Radiation Therapy for Glioblastoma: An ASTRO Evidence-Based Clinical Practice Guideline

Alvin R. Cabrera, MD[1], John Kirkpatrick, MD, PhD[2], John Fiveash, MD[3], Helen A. Shih, MD[4], Eugene Koay, MD, PhD[5], Stephen Lutz, MD[6], Joshua Petit, MD[7], Samuel Chao, MD[8], Paul D. Brown, MD[5], Michael Vogelbaum, MD, PhD[9], David Reardon, MD[10], Arnab Chakravarti, MD[11], Patrick Y. Wen, MD[10], Eric Chang, MD[12]

1. Department of Radiation Oncology, Group Health Cooperative, Seattle, Washington
2. Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina
3. Department of Radiation Oncology, University of Alabama, Birmingham, Alabama
4. Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts
5. Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston, Texas
6. Department of Radiation Oncology, Blanchard Valley Regional Health Center, Findlay, Ohio
7. Department of Radiation Oncology, University of Colorado Health, Fort Collins, Colorado
8. Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio
9. Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio
10. Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts
11. Department of Radiation Oncology, Ohio State University, Columbus, Ohio
12. Department of Radiation Oncology, University of Southern California, Los Angeles, California

CONFLICT OF INTEREST DISCLOSURE STATEMENT

Before initiating work on this guideline, all panelist completed disclosure statements and pertinent disclosures are published within this report. Where potential conflicts are detected, remedial measures to address them are taken and noted here.

JK: research funding, honoraria, and travel expenses from Varian, partner in ClearSight Radiotherapy Products, previous research funding from Genentech. **JF**: honoraria, travel expenses, and research funding from Varian. **HS**: advisory board for Genentech (started 10/2015), previous honoraria and travel expenses from Merck. **EK**: research funding from Phillips, pending patent on quantitative pancreatic image analysis. **SL**: previous stock in Tosk and Oculus. **MV**: consultant for NeuralStem; stock options, royalties, and patent licensing and copyright fees from Infuseon. **DR**: advisory boards for Roche/Genentech, EMD Serono, Novartis, Amgen, Abbvie, Bristol-Myers Squibb, Cavion, Celldex, Juno Pharmaceuticals, Momenta Pharmaceuticals, Novocure, Oxigene, Regeneron, and Stemline; previous advisory board for Apogenix; speaker bureaus for Merck/Scherin and Roche/Genentech; research funding from Celldex, Inovio, and Midatech. **PW**: advisory boards for Genentech/Roche, Novartis, Regeneron, Monteris, and Cavion; speaker for Merck; steering committee chair for Vascular Biogenics trial; previously on advisory boards for Abbvie, Cubist, Foundation Medicine, and Midatech. **EC**: honoraria from Abbvie and Elekta.

The panel chairs and ASTRO Guidelines Subcommittee reviewed these disclosures and took measures to mitigate the impact of potential conflicts. Due to relationships with Merck, Drs. Reardon, Shih, and Wen did not write the recommendations and narrative addressing temozolomide and were recused from consensus voting on these recommendations. Because of relationships with Genentech, Drs. Reardon and Kirkpatrick did not write the recommendations

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INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Incidence rises with age, peaking in the seventh decade of life. However, a substantial proportion of patients are younger than 60 and given its lethality, GBM exacts a significant toll on life-years worldwide and among the approximately 10,000 individuals diagnosed every year in the United States.[1]

Although the prognosis for GBM remains poor, therapeutic advances fueled by a large body of research have improved survival and quality of life. Optimal treatment is multidisciplinary and radiation therapy occupies an integral role, given GBM's proclivity for local recurrence.

This clinical practice guideline systematically reviews the evidence for effective treatment, focusing on the role of radiation therapy and the ways in which systemic therapies modify its effects. As significant variation exists in the technical aspects of radiation delivery, the guideline also focuses on the evidence for ideal dose-fractionation and target volume design. Recommendations seek to account for tumor-specific and patient-specific factors, including cytogenetics, performance status, and age. GBM nearly always recurs, so attention is also paid to the potential role of re-irradiation in this setting. This guideline is endorsed by the European Society for Radiotherapy & Oncology and the American Society of Clinical Oncology.

METHODS AND MATERIALS

Process

The guidelines subcommittee of the Clinical Affairs and Quality Council identified use of radiotherapy in GBM in both primary and recurrent settings as a high-priority topic in need of an

evidence-based practice guideline. In accordance with established ASTRO policy, the guidelines subcommittee recruited a guideline panel of recognized experts in GBM including radiation oncologists, neuro-oncologists, a neurosurgeon, and patient and caregiver representatives. The guideline panel members were drawn from academic settings, private practice, and residency. Four key questions (KQs) were proposed, which addressed the role of external beam radiation therapy after biopsy/resection (KQ1), the optimal dose-fractionation (KQ2), the ideal target volumes (KQ3), and the role of re-irradiation in recurrent GBM (KQ4). In September 2013, the ASTRO Board of Directors approved the proposal and panel membership.

Through a series of conference calls and emails between December 2013 and September 2015, the guideline panel, with ASTRO staff support, completed the systematic review, created literature tables, and formulated the recommendation statements and narratives for the guideline. The members of the panel were divided by key question into four writing groups, according to their areas of expertise. The initial draft of the manuscript was reviewed by four expert reviewers (see Acknowledgements) and ASTRO legal counsel. A revised draft was placed on the ASTRO website for public comment in August and September 2015. Following integration of the feedback, the document was submitted for approval to the ASTRO Board of Directors in January 2016. Going forward, the ASTRO guidelines subcommittee will monitor this guideline and initiate updates according to ASTRO policies.

Literature Review

A systematic review of the literature was performed in early 2014 to form the basis of the guideline. An analytic framework incorporating the population, interventions, comparators, and outcomes (PICO) was first used to develop and refine search strategies for each key question.

The searches were conducted in MEDLINE PubMed and designed to identify studies published in English between January 1966 and February 2014 that evaluated adults with GBM who had completed biopsy and/or resection (KQs 1-3) or had recurrent disease (KQ4). Both MeSH terms and text words were utilized and terms common to all searches included: *glioblastoma*, *malignant glioma*, *high-grade glioma*, *anaplastic glioma*, *radiation*, and *radiotherapy*. Additional terms specific to each key question were also incorporated. The outcomes of interest were overall and progression free survival, recurrence rates, toxicity, and quality of life. The initial literature review was conducted in January 2014 and a second round of searches was carried out in February 2014, following revision of the search strategies to include additional terms. The electronic searches were supplemented by hand searches of the reference lists of previous systematic reviews and other relevant papers.

A total of 3,059 abstracts were retrieved. The articles were then reviewed by ASTRO staff, the co-chairs of the guideline, and the writing groups for each KQ. During the first round of screening, 2163 articles were eliminated based on the inclusion and exclusion criteria. The inclusion criteria were: patients ≥18 years of age, primary or recurrent GBM, treatment with radiation therapy (including external beam radiation therapy [EBRT], brachytherapy, and stereotactic radiosurgery) with or without systemic therapy, and publication date 1966 to 2014. The exclusion criteria were: pre-clinical or non-human studies, case reports/series, non-English language, available in abstract only, pediatric patients, low-grade gliomas, absence of clinical outcomes reported, and otherwise not clinically relevant to the key clinical questions. Retrospective studies were also excluded for KQ1 as the presence of abundant prospective data obviated the need to include retrospective literature. The included articles subsequently underwent a second round of screening to select the most relevant studies and a further 739

articles were excluded during this stage, primarily due to poor relevance and/or poor quality. Ultimately, 157 full-text articles were chosen for inclusion and abstracted into detailed literature tables to provide supporting evidence for the clinical guideline recommendations.

