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REVIEW ARTICLE

Diffuse Infiltrating Oligodendroglioma and Astrocytoma

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ABSTRACT

The new 2016 WHO brain tumor classification defines different diffuse gliomas primarily according to the presence or absence of *IDH* mutations (*IDH*-mt) and combined 1p/19q loss. Today, the diagnosis of anaplastic oligodendroglioma requires the presence of both *IDH*-mt and 1p/19q codeletion, whereas anaplastic astrocytoma is divided into *IDH* wild-type (*IDH*-wt) and *IDH*-mt tumors. *IDH*-mt tumors have a more favorable prognosis, and tumors with low-grade histology especially tend evolve slowly. *IDH*-wt tumors are not a homogeneous entity and warrant further molecular testing because some have glioblastoma-like molecular features with poor clinical outcome. Treatment consists of a resection that should be as extensive as safely possible, radiotherapy, and chemotherapy. Trials of patients with newly diagnosed grade II or III glioma have shown survival benefit from adding chemotherapy to radiotherapy compared with initial treatment using radiotherapy alone. Both temozolomide and the combination of procarbazine, lomustine, and vincristine provide survival benefit. In contrast, trials that compare single modality treatment of chemotherapy alone with radiotherapy alone did not observe survival differences. Currently, for patients with grade II or III gliomas who require postsurgical treatment, the preferred treatment consists of a combination of radiotherapy and chemotherapy. Low-grade gliomas with favorable characteristics are slow-growing tumors. When deciding on the timing of postsurgical treatment with radiotherapy and chemotherapy, both clinical and molecular factors should be taken into account, but a more conservative approach can be considered initially in some of these patients. The factor that best predicts benefit of chemotherapy in grade II and III glioma remains to be established.

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INTRODUCTION

Diffuse grade II and III gliomas traditionally have been separated morphologically into two basic subtypes: oligodendroglioma and astrocytoma, with a third mixed category of oligoastrocytoma for those cases in which tumor morphology showed characteristics of both. The WHO 2016 edition of the classification of glioma has radically changed this, and glioma diagnosis is now primarily based on molecular characteristics.[1] Thus, the diagnosis of an anaplastic oligodendroglioma now requires the presence of both 1p/19q codeletion and mutation of isocitrate dehydrogenase 1 or 2 (*IDH1*-mt or *IDH2*-mt). Anaplastic astrocytoma has both *IDH*-mt and *IDH* wild-type (*IDH*-wt) variants. This new classification of diffuse gliomas is more robust and far more informative for treatment outcome than the classic morphologic approach, but it requires clinicians to digest this new reality and to rethink their approach to diagnostics and treatment of these tumors. This review summarizes the currently available clinical data for astrocytoma and oligodendroglioma from the perspective of the new WHO 2016 brain tumor classification.

CLINICAL PRESENTATION

Each year, in the United States, 4,500 to 5,000 patients are newly diagnosed with a grade II or III astrocytoma or oligodendroglioma.[2] Typically, patients with low-grade gliomas present between 25 and 45 years of age, whereas patients with anaplastic tumors tend to be slightly older. Astrocytoma with *IDH*-mt is occasionally diagnosed in adolescents (even younger than age 15 years) whereas some 1p/19q co-deleted *IDH*-mt oligodendrogliomas are first diagnosed in patients older than age 65 years. The likelihood of finding an *IDH* mutation in low-grade and anaplastic diffuse gliomas decreases with increasing age. The clinical presentation of brain tumors depends on tumor localization and growth rate. Most low-grade and anaplastic tumors present with seizures; early focal deficits are less common in these tumors. Most cases of low-grade glioma tend to

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be slow-growing lesions, with an annual growth rate (if left untreated) of 4 to 6 mm per year.[3] Well-known clinical prognostic factors include age and performance status of the patient, size of the tumor, and frontal location.[4,5]

