Public Comment Draft

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

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Table of Contents

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 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, gender, 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 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 submission of the document 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.

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, due to 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.

1. Introduction

Glioblastoma (GBM) classified as World Health Organization (WHO) grade 4 diffuse astrocytoma, is the most aggressive and common primary malignant brain tumor in adults. Despite advances in surgical techniques, RT, and chemotherapeutic 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 GBM, 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 have become both more available and allowed for more accuracy in diagnosis and prognosis. The characterization of high-grade glioma, and specifically histological GBM defined as WHO grade 4 diffuse glioma is an evolution of the WHO Classification of Tumors of the Central Nervous System.[4] Similarly, clinical trials have improved the median outcomes of patients with high-grade glioma since the standard of care of radiation therapy (RT) to 6000 cGy with concurrent and adjuvant temozolomide (TMZ) and was established in 2006.[5,6] This guideline updates 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 grading system rather than a full review of GBM practice. Nuances in care delivery are incorporated in this guideline to include patients with GBM that have experienced disparity in elements of their care. In addition, reviewing the health equity and disparities literature within GBM management is a precedent-setting endeavor ASTRO guidelines have begun incorporating to create opportunities for future research.

As the understanding of the biology and molecular genetics of malignant glioma has evolved, so has the taxonomy and nomenclature of WHO Classification of Tumors of the Central Nervous System entities.[4,8] It is now recognized that diffuse glioma in adults are biologically and genetically distinct from their pediatric counterparts.[8] Therefore, the discussion herein is limited to adult-type diffuse glioma. The emergence of biomarkers not only impacts how to subtype diffuse glioma but how they are graded. No longer is diffuse glioma grading based on histology alone. Diffuse glioma grading now incorporates additional molecular information.[8,9] Whereas the presence of vascular proliferation and/or necrosis 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 histological WHO grade 2/3 tumors now define these entities as molecular GBM. 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.[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 these guidelines are intended for adult-type WHO grade 4 diffuse glioma as defined in the 2021 WHO

classification, the task force recognizes and acknowledges that most of the available literature cited in developing the guideline pertain to what we regard today as histologically defined GBM, IDH-wildtype, WHO grade 4 tumors.

2. Methods

2.1. 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.

2.2. Document review and approval

The guideline was reviewed by XX 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 TBD.

2.3. 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. Allowable publication types included prospective studies including randomized controlled trials (RCTs), meta-analyses, and retrospective studies. The population of interest was adults (age ≥18 years) with a diagnosis of grade 4 adult-type diffuse glioma. Trial size required for inclusion was ≥50 patients for RCTs, ≥75 patients for prospective studies, ≥300 patients for meta-analyses (for KQ3 and KQ4 only), ≥100 patients if retrospective except for KQ1 which excluded retrospective studies, and ≥200 patients for studies on health disparities. RCTs from ASTRO's 2016 Radiation Therapy for Glioblastoma guideline evidence review were also used to supplement a lack of new data in key areas.[7]

Universal exclusion criteria included preclinical and nonhuman studies; publication types including abstract only, review articles, comments, or editorials; 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 were also excluded. For specific subquestions where limited data were available, expert opinion was relied upon 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 includes 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.

2.4. Scope of the guideline

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

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/chemotherapy alone regimens, the role of systemic/chemotherapy in the recurrent setting, multifocal/multicentric or disseminated GBM, and management for molecular GBM. The key outcomes of interest are local control, local failure, local progression, progression-free survival (PFS), overall survival (OS), and toxicity/morbidity.

Health disparities were searched separately for data specifically including RT for GBM. It 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 among others. Studies describing generalized patterns of care were potentially excluded if the focus was not to address a disparity or equity hypothesis.

This manuscript aims to provide a comprehensive and up-to-date set of recommendations for the management of GBM, 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 chemotherapy. By synthesizing the latest evidence and expert consensus, this guideline intends to standardize

care, promote the adoption of best practices, and ultimately improve the quality of life (QoL) and survival of patients with a GBM.

The most recent research findings have been incorporated, as well as expert insights from clinical practice, to address the current challenges and opportunities in GBM 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.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications for RT and/or adjunctive therapies (eg, chemotherapy, alternating electric fields) in patients with newly diagnosed grade 4 adult-type diffuse glioma?**			
	Adults with high-grade glioma/ astrocytomas, IDH-wildtype glioma, glioblastoma, WHO grade 4 glioma	• Surgery • RT • Chemo • Alternating electric field therapy (TTF) • 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 EBRT after biopsy/resection in patients with 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 EBRT • Hypofractionation • Hyperfractionation • Accelerated fractionation • Stereotactic radiosurgery • Pulsed RT • Chemo: alone or concurrent/adjuvant • Brachytherapy	• 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 definitive EBRT in patients with grade 4 adult-type diffuse glioma?**			
	Same as KQ1	• IMRT • Proton therapy • Smaller CTV expansions (eg, 0.5 cm, 1-1.5 cm) • 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 grade 4 adult-type diffuse glioma whose disease recurs following completion of standard first-line therapy?			
	Same as KQ1	• EBRT (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; EBRT = external beam radiation therapy; 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; LITT = laser interstitial thermal therapy; MRI = magnetic resonance imaging; OARs = organs at risk; PTV = planning target volume; preop = preoperative; postop = postoperative; RT = radiation therapy; SIB = simultaneous integrated boost; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy; VMAT = volumetric modulated arc therapy.

3. Key Questions and Recommendations

3.1. KQ1: Indications for RT and/or adjunctive therapies (Table 3)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1 and Figure 1.

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

Table 3 Indications for RT and/or adjunctive 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, 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 [3,15,16]
3. For patients with supratentorial glioblastoma, alternating electric field therapy for ≥18 hours per day is conditionally recommended after biopsy or resection and concurrent chemoradiation with TMZ.	Conditional	Moderate [5,17,18]

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

In patients with adequate performance status (PS), the standard of care following biopsy or resection of WHO grade 4 diffuse glioma is adjuvant fractionated external beam radiation therapy (EBRT) based on numerous RCTs performed primarily in the 1970s and 1980s that showed a significant benefit in OS following RT compared with chemotherapy or supportive care alone.[14,19-22] It is noteworthy that these studies enrolled a heterogenous patient population including both GBM and grade 3 glioma. Furthermore, most of these studies employed archaic radiation techniques including whole brain RT, which has been shown in the interim to be associated with cognitive sequelae compared with more conformal approaches used in modern radiation oncology practices. In addition, these studies were performed before magnetic resonance imaging (MRIs) were incorporated into RT treatment planning. Nonetheless, given the clear benefit of RT in these historical studies, re-evaluation with modern techniques would not be deemed ethical. There is 1 phase III trial in patients age ≥70 years performed in the last 2 decades using more modern treatment planning approaches which confirmed a benefit in OS compared with supportive care alone.

Although there is no high-quality data to guide the optimal timeline to initiate RT, expert opinion suggests that approximately 3 to 6 weeks following surgery may be most appropriate to allow adequate time for healing but minimize the risk of symptomatic progression in the interval period. MRI should be repeated as a part of simulation ideally within 1 to 2 weeks of initiation of RT given the high risk of progression over short time intervals. In patients with needle biopsy only, it is suggested that this timeline be expedited to approximately 1 to 2 weeks of pathology being available given the aggressive nature of the disease and the fact that needle biopsy alone is most performed in patients with tumors in eloquent and unresectable locations of the brain.

