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Clinical Practice Guideline

Radiation Therapy for WHO Grade 4 Adult-Type Diffuse Glioma: An ASTRO Clinical Practice Guideline

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Purpose: The central nervous system World Health Organization (WHO) grade 4 adult-type diffuse glioma represents one of the most aggressive and challenging primary brain tumors. This guideline aims to provide evidence-based recommendations for the multidisciplinary management of these tumors, focusing on diagnosis, initial treatment, reirradiation, and health disparities, while acknowledging that present literature primarily represents historical histologic grade 4 glioblastoma.

Methods: The American Society for Radiation Oncology convened a task force to address 4 key questions focused on indications for radiation therapy (RT) and/or adjunctive therapies (eg, systemic therapy, alternating electric field therapy), appropriate regimens for external beam RT after initial biopsy/resection including variables such as pretreatment characteristics, target volumes, technique, dose, reirradiation indications and techniques, and health disparities. Recommendations are based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Following maximum safe resection, molecular and pathologic diagnosis, and prognostic stratification of WHO grade 4 adult-type diffuse glioma, concurrent RT with temozolomide followed by adjuvant temozolomide is recommended for eligible patients and incorporation of alternating electric field therapy is conditionally recommended. In elderly patients, hypofractionated RT with concurrent and adjuvant temozolomide is conditionally recommended. In frail patients, supportive and palliative care is conditionally recommended following multidisciplinary, patient-centered discussion. Appropriate reirradiation techniques, with or without additional systemic therapies, can be considered and are conditionally recommended in patients following pathologic or advanced imaging confirmation of WHO grade 4 diffuse glioma recurrence. Health disparities exist in patients with WHO grade 4 adult-type diffuse glioma and attention is necessary to improve outcomes and increase clinical trial enrollment for underserved populations.

Conclusions: These evidence-based recommendations and current practice adoption patterns inform best clinical practices on the management of WHO grade 4 adult-type diffuse glioma. Future advancements in personalized medicine, biomarker discovery, and novel therapies are essential to improving outcomes. The integration of multidisciplinary care and participation in future clinical trials, especially in underserved populations, is crucial in addressing the poor outcomes among WHO grade 4 adult-type diffuse glioma.

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision-making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before the initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, sex, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or well-conducted meta-analyses of such randomized trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis including such a trial **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, because of absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower QoE, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submitting for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Introduction

Glioblastoma (GBM), now classified as central nervous system (CNS) World Health Organization (WHO) grade 4 adult-type diffuse glioma (histologic GBM), is the most aggressive and common primary malignant brain tumor in adults (Fig. 1). Even with optimal treatment, including advances in surgical techniques, radiation therapy (RT), and systemic therapy options, the prognosis remains poor, with a median survival of 15 to 17 months and a 5-year survival rate of <10%.[3] The highly infiltrative nature of WHO grade 4 diffuse glioma, coupled with its genetic and molecular heterogeneity, presents significant challenges in its management. Interpretation of the evidence has been further complicated by study cohorts defined by heterogeneous histologic classifications until recent years when molecular markers became both more available and allowed for more accuracy in diagnosis and prognosis. The characterization of high-grade glioma, and specifically histologic GBM being defined as WHO grade 4 diffuse glioma, is an evolution of the WHO Classification of Tumors of the Central Nervous System.[4] Similarly, median outcomes of patients with high-grade glioma have improved in clinical trials because the conventional treatment of RT to 6000 cGy with concurrent and adjuvant temozolomide (TMZ) was established in 2006.[5,6] This guideline replaces the 2016 ASTRO Guideline on Radiation Therapy for Glioblastoma[7] to reflect changes from the past decade, particularly in the context of the 2021 WHO Classification of Tumors of the Central Nervous System entities.[4,8] Additionally, health equity and disparities literature within WHO grade 4 diffuse glioma management was reviewed with the purpose of creating opportunities for future research.

As the understanding of the biology and molecular genetics of malignant glioma has evolved, so has the nomenclature of the 2021 CNS WHO classification system.[4,8] It is now recognized that diffuse glioma in adults are biologically and genetically distinct from their pediatric counterparts.[8] Therefore, the discussion is limited to adult-type diffuse glioma. The emergence of biomarkers affects the subtyping of diffuse glioma and how they are graded. Diffuse glioma grading is no longer based on histology alone and now incorporates additional molecular information.[8,9] Whereas the presence of vascular proliferation and/or necrosis

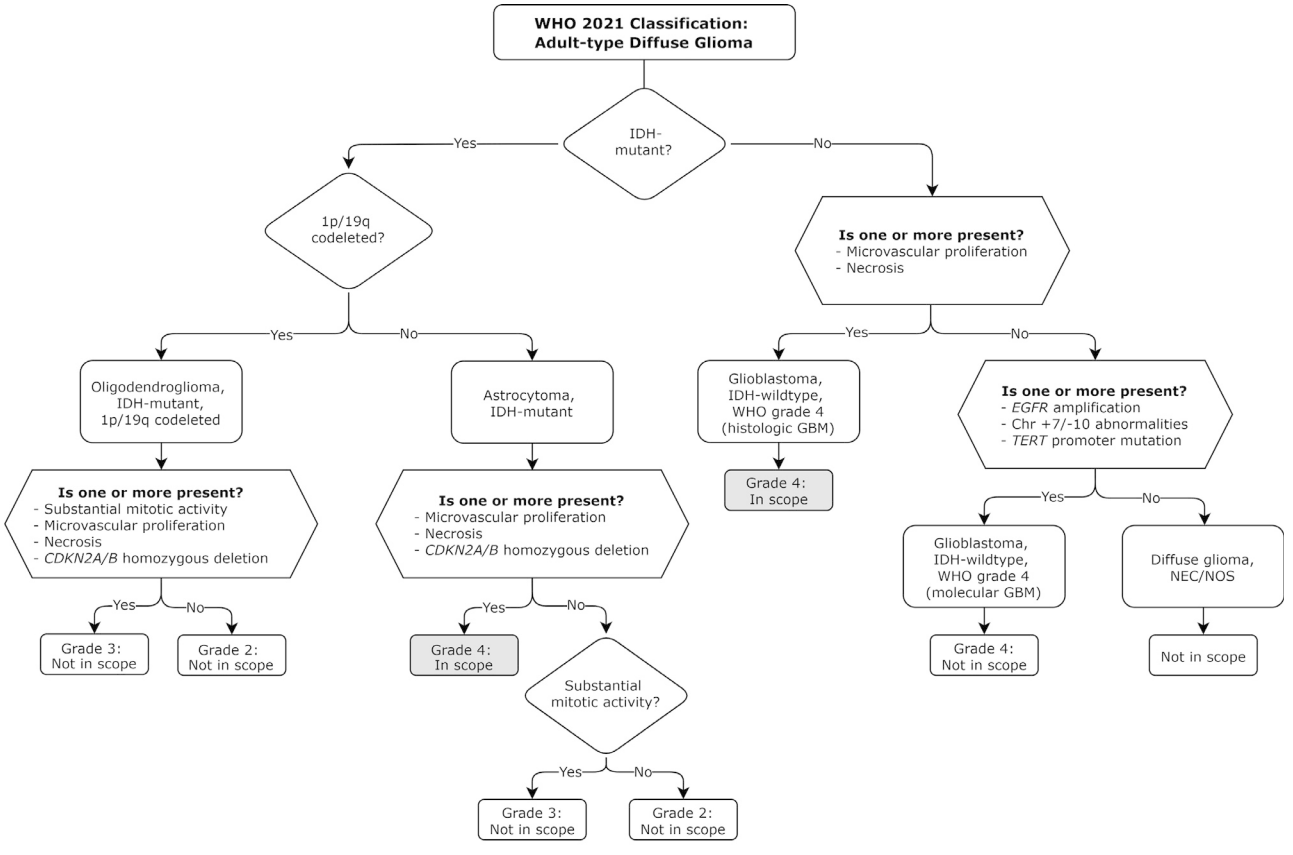


Figure 1 WHO 2021 classification: adult-type diffuse glioma.

