Imaging Findings of New Entities and Patterns in Brain Tumor

Isocitrate Dehydrogenase Mutant, Isocitrate Dehydrogenase Wild-Type, Codeletion, and MGMT Methylation

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KEYWORDS

• Glioma molecular status • IDH • Codeletion • MGMT • Radiomics

KEY POINTS

- Molecular features are necessary for diagnosis of glioma subtype and greatly impact prognosis and treatment response.
- Increased contrast enhancement, sharp tumor margins, and homogenous signal intensity are characteristic of IDH-mutant gliomas, whereas degree of necrosis is not.
- T2-FLAIR mismatch is specific to IDH-mutant, 1p19q nondeleted gliomas (diffuse astrocytoma).
- Advanced MR imaging techniques, such as sodium MR imaging, deep learning, diffusion kurtosis imaging, and texture analysis, are used to predict molecular subtypes.

BACKGROUND

The 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System set forth a revised classification system for brain tumors. This update included molecular aberrations in the definition of particular brain tumors and, to some extent, explained why some tumors of identical cell types appear similar on histology but respond differently to the same therapy and have different prognoses.[1] Today, this is thought to be caused by different genetic makeups of tumors, generating tremendous interest in the reclassification of cancers. Several molecular markers including isocitrate dehydrogenase (IDH), 1p/19q codeletion, O6-methylguanine-DNA methyltransferase methylation (MGMT), telomerase reverse transcriptase gene (TERT), α-thalassemia/mental retardation syndrome X-linked gene (ATRX), and p53, were identified as necessary for diagnoses of various gliomas (**Fig. 1**).[1–3]

There is parallel effort from an imaging perspective to be able to obtain molecular and genetic information from structural and molecular imaging techniques to match the new genotypic classifications. A major initiative to accomplish this was The Cancer Genome Atlas, undertaken by the National Institutes of Health.[4] This led to the Cancer Imaging Program, which obtains radiologic imaging data for The Cancer Genome Atlas patients and makes it available via The Cancer Imaging Archive.[4] The first large-scale imaging genomic study performed in glioblastomas (GBM) paved the way for the potential correlation between imaging features and histologic patterns and genetic profiles of the tumor, known collectively as

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"radiohistogenomic interpretation."[5] Radiomic-imaging features play an important role in accurate and early prediction of tumor genotype when genetic sequencing is not available.

GENETIC FACTORS

The 2016 central nervous system (CNS) WHO classification offered an attempt to standardize the terminology combining histopathologic and molecular features. Today CNS tumor naming includes histologic appearance (ie, astrocytoma or oligodendroglioma), WHO grade (II, III), and genetic features. Work on genotyping and identifying specific markers for brain tumors is ongoing. Histologic appearance is decided by routine staining techniques used in histopathology, which decides the cell lineage for the tumor. WHO grading (WHO I, II, III, and IV) of the diffuse glioma depends on cellularity, cortical infiltration, nuclear pleomorphism, hyperchromasia, and mitotic figures. The new classification posits grade I gliomas as virtually nonexistent in adults. Currently, the main molecular makers of diagnostic significance for gliomas include IDH, 1p19q deletion, MGMT, TERT, ATRX, and a tumor protein p53 gene (TP53).[2,3]

Diffuse gliomas based on gene expression and available molecular markers are classified as follows: grade II (diffuse astrocytoma, *IDH* mutant) and grade III astrocytic tumors (anaplastic astrocytoma, *IDH* mutant), grade II (oligodendroglioma *IDH* mutant and 1p/19q codeleted) and grade III oligodendrogliomas (anaplastic oligodendroglioma *IDH* mutant and 1p/19q codeleted), grade IV GBM (GBM *IDH* mutant and *IDH* wild-type), and diffuse gliomas of childhood (diffuse midline glioma, H3-K27M-mutant) (see **Fig. 1**).[2,3] Whenever molecular diagnostic testing is not available or genetic assay testing is inconclusive, the Not Otherwise Specified (NOS) category is used.

Neuro-oncology teams are of the opinion that much work still needs to be done to have a clear understanding of the genetic basis for many of the other brain tumors, including GBM. Following the 2016 classification, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was created in late 2016 under the sponsorship of the International Society of Neuropathology to provide a forum to evaluate and recommend proposed changes to future CNS tumor classifications.[6] cIMPACT-NOW updates are intended to provide guidance for diagnosticians and potentially inform future WHO classifications. This article focuses on correlating the phenotypic and genotypic features of gliomas, gliomagenesis of GBM, IDH mutation, other molecular markers and mutations in diffuse gliomas, and their imaging correlates on various MR imaging techniques.

Isocitrate Dehydrogenase Status

In humans, IDH exists in three isoforms (IDH1, IDH2, and IDH3). IDH1 and IDH2 are proteins in the cytosol and mitochondria, respectively, that

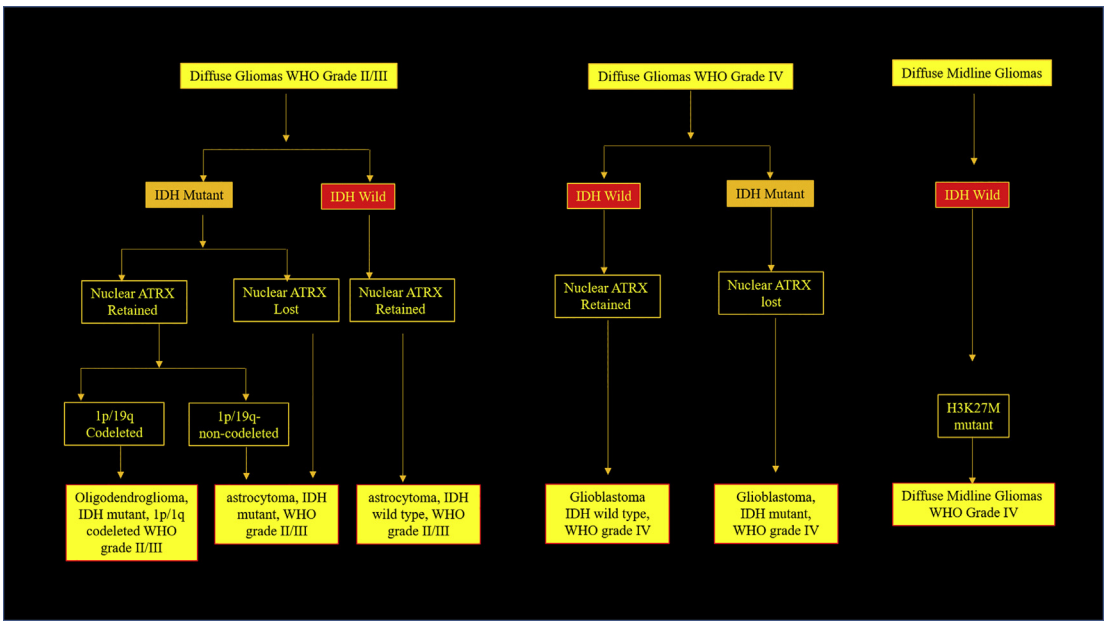

Fig. 1. WHO 2016 classification update on glioma molecular markers.

