Brain Neurorehabil. 2022 Nov;15(3):e24
https://doi.org/10.12786/bn.2022.15.e24
pISSN 1976-8753·eISSN 2383-9910

Brain & NeuroRehabilitation

Focused Review

Diagnosis, Treatment, and Rehabilitation for Adult Glioma

Treatment of Adult Gliomas: A Current Update

Joo Ho Lee, Chan Woo Wee

Received: Oct 13, 2022
Revised: Nov 21, 2022
Accepted: Nov 22, 2022
Published online: Nov 29, 2022

Correspondence to
Joo Ho Lee
Department of Radiation Oncology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Email: jooholee@snu.ac.kr

HIGHLIGHTS

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

Brain Neurorehabil. 2022 Nov;15(3):e24
https://doi.org/10.12786/bn.2022.15.e24
pISSN 1976-8753·eISSN 2383-9910

bnr
Brain & NeuroRehabilitation

Focused Review

Diagnosis, Treatment, and Rehabilitation for Adult Glioma

Check for updates

Treatment of Adult Gliomas: A Current Update

Joo Ho Lee [1,2] **Chan Woo Wee** [1,3]

[1]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea
[2]Department of Radiation Oncology, Seoul National University Hospital, Seoul, Korea
[3]Department of Radiation Oncology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

OPEN ACCESS

Received: Oct 13, 2022
Revised: Nov 21, 2022
Accepted: Nov 22, 2022
Published online: Nov 29, 2022

Correspondence to
Joo Ho Lee
Department of Radiation Oncology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Email: jooholee@snu.ac.kr

ORCID iDs
Joo Ho Lee
https://orcid.org/0000-0001-7248-3214
Chan Woo Wee
https://orcid.org/0000-0002-0631-7549

Funding
None.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

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-

https://doi.org/10.12786/bn.2022.15.e24

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.

https://doi.org/10.12786/bn.2022.15.e24

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/m^2/day × 6 weeks) and adjuvant temozolomide (150–20 mg/m^2/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,

https://doi.org/10.12786/bn.2022.15.e24

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 additional 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].

https://doi.org/10.12786/bn.2022.15.e24

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.

REFERENCES

1. Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med 2008;359:492-507.
PUBMED | CROSSREF
2. Lee JH, Lee JH. The origin-of-cell harboring cancer-driving mutations in human glioblastoma. BMB Rep 2018;51:481-483.
PUBMED | CROSSREF
3. Lee JH, Lee JE, Kahng JY, Kim SH, Park JS, Yoon SJ, Um JY, Kim WK, Lee JK, Park J, Kim EH, Lee JH, Lee JH, Chung WS, Ju YS, Park SH, Chang JH, Kang SG, Lee JH. Human glioblastoma arises from subventricular zone cells with low-level driver mutations. Nature 2018;560:243-247.
PUBMED | CROSSREF
4. Figarella-Branger D, Appay R, Metais A, Tauziède-Espariat A, Colin C, Rousseau A, Varlet P. The 2021 WHO classification of tumours of the central nervous system. Ann Pathol 2022;42:367-382.
PUBMED | CROSSREF
5. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy GroupsNational Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-996.
PUBMED | CROSSREF
6. van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, Malmström PO, Collette L, Piérart M, Mirimanoff R, Karim AB; EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005;366:985-990.
PUBMED | CROSSREF
7. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21:v1-v100.
PUBMED | CROSSREF
8. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med 2000;343:1350-1354.
PUBMED | CROSSREF
9. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, Pekmezci M, Rice T, Kosel ML, Smirnov IV, Sarkar G, Caron AA, Kollmeyer TM, Praska CE, Chada AR, Halder C, Hansen HM, McCoy LS, Bracci PM, Marshall R, Zheng S, Reis GF, Pico AR, O'Neill BP, Buckner JC, Giannini C, Huse JT, Perry A, Tihan T, Berger MS, Chang SM, Prados MD, Wiemels J, Wiencke JK, Wrensch MR, Jenkins RB. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 2015;372:2499-2508.
PUBMED | CROSSREF
10. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7:392-401.
PUBMED | CROSSREF

https://doi.org/10.12786/bn.2022.15.e24

11. Kim SM, Kim SH, Seo DW, Lee KW. Intraoperative neurophysiologic monitoring: basic principles and recent update. J Korean Med Sci 2013;28:1261-1269.
PUBMED | CROSSREF

12. Gulati S, Jakola AS, Nerland US, Weber C, Solheim O. The risk of getting worse: surgically acquired deficits, perioperative complications, and functional outcomes after primary resection of glioblastoma. World Neurosurg 2011;76:572-579.
PUBMED | CROSSREF

