REVIEW ARTICLE

Adult Gliomas

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RELATIONSHIP DISCLOSURE:
Dr Colman has served as an associate editor for *Neuro-Oncology* and on the editorial board for *Neuro-Oncology Practice* and has received personal compensation for serving on the advisory boards for AbbVie Inc, Bayer AG, Deciphera Pharmaceuticals, Inc, Forma Therapeutics, Karyopharm, NewLink Genetics Corporation, and Orbus Therapeutics and as a consultant for Best Doctors/Teladoc Health, Inc, and Private Health. Dr Colman has received grant support from the Alliance for Clinical Trials in Oncology (LAPS-UT003), The Hope Foundation, the Huntsman Cancer Foundation, the Musella Foundation
Continued on page 1475

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Colman discusses the unlabeled/investigational use of agents targeting mutations/alterations in *BRAF* (including vemurafenib), *EGFR, FGFR, IDH,* and *NTRK* to treat gliomas that harbor alterations in those genes and the use of checkpoint inhibitors, chimeric antigen receptor T cells, and pembrolizumab to treat glioblastoma.

ABSTRACT

PURPOSE OF REVIEW: This article highlights important aspects of the evaluation, diagnosis, and treatment of adult gliomas, including lower-grade astrocytomas and oligodendrogliomas, glioblastomas, and ependymomas.

RECENT FINDINGS: The appropriate initial evaluation and accurate diagnosis of gliomas require an understanding of the spectrum of clinical and radiographic presentations. Recent advances in the understanding of distinct molecular prognostic subtypes have led to major revisions in the diagnostic classification of gliomas. Integration of these new diagnostic and molecular classifications is an important part of the modern management of gliomas and facilitates better understanding and interpretation of the efficacy of different therapies in specific glioma subtypes.

SUMMARY: The management of adult gliomas is a multidisciplinary endeavor. However, despite recent molecular and treatment advances, the majority of diffuse gliomas remain incurable, and efforts aimed at the development and testing of new therapies in clinical trials are ongoing.

INTRODUCTION

Gliomas are a heterogeneous group of primary brain tumors that present multiple diagnostic and therapeutic challenges. Important issues facing the clinician evaluating a patient with possible or confirmed glioma include the initial (prediagnosis) evaluation, need for neurosurgical referral, prognostic considerations, and decisions about treatment. Recent developments have demonstrated the central role of molecular markers in the diagnosis, subtyping, and treatment of gliomas and their relationship with specific clinical and radiographic presentations. This article highlights some of the important clinical, radiographic, pathologic, and molecular considerations when evaluating a patient with a possible or confirmed diagnosis of glioma.

PRESENTATION AND INITIAL EVALUATION

Gliomas most commonly present with signs and symptoms related to a space-occupying lesion with symptoms often related to anatomic location. The time course and nature of symptoms vary significantly based on growth rate, location, degree of associated edema, degree of increased intracranial pressure, and whether seizures are part of the presentation. In general, lower-grade and slower-growing tumors present with gradually progressive symptoms and more

subtle neurologic deficits, except in the case of a new-onset seizure. Higher-grade and faster-growing tumors can present more acutely in terms of progressive neurologic deficits.

For initial diagnosis, contrast-enhanced MRI is much more sensitive for gliomas and other primary or metastatic brain tumors than CT imaging.[1] Thus, CT alone is not a sufficient evaluation, and MRI should be performed promptly for patients in whom brain tumor is part of the differential.

Indeterminate MRI Abnormalities and Neurosurgical Decision Making

While some combinations of clinical presentation and radiographic findings are more definitive for glioma, other presentations can be more difficult to interpret with certainty. One important aspect of the initial evaluation is assessment of the likelihood that a patient with an MRI abnormality actually has a glioma versus other neoplastic or non-neoplastic diseases because the assessed probabilities drive appropriate next steps in the diagnostic workup. When clinical and radiographic presentations suggest a high-grade neoplasm, early maximal safe resection for diagnosis, reduction of mass effect, and therapeutic benefit is usually the first step. However, care must be taken for potential mimickers of glioma in which surgery or more extensive surgery is not indicated, including tumefactive multiple sclerosis, central nervous system lymphoma, abscess, and stroke.[2]

One of the most significant challenges facing a neurologist in practice is how to approach the patient with an MRI abnormality, particularly if asymptomatic, for which glioma is a consideration but imaging and clinical presentation are indeterminate. It should be noted that conventional MRI and even advanced imaging modalities alone are not sufficiently sensitive and specific to make a definitive diagnosis of glioma, particularly when imaging is suggestive of a lower-grade neoplasm. The indications and limitations of both conventional MRI and advanced imaging for diagnosis of glioma have been well described in prior publications and reviews.[1,3]

Given the limitations of conventional and advanced imaging in the absence of pathologic confirmation, neurologists need to be aware that anecdotal interpretation of the significance of various clinical or radiographic findings can sometimes lead to an early or incorrect conclusion regarding the certainty of the underlying diagnosis. In the situation where interpretation of the initial clinical and radiographic presentation leads to an incorrect diagnosis of something other than glioma (eg, demyelination, stroke, herpes encephalitis, and others), a delay in neurosurgical intervention and the diagnosis of and treatment of glioma is the main danger. However, a mistaken presumptive diagnosis of a glioma when a different underlying diagnosis is present can result in exposure of the patient to unnecessary neurosurgical interventions and risk, as well as delay in the treatment of the real diagnosis (eg, demyelination, cortical dysplasia, infection). The goal of additional diagnostic evaluation is often to provide confidence that the diagnosis is something other than glioma, and one that does not require neurosurgical intervention, with higher confidence. However, care must be taken not to delay neurosurgical intervention unnecessarily in the case of an apparently higher-grade neoplasm or rapidly progressive symptoms. In these cases, the benefits of arriving at a definitive pathologic diagnosis quickly (whether glioma or not) often outweighs the additional risk of delay that more extensive preoperative diagnostic evaluations may incur.

KEY POINTS

- Adult gliomas are a clinically, radiographically, histologically, and molecularly heterogeneous group of tumors.
- The clinical presentation and symptoms of gliomas are often related to anatomic location.
- The acuity of symptoms and presentation are often related to the tumor growth rate.
- MRI is more sensitive than CT for the diagnosis of potential gliomas and other brain tumors.

One of the key decisions in the evaluation of a patient with a possible glioma is whether to pursue immediate referral for neurosurgical intervention and tissue diagnosis, pursue additional diagnostic evaluations, or initially observe with follow-up MRI studies to better determine the natural history and refine the differential diagnosis before pursuing a tissue diagnosis. Some of the key considerations in whether a patient requires immediate biopsy or resection of an indeterminate lesion include the pattern and timing of clinical presentation, imaging features (including size, location, and mass effect), whether the MRI abnormality is symptomatic or asymptomatic, patient age, and assessment of the likelihood that the lesion represents an infiltrating glioma versus a lower-grade (grade I neoplasm) or non-neoplastic process, among others. The use of steroids should also be avoided, when possible, when lymphoma, immune/inflammatory, or infectious processes are in the differential diagnosis because of the potential to decrease diagnostic yield from a biopsy or to negatively affect disease course. These considerations highlight the need for a comprehensive history and evaluation of symptoms and time course, careful evaluation of clinical and radiographic findings, and when appropriate, consultation with a neuro-oncologist or a neurosurgeon with experience in this area before going to surgery. In one study, the time to diagnosis, length of hospitalization, and number of unnecessary diagnostic studies were reduced by establishing a dedicated

TABLE 1-1 **Molecular and Clinical Features of Selected World Health Organization 2016 Glioma Diagnoses**

World Health Organization 2016 Integrated Diagnosis	Diagnostic Molecular Markers	Other Common Genomic Alterations	Characteristic Clinical and Radiographic Features
Diffuse astrocytoma and anaplastic astrocytoma, *IDH*-mutant (grade II and III)	*IDH*-mutant, 1p/19q-intact	*ATRX*, *TP53*	Younger adults, supratentorial, frontal predominance
Glioblastoma, *IDH*-mutant (grade IV)	*IDH*-mutant, 1p/19q-intact	*ATRX*, *TP53*; some cases: *CDKN2* loss	Younger adults, supratentorial, frontal predominance, enhancement common
Oligodendroglioma and anaplastic oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted (grade II and III)	*IDH*-mutant, 1p/19q codeleted	*CIC*, *FUBP1*, *TERT* promoter	Younger adults, supratentorial, frontal predominance
Diffuse midline glioma, H3K27M-mutant	*IDH*-wildtype, H3K27M-mutant	None	Midline (infratentorial and supratentorial), younger adults
Diffuse astrocytoma, *IDH*-wildtype (grade II and III)	*IDH*-wildtype	Chromosome 7 gain, chromosome 10 loss, *EGFR* amplification, *PTEN*; rare: *BRAF*, *NTRK*, *FGFR*	Older adults, supratentorial more common than infratentorial
Glioblastoma, *IDH*-wildtype (grade IV)	*IDH*-wildtype	Chromosome 7 gain, chromosome 10 loss, *EGFR* amplification, *PTEN*; rare: *BRAF*, *NTRK*, *FGFR*	Older adults, supratentorial more common than infratentorial, enhancement common

inpatient service for the evaluation of patients presenting with new brain masses on MRI,[4] highlighting the early and critical role of subspecialty expertise in the management of these complex cases.