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generate reduced nicotinamide adenine dinucleotide phosphate from $NADP^+$ by catalyzing the oxidative decarboxylation of isocitrate to α-ketoglutarate outside of the Krebs cycle (**Fig. 2**).[7–9] IDH3 functions to convert isocitrate to α-ketoglutarate and NAD^+ to NADH in the Krebs cycle. IDH plays an important role in cellular defense against oxidative stress. Cells with low levels of IDH become more sensitive to oxidative damage. IDH1 mutations involve an amino acid substitution (glycine to arginine) in the active site of the enzyme in codon 132 (R132H).[7–9] This mutation results in the abnormal production of 2-hydroxyglutarate (2HG), which causes histone and DNA methylation, thereby promoting tumorigenesis. IDH2 mutations occur in codon 172 and are associated with 2-hydroxyglutaric aciduria. These result in seizures, weak muscle tone (hypotonia), and progressive damage to the brain parenchyma.[7–9] Inhibition of these enzymes results in widespread histone and DNA methylation, which in turn leads to increased tumorigenesis.[4] Mutant IDH1 and IDH2 occur in more than 70% of WHO grade II and III astrocytomas, oligodendrogliomas, and in secondary GBM that developed from the previously mentioned lower-grade lesions.[10]

IDH1 and IDH2 are enzymes that function at the crossroads of cellular metabolism, epigenetic regulation, redox states, and DNA repair. The pro-oncogenic effect of *IDH* mutations is caused by the damage produced by high levels of reactive oxygen species to DNA and by 2HG, an oncometabolite that alters cell proliferation.[8,11] 2HG impairs the maturation of extracellular collagen in the brain capillary network basement membrane, which promotes cell migration to the extravascular space and intravascular fluid leakage into the extracellular space. This leakage is reflected as enhancement on contrast-enhanced MR imaging and permeability on MR perfusion imaging.

The Cancer Genome Atlas Research Network found an *IDH* mutation rate of 80% of grade II/III gliomas (diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas) and only 10% in GBM.[12,13] Based on these results, the WHO now recognizes the *IDH* mutation as a critical biomarker in glioma classification. Among the GBM, IDH1/IDH2 mutations are more commonly seen in secondary GBM originating from lower-grade diffuse gliomas than in primary GBM. When both IDH1/IDH2 mutant are negative, as in the primary GBM, it is labeled as IDH wild-type.[12–14] If IDH testing is not available, cannot be fully performed, or is inconclusive, the GBM is labeled IDH NOS. *IDH* status is considered an independent determinant of prognosis in patients

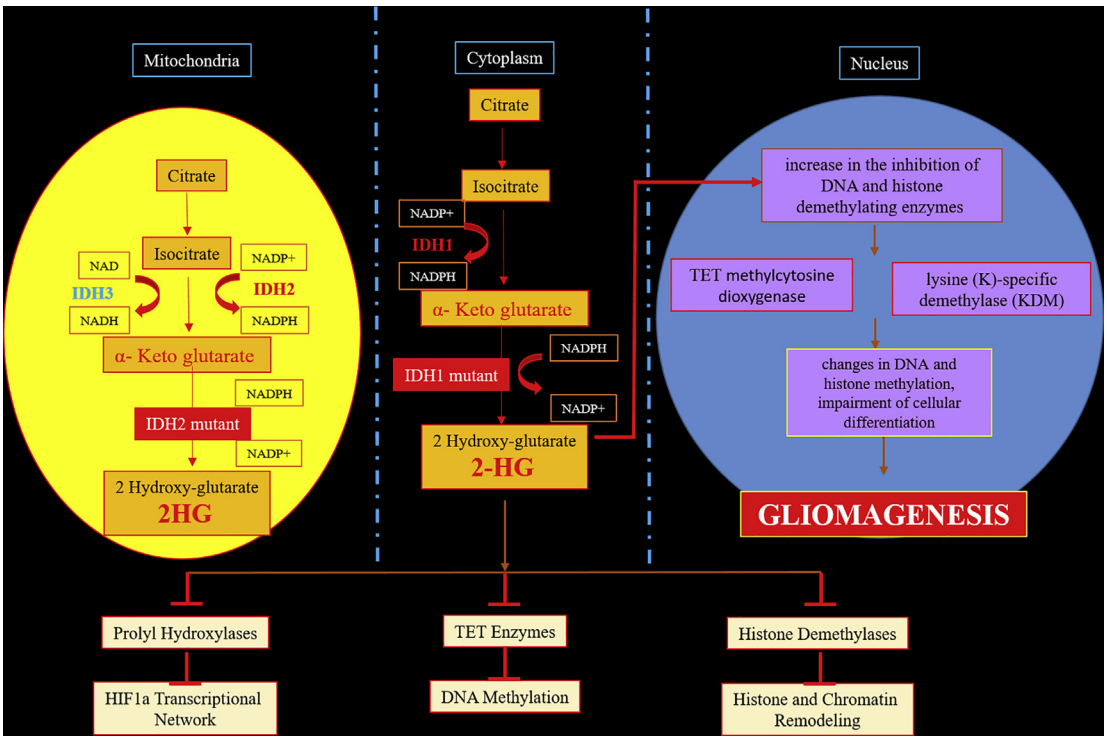

Fig. 2. Diagrammatic presentation of gliomagenesis.

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with diffuse gliomas. Survival is higher in *IDH*-mutant patients than in *IDH* wild-type patients.

MGMT Methylation

MGMT is an apoptotic enzyme and DNA repair protein that inhibits the cross-linkage of double-stranded DNA, and repairs premutagenic, precarcinogenic, and pretoxic DNA damage.[15–17] Methylation within the MGMT gene promoter on chromosome 10q26.3 induces loss of function of the protein, ultimately leading to insufficient DNA repair and tumorigenesis.[16,17] For brain tumors, MGMT activity declines as glioma grade increases.

Alkylating chemotherapeutics (ie, methylating agents [procarbazine, dacarbazine streptozotocin, and temozolomide] and chloroethylating agents [carmustine, lomustine, nimustine, and fotemustine]) are commonly used in the treatment of brain tumors, malignant melanoma, and lymphoma because they are powerful inducers of apoptosis.[16–19] These alkylating agents cause mutations, sister chromatid exchanges, recombination and chromosomal aberrations, and DNA mismatch repair to DNA double-strand breaks that trigger cell death. However, their efficacy largely depends on MGMT expression. The loss of MGMT protein expression caused by MGMT promoter methylation reduces the DNA repair activity of glioma cells, preventing their resistance to alkylating agents. Patients with GBM and a methylated MGMT promoter are more sensitive to the killing effects of alkylating drugs because tumor cells with low MGMT expression are unable to repair such DNA lesions and are prone to apoptosis.[16–19] Cancer cells that overexpress MGMT are resistant to alkylating agents. Therefore, MGMT promoter methylation is the most relevant prognostic marker and is used to predict a therapeutic response to alkylating agents. Documentation of MGMT promoter methylation is important to decide the choice of chemotherapy or radiotherapy in patients with brain tumors.

Methylation of the promoter region of the MGMT gene is more frequently found in secondary GBMs compared with primary GBMs (75% vs 36%).[17,18] By knowing whether or not the MGMT promoter is methylated, response to temozolomide, a standard adjuvant chemotherapy treatment of GBMs, may be predicted.[16] Overall survival (OS) in methylated patients is better when temozolomide is given concurrently with radiation therapy. In unmethylated patients, radiotherapy alone is more effective.[16,18,19] In addition, GBM patients with MGMT promoter methylation have better OS and progression-free survival (PFS) than those without methylated MGMT promoters regardless of therapeutic intervention. MGMT promoter methylation is also a strong predictor of pseudoprogression and IDH mutation to the extent that almost all patients with an IDH mutation also exhibit MGMT promoter methylation.