Conference abstracts from ASTRO, American Society of Clinical Oncology, Society for Neuro-Oncology, and American Association of Neurological Surgeons meetings between 2011 and 2014 (as of July 2014), were separately reviewed but were not used to support the recommendation statements. This was done to ensure that no practice changing trials had been reported in abstract form that would have substantially changed or rendered obsolete any of the guideline's recommendations.

Grading of Evidence, Recommendations, and Consensus Methodology

Guideline recommendation statements were developed based on the body of evidence and, when available, high-quality evidence formed the basis of the statements in accordance with Institute of Medicine (IOM) standards.[2] The level of consensus among the panelists on the recommendation statements was evaluated through a modified Delphi approach. An online survey was sent by ASTRO staff to the panel members, who independently rated their agreement with each recommendation on a five-point Likert scale, ranging from strongly disagree to strongly agree (higher score corresponds with stronger agreement). A pre-specified threshold of $\geq$ 75% of raters was determined to indicate when consensus was achieved.[3] Following the survey, the panel reviewed the results, which were provided in aggregate only. Changes were made to three recommendation statements to increase panel consensus. Using the same process, a second survey was sent to assess agreement on the revised statements.

For each guideline statement, the strength of the recommendations and the quality of supporting evidence were rated using the *American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence* (see Appendix).[4] Whether particular recommendations were rated "strong" or "weak" depended on the evidence clarifying the balance of risks and benefits (where applicable) and on the level of consensus established on the survey described above. The evidence supporting respective guideline statements was rated high quality evidence (HQE), moderate quality evidence (MQE), or low quality evidence (LQE). The ratings were initially assigned by the chairs of the guideline and were later approved by all panel members. The guideline statements, along with respective ratings of evidence quality, recommendation strength, and level of consensus, are listed in Table 1.

RESULTS

Key Question (KQ) 1: When is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?

Guideline Statements:

A. Fractionated radiotherapy improves overall survival compared to chemotherapy or best supportive care alone following biopsy or resection of newly diagnosed glioblastoma (**HQE**). Whether radiotherapy is indicated in a particular individual may depend on patient characteristics such as performance status (see KQ2). (Strong recommendation)

B. Adding concurrent and adjuvant temozolomide to fractionated radiotherapy improves overall survival and progression free survival compared to fractionated radiotherapy alone, with a reasonably low incidence of early adverse events and without impairing

quality of life (**HQE**). The guideline panel endorses fractionated radiotherapy with concurrent and adjuvant temozolomide as the standard of care following biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age (see KQ2 for recommendations regarding patients older than 70). (Strong recommendation)

C. Adding bevacizumab to standard therapy for newly diagnosed glioblastoma (i.e., fractionated radiotherapy with concomitant and adjuvant temozolomide) does not improve overall survival and is associated with a higher incidence of early adverse events (**HQE**). Bevacizumab may, however, prolong progression free survival (**MQE**). The panel does not recommend the routine addition of bevacizumab to standard therapy for newly diagnosed glioblastoma outside of a clinical trial. (Strong recommendation)
D. The addition of other systemic therapies to conventional radiotherapy with or without temozolomide remains investigational. (Strong recommendation)

KQ1A. Benefits of adjuvant radiotherapy (Table 2)

Multiple prospective, randomized controlled trials (RCT) in the 1970s and 1980s established the efficacy of radiotherapy following biopsy or resection over chemotherapy alone or best supportive care.[5-8] Brain Tumor Cooperative Group (BTCG) 69-01, a seminal RCT, randomized 303 patients with anaplastic glioma to whole brain radiation therapy (WBRT) to 50-60 Gy, WBRT with carmustine (BCNU), BCNU alone, or best supportive care.[5] Patients who received radiation therapy (with or without BCNU) had improved survival (median survival 35 weeks) compared to those who received best supportive care (14 weeks) or BCNU alone (18.5 weeks). A subsequent RCT of 467 patients confirmed the benefit of radiotherapy (with or without semustine [MeCCNU] or BCNU) over MeCCNU alone, showing similar survival

outcomes as the prior trial.[6] An RCT from the Scandinavian Glioblastoma Study Group involving 118 malignant glioma patients also demonstrated a survival advantage from WBRT (with or without bleomycin) compared to supportive care.[8] The overall survival benefit of radiotherapy was seen or suggested in other studies,[9-11] including two RCTs comparing chemoradiation to chemotherapy alone.[9,10] A Canadian meta-analysis pooling six randomized trials confirmed a significant survival benefit from postoperative radiotherapy compared to no radiotherapy (risk ratio 0.81, confidence interval 0.74-0.88, $p<0.00001$).[12]

Many of these older studies used older radiation techniques and included grade III glioma patients in addition to ones with GBM (World Health Organization [WHO] grade IV). A modern French RCT, which employed magnetic resonance imaging (MRI) to create focal radiation plans for 81 elderly GBM patients (70 years or older with Karnofsky performance status [KPS] 70 or greater), confirmed the benefits of conformal radiotherapy (50.4 Gy) versus best supportive care. Patients who received radiotherapy following biopsy or resection had improved survival (median 29 vs. 16.9 weeks, $p=0.002$).[13] This trial demonstrated no severe adverse events related to radiotherapy, while quality of life (QOL) and cognitive evaluations over time did not differ significantly between treatment groups.

Collectively, these studies illustrate that radiotherapy (using 2D and 3D techniques) after biopsy or resection of GBM improves overall survival compared to best supportive care or older forms of chemotherapy (e.g., BCNU, CCNU), while not detracting from QOL. These studies also inspired investigations combining radiotherapy with various radiation sensitizers.[14-21] Meta-analyses concluded that combining these older chemotherapy regimens with radiotherapy conferred a small survival advantage.[22,23] Specific questions relating to modern systemic

therapies are discussed in the next section, while issues pertaining to radiation dose and fractionation are explored in detail in KQ2.

KQ1B. Benefits of concurrent and adjuvant temozolomide (Table 3)

In the 1990s, the alkylating agent temozolomide (TMZ) was tested as a single agent in the treatment of recurrent glioma and demonstrated anti-tumor activity.[24,25] A pilot phase II trial demonstrated the feasibility of concomitant and adjuvant TMZ with conventionally fractionated radiotherapy, with a two-year survival rate of 31%.[26] This led to the landmark phase III trial from the European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada, EORTC/NCIC 26981-22981, which randomized 573 patients (18-70 years old, WHO performance status 0-2) to partial brain radiotherapy alone (60 Gy) versus radiotherapy with concomitant and adjuvant TMZ (six adjuvant cycles). The dosing of TMZ during radiotherapy was 75 mg per square meter per day, given 7 days per week during the radiotherapy course, but no longer than 49 days. The adjuvant TMZ dose was 150 mg per square meter for the first five days of the first 28-day cycle and 200 mg per square meter for the first five days of each subsequent cycles beginning with cycle 2, so long as there were no hematologic toxic effects.