Abbreviations: CDKN2A/B = cyclin-dependent kinase inhibitor 2A/B; Chr = chromosome; EGFR = epidermal growth factor receptor; GBM = glioblastoma; IDH = isocitrate dehydrogenase; NEC = not elsewhere classified; NOS = not otherwise specified; TERT = telomerase reverse transcriptase; WHO = World Health Organization.

historically characterized grade 4 diffuse glioma, the definition has now been expanded to incorporate entities previously regarded as lower-grade. Specific molecular alterations within previously characterized histologic WHO grade 2 or 3 tumors now define these entities as molecular GBM, which is out of scope for this guideline. These include isocitrate dehydrogenase (IDH)-wildtype astrocytoma harboring (1) epidermal growth factor receptor amplification, (2) concurrent gain of whole chromosome 7 and loss of whole chromosome 10, or (3) telomerase reverse transcriptase promoter mutation. Homozygous deletion of CDKN2A/B also indicates a WHO grade 4 distinction in IDH-mutant diffuse glioma.[9-11] IDH-mutant, WHO grade 4 astrocytoma are no longer classified as GBM with the latter designation exclusively reserved for IDH-wildtype diffuse glioma.[9] While this guideline is intended for adult-type WHO grade 4 diffuse glioma as defined in the 2021 CNS WHO classification,[4] the task force recognizes and acknowledges that most available literature cited in developing the guideline pertains to what is regarded today as histologic GBM, IDH-wildtype, WHO grade 4 tumors.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and neurosurgical oncologists; a neuropathologist; a radiation oncology resident; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Association of Neurological Surgeons/Congress of Neurological Surgeons, American Association of Neuropathologists, American Society of Clinical Oncology, and Society for Neuro-Oncology, who provided representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 23 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from December 2024 to January 2025. The final guideline was approved by the ASTRO Board of Directors and endorsed by the European Society for Radiotherapy and Oncology, the Royal Australian and New Zealand College of Radiologists, and the Society for Neuro-Oncology.

Evidence review

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs and then reviewed by the full task force. Using the PICOTS framework (Table 2), a systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English-language publications between March 2014 through December 7, 2023. The population of interest was adults (age ≥18 years) diagnosed with grade 4 adult-type diffuse glioma. Allowable publication types comprised prospective studies including randomized controlled trials (RCTs), meta-analyses, and retrospective studies. The following requirements for study size were applied: (1) ≥50 patients for RCTs; (2) ≥75 patients for prospective studies; (3) ≥300 patients for meta-analyses (for KQ3 and KQ4 only); (4) ≥100 patients for retrospective studies except for KQ1 which excluded retrospective studies; and (5) ≥200 patients for studies on health disparities. RCTs from ASTRO's 2016 Radiation Therapy for Glioblastoma guideline evidence review were used to continue to support recommendations where appropriate.[7]

Universal exclusion criteria included preclinical and nonhuman studies; publication types including abstract only, review articles, comments, or editorials; and study types such as health economics/cost analyses or large registry/database studies (except for studies related to health disparities). Treatment of patients with grade 1, IDH-mutant grade 2 and grade 3 tumors, metastatic or disseminated disease was also excluded. For specific subquestions where limited data were available, expert opinion was relied on to support recommendations. Full-text articles were assessed by the task force to determine the final included study list resulting in 105 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram showing the number of articles screened and included/excluded in the evidence review) and Appendix E3 in Supplementary Materials for the literature search strategy, which include the evidence search parameters.

The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

Scope of the guideline

The scope of this guideline is to provide updated recommendations on RT for patients with WHO grade 4 adult-type diffuse glioma, previously histologic GBM. It will address specific recommendations for diagnosis and treatment, acknowledging the integration of molecular markers, advanced imaging techniques, and novel therapeutics.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications for RT and/or adjuvant therapies (eg, systemic therapies, alternating electric fields) in patients with newly diagnosed WHO grade 4 adult-type diffuse glioma?**			
	• Adults with high-grade glioma/astrocytomas, IDH-wildtype glioma, glioblastoma, WHO grade 4 diffuse glioma, WHO grade 4 IDH-mutant diffuse glioma/astrocytoma	• Surgery • RT • Chemo • Alternating electric field therapy (tumor treating fields) • Monotherapies and/or combination systemic therapies	• Biopsy alone • Surgery alone • RT alone • Chemo alone • Surgery + postop RT alone • Surgery + postop chemoRT alone	• Local control • Local failure • Local progression • Progression-free survival • Overall survival • Toxicity/morbidity • Quality of life
2	**What are appropriate dose-fractionation regimens for RT after biopsy/resection in patients with WHO grade 4 adult-type diffuse glioma, and how might treatment vary based on pretreatment characteristics (eg, age or performance status)?**			
	• Same as KQ1	• Dose-escalated RT • Hypofractionation • Hyperfractionation • Accelerated fractionation • Stereotactic radiosurgery • Chemo: alone or concurrent/adjuvant • Brachytherapy • Temporally-modulated pulsed RT (pLDR)	• Lower total doses of RT • Conventional fractionation • Hypofractionation • Brachytherapy • Best supportive care	• Same as KQ1
3	**What are the appropriate target volumes and techniques for RT in patients with WHO grade 4 adult-type diffuse glioma?**			
	• Same as KQ1	• IMRT • Proton therapy • Smaller CTV expansions • Smaller GTV (enhancing lesion[s]/postop bed only) • 2-volume (primary + boost) and single-volume treatment plans • Dose painting, SIB, sequential boost • Dose-fractionation: conventional, hypofractionation, hyperfractionation • Imaging: MRI, CT, T1, T2, FLAIR	• 3-D CRT • Larger CTV expansions • Larger GTV (T2/FLAIR extent + enhancing lesion[s]/postop bed) • Use of MRI vs CT	• Same as KQ1
4	**What are the indications and appropriate techniques for reirradiation in patients with WHO grade 4 adult-type diffuse glioma whose disease recurs following completion of standard first-line therapy?**			
	• Same as KQ1	• RT (3-D CRT, IMRT, including VMAT, +/- systemic therapy) • SRT/SRS • Particle therapy (proton, carbon, boron neutron capture therapy) • Brachytherapy • Temporally-modulated pulsed RT (pLDR) • Alternating electric field therapy	• Systemic therapy alone • Surgery • Best supportive care	• Same as KQ1

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; chemo = chemotherapy; chemoRT = chemoradiation; CT = computed tomography; CTV = clinical target volume; FLAIR = fluid-attenuated inversion recovery; GTV = gross tumor volume; IDH = isocitrate dehydrogenase; IMRT = intensity modulated radiation therapy; KQ = key question; PICO = Population, Intervention, Comparator, Outcome; pLDR = pulsed low-dose radiation therapy; postop = postoperative; MRI = magnetic resonance imaging; postop = postoperative; RT = radiation therapy; SIB = simultaneous integrated boost; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy; VMAT = volumetric modulated arc therapy; WHO = World Health Organization.

This guideline addresses only the subjects specified in the KQs (Table 2). There are several important questions in the management of high-grade glioma that are outside the scope of this guideline, including surgical approaches, systemic therapy alone regimens, the role of systemic therapy in the recurrent setting, multifocal/multicentric or disseminated WHO grade 4 diffuse glioma, and management of molecular GBM. The key outcomes of interest

are local control (successful prevention of tumor growth at the original site of a cancer), local failure (cancer has recurred or progressed at the primary tumor site), local progression (tumor is actively growing and spreading within the original area where it first developed), progression-free survival (PFS), overall survival (OS), and toxicity/morbidity.