The treatment for WHO grade 4 diffuse glioma 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 was associated with a significant benefit in OS.[3,15] This study enrolled adults age 18 to 70 years with a WHO PS of 0 to 2. In another study, patients age ≥65 years were randomized to either hypofractionated RT to a dose of 4005 cGy in 15 fractions alone or the same RT regimen with concurrent and adjuvant TMZ and a significant benefit of TMZ was once again demonstrated.[16] However, the OS of both groups in this study was poorer than in the preceding study using 6000 cGy of RT and the study was assuming 4005 cGy in 15 fractions as the standard treatment for elderly patients. The nuances of these fractionation decisions are discussed in KQ2 (Table 4).

Two additional smaller scale studies have similarly shown a benefit in OS with the addition of TMZ to adjuvant RT. While a third study failed to confirm this benefit; it was stopped prematurely and was meaningfully underpowered.[23] Importantly, a meta-analysis demonstrated that adding concurrent and adjuvant TMZ to RT is associated with a significant benefit in OS in this patient population.[24] The EORTC study

driving the utilization of TMZ delivered 6 cycles of TMZ after concurrent RT plus TMZ.[3,15] Up to 12 cycles may be considered 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.[25] Ultimately, more data are needed to inform this decision.

Notably, the data overwhelmingly examined patients with what would be characterized as GBM according to the WHO 2021 definition.[4] Only a single post-hoc analysis has examined patients with molecular GBM that were previously histological grade 3 glioma and it did not demonstrate a benefit to adding TMZ concurrently to RT.[26]

Clinical trials exploring adjuvant bevacizumab in newly diagnosed GBM failed to show a statistically significant benefit in OS.[23,27] The use of immunotherapy remains an area of active investigation, although nivolumab versus placebo in combination with concomitant TMZ with RT did not show any benefit over chemoradiation with TMZ alone.[28,29] 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.[29] Lomustine-TMZ has also been explored and demonstrated increased hematologic toxicity compared with the TMZ alone arm in addition to increased reports of brain edema and neurological symptoms.[6] In patients with MGMT methylated tumors with acceptable toxicity levels, there may be an added benefit that leads to improved OS though the results should be interpreted with caution.[6]

Other adjuvant therapies may be considered at the time of surgery itself. Specifically, carmustine wafer implantation[30] and brachytherapy[31] have been explored. 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 GBM management. The overall effect of intraoperative RT remains inconclusive due to 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 GBM following resection or biopsy.[5,18] Alternating electric field therapy was well tolerated with an associated improvement in health-related QoL at 3 and 6 months, which did not persist at later time points due to increased dermatologic toxicity. In the study, the device was intended to be worn for 18 hours per day.[18] Nonetheless, the optimal time remains uncertain and there are remaining questions as to whether the cumulative time the device is worn drives outcomes rather than use on an individual day.

While the study represents high-quality data, several criticisms have been raised. Specifically, there is limited basic science data to understand the mechanism through which the device acts. The control arm did not include a sham device which may have biased subsequent patient management and surveillance or caused

a placebo effect. Randomization was also performed 2 months postoperatively such that patients with more aggressive tumors would not have been included. Ultimately, longer term observational studies will be beneficial as will data regarding the device in combination with hypofractionated RT regimens. The recommendation is conditional because of the limitations noted above and the variable consensus in adoption in national practices. The conditional recommendation reflects that most informed clinicians would choose the recommended course, though a substantial number may not, pending further data.

Despite aggressive management, most patients with WHO grade 4 diffuse glioma will ultimately succumb to their disease. As such, providers must remain acutely aware of the patients' QoL and address areas of physical and psychological distress. Early engagement of palliative care and symptomatic care services are highly encouraged in all patients to holistically address the challenges faced by patients and their families. It is critical to be aware that palliative care is unique from hospice and may be utilized cohesively with aggressive treatment including chemoradiation.

In frail patients or those with poor PS, hospice or supportive care may be an alternative to aggressive management. Patients and their families should be counseled that chemoradiation is likely to extend life but is not likely to improve a patient's baseline functional status. Therefore, if patients do not find their current QoL acceptable, they may prefer to forego aggressive management and focus on symptom management and minimizing time spent undergoing treatment. The physician'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 their goals of care.

3.2. KQ2: Appropriate dose-fractionation regimens for EBRT 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 EBRT after biopsy/resection in patients with grade 4 adult-type diffuse glioma, and how might treatment vary based on pretreatment characteristics (eg, age or performance status)?

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

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients age <70 years, KPS ≥60, with WHO grade 4 diffuse glioma, partial brain irradiation with 6000 cGy in 30 fractions with concurrent and adjuvant TMZ is recommended.	Strong	High [3,15,32,33]
2. For patients age ≥70 years, KPS ≥50, with WHO grade 4 diffuse glioma, partial brain irradiation with 4005 cGy in 15 fractions	Conditional	Moderate [16,34-36]

with concurrent and adjuvant TMZ is conditionally recommended.		
3. For patients with WHO grade 4 diffuse glioma who are frail, 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 physiological reserve and increased vulnerability to adverse health outcomes.	Conditional	Low [37,38]
4. For patients with WHO grade 4 diffuse glioma who are very frail or with KPS ≤40, supportive care in lieu of RT and chemotherapy is conditionally recommended.	Conditional	Expert Opinion

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

Historically, trials using EBRT 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.[33] The demonstration of improved OS with the addition of concurrent temozolomide to a backbone of 6000 cGy of RT followed by adjuvant TMZ in the landmark EORTC-NCIC trial[15] serves as the basis for the incorporation of this regimen as the standard arm in contemporary clinical trials.[23,27,39] For patients 18 to 70 years old and KPS ≥60, this regimen has remained the standard dose-fractionation for patients with newly diagnosed GBM.

Randomized studies evaluating dose-escalated RT strategies including hypofractionation, hyperfractionation, stereotactic radiosurgery and sequential/integrated boost, with or without older chemotherapeutics, have not demonstrated an improvement in OS in patients with newly diagnosed GBM.[15,40-44] An RCT evaluating dose-escalated radiotherapy using integrated boost and temozolomide demonstrated no initial improvement in OS.[45] These studies are based on conventional magnetic resonance imaging (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.[32,46-48]

Therapeutic decisions depend in part on prognosis, and among the most important patient factors affecting survival are age and PS. Analyses of prospective data have strongly associated older age and/or poor PS with limited life expectancy.[49,50] A RCT from France demonstrated, however, that even among patients age ≥70 years with KPS >70, RT improved median survival compared with supportive care alone (29.1 weeks versus 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.[15] Two other phase 3 RCTs compared conventionally fractionated RT (6000 cGy in 30 fractions over 6 weeks) with moderately hypofractionated RT in older patients.[35,38] A Canadian trial randomized patients ≥60 years old with KPS ≥50 to conventionally fractionated RT versus 4005 cGy in 15 fractions over 3 weeks. Results showed no difference in median survival, but patients receiving conventional fractionation required more corticosteroids.[35] 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 between the RT groups as a whole or among patients 60 to 70 years old was shown, but in patients age >70 years, hypofractionated RT resulted in significantly better survival.[38]

The Canadian[35] and Nordic[38] trials provide the only randomized data directly comparing hypofractionation with conventional fractionation among older patients with fair to good PS, and both support the conditional recommendation for moderate hypofractionation. Neither included concurrent or adjuvant TMZ in any of the treatment arms, however. NCIC 26052, a phase 3 RCT, later demonstrated that among patients age ≥65 years with an Eastern Cooperative Oncology Group (ECOG) 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.[16]

While 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 GBM age ≥65 years.[34,36] An analysis from Harvard found similar median overall and PFS times between conventionally fractionated and moderately hypofractionated chemoradiation.[34] Another propensity-matched analysis from Italy also found no difference in overall 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.[36] 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.[34,36] Based on these propensity-matched analyses[34,36] and RCTs,[16,35] 4005 cGy in 15 fractions with concurrent and adjuvant TMZ is conditionally recommended for patients age ≥70 years with a KPS ≥50. This recommendation is conditional because of the absence of randomized data directly comparing conventionally fractionated with hypofractionated regimens in the setting of TMZ.

