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Controversies in the Therapy of Low-Grade Gliomas

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Opinion statement

In the context of the new WHO classification system, all low-grade gliomas must have an IDH mutation, with or without 1p/19q codeletion. Upon discovery of the tumor, maximal safe surgical resection is the most appropriate first step due to the current inability to differentiate between IDH mutant and IDH wild–type tumors by imaging alone. In the postoperative setting, based on the synthesis and interpretation of the available data, we recommend utilizing conventional radiation therapy and PCV in all high-risk–low-grade gliomas. For patients felt to be in a low risk category, we recommend maintaining a low threshold to initiate treatment. In the setting of tumor recurrence, consideration of all treatment options is reasonable, but treatment with alkylator therapy has the strongest supporting data.

Introduction

With a worldwide effort and many years of study, significant progress has occurred in our understanding of the biology and treatment of low-grade gliomas. However, numerous controversies continue in many aspects of patient care, from initial diagnosis to tumor recurrence. The recent revision to the WHO classification system has been a critical step forward, since we now understand some of the key genetic drivers of diagnosis, prognosis, and treatment responsiveness [1]. Beyond key elements of diagnosis, the role of additional genetic testing, such as CIC, FUBP1, NOTCH1, and new technology, such as proton therapy, is currently unclear. Furthermore, timing and selection of treatment continue to be areas of

controversy. In this review, we discuss questions involving [1] the current definition of a low-grade glioma; [2] the timing of treatment; [3] the choice of chemoradiation; and [4] the treatment of recurrences.

What is a low-grade glioma? What is the current role of histologic grading?

Low-grade gliomas have traditionally been defined as histologic grade 2 oligodendrogliomas and astrocytomas. However, more recent evidence confirms marked genetic heterogeneity and clinical variability in these tumors [2–4]. The development of the revised WHO classification system [1] incorporates molecular markers and defines more homogeneous diagnostic categories. Since predicting clinical outcomes based on molecular markers has been shown to be more accurate than histology alone [5–9], clinical practice has shifted to relying primarily on 1p/19q codeletion and IDH status not only for diagnosis but also to determine treatment plans. Utilization of histologic grading can potentially provide useful adjunct information to assist in prognostication within the same molecular subgroup [3, 9].

Based on the new classification system, a new framework for gliomas consists of "molecular low-grade" tumors, namely those with IDH mutations, with or without 1p/19 codeletions. These tumors are thought to share a common pathway in development and arise from sequential steps beginning with IDH mutation followed by CpG island methylation phenotype to 1p/19q codeletion or TP53 mutation [8, 10–12]. No IDH wild–type tumors should be considered low grade given their overlap in clinical and genetic characteristics with glioblastoma [9, 13].

The role of additional genetic testing such as MGMT status continues to be unclear in low-grade gliomas. In EORTC 22033 [14] and The Cancer Genome Atlas [8], all 1p/19q codeleted tumors and the majority of IDH mutant 1p/19q not codeleted tumors had MGMT promoter methylation and no independent predictive value for MGMT testing was found. Testing of MGMT status in RTOG 0424 cited MGMT as an independent prognostic biomarker with a difference in PFS and OS between methylated and unmethylated groups, but the methylated patients were more frequently IDH wild type [15]. At this time, MGMT testing should be utilized primarily for IDH wild–type gliomas. Similarly, the direct clinical significance of mutations in CIC, FUBP1, NOTCH1, and TP53 is currently also unclear, although these appear to be markers of more indolent (CIC, FUBP1, NOTCH1) and more aggressive (TP53) IDH mutant tumors [8].

When should surgery be initiated?

Although difficult to estimate accurately, a significant percentage of patients, particularly those with tumors discovered incidentally, have lived with their tumor for years prior to diagnosis. Based on the indolent nature of most low-grade gliomas and their subsequent rate of growth, choosing the most appropriate time for treatment continues to be a complex, controversial topic.

For all patients with large tumors or tumors with neurologic symptoms, current practice favors early surgical intervention. For other scenarios, early surgery has not been proven to have a clear benefit, but several studies have suggested a positive trend favoring early intervention [16–19]. Despite some controversy about the exact timing of surgery, given the present inability to distinguish between IDH mutant and IDH wild–type gliomas [20–22], it is prudent to recommend surgical intervention soon after the discovery of the tumor in order to establish a genetic diagnosis. Although definitive evidence for maximizing the extent of tumor resection is absent, available data support a goal of maximal safe surgical resection, particularly for IDH mutant astrocytomas [17, 23–25].

