NCCN Guidelines® Insights

Central Nervous System Cancers, Version 1.2015

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System (CNS) Cancers provide interdisciplinary recommendations for managing adult CNS cancers. Primary and metastatic brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. These NCCN Guidelines Insights summarize the NCCN CNS Cancers Panel's discussion and highlight notable changes in the 2015 update. This article outlines the data and provides insight into panel decisions regarding adjuvant radiation and chemotherapy treatment options for high-risk newly diagnosed low-grade gliomas and glioblastomas. Additionally, it describes the panel's assessment of new data and the ongoing debate regarding the use of alternating electric field therapy for high-grade gliomas. (J Natl Compr Canc Netw 2015;13:1191–1202)

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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

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The full and most current version of these NCCN Guidelines are available at NCCN.org.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Central Nervous System Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Central Nervous System Cancers

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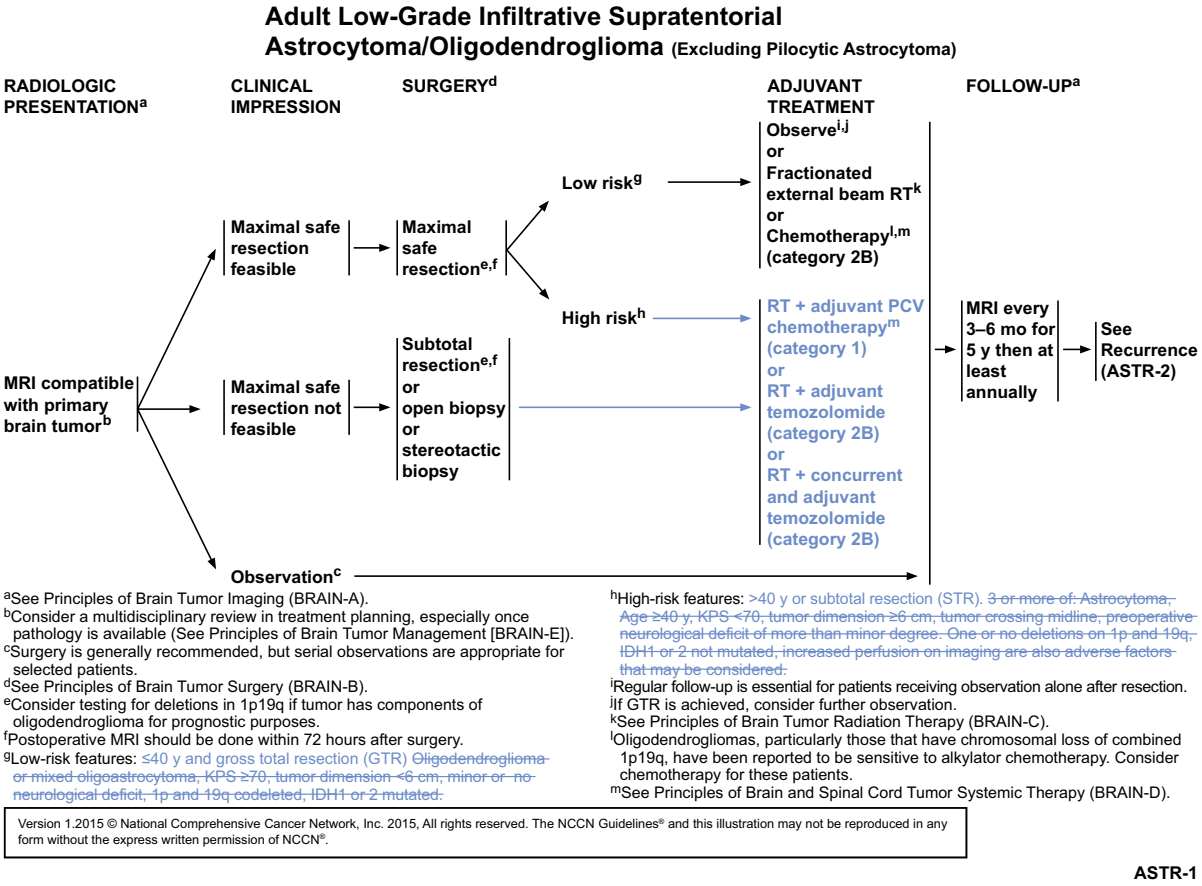