Diagnosis According to the WHO 2016 Classification

Before the 2016 update of the WHO classification for brain tumors, histology was the gold standard for diagnosis.[6] However, the usefulness of this classification was limited because of major inter- and intraobserver variability, and the heterogeneous clinical outcome among similar histologically diagnosed tumors.[7] Several developments have shifted the focus for glioma classification from histology to genetics. In 2008, a large-scale genetic analysis of a series of glioblastomas revealed mutations in the gene encoding for *IDH1* or *IDH2* that subsequently proved to be present in 70% to 80% of grade II or III gliomas.[8] Tumors with these mutations are associated with an improved survival compared with histologically similar tumors without the mutations.[8-10] IDH mutations represent early stable mutations and seem to be a driving mutation in diffuse glioma. All mutations in *IDH1* and *IDH2* are somatic, missense, and heterozygous, and they affect codon 132 (*IDH1*) or codon 172 (*IDH2*). Ninety percent of all *IDH* mutations concern the *IDH1* R132H position for which a sensitive and reliable immunohistochemistry assay is available. If immunohistochemistry is used for *IDH* mutation analysis, then negative cases should have follow-up sequencing of both *IDH1* and *IDH2*.

The grading of diffuse glioma is based on the presence or absence of certain characteristics such as nuclear atypia, high cellularity, presence of mitosis, endothelial proliferation, and necrosis. The clinical significance of grading of the diffuse gliomas within the WHO 2016 classification needs to be re-evaluated: grading of *IDH*-mt tumors seems clinically less relevant compared with grading of *IDH*-wt tumors.[11,12] The mutation induces an altered substrate affinity of the enzyme resulting in increased levels of 2-hydroxyglutarate and decreased levels of α-ketoglutarate and NADPH.[13] One of the consequences of the mutation is the development of a global methylation of CpG islands (often including the *MGMT* promoter).[13,14] This may in part explain the chemotherapy sensitivity of *IDH*-mt tumors. Another explanation is that some resistance mechanisms against alkylating chemotherapy are correlated with levels of α-ketoglutarate.[15] Similarly, decreased NADPH production by *IDH*-mt cells have been correlated with increased sensitivity to radiotherapy.[16]

Previously, genetic analysis demonstrated combined loss of 1p/19q as the most typical lesion for anaplastic oligodendroglioma, which was subsequently linked to improved responsiveness to procarbazine, lomustine, and vincristine (PCV) and temozolomide chemotherapy.[17-19] The 1p/19q co-deletion is an early event that typically remains present at the time of further progression. However, the current data indicate that 1p/19q co-deletion develops in tumors that have already accumulated an IDH mutation.[20] The 1p/19q co-deletion represents a balanced t(1;19)(q10;p10) translocation in which both the entire 1p and 19q arm are lost.[21] Ideally, the diagnostics for 1p and 19q should therefore cover the entire length of these chromosomal arms. Fluorescent in situ hybridization assays typically assess loss only at the ends of these chromosomal arms.[22]

Several clinical studies have now shown the superior prognostic and predictive significance of a molecular glioma classification based primarily on 1p/19q status and IDH mutations.[20,23,24] As a consequence, these two genetic lesions are now at the core of astrocytoma and oligodendroglioma diagnostics (Table 1).[1,25] Irrespective of the histologic findings, the presence of combined 1p/19q loss and an IDH mutation results in the diagnosis of an oligodendroglioma; the presence of an *IDH* mutation in the absence of a 1p/19q co-deletion results in the diagnosis of astrocytoma (Fig 1). The term "not otherwise specified" is used only for those gliomas in which molecular testing was not possible or was inconclusive. As a consequence of this change, the category of mixed oligoastrocytoma has ceased to exist.[26] Clearly, conclusions of published series of glioma need to be re-examined in the light of the shifts that are brought about by the new WHO classification. Table 2 summarizes overall survival (OS) and progression-free survival (PFS) observed in the molecular strata that reflect the WHO 2016 classification in recently reported prospective trials on diffuse grade II and III gliomas.