TMZ increased median survival from 12.1 months to 14.6 months, and improved 5-year overall survival from 1.9% to 9.8%, $p<0.0001$.[27,28] The investigators detected an increase in early hematologic toxic events with TMZ (7% with any grade 3 or 4 hematologic toxicity) compared to the control group (0%), but there was no adverse impact on QOL due to TMZ.[29] As these outcomes were superior to those from any prior phase III trial, this study defined the current standard of care for GBM patients with reasonable performance status up to 70 years of age.[27,28]

Three other RCTs interrogated the efficacy of adding TMZ to radiation. A phase II trial from Greece that randomized 130 GBM patients also demonstrated a survival advantage from adding concomitant and adjuvant TMZ to radiotherapy.[30] A smaller randomized study of radiotherapy with or without concomitant TMZ (but not adjuvant TMZ) was stopped after accruing only 65 of 500 planned patients due to the publication of the EORTC/NCIC trial. This study did not show a benefit for TMZ, but was severely underpowered.[31] Another study from Poland randomized 58 newly diagnosed GBM patients to radiotherapy alone (60 Gy) versus TMZ and radiotherapy. TMZ in this study was given before, during, and after radiotherapy, and significantly improved median overall survival (16 months vs 12.5 months) and 2-year survival (23.1% vs. 6.7%).[32] A recent meta-analysis confirmed that adding concomitant and adjuvant TMZ to radiotherapy improves overall and progression free survival following biopsy or resection in the initial treatment of GBM.[32,33]

Although the combination of TMZ and radiotherapy improved outcomes for GBM, few patients survive beyond five years, and multiple groups have attempted to augment the effects of TMZ and radiotherapy. For example, intensified dosing of adjuvant TMZ was attempted in the Radiation Therapy Oncology Group (RTOG) 0525 randomized phase III trial (n=833). The investigators compared standard adjuvant TMZ with a dose-dense schedule, but did not demonstrate improved efficacy over standard treatment.[34]

KQ1C. Adding bevacizumab to standard therapy (Table 4)

Another attempt to improve upon standard therapy involved targeting angiogenesis through the vascular endothelial growth factor (VEGF) signal-transduction pathway. This emerged as a promising strategy for newly diagnosed GBM partly due to the demonstration of

clinical activity in recurrent GBM.[35,36] Unfortunately, two large phase III trials, Radiation Therapy Oncology Group (RTOG) 0825 (N=637) and AVAglio (N=921), failed to show improvement in overall survival with the addition of bevacizumab to standard radiotherapy with concomitant and adjuvant TMZ.[37,38]

Both trials did suggest prolonged progression free survival with bevacizumab, although a pre-specified level of significance was not met in RTOG 0825.[38] One limitation of the progression free survival data is that both trials based progression on the Macdonald criteria, which do not account for growth of non-enhancing tumor; AVAglio used "adapted" Macdonald criteria to evaluate non-enhancing lesions qualitatively, but it is unclear how standardized this was. Moreover, patients on RTOG 0825 receiving bevacizumab experienced worse QOL, increased symptom burden, and more frequent decline in neurocognitive function.[38] In contrast, patients in the bevacizumab arm of AVAglio demonstrated longer maintenance of baseline health-related QOL and performance status, as well as lower glucocorticoid requirements. Concordant with RTOG 0825, however, bevacizumab patients on AVAglio experienced more grade 3 or higher adverse events.[30] These data do not support the routine addition of bevacizumab to standard chemoradiation in the upfront treatment of GBM.

KQ1D. Frontiers of therapy

A small, single-institution phase II study investigated combining bevacizumab with standard chemoradiation followed by adjuvant bevacizumab, irinotecan, and TMZ,[39] but no randomized data interrogating this regimen are available. Similarly, other systemic agents have not yet been shown to improve survival over standard radiotherapy with concomitant and adjuvant TMZ. Agents that have been investigated include topotecan,[40] sorafenib,[41] cilengitide,[42]

and erlotinib,[43,44] among others. Thus, the use of systemic agents with radiotherapy other than concomitant and adjuvant TMZ remains investigational.

Tumor Treating Fields (TTF), low intensity alternating electric fields which have been found to disrupt cell division *in vitro*, are being investigated in the treatment of GBM. At the time this systematic review was performed, results from a phase III trial (EF-14) interrogating the addition of TTF to temozolomide following standard chemoradiation had been presented at the Society for Neuro-Oncology 2014 Annual Meeting, but had not been published beyond abstract form. As we had decided *a priori* to exclude studies available only as abstracts and because EF-14 does not answer any questions directly related to radiotherapy (TTF in EF-1 was employed concomitantly with adjuvant temozolomide rather than with radiation), a comprehensive discussion of EF-14 or TTF in the upfront treatment of GBM is not included in this document.

The prognosis for GBM patients receiving the contemporary standard of care remains poor, with a median survival of approximately 15 months. The guideline panel supports consideration of participation in clinical trials and registries for appropriate patients in both upfront and recurrent settings to improve treatment of this challenging disease.

Biomarkers of response

A major goal of contemporary oncology is to individualize therapy based on tumor characteristics. In multiple studies, low levels of O-6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme, have been associated with longer survival among GBM patients receiving alkylating agents. Epigenetic silencing of MGMT by promoter methylation has been associated with improved survival in patients receiving TMZ, with or without

radiotherapy.[45-47] In the EORTC/NCIC trial, for example, MGMT methylation status was a significant prognostic factor, though not necessarily predictive. More specifically, adding temozolomide to radiation improved overall survival regardless of MGMT methylation, but survival differences were more pronounced among those with methylated MGMT promoters. These studies indicate that testing and stratification by MGMT status is feasible. Potentially using MGMT promoter methylation to guide therapy is the subject of ongoing study. Given that the benefit of temozolomide appears to be modest in those with unmethylated MGMT promoters, the Panel believes such patients can be ethically treated *on clinical trials* with investigative agents while withholding temozolomide.

Molecular characterization of GBM has identified other biomarker candidates. Prominent prognostic biomarkers include isocitrate dehydrogenase-1 (IDH1) mutations and epidermal growth factor receptor (EGFR) mutations.[48,49] As with MGMT, IDH1, EGFR and other biomarker candidates have been used primarily as prognostic rather than predictive factors to this point.

While efforts to tailor therapy according to molecular biomarkers continue, radiotherapy with concomitant and adjuvant TMZ remains the standard of care for GBM patients under the age of 70 with reasonable performance status. Recent studies suggest that in elderly patients, MGMT status may be useful in guiding management; this is explored more fully in KQ2.

Key Question (KQ) 2: What is the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma and how might treatment vary based on pretreatment characteristics such as age or performance status?

Guideline Statements:

A. For patients under 70 with good performance status (Karnofsky performance status [KPS] ≥ 60), the optimal dose-fractionation schedule for external beam radiation therapy following resection or biopsy is 60 Gy in 2-Gy fractions delivered over 6 weeks (**HQE**). Numerous other dose schedules have been explored without definitive benefit. Care should be taken to keep dose to critical structures (e.g., brainstem, optic chiasm/nerves) within acceptable limits. (Strong recommendation)

B. Older age and poor performance status are associated with shorter survival in GBM patients (**MQE**). Prognostic considerations should help guide treatment recommendations for individual patients. (Strong recommendation)

C. Among elderly patients (≥ 70 years old) with fair-good performance status (KPS ≥ 50), the panel recommends external beam radiation therapy following biopsy or resection, as radiotherapy (compared to supportive care alone) improves overall survival without impairing quality of life or cognition (**HQE**). The efficacy of concurrent and adjuvant temozolomide in this population has not been evaluated in a randomized trial, but may be considered for selected patients (**LQE**; see KQ2F). (Strong recommendation)

D. Among elderly patients, there is no evidence that conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiotherapy (e.g., 40 Gy in 15 fractions over 3 weeks) (**HQE**). Compared to conventionally fractionated radiotherapy, hypofractionated radiotherapy has been associated with superior survival and less corticosteroid requirement (**MQE**). (Strong recommendation)

E. Given the absence of proven superiority for conventionally fractionated radiotherapy, the panel recommends hypofractionated radiotherapy for elderly patients with fair-good

performance status (**HQE**). Temozolomide monotherapy is an efficacious alternative for elderly patients with MGMT promoter methylation (**HQE**), but the panel does not recommend temozolomide monotherapy as first-line therapy for patients with unmethylated MGMT promoters (**MQE**). Temozolomide monotherapy confers a higher risk of adverse events than radiotherapy, particularly with respect to hematologic toxicity, nausea, and vomiting (**MQE**). (Strong recommendation)