1p/19q Codeletion

According to the 2016 WHO classification of CNS tumors, 1p19q codeletion is required for the diagnosis of oligodendroglioma.[20] A 1p/19q codeletion is the complete deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q).[3,12] It is a definitive marker for grades II and III (anaplastic) oligodendroglioma. In contrast, a patient that is IDH positive and lacks a 1p19q codeletion carries a diagnosis of a diffuse astrocytoma (see **Fig. 1**).[20,21]

It is important to remember that oligodendroglial tumors have neither *ATRX* nor *TP53* gene mutations. An oligodendroglioma that is IDH-mutant but has not been analyzed for 1p/19q status is designated as oligodendroglioma NOS, whereas an oligodendroglioma that is IDH-mutant with a 1p deletion but an intact 19q is designated as diffuse glioma, IDH-mutant with 1p loss/19q retention, Not Elsewhere Classified (NEC).[3,12,22,23] Histopathologically diagnosed oligodendrogliomas without 1p19q codeletion is classified as a diffuse glioma of the oligodendroglial phenotype. Pediatric oligodendrogliomas are IDH negative, do not display 1p/19q codeletion, and are classified as NOS.

The presence of 1p/19q codeletion is associated with a favorable response to chemotherapy and radiotherapy and ultimately patient prognosis and survival.[20,21,24] 1p/19q codeletion is also linked to sensitivity to procarbazine-lomustine-vincristine chemotherapy and improved outcomes in patients with oligodendroglioma.[22,24]

MOLECULAR GENETICS OF GLIOBLASTOMA AND GLIOMAGENESIS

Gliomas are CNS tumors of glial origin, and GBM are the most common and aggressive subtype. On the phenotyping and genotyping features, GBM is classified into primary (95%) and secondary GBMs (5%). Primary GBMs are aggressive, highly invasive, and more commonly seen in the elderly.[2,3,25,26] Secondary GBMs are much less common, arise from low-grade gliomas, mostly seen younger than the age of 45, and have a better prognosis. GBMs are histologically indistinguishable but show distinctive genetic alterations that allows differentiation.

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Genetic alterations occur in major key pathways to form GBMs. Gliomagenesis is a multifactorial process involving several genetic mutations. The introduction of genotyping has had a major impact on the classification, treatment, and understanding of outcome for GBMs. IDH status classifies GBMs into three types: IDH wild-type, IDH-mutant, and IDH NOS.[2,3,11,12]

1. IDH wild-type GBMs are also called primary or de novo GBMs. They form around 95% of the total GBMs and are primarily seen in patients older than 55. In contrast to the IDH-mutant, IDH wild-type follow an aggressive course and have poor prognosis. They are associated with various genetic alterations including epidermal growth factor receptor (EGFR), MGMT, the phosphatase and tensin homolog, *TP53*, platelet-derived growth factor receptor-α (PDGFRA), neurofibromin 1 (NF1), cyclin-dependent kinase inhibitor 2A and B (CDKN2A/B) genes, and telomerase reverse transcriptase (TERT) promoter.[27–29]
   The most commonly pathway involved is receptor tyrosine kinases, which bind with growth factors inducing a conformational shift.[27–29] This shift activates the kinase function of the receptor tyrosine kinases allowing cross-phosphorylation of tyrosine residues in preparation for downstream signaling cascades. EGFR functions in the proliferation, migration, differentiation, and survival of all types of CNS cells.[28,29] In GBM cells, EGFR signaling gets activated either through overexpression of the receptor and its ligand amplifying the EGFR function. Amplification of the EGFR gene and activating mutations of its protein product are hallmarks of primary GBM and are associated with TP53 mutations.[3,13,28,29] PTEN amplification and loss of chromosome 10 are additional features of primary GBMs. Verhaak and colleagues[30] described a robust gene expression–based molecular classification of GBMs into proneural, neural, classical, and mesenchymal subtypes that integrate multidimensional genomic data to establish patterns of somatic mutations and DNA copy number. Primary GBMs represent the classical, mesenchymal, and neural subtypes. The mesenchymal and classical subtypes are typically associated with more aggressive, higher-grade gliomas. The classical subtype demonstrates a greater preponderance of EGFR amplification, decreased rates of *TP53* mutation, and *p16INK4A* and *p14ARF* deletion.[30]
2. IDH-mutant GBMs, also called secondary GBMs, usually arise from diffuse WHO grade II or III gliomas. Genetic alterations common to secondary GBMs include TP53 mutations and IDH1/2 mutations.[27,28,31] TP53 mutations are detectable in the early stages of secondary GBM. IDH1/2 mutations rarely occur in primary GBMs and are therefore the most reliable indicator to differentiate between primary and secondary GBMs. Secondary GBMs are also associated *ATRX* (80%) and retinoblastoma protein 1 (Rb1) mutations, reflecting its origin from lower-grade gliomas.[27,28] It is primarily seen within the frontal lobe and corresponds to the proneural histologic subtype on the Verhaak and colleagues[30] classification. The proneural subtype is less aggressive; seen in younger patients; and has alterations in TP53, PDGFRA, PIK3C, and IDH1[30]
3. The NOS group includes tumors for which the *IDH* status cannot be determined.[3,6] Another recently introduced category is NEC, used when diagnostic testing has been successfully performed, but the results do not allow for a WHO categorization. In contrast, the NOS designation is used when a full molecular work-up has not been undertaken or was not successful. NEC diagnoses are descriptive diagnoses where the pathologist uses a non-WHO term to describe the tumor.

Tumor heterogeneity, one of the hallmarks of GBM, is the presence of multiple different cell subpopulations within a single tumor. It is caused by cancer stem cells that possess varying degrees of stemness, the ability to self-renew and differentiate into different tumor cell types, and clonal evolution that may enhance genetic diversity within the affected tissues.[32,33] This heterogeneity varies from different zones of the GBM, namely the core, interface, and peripheral brain zones. Because tumor fragments from the same patient may have different molecular subtypes in different zones, GBM grading is complex. GBM also shows epithelial to mesenchymal transitions, thought to be caused by signaling pathways of Wnt, transforming growth factor-β, and NOTCH.[32,33] This transition is partly responsible for the migration, diffusion invasion, and angiogenesis of GBM. By virtue of the inherent heterogeneity of these tumors, not all of the cells within a glioma respond to chemotherapy and radiation, resulting in tumor progression/recurrence.

IMAGING

Phenotyping and genotyping using tumor tissue remains the gold standard for characterizing the histologic type and genetic make of the tumor; it

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is thereby the predominant factor in deciding choice the treatment and prognosis. However, pathology and genotyping have their own limitations. One major downside of pathologic analysis is intratumoral heterogeneity, even across molecular subtypes. It is often not feasible to study every section of invasive tumor, and the availability of the newer diagnostic tools, such as immunohistochemistry, genotyping, and molecular markers, is limited and expensive. Another clinical limitation of genotyping is that the study of a tumor's genetic profile can only be done on tumor tissue samples processed in the primary institution or laboratory. Furthermore, the usefulness of these techniques is limited once the patient is on radiation or chemotherapy. Unfortunately, there is still no worldwide standard for processing and analyzing tissue samples. The quest for developing a noninvasive, cheaper, and specific technique to identify the molecular/genomic makeup of tumors is still ongoing.

ROLE OF MR IMAGING

At present, imaging modalities have limitations in locating the point mutation of a tumor's genetic material. However, the Cancer Imaging Program and The Cancer Imaging Archive have paved the way to correlate imaging features and histologic patterns with the genetic profile of the tumor; this is called "radiohistogenomic interpretation."[13,27,34] Thus, in the absence of genetic sequencing, imaging modalities play an important role.