Less data are available to guide decisions on dose-fractionation among patients with poor PS or frailty, the latter characterized by reduced physiological reserve and increased vulnerability to adverse health outcomes.[51] Frailty is especially prevalent among older patients with cancer. Defined either as a clinical syndrome due to altered metabolism and abnormal stress responses or as a state of accumulated health-related deficits exacerbated by aging, frailty heightens the risk of complications from intensive cancer treatments like RT or chemotherapy.[51] 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.[51]

The International Atomic Energy Agency (IAEA) completed a phase 3 RCT[37] comparing ultrahypofractionation (2500 cGy in 5 fractions over 1 week) with moderate hypofractionation (4005 cGy in 15 fractions over 3 weeks) 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%). Ultrahypofractionation was found to be noninferior to moderate hypofractionation, demonstrating no intergroup difference in OS, PFS, or QoL.[37] The task force extrapolated from the IAEA[37] and Nordic[38] 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. The recommendation was conditional as the IAEA trial included patients based on age and PS rather than frailty as currently defined, and the Nordic trial included patients with a fair to good PS.[37,38]

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[14,52] and the Nordic trial.[38] Patients who are very frail with poor functional status and major comorbidities may experience increased chemotherapy-related toxicities and may optimally be managed with best supportive care alone.

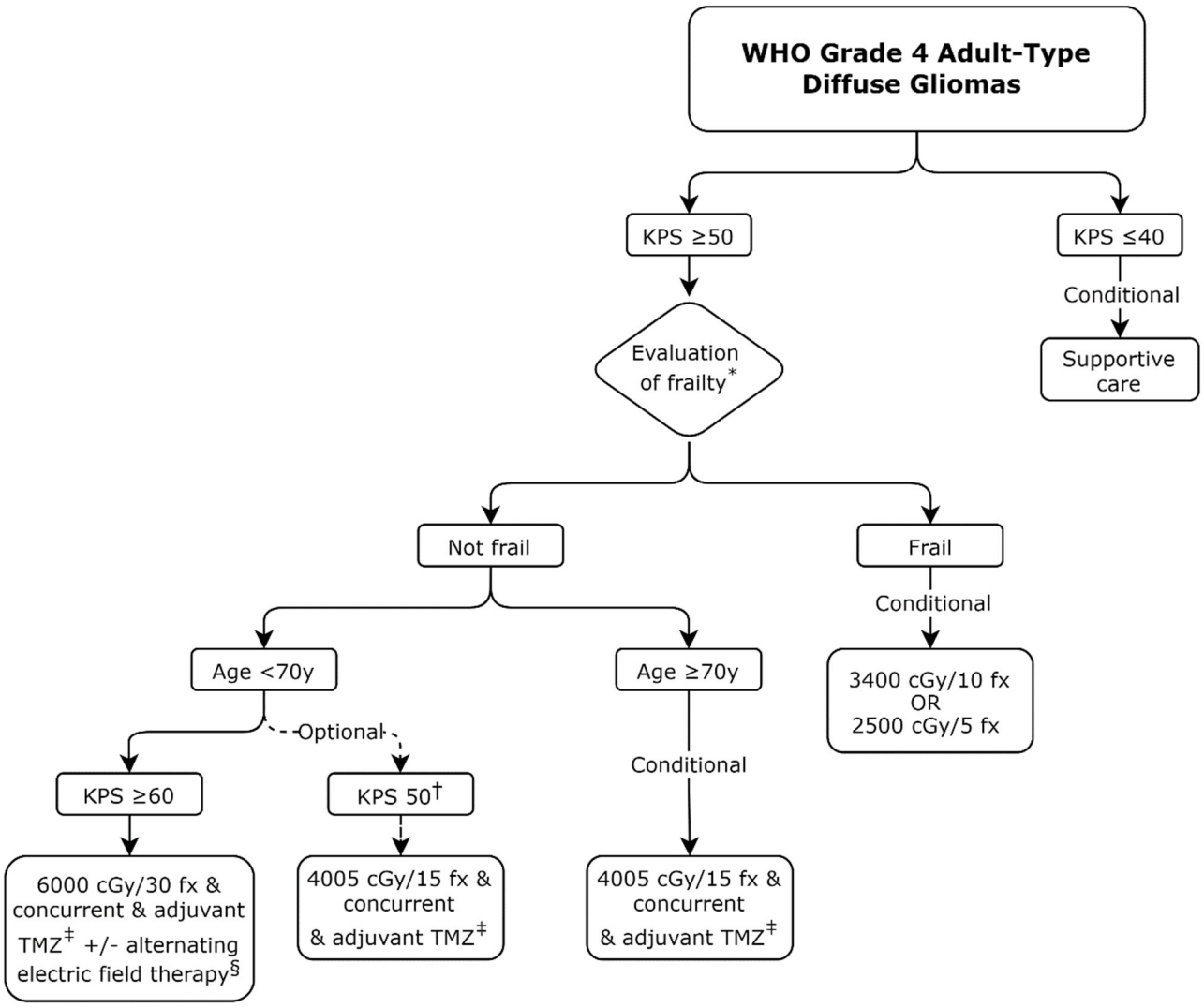

Figure 1 Management of WHO Grade 4 Adult-Type Diffuse Glioma

Abbreviations: fx = fraction(s), GBM = glioblastoma; KPS = Karnofsky performance status, RT = radiation therapy, TMZ = temozolomide, WHO = World Health Organization.

*Frailty is characterized by reduced physiological reserve and increased vulnerability to adverse health outcomes.

†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 GBM.

3.3. KQ3: Appropriate target volumes and techniques for definitive EBRT (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 definitive EBRT in patients with grade 4 adult-type diffuse glioma?

Table 5 Appropriate target volumes and techniques for definitive EBRT

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 [53,54]
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, + 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 [46,53,55-60]
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 and T2/FLAIR signal changes (non-enhancing tumor) revised to respect natural barriers to tumor spread (bone, dura, etc.) • PTV = CTV + 3-5 mm expansion	Strong	Low [16,53,54,61,62]
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 planning.	Strong	Expert Opinion
5. For patients with WHO grade 4 diffuse glioma, daily image guidance is recommended during treatment to facilitate reduced CTV to PTV expansions.	Strong	Expert Opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; CTV = clinical target volume; EBRT = external beam radiation therapy; 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.