NCCN Categories of Evidence and Consensus

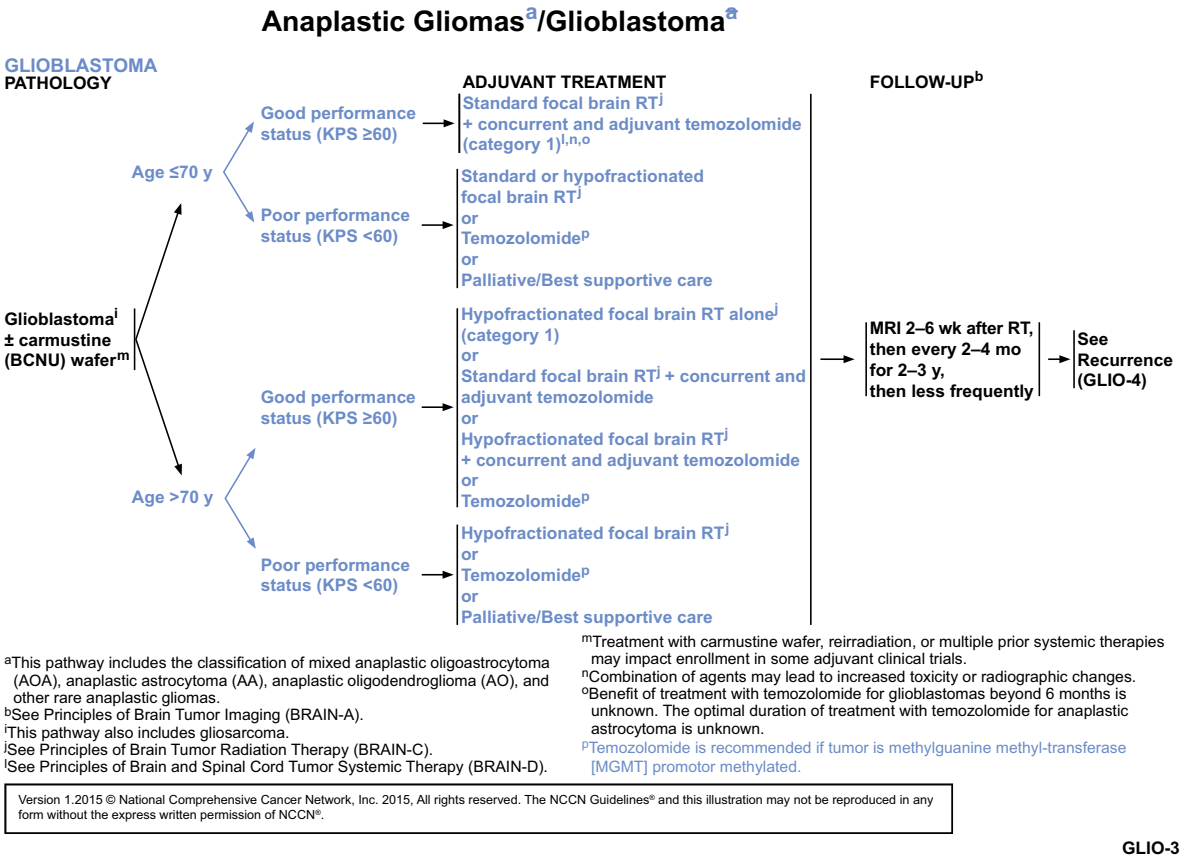
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

In 2015, an estimated 22,850 people in the United States will be diagnosed with primary malignant brain or other central nervous system (CNS) neoplasms, and these tumors will be responsible for approximately 15,320 deaths.[1] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CNS Cancers focus on management of adult CNS cancers: anaplastic gliomas and glioblastoma, low-grade infiltrative astrocytomas, oligodendrogliomas, ependymomas, brain metastases, leptomeningeal metastases, non–AIDS-related primary CNS lymphomas (PCNSLs), metastatic spinal tumors, meningiomas, primary spinal cord tumors, and primitive neuroectodermal tumors. These NCCN Guidelines Insights focus on changes to the recommendations for treatment of gliomas based on new data, including changes to the chemotherapy, radiation therapy (RT), and chemoradiation regimens recommended for postoperative adjuvant treatment



[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain Tumor Imaging (BRAIN-A).
[i]This pathway also includes gliosarcoma.
[j]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[l]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[m]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[n]Combination of agents may lead to increased toxicity or radiographic changes.
[o]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.
[p]Temozolomide is recommended if tumor is methylguanine methyl-transferase [MGMT] promotor methylated.

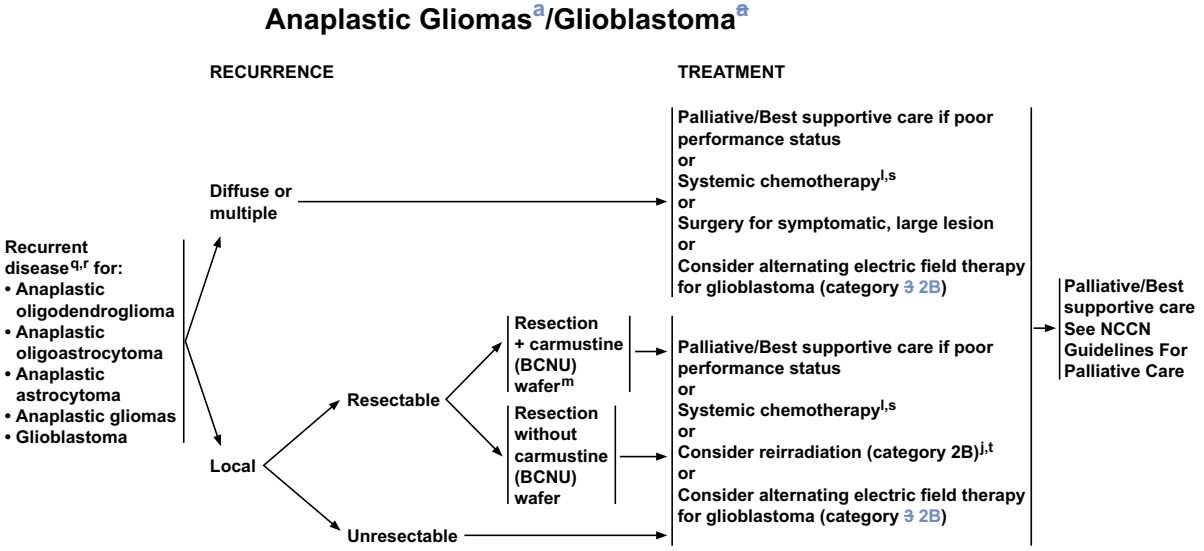
GLIO-3

of newly diagnosed high-risk low-grade gliomas (see ASTR-1, page 1193) and glioblastomas (see GLIO-3, this page). This article also summarizes the panel's assessment and discussion of the clinical data on alternating electric field therapy for newly diagnosed and recurrent glioblastoma.

