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Neuro-Oncology Practice Clinical Debate: Early treatment or observation for patients with newly diagnosed oligodendroglioma and small-volume residual disease

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Abstract

Advances in treatment of oligodendroglioma represent arguably the most significant recent development in the treatment of brain tumors, with multiple clinical trials demonstrating that median survival is approximately doubled in patients with World Health Organization grade II and III 1p/19q codeleted gliomas (ie, oligodendrogliomas) treated with procarbazine, lomustine, vincristine chemotherapy and radiation vs radiation alone. However, chemoradiotherapy itself is not without morbidity, including both short-term toxicities primarily related to chemotherapy and longer-term cognitive issues likely due to radiation. Patients and physicians both desire maximally effective therapy with minimal toxicity, and it remains unclear whether some patients with macroscopic residual disease after surgery can safely delay therapy, to avoid or delay toxicity, while simultaneously preserving the full benefits of treatment. In this article, experts in the field discuss the rationale for the approaches of up-front treatment with chemoradiotherapy and initial observation, respectively.

Keywords

cognition | observation | oligodendroglioma | radiation | toxicity

Clinical Scenario

A 31-year-old engineer presents with a first-time seizure and is found to have a nonenhancing left frontal lobe mass. She undergoes maximal safe resection, but gross total resection is not possible because of tumor involvement of an eloquent language area. Pathology reveals World Health Organization (WHO) grade II oligodendroglioma, isocitrate dehydrogenase (*IDH*) mutant and 1p/19q codeleted. After recovery from surgery her Eastern Cooperative Oncology Group performance status is 0, and she comes to your clinic for advice on treatment. She has researched her options and is aware of the data demonstrating that chemoradiotherapy improves survival in patients with oligodendroglioma, but she is also worried about the potential side effects of therapy, particularly with respect to cognition and her ability to continue to work as an engineer. Would you recommend she undergo chemoradiotherapy now, or initial observation with further therapy at the time of tumor progression?

Pro Side: Evidence Supports Early Treatment

S.E. Fogh, L. Boreta, and J.L. Nakamura

WHO grade II oligodendrogliomas represent a relatively indolent tumor on the spectrum of gliomas with a heterogeneity of reported median progression-free survival (PFS) and overall survival (OS) ranging from 3 years to in excess of a decade dependent on factors including but not limited to age, size of tumor, anatomic location, histology, seizures at presentation, and extent of surgical resection.[1,2] Since 2016, the tumor has been genetically defined by the molecular characteristics of mutation in *IDH1* or *IDH2* and codeletion of 1p/19q, rather than traditionally described microscopic features such as "fried egg" cells and "chicken-wire" vasculature.[3,4] Oligodendrogliomas tend to affect a younger patient population than more aggressive gliomas.

Treatment begins with maximal safe resection, and surgery has been shown to improve survival. However, surgical resection is dependent on technique and necessarily limited when tumors invade eloquent areas of the brain. Maximal safe resection is beneficial both to reduce disease burden and ensure accurate diagnosis, because more than 33% of grade III tumors are nonenhancing and thus cannot be reliably distinguished from WHO grade II tumors by standard magnetic resonance imaging.

