LOW-GRADE GLIOMAS: A DEFINITION IN TRANSITION

**IDH1 Mutant Low-Grade Gliomas**

For the purpose of this article, low-grade gliomas refers exclusively to World Health Organization (WHO) grade II diffuse astrocytic and oligodendroglial tumors (Table 1). These tumors are homogeneous in terms of bearing the hallmark IDH1/2 mutations and yet have striking variation in the propensity for malignant transformation. As summarized in detail elsewhere in this issue, WHO grade II astrocytomas are characterized by IDH gain-of-function mutations and loss of TP53 and ATRX. The median age of diagnosis is 36 years old, with a median survival of 10.9 years.1 WHO grade II oligodendrogliomas are genetically defined by IDH mutations, 1p/19q codeletions (frequently with FUBP1 or CIC mutations), and activating TERT promoter mutations. The median age of diagnosis for this tumor is older (age 43 years)2 with a median survival of 17.1 years.3 Grade II oligoastrocytomas, a categorization treated by the WHO 2016 as more reflective of inadequate molecular testing, traditionally have been thought to have a survival intermediate between astrocytomas and oligodendrogliomas.

For both low-grade glioma lineages, the diagnostic IDH1 neomorphic mutation generates the oncometabolite 2-HG, leading to dysregulation of histone lysine demethylase and ultimately global hypermethylation of CpG islands (G-CIMP).4,5 The mechanism of malignant progression in IDH1 mutant low-grade gliomas is an area of intensive study. An integrated genomic approach, including sequencing, copy number, expression, and DNA methylation data from patient-matched low-grade and progressed IDH1 mutant gliomas, revealed...
activation of Myc signaling, RTK-RAS-PI3K signaling, alterations in CDKN2A-CDKN2B, and increased methylation in embryonic targets of Polycomb repressive complex 2 (PRC2).6

**IDH1 Wild-Type Low-Grade Gliomas**

The subgroup of *IDH1* wild-type diffuse glioma is treated as transitional by the WHO 2016 and recent studies reveal heterogeneity in the survival of patients with histologically low-grade diffuse astrocytomas but no detectable *IDH1/2* mutations.7–9 Molecularly, the majority of tumors in this group resemble glioblastoma despite a low-grade histologic appearance, although a smaller subset bear a genomic profile aligned with grade I astrocytomas (eg, pilocytic). In a study of 212 WHO grade II diffuse astrocytomas defined histologically, all 25 of the noncontrast enhancing, truly *IDH1/2* wild-type (by sequencing) tumors could be reclassified using a combination of sequencing, methylation profiling, and copy number profiling into glioblastoma multiforme, diffuse midline glioma with H3K27M mutation, pilocytic astrocytoma, or normal brain tissue.7 In this study, 0 of 25 *IDH1* wild-type, with a histologic appearance consistent with diffuse low-grade gliomas could not be reclassified into another tumor type. This finding is consistent with the findings of Poulen and colleagues,9 where a subset of the 31 “*IDH1 wt*” grade II astrocytomas had a median survival of 3.5 years, whereas others had a 5-year survival of 77%. Additional work by Albaidula and colleagues9 of 168 *IDH1* wt grade II and III gliomas demonstrated that these tumors could be grouped into molecularly high grade and molecularly low grade, irrespective of histologic grade, which bore molecular hallmarks characteristic of primary glioblastoma multiforme (molecularly high grade) or characteristic of pediatric diffuse low-grade gliomas (molecularly low grade), which tended to occur in younger adults and may reflect the true extension of pediatric low-grade gliomas.

**EXTENT OF RESECTION AND THE IMPACT ON SURVIVAL**

Any discussion regarding the impact of the extent of resection (EOR) on improving survival, malignant progression, and/or quality of life in patients with low-grade gliomas must begin with the acknowledgment that there are no randomized, controlled trials evaluating these clinical questions.10 Part of the challenge in combining studies from the available literature into metaanalyses includes variations in the precision of the classification and measurement of the degree of surgical resection. For example, the scale of resection is treated by some studies as binary (eg, resection
vs biopsy), whereas other studies use sophisticated MRI volumetrics characteristics based on fluid-attenuated inversion recovery to quantify the EOR, creating difficulties in direct comparisons between studies. Complicating this also is timing of surgical resection—a short-term “watch and wait” strategy followed by complete resection may not negatively impact survival compared with upfront complete resection, but the time of observation may be affected by the baseline aggressiveness of the tumor (eg, more aggressive tumors progress earlier and are resected earlier). Additionally, available studies are not uniform in terms of postoperative management; for example, EOR studies are not controlled for adjuvant chemotherapy or radiation therapy, both of which may affect survival, progression, and cognition. Furthermore, the new WHO diagnostics reclassify the very definition of WHO grade II gliomas, with oligodendrogliomas as defined by IDH1/1p-19q codeletions having intrinsically better survival compared with astrocytomas as defined by IDH1/ATRX/TP53 mutations (see Table 1). Previous studies lacking these molecular distinctions are fundamentally susceptible to sample bias, and there is no way to control and stratify for mutational underpinning in nonrandomized studies that have compared maximal EOR versus biopsy. Additionally, there is evidence that tumor size at the time of diagnosis portends a worse prognosis, regardless of the degree of resection achieved, and these tumors are also less likely to undergo true gross total resection (GTR) as a technical limitation.