New Adjuvant Treatment Options for High-Risk Low-Grade Gliomas

Whereas noninfiltrative astrocytomas, usually pilocytic astrocytomas (WHO grade I), are typically noninvasive and curable by surgery alone, diffuse astrocytomas are poorly circumscribed and invasive, and most gradually evolve into high-grade astrocytomas.[2,3] Diffusely infiltrative low-grade gliomas include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas; they are a diverse group classified as grade II under the WHO grading system[4] that make up approximately 10% of newly diagnosed primary brain tumors.[5] The aggressiveness of these tumors varies by subtype, and patients with grade II oligodendrogliomas have a much better 5-year survival rate (70%) than those with mixed gliomas (56%) and astrocytomas (37%).[5] Other factors prognostic for progression-free survival (PFS) or overall survival (OS) in patients with grade II gliomas include age, tumor diameter, tumor crossing midline, neurologic or performance status prior to surgery, and the presence of certain molecular markers, such as a 1p19q codeletion in oligodendrogliomas and the presence of an isocitrate dehydrogenase (IDH) 1 or 2 mutation in grade II astrocytomas.[6–15]

For supratentorial WHO grade II gliomas, the NCCN Guidelines recommend that primary treatment aim to achieve as complete an excision as possible (based on postsurgical MRI verification) without compromising function. Multivariate analysis from a number of studies in patients with primary low-grade gliomas show that extent of resection is a significant



[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[j]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[l]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[m]Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.
[q]Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.
[r]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.
[s]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[t]Especially if long interval since prior RT and/or if there was a good response to prior RT.

GLIO-4

prognostic factor for PFS and/or OS.[8–13,16–20] Patients who undergo a subtotal resection, open biopsy, or stereotactic biopsy are therefore considered to be at higher risk for progression (see ASTR-1, page 1193).

Adjuvant RT after resection is supported by data from several retrospective studies comparing outcomes in patients with newly diagnosed low-grade gliomas who after surgery received no adjuvant treatment versus RT.[17,21,22] The recommended dosing for postoperative RT is based on results from 2 phase III randomized trials showing that higher dose RT had no significant effect on OS or time to progression,[8,10] and several retrospective analyses showing similar results.[9,11,21] Because higher doses offer no clear advantages, the NCCN CNS Cancers Panel recommends low-dose RT (45–54 Gy) for treatment of low-grade gliomas (grades I/II), including high-risk cases (see ASTR-1, page 1193). The timing of postoperative RT was tested in a phase III multicenter study (EORTC 22845) that showed improved PFS and greater reduction in seizure frequency in patients who received RT soon after surgery versus at time of disease progression.[23] Early versus late postoperative RT did not significantly affect OS, however, suggesting that observation is a reasonable option for some patients with newly diagnosed gliomas.[23] Results of EORTC 22845 were corroborated by several other analyses. The positive effect of RT on seizure control was confirmed in a retrospective study in patients with low-grade gliomas and medically intractable epilepsy.[24] A large meta-analysis, including data from 4 phase III trials (EORTC 22844 and 22845,[8,23] RTOG 9802,[25] and NCCTG 86-72-51[10]), confirmed that surgery followed by RT significantly improves PFS but not OS.[26] A retrospective study (N=95) showed that administering RT within 3 months of surgery versus delaying RT until progression improved PFS but not OS.[27] Although no consensus exists on the optimal timing of postoperative RT for low-grade gliomas in young healthy patients, the panel recom-

mends immediate postoperative RT in patients who are older, symptomatic, or have less-than-total resection (see ASTR-1, page 1193).

Combination chemotherapy with procarbazine, lomustine, and vincristine (PCV) has been used in the adjuvant setting for patients with newly diagnosed low-grade gliomas based on small retrospective and phase II studies showing positive outcomes in patients who had partial resection or biopsy.[28–30] These data showing clinical activity of PCV as adjuvant therapy for newly diagnosed low-grade gliomas prompted a multicenter phase III randomized clinical trial, RTOG 9802, which assessed the efficacy of adjuvant RT versus RT followed by 6 cycles of PCV in patients with newly diagnosed supratentorial WHO grade II gliomas and at least 1 of 2 risk factors for disease progression: subtotal resection or age of 40 years or older.[25] For randomization, patients were stratified by age, tumor histologic subtype, Karnofsky performance status (KPS), and presence of enhancement on preoperative MRI. Although the interim analysis (median follow-up, 5.9 years) showed that addition of PCV significantly improved PFS but not OS,[25] results from long-term follow-up (median, 11.9 years) showed significant improvements in both PFS and OS.[31,32] With the addition of PCV, median survival time increased from 7.8 to 13.3 years (P=.02), and the 10-year survival rate increased from 41% to 62%. Based on these results, the NCCN CNS Cancers Panel voted to include RT plus adjuvant PCV chemotherapy as a category 1 recommendation for adjuvant treatment of patients with newly diagnosed low-grade gliomas at high risk for recurrence as per the trial criteria: patients older than 40 years or of any age with residual disease after surgery (subtotal resection, open biopsy, stereotactic (see ASTR-1, page 1193). It is important to note, however, that roughly three-quarters of the study patients had a KPS of 90 to 100, and the median age was approximately 40 years.[25] Given that the addition of PCV to adjuvant RT significantly increased the percent of patients who experienced grade 3 or 4 adverse events,[25] the risk versus benefit of adjuvant PCV has yet to be determined for patients who are elderly or infirm. Furthermore, whether PCV is appropriate for all patients with high-risk low-grade glioma is not yet clear. For example, for patients with astrocytoma, the benefit provided by PCV (vs observation) was diminished relative to those with other tumor subtypes, such as oligodendroglioma or oligoastrocytoma. Significant improvement was observed for PFS but not OS in the patients with astrocytoma.[32]