As with all brain tumors, the goals of treatment are to maximize PFS and OS while minimizing treatment toxicities. The benefit of maximizing OS is self-evident, whereas maximization of PFS is desirable on the assumption that tumor growth measurable on imaging carries a risk of associated symptomatic decline. In this case of a young engineer with residual tumor in an eloquent language area, we are therefore concerned that, if left untreated, the tumor itself may lead to worsening and potentially permanent language deficits over time. With complete resection of a molecularly defined oligodendroglioma, most practitioners would currently favor observation, whereas most would conversely favor therapy in patients with large-volume residual disease. However, in the setting of a subtotal resection (STR) with relatively minimal residual disease, evidence exists that recurrence/progression rates are higher than after gross total resection, and these tumors fall into a higher-risk category. This allocation to a high-risk group results from several studies that have demonstrated inferior survival in the setting of gross residual disease. A study by Smith et al examined the impact of resection on low-grade tumors and found that a 90% or greater resection had excellent OS rates at 5 and 8 years (97% and 91%, respectively), whereas patients with less than a 90% resection had significantly inferior 5- and 8-year OS rates (76% and 60%, respectively).[5] This has been replicated in clinical trials showing that residual tumor increased the risk of recurrence. Specifically, less than 1 cm of residual tumor was associated with a risk of recurrence of 26%, whereas 1- to 2-cm residual disease carried a risk of 68%, and greater than 2 cm a risk of 89%.[6] In the molecular era, Wijnenga and colleagues examined the impact of surgical resection of molecularly defined low-grade glioma subtypes and found that postoperative volume correlated with OS, with risk increasing linearly with increase in volume of residual disease.[7]

Radiographically evident residual disease therefore puts patients in a high-risk category, and guidelines suggest postoperative therapy including radiation and chemotherapy therapy.[8] This recommendation stems from the long-term results of Radiation Therapy Oncology Group (RTOG) 9802, a phase 3 randomized trial examining the role of the addition of PCV (procarbazine, lomustine, vincristine) chemotherapy to radiation therapy (RT) in high-risk low-grade glioma patients. Although at short-term follow-up chemoradiotherapy was reported to improve only PFS, updated results of this trial also showed a significant improvement in OS for those who received PCV chemotherapy plus RT (13.3 years median survival time) compared to those receiving RT alone (7.8 years median survival time).[2,9] Importantly, this trial was *not* designed to assess the timing of therapy and although all patients inevitably require postoperative treatment, the timing of treatment is thus controversial. In short, although upfront chemoradiotherapy is unambiguously superior to upfront radiotherapy alone, we do not have the same level of certainty regarding the question of upfront vs delayed chemoradiotherapy, and given the long timeline necessary for completion of clinical trials in this disease, this information will not be available in the near future.

RT is typically delivered in doses ranging from 45 to 54 Gy in 1.8- to 2-Gy fractions using postoperative imaging with a 1- to 2-cm margin encompassing the T2 or fluid-attenuated inversion recovery abnormalities, because WHO grade II gliomas are typically nonenhancing tumors.[10,11] Given the volume of brain affected by incorporating the tumor and microscopic disease in the margin, RT is associated both with short- and long-term side effects with the most worrisome being permanent neurocognitive sequela. This may be less relevant in the setting of a high-grade glioma but is of particular concern with younger patients facing a protracted survival with this less aggressive tumor. Unfortunately, RTOG 9802 and other historic trials did not use robust methods to assess the neurocognitive impact of treatment, and few studies have rigorously studied long-term neurocognition with serial testing in patients with low-grade gliomas. Douw et al examined 65 patients with low-grade gliomas, with approximately half of the patients receiving RT.[12] No real differences in cognition were noted between the groups at 6 years but at 12 years, a 53% rate of neurocognitive deficits was noted in the group receiving radiation. Of note, 27% of patients who did not have radiation experienced significant neurocognitive deficits, further corroborating previous research that indicates the presence of tumors or tumor progression can affect neurocognitive function, highlighting the complex relationship between side effects from tumor progression vs side effects from treatment. As in clinical practice patients receiving radiation are often those judged to be higher risk in some way, it is possible that preexisting factors rather than RT itself account for some of this difference. Despite these concerns for RT-associated side effects, however, one could argue that in contrast to the radiation field of a progressive tumor, the area of the brain receiving radiation will be

relatively small shortly after STR, potentially reducing the severity of RT-associated toxicity.

