas. Data were derived from 1,193 molecularly classified adult-type diffuse gliomas with a median follow-up period of 51.0 months (interquartile range 24.0–87.9) from Severance Hospital.

grade 3.[30,32] On advanced imaging, oligodendrogliomas may show lower ADC value and higher rCBV than astrocytomas, IDH-mutant, WHO grade 2 or 3,[33] and these imaging findings should not be confused with those of glioblastoma, IDH-wildtype. Figure 6 shows typical imaging features of with oligodendroglioma, IDH-mutant and 1p/19q codeleted, according to different WHO grades.

ASTROCYTOMA, IDH-MUTANT. Astrocytoma, IDH-mutant, is defined as an adult-type diffuse glioma with IDH1/2 mutation without 1p/19q codeletion. Loss of nuclear ATRX expression and *TP53* mutation, which are shown in a large proportion of astrocytoma, IDH-mutant, strongly support the diagnosis of IDH-mutant astrocytoma. Grading is primarily based on histopathology, however, if tumor shows *CKDN 2A/B* homozygous deletion even in the absence of necrosis or microvascular proliferation, this tumor is assigned as CNS WHO grade 4. This is based on the fact that CDKN2A/B homozygous deletion has been proven to be an independent prognostic marker in all grades of astrocytomas, IDH-mutant, even within CNS WHO grade 4 astrocytomas, IDH-mutant.[34] The reported frequencies of *CDKN2A/B* homozygous deletions range from 0% to 12% in histological grade 2, 6% to 20% in histological grade 3, and 16% to 34% in histological grade 4, all of which are WHO CNS grade 4 by definition according to the 2021 WHO classification.[34,35]

Typical imaging findings include frontal location, with a slightly less frequent proportion than oligodendrogliomas[36]; 47%–57% of astrocytoma, IDH-mutant, were located in the frontal lobe compared to 53%–67% of oligodendroglioma, IDH-mutant and 1p/19q codeleted.[16,37] In WHO grade