Molecular imaging using MR imaging techniques, such as diffusion-weighted imaging/apparent diffusion coefficient (ADC), MR spectroscopy, MR perfusion, dynamic susceptibility contrast MR perfusion, and diffusion tensor imaging has shown promising results in understanding the genetic profile and biologic behavior of the tumor. Both structural and molecular imaging play an important role in the radiohistogenomic classification of the brain tumor. Markers that have been found useful in these classifications include location of the tumor, ADC values, FLAIR/T2 hyperintensities, chemical analysis of the tumor mass and surrounding brain using MR spectroscopy, and texture analysis using a combination of the previously mentioned techniques. These techniques are widely used to diagnose the IDH status; MGMT methylation; and, to a lesser extent, 1p/19q codeletion.[13,18,27,34] Extensive radiogenomic research is in progress to find imaging correlates of the other new molecular markers, such as TERT promoters, ATRX, TP53 mutations, TP53, diffuse midline gliomas, H3 K27M-mutant, and wingless and sonic hedgehog activation.[13,18,27,30,34] A noninvasive prediction of IDH mutation is important because maximal surgical resection, including enhancing and nonenhancing tumors, may contribute to a better prognosis in IDH1-mutant gliomas. Although a survival benefit was noted in the complete resection of enhanced IDH1 wild-type gliomas, no survival benefit was observed in further resection of the nonenhanced portion.

KEY IMAGING FINDINGS

MGMT Methylation

Standard methods of imaging are limited in their ability to distinguish molecular subtypes of gliomas. These imaging modalities have not been able to clearly differentiate MGMT methylated from unmethylated tumors. Several investigations have evaluated the value of ADC for predicting MGMT promoter methylation, but the results are inconclusive.[35,36] However, a minimum ADC value may have some prognostic value in preoperatively estimating the status of MGMT promoter methylation (84% sensitive, 91% specific).[35] If a relationship were to be found between ADC and MGMT promoter methylation, this would be especially useful in noninvasively predicting methylation because accurate measurement of methylation is difficult because of small biopsy specimens and regional heterogeneity of GBM.

Knowing that MGMT promoter methylation has been used as a prognostic biomarker, researchers have also addressed the role of MGMT methylation via imaging in GBMs.[37] Using various MR imaging techniques, it was noted that the diagnostic performance of MR imaging for prediction of MGMT promoter methylation with recently diagnosed GBM patients was clinically viable.[37] This study found that MGMT promoter methylation in GBMs shows less edema, high ADC, and low perfusion on MR imaging, with a sensitivity at 79% (95% confidence interval, 72%–85%), a specificity of 78% (95% confidence interval, 71%–84%), and the area under the receiver operating curve (AUC) at 0.86 (95% confidence interval, 0.82–0.88).[37]

Another study evaluating MGMT promoter methylation in primary GBMs through imaging looked at the relationship between ADC and relative cerebral blood flow (rCBF) values in a manually drawn region of interest.[38] Using a combination of tumor location, necrosis, ADC, and rCBF, the highest AUC resulted in 0.914.[38] This suggests that ADC and rCBF, when used with other known factors of GBMs, are associated with the prediction of MGMT promoter methylation.[38]

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Isocitrate Dehydrogenase Mutation

Determination of IDH mutation status is important and is usually determined via polymerase chain reaction, gene sequencing, and immunohistochemistry.[39] However, recent advances in imaging have afforded the potential to define the IDH status of diffuse gliomas (**Table 1**).[39,40] Radiogenomic texture analysis may show that a tumor's molecular differences and biologic behavior are mirrored in imaging features and that these parameters can be used for patient stratification to optimize glioma treatment.[39,40] This classification is clinically significant because IDH wild-type tumors have worse prognoses compared with secondary IDH-mutant tumors or others with more aggressive biologic behavior. The following is a compiled list of imaging findings correlated with IDH status:

- IDH-mutant tumors are primarily located in the frontal lobe or subventricular region of the frontal horns of the lateral ventricles and are less likely to invade eloquent areas of the brain.[18,21,41,42] IDH-mutant tumors are rare in the occipital lobe. IDH-mutant gliomas tend to be larger, exhibit slower growth, and have better defined contours than IDH wild-type gliomas.[18,42]
- Gliomas with IDH wild-type usually are multilobar; cross the midline; involve the corpus callosum; involve more than one lobe; and commonly affect eloquent areas and deeper structures, such as the diencephalon and brainstem.[18,42]
- IDH wild-type GBMs associated with unmethylated MGMT gene promoters are located predominantly in the right hemisphere and have poor prognoses. IDH-mutant MGMT methylated GBMs show better prognosis with temozolomide are located predominantly in the left hemisphere.[18,34]
- The presence of large portions of nonenhanced tumor in GBMs is strongly associated with the IDH1 mutation (**Fig. 3**). Large nonenhanced portions are caused by low VEGF levels in IDH-mutant tumors. IDH wild-type GBMs usually show smaller nonenhancing component.
- Yamashita and colleagues[43] suggested that percentage of cross-sectional necrosis area inside the enhancing lesion and necrosis area are significantly higher in patients with IDH1 wild-type than in those with IDH1 mutant GBMs (**Fig. 4**). The optimal cutoff for percentage of cross-sectional necrosis area inside the enhancing lesion was 22.5 with 72.7% sensitivity, 81.8% specificity, and 74.2% accuracy. The optimal cutoff for necrosis area was 151 mm^2 with 72.7% sensitivity, 81.8% specificity, and 74.2% accuracy. The AUCs for percentage of cross-sectional necrosis area inside the enhancing lesion and necrosis area were 0.739 and 0.772, respectively.
- Zhou and colleagues[44] used textural analysis and found that according to the Visually Accessible Rembrandt Images (VASARI) annotations, increased proportion of necrosis and decreased lesion size were the most predictive for IDH-mutation status.
- ADC values correlate inversely with the cellularity of the tumor. Because of the lower cellularity of IDH-mutant tumors than IDH wild-type tumors, ADC values of IDH-mutant grade II and III astrocytomas are higher than those of wild-types (see **Figs. 3**C and **4B**). An ADC mean of 1.2 can be used as a cutoff value to differentiate IDH wild-type and IDH-mutant gliomas. ADC means less than 1.08 have poor survival.[43] In addition, IDH-mutant tumors with codeletion 1p/19q, such as oligodendroglioma, have been shown to have greater ADC values and fractional anisotropy on diffusion tensor imaging imaging.
- Enhancement on postcontrast scans has historically been used to grade the aggressiveness of the tumor. However, the pattern of enhancement and perfusion largely depend on the chemical mediators that promote angiogenesis, such as EGFR, VEGF, and platelet-derived growth factors. Mutant GBMs show a more homogeneous, nodular, and less intense enhancement pattern compared with the wild-type tumors. IDH-mutant GBMs often have a greater proportion of nonenhanced tumor, whereas the ring enhancement with a central area of necrosis is a more common feature of IDH wild-type tumors.[18,45] It is found that a lower T2 abnormality to contrast enhancement volume ratio and central necrosis was predictive of the mesenchymal GBM subtype.
- MR imaging and computed tomography (CT) perfusion has been extensively studied to differentiate between the mutant and wild-type of GBMs. Because of low neovascularization, IDH-mutant GBMs have low relative cerebral blood volume value (1.09 ± 0.34 mL/100 g) compared with IDH wild-type GBMs (2.08 ± 0.54 mL/100 g) that show extensive angiogenesis.[46] Law and colleagues[47] demonstrated that the prognosis for patients with low-grade but highly perfused tumors was worse than that in

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Table 1
Common genetic aberration and markers in the glioma

