

Focused Review
**Diagnosis, Treatment, and
Rehabilitation for Adult
Glioma**



Treatment of Adult Gliomas: A Current Update

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HIGHLIGHTS

- Glioma treatment requires multimodal approaches.
- The treatment should be optimized by glioma, patient, and molecular characteristics.

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Conflict of Interest

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ABSTRACT

Gliomas are the most common type of primary brain tumor in adults. Glioma treatment requires a multidisciplinary approach involving surgery, radiotherapy, and chemotherapy. Multiple trials have been conducted to establish the appropriate choice of treatment to achieve long-term survival and better quality of life. This review provides up-to-date evidence regarding treatment strategies for gliomas.

Keywords: Glioma; Treatment; Surgery; Radiotherapy; Chemotherapy

INTRODUCTION

Gliomas, which are the most common type of primary brain tumor in adults, develop in the brain parenchyma [1-3]. Gliomas can be classified by the layered diagnosis defined by the World Health Organization (WHO) [4]. The classification layers include the histological classification, grade, and molecular information. The histological classification depends on pathological factors, such as nuclear atypia, mitotic activity, perivascular proliferation, necrosis degree, and clinical outcomes. The WHO classification has recently undergone a significant change; molecular information has become the primary evidence for classifying gliomas and even determining the grade of gliomas, which was previously determined by classic histology [4].

The treatment modalities for gliomas generally consist of surgery, radiotherapy, and chemotherapy. The survival outcomes of patients with gliomas vary widely according to the glioma type and prognostic factors. Glioblastoma, isocitrate dehydrogenase (IDH)-wildtype showed a poor prognosis, with a median survival of only 12–18 months [1,5], whereas low-grade glioma had a longer median survival of 5–7 years [6]. Therefore, the types and sequences of modalities should be decided based on the prognostic factors and the glioma classification. The major prognostic factors are younger age and better performance status at diagnosis in adults with gliomas [7]. Furthermore, molecular genetic factors, especially IDH mutation and 1p/19q codeletion, had critical prognostic value in the classification of gliomas and have become disease-defining factors in the updated WHO classification. The methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter is a vital prognostic

factor favoring better survival and response to alkylating agent-based chemotherapy [5,8]. Telomerase reverse transcriptase promoter mutations, epidermal growth factor receptor (EGFR) amplification, and chromosome 7 gain and 10 loss in astrocytoma, IDH-wildtype have become a prerequisite to define glioblastoma, IDH-wildtype [4,9].

The recent redefinition of clinical and molecular information as prognostic factors has driven updates in treatment strategies for gliomas. This review article aimed to discuss the current state of treatment for adult gliomas, focusing on the treatment modalities and strategies depending on the type of glioma.

SURGICAL TREATMENT

The therapeutic goal of surgery is the maximal safe resection of tumors (i.e., resecting as much tumor tissue as is safely feasible to preserve neurological conditions). Advances in surgical techniques, including surgical navigation systems with functional magnetic resonance imaging (MRI) or diffusion tensor imaging and intraoperative MRI, functional monitoring, and fluorescence tumor visualization using 5-aminolevulinic acid, have been widely adopted to reduce postoperative residual tumor volume while minimizing the risk of surgery-induced neurological deficits [10]. Furthermore, recent advances in intraoperative neurophysiological monitoring have made it possible to minimize or estimate more precisely neurological sequelae according to the surgical extent [11]. The prevention of surgery-induced neurological deficits, which reduce patients' independence and performance, needs to be emphasized in surgery. Neurological defects can delay or hinder subsequent treatment, such as radiotherapy or chemotherapy, which are also critical treatments, especially for high-grade glioma, which is not controlled with surgery alone [12]. Except in emergent cases, shared decision-making with patients and caregivers should be considered to discuss the anticipated deficits and decide on the surgical extent before surgery [13].