DIAGNOSIS AND GRADING OF GLIOMAS

Historically, gliomas were diagnosed based on histopathology alone. Astrocytoma and oligodendroglioma were named for the similarity in morphology of these tumor types to normal astrocytes and oligodendrocytes. Also, in the past, the term *mixed oligoastrocytomas* was used for tumors with mixed histology. Gliomas have also been graded based on histopathologic findings. The World Health Organization (WHO) grade for gliomas ranges from I to IV. Grade I gliomas are more common in children and young adults and are often either observed or treated primarily with surgical resection; for more information about this group of tumors, refer to the article "Pediatric Brain Tumors" by Sonia Partap, MD, and Michelle Monje, MD, PhD,[5] in this issue of *Continuum*. The most common gliomas seen in adults are the diffuse gliomas and include astrocytomas, which range from grade II (astrocytoma) to III (anaplastic astrocytoma) to IV (glioblastoma), whereas oligodendrogliomas are limited to grade II (oligodendroglioma) and III (anaplastic oligodendroglioma). The incidence of grade II and III diffuse gliomas is less than glioblastoma, with approximately 5000 new cases of grade II/III astrocytomas and oligodendrogliomas each year in the United States.[6] Grade III (anaplastic) tumors are differentiated from grade II gliomas by increased features of malignancy, including atypia, hypercellularity, and increased mitotic rate. Grade IV astrocytomas, also known as glioblastomas, are characterized by the presence of either vascular proliferation or necrosis. Glioblastoma is the most common glioma seen in adults with an incidence of approximately 3 per 100,000 people and 10,000 new cases in the United States each year.[6] Historically, both histologic diagnosis and grading of gliomas have been prone to significant interobserver variability under prior WHO diagnostic criteria.[7]

Revised 2016 World Health Organization Classification of Gliomas

The identification of distinct molecular subtypes of glioma (often with overlapping histologies) within this complex group of tumors has led to the 2016 revised classification by the WHO that has significantly improved diagnostic accuracy, reduced interobserver variability, and clarified the prognosis and treatment for distinct molecular subtypes. The revised 2016 World Health Organization Classification of Tumors of the Central Nervous System[8,9] combines histopathologic, molecular, and grading features into an integrated glioma diagnosis. Under this revised system, the prior WHO classification of tumors that covered diagnoses of astrocytoma, oligodendroglioma, and glioblastoma has been separated into a series of molecular subtypes (and grades) based on the presence or absence of several molecular alterations.[8,9] The major diagnostic molecular alterations that subdivide gliomas into different diagnostic categories are the presence or absence of (1) isocitrate dehydrogenase (*IDH*) mutations, (2) chromosome 1p/19q loss, and (3) H3K27M mutation. A summary of the key molecular and clinical features for these tumors is shown in **TABLE 1-1** and discussed in the following paragraph. The cIMPACT-NOW (Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) project is a multidisciplinary initiative to make

KEY POINTS

- Careful consideration of history, clinical factors, and imaging is needed to develop an accurate differential diagnosis in the evaluation of a newly presenting patient with imaging potentially consistent with glioma.
- The differing molecular features of diffuse gliomas are associated with distinct diagnoses and prognoses.
- The revised 2016 World Health Organization (WHO) classification of gliomas incorporates histologic and molecular features into an integrated diagnosis.
- The major molecular alterations used for diagnosis and classification of gliomas include isocitrate dehydrogenase (*IDH*) mutation status, chromosome 1p/19q status, and H3K27M mutation status.

ongoing recommendations for the classification of central nervous system tumors before the next edition of the World Health Organization Classification of Tumors of the Central Nervous System is to be issued in 2021.[10]

***IDH*-MUTANT GLIOMAS.** The majority of low-grade astrocytomas and oligodendrogliomas, particularly in younger patients (median age of 35 to 40 years for *IDH*-mutant gliomas versus median age of 55 to 60 years for *IDH*-wildtype glioblastoma), have mutations in either *IDH1* or *IDH2*, with mutations in *IDH1* being much more common. Thus, one of the first major diagnostic steps after determining that a newly diagnosed brain tumor is an infiltrating glioma is to determine *IDH* status either by immunohistochemical testing or by gene sequencing. The molecular marker used to differentiate *IDH*-mutant tumors into astrocytoma or oligodendroglioma is the combined loss of chromosomes 1p and 19q. The loss of both chromosomal arms (1p and 19q) through a balanced translocation is the molecular hallmark of oligodendroglial tumors. In the 2016 WHO classification, the official names for these entities are as follows:

- **oligodendroglioma, *IDH*-mutant and 1p/19q codeleted (grade II)**
- **anaplastic oligodendroglioma, *IDH*-mutant and 1p/19q codeleted (grade III)**

In addition to *IDH* mutation and 1p/19q loss, oligodendroglial tumors also demonstrate mutations in other genes, including *CIC* and *FUBP1*.[11–13] In contrast, intact chromosome 1p/19q (no loss) is part of the molecular diagnosis of *IDH*-mutant astrocytomas. When 1p/19q is intact or there is loss of only one chromosomal arm, additional testing for evidence of mutations in *ATRX* or *TP53* is often performed. Evidence of mutation of either of these genes in a tumor that is *IDH*-mutant and in which chromosome 1p or 19q is intact is generally consistent with an astrocytoma diagnosis. In the 2016 WHO classification, the official names for these entities are as follows:

- **diffuse astrocytoma, *IDH*-mutant (grade II)**
- **anaplastic astrocytoma, *IDH*-mutant (grade III)**
- **glioblastoma, *IDH*-mutant (grade IV)**

An example of the presentation, diagnostic findings, and treatment for a newly diagnosed grade II *IDH*-mutant astrocytoma is shown in **CASE 1-1**.

The 2016 WHO criteria have essentially eliminated the prior diagnosis of mixed oligoastrocytoma (when molecular features are known). Under the new criteria, tumors with a mixture of astrocytic and oligodendroglial histology are classified under either astrocytoma or oligodendroglioma based on *IDH* and 1p/19q status. It is also important to note that the diagnostic utility and presence or absence of these molecular alterations are often dependent on the histologic and molecular context. For instance, chromosome 1p/19q loss essentially occurs only in *IDH*-mutant tumors. However, the reciprocal is not necessarily true, in that a tumor can be intact for chromosome 1p/19q and show either *IDH* mutation or *IDH*-wildtype phenotype. In addition, *TERT* promoter mutations are common in oligodendroglial tumors but can also be seen in glioblastoma. *TERT* promoter mutation with *IDH* mutation is strongly suggestive of the diagnosis of oligodendroglioma, whereas *TERT* promoter mutation without *IDH* mutation is strongly suggestive of glioblastoma or other less common glioma diagnoses. Thus, specific molecular alterations may have different

diagnostic and prognostic implications depending on context and other molecular alterations that are present (or absent).