In addition to neurocognitive deficits and survival, health-related quality of life (HRQoL) is also an important consideration. As with neurocognition, some studies have demonstrated decreased quality of life at diagnosis that may decline over time, but it is unclear whether this decline is related to treatment or natural progression of disease. EORTC 22033-26033 compared temozolomide (TMZ) to RT and found no difference in HRQoL between the 2 groups.[13] It is worth noting that seizures can significantly decrease quality of life and although improvement in survival was not found when radiation was initiated following surgery, van den Bent et al did demonstrate a reduction in seizures from 41% to 25% at 1-year follow-up.[11]

Unfortunately, RTOG 9802 did not address the question of chemotherapy alone and used a more toxic chemotherapy (PCV) that preceded more modern therapies such as TMZ, creating a dissonance between what the first-line evidence shows and what some practitioners actually do.[14] In addition to the previously mentioned trial (EORTC 22033-26033) that showed no difference in PFS comparing TMZ to RT, RTOG 0424 examined radiation combined with TMZ in patients with high-risk factors. This study showed promising results compared to historical controls in 9802 but no phase 3 trials comparing these 2 regimens have been completed.[15,16]

In conclusion, given that the patient falls into a high-risk category with a STR, we would suggest that she receive the first-line therapy that has been proven to essentially double OS in patients with her tumor type, namely the combination of RT and PCV.

Con Side: Early Observation Is Reasonable

S.C. Kurz and A.S. Chi

Molecular correlative data from the RTOG 9802 trial has established the benefit of adjuvant PCV chemotherapy for patients with low-grade *IDH*-mutant, 1p/19q-codeleted oligodendroglioma.[9] Although the molecular associations were analyzed retrospectively, the considerably longer OS observed with PCV added to radiation vs radiation alone in this subset of patients has significantly affected practice patterns. Many providers recommend adjuvant radiation and PCV for all patients with residual disease, who would have been considered "high risk" per the RTOG 9802 study. However, this study did not address the timing of treatment, which is critical when considering the significant risk of delayed treatment-associated neurotoxicity in patients who are expected to be long-term survivors. Therefore, we would advocate for deferral of treatment and the associated risk of potentially disabling and permanent neurotoxicity in this young patient who is without sequelae from the tumor and surgery. Instead, careful surveillance and evaluation of the residual tumor growth rate of the residual disease could be a reasonable initial strategy, with future initiation of treatment if an accelerated tumor growth rate is observed and/or neurological symptoms arise.

The risk of radiation-induced neurocognitive decline is a major factor when considering delaying or withholding radiotherapy in people whose tumors harbor a molecular signature that predicts a favorable prognosis. Patients with low-grade, *IDH*-mutant, 1p/19q-codeleted oligodendroglioma have a median survival well beyond 10 years in recent data sets.[17–20] Although there are no randomized trial data on the effect of radiation on cognition in lower-grade glioma, and overall data are limited on the incidence and character of delayed neurotoxicity after radiotherapy, available evidence indicates the risk of severe cognitive decline exists for a significant subset of patients. Douw et al evaluated the long-term cognitive status of 65 patients with nonprogressive low-grade gliomas at time of diagnosis and after a mean of 12 years of follow-up using comprehensive neuropsychological assessments.[12] Of these 65 patients, 32 patients had received and 33 patients had not received radiotherapy. After a mean follow-up time of 12 years, those who received radiation had progressive decline in attentional functioning, and half (53%) of patients who had received radiation had developed cognitive dysfunction compared to 27% patients who had not received radiation.[12] Notably, differences in cognitive deficits between comparative groups were observed only after long-term follow-up and were not significant at a mean of 6 years after diagnosis,[21] and late cognitive decline was observed even in patients receiving 2 Gy or less per fraction, a dose generally regarded as safe.[12] It is worth noting, however, that cognitive dysfunction presumably due to tumor progression, potentially ongoing seizures, and/or surgery occurred in 27% of patients who did not receive radiotherapy. The multifactorial nature of cognitive dysfunction and the risks involved in deferring therapy highlights the complicated decision-making process involved in providing treatment recommendations for these patients.