Health disparities were searched separately for data specifically including RT for WHO grade 4 diffuse glioma. The literature search included a broad range of considerations including, but not limited to, socioeconomic status (SES), access to care, rural location, volume practice patterns, age, language disparities, sex, race, and ethnicity. Studies describing generalized patterns of care were potentially excluded if the focus was not to address a disparity or equity hypothesis.

This guideline aims to provide a comprehensive and up-to-date set of recommendations on the management of WHO grade 4 diffuse glioma, encompassing some components of advanced imaging, molecular updates to diagnosis, RT, emerging therapeutics, and when relevant to the role of RT, the sequence of surgical intervention, and systemic therapy.

The most recent research findings and expert insights from clinical practice have been incorporated to address the current challenges and opportunities in WHO grade 4 diffuse glioma management. The goal is to provide clinicians with a clear, evidence-based framework for decision-making, while also highlighting areas where further research is needed.

KQs and Recommendations

KQ1: Indications for RT and/or adjuvant therapies (Table 3)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1 and Fig. 2.

What are the indications for RT and/or adjuvant therapies (eg, systemic therapy, alternating electric field therapy) in patients with newly diagnosed WHO grade 4 adult-type diffuse glioma?

For patients with WHO grade 4 diffuse glioma who have undergone biopsy or resection, conventional treatment is adjuvant fractionated RT based on numerous RCTs performed primarily in the 1970s and 1980s that showed a significant benefit in OS after RT compared with chemotherapy or supportive care alone.[14,16-19] It is noteworthy that these studies enrolled a heterogeneous patient population with high-grade glioma, including both grade 4 and grade 3 diffuse glioma. Furthermore, most of these studies used older RT techniques including whole brain RT, which has more potential side effects including greater cognitive sequelae compared with more conformal approaches used in modern radiation oncology practices. Additionally, these studies were performed before magnetic resonance imaging (MRI) was incorporated into RT treatment planning. Nonetheless, given the clear benefit of RT in these historical studies, re-evaluation of modern RT techniques versus no RT is not necessary. There is 1 phase 3 RCT in patients age ≥70 years performed in the last 20 years using more modern treatment planning approaches which confirmed a benefit in OS compared with supportive care alone.[13]

Although there are no RCTs specifically evaluating optimal timing of RT initiation after surgery, task force expert opinion suggests that approximately 3 to 6 weeks after surgery may be most appropriate to allow adequate time for healing but minimize the risk of symptomatic progression in the interval period. Some data have identified improvements in outcomes for treatment initiated <4 weeks from surgery; however, a meta-analysis did not find a benefit to this time range.[20] Unfortunately, different factors may confound the interpretation of OS outcomes with the association of later initiation of adjuvant RT in studies that identify worse prognosis[21,22] with delayed therapy versus those that do not[20] in population-based studies. For example, while being of a specific racial group was associated with longer delay in RT initiation >30 days from surgery, so were clinical factors such as receipt of gross tumor resection and treatment at an academic facility.[22] Ongoing clinical trials (eg, BN001) may allow a window up to 7 weeks from surgery or biopsy depending on the extent of initial resection. In patients receiving needle biopsy only, it is preferred that treatment start be expedited to <3 weeks from final pathology being available given the aggressive nature of the disease and that needle biopsy alone is most often performed in patients with tumors in eloquent and unresectable locations of the brain. A treatment planning or diagnostic MRI performed within ≤3 weeks of initiation of RT is preferred given the risk of progression over a short time interval.

The conventional treatment for WHO grade 4 diffuse glioma after biopsy or resection is partial brain RT with concurrent and adjuvant TMZ based on a large RCT led by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) which found that adding concurrent (75 mg/m^2) and adjuvant (150-200 mg/m^2) TMZ to fractionated partial brain RT to a total dose of 6000 cGy in 30 fractions was associated with a significant benefit in OS.[3,23] This study enrolled adults age 18 to 70 years with a WHO performance status (PS) 0 to 2. In a second RCT, patients age ≥65 years or with a Karnofsky performance status (KPS) <60 were randomized to either hypofractionated RT with a dose of 4005 cGy in 15 fractions alone or the same

Table 3 Indications for RT and/or adjuvant therapies

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with WHO grade 4 diffuse glioma, fractionated RT after biopsy or resection is recommended.	Strong	High [12-14]
2. For patients with WHO grade 4 diffuse glioma who have undergone biopsy or resection, concurrent TMZ with RT followed by adjuvant TMZ is recommended. Implementation remarks: • Concurrent dosage is 75 mg/m^2, 7 days per week during RT. • Adjuvant dosage is 150-200 mg/m^2, 5 days per week of each 28-day cycle for 6 cycles.	Strong	High [3,15]
3. For patients with supratentorial WHO grade 4 diffuse glioma who have undergone biopsy or resection and concurrent chemoradiation with TMZ, alternating electric field therapy for ≥18 hours per day starting during adjuvant TMZ is conditionally recommended.	Conditional	Moderate [5]

Abbreviations: KQ = key question; RT = radiation therapy; TMZ = temozolomide; WHO = World Health Organization.

RT regimen with concurrent and adjuvant TMZ, resulting in a significant benefit of TMZ once again.[15] Of note, the OS of both groups in this study was poorer than in the preceding study using 6000 cGy of RT. Two RCTs using 2 different RT fractionation regimens identified a benefit in using concurrent and adjuvant TMZ supporting the high quality of evidence. The nuances of the fractionation decisions and population-specific guidance are discussed in KQ2 (Table 4).

Two additional smaller RCTs have similarly shown an OS benefit with the addition of TMZ to adjuvant RT.[24,25] Importantly, a meta-analysis demonstrated that adding concurrent and adjuvant TMZ to RT is associated with a significant OS benefit in this patient population.[26] The EORTC study driving the use of TMZ delivered 6 cycles of TMZ after concurrent RT plus TMZ.[3,23] Up to 12 cycles may be an option, although this may not improve outcomes and there is concern that this regimen may increase the risk of hematologic toxicity which could limit salvage options.[27,28]

The role of unmethylated O6-methylguanine-DNA methyltransferase (*MGMT*) status on the use of TMZ for patients with WHO grade 4 diffuse glioma is an ongoing area of discussion. Although there are data suggesting patients with unmethylated *MGMT* may derive less benefit from TMZ, the use of concurrent chemoradiation and adjuvant TMZ is presently the conventional treatment for patients with unmethylated *MGMT*[23] as we await further clinical trials to indicate otherwise. Patients with unmethylated *MGMT* tumors had a 1-month higher median OS that did not reach statistical significance, and 11% of patients with unmethylated *MGMT* tumors lived 3 years with use of concurrent chemoradiation and adjuvant TMZ compared with no living patients at 3 years without combined therapy.[3]

Clinical trials exploring adjuvant bevacizumab in newly diagnosed WHO grade 4 diffuse glioma failed to show a statistically significant benefit in OS.[29,30] The use of immunotherapy has also been evaluated. Nivolumab versus placebo in combination with concomitant TMZ with RT did not show a benefit over chemoradiation with TMZ alone.[31,32] In addition, nivolumab was associated with significantly higher rates of nausea, headache, and dysgeusia when compared with the placebo arm. Both arms demonstrated similar rates of serious adverse events including tumor flare, pancytopenia, and thrombocytopenia.[32] Lomustine-TMZ has also been explored and demonstrated increased hematologic toxicity compared with the TMZ alone arm and increased reports of brain edema and neurologic symptoms.[6] In patients with *MGMT* methylated tumors, there may be an improved OS though the results should be interpreted with caution because of the small sample size,[6] and thus warrant further clinical trial evaluation.