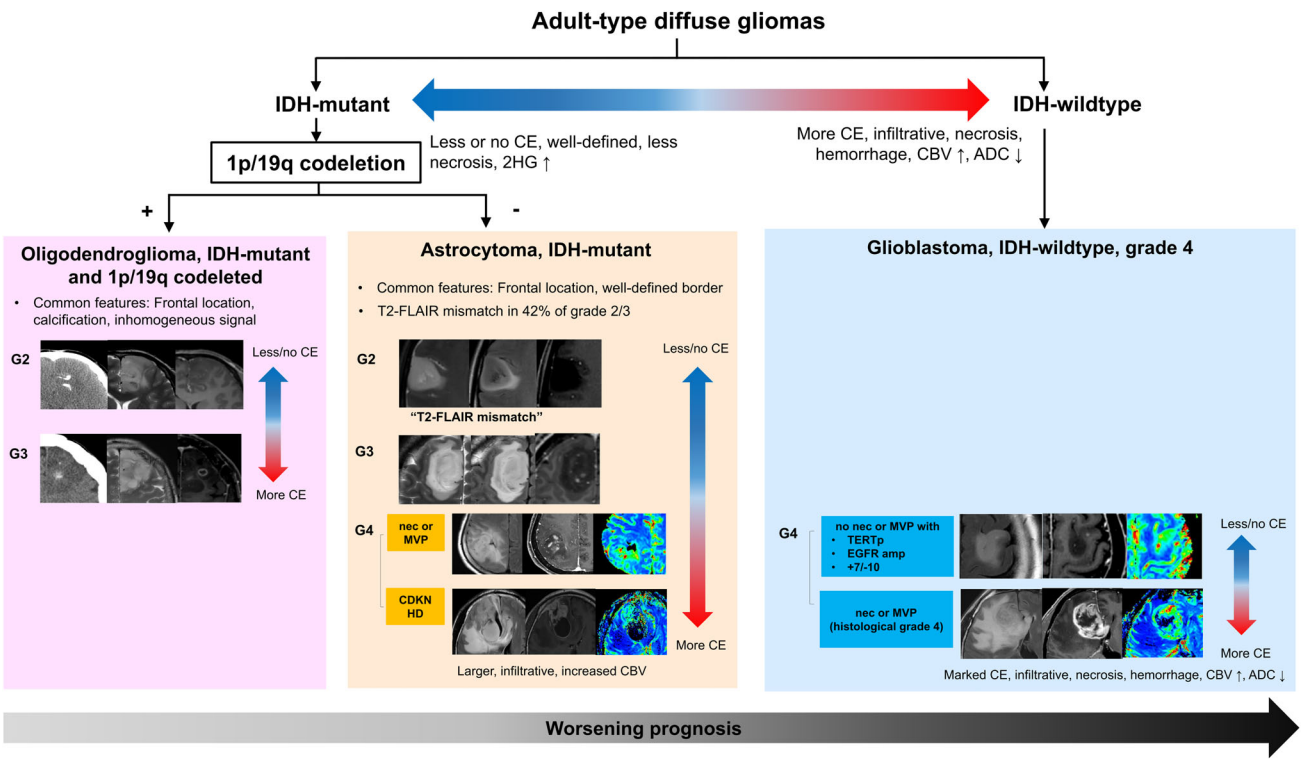

FIGURE 5: The imaging landscape of adult-type diffuse gliomas. Adult-type diffuse gliomas are divided into only three types according to presence of IDH mutation and 1p/19q codeletion: oligodendroglioma, IDH-mutant and 1p/19q-codeleted; astrocytoma, IDH-mutant; and glioblastoma, IDH-wildtype. Grading is performed within a single type. Common imaging features of each type and imaging features according to the grade or molecular status in each type are described. Note that there is no WHO grade 4 oligodendroglioma, IDH-mutant and 1p/19q codeleted, whereas there is no WHO grade 2 or grade 3 in glioblastoma, IDH-wildtype. 2HG = 2-hydroxyglutarate; amp = amplification; CE = contrast enhancement; HD = homozygous deletion; MVP = microvascular proliferation; nec = necrosis.