Other Mutations and IDH-*wt Tumors*

Ninety-five percent of *IDH*-mt astrocytomas show a *TP53* mutation, and 70% to 90% have inactivating alterations of *ATRX*. Fifty percent to 70% of *IDH*-mt 1p/19 co-deleted tumors have inactivating mutations of *CIC*, and 15% to 30% of tumors have mutations in *FUBP*, which is located on 1p.[33] 1p/19q co-deleted tumors typically also have mutations in the *TERT* promoter (*TERTp)* region, which are mutually exclusive with *ATRX* mutations often found in *IDH*-mt astrocytoma. *IDH*-wt astrocytomas are heterogeneous and merit further molecular testing. In

Table 1. The WHO 2016 Classification for Astrocytoma and Oligodendroglioma and ICD-10 Code

Diffuse Astrocytoma or Oligodendroglioma Molecular Subgroup	ICD-10 Code
Diffuse astrocytoma	9411/3
Gemistocytic astrocytoma	
IDH-mt	9400/3
Diffuse astrocytoma	
IDH-wt	9400/3
NOS	9400/3
Anaplastic astrocytoma	
IDH-mt	9401/3
IDH-wt	9401/3
NOS	9401/3
Diffuse midline glioma	
H3 K27M-mt	9385/3
Oligodendroglioma	
IDH-mt and 1p/19q co-deleted	9450/3
NOS	9450/3
Anaplastic oligodendroglioma	
IDH-mt and 1p/19q co-deleted	9451/3
NOS	9451/3
Oligoastrocytoma	
NOS	9382/3
Anaplastic oligoastrocytoma	
NOS	9382/3

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; mt, mutant; NOS, not otherwise specified; wt, wild-type.

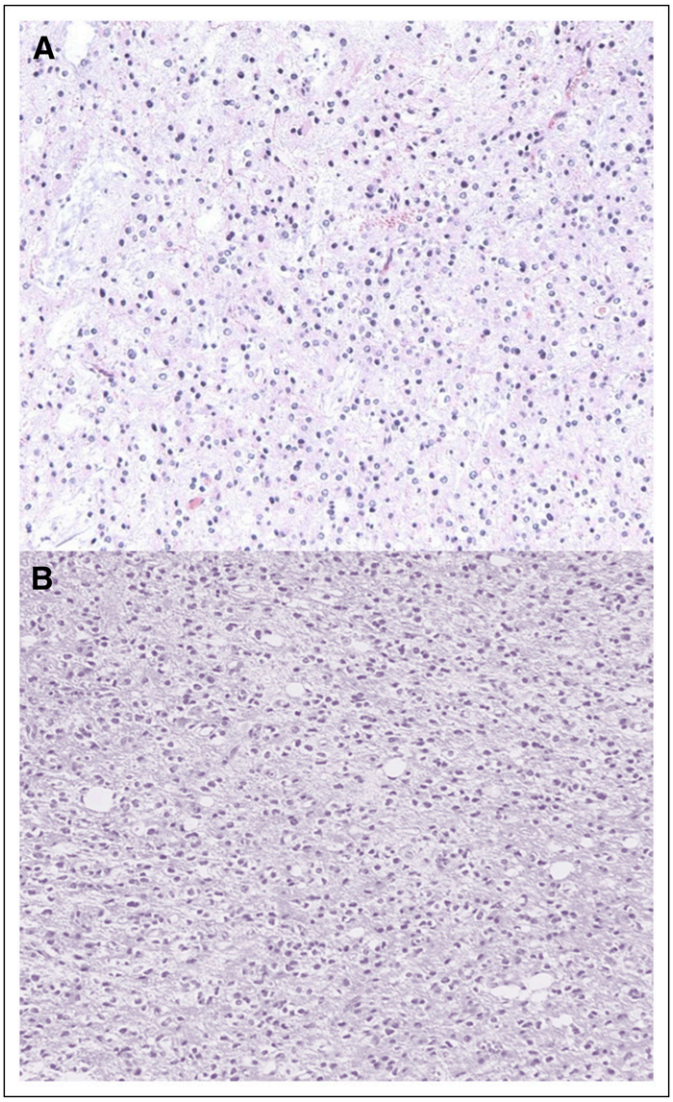

Fig 1. (A) Diffuse glioma showing histologic traits of oligodendroglioma. Molecular analysis revealed IDH1 mutation without 1p/19q co-deletion but with mutations in TP53 and ATRX, resulting in a diagnosis of astrocytoma *IDH*-mt. (B) Diffuse glioma that received the histologic diagnosis of mixed oligoastrocytoma. Molecular analysis yielded IDH1 mutation and 1p/19q co-deletion leading to the integrated diagnosis of oligodendroglioma *IDH*-mt and 1p/19q co-deleted.