Glioblastoma, *IDH*-mutant (WHO grade IV) accounts for approximately 10% of newly diagnosed glioblastoma. It is thought that virtually all of these grade IV *IDH*-mutant tumors represent so-called *secondary glioblastomas* that originated as a lower-grade astrocytoma that was not recognized clinically at an earlier time point and was diagnosed only after malignant transformation to grade IV. However, while currently given the name glioblastoma and/or the same grade as histologically similar *IDH*-wildtype tumors, the *IDH*-mutant tumors have a prognosis that is significantly better within any particular grade.[11–13] In addition, developing data suggest that the presence or absence of additional molecular features including *CDKN2* loss and others may be a better predictor of prognosis within *IDH*-mutant tumors than traditional histologic grading.[14–16] Furthermore, growing data suggest that traditional histologic features of grading, such as atypia and proliferation rate, may be less important in *IDH*-mutant tumors compared with *IDH*-wildtype tumors.[16]

KEY POINTS

- The majority of lower-grade (grade II and III) astrocytomas and oligodendrogliomas have *IDH* mutations.
- Loss of chromosomes 1p/19q is the molecular hallmark that distinguishes oligodendroglial from astrocytic gliomas within the *IDH*-mutant group.
- For the diagnosis of either astrocytoma or anaplastic astrocytoma with *IDH* mutation, the presence or absence of other molecular alterations including *CDKN2* loss may be more important than the actual WHO grade for prognosis.
- The vast majority of primary glioblastomas in older adults are *IDH*-wildtype, and even lower-grade *IDH*-wildtype astrocytic tumors with appropriate molecular alterations (*EGFR* or chromosome 7 gain/chromosome 10 loss or *TERT* promoter) can be classified as diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV.

IDH-WILDTYPE GLIOMAS AND GLIOBLASTOMAS. The vast majority of glioblastomas in older patients are glioblastoma, *IDH*-wildtype and represent the so-called *primary glioblastoma* (that do not arise from a known lower-grade precursor). In contrast to lower-grade gliomas, the majority of these glioblastomas demonstrate no mutation in *IDH* (*IDH*-wildtype). In general, patients with *IDH*-wildtype tumors have a worse prognosis than those with *IDH*-mutant tumors of the same histology and grade. *IDH*-wildtype astrocytomas and glioblastomas often share a mutational profile that can include alterations in *EGFR*, *NF1*, *TP53*, *PTEN*, *TERT* promoter, *CDKN2* loss, chromosome 7 gain, chromosome 10 loss, and others. A 2018 publication by the cIMPACT-NOW group specifically recommended that infiltrating gliomas that are *IDH*-wildtype and demonstrate (1) *EGFR* amplification, or (2) combined whole chromosome 7 gain and whole chromosome 10 loss, or (3) *TERT* promoter mutation should be more appropriately given the diagnosis of diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV.[17] Thus, even if histopathology is found to be lower grade (grades II and III), astrocytomas that harbor these glioblastomalike alterations tend to have a poor prognosis and behave similarly to histologic grade IV tumors. The recommended cIMPACT-NOW diagnosis for these patients (with diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV) is an attempt to assign a diagnosis appropriate with that prognosis, despite the lower-grade histologic features.[17–19] An example of a patient with lower-grade histology but molecular findings consistent with glioblastoma is shown in CASE 1-2.

OTHER CLINICALLY IMPORTANT *IDH*-WILDTYPE GLIOMA SUBTYPES. Although the majority of infiltrating gliomas fall into the WHO subtypes discussed earlier, several other clinically significant entities are important to identify from a diagnostic, prognostic, or therapeutic standpoint. These rarer subtypes are clinically relevant because they are associated with distinct clinical, radiographic, or molecular findings. In particular, the range of clinical behavior and prognoses within this group of *IDH*-wildtype (but not molecular glioblastomalike) tumors is quite broad. Some of these distinct diagnostic and molecular entities are described below.

DIFFUSE MIDLINE GLIOMA, H3K27M-MUTANT. This is a new and distinct diagnosis in the 2016 WHO criteria and is generally associated with younger age, midline (thalamic, basal ganglia) or posterior fossa location, diffuse infiltration, and typically a poor prognosis. A significant proportion of diffuse intrinsic pontine gliomas in children or younger adults are also members of this molecular subtype. In addition to the clinical and radiographic findings, this diagnosis is confirmed by molecular testing (either immunohistochemistry or DNA sequencing) that demonstrates the characteristic H3K27M mutation in

CASE 1-1

A 39-year-old woman presented with a new-onset seizure. Brain MRI demonstrated a nonenhancing mass in the left lateral frontoparietal regions, with fluid-attenuated inversion recovery (FLAIR) and T1 postcontrast images at diagnosis shown in FIGURES 1-1A and 1-1B, respectively. She underwent resection with pathology of diffuse astrocytoma, World Health Organization (WHO) grade II. Molecular testing at that time showed the tumor was mutant for *IDH1*, *ATRX*, and *TP53*, and chromosome 1p/19q was intact. By using the new WHO diagnostic criteria, this tumor would be classified as diffuse astrocytoma, *IDH*-mutant, WHO grade II. After surgery, she was treated with radiation to a dose of 54 Gy with concurrent temozolomide and six cycles of adjuvant temozolomide. She had been off treatment since, and MRI 8 years after diagnosis is shown in FIGURES 1-1C and 1-1D (FLAIR and T1 postcontrast, respectively) with no evidence of progression since the initial treatment. At her most recent visit, she had a Karnofsky Performance Status Scale score of 100, was working full time, and was seizure free.

COMMENT

This case illustrates some of the common clinical, radiographic, and diagnostic molecular features of *IDH*-mutant astrocytomas. The patient's good response to treatment, long progression-free interval, and excellent clinical status highlight the potential for good outcomes with this tumor type (as well as oligodendrogliomas, *IDH*-mutant and 1p/19q codeleted).

the histone 3 protein. An example of a midline glioma for which H3K27 testing confirmed the diagnosis of diffuse midline glioma, H3K27M-mutant is shown in CASE 1-3. Other rarer histone mutations are also seen but fall outside this narrower diagnostic entity.

DIFFUSE ASTROCYTOMAS, *IDH*-WILDTYPE, CHROMOSOME 1P/19Q-INTACT OF VARIABLE GRADES WITH *BRAF* GENE ALTERATIONS. This group of tumors can have variable histologic findings, with some indistinguishable from more typical *IDH*-mutant