Meanwhile, a lesser extent of surgery and greater residual tumor volume are negatively related to prognosis in high-grade glioma (e.g., glioblastoma) [14,15]. Furthermore, for maximal removal, supra-total resection beyond the MRI abnormalities has been recently suggested for high-grade glioma in non-eloquent regions [16,17]. In contrast, for IDH-mutant glioma, especially oligodendroglioma with IDH mutation and 1p/19q codeletion, the extent of resection has been shown to yield inconsistent prognostic results or even a negative correlation with survival [18,19].

After surgery, postoperative radiotherapy and chemotherapy should be performed according to the types, grades, and molecular features of gliomas as a standard treatment protocol.

LOW-GRADE GLIOMA, GRADE 2

Low-grade glioma consists of astrocytoma, IDH-mutant, WHO grade 2 and oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, WHO grade 2. Following surgery, a watch-and-wait policy can be cautiously adopted after gross total resection in young patients with no history of seizures related to the tumor. Postoperative radiotherapy for the involved field should be considered for patients with postoperative residual tumors or patients aged over 40 years. Early radiotherapy has been shown to improve seizure control and progression-

free survival (PFS) but not overall survival (OS) [6]. Chemotherapy alone with temozolomide might be considered only for patients who cannot tolerate radiotherapy. However, PFS after temozolomide alone is inferior to radiotherapy in astrocytoma, IDH-mutant, WHO grade 2 [20]. In RTOG 9802 trial, the addition of a procarbazine, lomustine, and vincristine (PCV) chemotherapy regimen to radiotherapy after resection prolonged the OS to 4–5 years in patients with high-risk low-grade glioma with young age (13–39 years) after subtotal resection or old age (over 40 years) [21]. This survival benefit was confirmed in patients with IDH-mutant tumors, but not those with IDH wild-type. Therefore, the standard postoperative treatment for high-risk patients with IDH-mutant glioma involves field radiotherapy followed by PCV. Radiotherapy doses ranging from 45 to 50 Gy can be sufficient in this group. A survival improvement with a high dose of 60 Gy or over was not observed in the EORTC 22844 and NCCTG/RTOG 9110 trials [22,23]. Moreover, late radiation-induced neurological deficits could be a concern for high doses in patients in whom long-term survival is expected.

OLIGODENDROGLIOMA, IDH-MUTANT, AND 1p/19q-CODELETED, WHO GRADE 3

For postoperative treatment, 2 large randomized controlled trials showed that the addition of PCV to radiotherapy improved OS [24,25]. The EORTC 26951 trial tested 6 cycles of PCV after radiotherapy, and the RTOG 9402 trial applied 4 cycles of PCV before radiotherapy. An absolute survival benefit of 5–6 years was observed in patients with oligodendroglioma, 1p/19q-codeleted, after the addition of PCV. Although these 2 studies analyzed small cohorts, the findings were validated by each other with similar results. However, alkylating chemotherapy alone seems not to have similar efficacy to radiotherapy with PCV. Temozolomide or PCV alone showed no difference in survival compared to radiotherapy alone in the NOA-04 trial [26]. Thus, PCV followed by radiotherapy (60 Gy) has become the standard treatment for this group. However, compliance for the completion of PCV cycles was problematic, as only 30%–50% of patients in the EORTC 26951 and RTOG 9402 trials complied. In contrast, temozolomide has shown a favorable safety profile with mild myelosuppression [5]. The modified CODEL trial will address whether temozolomide with radiotherapy can replace PCV with radiotherapy with better or similar outcomes [27].