With these caveats, several lines of evidence support maximal safe resection over biopsy alone or waiting for radiographic progression. In a study by Jakola and colleagues, the outcomes between 2 hospitals in Norway, one that tended to biopsy and then observe (71% of the time) and the other which tended to proceed with early resection (86% of the time), were compared. The hospital that tended to proceed with early resection had significantly better overall survival (OS) compared with the hospital that preferred biopsy and watchful waiting (P = .01), with expected 7-year survivals of 68% versus 44%, respectively. When considering tumors that underwent biopsy at the hospital where biopsy was preferred and compared with craniotomy at the hospital where craniotomy was preferred, the median survival was 5.8 years for the biopsy group, but the median survival was not reached at hospital B. This study was updated in 2017 to take into account the new WHO classification of low-grade glioma, at which point the median survival for the craniotomy group at hospital B was 14.4 years and the group treated at hospital B had better survival regardless of mutational profile. However, there are clear methodologic limitations to this study, including a lack of randomization and lack of data on the EOR, as well as a lack of data on postoperative treatment modalities (chemotherapy/radiation therapy).

In a study by Smith and colleagues, a series of 216 adult low-grade gliomas resected from 1989 to 2005 revealed that, after adjusting for age, Karnofsky Performance Score (KPS), tumor histology, and tumor location, tumors with at least 90% EOR (as defined by volumetric analysis of reduction of fluid-attenuated inversion recovery on postoperative MRI) had 5- and 8-year OS rates of 97% and 91%, respectively. In contrast, patients with less than 90% EOR had 5- and 8-year OS rates of 76% and 60%, respectively. As a caveat, the tumors that had greater than 90% resection tended to have a smaller preoperative volume, which may reflect differences in the underlying biology. Related to this, regardless of the EOR, tumors with a greater preoperative volume had statistically worse OS (hazard ratio, 4.442; P = .004) as well as worse progression-free survival (hazard ratio, 2.711; P < .001). Additionally, the subset of patients who received radiation therapy and/or chemotherapy after surgical resection (true for a subset of subtotally resected tumors) were combined in the analysis with the patients who did not.

A recent metaanalysis argued for a gradient of improved 5- and 10-year survival rates, with patients undergoing GTR having an improved survival compared with patients who underwent subtotal resection (STR), and patients with STR having an improved survival over patients who underwent biopsy alone. This analysis, which mainly combined retrospective studies published in 1990s, showed that the 5-year survival rate for patients with low-grade glioma was significantly higher in patients undergoing GTR compared with STR (odds ratio [OR], 3.90; 16 studies, 1328 cases) as well as to biopsy (OR, 5.43; 9 studies, 775 cases). A metaanalysis of 11 studies (1147 cases) showed that patients undergoing STR compared with biopsy had a significantly higher 5-year survival rates (OR, 1.75). This study also found that the 10-year survival rate for patients with low-grade glioma was higher in patients undergoing GTR compared with STR (OR, 7.91; 11 studies, 907 cases), GTR compared with biopsy (OR, 10.17; 5 studies, 186 cases), and STR compared with biopsy (OR, 2.21; 6 studies, 408 cases). Flaws associated with this analysis include the mix of adjuvant therapies that the patients underwent, as well as the nonstandardized definition of EOR between studies. For example, the majority of the included studies either did not specify how
EOR was determined or relied on the operative report or surgeon’s description instead of objective postoperative imaging characteristics. Additionally, the preoperative volume of the tumors were not considered, so there is possible confounding between the preoperative size of the tumors and the extent that was able to be resected (eg, the largest tumors were unable to undergo GTR and also had worse outcomes).