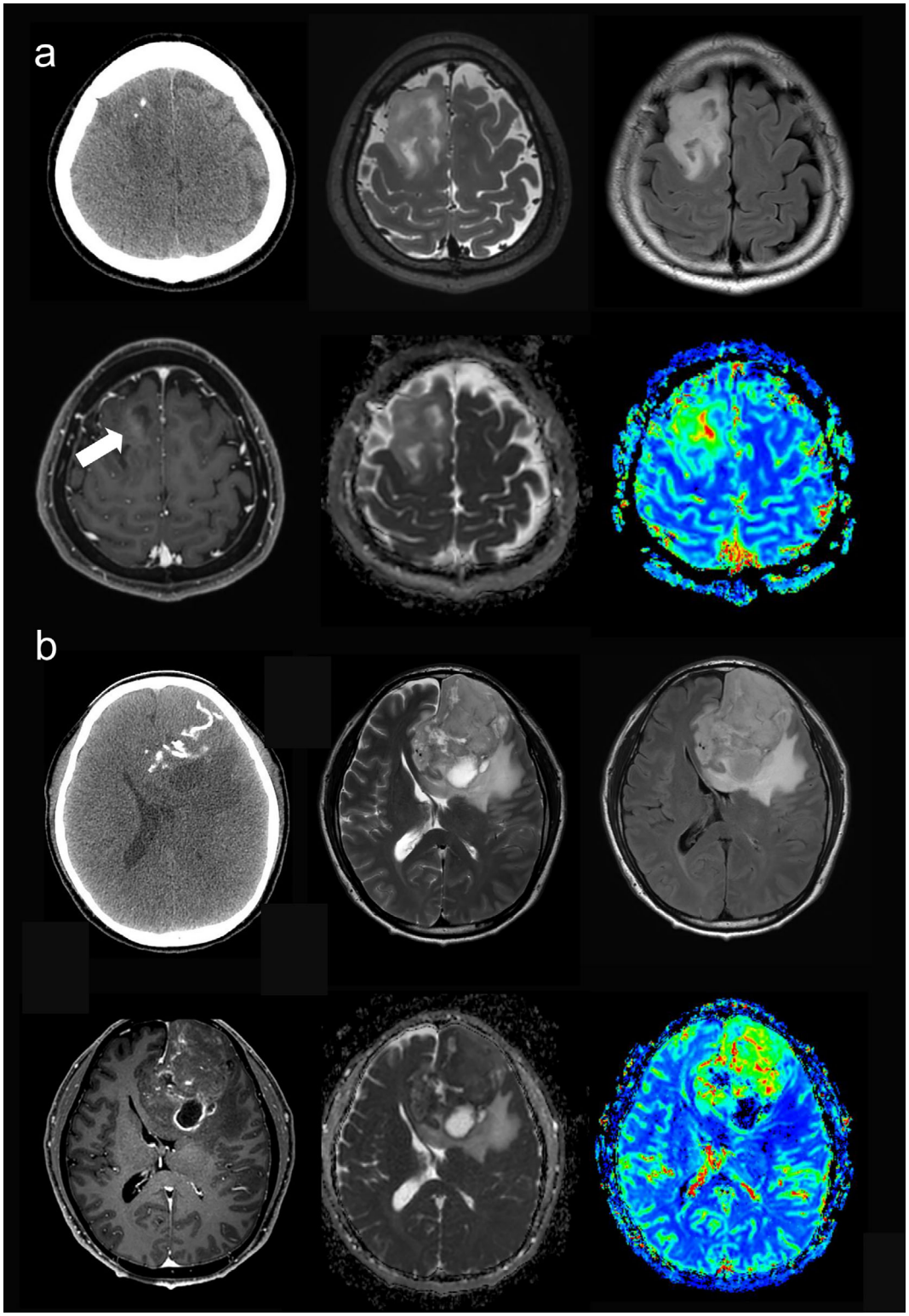

FIGURE 6: Images of two different patients with oligodendroglioma, IDH-mutant and 1p/19q codeleted. (a) Images in a 41-year-old male with WHO grade 2 tumor show focal calcifications on noncontrast CT. On T2-weighted and FLAIR images, areas of cystic changes are shown. There is focal faint enhancement (arrow). There is no cellularity increase on ADC map. There is an area of marked rCBV increase, which is characteristic in oligodendroglioma. (b) Images in a 49-year-old male with WHO grade 3 tumor show gyriform calcification on noncontrast CT. There is heterogeneous T2 signal intensity, and the tumor shows multifocal strong enhancement with necrosis. ADC map and CBV map show increased cellularity and increased rCBV at the solid portion.

2 and 3 astrocytomas, IDH-mutant, well-defined border, less contrast enhancement, high ADC value and low rCBV value are reported imaging findings.[15]

The "T2-FLAIR mismatch" sign, a highly specific imaging biomarker for astrocytoma, IDH-mutant, is defined by two distinct MRI findings: 1) a complete or