Use of temozolomide as adjuvant monotherapy for newly diagnosed low-grade gliomas after surgery is supported by results from noncomparative studies showing objective responses and reduced seizure frequency.[33–37] One retrospective comparative study showed that for patients with low-grade gliomas and new-onset seizures at presentation, adjuvant temozolomide monotherapy provided significant reduction in seizure frequency in significantly more patients compared with observation after surgery or biopsy.[38] Preliminary results from a large multicenter phase III randomized trial (EORTC 22033-26033, N=477) show that PFS is not significantly different for adjuvant RT versus dose-dense temozolomide in patients with resected or biopsied supratentorial grade II glioma and more than 1 risk factor: age of 40 years or older; progressive, new, or worsening neurologic symptoms; and intractable seizures.[39] Combined treatment with RT plus temozolomide is supported by a phase II multicenter trial (RTOG 0424) in patients with supratentorial WHO grade II tumors and at least 3 risk factors (age ≥40 years, astrocytoma, bihemispheric, tumor diameter ≥6 cm, neurologic function status >1).[40] Patients treated with concurrent and adjuvant temozolomide had OS rates at 3 and 5 years of 73.1% and 57.1%, respectively, which are positive results when compared with survival estimates for patients with similar risk factors treated with postoperative RT alone in previous trials (EORTC trials 22844 and 22845, and North American Intergroup trial 86-72-51).[6,7,26] However, because the historical controls included patients treated in an earlier period using different RT protocols, prospective controlled trials are needed to confirm the positive effect of adding temozolomide to adjuvant RT for the treatment of low-grade gliomas. Because panel consensus was nonuniform regarding the inclusion of RT with adjuvant temozolomide and RT with concurrent and adjuvant temozolomide, these options were included as category 2B recommendations for adjuvant treatment of patients with high-risk newly diagnosed low-grade gliomas (see ASTR-1, page 1193).

Based on the strength of the RTOG 9802 results, the panel agreed with adding RT with chemotherapy as a treatment option for patients with recurrent or

progressive low-grade gliomas who have not had prior RT (see ASTR-2, available online, in these guidelines, at NCCN.org). Although patients with recurrent or progressive low-grade gliomas were not included in RTOG 9802, there are very few data to inform treatment of these patients, because most of the studies in recurrent or progressive low-grade gliomas include patients who have had prior RT. There are a few small noncomparative studies in patients with no prior RT showing that temozolomide or PCV provide clinical responses (radiologic) and reduction in seizures or other neurologic symptoms.[41–44] In addition, as mentioned earlier, the EORTC 22033-26033 phase III trial included patients with progressive low-grade gliomas, and initial results suggest similar PFS for adjuvant temozolomide (monotherapy) versus RT.[39] Results from this and other randomized trials are needed to better inform treatment of recurrent/progressive low-grade gliomas.

Adjuvant Therapy for Glioblastomas

Glioblastomas (grade IV astrocytomas) are the most common primary malignant brain tumors in adults, accounting for 54.7% of all gliomas.[45] Glioblastomas are the most aggressive brain tumor, with fewer than 50% of patients surviving for 1 year, and only 5% living beyond 5 years.[45–47] For first-line treatment of glioblastomas, the NCCN Guidelines recommend maximal safe resection with or without placement of a carmustine (BCNU) wafer. If gross total resection is not feasible, then subtotal resection or stereotactic/open biopsy are options. After surgical intervention, the choice of adjuvant therapy for glioblastoma depends on a patient's age and performance status.[48–51] To improve readability, the panel reorganized the algorithm, providing recommendations for adjuvant treatment of newly diagnosed glioblastomas (see GLIO-3, page 1194). Table 1 shows the recommended adjuvant treatment options from the 2014 and 2015 NCCN Guidelines for specific subgroups of patients based on age and performance score. These recommendations are primarily based on results from large randomized trials (Table 2). The notable changes include (1) removing standard RT as a treatment option for elderly patients (age >70 years) with poor performance status (KPS <60), and (2) adding hypofractionated RT with concurrent and adjuvant temozolomide for elderly patients who have a good performance status.

Hypofractionated Radiation Therapy for Elderly Patients With a Poor Performance Status

Fractionated RT as adjuvant therapy for high-grade gliomas is based on several randomized trials showing improved survival compared with supportive care or BCNU alone.[52–55] Two randomized trials and a large retrospective analysis have shown that, in elderly patients (age >60 years), adjuvant therapy with hypofractionated RT (34-40 Gy in 10–15 fractions over 2–3 weeks) has similar or better efficacy compared with standard RT (60 Gy in 30–33 fractions over 6–7 weeks; Table 2).[48,50,56] The Nordic Clinical Brain Tumor Study Group (NCBTSG) phase III multicenter randomized trial also showed that, for patients aged 60 to 70 years, there was no significant difference in survival between standard versus hypofractionated RT, but patients older than 70 years had better median survival with hypofractionated versus standard RT (Table 2).[48] In the NCBTSG trial, hypofractionated RT was better tolerated than standard RT, and more patients were able to complete their full RT course. For elderly patients (age >70 years) with glioblastoma who opt for adjuvant treatment with RT alone, these findings support the recommendation to use hypofractionated RT rather than standard RT.

Hypofractionated Radiation Therapy With Concurrent and Adjuvant Temozolomide for Elderly Patients With a Good Performance Status

Standard RT with concurrent and adjuvant temozolomide is the standard of care for adjuvant treatment of newly diagnosed glioblastoma in patients who are younger and have a good performance status, based on the EORTC 26981-22981/NCIC CE3 multicenter international phase III randomized controlled trial showing significantly improved PFS and OS compared with RT alone (Table 2).[51] The use of this regimen in patients who are elderly or frail has been debated because this landmark clinical trial did not include patients older than 70 years and was not adequately powered to assess treatment effects in the subset of patients aged 60 to 70 years. For patients older than 70 years but with good performance, some evidence from small single-center studies suggests the usefulness of temozolomide in addition to adjuvant RT.[57,58]

Building on the findings that hypofractionated RT (monotherapy) has similar or better efficacy and safety compared with standard RT (monotherapy) for adjuvant treatment of glioblastoma in the elderly, a number of noncomparative studies have reported