particular, *IDH*-wt astrocytomas often show mutations in the *EGFR* and *PTEN* gene, and those that show polysomy of chromosome 7, loss of heterozygosity of chromosome 10q, and *TERTp* mutations are likely to behave like glioblastoma.[20,34-36] Subsets of *IDH*-wt astrocytomas may have other mutations such as BRAF or mutations in the histone *H3F3A* and *HIST1H3B* genes which are observed in clinically aggressive midline lesions (pontine, thalamic glioma) of adolescents and young adults. Thus, *IDH*-wt gliomas are not a single entity.

Imaging of Diffuse Grade II and III Gliomas

In general, *IDH*-mt tumors tend to be more often located in the frontal lobes.[37,38] Both oligodendroglioma and astrocytoma have low density on nonenhanced computed tomography, low signal intensity on T1-weighted and high signal intensity on T2-weighted magnetic resonance imaging (MRI). The hallmark features of oligodendroglioma are the presence of calcification, a cortical-subcortical location, heterogeneous signal intensity on T2-weighted MRI scans, and an indistinct border (Fig 2A). Coarse calcifications, which may be poorly visible on MRI scans and are best appreciated on nonenhanced computed tomography, are seen in up to 90% of patients. In contrast, astrocytomas typically do not calcify, do not involve the cortex, have homogeneous signal intensity on T2-weighted MRI scans, and commonly have a distinct border (Fig 2B).[39] After contrast administration, astrocytomas do not show enhancement, whereas minimal to moderate patchy, multifocal enhancement with a dot-like or lacy pattern is reported in up to 50% of tumors in patients with oligodendroglioma. This makes differentiation from anaplastic oligodendroglioma challenging: contrast enhancement is typically considered a feature of high-grade tumors, but it has only 63% sensitivity and 50% specificity in differentiating high- from low-grade oligodendroglioma.[40] In anaplastic astrocytoma, contrast enhancement is not usually seen, and if it is present, it has a patchy, focal, or nodular appearance (as opposed to glioblastoma, in which contrast enhancement is extensive, intense, and commonly ring-like). Perfusion MRI scans have reported high accuracy ($>$ 90%) in distinguishing high-grade from low-grade astrocytoma, with relative tumor blood volume being increased in high-grade astrocytoma.[41] In oligodendroglioma, perfusion is commonly moderately increased, again not adding to the differentiation from high-grade tumors. New enhancement in a previously nonenhanced untreated tumor is suggestive of malignant transformation as is a high growth rate of the mean tumor diameter.[42] MR spectroscopy may be helpful in grading oligodendroglioma, but it is inferior to MR perfusion imaging for grading astrocytoma.[43]

Treatment

Treatment via surgery in diffuse glioma has several objectives: obtaining tissue for diagnosis, improving the quality of life (relief of focal deficits, better seizure control), and increasing survival. The decision for surgery has to be made by taking into account risks and potential benefits and should not be delayed in clearly enhancing tumors because they are likely to behave more aggressively.[44] The role of early surgery or biopsy in nonenhancing and presumably low-grade glioma remains incompletely understood, in particular for incidentally discovered or relatively small lesions. To date, there have been no randomized controlled trials regarding the benefit of extensive surgery; all data on survival benefit after more extensive resections have been obtained in uncontrolled series that typically show the best outcome in patients with no or almost no residual disease after surgery.[5,45] However, the biases of these series as a result of patient selection are difficult to assess. A retrospective series from two geographically distinct centers in Norway reported better survival in the center that advocated early extensive surgery compared with biopsy only, but the patient characteristics of that series do not reflect those of patients with favorable low-grade glioma.[46] With the many series showing good survival after near total resection, it has become common practice to operate early on suspected and well-defined low-grade glioma-like lesions if an extensive resection is deemed safe and feasible. Intraoperative monitoring may allow a more extensive resection without