F. Among elderly patients with good performance status, adding concurrent and adjuvant temozolomide to hypofractionated radiotherapy appears to be safe and efficacious without impairing quality of life (**LQE**). In such patients, the panel recommends consideration of concurrent and adjuvant temozolomide. The combination of hypofractionated radiotherapy and temozolomide may be particularly efficacious in those with a methylated MGMT promoter (**LQE**). (Strong recommendation)

G. Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (**LQE**). (Strong recommendation)

KQ2A. Dose-fractionation for patients under 70 with good performance status (Table 5)

Multiple prospective studies have demonstrated improved survival with radiation dose escalation at standard fractionation (1.8-2 Gy daily) up to 60 Gy.[7,50,51] Walker and colleagues (1979) pooled treatment outcomes from three Brain Tumor Study Group protocols (66-01, 69-01, 72-01). Patients (621 high-grade gliomas, of which 534 were GBM) received a range of whole brain irradiation doses from 0 to 60 Gy. Dose escalation was associated with statistically significant improvements in median survival, at 18 weeks, 28 weeks, 36 weeks, and 42 weeks for

patients receiving 0 Gy, 50 Gy, 55 Gy, and 60 Gy, respectively. Patients receiving 45 Gy or less had a median survival of only 13.5 weeks, but were not felt to be comparable to the other groups due to worse performance status and a greater number of patients who died before completing radiotherapy.[7] The Medical Research Council subsequently conducted the BR2 study, a prospective RCT of 474 high- grade glioma patients age 18 to 70 years randomized to 45 Gy in 20 fractions vs 60 Gy in 30 fractions. Investigators used near complete supratentorial fields, with a smaller boost field for the 60 Gy arm after 45 Gy. Dose escalation to 60 Gy improved median survival by 3 months (12 vs 9 months, p=.04).[51]

Studies interrogating doses beyond 60 Gy using standard fractionation with or without concurrent chemotherapy have not demonstrated any survival benefit from additional dose escalation. A joint RTOG/ECOG trial launched in 1975 randomized malignant glioma patients to one of four arms. The control arm was 60 Gy to the whole brain, the second arm tested dose escalation to 70 Gy using a partial brain boost volume, and the other two study arms tested the addition of different chemotherapy regimens to 60 Gy. No arm demonstrated superiority in survival.[52,53] RTOG 98-03, a phase I/II study, attempted dose escalation at multiple dose levels up to 84 Gy with BCNU, but also demonstrated no convincing survival benefit; this study was not designed, however, to make comparisons of efficacy endpoints between dose levels.[54,55]

As noted in KQ3, the vast majority of patients progress within the high-dose region, implying the presence of radioresistant clones. Even dose escalation to 90 Gy with intensity modulated radiation therapy (IMRT) in a series of 34 malignant glioma patients resulted in a median survival of less than 12 months and predominantly in-field local failure (91%),[56] supporting the notion that standard dose escalation alone is insufficient to control this disease.

Moreover, dose escalation beyond 60 Gy may come with a cost. Whereas modern imaging and technology enable improved target definition and increasingly conformal high-dose radiation delivery, ample data demonstrate a correlation between higher doses and risk of radiation necrosis.[57,58] One institutional phase 2 study of 23 patients treated with mixed proton and photon therapy to 90 cobalt gray equivalent resulted in more than half of patients requiring second surgeries, all of which demonstrated significant radiation necrosis.[59] Their patients achieved a median survival of 20 months, but the absence of a control group obviates conclusions regarding efficacy relative to standard treatment. All long-term survivors exhibited significant steroid dependency and the investigators deemed treatment toxicity unacceptable. Adding concurrent TMZ to standard fractionated radiation therapy improves efficacy, but increases the risk of radiation necrosis as well.[27,28,58] Chemoradiation-associated necrosis should be assessed carefully in future dose escalation studies. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) paper modeling radiation dose-volume effects in the brain states that for standard fractionation (2 Gy per day), a 5% and 10% risk of symptomatic radiation necrosis is predicted to occur at doses of 72 Gy (range, 60-84) and 90 Gy (range, 84-102) in the context of partial brain irradiation. Risk of radiation necrosis increases with concurrent chemotherapy and larger volume of irradiated brain. The QUANTEC authors emphasize that for most brain tumors, there is no clinical indication for giving fractionated radiotherapy >60 Gy.[58]

Radiation biology suggests that hyperfractionation may enhance therapeutic index by preferentially sparing normal tissues and allowing delivery of higher dose to tumor, while accelerated fractionation (i.e., shorter overall treatment time) may counteract accelerated tumor repopulation. Unfortunately, no hyperfractionated or accelerated schedule has proven superior to

standard fractionation to 60 Gy. Hyperfractionated regimens have been tested with or without chemotherapy and/or radiosensitizing drugs, and with or without accelerated delivery (i.e., shorter overall treatment time). Investigated regimens have included BID schedules (1-2 Gy BID),[60-66] TID schedules (0.75-1.05 Gy TID),[67,68] and a QID schedule (1 Gy QID),[69] all demonstrating feasibility and safety but most failing to show any survival advantage.

Among the more relevant data include a prospective RCT of 231 GBM patients treated on one of four arms, with a conventionally fractionated control arm of 59.4 Gy and an accelerated, hyperfractionated, dose-escalated arm of 1.6 Gy BID to 70.4 Gy.[65] The other two arms delivered identical radiation regimens with difluoromethylornithine (DFMO), a polyamine inhibitor. No intergroup differences in median survival were observed. RTOG 8302 was a phase I/II trial of 786 high-grade glioma patients (81% GBM) testing various doses utilizing hyperfractionated and accelerated hyperfractionated dose escalation with BCNU.[70] Hyperfractionated schedules at 1.2 Gy BID ranged from 64.8 to 81.6 Gy, while accelerated hyperfractionated dose schedules were either 48 or 54.4 Gy. Toxicity was reportedly acceptable, though there was a trend toward increased late toxicity at higher doses, with grade 3+ toxicity at 5 years ranging from 3% in the 64.8 Gy arm to 6% and 5% in the 76.8 Gy and 81.6 Gy arms, respectively. Overall, no intergroup differences in median survival were observed. This study did not include a control arm using standard fractionation.

Given advances in radiation therapy and systemic therapy in recent years, the majority of published hyperfractionation studies have limited applicability, having employed older radiotherapy techniques (e.g., WBRT rather than partial brain irradiation) and/or concurrent administration of now obsolete drugs (e.g., CCNU, misonidazole in Fulton 1984,[71] BCNU in Werner-Wasik 1996[70]). Some contemporary studies have been promising but were

unrandomized, which subjects their results to confounds such as selection bias. For example, one single-arm study of 20 patients delivering mixed photons and protons to 96.6 Gy (RBE) in 56 fractions with nimustine reported favorable outcomes. But the study was small, chemotherapy was nonstandard, the trial lacked a control group, and eligibility was limited to tumors < 4 cm in size and located away from the brainstem, hypothalamus, and thalamus.[72] As such, this regimen and other nonstandard regimens remain investigational and require randomized comparison to standard therapy.