Additionally, a small cohort of nonprogressive long-term survivors (32 patients) from the EORTC 26951 anaplastic oligodendroglioma trial that randomly assigned patients with anaplastic oligodendroglial tumors to radiation alone or radiation plus PCV was evaluated for late cognitive adverse effects from treatment.[22] The median survival of this group was more than 12 years, and half of the patients had a 1p/19q-codeleted tumor (ie, oligodendroglioma by current definition). Cognitive assessment consisted of a battery of standardized neuropsychological tests covering a wide range of cognitive functions. Compared to healthy controls, the nonprogressive glioma patients performed worse in multiple cognitive domains. Notably, of the nonprogressive patients, 30% were severely cognitively disabled, and 19% required institutionalized care for activities of daily living.[22] These studies underscore the potential for severe, disabling late neurotoxicity in a significant fraction of patients receiving focal radiotherapy.

Considering these risks, can low-grade glioma patients with favorable molecular profiles be safely observed even with residual disease? Although no prospective randomized trial data are yet available for initial observation vs early radiation plus chemotherapy in low-grade glioma, the EORTC 22845 randomized phase 3 trial suggests that delaying radiation does not adversely affect OS in low-grade glioma. EORTC 22845 evaluated the long-term efficacy of adjuvant vs delayed radiation in patients with

Table 1. Synopsis of Key Arguments for Early Radiochemotherapy or Initial Observation, Respectively, in This Case of a 33-Year-Old Engineer With a Subtotally Resected *IDH*-Mutant, 1p19q-Codeleted Glioma (World Health Organization II)

Early radiochemotherapy (references)	Initial observation (references)
• If untreated, progressive tumor itself may cause worsening neurological deficits, including seizures and neurocognitive deficits.[11,12]	• Radiotherapy is associated with an increased rate of neurocognitive decline and impaired QoL, which would be detrimental, especially in a young, highly functioning individual.[11–13,21,22]
• Untreated residual disease is associated with significantly inferior OS rates.[5–7]	• Although RTOG 9802 demonstrated superiority of radiation + PCV chemotherapy over radiation alone, it did not address the question of timing of radiation (early vs late).[9,11]
• In RTOG 9802, up-front treatment with radiation + PCV has been associated with significantly prolonged PFS and OS.[9]	• EORTC 22845 demonstrated that OS is similar for patients who received early vs late radiation, therefore, one may be able to postpone treatment.[11]
• If untreated, tumors will invariably continue to grow and the appropriate time point to initiate treatment may be missed.[24]	• The growth pattern of oligodendrogliomas is slow and predictable. Therefore, careful initial observation of tumor growth rate may allow identification of patients whose tumors grow faster and require treatment sooner but would also identify patients whose tumors grow slowly and should be spared too-early treatment.[23–25]

Abbreviations: CCNU, lomustine; EORTC, European Organisation for Research and Treatment of Cancer; OS, overall survival; PCV, procarbazine; PFS, progression-free survival; QoL, quality of life; RTOG, Radiation Therapy Oncology Group; TMZ, temozolomide.

low-grade gliomas and demonstrated that although PFS was increased in patients who received adjuvant radiotherapy compared to patients who received radiation at time of tumor progression, median OS was not different (7.4 years vs 7.2 years; hazard ratio, 0.97, 95% CI, 0.71-1.34; $P = .87$).[11] It would be precarious to extrapolate conclusions from this trial to rationalize deferral both of radiation and chemotherapy until the time of progression; however, these data indicate the need for a study that evaluates the efficacy of early vs late radiation plus PCV for patients with low-grade, *IDH*-mutant, 1p/19q-codeleted gliomas and that includes longitudinal neuropsychological assessments as end points.