Table 2. Median Survival Regardless of Assigned Treatment in the Three Major Groups (*IDH*-wt, *IDH*-mt, and 1p/19q co-deleted) in Various Prospective Trials and Retrospective Molecular Analysis

Histology/Molecular Subgroup	First Author	Treatment	No. of Patients	Median PFS (years)	Median OS (years)
Low-grade glioma	Buckner[27]	Radiotherapy with or without PCV			
IDH R132H-mt			71		13.1
IDH-wt			42		5.1
Low-grade glioma	Baumert[28]	Radiotherapy or temozolomide			
IDH-mt 1p/19q co-deletion			104	5.2	NS
IDH-mt			165	4	NS
IDH-wt			49	1.7	NS
Anaplastic astrocytoma	Chang[29]	Radiotherapy with either temozolomide or either lomustine or carmustine			
IDH R132H-mt			49		7.9
IDH-wt			54		2.8
Anaplastic oligodendroglioma*	Dubbink[23]	Radiotherapy with or without PCV			
IDH-mt 1p/19q co-deleted			49		9.5
IDH-mt			20		3.1
IDH-wt			55		1.1
Anaplastic oligodendroglioma	Cairncross[30]	Radiotherapy with PCV			
IDH-mt 1p/19q co-deleted			42		14.7
IDH-mt			37		5.5
IDH-wt			26		1.3
Anaplastic glioma	Wick[31]; Wick[32]	Radiotherapy or chemotherapy with either temozolomide or PCV			
IDH-mt, 1p/19q co-deleted			69	7.5-8.7	NR
IDH-mt			83	2.1-3.0	7.0-7.3
IDH-wt			58	0.8	3.1-4.7

Abbreviations: mt, mutant; NR, not reported; NS, not significant; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PFS, progression-free survival; wt, wild-type.
*NGS data on a subset of patients.

increased morbidity, especially in tumors in eloquent areas.[47] In a prospective study of patients with favorable-prognosis low-grade glioma, residual disease, astrocytic histology, and preoperative tumor size were prognostic factors for PFS.[48] Studies of grade III glioma with radiologic confirmation of the extent of resection confirm the major impact of resection on outcome, which may be clinically even more relevant for *IDH*-mt tumors without co-deleted 1p/19q.[5,49]

Radiotherapy

Three trials have investigated the dosage and timing of involved field radiotherapy in histologically defined low-grade glioma. Trials on the dosage of radiotherapy found no survival difference between 45 Gy and 59.4 Gy and between 54 Gy and 65 Gy, with lower doses tending to be less toxic.[50,51] Current trials in low-grade glioma use 50.4 Gy in 28 fractions as a rule. Another trial observed no difference in OS between early and delayed radiotherapy, but a clear increase in PFS suggests that the timing is of less relevance as long as radiotherapy is given.[52] Separate randomized trials on the role and dosage of radiotherapy in grade III glioma have not been performed. It has become standard practice to treat anaplastic gliomas with 33 fractions of 1.8 Gy. With more advanced radiation techniques (eg, proton therapy), the damage to structures at risk can be minimized, but whether that will improve outcome in terms of fewer delayed toxicities with equal survival remains to be demonstrated in clinical trials.[53]

Chemotherapy

Chemotherapy sensitivity of grade II and III gliomas was initially established in trials on recurrent anaplastic oligodendroglioma and astrocytoma, which documented sensitivity to the PCV combination regimen and to temozolomide.[19,54-57] These trials showed more frequent and durable responses in oligodendroglioma (in particular in those with combined 1p/19q loss) compared with astrocytoma. Several randomized controlled trials have established the efficacy of chemotherapy in nearly all subtypes of newly diagnosed grade II and III glioma. Table 3 summarizes the hazard ratios observed in these trials. Four trials investigated adjuvant chemotherapy in addition to radiotherapy. Three used histologic criteria for eligibility and investigated PCV: two in anaplastic oligodendroglioma[58,59] and one in low-grade glioma.[27] The fourth trial investigated concurrent and adjuvant temozolomide in anaplastic glioma in which there was no co-deleted 1p/19.[60,61] These trials showed improved outcome with the addition of chemotherapy to radiotherapy, despite high crossover rates (56% to 79%) at the time of progression in the patients treated with radiotherapy only.[27,58,59,61] Both trials of PCV chemotherapy in anaplastic oligodendroglioma showed improved benefit with the addition of PCV to radiotherapy in patients with 1p/19q co-deleted tumors.[30,62] Within these trials, three intrinsically related candidate predictive markers for benefit from adjuvant PCV have been suggested: *IDH* mutational status, CpG island methylated phenotype, and *MGMT* promoter methylation. Analysis of one study suggested that *MGMT* promoter methylation assessed by a genomic-wide methylation assay was the best predictor for benefit of chemotherapy, whereas another study identified IDH mutational status as a predictive factor.[30,62]