Hypofractionation, which can increase biologically effective dose (BED) while accelerating treatment time, has also been attempted, but no schedule has proven superior to standard fractionation to 60 Gy in the general GBM population (i.e., up to 70 years of age with good performance status). Regimens have been tested with and without adjuvant or concurrent chemotherapy and/or radiosensitizers. Fraction sizes vary from 2.4-6 Gy to total doses of 30-65 Gy. Collectively, these studies are difficult to interpret and apply, given their wide variation in fraction size, total dose, treatment volume, overall duration of treatment, and use of concurrent drug. Eligibility criteria also vary with respect to patient factors such as age, performance status, and comorbidities. Most studies of hypofractionation in the general GBM population demonstrate feasibility and acceptable tolerance of therapy. Several recent studies have limited eligibility to contrast-enhancing tumors measuring no greater than 6 cm to reduce risk of underlying normal tissue injury.[73,74] One RCT did suggest a survival benefit from hypofractionation, but employed WBRT rather than modern partial brain techniques.[75] One concern of hypofractionation is the increased risk of normal tissue injury, including radiation necrosis, demonstrated in a few small series.[73,74,76] However, these series used particularly high doses per fraction, up to 5-6 Gy per fraction to a total of 50-60 Gy. The currently accruing NRG

BN-001 trial randomizes patients to 60 Gy via conventionally fractionated chemoradiation vs chemoradiation to 50 Gy in 30 fractions with a simultaneous integrated boost to 75 Gy in 30 fractions; the latter regimen can be delivered with photons or protons. Where more evidence already exists for hypofractionation is in elderly and/or poor performance status patients; in these populations, studies have generally employed more moderate hypofractionation, e.g., 2.66 Gy x15, 3.4 Gy x10 (see the following section).

Strategies combining standard fractionation schedules with hypofractionated boosts have also failed to demonstrate superiority. Hypofractionated boosts (5-7 Gy fractions, 4-5 fractions) integrated into 50-60 Gy standard fractionation schedules have not been shown to improve survival.[77,78] Many of these studies are limited by selection bias related to eligibility criteria requiring favorable patient and tumor characteristics, such as limitations on tumor size. For example, the EORTC 22972-26991/MRC BR10 trial, which provided a 20 Gy boost in 4 fractions following conventionally fractionated delivery of 60 Gy, included only favorable patients with enhancing tumors measuring no larger than 4 cm preoperatively.[77] Even stereotactic radiosurgery (SRS) boosts of 15-24 Gy in a single fraction have failed to improve outcomes, despite also being limited to the treatment of small tumors.[79] RTOG 9305 addressed this clearly in a prospective phase III RCT investigating the addition of a SRS boost to a conventionally delivered radiation course of 60 Gy. Near identical median survivals were observed: 13.6 vs 13.5 months in the standard and SRS boost arms, respectively (p=0.57). RTOG 9305 showed no effect on patterns of failure, with local recurrence a component of progression in 93%, possibly suggesting the presence of clones resistant to even extreme dose escalation. A single-arm phase II study of 36 GBM patients treated with concurrent TMZ and conventionally fractionated radiotherapy to 50.4 or 59.4 Gy followed by a 19 or 10 Gy SRS boost, respectively,

achieved a median survival of 28 months.[80] This study was limited by its size and lack of a control arm, and only included patients with relatively small targets located away from the brainstem and optic chiasm. Given these limitations and toxicity risks with SRS (e.g., radiation necrosis), further investigation is required before the panel can endorse such a treatment schedule, particularly given the results of RTOG 9305.

In summary, the preponderance of data support treating GBM patients following resection or biopsy to 60 Gy in 30 fractions over 6 weeks. This recommendation applies to patients under 70 years of age with good performance status, which is variably defined but generally includes patients with a KPS of 60 or greater; such patients are generally unable to work and require occasional assistance, but are able to care for most of their personal needs. The panel notes that the determination of performance status and appropriateness of standard chemoradiation requires individualized assessment by the treating physician. The data for patients who are elderly and/or have limited performance status will be discussed in the next section. In addition, the panel cautions that under certain circumstances (e.g., tumor extending into brainstem), prescription dose may be modified to keep dose to critical structures within acceptable limits.[81,82] Conformal techniques (e.g., three-dimensional conformal radiotherapy [3D-CRT], IMRT, volumetric modulated arc therapy [VMAT]) and image guidance may be necessary to facilitate normal tissue sparing, particularly when organs at risk are close to target. A comprehensive discussion of normal tissue tolerance is beyond the scope of this guideline.

KQ2B-G. Management options for elderly patients and patients with poor performance status (Table 6)

Therapeutic decisions for individual patients depend in part on prognosis, and the most important patient factors influencing survival are age and performance status.[83] Analyses of prospective data have strongly associated older age and/or poor performance status with shorter survival, and population-based studies demonstrate a median survival of approximately 4-5 months for patients older than 65, and a similar length of time for patients with poor performance status depending upon the cut-off score for that determination (**KQ2B**).[83,84] While EORTC/NCIC 26981-22981 established six weeks of radiotherapy with concomitant and adjuvant TMZ as the standard of care for patients under 70 with good performance status, patients older than 70 and those with World Health Organization performance scores (WHO PS) greater than 2 were excluded from the study.[85] The remainder of the KQ2 section reviews the evidence for various therapeutic approaches in patients who are elderly or have limited performance status.

The incidence of GBM rises with age, peaking in the seventh decade of life, and approximately half of GBM patients are older than 65, the segment of the population increasing fastest in the developed world.[86,87] While elderly age has been a consistently negative prognostic factor, the definition of 'elderly' varies between studies, with the cutoff generally ranging between 60 and 70 years old. Many reports that have assessed radiotherapy fractionation are single-institution, retrospective studies.[88,89] A review of the Surveillance, Epidemiology, and End Results registry from 1993 to 2005 for 2836 patients over 70 years of age revealed that delivery of any radiotherapy improved cancer-specific and overall survival and that increased age correlated with decreased survival (**KQ2B, KQ2C**).[90] Both single-institution retrospective and large registry analyses are limited by potential confounds, such as bias toward recommending intervention in patients with better performance status.

A number of studies have evaluated the potential benefits of surgery,[91,92] radiotherapy,[13] and systemic therapy[93,94] for elderly patients with GBM. A prospective RCT from the Association of French-Speaking Neuro-Oncologists randomized patients at least 70 years of age and with a KPS of 70 or higher to supportive care plus radiotherapy (50.4 Gy in 28 fractions) vs supportive care alone. The trial was stopped at the first interim analysis after enrolling 85 patients, which demonstrated superiority of the radiotherapy arm beyond the preset boundary of efficacy. Radiotherapy increased overall survival from 16.9 to 29.1 weeks without worsening quality of life or cognitive functioning compared to the control group **(KQ2C)**.[13]

The French study established the role of radiotherapy in elderly patients with good performance status,[13] but optimal dose-fractionation for this population remained unclear. Given these patients' limited life expectancy, interest grew in an abbreviated, hypofractionated course, which potentially could be more convenient, less morbid, and more likely to be completed than six weeks of conventionally fractionated radiotherapy. Building on several promising single arm studies interrogating hypofractionated radiation courses,[95-100] two phase III RCTs compared conventionally fractionated radiotherapy to hypofractionated regimens (**KQ2D**).[101,102] A Canadian trial randomized 100 patients aged 60 years or older and with a KPS of at least 50 to conventionally fractionated radiotherapy (60 Gy in 30 fractions over six weeks) or hypofractionated radiotherapy (40 Gy in 15 fractions over three weeks). Results showed no significant difference in overall survival between the two arms (5.1 and 5.6 months, respectively). There was also no intergroup difference in post-treatment KPS, but patients in the conventionally fractionated arm had greater corticosteroid requirements.[101] The Nordic phase III trial randomized 342 patients aged 60 or older (changed midway to 65 or older after positive results from EORTC/NCIC 26981-22981 had been released) with a good performance status

(WHO PS 0-2) to conventionally fractionated radiotherapy (60 Gy in 30 fractions over six weeks) vs hypofractionated radiotherapy (34 Gy in 10 fractions over two weeks) vs TMZ alone (200 mg/m2 on days 1-5 of every 28 days for up to six cycles). The Nordic study showed no significant difference between conventionally fractionated radiotherapy and hypofractionated radiotherapy among the groups as a whole or among patients aged 60-70, but in the subset of patients older than 70, hypofractionated radiotherapy was associated with better survival (hazard ratio [HR] 0.59, $p<0.02$). Fewer patients in the conventionally fractionated arm completed irradiation according to protocol than in the hypofractionated arm (72% vs 95%), owing primarily to deterioration or disease progression during treatment.[102] In short, randomized trials in the elderly have failed to show superiority of the six-week course to hypofractionated regimens, and suggest potential benefits to hypofractionation with respect to survival and treatment tolerance.