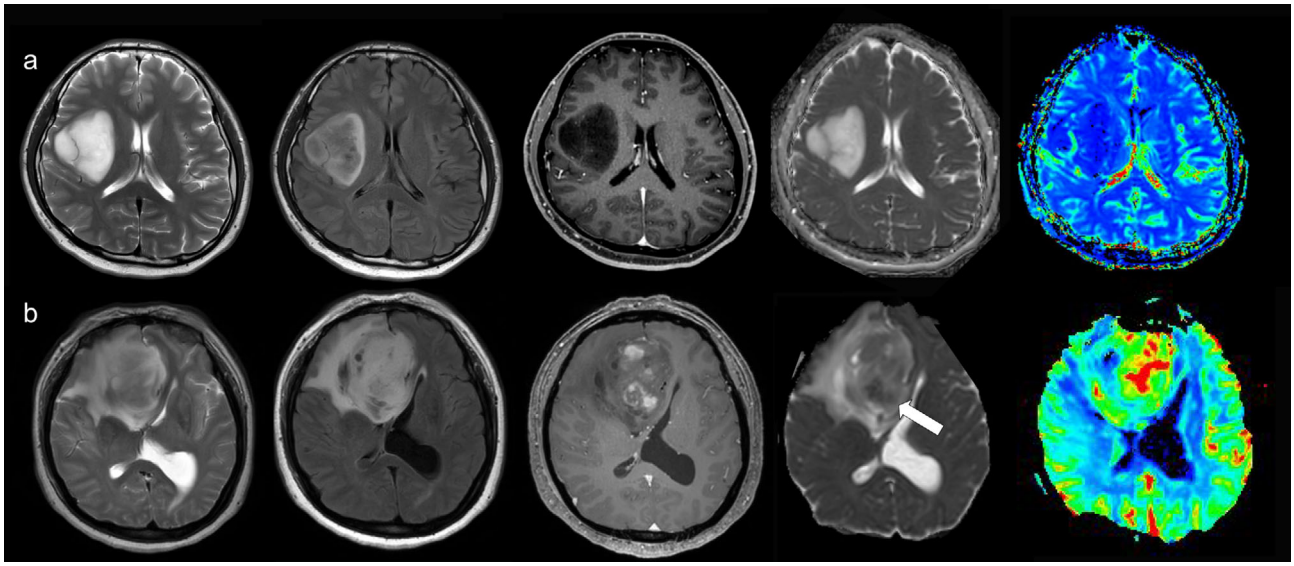

FIGURE 7: Images two different patients with astrocytoma, IDH-mutant. (a) Images in a 42-year-old male with astrocytoma, IDH-mutant, WHO grade 2, show an expansile nonenhancing mass centered in the right insula. There is a T2-FLAIR mismatch sign, which has a high positive predictive value for astrocytoma, IDH-mutant. There is no cellularity nor rCBV increase. (b) Images in a 47-year-old female with astrocytoma, IDH-mutant, WHO grade 4, with *CDKN 2A/B* homozygous deletion. A heterogeneously enhancing mass involving the right frontal lobe and corpus callosum genu is shown. There are foci of increased cellularity on ADC map (arrow), whereas the rCBV is markedly increased. Histologically, this patient lacked necrosis or microvascular proliferation, with histopathology fulfilling for grade 3, but due to the presence of *CDKN 2A/B* homozygous deletion, the final CNS WHO grade was 4.

near-complete and almost homogeneous hyperintense signal on T2-weighted images, and 2) a relatively hypointense signal on the T2-weighted FLAIR sequence except for a hyperintense peripheral rim.[38,39] This imaging finding had a pooled sensitivity and specificity for 42% and 100% for astrocytoma, IDH-mutant, respectively.[40] But several studies also reported few cases of false positive results, particularly in pediatric-type gliomas.[40] False positive results have also been reported in 28.5% among oligodendrogliomas,[41] but the authors in this study applied a more "relaxed"