Two trials compared chemotherapy with radiotherapy: temozolomide or PCV versus radiotherapy in the German trial on anaplastic glioma and temozolomide versus radiotherapy in low-grade glioma.[28,31] Both trials failed to show improvement in

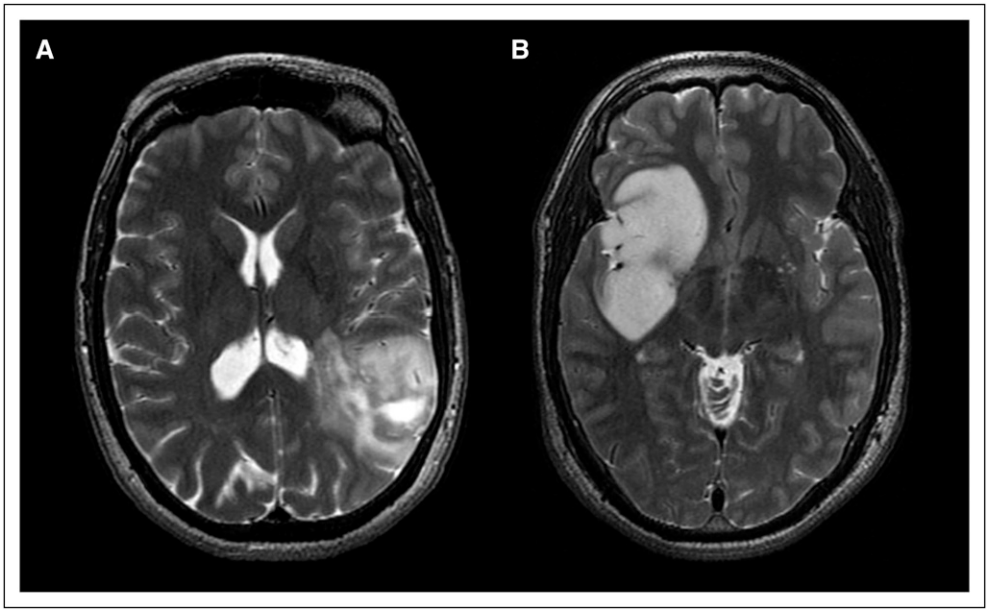

Fig 2. Typical axial T2-weighted magnetic resonance (MR) images of (A) an *IDH*-mt and 1p/19q co-deleted oligodendroglioma, and (B) an *IDH*-mt astrocytoma. Note the heterogeneous signal intensity, cortical involvement, and indistinct border of the oligodendroglioma. In contrast, there is homogeneous signal intensity, a sharp border, and no involvement of the cortex in the astrocytoma.

outcome after initial management with chemotherapy alone (and with the suggestion of decreased survival after initial chemotherapy in some molecular strata).[28,31] In the absence of the results of a trial that formally compared chemotherapy alone with chemotherapy and radiotherapy combined, it seems safe to conclude that combination therapy improves survival compared with single modality treatment (initial treatment with either radiotherapy alone or chemotherapy alone). One argument in favor of chemotherapy alone is that it may avoid or delay radiotherapy-induced delayed cognitive effects, but it should be realized that this strategy could jeopardize survival. Although better tolerated, the use of temozolomide has been associated with the development of a hypermutated tumor phenotype at relapse through temozolomide-induced mutations of the mismatch repair pathway genes.[63] Although this reflects resistance to temozolomide, from a patient management perspective, the DNA pattern at progression is less relevant than the duration of treatment response and OS.