Other adjuvant therapies have been considered at the time of surgery, specifically, carmustine wafer implantation[33] and brachytherapy.[34] Both may interfere with clinical trial eligibility and are therefore sometimes reserved for the recurrent setting. Similarly, there is weak evidence supporting survival benefit of intraoperative RT for WHO grade 4 diffuse glioma management.[35] The overall effect of intraoperative RT remains inconclusive because of the small number of patients and heterogeneous reporting of data. Additional clinical trials are needed to better understand the optimal implementation of these measures into routine clinical practice.

One RCT demonstrated a significant benefit in PFS (6.7 vs 4 months) and OS (20.9 vs 16 months) with the addition of alternating electric field therapy to adjuvant RT plus TMZ in patients with supratentorial WHO grade 4 diffuse glioma after resection or biopsy.[5,36] Alternating electric field therapy was well tolerated with an associated improvement in health-related quality of life (QoL) at 3 and 6 months,[37] but this did not persist at later time points because of increased dermatologic toxicity. In the study, the device was intended to be worn for at least 18 hours per day starting with adjuvant TMZ for a maximum of 24 months.[36]

In support of this impressive international RCT, the recommendation according to ASTRO's Guideline methodology is conditional with a moderate quality of evidence because there is presently 1 well-conducted RCT and currently variable consensus with adoption in national practices, reflecting that while most informed clinicians would choose alternating electric field therapy, a substantial minority may not (Table 1). Future studies might allow a better understanding of pathways associated with resistance to the device, thereby helping optimize patient selection. Although it would not be expected to impact the benefit of alternating electric field therapy in both arms, randomization was performed at a median of 3.8 months from diagnosis such that patients with more aggressive tumors may not have been included, potentially resulting in a study population having a better prognosis than studies that enroll patients at earlier time points. Lastly, the impact of additional supportive personnel for patients receiving alternating electric field therapy is unknown. Longer-term observational studies will also be beneficial as will data on the device in combination with hypofractionated RT regimens. Additional prospective studies may be important to assist in appropriately increasing adoption.

Despite intensive management, most patients with WHO grade 4 diffuse glioma will ultimately succumb to their disease. As such, providers should consider the patient's QoL and address areas of physical and psychological distress. Early engagement of palliative interventions and symptom management services is encouraged in patients to holistically address the challenges faced by patients and their families.[38] It is important to be aware that certain palliative care services are distinct from hospice and may be used cohesively with chemoradiation.

In frail patients or those with poor PS, hospice or supportive care alone may be a more appropriate alternative to intensive management. Patients and their families should be counseled that chemoradiation is likely to extend life but is unlikely to improve a patient's baseline functional status. Therefore, if patients do not find their current health-related QoL acceptable, they may prefer to forego intensive management and focus on symptom management alone and minimize time spent undergoing treatment. The clinician's role is to facilitate decision making and present patients and their families with appropriate management options, so they can make fully informed decisions consistent with patients' goals of care.

KQ2: Appropriate dose-fractionation regimens for RT after biopsy/resection (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2.

What are appropriate dose-fractionation regimens for RT after biopsy/resection in patients with WHO grade 4 adult-type diffuse glioma, and how might treatment vary based on pretreatment characteristics (eg, age or PS)?

Historically, trials using RT alone demonstrated prolongation of median OS, which provided evidence of the beneficial effects of sufficient tumoricidal doses of RT. However, the durability of tumor control was suboptimal in most patients.[40] The demonstration of improved OS with the addition of concurrent TMZ to 6000 cGy of RT followed by adjuvant TMZ in the landmark EORTC-NCIC trial[23] serves as the basis for the incorporation of this regimen as the standard arm in contemporary clinical trials.[29,30,46] For patients age 18 to 70 years and KPS ≥60, this regimen has remained the standard dose-fractionation for patients with newly diagnosed WHO grade 4 diffuse glioma. In fact, most patients receiving this regimen may likely have higher PS, given 87% of patients in the original clinical trial receiving chemoradiation had an Eastern Cooperative Oncology Group PS 0 to 1.[3]

Randomized studies evaluating dose-escalated RT strategies including hypofractionation, hyperfractionation, stereotactic radiosurgery and sequential/integrated boost, with or without older systemic therapies, have not demonstrated an improvement in OS in patients with newly diagnosed WHO grade 4 diffuse glioma.[23,47-51] An RCT evaluating dose-escalated RT using integrated boost and TMZ demonstrated no initial improvement in OS.[52] These studies are based on conventional MRI including T1-weighted gadolinium-enhanced and T2-weighted fluid-attenuated inversion recovery (FLAIR) images. Investigational approaches evaluating dose-escalation strategies using advanced imaging techniques (amino acid positron emission tomography [PET], advanced MRI techniques) are ongoing and will require validation.[39,53-55]

Age and PS are important factors to consider when making therapeutic decisions. Analyses of prospective data have strongly associated older age and/or poor PS with limited life expectancy.[56,57] However, an RCT from France demonstrated that even among patients age ≥70 years with KPS >70, RT improved median survival compared with supportive care alone (29.1 weeks vs 16.9 weeks).[13]

Whether older patients should receive the same dose-fractionation regimen as younger patients remains unclear following publication of the French RCT.[13] EORTC/NCIC 26981−22981 established 6 weeks of RT plus TMZ for patients age ≤70 years with good PS, but patients age >70 years or with poor PS were excluded from the study.[23] Two other phase 3 RCTs compared conventionally fractionated RT (6000 cGy in 30 fractions over 6 weeks) with moderately hypofractionated RT in older patients.[42,45] A Canadian trial randomized patients ≥60 years old with KPS ≥50 to conventionally fractionated RT versus 4005

Table 4 Appropriate dose-fractionation regimens for RT after biopsy/resection

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients age <70 years and KPS ≥60 with WHO grade 4 diffuse glioma who have undergone biopsy or resection, partial brain irradiation with 6000 cGy in 30 fractions with concurrent and adjuvant TMZ is recommended.	Strong	High [3,39,40]
2. For patients age ≥70 years and KPS ≥50 with WHO grade 4 diffuse glioma who have undergone biopsy or resection, partial brain irradiation with 4005 cGy in 15 fractions with concurrent and adjuvant TMZ is conditionally recommended.	Conditional	Moderate [15,41-43]
3. For patients with WHO grade 4 diffuse glioma who are frail and have undergone biopsy or resection, partial brain irradiation alone using 3400 cGy in 10 fractions or 2500 cGy in 5 fractions is conditionally recommended. Implementation remark: Frailty is characterized by reduced physiologic reserve and increased vulnerability to adverse health outcomes.	Conditional	Low [44,45]
4. For patients with WHO grade 4 diffuse glioma who are very frail or with KPS ≤40, supportive care in lieu of RT and/or systemic therapy is conditionally recommended.	Conditional	Expert Opinion

Abbreviations: KPS = Karnofsky performance status; KQ = key question; RT = radiation therapy; TMZ = temozolomide; WHO = World Health Organization.

cGy in 15 fractions over 3 weeks. Results showed no difference in median survival, but patients receiving conventional fractionation required more corticosteroids.[42] The Nordic trial randomized patients age ≥60 years with a WHO PS 0 to 2 to conventionally fractionated RT versus 3400 cGy in 10 fractions over 2 weeks versus TMZ alone. No survival difference was shown between the RT groups as a whole or among patients 60 to 70 years old, but in patients age >70 years, hypofractionated RT resulted in significantly better survival.[45]