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), rotational IMRT or

volumetric modulated arc therapy (VMAT), proton RT, and more experimental forms including carbon ion therapy.[53-55,59,60,63]

IMRT (including VMAT), when compared with 3-D CRT, improves target conformity and dosimetric indices, with lower RT doses being delivered to adjacent normal tissues, especially the uninvolved brain. These dosimetric differences result in significantly reduced rates of acute grade 1 and 2 neurological toxicities, most notably cerebral edema and impaired neurocognition, compared with 3-D CRT.[53,54] Of note, IMRT (including VMAT) can slightly increase the RT dose 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 the QUANTEC papers.[54,64] The data comparing IMRT (including VMAT) with 3-D CRT have been mixed with respect to OS, with some analyses showing improved survival with IMRT (including VMAT), and others noting no differences.[53,54] Based on the evidence of reduced RT dose to normal tissue and decreased toxicity, IMRT (including VMAT) is recommended over 3-D CRT.

In prospective clinical trials and retrospective series, proton therapy has been shown to reduce doses to normal tissues when compared with IMRT including the normal brain, cochlea, and optic pathway.[59,60,63] In an RCT comparing proton RT with IMRT for patients with GBM, patients receiving treatment with proton RT had significantly fewer grade 2+ toxicities compared with those treated with IMRT.[60] There have been no consistent differences found between proton RT and IMRT with respect to PFS or cognitive failure in GBM, however,[60] 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 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 and 4 glioma (including IDH-wildtype GBM) treated with a 1-phase versus 2-phase technique.[65] In this guideline, use of either a 1-phase technique with single set of targets or a 2-phase technique including a “cone-down” or “boost” targets are 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.[16,32,46,53-62,66-70]

For RT planning of WHO grade 4 diffuse glioma, there is consensus that brain MRI should be used for target delineation; however, the details on optimal timing of the MRI scans are often not reported.[16,32,53,54,57-59,62,66] 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 simulation.[46,56,60,67] While all reports that describe MRI scans for RT target

delineation detail using T2-weighted, FLAIR and post-contrast T1-weighted imaging sequences, only 2 studies specify acquisition of thin-cut, volumetric post-contrast T1-weighted images to facilitate treatment target contouring.[62,68] None of these studies discuss the need for distortion correction when fusing the MRI scans to the CT scans obtained at simulation. Given the paucity of evidence regarding optimal timing and sequences of MRI to be obtained for RT planning, patients with WHO grade 4 diffuse glioma should undergo volumetric MRI brain with and without contrast within 14 days of starting RT for treatment planning 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.[16,53,54,61,62] For this technique, the GTV is commonly accepted to be the surgical cavity plus residual tumor identified on post-contrast 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, 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 as employed by the Radiation Therapy Oncology Group (RTOG) 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.[23,39] How the 2-phase approach has been implemented, however, varies widely from the RTOG and from center to center, including the specifics of how the targets are defined (eg, 1[55-57] versus 2[58] GTVs), and the doses delivered to the initial (4000-5000 cGy in 20-25 fractions) and boost (1000-2000 cGy in 5-10 fractions) volumes.[55-58,68] Further, with wider use of IMRT (including VMAT), more institutions have transitioned away from sequential boosting to a simultaneous integrated boost technique,[32,55,56,58-60,66,67] with no difference in survival outcomes noted when these approaches were compared with 2 retrospective series.[55,58] The initial GTV ("GTV1") used in the 2-phase approach is the same as for the 1-phase, with or without the T2/FLAIR changes included, and the cone-down GTV ("GTV2") limited to the 1-phase GTV volume. 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 RT approach, various PTV expansions have been employed, ranging from 1 mm[67] to 10 mm,[55,68] with many studies using a 3 to 5 mm expansion.[16,32,46,53,54,56,58-62,66] 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.[69,70] 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.[53,54] Therefore, 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.

3.4. 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 grade 4 adult-type diffuse glioma whose disease recurs after completion of standard first-line therapy?

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 glioblastoma, establishing the diagnosis by either pathology or advanced imaging (eg, MR perfusion, spectroscopy, or PET) is conditionally recommended.	Conditional	Low 71-74
2. For patients with recurrent WHO grade 4 diffuse glioma with a KPS ≥70 and prior in-field RT interval of ≥6 months and/or focal tumor volume ≤6 cm, reirradiation is conditionally recommended following a multidisciplinary, patient-centered discussion. Implementation remark: Physicians are encouraged to enroll patients in clinical trials or multi-institutional registries.	Conditional	Moderate 72,73,75-78
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 72-88
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 72,73,79,86,88,89
5. For patients receiving reirradiation for recurrent WHO grade 4 diffuse glioma, concomitant bevacizumab is conditionally recommended to reduce toxicity.	Conditional	Moderate 71,73,90-92

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.

The prognosis for patients with recurrent GBM remains limited, with few effective salvage therapies. For patients with WHO grade 4 diffuse glioma with any suspected recurrence, establishing the diagnosis by

either resection, advanced imaging (ie, MR perfusion, MR spectroscopy, or PET) or repeat follow-up MRI to rule out predominately treatment effect changes and confirm recurrence is necessary prior to reirradiation.[71-74] Reirradiation is a treatment option for patients with recurrent GBM.[72,73,89] As there is considerable variance in approaches to salvage therapies, most data are retrospective with few randomized, prospective clinical studies.[72,73,75] Acknowledging that the majority of patients at first recurrence of GBM receive second-line systemic therapy, reirradiation for patients with recurrent WHO grade 4 diffuse glioma is conditionally recommended following a multidisciplinary, patient-centered discussion. Physicians are encouraged to enroll patients in clinical trials or prospective, multi-institutional registries. Appropriate patient selection for reirradiation include younger age, good PS, longer interval from initial RT and/or smaller tumor size.[75-78]

Modern RT techniques deliver highly conformal RT and have improved the safety of reirradiation.[74,75,79-87,93] 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), fractionated stereotactic RT, or brachytherapy.[74,75,79-87,93,94] 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.[72,73,79,86,88,89] 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.[95]

The role of systemic therapy in combination with reirradiation in recurrent WHO grade 4 diffuse glioma has been investigated with several retrospective studies suggesting the combination improves local control.[71,90-92] The addition of bevacizumab is conditionally recommended because it appears to reduce the risk of radiation necrosis and improves the safety of reirradiation.[71,90-92]

4. Health Disparities

Health disparities encompass a wide range of factors impacting access to care, such as therapy timing, type of therapies offered, impact of geography, SES, and race/ethnicity. The retrospective nature of health disparities literature in GBM has inherent limitations, with national database reviews lacking nuanced specificity on clinical characteristics,[96] while smaller institution series with more specific data 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.[97] The impact of this may be unclear. For instance, RT delayed by >42 days (6 weeks) or even 31 to 37 days has been associated with worse outcomes.[98,99] However, a different meta-analysis found no difference in OS per week of delay in 12 studies encompassing over 5,200 patients.[100] Different factors may confound the association of delays in treatment with OS outcomes in population-based studies. For example, while Black race was associated with greater treatment delays (>30 days from surgery), so were clinical factors such as receipt of gross tumor resection and treatment at an academic facility.[99]