Table 1 Recommendations for Adjuvant Treatment of Glioblastoma[a]

Age	KPS	2014 Treatment Options	2015 Treatment Options
≤70 y	≥60	• Fractionated external-beam RT + concurrent and adjuvant temozolomide (category 1)	• Standard focal brain RT + concurrent and adjuvant temozolomide (category 1)
≤70 y	<60	• Fractionated external-beam RT (hypofractionated or standard) • Chemotherapy • Palliative/Best supportive care	• Standard or hypofractionated focal brain RT • Temozolomide[b] • Palliative/Best supportive care
>70 y	≥60	• Fractionated external-beam RT (hypofractionated) (category 1) • Fractionated external-beam RT + concurrent and adjuvant temozolomide • Chemotherapy (temozolomide MGMT promoter methylation positive)	• Hypofractionated focal brain RT alone (category 1) • Standard focal brain RT + concurrent and adjuvant temozolomide • Hypofractionated focal brain RT + concurrent and adjuvant temozolomide • Temozolomide[b]
>70 y	<60	• Fractionated external-beam RT (hypofractionated or standard) • Chemotherapy • Palliative/Best supportive care	• Hypofractionated focal brain RT • Temozolomide[b] • Palliative/Best supportive care

Abbreviation: KPS, Karnofsky performance status; RT, radiotherapy.
[a]Changes to GLIO-3, see page 1194.
[b]Temozolomide is recommended if tumor is methylguanine methyl-transferase (MGMT) promotor methylated.

positive results from patients treated with hypofractionated RT plus concurrent and adjuvant temozolomide. These studies have shown median OS ranging from 15 to 20 months for adult populations with good performance status and broad age range,[59–66] and median OS of 12.4 to 14.4 months for studies in patients who were elderly or had other risk factors.[67–69] A large retrospective analysis of elderly patients treated with RT plus concurrent and adjuvant temozolomide found no significant differences in OS and PFS with standard versus hypofractionated RT (Table 2).[50] This finding was confirmed by analysis of 90 propensity-score matched pairs and by stratified analyses of prognostic factors. However, standard RT therapy was associated with increased rates of failure to complete the course of RT, grade 2/3 neurologic toxicities, decline in KPS scores during treatment, and corticosteroid dose increase during or soon after their RT course (Table 2). Patients included in this retrospective analysis had a KPS of 60 or greater, so these findings support the use of hypofractionated RT with concurrent and adjuvant temozolomide as a reasonable adjuvant treatment option for elderly patients with a good performance status.

Alternating Electric Field Therapy

Alternating electric field therapy for treatment of high-grade gliomas is a topic of ongoing debate as evidence continues to emerge. In 2011, the FDA approved a portable medical device that generates low-intensity alternating electric fields, termed *tumor treating fields* (TTF), for the treatment of recurrent glioblastoma. Approval was based on the results of a clinical trial (EF-11) that randomized 237 patients with recurrent glioblastoma to either TTF or the treating oncologist's choice of chemotherapy.[70] Although similar survival was observed in the 2 arms, TTF therapy was associated with lower toxicity and improved quality of life. This study was not blinded, however, and therefore quality-of-life assessments may have been compromised. A recent development in this area includes the publication of an analysis of the Patient Registry Dataset (PRiDe) reporting real-world outcomes for 457 patients who received TTF for recurrent glioblastoma.[71] Although OS with TTF was significantly higher in the PRiDE data set analysis than in the EF-11 phase III trial,[71] patients in the former may have received concomitant therapy that could account for the improvement in survival. Other recent developments that were discussed among the panel members were abstract presentations of EF-14,[72,73] a phase III trial in patients with newly diagnosed glioblastoma (n=700) that showed an improvement in median PFS and OS in patients treated after radiation and concurrent temozolomide with temozolomide plus TTF versus adjuvant temozolomide monotherapy (PFS, 7.1 vs 4.2 months; P=.0010; OS, 19.4 vs 16.6 months; P=.0222).[73]

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Table 2 Key Trials in Adjuvant Care for Newly Diagnosed Glioblastoma[a]