Genetic Aberration	CNS Tumor Association	Comments
IDH1/IDH2 mutation	Frequent in WHO grade II and III astrocytomas, oligodendrogliomas, secondary glioblastomas Required for diagnosis: Astrocytoma, IDH-mutant vs wild-type Anaplastic astrocytoma, IDH-mutant vs wild-type Glioblastoma, IDH-mutant vs wild-type Oligodendroglioma, IDH-mutant and lp/19q-codeleted Anaplastic oligodendroglioma, IDH-mutant and lp/19q-codeleted	IDH-mutant status signifies better prognosis compared with that of IDH wild-type even with the histologically same WHO grade
MGMT promoter hypermethylation	Reported as independent favorable prognostic factor in glioblastomas (irrespective of treatment)	Suggests improved prognosis in malignant glioma and predicts response to temozolomide chemotherapy and radiotherapy
EGFR amplification	Common in IDH wild-type glioblastomas (~40%)	Over expression of EGFR is responsible for proliferation and migration/infiltration in IDH wild-type
ATRX	Supportive for diagnosis of IDH-mutant diffuse astrocytoma/anaplastic astrocytoma/glioblastoma	ATRX mutations are almost always seen along with other mutations in the histone regulation, such as IDH, H3 K27M, and TP53
TP53 mutation	Supportive for diagnosis of IDH-mutant diffuse astrocytoma/anaplastic astrocytoma/glioblastoma	TP53 mutations also occur in IDH wild-type astrocytic tumors, but are rare in oligodendrogliomas
1p/19q codeletion	Required for diagnosis of: Oligodendroglioma, IDH-mutant, and 1p/19q codeleted Anaplastic oligodendroglioma, IDH-mutant, and 1p/19-codeleted	1p/19q codeletion is associated with sensitivity to procarbazine-lomustine-vincristine chemotherapy and improved outcome in patient with oligodendroglioma
H3 K27M mutation H3 Histone Family Member 3A (H3F3A) or Histone	Required for the diagnosis of diffuse midline glioma, H3 K27M-mutant	Signifies poor prognosis in diffuse midline glioma
TERT promoter mutation	Encountered in all grades of diffuse gliomas, ranging from WHO grade II to IV	TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas

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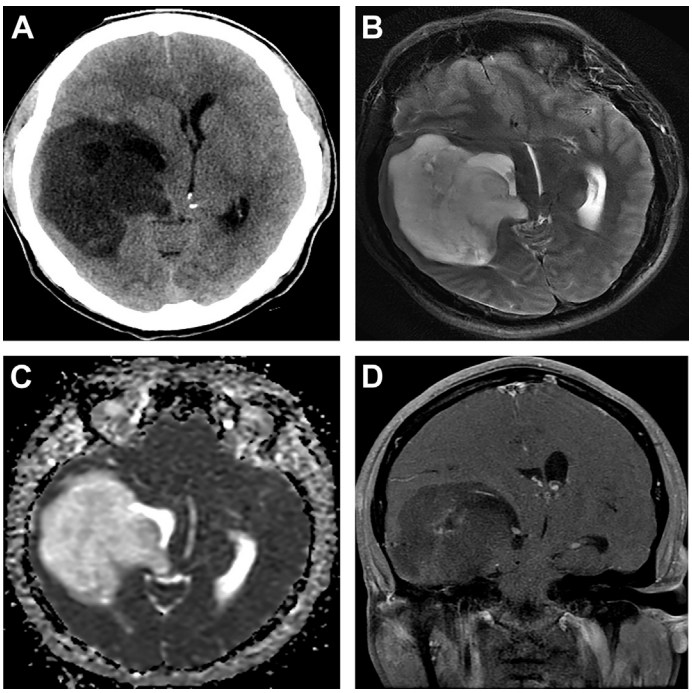

Fig. 3. IDH-mutant glioblastoma. A 53-year-old woman who presented with generalized fatigue and constitutional symptoms. Axial CT scan (*A*) shows a large mass in the right temporal lobe with severe mass effect on the surrounding brain parenchyma and midline shift to the left. Axial T2 image (*B*) shows large, well-defined hyperintense mass lesions without surrounding edema and high ADC value (*C*). Postcontrast coronal T1-weighted image (*D*) shows mild enhancement in the central portion of the tumor with severe mass effect on the brainstem and midline shift of 11 mm.

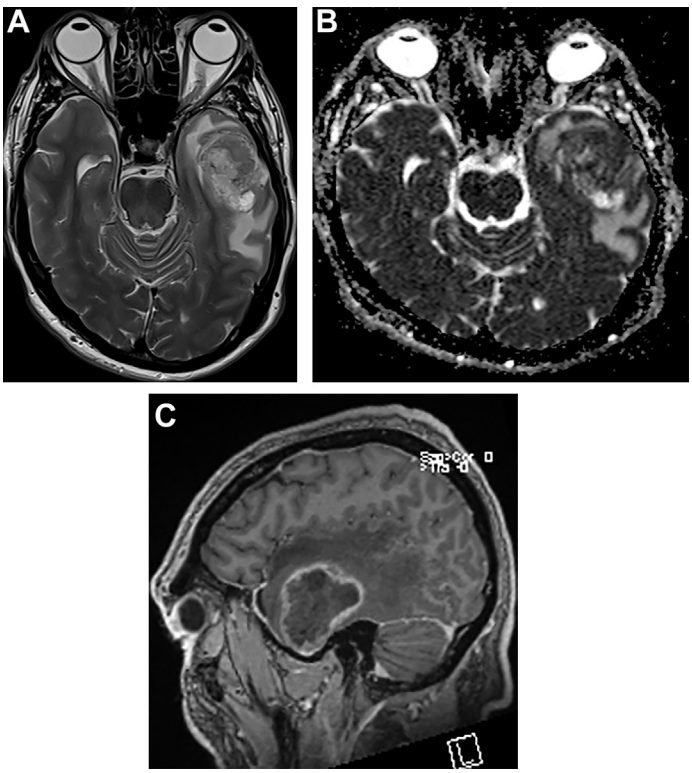

Fig. 4. IDH wild-type glioblastoma. A 62-year-old man presented to the emergency department with right-sided numbness and difficulties with fine motor skills. Axial T2-weighted image (*A*) shows heterointense mass in the left temporal lobe with large perilesional T2 hyperintensity. Axial ADC image (*B*) shows low ADC in the soft tissue component and few cystic areas. Sagittal postcontrast T1-weighted image (*C*) shows a necrotic mass with peripheral enhancement.

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patients with high-grade, low-perfusion tumors. Yamashita and colleagues[43] using the arterial spin labeling technique, demonstrated that absolute tumor blood flow (aTBF) and relative tumor blood flow (rTBF) were significantly higher in patients with IDH wild-type GBMs than in patients with IDH-mutant GBMs. The optimal cutoff for aTBF was 70.0 mL/100 g/min with 76.5% sensitivity, 88.9% specificity, and 79.1% accuracy. The optimal cutoff for rTBF was 1.55 with 88.2% sensitivity, 77.8% specificity, and 86.0% accuracy, with the AUCs for aTBF and rTBF being 0.850 and 0.873, respectively.

- MR spectroscopy has shown encouraging results in differentiating types of glioma mutation. Mutations of the IDH1 and IDH2 genes result in an overreduction of the a-ketoglutarate to 2HG metabolite, leading to an accumulation of 2HG.[8,9,39,40] Using special proton MR spectroscopy point-resolved spectroscopy sequences, 2HG accumulation is analyzed qualitatively and quantitatively. Choi and colleagues[39] showed the existence of 2HG and glutamate multiplets in patients with IDH-mutated grade II-III tumors with 100% sensitivity and specificity. A maximum 2HG peak was identified at approximately 2.25 ppm, near the γ-aminobutyric acid peak (at 2.2–2.4 ppm) and located to the left of the *N*-acetylaspartate peak, at 2.0 ppm. Documentation of the 2HG peak is seen with IDH-mutation gliomas, and its absence is consistent with IDH wild-type tumors. MR spectroscopy has also been found useful in documenting the treatment response with DH1/2-mutant inhibitors.