Insurance, geographic distribution, type of hospital facility, and trial eligibility can impact healthcare access disparities systemically. Based on multiple large retrospective analyses, including the National Cancer Database and the Surveillance, Epidemiology, and End Results Program patient data, males, Blacks and Hispanics are more likely to be "underinsured" with Medicaid or no insurance.[97,101-108] Adult patients with WHO grade 4 diffuse glioma who have Medicaid coverage are more likely to have larger tumors at diagnosis and less likely to receive triple-modality therapy (surgery, RT, and chemotherapy).[109] Data identified that patients in counties with fewer neurosurgeons and with higher Black populations experience greater delays in care, while those in rural communities were less likely to receive adjuvant RT.[110] Patients at safety net hospitals (those with the highest burden of patients who are uninsured or those with Medicaid) also had lower rates of receiving gross tumor resection and lower likelihood of receiving any adjuvant therapy, including RT.[106] Clinical trial access eligibility often reflects an inherently healthier population, illustrated in a review that only a small minority of cases would be eligible to participate based on standard clinical and laboratory eligibility criteria and were more likely to be younger, male and have a median OS double that of those not considered eligible (16 months vs 7 months).[111]

Data suggest lower likelihood of receipt of RT among Hispanic and Black patients.[102] However, quantifying how much this translates to differences in outcomes is unclear because of limitations in retrospective, population-based or registry data. Depending on the region of the United States, Hispanic patients were less likely to receive triple-modality therapy, which was also associated with lack of insurance, lower income, and living in regions with lower rates of high school graduates.[104] Yet, other single institution series found no difference in outcomes among Hispanic patients when adjusting for other clinical factors,[112] and that Latinos in the US had higher survival despite slightly lower rates of receipt of RT.[113] Amongst patients with GBM, Black and Asian/Pacific Islander patients had lower GBM specific mortality, despite Black patients having significantly higher non-GBM mortality overall in the cohort.[114] In multivariable models Black, Hispanic, and Asian patients had overall lower rates of death, but when stratifying delay in receipt of RT by race, the hazard ratio of death was instead higher in these patients suggesting there may be additional factors not adequately captured retrospectively in population-based models that confound the interpretation of survival

analysis.[102] These findings highlight the importance of having prospective data that better adjust for social determinants of health that may be tied to geographic and insurance access in addition to racial/ethnic factors to address the impact on survival outcomes.

Higher household income has been associated with higher survival with known clinical prognostic positive markers such as MGMT methylation.[115] While some data show lower SES is associated with worse OS,[114,116,117] other data also 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.[107] Marital status was also associated with improved outcomes favoring married patients,[118] while the Surveillance, Epidemiology, and End Results Program registry data showed widowed or unmarried status was associated with lower rates of receipt of RT and worse outcomes.[119,120] In a retrospective meta-analysis and the Cancer Genome Atlas Program analysis, female sex patients were more likely to have MGMT promoter methylation, and this combination of gender and methylation status was associated with improved outcomes.[121]

There are acknowledged limitations to these findings given a larger representative population of United States/Euro-centric data based on predefined thresholds in reported study cohort numbers. Meta-analyses aimed to mitigate some of these factors. Pertinent goals for the future of health disparities research discussed by the task force included addressing improving outcomes in a multifactorial approach. For instance, reporting data beyond race, SES, and sex to address additional barriers to care which can compound disparities. Primary hypothesis-based literature on health disparities and funding is warranted and would increase the rigor and quality of the analyses to investigate health disparities specifically. An emphasis on intervention-based or community-based research strategies for mitigating health disparities instead of reporting existing, known disparities is crucially needed. One unique aspect is the importance of social support structures in cancer care. In addition to current data on marital status, literature that recognizes non-traditional family or community support is warranted and could impact smaller ethnic communities, rural populations, faith-based or indigenous populations. Clinical trial data can also improve the literature in disparate outcomes by reporting adjusted ethnicity/race, SES and geographical patterns of enrollment consistently in the primary findings which could better inform the likelihood of application in a real-world setting. Gatekeepers to access to care (eg, primary care providers) may also impact health disparities because insurance access, number of specialty providers (eg, neurosurgeons, radiation oncologists, neuro- or medical oncologists) and geography alone may not address all issues. Lastly, factors may differ across countries due to the difference in healthcare structures, financing, and overall population health, so improved research in health disparities is encouraged to equitably provide optimal care.

5. Conclusions and Future Directions

GBM 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, chemotherapy, and supportive care. The recommendations highlight the significance of individualized, image-guided treatment planning, where patient-specific factors such as molecular markers and functional status guide treatment. There are emerging data for considering using smaller margin expansions for RT treatment planning. While initial reports indicate similar outcomes to traditional volume expansions, the data are not mature enough to include in this guideline.[95]

Emphasis on recent molecular and genetic discoveries also points to the growing potential of precision medicine, where therapies can be tailored to specific tumor characteristics, potentially improving outcomes and reducing toxicity. Furthermore, the use of circulating DNA is emerging to better inform treatment and surveillance.[122] Enrolling eligible patients in clinical trials, particularly minority populations, focused on novel drug therapies and experimental RT techniques, remains crucial, as these trials drive the discovery of novel therapeutics and further refine existing strategies. Ongoing trials that may address the use of protons versus photons (*NCT02179086*), management of molecular GBM (*NCT04623931*), and adaptive RT (*NCT06108206, NCT04075305, NCT04574856*), will likely help inform future practice beyond the publication of this guideline.[123,124]

Ultimately, the goal of this guideline is to provide a robust framework for optimizing GBM 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 these guidelines 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 GBM.

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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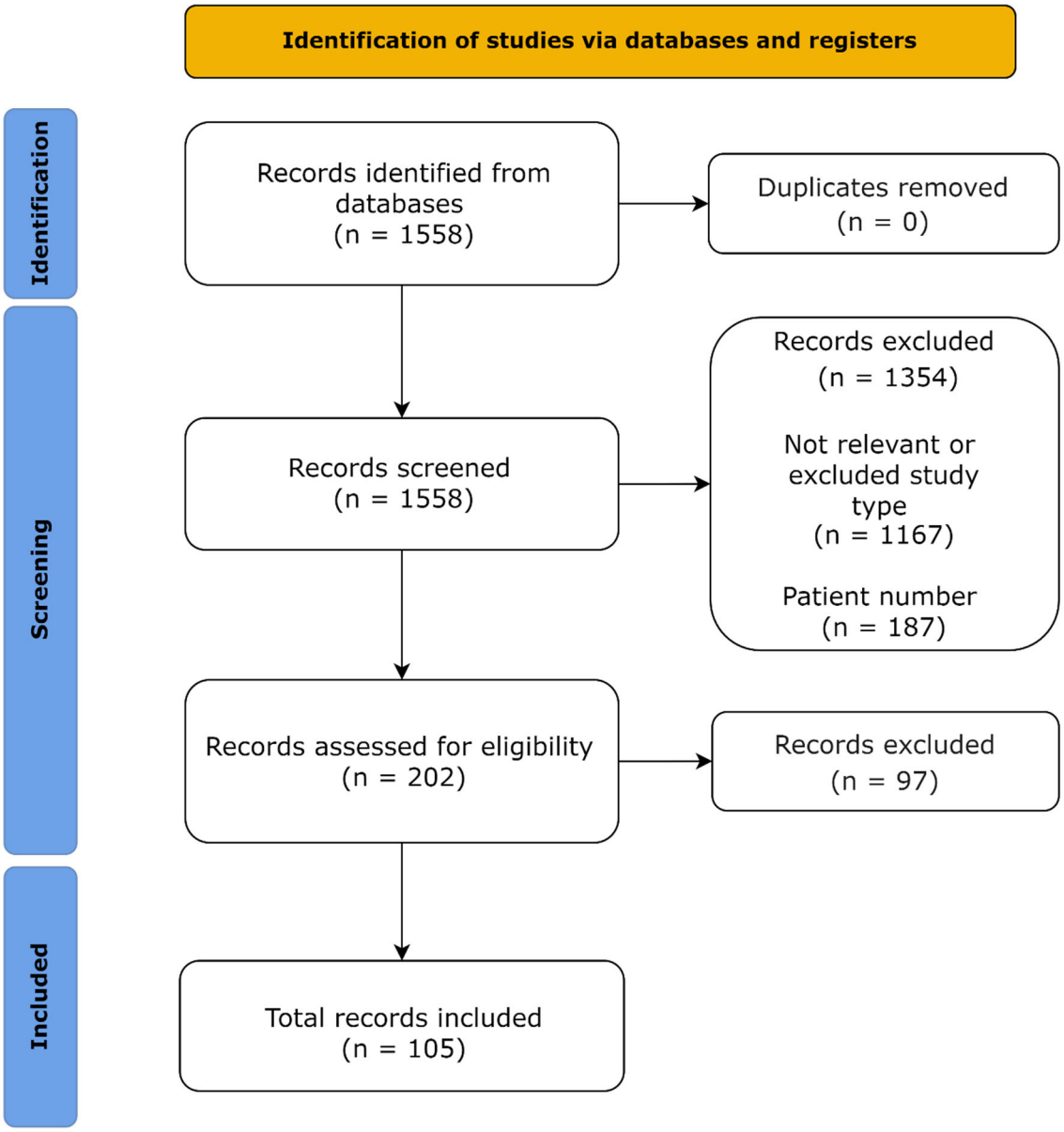