When should chemoradiation be initiated?

The current data support utilization of both radiation and chemotherapy when initiating postoperative therapy for patients at greatest risk for tumor recurrence [26••]. In high-risk patients, the combination of RT and PCV resulted in significant increases in both progression-free and overall survival compared to radiation therapy alone (Fig. 1; 10.4 years vs 4.0 years and 13.3 years versus 7.8 years, respectively).

While risk factors are relative and there is no consistent agreement between definitions of high risk, many studies including EORTC 22844, EORTC 22845, and RTOG 9802 have used similar variables to assign high risk status [26••, 27, 28]. These include age > 40, tumor-related symptoms, astrocytoma histology, initial tumor > 4 cm, and subtotal resection [26••, 27, 28]. Limitations to most stratification schemes include lack of consistent molecular testing. Of these risk factors, subtotal resection and astrocytoma histology have perhaps the most

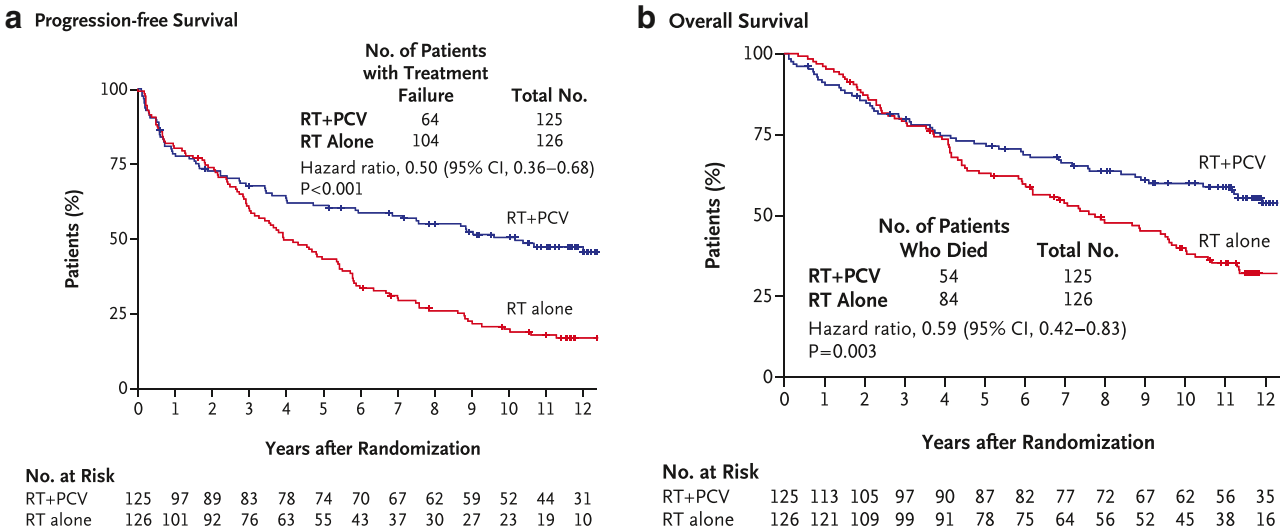

Fig. 1. **a** Progression-free and **b** overall survival of patients with low-grade gliomas receiving RT + PCV versus RT alone as reported in RTOG 9802. From *New England Journal of Medicine*, Buckner JC, Shaw EG, Pugh SL, et al., Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma, Volume No. 374, page 1344. Copyright© 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

data confirming high risk (Fig. 2), as multiple studies have shown association with decreased overall survival, including arm 1 from RTOG 9802 [16, 26••, 29, 30].

Our practice assigns risk largely based on criteria used in RTOG 9802 as this study contains the highest level of evidence to date in the treatment of low-grade gliomas. The decision is always individualized but our practice favors treating all patients assigned a high risk status in the immediate postoperative setting.