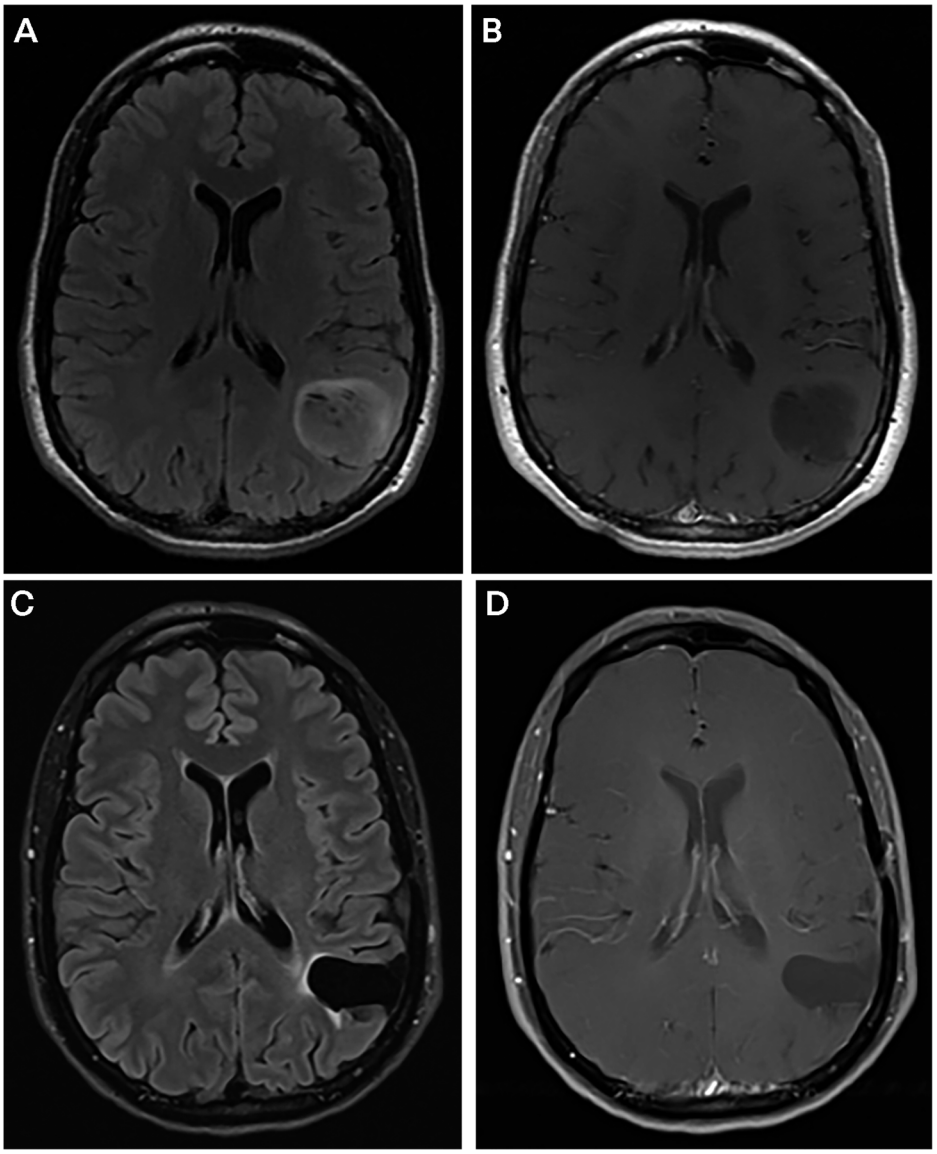

FIGURE 1-1
Imaging of the patient in CASE 1-1. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and postcontrast T1-weighted (*B*) brain MRI demonstrates a nonenhancing mass in the left lateral frontoparietal region at diagnosis. FLAIR (*C*) and postcontrast T1-weighted (*D*) images 8 years after diagnosis show a resection cavity with no evidence of progression since the initial treatment.

astrocytomas and others having potential overlap in histologic and molecular findings with other (often circumscribed) glioma variants. These variants are potentially clinically important as several therapies exist that specifically target *BRAF* alterations, and data are increasing regarding the therapeutic benefit of these agents in gliomas and other primary brain tumors. The most common *BRAF* alterations seen in infiltrating gliomas are a point mutation (*BRAF* V600E) and *BRAF* gene fusions (*BRAF-KIAA1549*), and these alterations are mutually

CASE 1-2

A 45-year-old man presented with a new-onset seizure and some subtle but progressive speech difficulty. Brain MRI demonstrated a nonenhancing mass in the medial left temporal lobe, with fluid-attenuated inversion recovery (FLAIR) and postcontrast T1-weighted images at diagnosis as shown in FIGURES 1-2A and 1-2B, respectively. He underwent almost complete resection of the tumor in the left temporal lobe with pathology of diffuse astrocytoma, World Health Organization (WHO) grade II. The tumor was determined to be *IDH*-wildtype by immunohistochemistry and sequencing. Next-generation DNA sequencing showed that the tumor was *EGFR* amplified and had chromosome 7 gain, *PTEN* loss, and a *TERT* promoter mutation. If the patient had been diagnosed by using the revised 2016 WHO criteria, this tumor would have been classified as diffuse astrocytoma, *IDH*-wildtype, WHO grade II. *O*-6-methylguanine-DNA methyltransferase (MGMT) promoter was unmethylated.

He received radiation to 60 Gy with concurrent temozolomide followed by six cycles of adjuvant temozolomide. Despite treatment typical for higher-grade astrocytoma (due to the unfavorable molecular findings), the patient experienced rapid recurrence involving the left insula, frontal lobe, and corpus callosum approximately 2 years later (FIGURES 1-2C and 1-2D).

COMMENT

This case illustrates the importance of the molecular alterations in diffuse gliomas relative to prognosis. Although age, presentation, imaging, pathology, and histologic grade were similar to those in CASE 1-1, this patient experienced a very different and much worse outcome despite receiving similar treatment. The findings of *EGFR* mutation, chromosome 7 gain, *TERT* promoter mutation, and others in a histologically low-grade *IDH*-wildtype astrocytoma are generally associated with a prognosis that is similar to glioblastoma, and the cIMPACT-NOW (Consortium to Inform Molecular and Practical Approaches to CNS Tumor) group recently published recommendations that these tumors are given the diagnosis diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV.[16] This case highlights the need for clinicians to be aware of these subtleties in the diagnosis and treatment of diffuse gliomas.

exclusive within a particular tumor.[20] *BRAF* fusions are seen most commonly in pilocytic astrocytomas but can also occur rarely in infiltrating gliomas. *BRAF* mutations exist in a variety of glioma histologies including pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma, ganglioglioma, and rarely in lower-grade infiltrating astrocytoma and glioblastoma. Epithelioid glioblastoma is recognized as a distinct glioblastoma subtype in the 2016 WHO classification, is seen predominantly in children and young adults, and has a

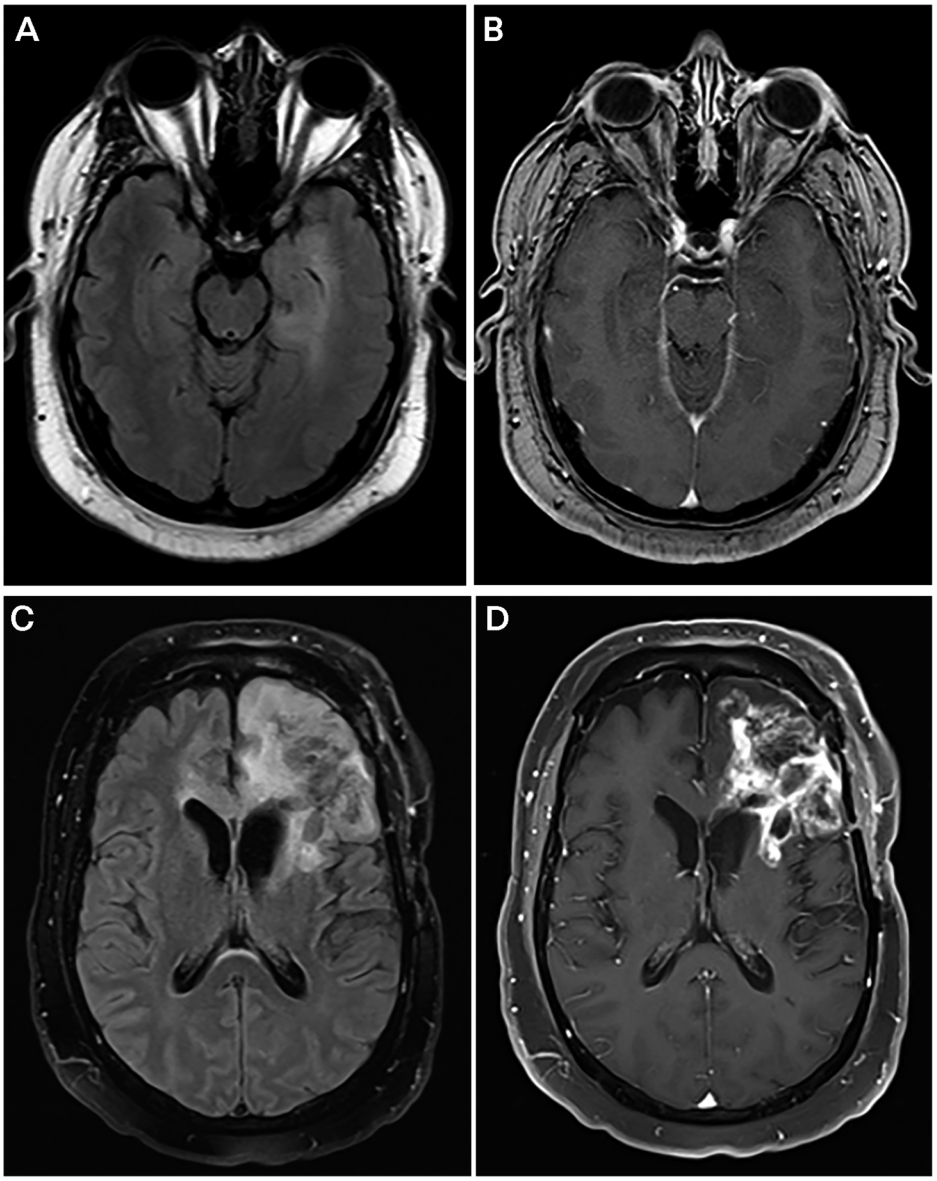

FIGURE 1-2
Imaging of the patient in CASE 1-2. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and postcontrast T1-weighted (*B*) brain MRI demonstrates a nonenhancing mass in the medial left temporal lobe at diagnosis. FLAIR (*C*) and postcontrast T1-weighted (*D*) images show aggressive recurrence approximately 2 years after initial treatment with radiation and temozolomide.

distinct cell morphology in which greater than 50% of tumors harbor the *BRAF* V600E mutation. Some debate exists about the overlap of epithelioid glioblastoma and anaplastic pleomorphic xanthoastrocytoma and whether these really represent distinct diagnoses.[20] Case reports and small series in the literature describe radiographic responses of various glioma subtypes harboring *BRAF* alterations to drugs targeting either *BRAF* V600E mutation and drugs that target mitogen-activated protein kinase, a downstream component in this pathway.[21] Thus, it is important to recognize these rare variants because of the potential for the use of targeted therapies in the appropriate clinical situation.