Additionally, the VASARI, created by the Cancer Imaging Archive is a set of MR imaging features that are used to create uniform descriptions for gliomas. Researchers found that several of these features were significant predictors of IDH1-mutation status and 1p/19q codeletion status.[48] The following were considered to be independently associated with predicting IDH1 mutation based on the model generated (AUCs for predictive model, 0.859 and 0.778 for the discovery and validation sets, respectively)[48]: nonlobar tumor location, proportion of enhancing tumors of greater than 33%, multifocal/multicentric diffusion, and well-defined nonenhancing margin.

Determining IDH-mutation status is not only potentially useful in distinguishing gliomas from other lesions, it may help influence surgical decision-making, and help monitor treatment response or failure.[39,40] This method may also be useful in distinguishing between gliosis and lower-grade gliomas, possibly avoiding unnecessary biopsies or repeat surgical resections in ambiguous cases.[39,40]

1p/19q Codeletion on Imaging

1p/19q testing is not readily available in many locations. When formal 1p/19q testing is not possible, MR imaging features are likely to be more specific for determining 1p/19q status than histologic phenotype.[49–51] Genetically defined IDH-mutant codeletion oligodendrogliomas and IDH-mutant noncodeleted astrocytic gliomas differ in regards to tumor margins, heterogeneity, and ADC values.[49,51] Johnson and colleagues[49] found that 1p/19q codeleted oligodendrogliomas had poorly circumscribed borders in comparison with non-1p/19q codeleted astrocytic gliomas (**Fig. 5**). Even though there seem to be correlations between MR imaging findings and biomarkers in lower-grade gliomas, it is widely believed that conventional MR imaging findings are not sufficiently specific enough to predict histologic and/or molecular subtype of a low-grade glioma in an individual patient.

On MR imaging, more than 50% T2-FLAIR mismatch is strongly predictive of a noncodeleted astrocytic gliomas. The T2/FLAIR mismatch sign is represented as a homogeneous high signal on T2 sequence but as a bright rim and dark center on FLAIR images (**Fig. 6**). Patel and colleagues[50] showed that the substantial T2-FLAIR mismatch is specific to the IDH-mutant-noncodeleted molecular subtype of *IDH*-mutant gliomas, with 100% positive predictive value in the test and validation sets, with a high level of interrater agreement.[52] A T2-FLAIR mismatch on CT correlates with a markedly hypodense tumor. If a glioma were to be IDH-mutant, patients would significantly benefit from a gross total tumor resection compared with partial resection. Therefore, the T2-FLAIR mismatch sign may provide useful information to neurosurgeons before treatment planning stages of patient care encounters (see **Fig. 2**). Identification of this MR imaging biomarker may contribute to pretreatment planning and promote accurate and timely patient counseling.

The tumor is likely 1p/19q-codeleted if there are calcifications identified on CT or susceptibility weighted images. Johnson and colleagues[49] have also documented that noncircumscribed borders correlate with 1p/19q codeletion, but this appearance is also seen in 45% of noncodeleted tumors. Sharp borders are thought to be a better indicator for a noncodeleted tumor. Additionally, oligodendrogliomas are heterogenous on T1 and/or T2-weighted MR imaging and show ADC value less

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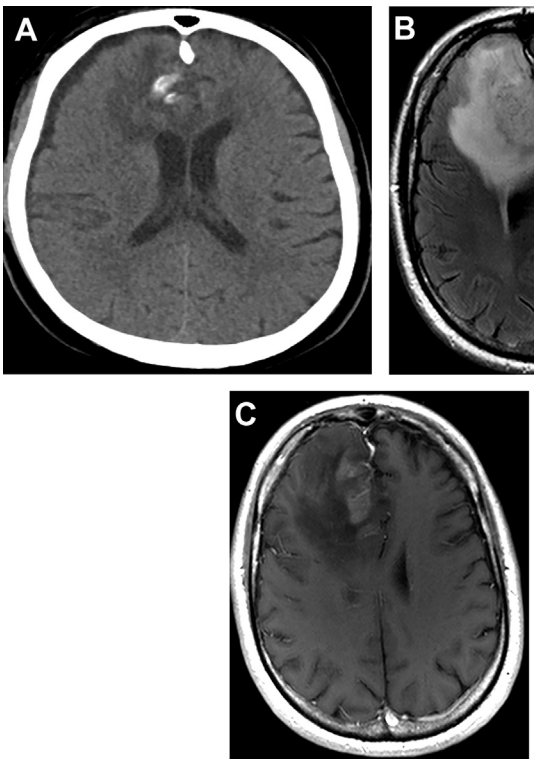

Fig. 5. Codeleted oligodendroglioma. A 39-year-old man with right frontal lobe oligodendroglioma, *IDH*-mutant, and 1p/19q codeleted, showing characteristic imaging features. Axial CT image (*A*) shows the right frontal lobe calcified mass with mild mass effect on the ventricular system. Axial FLAIR image (*B*) shows a hyperintense infiltrative mass in the right frontal lobe, which shows mild fluffy enhancement on its medial side on postcontrast T1 weighted images (*C*).

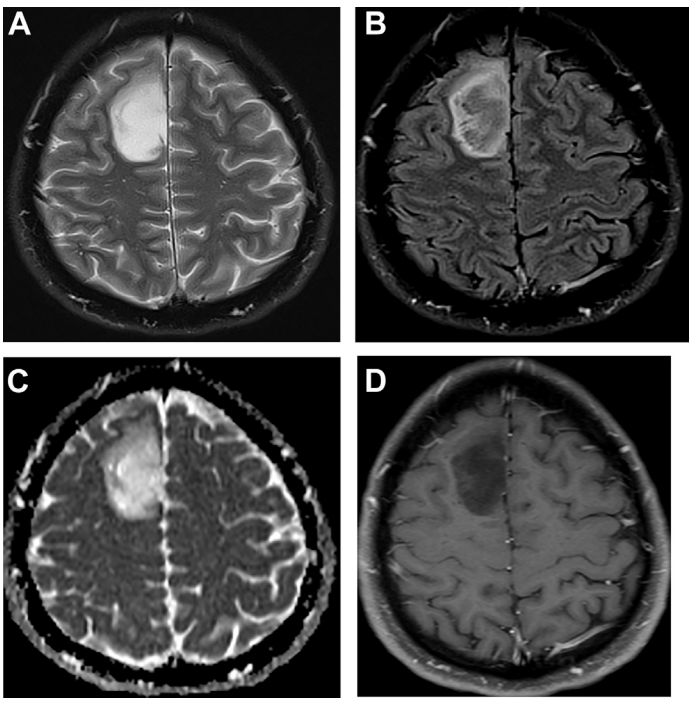

Fig. 6. Nondeleted astrocytoma. A 48-year-old man with a right frontal lobe diffuse astrocytoma, *IDH*-mutant, and 1p/19q noncodeleted, showing characteristic imaging features. Axial T2 image (*A*) shows a well-defined hyperintense mass in the right frontal lobe without much perilesional edema. Axial FLAIR image (*B*) shows hypointensity to isointensity in the central portion of the mass with surrounding hyperintensity. This is called T2-FLAIR mismatch sign. Mass shows high ADC and no enhancement on axial ADC (*C*) and postcontrast T1-weighted image (*D*).