In patients assigned some derivation of "low risk," selecting timing of additional treatment, such as radiation therapy, chemotherapy, or both, continues to be an area of active controversy. In these circumstances, there is no consistent threshold that prompts treatment; and significant variability is present in current clinical practice. A period of observation is considered a reasonable option if surgery results in complete or near-complete resection, particularly in patients with 1p/19q codeleted tumors. The rationale is based on the known indolent nature of these tumors and the risk of neurocognitive decline years following treatment [32–35]. Data about long-term outcomes with this approach are limited and whether this approach can be effectively applied to select higher risk patients is also unclear. RTOG 9802 included a prospective series of 111 patients that underwent gross tumor resection and no immediate postoperative treatment. Five-year overall survival was 93% but 5-year progression-free survival was 48% [31]. In EORTC 22033, after initial histologic diagnosis, patients could be observed prior to randomization. Reasons to initiate treatment were age 40 or older, radiological tumor progression, new or worsening neurologic symptoms or refractory seizures. Median time to initiation of therapy following initial biopsy was 5.1 months (range 2.9–25.7 months) and 6.0 months (range 2.7–30.0 months) in the radiation arm versus temozolomide arm, respectively. Thus, most patients required treatment rather early after initial biopsy. While it is possible that patients were observed

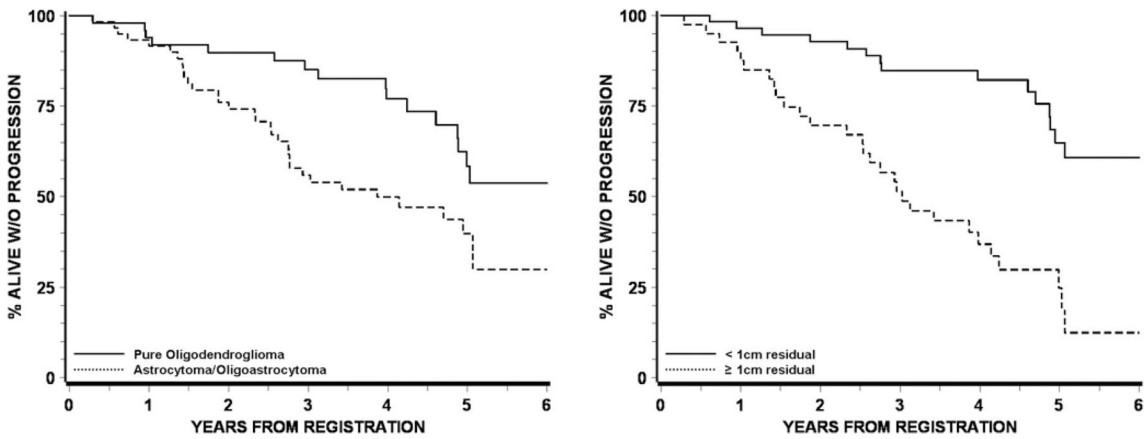

Fig. 2. Progression-free survival of low-grade glioma patients that underwent surgical resection followed by a period of observation, stratified by histologic appearance (left) and residual amount of tumor (right). From Shaw EG, Berkey B, Coons SW, Bullard D, Brachman D, Buckner JC, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. *Journal of Neurosurgery*, 2008 Nov;109 (5):835–41, reprinted with permission from the American Association of Neurological Surgeons.

for a significant length of time after radiologic detection of a suspected low-grade glioma and prior to the initial biopsy, the median time initiation of therapy after biopsy was relatively short, and no patient was observed more than 30.0 months prior to starting treatment in this study [14].

Given the large effect size of treatment with radiation plus chemotherapy, one could argue that even low-risk patients should receive early chemoradiation because 1) all patients develop progressive disease, 2) the radiation volume will be lowest immediately after diagnosis, thereby minimizing the risk of neurocognitive decline associated with larger radiation volume later, 3) lower doses of radiation therapy [27, 28, 36] appear to be as effective as higher doses and with lower long-term toxicity, and 4) there will be less time for spontaneous anaplastic transformation to a treatment-refractory genotype. In spite of insufficient evidence, certain low-risk patients may benefit from delayed chemoradiation; however, we recommend having a low threshold to initiate chemoradiotherapy and reserving delayed treatment only in the most favorable genetic and patient circumstances.

Is there a role for proton-based therapy?