DIFFUSE ASTROCYTOMAS, *IDH*-WILDTYPE, CHROMOSOME 1P/19Q-INTACT THAT HARBOR OTHER DISCRETE AND POTENTIALLY THERAPEUTICALLY TARGETABLE MOLECULAR ALTERATIONS. These alterations are rare (often less than 2% to 3% each in gliomas) but have shown promise in other tumor types as therapeutic

CASE 1-3

A 31-year-old woman presented with a 2- to 3-month history of progressive headaches. Brain MRI demonstrated a relatively well-circumscribed, nonenhancing mass involving the hypothalamus and inferior basal ganglia bilaterally, shown in FIGURES 1-3A and 1-3B (fluid-attenuated inversion recovery [FLAIR] and postcontrast T1-weighted images, respectively). Biopsy was performed, and the pathologic diagnosis was initially diffuse astrocytoma, World Health Organization (WHO) grade II, negative for *IDH* mutation by immunohistochemistry. However, subsequent tumor sequencing demonstrated an isolated H3K27M mutation, which under current WHO criteria would be diagnosed as diffuse midline glioma, H3K27M-mutant. Although the patient was diagnosed before the current WHO guidelines, the negative prognostic impact of this finding was known, and the patient was treated aggressively with radiation to 60 Gy with concurrent temozolomide followed by six cycles of adjuvant temozolomide.

The patient was lost to follow-up and presented again approximately 2.5 years later with seizures, encephalopathy, and left hemiparesis, and repeat brain MRI was performed (FIGURE 1-3C). Based on the patient's poor performance status requiring intensive care unit admission, the family chose not to pursue additional treatment.

COMMENT

As in the previous cases, this case demonstrates another example of the spectrum of molecular findings and prognoses that can occur in diffuse gliomas, sometimes with similar clinical and radiographic findings. Although this patient's tumor has a relatively "benign" and well-circumscribed appearance on the initial imaging, which might suggest a diagnosis of several grade I tumors such as pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor (DNET), or ganglioglioma based on imaging alone, the molecular findings here are diagnostic of the grade IV H3K27M midline tumor, and accurately predicted the poor prognosis of this patient despite aggressive treatment.

targets. These include *FGFR* gene fusions,[22] *NTRK* gene fusions, microsatellite instability–high, and *ROS1* gene fusions. In the case of *NTRK* fusions and microsatellite instability–high tumors, the US Food and Drug Administration (FDA) has approved targeted and immunotherapy agents, respectively, where the drug approval is "tissue agnostic." Thus, testing for these rare alterations can be important to identify those patients for whom these targeted or immunotherapies may be appropriate in addition to or instead of standard therapies in selected situations.

EPENDYMAL TUMORS. Ependymal tumors are glial neoplasms that are distinct from the diffuse gliomas and can present in both childhood and adulthood.[6] In contrast to the diffuse gliomas, this group of tumors is thought to arise from the ependymal lining of the ventricular cavities or from radial glia precursors in these regions.[23] Ependymal tumors comprise different histologies including

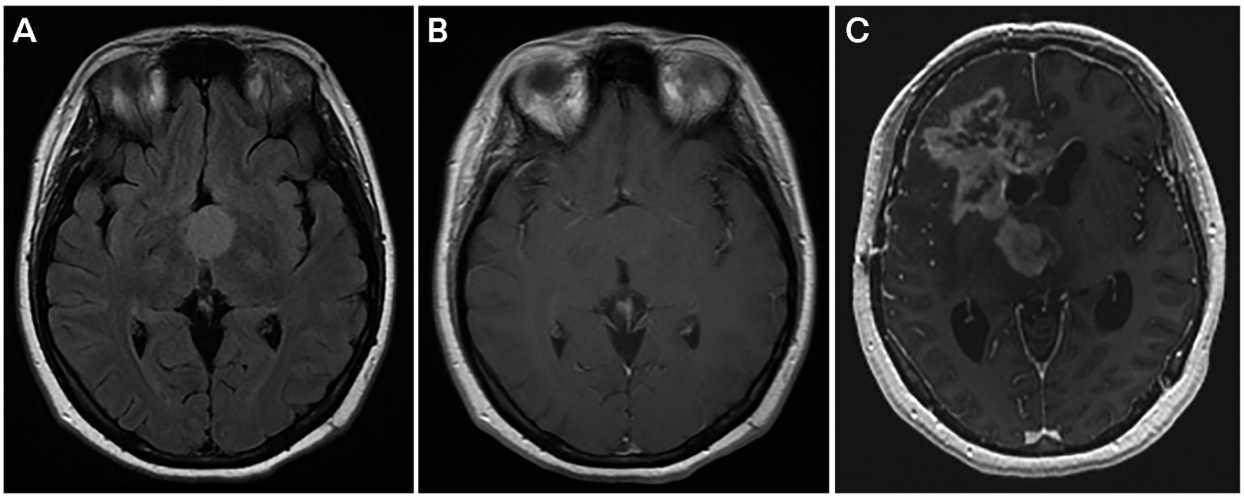

FIGURE 1-3
Imaging of the patient in CASE 1-3. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and postcontrast T1-weighted (*B*) brain MRIs demonstrate a relatively well-circumscribed, nonenhancing mass involving the hypothalamus and inferior basal ganglia bilaterally. A repeat brain postcontrast T1-weighted sequence (*C*) approximately 2.5 years after initial treatment with radiation and temozolomide shows aggressive recurrence in the midline and anteriorly and superiorly in the frontal lobe on the right.

ependymoma, subependymoma, and myxopapillary ependymoma that are associated with different clinical, radiographic, molecular, and grading features. Subependymomas are grade I tumors, most commonly located in the lining of the fourth ventricle, but they can be found elsewhere. These are slow-growing tumors that are often diagnosed as an incidental finding but when symptomatic are often associated with CSF obstruction and increased intracranial pressure. Subependymomas that are incidental, asymptomatic, or not clearly progressing might be observed without intervention. When symptomatic, the primary treatment is usually resection alone, with radiation used only in rare cases of multiply recurrent or unresectable and progressive subependymoma. Myxopapillary ependymomas are also WHO grade I tumors, most commonly found in the conus medullaris and cauda equina regions of the spine. Resection is the primary treatment, with radiation reserved for incomplete resection or tumors that progress after maximal resection. Rarely, myxopapillary ependymomas can behave much more aggressively than the grade I histology would suggest, with cases of CSF dissemination or invasion of adjacent bony structures. Ependymomas are either grade II or grade III (anaplastic ependymoma) with grading based on histologic findings. The histopathologic hallmark of ependymoma is the perivascular pseudorosette (FIGURE 1-4). As in diffuse gliomas, recent advances in the molecular understanding of ependymomas have led to the identification of distinct molecular subtypes. An important subtype is the *RELA-C11orf95* fusion variant observed in a high percentage of supratentorial ependymomas,[23,24] which led to the inclusion of ependymoma, *RELA* fusion–positive as a distinct diagnostic category in the 2016 revised WHO classification.[9,23,24] There are two subtypes of posterior fossa ependymoma (group A and group B) based on gene expression and epigenetic profiling.[25] Negative prognostic factors for ependymoma include intracranial (versus spinal) location, younger age, male sex, higher grade, and incomplete resection.[23]

In terms of treatment, maximal safe resection is the primary initial treatment for ependymoma. Staging of the neuraxis with contrast-enhanced MRI of both brain and spine and CSF cytology before surgery is preferred when ependymoma is suspected preoperatively, but staging can also be performed after a histologic diagnosis is made. Adjuvant radiation after surgery is generally part of treatment for all grade III ependymomas and incompletely resected grade II ependymomas.[26] In addition, one retrospective series indicated that, even with complete resection, posterior fossa grade II ependymomas have a higher recurrence rate without adjuvant radiation.[27] The role for adjuvant radiation for completely resected supratentorial ependymoma is a topic of debate.