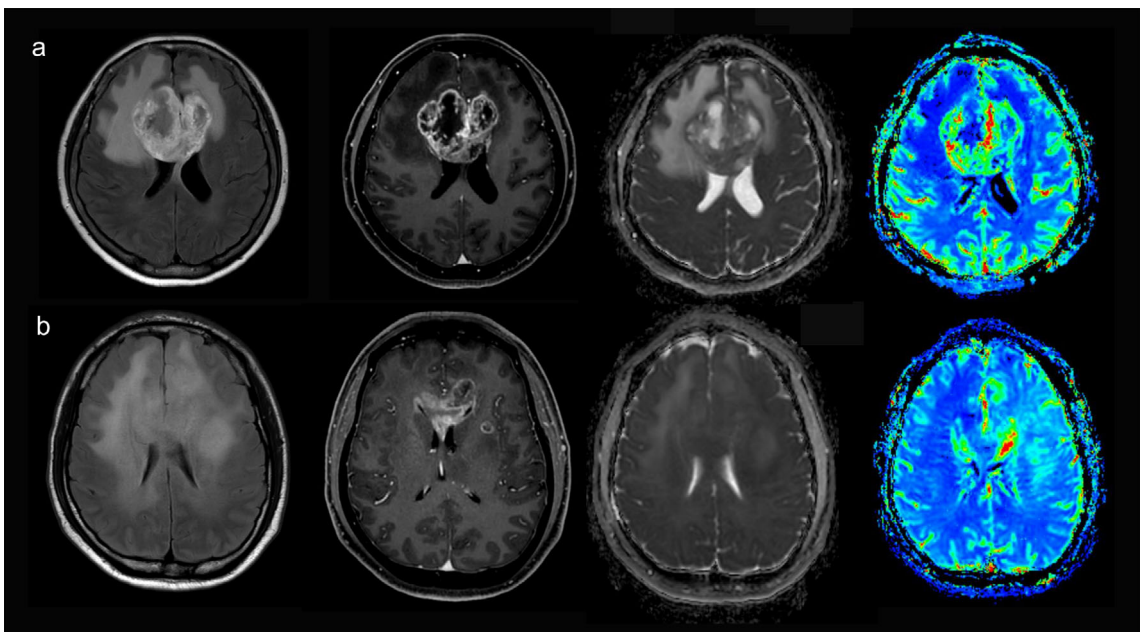

FIGURE 8: Images in two different patients with glioblastoma, IDH-wildtype, grade 4, with necrosis and microvascular proliferation on histopathology. (a) Images in a 68-year-old female with an enhancing necrotic tumor involving the bifrontal lobes and corpus callosum with edema. ADC map and CBV map show increased cellularity and increased rCBV at the enhancing portion. (b) Images in a 40-year-old male with enhancing tumors at the corpus callosum and left basal ganglia show strong enhancement with necrosis. Note that the nonenhancing infiltrative tumor component (not edema) diffusively involves the bilateral cerebral hemispheres on FLAIR. ADC map and CBV map shows slightly increased cellularity and increased rCBV at the enhancing portion.