Conventional radiation therapy is well established in the treatment of low-grade gliomas at a total dose of 50–54 Gy delivered in individual fractions less than 2 Gy [27, 28, 36]. The goal of proton therapy is to maintain tumor control while reducing late cognitive decline. However, limited data are currently present in the medical literature. A single arm, prospective trial of 20 patients with grade 2 gliomas safely utilized proton therapy at a dose of 54 Gy in 30 fractions [37]. The median follow-up was 5.1 years with a PFS of 85% at 3 years and 40% at 5 years. All patients tolerated the full treatment with a subset of patients developing new endocrine dysfunction. There was no change to quality of life assessment [38] and patients were reported to have stable cognitive function [39]. At this time, there are also limited data about side effects with proton therapy. However, initial studies reveal similar rates, but earlier development, of pseudoresponse in low-grade glioma patients treated with proton therapy [38]. No other applicable studies are currently available but NRG-BN005, which directly compares proton versus photon therapy in grade 2 and 3 IDH-mutated tumors, has the potential to provide not only data about differences in progression-free and overall survival, but also in cognition and quality of life [40].

What is the optimal chemotherapy regimen for low-grade gliomas?

A persistent source of controversy in the treatment of low-grade gliomas revolves around the selection of chemotherapy. Prior to the publication of the mature results from RTOG 9802, clinical practice had shifted significantly to the use of temozolomide as initial therapy. However, RTOG 9802, the landmark phase 3, randomized trial in high risk grade 2 glioma patients treated with RT + PCV versus RT, provided level 1 evidence supporting the use of PCV therapy as part of the treatment protocol applied to all high-risk IDH mutant low-grade gliomas [26••]. Although the benefit was particularly noticeable in histologic

oligodendrogliomas and oligoastrocytomas, the astrocytoma group also trended toward benefit ($n = 46$; HR, 0.73; 95% CI, 0.4–1.34). Use of PCV in grade 2 astrocytomas did not ultimately result in a statistically significant difference in progression-free and overall survival, but this group contained IDH wild–type patients. Subsequent analysis of outcomes by IDH mutation and 1p/19q codeletion confirmed maximum benefit in patients with 1p/19 codeletion, intermediate benefit in IDH mutant non-codeleted tumors, and minimal or no benefit in IDH wild–type tumors [41]. Similar outcomes were reported from EORTC 26951 and RTOG 9402, both phase 3 trials examining the role of PCV in the treatment of anaplastic oligodendrogliomas, and demonstrated significant improvement in survival with the addition of PCV to radiation in patients with IDH mutations, with or without 1p/19q codeletions (Fig. 3).

Similar to RTOG 9802, in EORTC 26951 and RTOG 9402, IDH wild–type tumors do not respond to PCV [42, 43]. In each of these trials, the separation of the progression-free survival curves began approximately 2 years after randomization, suggesting that a chemorefractory cohort of tumors exists.

However, in current clinical practice, some academic centers continue to use temozolomide in the treatment of low-grade gliomas. The proponents of temozolomide note that no head-to-head comparison between the chemotherapies currently exists that supports the superiority of PCV compared with temozolomide. Although temozolomide has been shown to have efficacy in treatment of patients with low-grade gliomas, current data are limited. Examples include the EORTC 26971 study [44] in which a subset of 38 patients with recurrent oligodendrogliomas was treated with temozolomide after initial therapy with radiation. Half of them experienced a complete or partial response and, at 12 months, 80 % of these patients had not experienced progression. In a single-arm phase 2 study, RTOG 0424 [45], which examined high-risk low-grade gliomas treated with RT and concurrent and adjuvant TMZ compared to historical controls, the median survival was not reached at 4 years and the 3 years overall survival was 73.1% (95% CI, 65.3%–80.8%). The use of TMZ resulted in statistically improved overall survival compared to the historical controls. In the CATNON trial, a randomized phase 3 trial of newly diagnosed 1p/19q not codeleted anaplastic gliomas, showed a survival benefit in adjuvant TMZ treatment groups, although IDH mutational status has not yet been reported [46••]. Furthermore, in RTOG9813, patients with anaplastic astrocytoma were randomized to receive radiation plus temozolomide or radiation plus a nitrosourea (either CCNU or BCNU). Survival outcomes were identical between the two arms, but there was no analysis of results by IDH mutations or 1p/19 codeletion [47]. Proponents of TMZ cite incomplete molecular classification and the subsequent lack of statistical power in IDH mutant gliomas as a limitation to RTOG 9802, albeit these data are available in a subset of patients [41]. In addition, they note that the magnitude of the survival benefit is driven by 1p/19q codeleted tumors and question whether PCV is as effective in astrocytoma lineages.