Trial	Patients Analyzed	Adjuvant Treatments and Median Follow-up	Efficacy Results	Safety/HRQoL Results
Prospective, randomized, multicenter, Canadian Roa et al,[56] 2004	N=95 Age ≥60 y KPS ≥50	• Standard RT[b] (n=47) • HypoRT[c] (n=48) Stratification: biopsy vs resection, KPS <70 vs ≥70 Follow-up: until all dead	Failed to complete RT: 26% vs 10% No effect on survival[d]: • Median 5.1 vs 5.6 mo (*P*=.57) • 6-mo: 44.7% vs 41.7% • Similar results when stratified by extent resection	• KPS scores: effect of treatment NS difference between arms • Required corticosteroid dose increase (n=78 completed treatment): 49% vs 23% (P=.02)
EORTC 26981-22981/ NCIC CE3 Phase III, randomized, multicenter, international ClinicalTrials.gov identifier: NCT00006353 Stupp et al,[51] 2009	N=573 Age 18–70 y WHO PS 0–2	• Standard RT[b] (n=286) • Standard RT[b] + concurrent and adjuvant TMZ (n=287) Stratification: WHO PS, surgery type, institution Follow-up: 69 mo (11 d–79 mo)	TMZ improves OS: • Median 12.1 vs 14.6 mo • P<.0001 throughout follow-up • TMZ improved OS for both MGMT promoter methylated (*P*=.004) and unmethylated (*P*=.035) TMZ improves PFS: *P*<.0001	• HRQoL maintained in both arms • Toxicity low and HRQoL maintained in both arms • Late (>9 mo after RT completion) grade 3–4 AEs: 1 (fatigue) vs 2 (visual deficit, seizures)
NCBTSG Phase III, randomized, open-label, multicenter, international ISRCTN81470623 Malmstrom et al,[48] 2012	N=342 Age: ≥60 y WHO PS 0–2[e]	3-group randomization: • TMZ (n=93) • HypoRT[f] (n=98) • Standard RT[b] (N=100) 2-group randomization: • TMZ (n=26) • HypoRT (n=25) Stratification: institution[g]	Completed RT: 95% vs 72% Median OS • Age 60–70 y: NS for all treatment comparisons • Age >70 y: Standard RT vs TMZ: 5.2 vs 9.0 mo (*P*<.0001) Standard RT vs HypoRT: 5.2 vs 7.0 (*P*=.02) TMZ vs HypoRT: NS	AEs: • TMZ vs either RT arm: more nausea, vomiting, infection/ fever, hematologic AEs • Standard RT vs HypoRT: more infection/ fever, intracranial hemorrhage, seizures, nausea, vomiting; fewer thromboembolic events, bleeding
NOA-08[a] Phase III, randomized, multicenter, Germany and Switzerland ClinicalTrials.gov identifier: NCT01502241 Wick et al,[74] 2012	N=373 Age >65 y KPS ≥60	• RT[h] (n=178) • TMZ (n=195) Follow-up: 25.2 mo, minimum 12 mo	Survival: • Median 9.6 vs 8.6 mo • 1-y rate: 37.4% vs 34.4% • TMZ noninferior to RT EFS: • Median 4.7 vs 3.3 mo • 1-y rate: 12.0% vs 9.3% • TMZ noninferior to RT • For MGMT methylation positive, TMZ significantly better than RT; for unmethylated, RT is significantly better	AEs: More frequent with TMZ in all categories except cutaneous AEs
Retrospective, multicenter, Italy Minniti et al,[50] 2015	N=243 Age: ≥65 y KPS ≥60	Concomitant and adjuvant TMZ + • Standard RT[h] (n=127) • HypoRT[c] (n=116) Follow-up: 24.0, 22.5 mo	Failed to complete RT course: 8.5% vs 1.7% OS median: 12 vs 12.5 mo (NS) PFS median: 5.6 vs 6.7 mo (NS)	• Grade 2–3 neurologic toxicities: 40% vs 14% (P=.01) • KPS score worsened: 44% vs 23% (P=.01) • Corticosteroid dose increased (≥4 mg during and/or early after RT): 48% vs 32% (P=.02)

Abbreviations: AC, astrocytoma; AE, adverse events; EORTC, European Organization for Research and Treatment of Cancer; GBM, glioblastoma; HRQoL, health-related quality of life; hypoRT, hypofractionated radiotherapy; KPS, Karnofsky performance status; NCBTSG, Nordic Clinical Brain Tumor Study Group; NCIC, National Cancer Institute of Canada; NOA, Neuro-oncology Working Group of the German Cancer Society; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; PS, performance status; RT, radiotherapy; STR, subtotal resection; TMZ, temozolomide.

[a]Patients included in these trials were newly diagnosed with glioblastoma, defined as WHO grade IV astrocytoma, except for 11% of the patients in the NOA-08 trial with anaplastic astrocytoma. All patients received resection or biopsy before adjuvant therapy.

[b]Standard RT: 60 Gy, 30 fractions, 5 d/wk, 6 wk.

[c]HypoRT: 40 Gy, 15 fractions.

[d]Trial was powered to show that there is not a >14% difference in 6-mo survival rate.

[e]WHO PS =3 allowed if only due to neurologic deficits.

[f]HypoRT: 34.0 Gy total, 10 fractions, 2 wk, 5 d/wk, allowed daily fractionation.

[g]Arms were balanced for age, percent patients with biopsy vs resection, WHO PS, percent patients with concomitant steroids.

[h]Standard RT: 60.0 Gy, 1.8-2.0 Gy/fraction, 6–7 wk.

[i]All discontinuations were due to clinical deterioration.

Some panelists expressed the opinion that the results from EF-14 and PRiDE provide additional evidence of clinical activity and thus give further support for TTF treatment in patients with recurrent glioblastoma. Others argued that data from the prospective, randomized EF-11 study provided a more accurate measure of the true efficacy in recurrent disease than the PRiDE data. Based on the 2015 panel vote, the inclusion of "Consider alternating electric field therapy for glioblastoma" changed from a category 3 to a category 2B recommendation (see GLIO-4, page 1195). The panel awaits peer-reviewed publication of results from the EF-14 trial before deciding whether to add TTF as a treatment option for newly diagnosed glioblastoma.