Two randomized trials have evaluated whether TMZ monotherapy could be a reasonable alternative to radiotherapy in elderly GBM patients (**KQ2E**). The previously described Nordic trial demonstrated improved survival with TMZ monotherapy compared to conventionally fractionated radiotherapy, but no difference between TMZ and hypofractionated radiotherapy. Adverse event rates were generally higher in the temozolomide arm than in the radiotherapy arms, particularly with respect to nausea, vomiting, and hematologic toxicity.[102] The NOA-08 study, a phase III non-inferiority trial, randomized 412 patients greater than 65 years old and with a KPS of at least 60 to TMZ (100 mg/m2 daily x 7 days, every other week) vs conventionally fractionated radiotherapy (60 Gy in 30 fractions). Median overall survival in the chemotherapy arm versus the radiotherapy arm was 8.6 versus 9.6 months, respectively (non-inferiority = 0.033). As the investigators had pre-specified a non-inferiority margin of 25%, they

concluded that TMZ was not inferior to conventionally fractionated radiotherapy for this group. They found that TMZ conferred a higher risk of toxicity, however, with the most frequent grade 3-4 intervention-related adverse events being neutropenia, lymphocytopenia, thrombocytopenia, elevated liver enzymes, infections, and thromboembolic events. Grade 2-4 adverse events were more frequent with temozolomide than with radiotherapy in all categories except cutaneous adverse events.[103]

In both the Nordic study and the NOA-08 study, on subgroup analysis MGMT promoter methylation was associated with improved survival among patients receiving TMZ, but not among those receiving radiotherapy. In the NOA-08 study, event free survival was actually worse among patients with unmethylated MGMT promoters who received TMZ compared to radiotherapy. A nonrandomized ANOCEF phase II trial evaluated TMZ alone in 70 patients aged 70 years or older with poor performance status (KPS < 70), and concluded that TMZ was tolerable and associated with improved functional status in 33%. Patients in this study had a median survival of 25 weeks, which seems favorable in this population (**KQ2G**).[83,84,104] However, randomized data investigating TMZ monotherapy in elderly patients with poor performance status is lacking.

No phase III trials have been published interrogating the efficacy of conventionally fractionated chemoradiation (60 Gy in 30 fractions) with TMZ in patients older than 70. RTOG 0525 and RTOG 0825 did not specifically exclude patients older than 70, but the publications do not indicate how many elderly patients enrolled or analyze interactions between outcomes and age.[34,38] Nonrandomized phase II data in this population suggest that hypofractionated radiotherapy with concomitant and adjuvant TMZ is safe and efficacious (**KQ2F**). A nonrandomized, phase II multi-center Italian trial combined hypofractionated radiotherapy (40

Gy in 15 fractions) with concurrent and adjuvant TMZ in patients at least 70 years of age and with a KPS of at least 60. Median overall survival was 12.4 months and quality of life was found to be stable or improved until the time of disease progression. MGMT methylation status was the strongest prognostic factor associated with overall and progression free survival.[105,106] These results are promising, but phase III data comparing this approach to hypofractionated radiotherapy alone are lacking.

Randomized trials comparing conventionally fractionated radiation to hypofractionated regimens in the setting of concurrent chemotherapy are also lacking, but other data are available. A propensity-matched analysis comparing 127 patients who received conventionally fractionated chemoradiation (60 Gy in 30 fractions with 6 weeks of TMZ) to 116 patients who received hypofractionated chemoradiation (40 Gy in 15 fractions with 3 weeks of TMZ) found similar median overall and progression free survival times between the two groups. Conventionally fractionated chemoradiation was associated, however, with increased grade 2-3 neurologic toxicity, worsened performance status, and higher corticosteroid requirements.[107]

Ongoing RCTs in the elderly GBM population include three trials interrogating the addition of systemic therapy (TMZ, bevacizumab, or hydroxychloroquine, respectively) to hypofractionated radiotherapy. EORTC 26062-22061 NCIC CTG CE6, which randomized 562 elderly patients to hypofractionated radiotherapy (40 Gy in 15 fractions) with or without concomitant and adjuvant temozolomide, has completed accrual and should answer more definitively whether adding temozolomide to hypofractionated radiotherapy improves survival. The International Atomic Energy Agency published a RCT comparing two hypofractionated regimens (3 weeks vs 1 week) in elderly and/or frail patients prior to release of this guideline, but not early enough for inclusion in our systematic review.[108] Other high quality studies which

specifically assess the use of conventionally fractionated or hypofractionated radiotherapy in patients with poor performance status are lacking. However, the poor prognosis of this patient group combined with practical considerations, including the logistical (e.g., transportation) demands of prolonged radiotherapy courses merits strong consideration of hypofractionated radiotherapy,[94,97,98] TMZ alone, or best supportive care alone in these circumstances (**KQ2G**).

Key Question (KQ) 3: What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?

Guideline Statements:

A. Although glioblastoma is thought to be diffusely infiltrative, partial brain radiation therapy leads to no worse survival than whole brain radiation therapy (**HQE**). The panel endorses partial brain radiation therapy as the standard treatment paradigm for glioblastoma. (Strong recommendation)

B. Several strategies for target volume definition produce similar outcomes (**LQE**). All confer a low risk of isolated marginal or distant failure, with a high risk of local failure as a component of disease progression (**MQE**). Acceptable strategies include but are not limited to the following: (strong recommendation)

    1. Two-phase: 1) primary target volume encompasses edema (hyperintense region on T2 or FLAIR on MRI) and gross residual tumor/resection cavity; 2) boost target volume encompasses gross residual tumor/resection cavity. A range of acceptable clinical target volume margins exists.
    2. One-phase: single target volume includes gross residual tumor/resection cavity with wide margins, without specifically targeting edema.

C. Reducing target volumes allows less radiation to be delivered to radiographically normal brain. Delivering less radiation to normal brain should result in less late toxicity (**LQE**), but this remains to be validated. (Weak recommendation)

KQ3A. Although glioblastoma is thought to be diffusely infiltrative, partial brain radiation therapy leads to no worse survival than whole brain radiation therapy

Despite usually appearing focal on imaging, GBM is considered an infiltrative disease. This understanding derives in part from the failure of even extensive resection to control disease: in the early twentieth century, attempts at ipsilateral hemispherectomy resulted in progression in the contralateral hemisphere.[109,110] As such, radiation therapy when initially applied was delivered to the whole brain, with the earliest randomized trials demonstrating the benefit of whole brain radiation therapy to 45-60 Gy with opposed lateral beams compared to chemotherapy alone or best supportive care.[5,8]

Over the last several decades, however, radiation therapy for GBM has evolved from whole brain radiotherapy to partial brain irradiation, treating only the areas at highest risk of recurrence. CT-based patterns of failure studies helped establish the rationale for this shift, demonstrating that approximately 80-90% of GBM patients recur within 2 cm of the primary site.[111-114] Data from prospective RCTs also support the efficacy of partial brain irradiation. Brain Tumor Cooperative Group 8001, which randomized patients to whole brain radiotherapy to 60.2 Gy versus whole brain radiotherapy to 40.3 Gy plus a 17.2 Gy partial brain boost (gross tumor/resection cavity + 2 cm), showed that coning down to a smaller boost volume did not affect overall survival.[20] One small, randomized trial directly compared whole brain radiation therapy to partial brain radiation therapy and found no difference in survival, but better

performance status in those who received partial brain irradiation, suggesting that reducing target volumes decreases toxicity.[115] All contemporary GBM trials, the outcomes of which compare favorably to historical trials, utilize the partial brain radiotherapy paradigm.