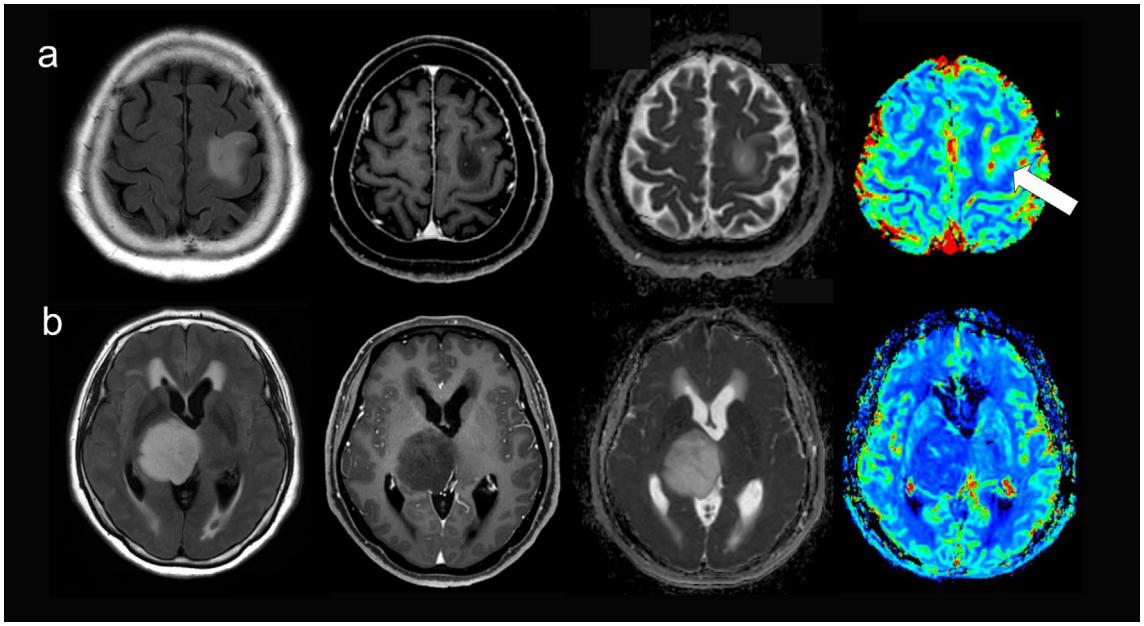

FIGURE 9: Images in two different patients with glioblastoma, IDH-wildtype, WHO grade 4, with diagnosis established by molecular data. There was no necrosis or microvascular proliferation on histopathology of both patients. (a) Images in a 79-year-old female with a nonenhancing expansile mass at the left frontal lobe. There is no cellularity increase on ADC map. However, there is focal rCBV increase (arrow). The patient had IDH-wildtype astrocytic glioma, without necrosis or microvascular proliferation (histologically grade 3), but there are *TERT*p mutation and *EGFR* amplification, sufficient for diagnosis of glioblastoma, IDH-wildtype, WHO grade 4. (b) Images in a 57-year-old female with a nonenhancing expansile mass at the right thalamus. ADC map and CBV map show- no cellularity nor rCBV increase. Note that in this case it is virtually impossible to differentiate this tumor from diffuse midline glioma, H3 K27-altered, or other low-grade tumors. The patient had astrocytic glioma, without necrosis or microvascular proliferation (histologically grade 2), but there is *TERT*p mutation and combined chromosome 7 gain and chromosome 10 loss, sufficient for diagnosis of glioblastoma, IDH-wildtype, grade 4. There is no mutation in histone H3, excluding the possibility of diffuse midline glioma, H3 K27-altered.

criteria for "T2-FLAIR mismatch" rather than applying the aforementioned strict criteria.[38,39] T2-FLAIR mismatch sign is reported to reflect enlarged intercellular space on pathology and overexpression of mTOR-related genes on molecular analysis.[42] Figure 7a shows a representative case with "T2-FLAIR" mismatch in a patient with astrocytoma, IDH-mutant, WHO grade 2.

Imaging findings in WHO grade 4 have been less commonly reported due to the small proportion (less than 20%) within astrocytomas, IDH-mutant.[16,34] The imaging findings of astrocytomas, IDH-mutant, WHO grade 4, with *CDKN 2A/B* homozygous deletion have been recently reported by our group in relatively small multi-center dataset, and consist of infiltrative pattern, larger tumor size, and higher rCBV.[43] Figure 7b shows a representative case with *CDKN 2A/B* homozygous deletion, leading to WHO grade 4.

GLIOBLASTOMA, IDH-WILDTYPE. In the 2021 WHO classification, there are essential diagnostic criteria for glioblastoma (CNS WHO grade 4). First, glioblastomas are by definition diffuse astrocytic glioma with no mutation in either IDH1 or IDH2 genes, also known as IDH-wildtype. In addition, there should be necrosis or microvascular proliferation histologically or one of the following three molecular features: *TERT* promoter mutation; *EGFR* amplification; and combined chromosome +7/−10. Therefore, there is no longer IDH-mutant glioblastoma, which is now reclassified as astrocytoma, IDH-mutant, CNS WHO grade 4, due to the biologically distinct behavior between astrocytoma, IDH-mutant and glioblastoma, IDH-wildtype. For histological grade 2–3 IDH-wildtype diffuse gliomas without necrosis or microvascular proliferation, testing of *TERT* promoter mutation, *EGFR* amplification, and chromosome +7/−10 should be performed to establish the molecular diagnosis of glioblastoma, IDH-wildtype. Presence of one or more of these molecular markers leads to diagnosis of glioblastoma, IDH-wildtype, WHO grade 4, even in the absence of necrosis or microvascular proliferation.