Conclusions

The NCCN Guidelines for CNS Cancers are updated annually to include new information or treatment philosophies as they become available. The NCCN Guidelines are sometimes updated more often if new high-quality clinical data become available. Because this field evolves continually, practitioners should use all of the available information to determine the best clinical options for their patients. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient for providing optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN CNS Cancers Panel strongly encourages participation in prospective clinical trials.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Piepmeier J, Christopher S, Spencer D, et al. Variations in the natural history and survival of patients with supratentorial low-grade astrocytomas. Neurosurgery 1996;38:872–878; discussion 878–879.
3. Afra D, Osztie E, Sipos L, Vitanovics D. Preoperative history and postoperative survival of supratentorial low-grade astrocytomas. Br J Neurosurg 1999;13:299–305.
4. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109.
5. CBTRUS: Statistical report: Primary Brain Tumors in the United States, 1995-1999. Chicago, IL: Central Brain Tumor Registry of the United States; 2002.
6. Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002;20:2076–2084.
7. Daniels TB, Brown PD, Felten SJ, et al. Validation of EORTC prognostic factors for adults with low-grade glioma: a report using intergroup 86-72-51. Int J Radiat Oncol Biol Phys 2011;81:218–224.
8. Karim AB, Maat B, Hatlevoll R, et al. 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.
9. Lo SS, Cho KH, Hall WA, et al. Does the extent of surgery have an impact on the survival of patients who receive postoperative radiation therapy for supratentorial low-grade gliomas? Int J Cancer 2001;96(Suppl):71–78.
10. Shaw E, Arusell R, Scheithauer B, et al. 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.
11. Lo SS, Hall WA, Cho KH, et al. Radiation dose response for supratentorial low-grade glioma--institutional experience and literature review. J Neurol Sci 2003;214:43–48.
12. Jeremic B, Milicic B, Grujicic D, et al. Hyperfractionated radiation therapy for incompletely resected supratentorial low-grade glioma: a 10-year update of a phase II study. Int J Radiat Oncol Biol Phys 2003;57:465–471.
13. Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg 2008;109:835–841.
14. Nitta M, Muragaki Y, Maruyama T, et al. Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection. Neurosurg Focus 2015;38:E7.
15. Houillier C, Wang X, Kaloshi G, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 2010;75:1560–1566.
16. Philippon JH, Clemenceau SH, Fauchon FH, Foncin JF. Supratentorial low-grade astrocytomas in adults. Neurosurgery 1993;32:554–559.
17. Kang HC, Kim IH, Eom KY, et al. The role of radiotherapy in the treatment of newly diagnosed supratentorial low-grade oligodendrogliomas: comparative analysis with immediate radiotherapy versus surgery alone. Cancer Res Treat 2009;41:132–137.
18. Kaya V, Aksu MG, Korcum AF, et al. Clinical prognostic factors of adjuvant radiation therapy for low-grade gliomas: results of 10 years survival. Int J Clin Exp Med 2014;7:1336–1343.
19. Schomas DA, Laack NN, Rao RD, et al. Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic. Neuro Oncol 2009;11:437–445.
20. Turkoglu E, Gurer B, Sanli AM, et al. Clinical outcome of surgically treated low-grade gliomas: a retrospective analysis of a single institute. Clin Neurol Neurosurg 2013;115:2508–2513.
21. Shaw EG, Daumas-Duport C, Scheithauer BW, et al. Radiation therapy in the management of low-grade supratentorial astrocytomas. J Neurosurg 1989;70:853–861.
22. Yeh SA, Lee TC, Chen HJ, et al. Treatment outcomes and prognostic factors of patients with supratentorial low-grade oligodendroglioma. Int J Radiat Oncol Biol Phys 2002;54:1405–1409.
23. van den Bent MJ, Afra D, de Witte O, et al. 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.
24. Ruda R, Magliola U, Bertero L, et al. Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. Neuro Oncol 2013;15:1739–1749.
25. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol 2012;30:3065–3070.
26. Gorlia T, Wu W, Wang M, et al. New validated prognostic models and prognostic calculators in patients with low-grade gliomas diagnosed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. Neuro Oncol 2013;15:1568–1579.
27. Buglione M, Pedretti S, Gipponi S, et al. Radiotherapy in low-grade glioma adult patients: a retrospective survival and neurocognitive toxicity analysis. Radiol Med 2014;119:432–439.
28. Lebrun C, Fontaine D, Bourg V, et al. Treatment of newly diagnosed symptomatic pure low-grade oligodendrogliomas with PCV chemotherapy. Eur J Neurol 2007;14:391–398.
29. Iwadate Y, Matsutani T, Hasegawa Y, et al. Favorable long-term outcome of low-grade oligodendrogliomas irrespective of 1p/19q status when treated without radiotherapy. J Neurooncol 2011;102:443–449.
30. Buckner JC, Gesme D, Jr., O'Fallon JR, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol 2003;21:251–255.