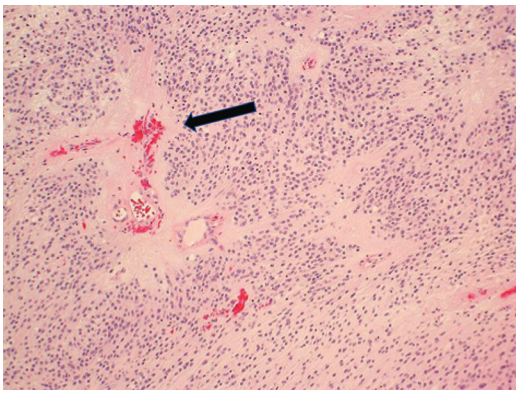

FIGURE 1-4
A perivascular pseudorosette (*arrow*) characteristic of ependymoma.
Image courtesy of Cheryl Ann Palmer, MD.

DIFFUSE GLIOMA TREATMENT

Several treatment modalities including surgical resection, radiation, chemotherapy, and

more recently tumor treating fields have been shown to have overall or progression-free survival benefits in gliomas. However, the relative benefit of each modality can differ based on specific histologic, grade, and molecular features. The current evidence for these treatment modalities in specific clinical situations is reviewed here.

KEY POINTS

- H3K27M mutations are the hallmark of diffuse midline glioma, which most commonly occur in the pons and diencephalon in younger patients and are associated with poor prognosis.
- Initial treatment for most diffuse gliomas starts with maximal safe resection.

Surgery

Initial treatment for all grades of gliomas starts with maximal safe resection. In addition to providing definitive histologic and molecular diagnosis, surgery also can provide a clinical benefit from a reduction of mass effect, and more extensive resection has been associated with better survival in several glioma subtypes. For newly diagnosed glioblastoma (and by extension higher-grade *IDH*-wildtype gliomas), a greater extent of resection of an enhancing tumor has been associated with better overall survival. In some retrospective studies, resection of greater than 95% of presurgical enhancement is needed for significant improvement in survival,[28,29] although in one analysis from a large retrospective series the volume of residual enhancement after resection was more important than the percentage of resection.[30]

Only recently have outcomes relative to the extent of resection in gliomas been analyzed based on molecular subtypes. In the case of lower-grade gliomas, a greater extent of resection and a smaller volume of residual (often nonenhancing) tumor have been found to be positive prognostic factors in several retrospective analyses.[31] In analyses of gliomas that compared surgical outcomes of *IDH*-mutant versus *IDH*-wildtype gliomas, the extent of resection of enhancing disease (but not nonenhancing tumor) was prognostic in *IDH*-wildtype tumors, whereas the extent of resection of total tumor volume (enhancing and nonenhancing disease) was prognostic in *IDH*-mutant tumors.[32] These findings suggest that the role and surgical target for maximal resection may differ based on the molecular subtype of glioma.

In suspected lower-grade gliomas, the timing of surgery is also an important clinical decision. The effect of early resection versus initial observation of presumed low-grade gliomas has not been evaluated in a randomized trial. Uncontrolled and retrospective analyses have suggested a survival benefit of early and more complete resection.[31–33] To date, no studies have convincingly defined a population of patients in which delayed or incomplete resection has demonstrated clinical benefit. As a result, the most common approach in specialized centers is to proceed with maximal safe resection in patients with suspected lower-grade gliomas, as recommended in National Comprehensive Cancer Network guidelines for suspected low-grade gliomas.[17,34]

Radiation, Chemotherapy, and Tumor Treating Fields for Newly Diagnosed Glioblastoma

The benefit of radiation in prolonging survival with high-grade gliomas dates back several decades. In terms of radiation dosage for glioblastoma, historical studies have suggested that dosages greater than 65 Gy have efficacy similar to that of 60 Gy but with higher toxicity and increased risk of radiation necrosis. Thus, current guidelines recommend a standard dose of 60 Gy in 2.0-Gy fractions or 59.4 Gy in 1.8-Gy fractions.[35] Tumor volumes (enhancing and nonenhancing) for radiation treatments are defined by the postoperative (preradiation) MRI and include the volume of abnormalities on T1-weighted and

T2-weighted sequences (gross tumor volume) plus a margin that can range from 1 cm to 3 cm. The therapeutic effect of radiation is generally related to dose, not modality (eg, photons versus protons), with current clinical trials comparing intensity-modulated radiation therapy to proton therapy mainly aimed at determining if there is any benefit of proton therapy in terms of reduced neurotoxicity.

The role of chemotherapy as a standard part of treatment in newly diagnosed glioblastoma was established in a 2005 randomized trial of temozolomide plus radiation versus radiation alone. This study showed a significant survival benefit (14.6 months versus 12.1 months) with the addition of temozolomide to radiation and 6 additional months of postradiation temozolomide.[35] Dosing of temozolomide was 75 mg/m^2 daily during the 6 weeks of radiation, 150 mg/m^2 days 1 to 5 of the first 28-day adjuvant cycle after radiation, and then (if tolerated) 200 mg/m^2 for days 1 to 5 of the 28-day cycles 2 through 6 after radiation. Longer-term follow-up of patients from this study also demonstrated an improvement in long-term survival, with overall 5-year survival of 9.8% in the radiation plus temozolomide group versus 1.9% in the radiation alone group.[36] The most common adverse effects of temozolomide include fatigue, nausea, constipation, and bone marrow suppression, with lymphopenia and thrombocytopenia the most common cytopenias. Temozolomide remains the only chemotherapy that is FDA approved specifically for newly diagnosed glioblastoma. As a result of this study, radiation plus temozolomide is the standard initial treatment for patients with newly diagnosed glioblastoma, particularly in patients with favorable clinical prognostic factors (younger age, better performance status, better extent of resection) and in those patients in whom the tumor shows evidence of *O*-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

MGMT Promoter Methylation

The initial randomized study of temozolomide in newly diagnosed glioblastoma also identified MGMT promoter methylation as a marker of better prognosis and a predictive marker of temozolomide benefit.[37] MGMT removes methyl groups from DNA, thereby conferring resistance to methylating agents such as temozolomide. Thus, high MGMT levels act as a potential resistance mechanism to temozolomide treatment. High levels of methylation of the MGMT promoter are associated with lower expression levels of MGMT resistance enzyme and increased sensitivity to temozolomide treatment. Longer-term follow-up from the 2005 temozolomide study also demonstrates a strong prognostic and predictive effect of MGMT promoter methylation.[36] In patients who received radiation alone, patients with MGMT promoter methylation had better 5-year survival than those without MGMT promoter methylation (5.2% versus 0%), suggesting a better prognosis even without chemotherapy (at least at initial diagnosis). However, the benefit of MGMT promoter methylation was strongest in the patients who received temozolomide with radiation as the initial treatment with a 5-year survival of 23.4% (methylated) versus 12.6% (unmethylated). These data indicate that when patients with *IDH*-wildtype glioblastoma have a combination of positive clinical prognostic factors and MGMT promoter methylation, the likelihood of longer-term survival with standard treatments is higher.[38]

Tumor Treating Fields

The only other treatment modality beyond radiation and temozolomide that has a survival benefit in newly diagnosed glioblastoma is tumor treating fields.[39] The

potential mechanism of action that led to the development of tumor treating fields as a treatment modality is the concept that DNA and mitotic spindles within a cell are electrically charged, and it was hypothesized that an electrical field of sufficient strength delivered across the tumor cells could inhibit DNA replication and mitosis. The tumor treating fields are delivered to the glioblastoma tumor by using multiple electrode arrays that are attached to the shaved scalp of the patient, and the electric fields are delivered via a battery pack that is worn as a shoulder or backpack and attached to the electrodes via a wiring harness. The randomized study examining the effect of tumor treating fields in newly diagnosed glioblastoma involved random assignment of patients after they completed radiation and temozolomide to either temozolomide alone (control) or temozolomide and tumor treating fields (experimental) groups. This was not a placebo-controlled study, and thus, it is not possible to determine whether differences in supportive care or follow-up between arms played some role in the outcomes.[40] However, the study did demonstrate a survival benefit in the tumor treating fields group versus control (20.9 months versus 16.0 months, respectively).[39] Tumor treating fields are FDA approved for use in newly diagnosed glioblastoma along with temozolomide after radiation based on these data.