KQ3B. Target Volume Design

CT and MRI help delineate tumor and are routinely used for treatment planning. A seminal study by Kelly et al. correlating MRI findings and histology for 177 biopsy specimens from 39 patients with glial neoplasms showed that enhancing volumes most often corresponded to tumor without intervening brain parenchyma, whereas T2 hyperintensity often corresponded to parenchyma infiltrated by isolated tumor cells.[116] The ability of conventional imaging to delineate tumor is, however, limited. T2 and FLAIR abnormalities are nonspecific, potentially representing infiltrating tumor cells, low-grade tumor or simply edema. While MRI is more sensitive than CT, not all areas of brain involved by glioma demonstrate T1 enhancement or T2 hyperintensity. Indeed, Kelly et al found that stereotactic biopsy frequently revealed tumor in regions of brain appearing normal on MRI.[116]

While consensus has been achieved regarding the appropriateness of partial brain irradiation, variation in target volume design exists. North American radiation oncology cooperative groups generally treat patients in two phases, with an initial phase directed at edema (hyperintense region on T2/FLAIR on MRI) in addition to the resection cavity and gross residual tumor (enhancing lesion on T1) followed by a boost directed only at the resection cavity and gross residual tumor. T2 hyperintense regions are targeted in this paradigm because of evidence that T2 hyperintensity sometimes reflects infiltrative and/or low-grade tumor. Some institutions, however, utilize a two-phase treatment paradigm targeting resection cavity and gross tumor

alone *without* specifically targeting edema, citing similar patterns of failure with this approach.[117] The EORTC has adopted a single-phase approach, targeting the enhancing tumor plus cavity with a wide margin throughout the entire treatment, without specifically targeting edema. Among North American cooperative groups, variability exists in clinical target volume (CTV) margin size, with the American Brain Tumor Consortium (ABTC) utilizing the smallest volumes. Table 8 summarizes the cooperative group margins being used in contemporary GBM clinical trials. Few data exist on practice patterns outside these consortia, but one survey of Canadian centers published in 2010 found 60% of respondents utilizing a single-phase treatment.[118] Center-specific guidelines were more prevalent than strict adherence to either RTOG or EORTC protocol guidelines.

As treatment planning increased in complexity, new challenges in target design arose. The definition of margin changed from a two dimensional distance to block edge to a three dimensional (3D) distance describing a margin of dose to account for microscopic infiltration (CTV) and setup error (planning target volume [PTV]). In retrospect, decisions defining CTV and PTV may have derived primarily from older block edge treatment techniques rather than data. The transition to 3-dimensional treatment planning has in some cases resulted in systematically larger target volumes. For example, RTOG 9710 utilized a 2 cm margin from edema to block edge, while more recent studies have utilized a 2 cm PTV margin, requiring additional margin to block edge for adequate coverage.

Patterns of Failure with Concurrent Temozolomide

The most relevant data for defining target volumes relate to patterns of failure in patients who received concurrent TMZ with radiation therapy plans designed using contemporary, MRI-

based planning. These studies comprise secondary analyses of prospective cooperative group trials and single institution retrospective studies, and employed different methodologies including various definitions of "central" and "marginal". Nearly all studies demonstrate that at least 80-90% of recurrences have a component of failure within the high-dose volume (Table 7). Central failure seems to predominate regardless of target volume design, whether in plans targeting edema (two-phase treatment planning), plans not specifically targeting edema (i.e., single phase), or plans using smaller CTV margins.[119] Several institutions in the ABTC consortium have published retrospective studies evaluating smaller CTV margins.[120-122] These studies suggest that CTV margins as low as 5 mm may be clinically feasible without increasing the risk of marginal recurrence (see Table 8). Of note, most of these plans incorporated an additional PTV margin (3-5 mm).

Preliminary evidence suggests that MGMT status may impact patterns of failure. In a prospective study of 95 patients receiving standard chemoradiation per EORTC 26871/22981, 85% of patients with unmethylated MGMT promoters experienced in-field or marginal failures, while only 58% of patients with methylated MGMT promoters developed in-field or marginal failures (p=.01).[123] Importantly, recurrences in the methylated MGMT population generally would have been distant to margins for any typical partial brain radiotherapy plan. Single-institution retrospective studies from Italy and Germany demonstrated similar trends, though in the German study the difference in failure patterns failed to reach statistical significance and further study in this area is required.[119,124]

One hypothesis regarding the relative resistance of GBM to radiation therapy is that glioma stem cells reside in the subventricular zone (SVZ). If this hypothesis were true, higher radiation dose to the SVZ could conceivably improve tumor control. Several investigators have

retrospectively examined SVZ dosimetry in a homogeneously treated group of GBM patients. In two studies, patients who received higher SVZ doses exhibited more favorable overall survival than similar patients who received lower SVZ doses.[125,126] In another report, higher doses to the SVZ independent of the extent of surgery were associated on multivariate analysis with improved progression free survival, but no overall survival benefit.[127] Well-designed, prospective studies are required to validate these findings. At this time, high-level evidence does not exist to support routine expansion of CTV beyond standard margins in order to include the SVZ.

KQ3C. Potential Significance of Smaller Target Volumes

Reducing target volumes by omitting intentional treatment of edema, using smaller CTV margins, using image-guidance to reduce PTV margins, or employing conformal techniques (e.g., 3d-CRT, IMRT, VMAT), may decrease radiation dose to normal brain, but the clinical significance of this has not been well studied.[117,122] EORTC 22844 randomized patients with low-grade gliomas to 45 Gy versus 59.4 Gy and found that patients receiving higher doses of radiation reported lower levels of functioning and more symptoms after radiation.[128] Effects on neurocognition may be related to treatment volume as well. A recent phase II trial of hippocampal-sparing, intensity modulated whole brain radiation therapy for brain metastases demonstrated a lower risk of memory decline compared to historical controls receiving conventional whole brain radiation therapy.[129] Reducing treatment volumes in GBM patients could facilitate protection of the hippocampus and other uninvolved brain structures, but understanding the neurocognitive implications of target volume reduction requires additional

study. Given the absence of published data for hippocampal sparing in GBM patients, the Panel does not recommend compromising target coverage for hippocampus protection.

Caveats in Patterns of Progression Studies and Target Definition

Conventional imaging (i.e., MRI) is limited in its ability to distinguish local recurrence from radiation-related changes. These limitations will be discussed in greater detail in KQ4, but are relevant to the current discussion insofar as these challenges may bias attempts to analyze patterns of failure. Most patterns of failure studies have relied on institutional criteria to define progression, and in some cases it is possible that treatment effect (pseudoprogression) was interpreted as tumor progression. False positive errors are most likely to occur in the high-dose volume, biasing patterns of failure data. It will be important for future studies to utilize standard recurrence criteria, such as the Response Assessment in Neuro-Oncology (RANO) criteria.[130]

The acquisition of MRI for radiation planning usually occurs within 48 hours from surgery. If MRI is obtained between four days and three weeks after surgery, blood product and tissue changes related to the operation may enhance on T1 and interfere with definition of residual enhancing disease.[131] If therapy is delayed beyond 3-5 weeks postoperatively, an additional MRI should be considered as tumor may progress or postoperative edema may improve.[132] The latter consideration may be especially important for tumors causing profound edema and/or mass effect, as these effects may resolve following resection, altering anatomy and target volumes. Although some centers use the preoperative MRI to delineate the hyperintense region on T2/FLAIR (assuming two-phase target volume design), current RTOG protocols specify and the majority of the panel utilizes the postoperative MRI to define the T2/FLAIR hyperintense region in addition to any residual gross disease and the resection cavity. This

approach derives from the notion that T2/FLAIR hyperintense areas prior to resection may largely reflect reactive edema rather than infiltrative tumor.