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31. Buckner JC, Pugh SL, Shaw EG, et al. Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG [abstract]. J Clin Oncol 2014;32(Suppl):Abstract 2000.
32. Buckner J, Shaw E, Pugh S, et al. R9802: Phase III study of radiation therapy (RT) with or without procarbazine CCNU, and vincristine (PCV) in low-grade glioma: results by histologic type [abstract AT-13]. Neuro-Oncology 2014;16:v11.
33. Brada M, Viviers L, Abson C, et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. Ann Oncol 2003;14:1715–1721.
34. Hoang-Xuan K, Capelle L, Kujas M, et al. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. J Clin Oncol 2004;22:3133–3138.
35. Kesari S, Schiff D, Drappatz J, et al. Phase II study of protracted daily temozolomide for low-grade gliomas in adults. Clin Cancer Res 2009;15:330–337.
36. Everhard S, Kaloshi G, Criniere E, et al. MGMT methylation: a marker of response to temozolomide in low-grade gliomas. Ann Neurol 2006;60:740–743.
37. Pouratian N, Gasco J, Sherman JH, et al. Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. J Neurooncol 2007;82:281–288.
38. Sherman JH, Moldovan K, Yeoh HK, et al. Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. J Neurosurg 2011;114:1617–1621.
39. Baumert BG, Mason WP, Ryan G, et al. Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade glioma: a randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033) [abstract]. J Clin Oncol 2013;31(Suppl):Abstract 2007.
40. Fisher BJ, Hu C, Macdonald DR, et al. Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys 2015;91:497–504.
41. Levin N, Lavon I, Zelikovitsh B, et al. Progressive low-grade oligodendrogliomas: response to temozolomide and correlation between genetic profile and O6-methylguanine DNA methyltransferase protein expression. Cancer 2006;106:1759–1765.
42. Kaloshi G, Benouaich-Amiel A, Diakite F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. Neurology 2007;68:1831–1836.
43. Tosoni A, Franceschi E, Ermani M, et al. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. J Neurooncol 2008;89:179–185.
44. Peyre M, Cartalat-Carel S, Meyronet D, et al. Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherapy in low-grade gliomas. Neuro Oncol 2010;12:1078–1082.
45. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol 2014;16 Suppl 4:iv1–63.
46. Wachtel MS, Yang S. Odds of death after glioblastoma diagnosis in the United States by chemotherapeutic era. Cancer Med 2014;3:660–666.
47. Darefsky AS, King JT Jr, Dubrow R. Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of Surveillance, Epidemiology, and End Results registries. Cancer 2012;118:2163–2172.
48. Malmstrom A, Gronberg BH, Marosi C, et al. 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.
49. Chang CH, Horton J, Schoenfeld D, et al. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. Cancer 1983;52:997–1007.
50. Minniti G, Scaringi C, Lanzetta G, et al. Standard (60 gy) or short-course (40 gy) irradiation plus concomitant and adjuvant temozolomide for elderly patients with glioblastoma: a propensity-matched analysis. Int J Radiat Oncol Biol Phys 2015;91:109–115.
51. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459–466.
52. Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 1978;49:333–343.
53. Kristiansen K, Hagen S, Kollevold T, et al. Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer 1981;47:649–652.
54. Andersen AP. Postoperative irradiation of glioblastomas. Results in a randomized series. Acta Radiol Oncol Radiat Phys Biol 1978;17:475–484.
55. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527–1535.
56. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 2004;22:1583–1588.
57. Brandes AA, Vastola F, Basso U, et al. A prospective study on glioblastoma in the elderly. Cancer 2003;97:657–662.
58. Minniti G, De Sanctis V, Muni R, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma in elderly patients. J Neurooncol 2008;88:97–103.
59. Reddy K, Damek D, Gaspar LE, et al. Phase II trial of hypofractionated IMRT with temozolomide for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2012;84:655–660.
60. Iuchi T, Hatano K, Kodama T, et al. Phase 2 trial of hypofractionated high-dose intensity modulated radiation therapy with concurrent and adjuvant temozolomide for newly diagnosed glioblastoma. Int J Radiat Oncol Biol Phys 2014;88:793-800.
61. Ney DE, Carlson JA, Damek DM, et al. Phase II trial of hypofractionated intensity-modulated radiation therapy combined with temozolomide and bevacizumab for patients with newly diagnosed glioblastoma. J Neurooncol 2015;122:135-143.
62. Miwa K, Matsuo M, Ogawa S, et al. Hypofractionated high-dose irradiation with positron emission tomography data for the treatment of glioblastoma multiforme. Biomed Res Int 2014;2014:407026.
63. Terasaki M, Eto T, Nakashima S, et al. A pilot study of hypofractionated radiation therapy with temozolomide for adults with glioblastoma multiforme. J Neurooncol 2011;102:247-253.
64. Jastaniyah N, Murtha A, Pervez N, et al. Phase I study of hypofractionated intensity modulated radiation therapy with concurrent and adjuvant temozolomide in patients with glioblastoma multiforme. Radiat Oncol 2013;8:38.
65. Yoon SM, Kim JH, Kim SJ, et al. Hypofractionated intensity-modulated radiotherapy using simultaneous integrated boost technique with concurrent and adjuvant temozolomide for glioblastoma. Tumori 2013;99:480-487.
66. Chen C, Damek D, Gaspar LE, et al. Phase I trial of hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2011;81:1066-1074.
67. Panet-Raymond V, Souhami L, Roberge D, et al. Accelerated hypofractionated intensity-modulated radiotherapy with concurrent and adjuvant temozolomide for patients with glioblastoma multiforme: a safety and efficacy analysis. Int J Radiat Oncol Biol Phys 2009;73:473-478.
68. Minniti G, Lanzetta G, Scaringi C, et al. Phase II study of short-course radiotherapy plus concomitant and adjuvant temozolomide in elderly patients with glioblastoma. Int J Radiat Oncol Biol Phys 2012;83:93-99.
69. Floyd SR, Kasper EM, Uhlmann EJ, et al. Hypofractionated Radiotherapy and Stereotactic Boost with Concurrent and Adjuvant Temozolamide for Glioblastoma in Good Performance Status Elderly Patients - Early Results of a Phase II Trial. Front Oncol 2012;2:122.
70. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192-2202.
71. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol 2014;41 Suppl 6:S4-S13.
72. Stupp R, Taillibert S, Kanner A, et al. Tumor treating fields (TTFields): A novel treatment modality added to standard chemo- and radiotherapy in newly diagnosed glioblastoma--First report of the full dataset of the EF14 randomized phase III trial. ASCO Meeting Abstracts 2015;33:2000.
73. Stupp R, Wong E, Scott C, et al. NT-40Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM. Neuro-Oncology 2014;16:v167.
74. Wick W, Platten M, Meisner C, et al. 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.

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Posttest Questions

1. A 45-year-old woman is diagnosed with WHO grade II oligodendroglioma. The tumor has been completely resected. Which adjuvant treatment is recommended based on category 1 evidence and consensus?
   There is only one correct answer:
   a. Fractionated external-beam radiation therapy (without chemotherapy)
   b. Chemotherapy (without radiation therapy)
   c. Radiation therapy followed by adjuvant PCV (procarbazine, lomustine, and vincristine) chemotherapy
   d. Radiation therapy followed by adjuvant temozolomide
2. True or false: For elderly patients (age >70 years) with glioblastoma who opt for postoperative adjuvant treatment with radiation therapy (RT) alone, hypofractionated RT is preferred over the standard radiation regimen.
3. For patients with glioblastoma who are elderly (age >70 years) but have good performance status (Karnofsky performance status ≥60), which of the following postoperative adjuvant treatments are recommended?
   1. Hypofractionated focal brain radiotherapy (alone)
   2. Temozolomide (alone)
   3. Standard focal brain radiation with concurrent and adjuvant temozolomide
   4. Hypofractionated focal brain radiation with concurrent and adjuvant temozolomide

   There is only one correct answer:
   a. 1 and 2
   b. 4 only
   c. All of the above (1–4)