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than or equal to 1.41 mm^2/s with 73.7% sensitive and 74.1% specific for 1p/19q codeleted oligodendroglioma.[49,51] A single 1p19q codeleted tumor with immunohistochemistry negative for *IDH1* does not exhibit calcifications or greater than 50% T2-FLAIR mismatch. Simple MR imaging markers may be helpful in predicting the 1p/19q status, but an accuracy of 82% is insufficient to replace formal 1p/19q testing for all patients.[49–51]

OTHER MOLECULAR MARKERS AND MUTATIONS IN DIFFUSE GLIOMAS

Today, neuro-oncologic practice is increasingly dependent on molecular diagnostics of tumor tissue. Various mutations and molecular markers have been identified in brain tumors (**Table 2**). Depending on the genetic analysis of the tumor, tumor treatment has become personalized and identifying these mutations has become mandatory to select therapies promoting better OS and PFS. With the development of next-generation sequencing panels, multiple mutations are detected in a single analysis. Next-generation sequencing panels also allow for the simultaneous detection of genome-wide methylation profiling and fusion and chromosomal copy aberrations. Mutations of the ATRX, TP53, and MGMT genes usually occur after the IDH mutation.[2,3,6] Currently, there is no specific imaging marker to diagnose these mutations; however, ancillary and indirect imaging findings may help in the search for a genetic mutation or molecular marker.

α-Thalassemia/Mental Retardation Syndrome X-Linked and TP53 Mutations

ATRX encodes a chromatin remodeling protein important in DNA replication, telomere stability, gene transcription, chromosome congression, and cohesion during cell division. ATRX mutation results in the abnormal lengthening of telomerase, an enzyme important for chromatin maintenance and remodeling.[3,6,53] ATRX mutations are rarely seen without other mutations in the genes for histone regulation proteins, such as IDH, H33 K27M,

Table 2
Distinguishing MR imaging features between IDH wild-type and IDH-mutant glioma

MR Parameters	IDH Wild-Type	IDH-Mutant
	Primary/de novo glioblastoma (90%)	Secondary glioblastomas (10%) (from diffuse or anaplastic astrocytoma)
Location/age	Supratentorial, >60 y	Frontal lobe, <45 y
Lobes	Multilobar, cross the midline	Single lobe, sparing of eloquent areas
Size and contours	Usually smaller, ill-defined, infiltrative margins	Larger and better defined contours
Growth	Faster growth, % NEC and NEC area significantly higher	Slow growth, limited necrosis
Enhancement	Heterogeneous, ring enhancement with central area of necrosis is a common feature	More homogeneous or nodular and less intense enhancement, large nonenhacing portion
DWI-ADC	ADC_{mean} low, <1.2 and low FA	ADC_{mean} higher FA: high
Promoter methylation	High relative CBV value (2.08 ± 0.54 mL/100 g), which shows extensive angiogenesis	Low relative CBV value (1.09 ± 0.34 mL/100 g),
MR spectroscopy	Absence of a 2HG peak	Maximum 2HG peak was identified at approximately 2.25 ppm
Median overall survival Surgery + RT Surgery + RT + CTX	9.9 mo 15 mo	24 mo 31 mo

Abbreviations: CBV, cerebral blood volume; CTX, chemotherapy; DWI, diffusion-weighted imaging; FA, fractional anisotropy; NEC, necrosis area; % NEC, percentage of cross-sectional necrosis area inside the enhancing lesion; RT, radiotherapy.

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or TP53.[53,54] TP53 is a tumor suppressor gene located on the short arm of chromosome 17. TP53 is a cell-cycle regulatory protein that slows or prevents the passage from the G1 phase to the S phase of mitosis if the genetic material has undergone DNA damage. Loss of TP53 leads to DNA damage, hypoxia, oncogene activation, microtubule disruption, and oxidative damage, which contribute to CNS tumors pathogenesis including medulloblastoma, GBM, IDH-mutant astrocytomas, and hereditary syndromes.[53–55] IDH-mutant astrocytic tumors frequently carry an ATRX and a TP53 gene mutation. Loss of nuclear ATRX during immunohistochemical staining is a strong predictor an of ATRX mutation, whereas strong and extensive nuclear staining for TP53 signifies the presence of a TP53 mutation.

Pediatric Gliomas

Before the 2016 tumor classification, pediatric and adult gliomas were under one umbrella because of their histologic similarities. Now they are independent of one another because their varying genetic profiles. Unlike adult gliomas, pediatric diffuse gliomas do not have changes in the *IDH* or *ATRX* genes, nor do they exhibit the 1p/19q codeletion.[3] Some differences include that WHO grade I gliomas are almost exclusively in pediatric or young adult patients and that GB incidence is rarer in childhood. *IDH* and *ATRX* gene mutations commonly seen in adult diffuse gliomas are not found in pediatric GBMs; rather, more than 95% of pediatric GBM cases exhibit the H3-K27M gene mutation.[56]

Diffuse Midline Glioma and H3 K27M-Mutant

Diffuse intrinsic pontine gliomas are malignant brain tumors that account for 75% to 80% of brainstem tumors in children.[56,57] Histone H3 K27M is a mutation in the H3F3A gene that encodes histone H3.3, a protein that replaces lysine by methionine at position 27 (H3-K27M-mutant).[56] This leads to a global reduction of H3 K27 trimethylation and a lateration in the epigenetic setting of the cell including DNA methylation. This drives gene expression patterns thought to block glial differentiation and promote gliomagenesis. H3 K27M mutations are commonly seen with diffuse midline gliomas but are not exclusive to them. This mutation has been identified in a subset of posterior fossa ependymomas; anaplastic gangliogliomas; and, although rarely, pilocytic astrocytomas. Tumors with an H3 K27M mutation exhibit more aggressive behavior. Diffuse midline gliomas have a predilection for young adults and children but may also occur in adults. With an H3 K27M mutation diffuse midline gliomas carry a poor prognosis, with a 2-year survival rate less than 10%.

As the name suggests, diffuse midline gliomas are seen along the midline involving CNS structures, including the thalamus, hypothalamus, third ventricle, pineal region, cerebellum, brainstem (previously known as diffuse intrinsic pontine glioma), and spinal cord. The imaging features of histone H3 K27M mutant gliomas are heterogeneous. Thalamic gliomas (**Fig. 7**) demonstrate contrast enhancement and necrosis in 50% of patients, pontine gliomas demonstrate variable contrast enhancement in 67% of patients, and cervical spine gliomas demonstrate uniform enhancement.[58] Cervical spine gliomas with histone H3 K27M mutation demonstrate leptomenigeal metastatic spread, whereas thalamic and pontine gliomas demonstrate local spread and recurrence. The prognosis is dependent on multiple factors, such as patient age, symptom duration, treatment type, and radiologic presence of contrast ring enhancement within diffuse intrinsic pontine gliomas. The type and site of mutation play a vital role in survival. Correlating imaging findings with molecular/genetic analysis remains challenging because of the morbidity associated with biopsies. H3 K27M mutant diffuse intrinsic pontine gliomas have worse OS than the H3.1-mutated subgroup. On imaging, poor outcomes correlate with ring enhancement and lower baseline ADC values.[58]

TERT Promoter Mutations

TERT promoter mutations are encountered in all grades of diffuse gliomas ranging from grade II oligodendrogliomas, the best prognosis, to grade IV GBM, the worst prognosis. The prevalence of TERT mutations is most common in GBMs (IDH wild-type, 1p19q not codeleted) and oligodendrogliomas (IDH-mutant, 1p19q codeleted).[59–61] These genetic aberrations are valuable diagnostic markers. The interaction of TERT mutations, IDH mutations, and 1p19q codeletion status is complex and depends on other combinations to determine survival.[60] For example, IDH wild-type diffuse astrocytomas (not 1p19q codeleted) of all grades (II to IV) that have a TERT mutation exhibit significant reductions in survival rate, most strikingly in grade II and III tumors. TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas.