Typical imaging findings of glioblastoma, IDH-wildtype include infiltrative nature on T2-weighted or FLAIR imaging, heterogeneous signal intensity, larger tumor size, peripheral rim enhancement with prominent central necrosis, regions of internal hemorrhage, regions of low ADC and high rCBV on dynamic susceptibility contrast imaging within solid component. IDH-wildtype glioblastomas are more likely to have a multifocal and nonlobar location.[29,44–46] Figure 8 shows representative cases of typical imaging features of glioblastoma, IDH-wildtype.

Further reports have shown that several molecular features of glioblastoma, IDH-wildtype, with necrosis or

microvascular proliferation can be predicted with imaging. Studies have shown that multifocal or multicentric distribution highly correlate with *EGFR* amplification.[47,48] Another study showed that high proportion of necrosis was correlated with *TERT* promoter mutation.[49] However, caution should be taken in interpreting whether *MGMT* promoter methylation status could be predicted preoperatively with imaging; we believe that current results are inconclusive and there is no validated imaging finding to predict the *MGMT* promoter methylation status, not even in advanced technique such as radiogenomics.[50] *MGMT* promoter methylation status is a crucial predictive and prognostic biomarker only in glioblastoma, IDH-wildtype, but not in other types of adult-type diffuse gliomas.[11] A high correlation between IDH mutation and *MGMT* promoter methylation has been reported.[16,51] Thus, previous studies prior to the 2021 WHO classification reporting relevant imaging findings to predict *MGMT* promoter methylation in glioblastoma, IDH-wildtype, and astrocytoma, IDH-mutant, WHO grade 4 may be inherently biased because it may simply reflect imaging findings from astrocytoma, IDH-mutant, WHO grade 4.[52]

As stated before and emphasized again to avoid confusion, in histological grade 2–3 IDH-wildtype diffuse gliomas, testing of *TERT* promoter mutation, *EGFR* amplification, and chromosome +7/−10 should be performed to establish the molecular diagnosis of glioblastoma, IDH-wildtype. The presence of at least one of these aberrations in an IDH-wildtype diffuse glioma leads to diagnosis of glioblastoma, IDH-wildtype, even in the absence of microvascular proliferation or necrosis.[10] Identifying molecular features of glioblastoma in histological grade 2 or 3 IDH-wildtype diffuse gliomas on preoperative imaging may be difficult because they are commonly nonenhancing or merely show a small proportion of contrast enhancement. Several studies have reported imaging findings of molecular features of glioblastoma, IDH-wildtype, in the absence of necrosis or microvascular proliferation.[53–56] Cortical involvement, infiltrative appearance, lower ADC and higher rCBV are reported imaging findings to predict molecular features of glioblastoma, IDH-wildtype. However, another recent study demonstrated discrepant results showing that *TERT* promoter mutation status may not necessarily be reflected on advanced imaging in IDH-wildtype gliomas.[57] Future developments in characterization of these gliomas are needed. An example in Fig. 9a shows a case demonstrating that advanced imaging findings raise suspicion of a more aggressive pathology. However, as shown in Fig. 9b, it is sometimes virtually impossible to correctly predict the tumor type on preoperative imaging.

Conclusion

The key points in 2021 WHO classification and imaging features of adult-type diffuse gliomas were reviewed and summarized in a radiologist's viewpoint. A deep understanding in the current classification and the imaging features according to each tumor type not only enhances the overall quality of our interpretation in daily practice but also improves communication with clinicians. Although imaging features are not included in the diagnostic criteria in the 2021 WHO classification, this does not mean that radiologists may remain in a passive role in the clinical practice. We believe that qualified radiologists may play an active role in the whole process of diagnosis and management of glioma patients; to predict the tumor type, indicate the tissue acquisition site, discuss whether discrepancy exists between the imaging and the pathological results, and predict the clinical course. This is enabled by taking additional time not only into studying the imaging features of gliomas, but also intensively studying the epidemiology, clinical course, and treatment of gliomas, and actively interacting with clinicians and receiving feedbacks. We hope this review series serve as a rough guide to the current concepts and encourage future studies to fully elucidate the glioma classification system.

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Conflict of Interest

None.

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