In addition, careful surveillance would enable the assessment of tumor growth rate, which could potentially be used in the decision of when to initiate treatment. Untreated low-grade gliomas generally grow at a slow, linear rate that can be predicted within a narrow range, with a median rate of approximately 4 to 6 mm/year and with the growth rate of untreated 1p/19q-codeleted tumors being in the lower range of growth rate.[23,24] A large study of 143 patients with untreated low-grade, noncontrast-enhancing gliomas suggested that growth rates generally distribute into 2 groups; a majority (84.6%) of tumors grow at a rate of less than 8 mm/year and have a median survival of more than 15 years, whereas a minority (15.4%) of tumors grow faster than 8 mm/year and carry a median survival of only 5.16 years ($P < .001$).[25] Therefore, close surveillance of residual tumor is likely safe for a significant majority of low-grade gliomas, and treatment could be initiated if/when a faster than expected growth rate is detected.

Another provocative factor that could be considered in the timing of treatment initiation is the risk of developing chemotherapy-induced "hypermutator phenotype," which has been reported with the use of TMZ and CCNU (lomustine)-based chemotherapy in glioma.[26,27] In *IDH*-mutant glioma, Johnson and colleagues initially demonstrated the development of hypermutator phenotype after TMZ exposure in paired *IDH*-mutant astrocytoma, and this was associated with malignant transformation to a glioblastoma.[28] Chemotherapy-induced hypermutator phenotype has since been demonstrated both in 1p/19q-codeleted and *p53*-mutant subsets of *IDH*-mutant glioma.[29,30] Notably, however, the clinical significance of this phenomenon remains highly uncertain as questions remain regarding whether development of hypermutator phenotype definitively contributes to malignant transformation, the amount of chemotherapy required to induce a hypermutator phenotype, the incidence, the latency period, and the prognosis and treatment sensitivity once the hypermutator phenotype develops. Therefore, consideration of the risk of this phenomenon in clinical decision making is not yet recommended.[31]

In summary, we would advocate for deferring adjuvant tumor-directed therapy in this young patient with an STR low-grade glioma characterized by a favorable molecular profile that predicts long-term survival. In our opinion, the patient's relatively long life expectancy is an even greater reason to defer the potentially permanent and disabling risk of neurotoxicity associated with treatment. With the knowledge that the majority of low-grade gliomas, and in particular 1p/19q-codeleted gliomas, have slow, linear, predictable growth rates, *IDH*-mutant, 1p/19q-codeleted oligodendrogliomas can potentially be safely observed if monitored closely. Treatment can be initiated if/when growth rates accelerate or if new clinical or radiographic situations emerge, such as neurological progression or development of contrast enhancement.

Pro-Early Treatment Reply

The authors make excellent points and eloquently highlight the controversy surrounding this diagnosis, particularly in young, highly functional patients. We agree that the current standard definition for "high-risk patients" might

be outdated, particularly as it relates to age. The concept of a STR with residual disease is still controversial, with limited data in the era of molecular diagnosis. Although many of the studies preceding molecular diagnosis showed significant impact on outcomes in patients with residual disease, in the molecular era, this is still an area of controversy. Wijnenga et al reported a significant relationship between postoperative volume and outcomes, strongest in *IDH*-mutated astrocytoma patients.[7] Although not clinically significant, a trend was noted in oligodendroglioma patients with more extensive resections. Patel and colleagues also looked at the role of resection in the molecular era and although they report a benefit to extent of resection in all patients, when stratifying by *IDH* status, the benefit seemed to be limited to patients with *IDH* wild-type tumors.[32] It is important to recognize, however, that these studies are confounded by their sample size because of the small number of patients with known mutational status, leaving this an open area of study.

With regards to the arguments raised about the relatively slower growth rate in some low-grade gliomas compared to others, it is also worth noting that, although these tumors may grow extremely slowly over time, they nevertheless continue to grow if untreated, as demonstrated by Mandonnet et al.[24] In clinical practice and because of the insidious tumor growth, this may be overlooked and the appropriate time point to initiate treatment may be missed.