PRISMA 2020 Study Selection Diagram[125,126]

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Appendix E1 Peer Reviewers and Disclosures (Comprehensive)

Added to the draft prior to publication.

Appendix E2 Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy
cGy = centiGray
CT = computed tomography CTV = clinical target volume
EBRT = external beam radiation therapy
EORTC = European Organisation for Research and Treatment of Cancer
GBM = glioblastoma
GTV = gross tumor volume
FLAIR = fluid attenuated inversion recovery
fx = fraction(s)
IDH = isocitrate dehydrogenase
IMRT = intensity modulated radiation therapy
KPS = Karnofsky performance status
KQ = key question
PET = positron emission tomography
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PTV = planning target volume
PFS = progression-free survival
PS = performance status
SES = socio-economic status
QoE = quality of evidence
QoL = quality of life
MRI = magnetic resonance imaging
OS = overall survival
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT = randomized controlled trial
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
TMZ = temozolomide
VMAT = volumetric modulated arc therapy
WHO = World Health Organization

Appendix E3 PICOTS Questions / Literature Search Strategy

Appendix A PICOTs Questions

Search Limits:

Search Date(s):	February 1, 2014 – December 15, 2023
Age Range	Adults (≥18 years old)
Language	English only
Species	Humans
Publication Types	• RCTs (≥50 pts) • Meta-analyses (KQ3 & 4 only; ≥300 pts) • Prospective trials (≥75 pts) • Retrospective studies (excluded from KQ1; ≥100 pts for KQs 2, 3, 4) • Health disparities (≥200 pts)
Timeframe	• New search: February 1, 2014 – December 15, 2023 • Additional search from January 1966 – February 2014 to confirm 2016 guideline search was comprehensive; RCT data from this search was used by the task force.

Universal Exclusion Criteria:

1. Preclinical, nonhuman studies
2. Feasibility and phase I studies
3. Health economics, cost analysis studies
4. Studies available in abstract only
5. Comment, review articles, editorial, guidelines, or case reports
6. Pediatric patients
7. Grade 1, IDH-mutant grade 2 and grade 3
8. Metastatic disease or disseminated disease
9. Brainstem gliomas
10. SEER and NCDB (included only for health disparities)
11. Otherwise not relevant or out of scope

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 1: What are the indications for radiation therapy and/or adjunctive therapies (eg, chemotherapy, alternating electric fields) in patients with newly diagnosed grade 4 adult-type diffuse gliomas?**
Definitions	• RT: photons, SRS, SRT, IMRT, 3-D CRT, VMAT, protons, brachytherapy • Chemotherapy • ChemoRT • Tumor treating fields (TTF), alternating electric fields (Optune, NovoTTF)
Participants/ population	Adults with high-grade gliomas/astrocytomas, IDH-wildtype gliomas, glioblastoma, WHO grade 4 (IV) gliomas, WHO grade 4 (IV) IDH-mutant gliomas *(the nomenclature has changed over the years so it was kept broad for all KQs)*

Intervention(s)/ exposure(s)	• Surgery: biopsy, subtotal resection, gross total resection, LITT (laser interstitial thermal therapy) • RT: photons, SRS, SRT, IMRT, 3-D CRT, VMAT, protons, brachytherapy • Chemotherapy: concurrent chemotherapy, adjuvant chemotherapy, carmustine implant (eg, Gliadel wafer), other systemic therapy (eg, bevacizumab) • TTF, alternating electric fields • Monotherapies and/or combination systemic therapies. For combination therapies, sequential and/or concurrent therapies (immunotherapy and others), hyperthermia
Comparator(s)/ control	Comparisons include all of the management options listed above (eg, surgery alone, RT alone, chemotherapy alone, surgery + postoperative RT alone, surgery + postoperative chemoRT alone), and biopsy alone
Outcomes: primary/critical	• Local control, local failure, local progression • Progression-free survival • Overall survival • Acute and late toxicity/morbidity • Quality of life (eg, adverse effects, neurocognitive function, cognitive function, memory, executive function)
Timing	Any
Setting/context	Any

Study design	• RCTs
	  ○ Surgery/biopsy vs surgery + RT
	  ○ Surgery/biopsy vs surgery/biopsy + chemoRT
	  ○ Surgery/biopsy vs surgery/biopsy + RT and adjuvant chemo
	  ○ Surgery/biopsy followed by chemotherapy vs RT
	  ○ Postoperative RT vs postoperative chemoRT
	  ○ Postoperative RT vs postoperative RT and sequential chemo
	  ○ Postoperative chemoRT vs postoperative chemoRT + TTF
	• Prospective trials

Health disparity considerations	Are there groups that might be disadvantaged in relation to the problem or intervention of interest, and are there considerations that people implementing the intervention should consider for reducing associated inequities? (SEER/NCDB data used for health disparities only)
Key search selection criteria	**Inclusion criteria: as above** **Exclusion criteria: as above**
Validation set/ key studies	**PMIDs**: 7001230; 355604, 19269895, 29260225, 24552317, 30782343, 34838156, 27310651, 24285550, RTOG 0525

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Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**<u>Key Question 2</u>: What are appropriate dose-fractionation regimens for EBRT after biopsy/resection in patients with grade 4 adult-type diffuse gliomas, and how might treatment vary based on pretreatment characteristics (eg, age or performance status)?**
Definitions	• Conventional fractionation (180-200 cGy/fraction) • Hypofractionation (>200 cGy/fraction) • Hyperfractionation (≥2 fractions daily of smaller than conventional fraction size) or accelerated fractionation (dosing more than once daily to shorten total treatment time) • Pretreatment characteristics (age, performance status, etc.)
Participants/ population	Adults with high-grade gliomas/astrocytomas, IDH-wildtype gliomas, glioblastoma, WHO grade 4 (IV) gliomas, WHO grade 4 (IV) IDH-mutant gliomas
Intervention(s)/ exposure(s)	• Head-to-head studies of same intervention, different dose/technique/regimen • Dose-escalated EBRT • Hypofractionation