**SUPRATOTAL RESECTION**

A biopsy study of 101 stereotactic biopsies (64 within regions of radiographic abnormalities, 37 from outside the regions of radiographic abnormalities) from 16 patients for diffuse low-grade oligodendrogliomas revealed isolated tumor cells up to 20 mm beyond radiographic evidence of tumor per MRI. To test whether supratotal resection (removing the fluid-attenuated inversion recovery abnormality as well as an additional margin) of diffuse low-grade gliomas would provide superior outcomes, the rates of malignant transformation and recurrence were compared between patients undergoing supratotal resection versus GTR. Using awake functional stimulation to define functional boundaries, supratotal resection was achieved in 15 patients with low-grade gliomas. For these patients, there were no instances of malignant transformation over an average of 35.7 months of postoperative follow-up and tumor recurrence was observed in 4 of 15 patients (average time to recurrence, 38 months). In contrast, a control group of 29 patients who underwent GTR had anaplastic transformation in 7 cases. In a study with more extensive follow-up (mean follow-up, 132 months), Duffau studied the clinical outcomes of 16 patients who underwent awake surgery with intraoperative stimulation to define the functional boundaries of resection. None of the tumors underwent malignant transformation, none of the patients died during the time of follow-up, and only 8 of the tumors recurred (average, 70.3 months; see Hugues Duffau’s article, “Higher Order Surgical Questions for Diffuse Low-Grade Gliomas: Supramaximal Resection, Neuroplasticity and Screening,” in this issue). In combination, these studies suggest a rationale for and potential benefit to supratotal resection to delay malignant transformation of low-grade glioma; however, studies with larger sample sizes are needed.

**EXTENT OF RESECTION AND MOLECULAR SUBTYPING**

More recent EOR studies have used molecular definitions of grades II and III gliomas and have suggested differences in the impact of maximal resection in astrocytomas versus oligodendrogliomas (see Table 1). For grade III anaplastic astrocytomas (defined as IDH mutant, 1p/19q retained), patients who underwent GTR had statistically significant improved survival ($P = .005$). However, for grade III anaplastic oligodendrogliomas (defined as IDH mutant, 1p/19q codeleted), there was no significant survival difference in patients who underwent GTR versus STR ($P = .14$). This pattern was also reflected in a later analysis comparing the survival benefit granted by the EOR in grade II astrocytomas ($IDH1$ mutant, 1p/19q retained) versus grade II oligodendrogliomas ($IDH1$ mutant, 1p/19q codeleted). In this study, a residual volume of 0.1 to 5.0 cm$^3$ for grade II astrocytomas granted a significantly worse OS compared with GTR; however, even up to 25 cm$^3$ of residual tumor had a significantly better OS compared with greater than 25 cm$^3$. In contrast, there was no significant improvement in the survival of grade II oligodendrogliomas in patients with GTR versus small residual tumor (0.1–5.0 cm$^3$).

**EXTENT OF RESECTION AND QUALITY OF LIFE**

Regardless of the EOR, patients with low-grade gliomas survive on the scale of years; therefore, quality of life metrics are important endpoints for clinical consideration. In a retrospective study by Chang and colleagues, 81% of patients (269/332) with low-grade gliomas presented with seizures, and 49% of these patients (132/269) had medication-refractory epilepsy. At both 6 and 12 months, 91% of patients who presented with seizures had at least meaningful improvement (Engel class I–III) in their seizure control postoperatively. Of patients who presented with seizures, 67% had no seizures at 6 and 12 months of follow-up after resection, including approximately 50% of patients who presented with medication-refractory epilepsy. GTR was significantly associated with freedom from seizures (OR, 16; $P = .0064$) and a preoperative seizure history of more than 1 year was associated with worse postoperative seizure control (OR, 0.285; $P = .003$). This finding argues for early and aggressive surgical intervention for patients with low-grade gliomas presenting with seizures.

Similarly, in a study of low-grade gliomas of the insula, all of the 52 patients analyzed presented with seizures. An analysis of postoperative seizure control and the EOR by volumetric analysis using preoperative and postoperative MRI demonstrated that increased EOR was associated with increased rate of achieving Engel class I (seizure...
The rate of Engel class I in patients with more than 90% EOR was 85.71%; for patients with an EOR of 70% to 89%, the rate was 65.22% and it was 0% for patients with less than a 70% EOR. Ultimately, however, on multivariate analysis EOR was not associated with improved seizure control and the only factor significantly impacting postoperative seizure control was a quantification of how diffuse the tumor’s growth pattern (as defined by preoperative increased delta VT2T1 value), which also had a negative association with EOR.