Nitrosourea-Based Regimens or Temozolomide?

Survival improvement in newly diagnosed grade II or III tumors was initially demonstrated in trials that investigated adjuvant PCV chemotherapy. Regarding the results of the CATNON (Phase III Trial of Anaplastic Glioma Without 1p/19q LOH; NCT00626990) trial, the use of temozolomide seems at least warranted for both grade II and III tumors without co-deleted 1p/19q. Another trial on anaplastic astrocytoma compared radiation and temozolomide with radiation and adjuvant carmustine or lomustine; it showed no survival difference between the two treatment arms but significantly more myelosuppression in the patients treated with nitrosourea, which led to frequent early discontinuation of treatment.[24] There are retrospective reports and subgroup analyses of larger studies that suggest a better outcome after PCV treatment compared with temozolomide treatment in 1p/19q co-deleted tumors.[31,64,65] The ongoing CODEL (NCT00887146; Radiation Therapy With Concomitant and Adjuvant Temozolomide Versus Radiation Therapy With Adjuvant PCV Chemotherapy in Patients With Anaplastic Glioma or Low Grade Glioma) trial in 1p/19q co-deleted grade II or III tumors will answer this question, but finding the answer will take many years.

Postsurgical Treatment: Timing of Treatment

Because of the potential (delayed) adverse effects of surgery and radiotherapy, a wait-and-see policy has been advocated in patients with presumed low-grade glioma who have expected favorable prognosis and in those who have had an extensive resection. Data are limited on the incidence of delayed toxicities and in particular on the development of cognitive decline after radiotherapy in the absence of tumor progression. In randomized studies, assessment with the mini-mental status examination did not reveal a significant decline in patients with low-grade glioma who were treated with radiotherapy nor a difference between patients treated with radiotherapy and those treated with chemotherapy, but this instrument has limited sensitivity.[66,67] After a mean follow-up of 12 years, a pivotal study in long-term survivors of low-grade glioma showed stable radiologic and cognitive status in patients who did not have radiotherapy, whereas those who received radiotherapy showed a progressive decline in attentional functioning, even those who received fraction doses that are regarded as safe ($\leq$ 2 Gy).[68] A cohort study on long-term survivors of the EORTC 26951 trial[59] on the addition of PCV to radiotherapy in anaplastic oligodendroglioma showed that of progression-free patients, 26% were not severely cognitively impaired and 30% were; 41% were employed and 81% were able to live independently.[69] Of note, cognitive complications are primarily relevant for patients who actually achieve long-term survivorship; the few patients whose disease had progressed during follow-up seemed to be doing worse compared with patients without progression. These data on cognitive deficits in

Table 3. HRs and 95% CIs Observed in Recently Reported Trials of Grade II and III Glioma

Histology	First Author	Trial Question	No. of Patients	OS	
				HR	95% CI
Anaplastic oligodendroglioma	van den Bent[59]	Radiotherapy/PCV *v* radiotherapy	368	0.75	0.60 to 0.95
Anaplastic oligodendroglioma	Cairncross[58]	Radiotherapy/PCV-i *v* radiotherapy	291	0.79	0.60 to 1.04
Low-grade glioma	Buckner[27]	Radiotherapy/PCV *v* radiotherapy	251	0.59	0.42 to 0.83
Anaplastic astrocytoma	Hildebrand[60]	Radiotherapy/carmustine + dibromdulcitol *v* radiotherapy	193	0.77	0.56 to 1.06
Anaplastic glioma, 1p/19q intact	van den Bent[61]	Radiotherapy *v* radiotherapy/ temozolomide	745	0.65*	0.45 to 0.93
Anaplastic glioma	Wick[31]	Temozolomide or PCV *v* radiotherapy	318	1.11	0.8 to 1.55
Low-grade glioma†	Baumert[28]	Radiotherapy *v* temozolomide	447	1.16	0.9 to 1.5
Anaplastic astrocytoma	Chang[29]	Radiotherapy/temozolomide *v* radiotherapy/lomustine or carmustine	197	0.94	0.67 to 1.32

Abbreviations: HR, hazard ratio; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PCV-i, PCV intensified.
*99.145% CI.
†Primary end point, progression-free survival.

long-term survivors have been used as an argument to postpone radiotherapy and treat initially with chemotherapy only; however, the current randomized trial data indicate that chemotherapy alone may jeopardize survival, and tumor growth may also affect cognitive functioning.