Despite numerous trials, it is unclear if the efficacy of treatment with TMZ is equal to that of PCV. Some data suggest that TMZ may be inferior. The original study design of the CODEL trial, which randomized adult patients with newly diagnosed anaplastic gliomas with 1p/19p codeletion to receive RT alone, RT+TMZ, or TMZ alone, was altered based on recommendations from the Data Safety Monitoring Committee due to more frequent tumor progression in the TMZ monotherapy group ($n = 6/12$; 50%) than in the radiation therapy arms

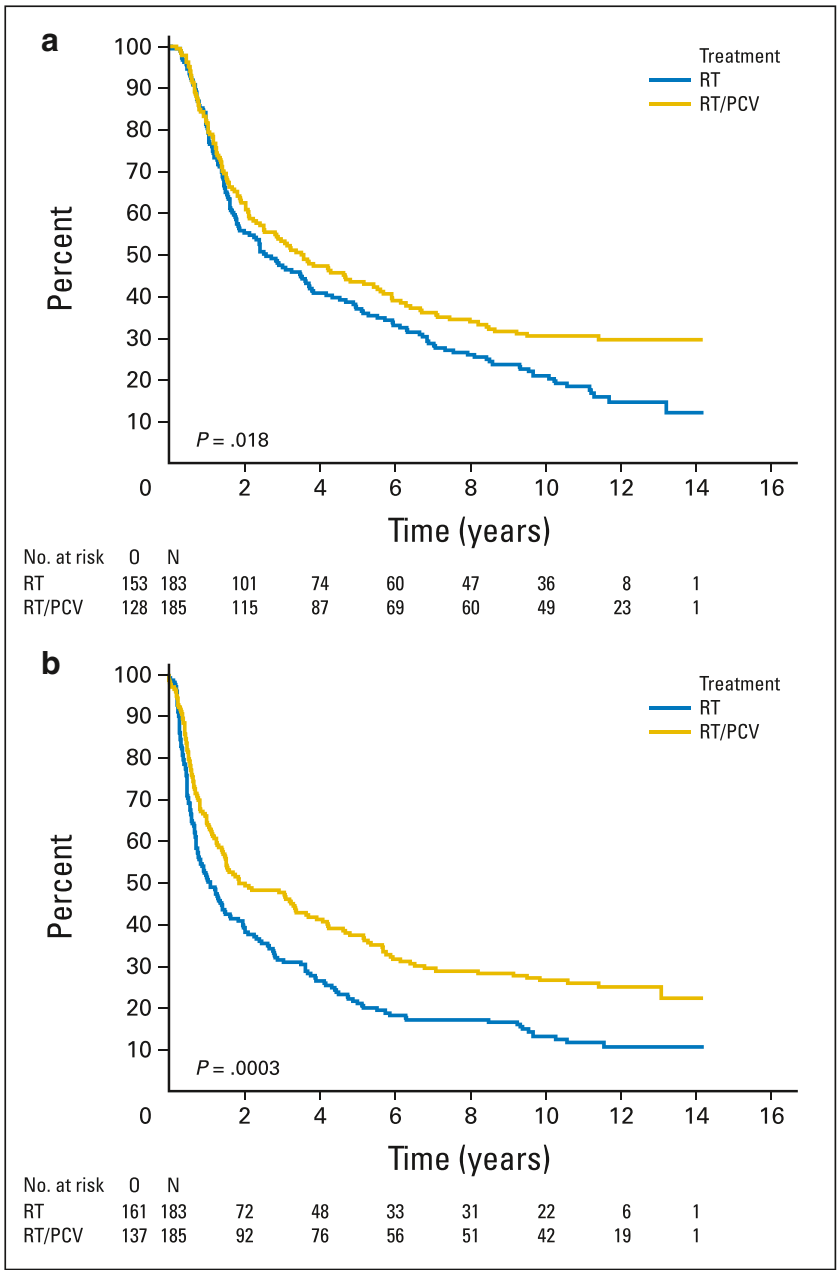

Fig. 3. Overall and progression-free survival of patients with anaplastic oligodendroglioma treated with RT + PCV versus RT as reported in EORTC 26951. Reprinted with permission. ©2012 American Society of Clinical Oncology. All rights reserved. Van den Bent MJ, et al.: Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951 31 (3), 2012:344–350.