ASTROCYTOMA, IDH-MUTANT, WHO GRADE 3–4

Postoperative radiotherapy is also recommended after surgery for astrocytoma, IDH-mutant, WHO grade 3–4. The radiotherapy dose is similar to that for other high-grade gliomas (60 Gy). The evidence for postoperative treatment primarily comes from subgroup analyses in trials of high-grade glioma, WHO grade 3. The EORTC 26053 (CANTON) trial compared the survival outcomes among radiotherapy alone, radiotherapy with concurrent temozolomide, and radiotherapy with adjuvant temozolomide [28]. The patients in this trial had 1p/19q non-codeleted glioma, including IDH-mutant astrocytoma and glioblastoma, IDH-wildtype. The updated results in 2021 showed no benefit from the addition of concurrent temozolomide, but improved survival with the addition of adjuvant temozolomide. Notably, only patients with IDH-mutant glioma showed survival benefits from temozolomide. Therefore, this ongoing trial needs to analyze further the benefit of temozolomide with concurrent or adjuvant use.

Astrocytoma, IDH-mutant, WHO grade 4 is newly defined in the WHO 2021 classification; this category was referred to as glioblastoma, IDH-mutant in the previous version of the WHO classification [4,29]. This type is frequently related to a long history and dedifferentiation of prior low-grade glioma and younger age. Even though it has a much more favorable prognosis than glioblastoma, IDH-wildtype, WHO grade 4, the appropriateness of treatment deintensification has not yet been proven. Furthermore, this type was included as glioblastoma in the landmark studies of glioblastoma [5]. Thus, the standard treatment for glioblastoma, IDH-wildtype is also recommended for this type.

GLIOBLASTOMA, IDH-WILDTYPE, WHO GRADE 4

Glioblastoma, IDH-wildtype, WHO grade 4 is the most common type of primary central nervous system malignancies and has the worst survival outcomes, with a 5%–10% OS rate in 5 years [2,7]. After maximal safe resection, radiotherapy with concurrent (75 mg/m²/day × 6 weeks) and adjuvant temozolomide (150–20 mg/m²/day × 5 days for six 28-day cycles) have been widely adopted as the standard of treatment for newly diagnosed glioblastoma patients. This regimen, called the Stupp regimen, showed a survival gain in a comparison between concurrent chemoradiation with adjuvant temozolomide and radiotherapy alone in the EORTC-NCI trial, a randomized phase III trial [5]. In this trial, MGMT methylation was a strong predictive factor for better responses and outcomes of the temozolomide regimen. However, the patients without MGMT methylation also received a smaller, but significant, survival gain. Therefore, regardless of MGMT methylation, the concurrent and adjuvant use of temozolomide with radiotherapy can be recommended for this group.

However, no additional change in regimens has appeared after the Stupp regimen. Neither increasing the dose of temozolomide [30] nor extending the length of adjuvant temozolomide over 6 cycles [31] resulted in survival benefits. The addition of bevacizumab to the Stupp regimen prolonged PFS at 3–4 months, but not OS, in 2 randomized phase III trials [32,33]. Furthermore, the toxicity related to bevacizumab increased, and PFS prolongation did not reach the prespecified range [32,33]. Thus, bevacizumab is not widely adopted as a first-line treatment. Targeted therapy has long been investigated for the receptor tyrosine kinase-PI3K, PT53, and Rb pathway, which is considered a frequent and crucial tumorigenic pathway in glioblastoma, IDH-wildtype [34]. However, a tumor-specific antibody-drug conjugate consisting of an antibody (ABT-806) directed against activated EGFR failed to achieve survival benefits in combination with standard therapy for newly diagnosed EGFR-amplified glioblastoma [35], despite the promising results for recurrent tumors [36]. In a phase III trial of immunotherapy testing Rindopepimut, an EGFR-targeted vaccine showed negative results in patients with EGFRvIII-positive glioblastoma [37]. Currently, the first-line chemotherapy has remained in the standard Stupp regimen. Although immune therapy or targeted therapy trials failed to yield first-line treatments, a multimodal approach with novel therapies combined with the standard treatment might improve survival outcomes in the future.