KEY POINTS

- *O*-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is both a prognostic marker in glioblastoma and a predictive marker of a better outcome with temozolomide.
- Standard treatment options with survival benefit in randomized studies for newly diagnosed glioblastoma include radiation, temozolomide, and tumor treating fields.

Recurrent Glioblastoma

Despite initial therapy, glioblastoma progresses in virtually every patient. While clinical and molecular prognostic markers such as *IDH* mutation and MGMT promoter methylation have been associated with better outcomes in recurrent tumors in at least some studies, the survival of recurrent glioblastoma is generally poor, with one randomized study showing a median survival of approximately 9 months from the time of first progression.[41] Patients with poor prognostic factors (eg, older age, poor performance status) have even worse survival outcomes. Despite the testing of many different agents with various mechanisms of action in recurrent glioblastoma, no treatment has been shown to improve overall survival in this group of patients. Cytotoxic chemotherapies have very low radiographic response rates in recurrent glioblastoma.[42] Thus, the antiangiogenic agent bevacizumab (a humanized monoclonal antibody against vascular endothelial growth factor [VEGF]) created some excitement when it was found to have a high response rate (40% to 60%) in initial single-arm studies, as well as improved progression-free survival compared with historical controls.[43] The observation of a high response rate and improved progression-free survival with bevacizumab led to accelerated approval by the FDA for the treatment of recurrent glioblastoma. However, the provisional FDA approval in 2009 stipulated that confirmatory phase 3 studies be performed. Two phase 3 randomized, placebo-controlled studies of radiation, temozolomide, plus bevacizumab versus radiation and temozolomide alone were performed with patients with newly diagnosed glioblastoma,[44,45] and subsequently a separate phase 3 study of bevacizumab plus lomustine versus lomustine alone in recurrent glioblastoma.[41] The results of all of these studies were similar (despite the different patient populations) in that all confirmed a high proportion of radiographic responses to bevacizumab in glioblastoma and improvement of progression-free survival in the 3- to 5-month range. However, none of these studies demonstrated a significant benefit on overall survival. Despite these findings, it was concluded that the net clinical benefit observed in terms of response rate, progression-free survival, and maintenance of performance status

was important, and this led to conversion of bevacizumab to full approval by the FDA in 2019. Several other agents including lomustine, tumor treating fields, carmustine, carboplatin, and others have shown some activity in recurrent glioblastoma and are listed in National Comprehensive Cancer Network guidelines,[34] but as with bevacizumab, none of these have demonstrated an overall survival benefit in recurrent glioblastoma in a randomized study.

Older Adults With Glioblastoma

Older age is generally associated with worse prognosis in glioblastoma. Randomized studies have examined the role of a shorter course (hypofractionated) of radiation with and without temozolomide in older patients (generally older than 60 or 65 years depending on the study). In one randomized study examining standard versus hypofractionated radiation alone (before temozolomide was part of the standard of care), no significant difference in survival was found between a total dose of 40 Gy in 15 fractions compared with standard 60 Gy in 30 fractions.[46] In a separate study of anaplastic astrocytoma and glioblastoma in patients older than 65, patients were randomly assigned to standard radiation (60 Gy) alone versus a regimen of temozolomide alone.[47] This study demonstrated that temozolomide alone was not inferior to radiation in the overall population and that, within the group of patients with MGMT promoter methylation, survival was better in the temozolomide monotherapy group versus the radiation group. Results of a three-arm study of standard-dose temozolomide versus standard radiation (60 Gy) versus a hypofractionated schedule (34 Gy in 3.4-Gy fractions) in patients older than 60 showed that survival with temozolomide was longer than with standard radiation but similar to hypofractionated radiation.[48] Again, patients whose tumors had MGMT promoter methylation had better survival with temozolomide treatment. These studies led to the concept that, in older patients with glioblastoma with MGMT promoter methylation, temozolomide alone (no radiation) is an option for initial treatment, and, in MGMT unmethylated tumors, hypofractionated radiation may be a reasonable alternative to standard radiation. However, a subsequent phase 3 study comparing hypofractionated radiation alone to hypofractionated radiation (40 Gy in 15 fractions) plus temozolomide in patients older than 65 with newly diagnosed glioblastoma showed an improvement in median survival with the addition of temozolomide in the overall population (9.3 months versus 7.6 months). Somewhat surprisingly, the benefit of the addition of temozolomide was seen in both the MGMT unmethylated (10.0 months versus 7.9 months) and MGMT methylated groups (13.5 months versus 7.7 months).[49] Based on these results in older patients with glioblastoma, National Comprehensive Cancer Network guidelines for patients older than 70 with good performance status currently include all combinations of standard and hypofractionated radiation with or without temozolomide as reasonable treatment options for MGMT methylated or unmethylated tumors and temozolomide alone as an additional potential option for MGMT methylated tumors.[34] Tumor treating fields are also part of National Comprehensive Cancer Network guidelines for treatment of both methylated and unmethylated tumors in this age group.

Grade II and III Diffuse Infiltrating Astrocytoma and Oligodendroglioma

As described earlier, recent developments have clarified the molecular distinctions between lower-grade (grades II and III) astrocytomas and

oligodendrogliomas, and 2016 updated WHO diagnostic criteria combine histologic findings with *IDH* mutation status and chromosome 1p/19q deletion status into an integrated diagnosis and grading system. The majority of lower-grade gliomas are *IDH*-mutant, and, in general, lower-grade *IDH*-wildtype tumors either fall into the glioblastomalike category or represent rarer molecular variants (eg, H3K27 mutant, *BRAF* alterations). This discussion of lower-grade gliomas focuses on the more common *IDH*-mutant subtypes, with the majority of *IDH*-wildtype tumors falling under the category of glioblastoma in terms of recommended treatment. Prognosis is generally much better for lower-grade *IDH*-mutant astrocytoma and oligodendroglioma compared with grades II through IV *IDH*-wildtype and better than *IDH*-mutant grade IV tumors.[12,13] Prognosis is generally better for oligodendroglioma, *IDH*-mutant compared with astrocytoma, *IDH*-mutant across grades II and III, regardless of whether the treatment being tested in the study was radiation, chemotherapy, or some combination. In addition, within all *IDH*-mutant lower-grade gliomas, several important clinical prognostic factors have been identified including age, performance status, size of tumor at presentation, the amount of residual tumor burden after resection, tumor location, and other molecular features beyond *IDH* mutation (discussed earlier), and all appear to play an important role in outcomes, regardless of treatment modality.

Radiation dosage for grade II and III gliomas has been evaluated in several randomized trials. Based on the results of these studies, lower radiation doses (eg, 50.4 Gy in 28 fractions) are often used for grade II tumors, whereas higher doses (59.4 Gy) are commonly used in grade III tumors.[34] These dosages were determined before the understanding of molecular subtypes and determinants in infiltrating gliomas. The finding that traditional histopathologic grading is not prognostic in *IDH*-mutant gliomas does suggest that these differences in radiation dose based on histologic grade may need to be revisited in the modern era, but, to date, no comparative data on the use of different doses in molecularly defined subtypes of glioma are available to guide these decisions. Relevant to this issue, current National Comprehensive Cancer Network guidelines suggest that patients with grade II diffuse gliomas receive 45 Gy to 54 Gy in 1.8- to 2.0-Gy fractions, but dose escalation to 59.4 Gy to 60 Gy should be considered for *IDH*-wildtype grade II gliomas.[34] For anaplastic gliomas, National Comprehensive Cancer Network recommendations are to treat to 60 Gy in 2.0-Gy fractions or 59.4 Gy in 1.8-Gy fractions, regardless of *IDH* status.