Because the pivotal PCV trial in low-grade glioma used incomplete resections and/or age older than 40 years as inclusion criteria, it is now frequently assumed that these are the decisive factors for starting adjuvant treatment in patients with low-grade glioma.[27] However, these inclusion criteria have a limited clinical rationale and are not based on treatment sensitivity.[70] There is no clinical justification for a strict age cutoff, and other prognostic factors should be considered when deciding on adjuvant treatment. Delaying postoperative treatment is particularly attractive if prognostic factors indicate that a delay of progression for several years is likely. Uncontrolled seizures are a reason for not delaying postoperative treatment, because both chemotherapy and radiotherapy may improve seizure control.[52,71] The use of antiepileptic drugs is associated with decreased cognitive functioning, and lowering the dosage once better seizure control is achieved may improve cognitive functioning and will reduce other adverse effects.[68]

Future Perspectives

Current research approaches include the development of personalized therapies that target the metabolic and cytogenetic characteristics of astrocytic and oligodendroglial tumors. The PI3K/Akt/mTOR pathway regulates cellular proliferation and is frequently activated in low-grade gliomas, and ongoing trials are evaluating everolimus (an inhibitor of mTOR) in high-risk low-grade glioma.[72] Other strategies target the mutated IDH complex using IDH inhibitors.[73] Combining these agents with other treatment modalities may be complicated, because in vitro studies suggest the metabolic changes induced by IDH mutations may sensitize cells for radiotherapy and chemotherapy.[15,16] Different approaches to targeting the immune system are being evaluated in early-phase trials in grade II glioma. One approach is vaccine therapies targeting the IDH mutation, and other approaches are peptide vaccines such as GBM6-AD-poly-ICLC and vaccines created from autologous dendritic cells pulsed with autologous tumor lysate.[74]

CONCLUSION AND TREATMENT RECOMMENDATIONS

The diagnosis of diffuse grade II or III glioma is now based on molecular characteristics. Patients with *IDH*-mt grade II or III glioma have a more favorable prognosis, especially in the presence of 1p/19q co-deletion. *IDH*-wt gliomas are a heterogeneous group of tumors, many of which have a glioblastoma-like molecular profile and clinical outcome and which typically affect older patients.

Early resection, if safely possible, is currently considered standard of care in presumed low-grade gliomas, but the role of a biopsy is unclear in patients who are assumed to have a favorable prognosis (young patients with well-controlled seizures only, in the absence of a large lesion) if no extensive resection is safely possible and a wait-and-see policy appears justified. An alternative approach is then to wait until tumor growth has been documented. If a patient with a favorable prognosis who has a grade II IDH-mt tumor has undergone an extensive resection, further treatment can be postponed until tumor growth is documented. Definitive guidelines on what amount of growth is sufficient to initiate further treatment are not available and should be decided on a case-by-case basis; repeat surgery should also be considered at that time.

Combined chemoradiation with temozolomide should be considered in IDH-wt grade II or III glioma. The optimal postsurgical treatment of patients with grade II or III IDH-mt glioma consists of a combination of radiotherapy and chemotherapy. For patients with IDH-mt tumors without co-deleted 1p/19q, the evidence for using temozolomide is now established. Whether PCV is indeed the regimen of choice for patients with 1p/19q co-deleted tumors remains a matter of debate. Treatment with chemotherapy only should be limited to those patients for whom radiotherapy implies a large treatment volume and thus increased risk of delayed cognitive effects of treatment. The potential for decreased survival with this approach should be discussed with the patient. Finally,

offering these patients access to a rehabilitation program is important. With longer survival in the majority of patients, many will suffer from some level of cognitive dysfunction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Diffuse Infiltrating Oligodendroglioma and Astrocytoma

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