In addition, we agree that the results of EORTC 26951 are worrisome with respect to the long-term effects of radiation; however, it is important to realize that 37 patients is an extremely small sample size, that most cognitive deficits were found in patients who had progressive disease, and that HRQoL was stable in those with no progression of disease. Thus, it is plausible that if radiation therapy successfully delays disease progression, it could have a neutral or even beneficial impact on these other outcomes. As mentioned previously, other authors have also noted cognitive deficits in patients who have not received radiation, and identifying the patients most at risk is challenging.

It is also important to note that many of these studies reporting long-term deficits have used less conformal radiation techniques with inferior imaging, together resulting in larger treatment volumes. RTOG 9802 was conducted before intensity modulated RT or more conformal techniques were widely used. EORTC 22844 and 22845 also both preceded the use of intensity modulated RT and magnetic resonance imaging used for planning and allowed parallel opposing, oblique wedge fields or 3-dimensional conformal plans with 2-cm margins. EORTC 26951 used computed tomography planning and targeted the preoperative tumor volume with a 2.5-cm expansion.

While the impact of margin size on regional failure is still debated, many papers have reported increased neurocognitive deficits and toxicity with larger margins that translate into significantly larger radiation target volumes and in many cases increased doses to eloquent structures such as the hippocampus.[21,33,34] For example, Gondi and colleagues noted a dose response relationship to the hippocampal dose and subsequent risk of neurocognitive effects and memory in patients treated with radiation with low-grade and benign tumors.[35] It is therefore of critical importance to be thoughtful about clinical target volume expansions, respect normal tissue boundaries without reflexively adding margin to anatomic areas not at risk for tumor expansion, as well as continue to expand on our knowledge about the eloquent structures driving this impact without compromising tumor control and to reach consensus about how the tumor volumes are drawn.

Lastly, location of the tumor certainly plays a large role in predicting how residual disease may affect functional and cognitive outcomes. In this scenario, although we are told the tumor is in eloquent territory, we do not know how much residual there is and where the residual is located. For example, does the tumor cross midline or is it in the brainstem? Gliomas are infiltrative and progression can result in more extensive anatomic involvement (for example, contralateral spread, multilobar disease) that not only produces more debilitating symptoms but necessitates larger radiotherapy volumes, and potentially more posttreatment complications as a result. One can imagine the same scenario but with 2 extremes of STR and the level of concern being very different.

Pro-Observation Reply

We appreciate the thoughtful opinion statement in support of early treatment for this 31-year-old engineer with an STR left frontal WHO II, *IDH*-mutant, 1p19q codeleted oligodendroglioma. We agree that, based on the data from RTOG 9802, aggressive chemoradiation with PCV chemotherapy will improve survival of high-risk low-grade gliomas compared to radiation alone. However, we highlight 2 of the outstanding issues that this study did not address. One is the definition of "high-risk," which, in this study, was age older than 40 years and/or presence of residual tumor. This high-risk classification was not based on strong evidence, and, in our opinion, is antiquated in the era of molecular classification. Notably, in a seminal study by Olar et al, patient age was found not to be independently predictive of survival within *IDH*-mutant diffuse grade II to III gliomas (hazard ratio, 1.01, $P = .12$).[19] This study also specifically evaluated the age cutoff of 40 years within *IDH*-mutant patients only and found no difference in OS of patients older than 40 compared to those 40 years and younger ($P = .66$). This finding highlights our opinion that the classical definition of "high-risk" in low-grade glioma requires reconsideration. Although the patient being considered here may be considered "high-risk" based on her residual tumor, her molecular profile would independently predict a protracted survival.