($n = 2/24$; 8%; $P = 0.002$) after a median follow-up of 3.4 years [48]. In this TMZ group, 3 of 12 patients who progressed on TMZ died. In the NOA-4 trial [49], patients with newly diagnosed anaplastic gliomas were randomized to initial therapy with RT followed by TMZ or PCV at progression versus TMZ or PCV followed by RT at progression. There was no difference in survival between

the two primary treatment arms, i.e., initial radiation versus initial chemotherapy. While the study was not designed to assess the difference between PCV and temozolomide, there was a trend toward improved progression-free survival, time to treatment failure, and overall survival with PCV versus temozolomide in patients with 1p/19q codeletions. In the large retrospective study by Lassman, 49% of patients with 1p/19q codeletion who received RT + PCV were alive at 10 years, compared to 15% of patients who were treated with RT + TMZ [50]. Proponents of PCV also cite the potential for TMZ use to result in the development of a hypermethylated, aggressive tumor phenotype. Genetic analysis of gliomas exposed to TMZ revealed disruption of the retinoblastoma-associated protein tumor suppressor pathway and activation of the Akt–mTOR pathway [51], changes resembling those found in glioblastoma, and suggesting that TMZ use can potentially accelerate transformation. Whether this phenotype results in clinically significant differences is not yet clear.

However, temozolomide is felt to be overall much better tolerated and the toxicities of PCV therapy are frequently cited in arguments against its use. In part, this is a consequence of toxicities encountered in earlier trials, such as RTOG 9402 [43], which utilized a higher dose regimen than is currently standard. In NOA-4 [49], hematologic toxicity delayed 18% of cycles in PCV arm and 6% of cycles in TMZ arm. The median number of completed cycles was 4 (range, 1–5 cycles) for PCV and 8 (range, 0–12 cycles) for TMZ. In contrast, the regimen in RTOG 9802 utilized lower doses of lomustine and cycles were repeated every 8 weeks [26••]. This regimen was much better tolerated and most symptoms comprised of grade 1 or grade 2 fatigue, nausea, anorexia, and vomiting. Only approximately 10% experienced grade 4 hematologic side effects. Three patients received red cell transfusions, one received platelet transfusions, and there was one case of neutropenic fever.

Though the final answer to the choice of chemotherapy may come with the results of the CODEL trial, which currently randomizes patients with 1p/19q codeleted anaplastic gliomas to receive RT followed by PCV versus RT + TMZ followed by TMZ, the efficacy of temozolomide for treatment of IDH-mutated low-grade gliomas does not currently have the same level evidence as PCV. It is therefore prudent to treat patients with IDH mutant low-grade gliomas, especially those with 1p/19q codeletions, with PCV as the current data best support this practice.

What treatment should be selected for tumor recurrences?

Treatment of recurrences is subject to wide variation in clinical practice in large part due to the lack of studies that can be used to guide decision-making. There is no consensus on the optimal threshold for or timing of retreatment. In essentially all cases, repeat surgery is considered, and depending on the opinions of the treatment team members, some centers utilize repeat surgery more than others. However, no clinical trials have substantiated the practice. Reirradiation with conventional beam therapy is usually not recommended at first recurrence due to concern for side effects and radiation necrosis. Some studies have suggested a role for stereotactic radiotherapy in select cases and have published results of delivering an additional 36 Gy at recurrence [52]. Median overall survival after stereotactic radiotherapy for recurrent low-grade gliomas was 22 months (range 2 to 104 months). This practice resulted in

minimal side effects, but the data are limited by small numbers, heterogeneous initial treatments, and lack of genetic characterization.

Chemotherapy with alkylating agents is often the mainstay of treatment for recurrent gliomas. Multiple previous trials have explored the role of TMZ and have reported a response rate of 47–61% and 6 month progression-free survival of 76–98% in recurrent low-grade gliomas [53–55]. Other chemotherapies have not yet been shown to improve progression-free or overall survival. For example, adding bevacizumab to temozolomide in recurrent grade 2 or 3 1p/19q not codeleted gliomas did not improve overall survival compared to temozolomide monotherapy [56•]. Bevacizumab is therefore currently utilized primarily for symptomatic management. Finally, the role of targeted molecular therapies such as everolimus [57] is promising but unproven. Although we reconsider all treatment options when assessing a patient with tumor recurrence, our practice primarily utilizes surgery or chemotherapy in the treatment of low-grade gliomas. Reirradiation is reserved for patients not eligible for surgery, further chemotherapy, or clinical trials.

Compliance with Ethical Standards

Conflict of Interest
Ivan D. Carabenciov and Jan C. Buckner declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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- • Of importance
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