The Canadian[42] and Nordic[45] trials provide the only randomized data directly comparing hypofractionation with conventional fractionation among older patients with fair to good PS, and both support moderate hypofractionation. However, neither included concurrent or adjuvant TMZ in any of the treatment arms. Although RCTs comparing conventionally fractionated with hypofractionated regimens in the setting of concurrent and adjuvant TMZ are lacking, 2 propensity-matched analyses performed this comparison among patients with WHO grade 4 diffuse glioma age ≥65 years.[41,43] An analysis from Harvard found similar median OS and PFS times between conventionally fractionated and moderately hypofractionated chemoradiation.[41] Another propensity-matched analysis from Italy also found no difference in OS or PFS between conventionally fractionated and moderately hypofractionated chemoradiation, but found that conventional fractionation was associated with increased grade 2 to 3 neurologic toxicity, worse PS, and higher corticosteroid requirements.[43] In the Harvard study, >70% had a KPS ≥70 and >90% had a KPS ≥50, while in the Italian study all patients had a KPS ≥60.[41,43] Additionally, NCIC 26052, a phase 3 RCT, demonstrated that among patients age ≥65 years with an Eastern Cooperative Oncology Group PS 0 to 2, adding concurrent and adjuvant TMZ to RT (4005 cGy in 15 fractions over 3 weeks) improves survival compared with RT alone.[15] Based on these propensity-matched analyses[41,43] and RCTs,[15,42] 4005 cGy in 15 fractions with concurrent and adjuvant TMZ is conditionally recommended for patients age ≥70 years with a KPS ≥50, acknowledging that some clinicians may choose other approaches for older patients with excellent KPS.

Less data are available to guide decisions on dose-fractionation among patients with poor PS or frailty, the latter characterized by reduced physiologic reserve and increased vulnerability to adverse health outcomes.[58] A recognized gap in the recommendations is the population of patients age <70 years with KPS <60 or with degrees of frailty. Various hypofractionated regimens (eg, 4005 cGy in 15 fractions, 3400 cGy in 10 fractions, 2500 cGy in 5 fractions) may be appropriate in this population although in select cases some might consider conventional fractionation (Fig. 2). Independent from KPS and age is frailty, defined either as a clinical syndrome because of altered metabolism and abnormal stress responses or as a state of accumulated health-related deficits.[58-60] Frailty is especially prevalent among older patients with cancer, and heightens the risk of complications from intensive cancer treatments like RT or systemic therapy because of reduced physiologic reserve and increased vulnerability to adverse health outcomes. Assessing frailty allows oncologists to customize treatments to optimize patient-centered care. Various instruments are available to measure frailty, from brief screening tools to comprehensive multidomain geriatric assessments, and those tailored for specific treatment populations to inform decision-making. Resources for selecting an appropriate frailty assessment tool and electronic calculators for common instruments are accessible at eFrailty.org.[58]

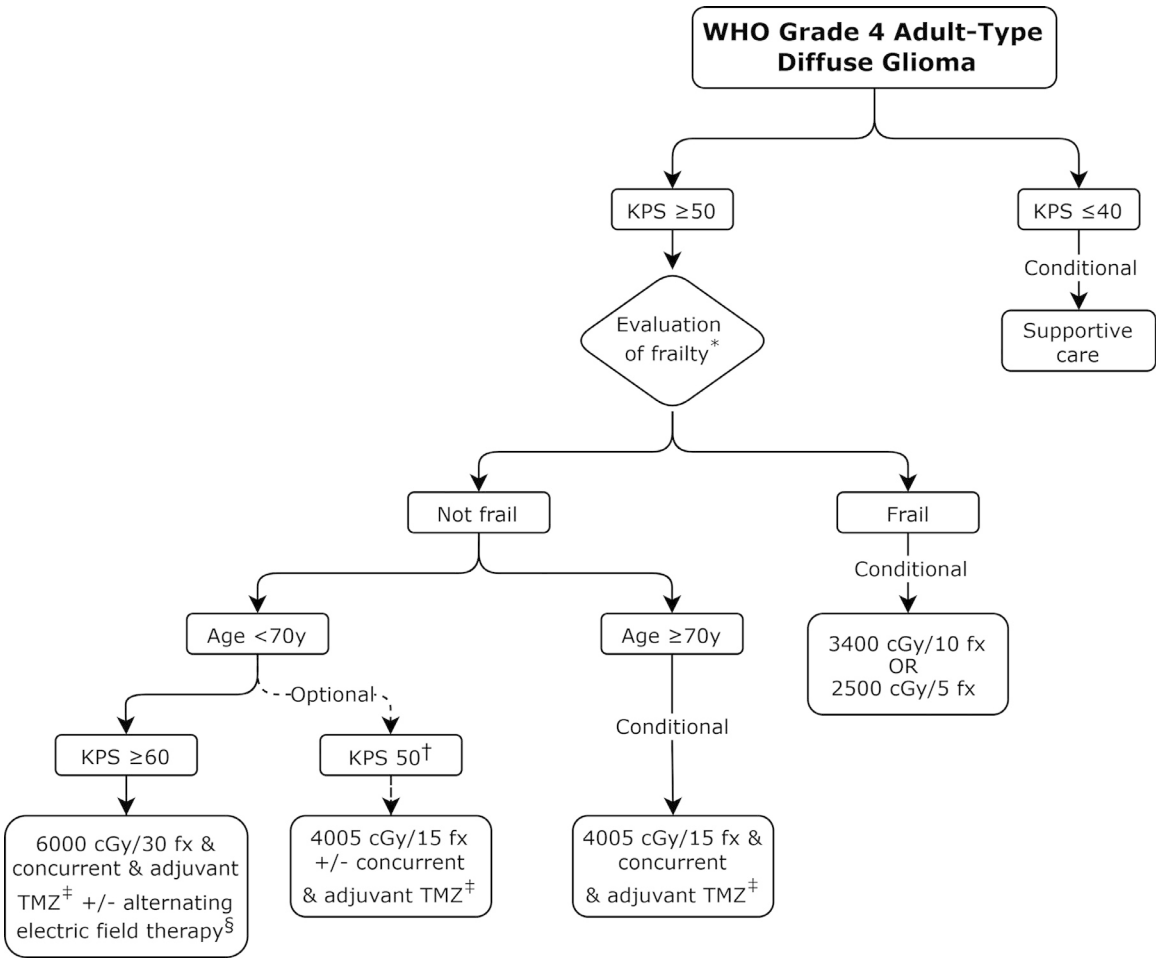


Figure 2 Management of WHO grade 4 adult-type diffuse glioma.
Abbreviations: fx = fraction(s), GBM = glioblastoma; KPS = Karnofsky performance status, RT = radiation therapy, TMZ = temozolomide, WHO = World Health Organization. *Frailty is characterized by reduced physiologic reserve and increased vulnerability to adverse health outcomes.[58-60,65] †May be an option based on consensus of the task force though not reflective of a specific recommendation because patients age <70 years with a KPS of 50 were poorly represented in trials. ‡Concurrent TMZ dosage is 75 mg/m^2, 7 days per week during RT; adjuvant TMZ dosage is 150 to 200 mg/m^2, 5 days per week of each 28-day cycle for 6 cycles. §Consider for patients with supratentorial WHO grade 4 diffuse glioma.