Secondly, as previously mentioned, RTOG 9802 did not address the timing of treatment after surgery. The only randomized, prospective data with regards to treatment timing in low-grade glioma remain EORTC 22845 (early vs late RT), which showed no difference in OS between treatment groups.[11] Moreover, recent retrospective analyses have suggested low-grade glioma patients considered "high-risk" by classical criteria (age > 40 and/or presence of residual tumor) have excellent OS times with initial observation alone, comparable to aggressive chemoradiation.[36,37] Surprisingly, Pal'a et al found that *IDH*-mutant, low-grade glioma patients lived significantly

longer without adjuvant treatment compared to immediate therapy with either chemoradiation, radiation alone, or chemotherapy alone, even among those patients who would classically be considered "high-risk" based on age older than 40 and/or residual tumor.[36] These studies are obviously limited by their retrospective nature, which leads to possible selection bias and other limiting factors such as short follow-up time (median follow-up time was only 6 years in Pal'a et al and 10.6 years in Youland et al[37]) and differences in type of chemotherapy used (the vast majority of chemotherapy-treated patients in Pal'a et al were given TMZ and not PCV). Nevertheless, these studies do highlight the fact that there remains considerable uncertainty regarding the significance of treatment timing on OS of patients with low-grade gliomas, particularly those who have molecular profiles predictive of indolent tumor behavior. We do agree that the currently available data on quality of life and neurocognitive side effects can be interpreted as conflicting and of suboptimal quality. Nevertheless, we consider the data provided by Douw and colleagues as robust enough to at least raise concern for neurocognitive side effects and inferior quality of life associated with radiation.[12,21]

Therefore, if we now consider the individual patient in front of us—a young, high-functioning person with a good prognostic molecular profile who depends on high-level cognitive ability for her employment—and aim to personalize the treatment based on the best current available data, we conclude that a period of careful clinical and radiographic surveillance and treatment at time of accelerated tumor growth or clear radiographic or clinical progression would be reasonable. This approach would allow this young woman to experience a longer life time period at her maximum cognitive capacity and, in our opinion, with potentially little or no compromise to her OS time. However, we acknowledge that prospective data are still lacking with regards to timing of adjuvant chemoradiation for these patients, and we emphasize that this case highlights the need for such prospective and randomized studies. Meanwhile, we hope that the ongoing CODEL (NCT00887146) and other clinical trials will shed further light on the effects of radiation and chemotherapy on neurocognition and quality of life in patients who receive treatment for *IDH*-mutant, 1p19q-codeleted oligodendrogliomas.

Discussion

Recent advances in the treatment of oligodendroglioma have significantly prolonged survival but also raised important questions regarding how to balance the benefits and toxicities associated with therapy. In patients with aggressive brain tumors such as glioblastoma, long-term toxicities of therapy are a relatively minor concern, experienced only by the fortunate subset of patients who significantly surpass median survival expectations. The situation is much different in tumors such as oligodendroglioma, with a median survival in excess of a decade. At the moment, we have high-quality evidence from multiple randomized trials that upfront treatment with PCV-based chemoradiotherapy significantly improves survival in patients with oligodendroglioma relative to radiation alone, and some evidence that delayed RT does not negatively affect survival compared to up-front radiation. Thus, one might conclude that delayed chemoradiotherapy may be equivalent to up-front chemoradiotherapy in terms of OS. However, this hypothesis remains to be proven, and the consequence of being incorrect is potentially years of patient survival. On the other hand, there is ample evidence in the literature that brain radiation is detrimental to cognition, in addition to the extensive anecdotal experience of neuro-oncologists who can recall long-term glioma survivors who were cognitively devastated by therapy. If the growth pattern of oligodendroglioma is slow and predictable, and the treatment of small-volume disease is equally effective in the initial postoperative setting or at time of progression, it could be in a patient's interest to delay chemoradiotherapy and subsequent toxicity as long as possible. Unfortunately, no large clinical trials are currently evaluating the question of early chemoradiotherapy vs observation in patients with high-risk oligodendroglioma (either WHO grade II or grade III), so no definitive answer to this controversy is forthcoming. For the foreseeable future clinicians and patients will need to continue to critically evaluate the available evidence and make decisions based on their judgment of the perceived risks and benefits of therapy. Consideration of the key points of this debate, as summarized in Table 1, may assist them in this effort.

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