A radiotherapy dose of 60 Gy in 1.8–2 Gy per fraction has been the standard radiotherapy regimen, the same as the Stupp regimen [5]. Increasing doses beyond 60 Gy and using radiosurgery or brachytherapy did not show survival improvements [38,39]. Still, the standard dose of 60 Gy in 30 fractions with concurrent and adjuvant temozolomide is the standard of care for patients with good performance or young age (< 70 years). Otherwise, an abbreviated course of radiotherapy has been explored for patients with poor prognoses,

especially the elderly. Although only supportive care without radiotherapy compromised OS in patients aged ≥ 70 years with good performance (Karnofsky Performance Scale ≥ 70) [40], short-course hypofractionated radiotherapy of 40 Gy in 15 fractions or 34 Gy in 10 fractions has shown similar efficacy to conventional irradiation with 60 Gy in 30 fractions in patients with unfavorable prognostic factors in age or performance [41,42]. Ultra-short radiotherapy with 5×5 Gy doses also showed no difference in OS for patients with poor performance or old age [43]. Although hypofractionation needs to be used cautiously due to concerns about neurotoxicity compared to conventional fractionation, hypofractionation with short-course radiotherapy can be recommended for frail patients with old age or poor performance. The addition of temozolomide to hypofractionated radiotherapy has also improved OS in patients with age ≥ 65 years [41]. However, the survival gains with temozolomide in hypofractionated radiotherapy regimens are limited in patients with methylated MGMT. Furthermore, in 2 phase 3 trials, temozolomide alone without radiotherapy showed similar survival to hypofractionated radiotherapy in patients with old age or poor performance when the MGMT promoter was methylated [42,44,45]. Thus, temozolomide alone without radiotherapy can be considered for frail patients with MGMT methylation who would not be able to tolerate multimodal treatments. However, it remains a matter of debate whether frail patients with old age or poor performance should receive temozolomide in addition to short-course hypofractionated radiotherapy. If MGMT is unmethylated, the omission of temozolomide with radiotherapy alone could be considered based on findings showing a minimal gain of survival in these patients [41]. However, compliance with treatment and severe toxicity were not significantly different between temozolomide alone and chemoradiotherapy [41]. Furthermore, the addition of temozolomide showed survival gain in all frail patients with old age or poor performance, similar to Stupp's trial [5,41]. Therefore, hypofractionated radiotherapy with or without temozolomide can be the standard treatment for the elderly, and the addition or omission of temozolomide to hypofractionated radiotherapy needs to be evaluated in further trials [46].

REHABILITATION AND SUPPORTIVE CARE

Patients with glioma frequently experience neurological dysfunction throughout the disease course. Especially with the progression of the disease, medical and social support have become mandatory for patients and their caregivers [47]. Therefore, an early discussion and integration of rehabilitation and supportive care will be required for all patients with glioma. Furthermore, the best supportive care without oncological interventions would be appropriate for patients who have severe neurologic deficits that cannot be restored by surgery or radiotherapy [48].

Steroids are often necessary to control tumor-associated edema, improve clinical symptoms, and facilitate the treatment of gliomas. However, steroids should not be considered for prophylactic aims in asymptomatic patients with edema. The usage of steroids has been shown to have a negative prognostic effect on OS in patients in large cohorts [49]. Moreover, the long-term use of steroids can induce steroid-related toxicity, such as Cushing syndrome or immune dysfunction. Seizure is a common symptom at presentation. Like steroids, antiepileptic drugs need to be maintained at the lowest possible level for seizure control [50]. Furthermore, the routine prophylactic use of antiepileptic drugs after surgery is not recommended for patients without a seizure history [51].

CONCLUSION

The treatment of glioma requires a multidisciplinary approach incorporating surgery, radiotherapy, and chemotherapy. The clinical outcomes have been improved with advances in multimodal treatments. The appropriate choice of treatment modality will be different according to the type of glioma, categorized by the clinical-histological features, molecular evidence, and anticipated prognosis. Recent progress in understanding the molecular pathogenesis of gliomas has been applied to the classification of glioma types. However, progress in improving survival outcomes is still limited and challenging in gliomas. Novel therapies based on molecular biology should be explored through further experimental studies and clinical trials.

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