The International Atomic Energy Agency (IAEA) completed a phase 3 RCT[44] comparing ultrahypofractionation (2500 cGy in 5 fractions over 1 week) with moderate hypofractionation (4005 cGy in 15 fractions over 3 weeks) without use of chemotherapy in either arm in patients deemed "frail" (≥50 years old with KPS 50%-70%), "elderly" (≥65 years old with KPS 80%-100%), or "elderly and frail" (≥65 years old with KPS 50%-70%). These definitions were specific to that trial, though the general definition for frailty assessments in the literature encompasses a broader definition independent of KPS or age.[58,59] Ultrahypofractionation was found to be noninferior to moderate hypofractionation, demonstrating no intergroup difference in OS, PFS, or health-related QoL.[44] The task force extrapolated from the IAEA[44] and Nordic[45] RCTs to conditionally recommend 2500 cGy in 5 fractions or 3400 cGy in 10 fractions for patients with frailty, noting that for patients with a short life expectancy, truncating the RT course may have even greater importance. Evidence in support of the recommendation was limited because only 1 RCT supported each fractionation regimen (2500 cGy in 5 fractions or 3400 cGy in 10 fractions), there is minor variation in the definition of frailty, and the Nordic trial also included patients with fair to good PS.[44,45]

There are smaller phase 1 and 2 single-arm protocols with ≤30 patients evaluating the use of stereotactic RT of 2500 to 3500 cGy in 5 fractions or 5250 cGy in 15 fractions.[61,62] However, given the smaller sample size and lack of RCTs, the task force deferred making a recommendation as we await further data.

TMZ as a single modality may be considered for older patients with *MGMT* methylated tumors who are not candidates for a combined modality approach or RT alone because of poor PS or significant comorbidities. In this patient population, TMZ may also be an alternative to RT based on the results of the NOA-08 trial[14,63] and the Nordic trial.[45] Regarding *MGMT* status in older patients

eligible for RT, 2 other RCTs[3,16] included older patients with unmethylated *MGMT* tumors supporting the present concurrent use of TMZ, though additional trials on the risk/benefit for unmethylated *MGMT* may be needed in the future.[3,15,64]

KQ3: Appropriate target volumes and techniques for RT (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3.

What are the appropriate target volumes and techniques for RT in patients with WHO grade 4 adult-type diffuse glioma?

RT treatment techniques for patients with WHO grade 4 diffuse glioma include 3-dimensional conformal radiation therapy (3-D CRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), proton RT, and more experimental forms including carbon ion therapy.[66-68,72,73,76]

IMRT (including VMAT), when compared with 3-D CRT, improves target conformity and dosimetric indices especially to the uninvolved brain. These dosimetric differences result in significantly reduced rates of acute grade 1 and 2 neurologic toxicities, most notably cerebral edema and impaired neurocognition, compared with 3-D CRT.[66,67] Of note, IMRT (including VMAT) can slightly increase the low-dose radiation exposure to organs at-risk adjacent to the targeted tumor compared with 3-D CRT, but toxicity can be mitigated by using the dose limitations recommended in Quantitative Analyses of Normal Tissue Effects in the Clinic.[67,77] The data comparing IMRT (including VMAT) with 3-D CRT have been mixed with respect to OS, with some analyses showing improved OS with IMRT (including VMAT), and others noting no differences.[66,67] Based on the evidence of improved RT dosimetry and decreased toxicity, IMRT (including VMAT) is recommended over 3-D CRT.

In prospective clinical trials and retrospective series, proton RT has been shown to reduce doses to normal tissues when compared with IMRT including the normal brain, cochlea, and optic pathway.[72,73,76] In an RCT comparing proton RT with IMRT for patients with WHO grade 4 diffuse glioma, patients who received treatment with proton RT had significantly fewer grade 2+ toxicities compared with those treated with IMRT.[73] There have been no consistent differences found between proton RT

Table 5 Appropriate target volumes and techniques for RT

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with WHO grade 4 diffuse glioma, IMRT (including VMAT) is recommended over 3-D CRT to reduce toxicity.	Strong	Moderate 66,67
2. For patients with WHO grade 4 diffuse glioma, the following target volumes defined by MRI are recommended if cone-down/boost is desired: • GTV1 = resection cavity, residual enhancement on postoperative T1 postcontrast, and T2/FLAIR changes (non-enhancing tumor) • GTV2 = resection cavity and residual enhancement on postoperative T1 postcontrast • CTV1/2 = GTV1/2 + 10-20 mm expansion, modified to respect natural barriers to tumor spread (bone, dura, etc.) • PTV1/2 = CTV1/2 + 3-5 mm expansion.	Strong	Low 53,66,68-73
3. For patients with WHO grade 4 diffuse glioma, the following target volumes defined by MRI are recommended if **no** cone-down/boost is desired: • GTV = resection cavity and residual enhancement on T1 postcontrast • CTV = GTV + 10-20 mm expansion with additional expansion as needed to include T2/FLAIR signal changes (non-enhancing tumor) modified to respect natural barriers to tumor spread (bone, dura, etc.) • PTV = CTV + 3-5 mm expansion.	Strong	Low 15,66,67,74,75
4. For patients with WHO grade 4 diffuse glioma, a volumetric brain MRI with and without contrast preferably ≤14 days before starting RT is recommended for treatment planning.	Strong	Expert Opinion
5. For patients with WHO grade 4 diffuse glioma receiving RT, daily image guidance is recommended to facilitate reduced CTV to PTV expansions.	Strong	Expert Opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; CTV = clinical target volume; FLAIR = fluid-attenuated inversion recovery; GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; KQ = key question; MRI = magnetic resonance imaging; PTV = planning target volume; RT = radiation therapy; VMAT = volumetric modulated arc therapy; WHO = World Health Organization.

and IMRT with respect to PFS or cognitive failure in WHO grade 4 diffuse glioma,[73] however, and given the limited availability of proton RT, there is no consensus to recommend using proton RT over IMRT in this patient population.

Partial brain RT is generally used for treating WHO grade 4 diffuse glioma. This allows for more focused targeting of those areas at highest risk for tumor recurrence and sparing of uninvolved brain.[7] A recent RCT demonstrated no difference in PFS or OS, and no difference in treatment-related adverse events among patients with grade 3 or 4 glioma (including IDH-wildtype GBM) treated with a 1-phase versus 2-phase technique.[78] Use of either a 1-phase technique with single set of targets or a 2-phase technique including a "cone-down" or "boost" targets is considered acceptable RT strategies.[7] Regardless of the treatment strategy used, there remains a wide variety of target volume definitions described for gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) in the published literature for this patient cohort. These include several prospective studies with the GTV and CTV based on clinical concern of tumor involvement, and the PTV dependent on patient set-up variability based on immobilization and type of image guidance used.[15,39,53,66-75,79-83]

For WHO grade 4 diffuse glioma RT planning, there is consensus that a brain MRI should be used for target delineation; however, the details on optimal timing of MRI scans are often not reported.[15,39,66,67,70-72,75,79] When timing has been reported, the time range for the scan has varied widely from <48 hours after surgery to within 14 to 30 days of the start of treatment.[53,69,73,80] Although all reports that describe MRI scans for RT target delineation detail using T2-weighted, FLAIR and postcontrast T1-weighted imaging sequences, only 2 studies specify acquisition of thin-cut, volumetric postcontrast T1-weighted images to facilitate treatment target contouring.[75,81] None of these studies discuss the need for distortion correction when fusing MRI scans to CT scans obtained during simulation. Given the paucity of evidence regarding optimal timing and sequences of MRI to be obtained for RT planning, a volumetric brain MRI with and without contrast within 14 days of starting RT for treatment planning is preferable based on expert opinion.

The 1-phase approach for target delineation uses a single dose target based on a CTV expansion from the GTV to cover the adjacent at-risk tissue, and this volume is treated with the full planned dose to treat the WHO grade 4 diffuse glioma, as has been espoused by the EORTC and is still variably employed in studies from institutions outside the United States.[15,66,67,74,75] For this technique, the GTV is commonly accepted to be the surgical cavity plus residual tumor identified on postcontrast T1-weighted MRI images, and the CTV to be a 10 to 20 mm expansion from the GTV, then adjusted to include abnormal FLAIR/T2-weighted imaging changes (non-enhancing tumor), and finally modified to respect anatomic barriers of tumor spread.