	• Hyperfractionation • Accelerated fractionation • SRS • Pulsed RT/Temporally modulated pulsed radiotherapy (pLDR) • Chemotherapy: alone or concurrent/adjuvant • Brachytherapy
Comparator(s)/ control	• Lower total RT doses • Conventional fractionation • Hypofractionation (eg, IAEA elderly and/or frail study) • Brachytherapy • Best supportive care
Outcomes: primary/critical	Same as KQ1 plus quality of life, elderly, or lower KPS
Timing	Any
Setting/context	Any

Study design	• RCTs
	  ○ Low-dose RT (<60 Gy vs current conventional dosing 60 Gy)
	  ○ Dose-escalation (conventional dosing 60 Gy vs >60 Gy)
	  ○ Conventional fractionation vs hypofractionation
	  ○ Conventional fractionation vs hyperfractionation or accelerated fractionation
	  ○ Conventional fractionation vs conventional fractionation + radiosurgery boost
	  ○ Chemotherapy vs RT (conventional or hypofractionated) (eg, NOA-08, Nordic)
	  ○ Brachytherapy
	• Prospective trials
	• Retrospective studies

Health disparity considerations	Same as KQ1
Key search selection criteria	**Inclusion criteria: as above** **Exclusion criteria: as above**
Validation set/ key studies	**PMIDs:** 25442339, 25841623, 21709196, 28296618, 3281031, 17429084, 15051755, 22877848, 22578793, 231022, 22065084, 36225241, 32599030

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**<u>Key Question 3</u>: What are the appropriate target volumes and techniques for definitive EBRT in patients with grade 4 adult-type diffuse gliomas?**
Definitions	• GTV, CTV, PTV • OARs • Imaging: MRI, CT, T1, T2, FLAIR
Participants/ population	Adults with high-grade gliomas/astrocytomas, IDH-wildtype gliomas, glioblastoma, WHO grade 4 (IV) gliomas, WHO grade 4 (IV) IDH-mutant gliomas
Intervention(s)/ exposure(s)	• 3-D CRT • IMRT • Proton therapy • Photon therapy • Smaller CTV expansions (eg, 0.5 cm, 1-1.5 cm) • Smaller GTV (enhancing lesion[s]/postoperative bed only) • 2-volume (primary + boost) and single-volume treatment plans • Dose painting, SIB, sequential boost • Dose-fractionation: conventional, hypofractionation, hyperfractionation

Comparator(s)/ control	• 3-D CRT • Larger CTV expansions (eg, 2-3 cm) • Larger GTV (T2/FLAIR extent + enhancing lesion[s]/postoperative bed) • Use of MRI vs CT-based planning
Outcomes: primary/critical	Same as KQ1
Timing	Any
Setting/context	Any
Study design	• RCTs • Meta-analyses • Prospective trials • Retrospective studies
Health disparity considerations	See comment in KQ1
Key search selection criteria	**Inclusion criteria: as above** **Exclusion criteria: as above**
Validation set/ key studies	**PMIDs**: 20855119, 24906388, 16735709, 30195927, 23211224, 36736621, 32278653

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Item	Details
	Key Question and PICO(TSS) Framework
Key clinical question(s)	**Key Question 4: What are the indications and appropriate techniques for reirradiation in patients with grade 4 adult-type diffuse gliomas whose disease recurs following completion of standard first-line therapy?**
Definitions	• Reirradiation • Salvage RT
Participants/ population	Adults with high-grade gliomas/astrocytomas, IDH-wildtype gliomas, glioblastoma, WHO grade 4 (IV) gliomas, WHO grade 4 (IV) IDH-mutant gliomas
Intervention(s)/ exposure(s)	• EBRT (LINAC/3-D CRT/VMAT/IMRT +/- systemic therapy (eg, bevacizumab, temozolomide) • SRT/SRS • Particle therapy (proton, carbon [CINDERELLA], boron neutron capture therapy) • Brachytherapy • Temporally modulated pulsed radiotherapy (pLDR) • TTF
Comparator(s)/ control	Systemic therapy alone, surgery, best supportive care
Outcomes: primary/critical	Same as KQ1
Timing	Any
Setting/context	Any
Study design	• RCTs • Meta-analyses • Prospective trials • Retrospective studies
Health disparity considerations	See comment in KQ1
Key search selection criteria	**Inclusion criteria: as above** **Exclusion criteria: as above**

Validation set/ key studies	**PMIDs:** 19167838, 23725997, 21489708, 36260832, 30523605, 32599030, 35740612, 33083661

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; chemoRT = chemoradiation; CT = computed tomography; CTV = clinical target volume; EBRT = external beam radiation therapy; FLAIR = fluid-attenuated inversion recovery; FSRT = fractionated stereotactic radiation therapy, GTV = gross tumor volume; IAEA = International Atomic Energy Agency; IDH = isocitrate dehydrogenase; IMRT = intensity modulated radiation therapy; KPS = Karnofsky performance scale; KQ = key question; LITT = laser interstitial thermal therapy; MRI = magnetic resonance imaging; OARs = organs at risk; PLDR = pulsed low-dose rate; PTV = planning target volume; RCT = randomized controlled trial; SIB = simultaneous integrated boost; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy; TTF = tumor treating fields; VMAT = volumetric modulated arc therapy.

Appendix B. Literature Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to December 07, 2023

#	Searches	Results
1	Glioblastoma/	33274
2	(("grade 4" or "grade four" or "high-grade" or "grade IV") adj3 (glioma or gliomas or astrocytoma*)).ti,ab,kf.	9877
3	Glioma/ or astrocytoma/ or brain neoplasms/	151543
4	("grade 4" or "grade four" or "high-grade" or "grade IV").ti,ab,kf.	97315
5	3 and 4	10380
6	glioblastoma*.ti,ab,kf.	51483
7	(diffuse* adj3 astrocytoma*).ti,ab,kf.	1036
8	((IDH-mutant or IDH wildtype or IDH wild-type) adj3 (astrocytoma* or oligodendroglioma*)).ti,ab,kf.	409
9	((diffuse* adj3 glioma*) and (IDH-mutant or IDH wildtype or IDH wild-type)).ti,ab,kf.	415
10	Pulsed-Reduced Dose Rate.ti. and (glioma* or Glioblastoma*).ti,kf.	5
11	or/1-2,5-10 [high grade gliomas]	64749
12	limit 11 to english language	61864
13	limit 12 to ez=20140201-20231215 [From Feb 2014 to current]	36930
14	(animals not (humans and animals)).sh.	5143714
15	13 not 14	35640
16	(animal* or mice or mouse or murine or rat or rats or rodent or cells or "in vitro" or "cell line").ti.	2919365
17	15 not 16	29358
18	((child or children or adolescent or pediatric* or paediatric*).ti. or (infant* or newborn*).ti,kf.) not childhood.ti.	1278009
19	17 not 18	28389
20	case report*.ti,jw.	441090
21	case reports.pt. not (exp clinical study/ or comparative study/ or evaluation studies/ or meta-analysis/ or multicenter study/ or validation studies/ or exp Cohort Studies/ or letter.pt. or (series or cohort or retrospective*).ti,ab.)	1985386
22	20 or 21	2091089
23	19 not 22	26903
24	(comment or editorial or news or preprint).pt.	1717073
25	23 not 24	25948
26	review.pt.	3249989