A key long-standing question in the treatment of lower-grade gliomas has been the issue of whether radiation alone, chemotherapy alone, or the combination of radiation and chemotherapy is optimal in different subtypes or glioma grades. In particular, the observation, along with the discovery of chromosome 1p/19q loss in oligodendrogliomas, was that these tumors appeared particularly sensitive to chemotherapy,[50] which led to the hypothesis that treatment with chemotherapy alone (no radiation) may be sufficient for some or all patients with these tumors. However, a series of randomized trials has demonstrated a survival benefit of radiation plus chemotherapy (most trials used either procarbazine, lomustine [CCNU], and vincristine [PCV] or temozolomide) versus radiation alone in either grade II gliomas[51] or grade III oligodendrogliomas[52,53] and grade III astrocytoma.[54] Subset analyses of these studies have confirmed that the largest magnitude of benefit of combined radiation and chemotherapy in grade II and III diffuse

KEY POINTS

- **Bevacizumab is US Food and Drug Administration (FDA)-approved for recurrent glioblastoma based on improved progression-free survival in randomized studies, but this agent has not demonstrated an overall survival benefit in glioblastoma.**
- **In older patients with newly diagnosed glioblastoma, a hypofractionated course of radiation is a consideration with or without temozolomide or tumor treating fields.**

gliomas is observed in the *IDH*-mutant and chromosome 1p/19q-codeleted tumors (oligodendrogliomas) followed by the *IDH*-mutant and chromosome 1p/19q-intact (astrocytoma) tumors. The smallest benefit is observed in the *IDH*-wildtype grade II and III tumors.[54,55] In addition, randomized studies comparing chemotherapy alone (PCV[56] or temozolomide[57]) to radiation alone did not show a benefit of chemotherapy alone and showed some indication of worse survival in some subgroups. The interpretation of these studies is that, despite the goal of seeking to spare patients the toxicity of either radiation or chemotherapy when possible, data from randomized trials indicate that when the decision is made to initiate treatment for lower-grade gliomas, the treatment with the best data for prolonging survival is a combination of radiation and chemotherapy. In terms of which radiation and chemotherapy combination to use (radiation followed by PCV or radiation with concurrent temozolomide followed by adjuvant temozolomide), a subsequent randomized clinical trial potentially supports the use of radiation and temozolomide in tumors that are *IDH* mutated and 1p/19q intact,[54] although this study did not evaluate the relative benefit of PCV versus temozolomide in addition to radiation. For *IDH*-mutated and 1p/19q-deleted tumors, some retrospective analyses suggested a better outcome with PCV compared with temozolomide but at the cost of higher toxicity with PCV.[58] The relative outcome of radiation plus PCV versus radiation and temozolomide in grade III *IDH*-mutated and 1p/19q-codeleted tumors is the central question being tested in the ongoing CODEL (Phase III Intergroup Study of Radiotherapy With Concomitant and Adjuvant Temozolomide Versus Radiotherapy With Adjuvant PCV Chemotherapy in Patients With 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma) trial (NCT00887146), but results of that trial are not expected for years.

FUTURE DIRECTIONS AND CLINICAL TRIALS

While surgery, radiation, chemotherapy, and tumor treating fields represent the standard and FDA-approved therapies for adult gliomas, the overall clinical benefit of these approaches is modest at best in the majority of patients with higher-grade tumors. As a result, the neuro-oncology field has continued to evaluate a wide variety of treatment options in the setting of clinical trials to identify more effective therapies for selected subgroups of patients.

Targeted Therapy

One of the modern breakthroughs in oncology was the identification of multiple genomic alterations that drive tumor initiation or maintenance, rendering such tumors to functional blockade by drugs that target the mutant protein or kinase or one of its downstream effectors. Examples of such targetable alterations in oncology are numerous but began with ones such as *BCR-ABL* fusions (in chronic myelogenous leukemia), *HER2* amplification (in breast cancer), and *EGFR* mutations (in lung cancer). There are several potentially targetable alterations observed in different subtypes of lower-grade glioma and glioblastoma. In *IDH*-mutant tumors, the *IDH* mutation itself has been a potential target with a number of drugs developed to inhibit the neomorphic function of the mutant *IDH* enzyme to block the production of 2-hydroxyglutarate. Two of these *IDH* inhibitors are FDA approved in acute myeloid leukemia with

IDH mutation, and other *IDH* inhibitors are in development. To date, the evidence of efficacy for *IDH*-mutant gliomas with these drugs is that they can alter the growth rate and result in stabilization of disease in a subset of patients with glioma with *IDH*-mutant tumors, but no drug has received FDA approval for gliomas. In glioblastoma and *IDH*-wildtype lower-grade gliomas, potential druggable targets include *EGFR* amplification and mutation (EGFRvIII), which are observed at higher frequencies, as well as other alterations that are seen at lower frequencies including *FGFR* gene fusions, *NTRK* gene fusions, and *BRAF* mutations and fusions. For *NTRK* and *BRAF* mutations and fusions, drugs that are FDA approved in other tumor types have potential efficacy in glioma. Case reports and small series suggest clinical benefit of specific *FGFR*, *BRAF*, and *NTRK* inhibitors, but the rarity of these alterations in glioblastoma has complicated attempts at larger studies to verify activity in this tumor type. In the case of inhibitors of the *BRAF* V600E mutation, initial data from a larger basket-type trial of multiple histologies, unfortunately, suggest that the activity of one drug, vemurafenib, may be less in higher-grade gliomas harboring this mutation than in other tumor types.[20] Multiple attempts to target *EGFR* alterations have been made with targeted tyrosine kinase inhibitors, vaccines, and *EGFR*-specific antibodies, but in all cases, the phase 3 studies of these drugs or vaccines have not demonstrated any survival benefit. Despite these disappointments, development continues on other approaches including newer kinase inhibitors, bifunctional antibodies, as well as chimeric antigen receptor (CAR) T cells engineered to target EGFRvIII mutation and other glioblastoma alterations.

Another breakthrough in oncology was the demonstration in multiple tumor types that drugs that modulate the immune response can have significant clinical efficacy. In some cases, these immunotherapy agents are possibly curative in subsets of patients who were previously incurable. Most of the currently FDA-approved immunotherapy agents are humanized monoclonal antibodies that act by blocking cell surface signaling proteins that inhibit activation of immune responses against tumor cells and/or tumor neoantigens. Several phase 2 and 3 studies have tested the activity of immune checkpoint inhibitors in newly diagnosed and recurrent glioblastoma. To date, all studies of single-agent checkpoint inhibitors in glioblastoma have been negative for a survival benefit. A small randomized phase 2 study of the checkpoint inhibitor pembrolizumab given before and after surgery for recurrent glioblastoma was the first to demonstrate a potential survival benefit in glioblastoma.[59] The fact that the benefit was observed in combination with surgery raises the hope that immunotherapy can be used successfully in the treatment of glioblastoma but also suggests that additional factors beyond the presence of a checkpoint inhibitor alone are necessary for efficacy in glioblastoma (in contrast to other solid tumors). However, the benefit of surgery plus pembrolizumab in a limited number of patients requires validation in larger studies.

KEY POINT

- **The combination of radiation and chemotherapy (either procarbazine, lomustine [CCNU], and vincristine [PCV] or temozolomide) has been proven more effective for prolonging survival than radiation alone in lower-grade diffuse gliomas with *IDH* mutation.**

Clinical Trials

To date, the only treatments that have demonstrated a survival benefit in diffuse gliomas and glioblastoma are radiation, cytotoxic chemotherapy, and tumor treating fields. Despite the growing evidence and information regarding genomic and epigenetic alterations that define molecular subgroups of glioma, no FDA-approved drug targeting a specific mutation or molecular alteration (beyond bevacizumab), or any immunomodulatory drug is FDA approved

KEY POINT

● **Participation in a clinical trial is an important consideration in the treatment of all histologies, grades, and molecular subtypes of glioma.**

specifically for gliomas. This situation highlights the need to increase enrollment of all histologies and grades of gliomas in clinical trials. In the current National Comprehensive Cancer Network guidelines, clinical trial enrollment is the preferred option for the treatment of both newly diagnosed and recurrent glioma for eligible patients.[33]

CONCLUSION

Adult gliomas represent a clinically and molecularly heterogeneous group of tumors. An understanding of the differences in presentation, diagnosis, and treatment is important for neurologists. The recent advances in the understanding of molecular subtypes of tumors have led to a dramatic revision of the approach to the diagnosis and treatment of adult gliomas. Much of this new knowledge is described in the 2016 World Health Organization Classification of Tumors of the Central Nervous System, although this field continues to evolve rapidly, and some diagnostic entities, such as the diagnosis of diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade IV, remain consensus recommendations and will presumably be incorporated into future WHO classifications. Despite the dramatic advances in the biologic understanding and classification of adult gliomas, the majority of these tumors remain incurable with standard approaches of surgery, radiation, chemotherapy, and tumor treating fields, and efforts aimed at the development and testing of new therapies for specific glioma subtypes in clinical trials are ongoing.

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DISCLOSURE

Continued from page 1452

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