TREATMENT, PROGNOSIS, AND ISOCITRATE DEHYDROGENASE MUTATIONS

A detailed discussion of glioma treatment is out of the scope of this article. We highlight the salient

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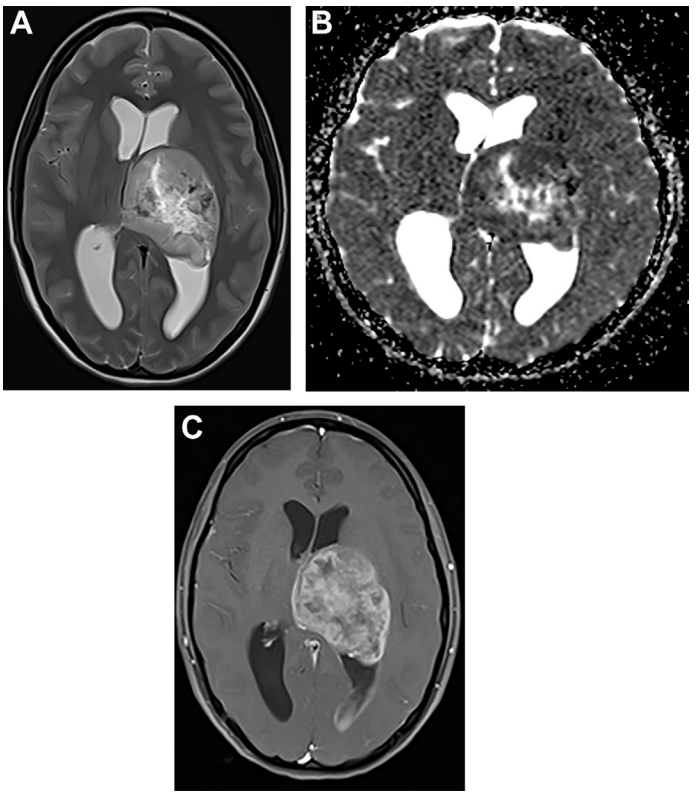

Fig. 7. Diffuse midline glioma with H3 K27M mutation. Axial T2-weighted image (*A*) demonstrates heterointense mass centered over the left thalamus with well-defined margins and without perilesional edema. On axial ADC image (*B*), mass shows low ADC except in the region of the necrosis. Contrast-enhanced T1-weighted image (*C*) shows intense enhancement of the thalamic mass with leptomeningeal enhancement along the left trigone and occipital horn.

genotyping and imaging features, which guide the oncology team in deciding an appropriate treatment. The main focus of glioma treatment has been to improve OS and have a PFS. By elevating the understanding of gliomagenesis and the phenotyping and genotyping classifications, the effort to develop therapeutic drugs, combined regimes, and minimally invasive surgeries to treat gliomas can continue.

IDH mutations are the initiating event in the oncogenesis of IDH-mutant gliomas. Noninvasive, preoperative identification of the IDH mutation is gaining ground, especially because genetic testing is not available across the globe. IDH1 mutation status is associated with a dramatic improvement in survival across the full spectrum of gliomas.[62] Therefore, pretreatment identification of IDH1 mutation in low-grade gliomas via radiographic characteristics may warrant early intervention as opposed to observation. Furthermore, IDH-mutant gliomas are found to be more susceptible to temozolomide as opposed to IDH wild-type lesions, which may be better targeted with alternative therapeutic interventions.[62,63] IDH-mutation status may also influence the extent of surgical resection.[62] High-grade IDH1-mutant may benefit from resection of nonenhancing surrounding tissue, but similar results were not found for IDH1 wild-type high-grade gliomas. IDH status plays a significant role in surgical treatment plans, patient counseling, and adjuvant therapy.

Today, the treatment of GBM and diffuse glioma is largely decided by the mutation status and other available markers besides the tumor histology. This is also applicable when deciding the surgical approach and resection. There are emerging data that resection of the nonenhancing tumor component improves survival in patients with IDH-mutant but not IDH wild-type GBM, further strengthening the argument for noninvasive, preoperative classification of gliomas.[64,65]

In accordance with the Stupp protocol, a temozolomide and radiotherapy combination followed by temozolomide maintenance treatment is recommended on diagnosis of GBM in a patient younger than 70 years of age regardless of IDH status.[66] In patients diagnosed with IDH wild-type, however, radiotherapy alone is recommended for patients with a negative MGMT methylation status, whereas the GBM protocol is recommended for patients with a positive MGMT methylation status. There is ongoing effort to find

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the appropriate DH1/2-mutant inhibitors to improve IDH1/2-mutant glioma treatment. These inhibitors can quantitatively inhibit IDH1/2 mutants and reduce 2HG to normal levels.[67,68] They also partially reverse histone modification and DNA hypermethylation, thereby playing a protective role. IDH1/2-mutant enzyme inhibitors have shown great potential in clinical trials: ivosidenib (AG-120) and enasidenib (AG-221) are the preferred reversible selective inhibitors of IDH1- and IDH2-mutant enzymes, respectively.[67,68] Enasidenib was approved by the Food and Drug Administration as a first-in-class inhibitor for the treatment of relapsed or refractory IDH2-mutated acute myeloid leukemia.

PROGNOSIS

Patients with an IDH-mutant GBM generally show substantially longer OS than those with IDH wild-type GBM. This prognostic impact also applies to the diffuse grade II and anaplastic grade III astrocytomas with *IDH* mutants. An interesting finding is that the OS of patients with IDH wild-type anaplastic astrocytoma was worse than patients with IDH-mutant GBM (WHO grade IV). However, this rule may not hold true for all *IDH* mutants and IDH wild-type gliomas. cIMPACT Update 3 clarifies that besides IDH status, prognosis also depends on other factors including the microvascular proliferation and necrosis. Therefore, cIMPACTNOW Update 3 requires the detection of an EGFR amplification, a TERT promoter mutation, or a complete gain of chromosome 7 combined with a complete deletion of chromosome 10 in addition to the histologic and IDH status of the tumor to establish the correct genotypic diagnosis.

SUMMARY

The treatment of the brain tumors is more personalized and is moving toward targeted therapeutics because of a better understanding of tumor genetics and molecular markers. However, the increase in the number and importance of distinct genetic mutations has led to a search of noninvasive and less expensive biomarkers to identify and classify these tumors. *IDH* gene mutations reflect alterations in metabolism, cellularity, and angiogenesis, which may manifest characteristic features on FLAIR-T2, diffusion-weighted imaging/ADC, MR spectroscopy, and DSC-PWI. Although imaging cannot replace the genetic panel at present, image findings have shown promising signs to identify and diagnose the types and subtypes of gliomas.

CLINICS CARE POINTS

- Molecular aberrations in the particular brain tumors, explains why some tumors of identical cell types appear similar on histology but respond differently to the same therapy and have different prognoses.
- Several molecular markers including isocitrate dehydrogenase (IDH), 1p/19q codeletion, O6-methylguanine-DNA methyltransferase methylation (MGMT), telomerase reverse transcriptase gene (TERT), athalassemia/mental retardation syndrome X-linked gene (ATRX), and p53, have been identified as necessary for to classify and understand the behavior and progression of the tumor.
- The Cancer Imaging Program and The Cancer Imaging Archive have paved the way to correlate imaging features and histologic patterns with the genetic profile of the tumor; this is called "radiohistogenomic interpretation."
- At present, imaging modalities have limitations in locating the point mutation of a tumor's genetic material.

DISCLOSURE

B.E. Zacharia: NICO Corp, Speaker's Bureau; Medtronic Inc, consultant.

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