In addition to seizure control, whether surgery improves or harms cognitive function in patients with low-grade glioma is another important consideration. Barzilai and colleagues performed a retrospective analysis of 49 patients with low-grade gliomas (including a subset of pilocytic astrocytomas and gangliogliomas) who underwent full neurocognitive testing before and after attempting maximal safe resection. At baseline, the 49 patients had normal intelligence and abstract thinking but showed significant impairment in memory ($z = -4.03$). For the 26 dominant-sided tumors (mean EOR of 76% by volumetrics), there was a significant improvement in memory and executive function. For the 23 nondominant sided tumors (mean EOR of 83%), there was a significant improvement in memory only after attempted maximal safe resection. The caveats to this study include a lack of comparison of cognitive improvement to patients undergoing biopsy alone, and the heterogeneity of tumors pooled together (eg, only 29 of the 48 patients included were mutated for IDH1).

MOLECULAR CLASSIFICATION AND NOVEL THERAPEUTICS

These studies suggest a benefit for maximal safe surgical resection of low-grade gliomas, an effect that seems to be more striking for grade II astrocytomas compared with grade II oligodendrogliomas.

For the tumors that cannot be safely resected or that recur despite radiographic GTR, the identification of the molecular mechanisms driving low-grade glioma formation as well as malignant progression have fueled a field of active translational study for targeted adjuncts to surgical resection (Fig. 1).

There is an ongoing clinical trial for the use of 2-HG suppressors AG-120 or AG-881 in recurrent grade II or III confirmed IDH1 mutant gliomas (NCT03343197). However, Johannessen and colleagues demonstrate that, in a transformed astrocyte culture model, mutant IDH1 is important in the initiation but not the maintenance of gliomagenesis and therapeutic targeting of mutant IDH1 loses effectiveness after 4 days in their model.

Another approach capitalizes on the finding that 2HG creates a defect in homologous recombination, rendering IDH1 mutant cell lines susceptible to PARP (poly(adenosine 5'-diphosphate–ribose) polymerase) inhibition. There is currently a phase II clinical trial (NCT03212274) studying the PARP inhibitor olaparib in recurrent or progressive IDH1/2 mutant gliomas as well as other IDH1 mutant solid tumor types.

Another strategy focuses on reversing the G-CIMP hypermethylation phenotype associated with IDH mutations. Decitabine, a DNA methyltransferase inhibitor, was demonstrated to reverse the G-CIMP phenotype in vitro, resulting in the upregulation of glial differentiation genes and reduced cell growth in patient-derived IDH1 mutant glioma cell lines.

In addition to direct pharmacologic inhibition of IDH1 or the perceived downstream effects (HR defects, G-CIMP), multiple clinical trials of immunotherapy with vaccines raised against the mutant epitope are currently recruiting. Schumacher and colleagues demonstrated that an IDH1 R132H vaccine induced a Th-mediated immune response and reduced tumor growth in a humanized mouse model. Currently, there are 3
phase I IDH1-specific immunotherapy trials underway, including the PEPIDH1M vaccine for grade II IDH1 mutant gliomas (recurrent or progressive, NCT02193347).

Because IDH1 targeted therapy has not yet come to clinical fruition, the application of adjuvant radiation therapy and/or chemotherapy after surgery has been studied relative to the subgroups of low-grade gliomas, as defined by the 2016 WHO classification. A study by Buckner and colleagues on patients with grade II gliomas (defined histologically, not by WHO 2016 mutational criteria) who had undergone STR or biopsy and were randomized to either radiation therapy alone or radiation therapy + PCV showed a survival benefit to all groups of grade II gliomas (oligodendrogliomas, astrocytomas, and oligoastrocytomas) that received both radiation therapy + PCV. A subgroup analysis of IDH1 mutated tumors also demonstrated improved survival to the patients who underwent radiation therapy + PCV versus radiation therapy alone ($P = .02$). The median OS was 13.3 years for the combined group of low-grade gliomas who received radiation therapy + PCV compared with 7.8 years with radiation therapy alone ($P = .003$).

**SUMMARY**

Although the pathways underlying grade II diffuse gliomas are increasingly elucidated, there are unfortunately no available targeted therapies leveraging this molecular knowledge available for clinical practice. There are, however, multiple clinical trials underway that aim to exploit the class-defining neomorphic IDH1 mutation to halt tumor progression. In the interim, the available literature supports the application of adjunctive therapies (specifically, the combination of radiation therapy + PCV) after maximal safe resection to improve the OS of low-grade gliomas. The benefit of maximal safe resection is more pronounced in astrocytomas, which may be a reflection of their intrinsically more aggressive clinical course compared with oligodendrogliomas.

**REFERENCES**