An alternative approach to treating WHO grade 4 diffuse glioma with RT involves the use of a cone-down or boost target volume to allow for dose intensification of the contrast-enhancing area accepted to correspond to the most aggressive tumor and a reduced dose delivered to the adjacent non-enhancing, potentially lower-grade, abnormal tissue. The original 2-phase technique used by the Radiation Therapy Oncology Group includes an initial large-field target covering the abnormal T2/FLAIR areas with additional margin for microscopic tumor spread followed by a sequential cone-down to the tumor bed and residual tumor with additional margin.[30,46] How the 2-phase approach has been implemented, however, varies widely from the Radiation Therapy Oncology Group and from center to center, including how the targets are defined (eg, 1 GTV[68-70] vs 2 GTVs[71]), and the doses delivered to the initial (4000-5000 cGy in 20-25 fractions) and boost (1000-2000 cGy in 5-10 fractions) volumes.[68-71,81] Further, with wider use of IMRT (including VMAT), more institutions have transitioned away from sequential boosting to a simultaneous integrated boost technique,[39,68,69,71-73,79,80] with no difference in survival outcomes noted when these approaches were compared with 2 retrospective series.[68,71] The initial GTV ("GTV1") used in the 2-phase approach includes the resection cavity and residual enhancement on postoperative T1 postcontrast MRI and T2/FLAIR changes (non-enhancing tumor) and the cone-down GTV ("GTV2") is limited to the resection cavity and residual enhancement on postoperative T1 postcontrast MRI. The initial and boost CTVs ("CTV1" and "CTV2," respectively) comprise a 10 to 20 mm expansion on the corresponding GTV, adapted to respect anatomic barriers.

Regardless of the RT approach, various PTV expansions have been employed, ranging from 1[80] to 10 mm,[68,81] with many studies using a 3 to 5 mm expansion.[15,39,67,73,75] With improved immobilization and daily image guidance, variability in daily patient set-up can be reduced, allowing for smaller PTV expansions to ensure adequate dose coverage of the CTV.[82,83] The determination of CTV to PTV expansion needs to be individualized based on the immobilization techniques and image guidance available at each practice. Reduction in PTV size translates to less normal tissue being irradiated, which by extrapolation from the studies comparing 3-D CRT with IMRT targets, may result in less acute RT-related toxicity.[66,67] Therefore, the use of daily image guidance to enable an appropriate reduction in the CTV to PTV expansion when treating patients with WHO grade 4 diffuse glioma with RT is recommended based on the expert opinion of the task force.

KQ4: Indications and appropriate techniques for reirradiation with recurrent disease after first-line therapy (Table 6)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ4.

What are the indications and appropriate techniques for reirradiation in patients with WHO grade 4 adult-type diffuse glioma whose disease recurs after completion of standard first-line therapy?

The prognosis for patients with recurrent WHO grade 4 diffuse glioma remains limited, with few effective salvage therapies. For patients with WHO grade 4 diffuse glioma with suspected recurrence, a biopsy/resection or advanced imaging (ie, MR perfusion, MR spectroscopy, or PET) is conditionally recommended before reirradiation to rule out treatment effect from recurrence.[84-87] Reirradiation is a treatment option for patients with recurrent WHO grade 4 diffuse glioma[85,86,102]; however, most data are retrospective with considerable variance in approaches.[85,86,88,106] Acknowledging that the majority of patients at first recurrence of WHO grade 4 diffuse glioma receive second-line systemic therapy, reirradiation for patients with recurrent WHO grade 4 diffuse glioma is conditionally recommended after a multidisciplinary, patient-centered discussion. Physicians are encouraged to enroll patients in clinical trials or prospective, multi-institutional registries. Appropriate patient selection for reirradiation includes good PS, longer interval from initial RT and/or smaller tumor size.[88-91]

Modern RT techniques deliver highly conformal RT and have improved the safety of reirradiation.[87,88,92-100,107] In patients with recurrent WHO grade 4 diffuse glioma who are candidates for and elect reirradiation, recommended RT techniques include conventionally fractionated RT (3600-5400 cGy in 180-200 cGy fractions), hypofractionated RT (3500 cGy in 10 fractions), stereotactic radiosurgery (2500-3500 cGy in 5 fractions or 1200-2000 cGy in a single fraction), pulsed low-dose RT (temporally-modulated pulsed RT) or brachytherapy.[87,88,92-100,107,108] Conditionally recommended target volumes for reirradiation include the GTV defined residual contrast-enhancing tumor identified on postcontrast T1-weighted MRI images, non-enhancing tumor, and/or the resection cavity.[85,86,92,99,101,102] An optional CTV expansion of the GTV of 3 to 5 mm is used for conventional or hypofractionated RT techniques and then modified to respect anatomic barriers of tumor spread (bone, dura, etc.). PTV expansions of ≤3 mm using improved immobilization and daily image guidance will translate to less normal tissue being reirradiated. Smaller PTV margins of ≤2 mm are used when stereotactic radiosurgery techniques are used.[109]

The role of systemic therapy in combination with reirradiation in recurrent WHO grade 4 diffuse glioma has been investigated in an RCT[86] and several retrospective studies suggest that the combination improves local control.[84,103-105] The addition of bevacizumab is

Table 6 Indications and techniques for reirradiation with recurrent disease after first-line therapy

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with suspected recurrent WHO grade 4 diffuse glioma, establishing the diagnosis by pathology or advanced imaging (eg, MR perfusion, spectroscopy, or PET) is conditionally recommended.	Conditional	Low 84-87
2. For patients with recurrent WHO grade 4 diffuse glioma with a KPS ≥70, in-field RT interval of ≥6 months and/or focal tumor maximum diameter of ≤6 cm, reirradiation is conditionally recommended following a multidisciplinary, patient-centered discussion. Implementation remark: Patient enrollment in clinical trials or multi-institutional registries is encouraged.	Conditional	Moderate 85,86,88-91
3. For patients with recurrent WHO grade 4 diffuse glioma who elect reirradiation, the following treatment options are conditionally recommended: conventionally fractionated RT, hypofractionated RT, stereotactic radiosurgery, fractionated stereotactic RT, or brachytherapy.	Conditional	Moderate 85-101
4. For patients with recurrent WHO grade 4 diffuse glioma who elect reirradiation, using a GTV defined as contrast-enhancing tumor, non-enhancing tumor, and/or resection cavity based on MRI is conditionally recommended.	Conditional	Moderate 85,86,92,99,101,102
5. For patients receiving reirradiation for recurrent WHO grade 4 diffuse glioma, concomitant bevacizumab is conditionally recommended to reduce toxicity.	Conditional	Moderate 84,86,103-105

Abbreviations: CTV = clinical target volume; GTV = gross target volume; IGRT = image-guided radiation therapy; KPS = Karnofsky performance status; KQ = key question; MR = magnetic resonance; PET = positron emission tomography; PTV = planning target volume; RT = radiation therapy; WHO = World Health Organization.

conditionally recommended because it appears to reduce the risk of radiation necrosis and to improve the safety of reirradiation.

Health Disparities

ASTRO has noted the importance of addressing health disparities where literature is available. However, given the lack of phase 3 RCTs with specific health disparities primary endpoints, no formal recommendations could be made, though it highlights a call to action included in future directions. Health disparities encompass a wide range of factors impacting access to care (eg, therapy timing, type of therapies offered, impact of geography, SES, and race/ethnicity). The retrospective nature of health disparities literature in WHO grade 4 diffuse glioma has inherent limitations, with national database reviews lacking nuanced specificity on clinical characteristics,[110] while smaller institution series with more specific data often lack the cohort numbers for broader application.