27	comparative study/ or evaluation studies/ or Clinical Trial/	2514451
28	systematic review*.ti,pt. or "cochrane database of systematic reviews".jn. or meta-analysis as topic/ or Meta-Analysis.pt. or (meta-analy* or metaanaly*).ti.	424792
29	27 or 28	2921495
30	26 not 29	2992353
31	25 not 30	21804
32	Practice Guideline/	30927
33	consensus development conference.pt.	12375
34	consensus development conference nih.pt.	801
35	(Guideline* or consensus).ti.	126203
36	((consensus or position) adj3 statement*1).ti.	8961
37	(practice adj3 parameter*).ti.	738
38	or/32-37	149981
39	31 not 38	21736
40	ncdb.ti. or ("National Cancer Data Base" or "National Cancer Database").ti,ab,kf. or SEER Program/	15522
41	39 not 40 [Remove unwanted types of studies]	21600
42	((metastatic or metastas?s) not primary).ti,kf.	233589
43	41 not 42	21118
44	(NRG or RTOG).ti.	1086
45	(tumo?r treating field* or TTField*).ti,ab,kf.	495
46	exp Radiotherapy/	209427
47	(radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or "intensity modulated" or IMRT or EBRT or VMAT or IGRT or photon* or proton* or radiosurgery or brachytherapy or "particle therapy").ti,ab,kf.	1116085
48	exp Radiotherapy Planning, Computer-Assisted/	25740
49	exp Radiation Oncology/	5900
50	or/44-49 [Radiation broader]	1154541
51	43 and 50 [glioma + radiation therapy broader]	4470
52	exp Treatment Outcome/	1261842
53	exp Survival Analysis/	335003
54	((overall or progression-free or disease-free) adj3 survival).ti,ab,kf. or survival.ti,kf.	461337
55	Neoplasm Recurrence, Local/	146626
56	((local* or locoregional or "loco-regional") adj3 (control or recurrence* or failure or progression)).ti,ab,kf.	92833
57	Kaplan-Meier.ab.	104561
58	((cox or hazard*) adj3 model*).ti,ab,kf.	107875
59	exp *"Quality of Life"/	114795
60	("quality of life" or "HR-QOL" or "health-related QOL" or toxicity or toxicities).ti,kf.	254889
61	adverse event*.ti,ab,kf.	233090
62	exp Radiotherapy/ae, co [Adverse Effects, Complications]	43042
63	exp Cognition Disorders/	118322
64	Attention/re [Radiation Effects]	131
65	exp *Memory Disorders/	22172

66	Executive Function/	19964
67	(cognitive or neurocognitive or cognition or neurocognition or memory or executive function*).ti,ab,kf.	769781
68	exp *Neuropsychological Tests/	32374
69	exp Psychomotor Performance/	121572
70	or/52-69 [outcomes]	3205435
71	51 and 70	2543
72	meta-analysis as topic/ or Meta-Analysis.pt. or (meta-analy* or metaanaly*).ti.	257217
73	random allocation.sh.	107047
74	double blind method.sh.	176892
75	single blind method.sh.	33096
76	(randomized or randomised or randomly).ti,ab.	1137635
77	exp Clinical Trial/	984556
78	((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab,kf.	229504
79	("4 arm" or "four arm").ti,ab,kf.	1622
80	trial.ti.	298788
81	(groups or placebo*).ab.	2774775
82	Research Design/	125974
83	Control Groups/	2064
84	exp Clinical Trials as Topic/	386509
85	multicenter study/ or (multicenter or "multi-center").ti.	357153
86	(phase 1* or phase1* or phase 2* or phase2* or phase 3* or phase3*).ti,kf.	16803
87	("phase* I*" or "phase* II*" or "phase* III*").ti,kf.	61103
88	Prospective Studies/ or prospective*.ti,ab,kf.	1077611
89	(NRG or RTOG).ti.	1086
90	or/72-89 [MA, RCT & prospective studies]	5102340
91	71 and 90 [KQ1]	1133
92	Brain/su [Surgery]	7372
93	Glioblastoma/su or Glioma/su or astrocytoma/su or brain neoplasms/su	24391
94	exp Biopsy/	309708
95	(surger* or surgical or resect* or excision or biops*).ti,ab,kf.	2876907
96	92 or 93 or 94 or 95	3025079
97	71 and 96	1416
98	exp Radiotherapy Planning, Computer-Assisted/	25740
99	exp radiotherapy dosage/	68731
100	((dose* or dosage* or technique*) adj2 (radiat* or radiotherapy or irradiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo*)).ti,ab,kf.	72210
101	(fraction* or hypofractionat* or hyperfractionat* or stereotactic radiosurgery or pulsed or regimens or brachytherapy).ti,ab,kf.	909940
102	(dose adj3 escalat*).ti,ab,kf.	18819
103	98 or 99 or 100 or 101 or 102	1025556
104	97 and 103 [KQ2]	373
105	(delineat* or margin*).ti,ab,kf.	353977

106	exp Organs at Risk/	4826
107	(OAR or OARs).ti,ab,kf.	5303
108	"organ* at risk".ti,ab,kf.	7619
109	(target volume* or "tumo?r volume*").ti,ab,kf.	43219
110	(dose* adj (paint* or boost*)).ti,ab,kf.	753
111	or/103,105-110 [target volume and techniques]	1383928
112	71 and 111 [KQ3 without limits to study type]	872
113	retrospective studies/ or follow-up studies/ or exp longitudinal studies/ or observational study/ or cohort studies/	2146374
114	("single-center" or "single-institut*").ti,ab.	127195
115	(retrospective* or cohort).ti,ab,kf.	1677456
116	(dosimetr* or contour*).ti,ab,kf.	87533
117	radiometry/ or exp radiation dosage/	115289
118	or/90,113-117	6985722
119	112 and 118 [KQ3 limit by study type]	729
120	Re-Irradiation/	630
121	"re-irradiation*".ti,ab,kf.	1400
122	Salvage Therapy/	16393
123	("re-irradiation*" or salvage).ti,ab,kf.	54461
124	120 or 121 or 122 or 123	60655
125	71 and 124 [KQ4 without limited by study type]	205
126	91 or 104 or 119 or 125	1494
127	exp Healthcare Disparities/	22547
128	(disparit* or inequalit* or inequit* or equalit* or equit*).ti,ab,kf.	212186
129	Medically Underserved Area/	7532
130	exp ethnicity/ or exp racial groups/	192996
131	exp Socioeconomic Factors/	516674
132	"social determinants of health"/	6873
133	(race* or racial* or ethnic* or socioeconomic or "socio economic*").ti,ab,kf.	493775
134	exp health inequities/	20438
135	("American Indian*" or "Alaska Native" or "native american*" or Asian or Latino* or African* or black or hispanic* or Caucasian).ti,ab,kf.	521316
136	or/127-135	1468651
137	39 and 50	4651
138	136 and 137 [KQ5 health disparity research- high grade giloma radiation therapy]	97
139	91 or 104 or 119 or 125 or 138 [all 5 key questions]	1567
140	remove duplicates from 91	1128
141	remove duplicates from 104	369
142	remove duplicates from 119	726
143	remove duplicates from 125	205
144	remove duplicates from 138	96

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