13. Sorensen von Essen H, Poulsen FR, Dahlrot RH, Piil K, Steffensen KD. Development of a patient decision aid to support shared decision making for patients with recurrent high-grade glioma. Int J Environ Res Public Health 2022;19:7396.
PUBMED | CROSSREF

14. Molinaro AM, Hervey-Jumper S, Morshed RA, Young J, Han SJ, Chunduru P, Zhang Y, Phillips JJ, Shai A, Lafontaine M, Crane J, Chandra A, Flanigan P, Jahangiri A, Cioffi G, Ostrom Q, Anderson JE, Badve C, Barnholtz-Sloan J, Sloan AE, Erickson BJ, Decker PA, Kosel ML, LaChance D, Eckel-Passow J, Jenkins R, Villanueva-Meyer J, Rice T, Wrensch M, Wiencke JK, Oberheim Bush NA, Taylor J, Butowski N, Prados M, Clarke J, Chang S, Chang E, Aghi M, Theodosopoulos P, McDermott M, Berger MS. Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. JAMA Oncol 2020;6:495-503.
PUBMED | CROSSREF

15. Grabowski MM, Recinos PF, Nowacki AS, Schroeder JL, Angelov L, Barnett GH, Vogelbaum MA. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg 2014;121:1115-1123.
PUBMED | CROSSREF

16. Roh TH, Kang SG, Moon JH, Sung KS, Park HH, Kim SH, Kim EH, Hong CK, Suh CO, Chang JH. Survival benefit of lobectomy over gross-total resection without lobectomy in cases of glioblastoma in the noneloquent area: a retrospective study. J Neurosurg 2019;132:895-901.
PUBMED | CROSSREF

17. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir (Wien) 2016;158:51-58.
PUBMED | CROSSREF

18. Ding X, Wang Z, Chen D, Wang Y, Zhao Z, Sun C, Chen D, Tang C, Xiong J, Chen L, Yao Z, Liu Y, Wang X, Cahill DP, de Groot JF, Jiang T, Yao Y, Zhou L. The prognostic value of maximal surgical resection is attenuated in oligodendroglioma subgroups of adult diffuse glioma: a multicenter retrospective study. J Neurooncol 2018;140:591-603.
PUBMED | CROSSREF

19. Yordanova YN, Duffau H. Supratotal resection of diffuse gliomas - an overview of its multifaceted implications. Neurochirurgie 2017;63:243-249.
PUBMED | CROSSREF

20. Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, Brandes AA, Kantor G, Taphoorn MJ, Hassel MB, Hartmann C, Ryan G, Capper D, Kros JM, Kurscheid S, Wick W, Enting R, Reni M, Thiessen B, Dhermain F, Bromberg JE, Feuvret L, Reijneveld JC, Chinot O, Gijtenbeek JM, Rossiter JP, Dif N, Balana C, Bravo-Marques J, Clement PM, Marosi C, Tzuk-Shina T, Nordal RA, Rees J, Lacombe D, Mason WP, Stupp R. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol 2016;17:1521-1532.
PUBMED | CROSSREF

21. Bell EH, Zhang P, Shaw EG, Buckner JC, Barger GR, Bullard DE, Mehta MP, Gilbert MR, Brown PD, Stelzer KJ, McElroy JP, Fleming JL, Timmers CD, Becker AP, Salavaggione AL, Liu Z, Aldape K, Brachman DG, Gertler SZ, Murtha AD, Schultz CJ, Johnson D, Laack NN, Hunter GK, Crocker IR, Won M, Chakravarti A. Comprehensive genomic analysis in NRG oncology/RTOG 9802: a phase III trial of radiation versus radiation plus procarbazine, lomustine (CCNU), and vincristine in high-risk low-grade glioma. J Clin Oncol 2020;38:3407-3417.
PUBMED | CROSSREF

22. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, Mascarenhas F, Horiot JC, Parvinen LM, van Reijn M, Jager JJ, Fabrini MG, van Alphen AM, Hamers HP, Gaspar L, Noordman E, Pierart M, van Glabbeke M. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 1996;36:549-556.
PUBMED | CROSSREF

23. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, Nelson D, Earle J, Jones C, Cascino T, Nichols D, Ivnik R, Hellman R, Curran W, Abrams R. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002;20:2267-2276.
PUBMED | CROSSREF

24. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, Fink K, Souhami L, Laperriere N, Curran W, Mehta M. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31:337-343.
PUBMED | CROSSREF

25. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Enting RH, French PJ, Dinjens WN, Vecht CJ, Allgeier A, Lacombe D, Gorlia T, Hoang-Xuan K. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344-350.
PUBMED | CROSSREF

26. Wick W, Roth P, Hartmann C, Hau P, Nakamura M, Stockhammer F, Sabel MC, Wick A, Koeppen S, Ketter R, Vajkoczy P, Eyupoglu I, Kalff R, Pietsch T, Happold C, Galldiks N, Schmidt-Graf F, Bamberg M, Reifenberger G, Platten M, von Deimling A, Meisner C, Wiestler B, Weller M; Neurooncology Working Group (NOA) of the German Cancer Society. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. Neuro Oncol 2016;18:1529-1537.
PUBMED | CROSSREF

27. Jaeckle KA, Ballman KV, van den Bent M, Giannini C, Galanis E, Brown PD, Jenkins RB, Cairncross JG, Wick W, Weller M, Aldape KD, Dixon JG, Anderson SK, Cerhan JH, Wefel JS, Klein M, Grossman SA, Schiff D, Raizer JJ, Dhermain F, Nordstrom DG, Flynn PJ, Vogelbaum MA. CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design. Neuro Oncol 2021;23:457-467.
PUBMED | CROSSREF

28. van den Bent MJ, Tesileanu CM, Wick W, Sanson M, Brandes AA, Clement PM, Erridge S, Vogelbaum MA, Nowak AK, Baurain JF, Mason WP, Wheeler H, Chinot OL, Gill S, Griffin M, Rogers L, Taal W, Rudà R, Weller M, McBain C, Reijneveld J, Enting RH, Caparrotti F, Lesimple T, Clenton S, Gijtenbeek A, Lim E, Herrlinger U, Hau P, Dhermain F, de Heer I, Aldape K, Jenkins RB, Dubbink HJ, Kros JM, Wesseling P, Nuyens S, Golfinopoulos V, Gorlia T, French P, Baumert BG. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2021;22:813-823.
PUBMED | CROSSREF

29. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803-820.
PUBMED | CROSSREF

30. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, Armstrong TS, Wefel JS, Won M, Blumenthal DT, Mahajan A, Schultz CJ, Erridge S, Baumert B, Hopkins KI, Tzuk-Shina T, Brown PD, Chakravarti A, Curran WJ Jr, Mehta MP. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol 2013;31:4085-4091.
PUBMED | CROSSREF

31. Balana C, Vaz MA, Manuel Sepúlveda J, Mesia C, Del Barco S, Pineda E, Muñoz-Langa J, Estival A, de Las Peñas R, Fuster J, Gironés R, Navarro LM, Gil-Gil M, Alonso M, Herrero A, Peralta S, Olier C, Perez-Segura P, Covela M, Martinez-García M, Berrocal A, Gallego O, Luque R, Perez-Martín FJ, Esteve A, Munne N, Domenech M, Villa S, Sanz C, Carrato C. A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GEINO 14-01). Neuro Oncol 2020;22:1851-1861.
PUBMED | CROSSREF

32. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L, Cloughesy T. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-722.
PUBMED | CROSSREF

33. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ Jr, Mehta MP. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
PUBMED | CROSSREF

34. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008;455:1061-1068.
PUBMED | CROSSREF

35. Lassman A, Pugh S, Wang T, Aldape K, Gan H, Preusser M, Vogelbaum M, Sulman E, Won M, Zhang P, Moazami G, Macsai M, Gilbert M, Bain E, Blot V, Ansell P, Samanta S, Kundu M, Seidel C, De Vos F, Hsu S, Cardona A, Lombardi G, Bentsion D, Peterson R, Gedye C, Lebrun-Frénay C, Wick A, Curran W, Mehta M. ACTR-21. A randomized, double-blind, placebo-controlled phase 3 trial of depatuxizumab mafodotin (ABT-414) in epidermal growth factor receptor (EGFR) amplified (AMP) newly diagnosed glioblastoma (nGBM). Neuro Oncol 2019;21:vi17.
CROSSREF

36. Van Den Bent M, Eoli M, Sepulveda JM, Smits M, Walenkamp A, Frenel JS, Franceschi E, Clement PM, Chinot O, De Vos F, Whenham N, Sanghera P, Weller M, Dubbink HJ, French P, Looman J, Dey J, Krause S, Ansell P, Nuyens S, Spruyt M, Brilhante J, Coens C, Gorlia T, Golfinopoulos V. INTELLANCE 2/EORTC 1410 randomized phase II study of Depatux-M alone and with temozolomide vs temozolomide or lomustine in recurrent EGFR amplified glioblastoma. Neuro Oncol 2020;22:684-693.
PUBMED | CROSSREF

37. Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, Ashby L, Mechtler L, Goldlust SA, Iwamoto F, Drappatz J, O'Rourke DM, Wong M, Hamilton MG, Finocchiaro G, Perry J, Wick W, Green J, He Y, Turner CD, Yellin MJ, Keler T, Davis TA, Stupp R, Sampson JH; ACT IV trial investigators. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol 2017;18:1373-1385.
PUBMED | CROSSREF

38. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys 2004;60:853-860.
PUBMED | CROSSREF

39. Malouff TD, Peterson JL, Mahajan A, Trifiletti DM. Carbon ion radiotherapy in the treatment of gliomas: a review. J Neurooncol 2019;145:191-199.
PUBMED | CROSSREF

40. Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, Guillamo JS, Jadaud E, Colin P, Bondiau PY, Meneï P, Loiseau H, Bernier V, Honnorat J, Barrié M, Mokhtari K, Mazeron JJ, Bissery A, Delattre JY; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-1535.
PUBMED | CROSSREF

41. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, Fisher B, Fulton D, Gulavita S, Hao C, Husain S, Murtha A, Petruk K, Stewart D, Tai P, Urtasun R, Cairncross JG, Forsyth P. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 2004;22:1583-1588.
PUBMED | CROSSREF

42. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, Abacioglu U, Tavelin B, Lhermitte B, Hegi ME, Rosell J, Henriksson R; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012;13:916-926.
PUBMED | CROSSREF

43. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, Hentati D, Guedes de Castro D, Dyttus-Cebulok K, Drodge S, Ghosh S, Jeremić B, Rosenblatt E, Fidarova E. International atomic energy agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 2015;33:4145-4150.
PUBMED | CROSSREF

44. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, Nikkhah G, Papsdorf K, Steinbach JP, Sabel M, Combs SE, Vesper J, Braun C, Meixensberger J, Ketter R, Mayer-Steinacker R, Reifenberger G, Weller M; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707-715.
PUBMED | CROSSREF

45. Wick A, Kessler T, Platten M, Meisner C, Bamberg M, Herrlinger U, Felsberg J, Weyerbrock A, Papsdorf K, Steinbach JP, Sabel M, Vesper J, Debus J, Meixensberger J, Ketter R, Hertler C, Mayer-Steinacker R, Weisang S, Bölting H, Reuss D, Reifenberger G, Sahm F, von Deimling A, Weller M, Wick W. Superiority

of temozolomide over radiotherapy for elderly patients with RTK II methylation class, MGMT promoter methylated malignant astrocytoma. Neuro Oncol 2020;22:1162-1172.
PUBMED | CROSSREF

46. Wee CW, Kim IH, Park CK, Kim N, Suh CO, Chang JH, Lim DH, Nam DH, Kim IA, Kim CY, Oh YT, Chung WK, Kim SH. Chemoradiation in elderly patients with glioblastoma from the multi-institutional GBM-molRPA cohort: is short-course radiotherapy enough or is it a matter of selection? J Neurooncol 2020;148:57-65.
PUBMED | CROSSREF

47. Bradley S, Sherwood PR, Donovan HS, Hamilton R, Rosenzweig M, Hricik A, Newberry A, Bender C. I could lose everything: understanding the cost of a brain tumor. J Neurooncol 2007;85:329-338.
PUBMED | CROSSREF

48. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, Henriksson R, Le Rhun E, Balana C, Chinot O, Bendszus M, Reijneveld JC, Dhermain F, French P, Marosi C, Watts C, Oberg I, Pilkington G, Baumert BG, Taphoorn MJ, Hegi M, Westphal M, Reifenberger G, Soffietti R, Wick W; European Association for Neuro-Oncology (EANO) Task Force on Gliomas. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 2017;18:e315-e329.
PUBMED | CROSSREF

49. Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, Dai C, Ozawa T, Chang M, Chan TA, Beal K, Bishop AJ, Barker CA, Jones TS, Hentschel B, Gorlia T, Schlegel U, Stupp R, Weller M, Holland EC, Hambardzumyan D. Corticosteroids compromise survival in glioblastoma. Brain 2016;139:1458-1471.
PUBMED | CROSSREF

50. van Breemen MS, Rijsman RM, Taphoorn MJ, Walchenbach R, Zwinkels H, Vecht CJ. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol 2009;256:1519-1526.
PUBMED | CROSSREF

51. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2000;54:1886-1893.
PUBMED | CROSSREF