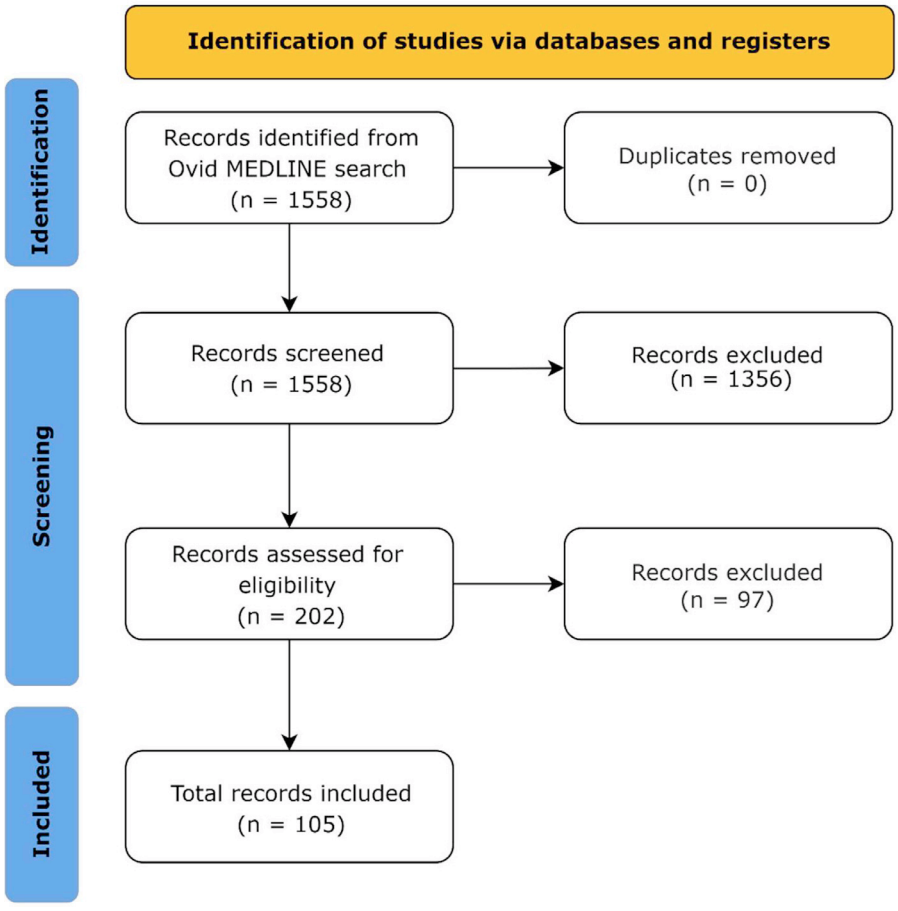
With regard to therapy delays, patients with lower SES and patients with US-based Medicaid may be at greater risk of initiating RT >42 days or beyond 6 weeks from surgery.[111] Unfortunately, insurance, geographic distribution, type of hospital facility, and trial eligibility can notably impact health care disparities systemically. Based on multiple large retrospective analyses, including the National Cancer Database and the Surveillance, Epidemiology, and End Results Program patient data, males, Black and Hispanic patients are more likely to be "underinsured" with Medicaid or no insurance.[111-118] These factors may lead to larger tumors at diagnosis and triple-modality therapy (eg, surgery, RT, and chemotherapy) not being offered.[119] Issues of health care access can also be impacted by geographic access to neurosurgeons or safety net hospitals, which have been associated with disparities in care.[112,117]

Appropriately quantifying the full impact on outcomes is challenging because of limitations in retrospective, population-based, or registry data. For instance, some series identified no difference in outcomes[120] or even higher OS among Latino populations.[121] Black and Asian/Pacific Islander patients had lower WHO grade 4 diffuse glioma-specific mortality, though Black patients had higher non-WHO grade 4 diffuse glioma mortality overall.[122] In multivariable models, Black, Hispanic, and Asian patients had lower rates of death, but when stratifying for delay in receiving RT by race, the hazard ratio of death was instead higher in these patients. Thus, findings identifying no correlation between receipt of treatment and survival suggest there may be additional factors not adequately captured retrospectively in population-based models that confound the interpretation of survival analysis. Adoption of newer technologies such as alternating electric field therapy may also be disparate among populations,[123] along with clinical trial participation. Clinical trial eligibility often reflects inherently healthier populations and is more likely to be younger and male.[124] Although some data suggest similar outcomes when evaluating SES as a reflection of a zip code area and when adjusting for factors including insurance status, employment status, PS, comorbidities, and presence of multifocal disease,[125] several studies show that lower SES is associated with worse OS.[122,126-128] These findings highlight the importance of having prospective data that better adjust for social determinants of health which may be tied to geographic and insurance access in addition to racial/ethnic and biological factors to address the impact on survival outcomes. Importantly, these disparities might be mitigated by upstream factors, such as equitable trial enrollment, broadening of enrollment criteria, increasing provider diversity, and attention to social factors limiting access.[129-131]

Conclusions and Future Directions

WHO grade 4 diffuse glioma remains one of the most challenging malignancies to treat, with a complex clinical course and limited survival despite advancements in care. This guideline underscores the critical importance of a multidisciplinary approach, combining advanced surgical techniques, RT, systemic therapy, alternating electric field therapy, and supportive care. Additionally, the importance of molecularly guided diagnoses, individualized, image-guided radiation treatment planning and delivery, and patient-specific factors such as age and PS guiding treatment recommendations is highlighted.

Emphasis on molecular and genetic discoveries also points to the growing potential of precision medicine, where therapies are tailored to specific tumor characteristics, potentially improving outcomes and reducing toxicity. For instance, tailored management of IDH-mutant WHO grade 4 tumors and other molecular WHO grade 4 diffuse glioma was beyond the scope of the guideline, as the field awaits future clinical trials to differentiate it from conventional therapy. Furthermore, the use of circulating tumor DNA is emerging to better inform treatment and surveillance.[132] Enrolling eligible patients in clinical trials, particularly minority populations, focused on novel therapies (drug and device) and experimental RT techniques, remains crucial, as these trials drive the discovery of novel therapeutics and further refine existing strategies. There are emerging data on using smaller margin expansions for RT treatment planning; however, the data are not mature enough to include in this guideline.[109] Ongoing trials may address the use of protons versus photons (*NCT02179086*), management of molecular GBM (*NCT04623931*), management of *MGMT* methylated GBM (*NCT05095376*) versus unmethylated GBM (RT sensitizers) (*NCT03970447,*



PRISMA 2020 Study Selection Diagram[135,136]
Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

NCT04555577), and adaptive RT (*NCT06108206, NCT04075305, NCT04574856*), will likely inform future practice beyond the publication of this guideline.[133,134]

Pertinent goals for the future of health disparities glioma research include improving outcomes in a multifactorial approach. Primary hypothesis-based literature on health disparities and funding is warranted and would increase the rigor of the analyses to investigate glioma health disparities specifically. An emphasis on intervention-based or community-based research strategies for mitigating health disparities instead of reporting existing, known disparities is crucial. Clinical trial data can also improve the literature on disparate outcomes in glioma by consistently reporting adjusted ethnicity/race, SES, and geographic patterns in the primary findings to better inform the likelihood of application in a real-world setting. Lastly, factors may differ across countries because of the difference in health care structures, financing, and overall population health, so increased research in health disparities is encouraged to equitably provide optimal care.

Ultimately, the goal of this guideline is to provide a robust framework for optimizing WHO grade 4 diffuse glioma care. However, the complexity of this disease requires ongoing research, adaptability in clinical practice, and a commitment to compassionate care. As the field evolves, future iterations of this guideline will integrate new findings to ensure that patients benefit from the latest advancements. Through continued innovation, interdisciplinary collaboration, and dedication to quality care, we can strive to improve outcomes and QoL for those affected by WHO grade 4 diffuse glioma.

Disclosures

All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

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The American Association of Neurological Surgeons/Congress of Neurological Surgeons Section on Tumors affirms the educational benefit of this document.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2025.05.014.

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