Novel Imaging Techniques

To augment conventional imaging, novel techniques to define a "biologic" target volume are being investigated. While high background glucose uptake in normal brain renders fluorodeoxyglucose (FDG)-based positron emission tomography (PET) relatively insensitive at tumor identification, early studies of novel PET tracers (e.g., amino acids), have demonstrated geometric and volume differences compared to MRI.[124,133] These studies often identify tumor outside areas of enhancement on T1 but within the region of FLAIR/T2 hyperintensity.[134] Even when these volumes are targeted, however, patterns of progression remain predominantly central.[135,136] Similar studies have been performed with MR spectroscopy, including an analysis in which the most common site of progression fell within the pre-existing morphologic and biologic volume.[137]

Some investigators have proposed higher doses to volumes demonstrating abnormal biologic activity, while others have suggested that biologic imaging could be used to tailor smaller, more specific target volumes.[137,138] All this requires clinical validation. The currently available evidence has not proven an incremental benefit to novel/biologic imaging for treatment planning over conventional MRI. Investigations are ongoing.

Key Question (KQ) 4: What is the role of re-irradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

Guideline Statements:

In younger patients with good performance status, focal re-irradiation (e.g., stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, brachytherapy) for recurrent glioblastoma may improve outcomes compared to supportive care or systemic therapy alone (**LQE**). Tumor size and location should be taken into account when deciding whether re-irradiation would be safe (**LQE**). (Weak recommendation)

Assessing Treatment Response and Defining Recurrence

Even following maximal safe resection, external beam radiotherapy, and concurrent and adjuvant TMZ, nearly all GBM patients recur. In EORTC/NCIC 26981-22981, which defined the current standard of care, respective 2- and 5-year progression free survivals of only 11% and 4% were observed, with fewer than 10% surviving more than 5 years from diagnosis.[27]

GBM presents challenges with respect to treatment response assessment and determination of recurrence. Heterogeneity in tumor composition and perfusion complicate delineation of tumor extent on imaging. Changes secondary to surgery, steroids, chemotherapy, radiotherapy, and/or anti-angiogenic agents may alter enhancement and edema. Treatment-related imaging changes that suggest increased tumor burden, but which do not reflect true progression, are termed pseudoprogression. This phenomenon, most often observed in the 12 weeks following chemoradiation, has been reported in 20-38% of patients, and even more commonly in patients with MGMT promoter methylation.[139-141] In contrast, treatment-related imaging changes that suggest reduced tumor burden but which do not reflect true response are termed *pseudoresponse* and occur primarily in patients receiving anti-angiogenic therapy.[142] In both scenarios, expectant management is often indicated to confirm the diagnosis over time.

Histopathologic confirmation remains the only definitive way to confirm tumor progression. That said, risks associated with biopsy are not trivial and must be weighed carefully against potential benefits when deciding whether biopsy is appropriate.

Often, serial imaging (typically, MRI) and clinical evaluation form the basis for classifying treatment response, defining recurrence, and informing clinical decisions. The Macdonald criteria, published in 1990, provided an objective methodology for tumor measurement and comparison over time based on the product of maximal cross-sectional dimensions of enhancing foci. These criteria standardized nomenclature for response assessment (i.e., complete response, partial response, stable disease, or progressive disease) according to changes in tumor size, while taking into account neurologic status and steroid use.

Over time, identification of limitations of the Macdonald criteria resulted in the development of the RANO criteria,[143] which built upon the Macdonald criteria by clarifying which lesions are sufficiently large and discrete to allow for accurate measurement, by accounting for non-enhancing disease, and by addressing pseudoprogression and pseudoresponse.[142,143] The RANO criteria are now used in the majority of clinical trials for treatment response assessment and definition of tumor recurrence.[144] These criteria define recurrence as any of the following: at least 25% increase in sum of the products of perpendicular diameters (SPD) of well-defined and "measurable" enhancing lesions or significant increase in T2/FLAIR non-enhancing lesion while on stable or increasing corticosteroid doses, development of a new lesion, clear progression of "nonmeasurable" disease (i.e., unidimensional, ill-defined or <10 mm), or clinical deterioration not attributable to causes apart from tumor.

Pseudoprogression should be strongly considered if the enhancing lesion grows within 12 weeks of chemoradiation. The RANO criteria only consider such growth "progression" if the

majority of new enhancement lies outside the high-dose region (i.e., 80% isodose line) or if there has been pathologic confirmation of disease. Failure to consider pseudoprogression may result in inappropriate discontinuation of effective adjuvant therapy. When pseudoprogression is assumed, however, it is important to monitor patients with frequent imaging and clinical assessment, as tumor progression remains possible even at early post-treatment time points.

Pseudoresponse should be considered in patients receiving anti-angiogenic therapy, which may cause rapid reductions in enhancement in tumors that subsequently demonstrate increased T2/FLAIR signal reflecting infiltrative tumor.[143]

The potential for pseudoprogression (and pseudoresponse in those receiving anti-angiogenic therapy) should be discussed with patients early in the course of their treatment to avoid confusion related to treatment response assessment and subsequent management recommendations.

Investigation of novel imaging techniques (e.g., intracranial SPECT, PET, dynamic contrast-enhanced MRI) is ongoing.

Prognostic factors in recurrent GBM

When tumor recurs, management options include supportive care, re-operation, re-irradiation, systemic therapies, and combined-modality therapy. Management decisions should involve collaboration between the patient and a multi-disciplinary medical team. The appropriate strategy depends in part on patient- and disease-specific factors that correlate with prognosis. The most consistently demonstrated prognostic factor is favorable performance status (KPS ≥ 70), which correlates with significantly improved PFS and OS following salvage therapy.[145-151] Younger age is the second most frequently reported prognostic factor to be associated with

improved survival.[145,147,152,153] Patient-specific factors that have been less frequently and less strongly correlated with improved survival include smaller tumor size (i.e., less than 42-50 cc), non-eloquent location, longer interval from first line therapy to recurrence, and lack of steroid dependence.

Surgical Resection

Resection of recurrent lesions can be diagnostic and therapeutic. Surgery tends to be most beneficial when a well-defined lesion in non-eloquent brain is producing symptomatic mass effect, and surgery or biopsy may play a role in distinguishing between disease progression and pseudoprogression. Surgery has also been used to deliver loco-regional, usually investigational, therapies. Re-operation may be complicated, however, by impaired wound healing related to prior irradiation or anti-angiogenic agents.[154] Moreover, many patients have previously undergone maximal safe resection, implying that additional surgery could encroach on eloquent areas.

Despite these limitations, reoperation can often be safely performed.[155,156] It does not follow, however, that reoperation should be performed any time surgery is deemed safe.[139] The overall benefit of surgery in the recurrent setting remains unclear, as the available retrospective and few prospective phase I/II studies are limited by selection bias and lack of suitable control populations.[139,145,149,151,155-157] A few small, retrospective studies suggest that a combination of resection and systemic adjuvant therapy may at times be beneficial.[139,157,158]

Systemic therapy

Comprehensive discussion of the many trials investigating systemic agents for recurrent GBM is beyond the scope of this guideline, but important results will be summarized to provide context for the studies on reirradiation.[159] Early studies of cytotoxic chemotherapeutic agents demonstrated short median PFS and OS following recurrence, on the order of 3-4 and 6-7 months, respectively.[149,160] In several phase II and retrospective studies, bevacizumab was associated with median survival ranging from 31-42 weeks.[35,36,161-167] The BELOB trial, a randomized phase II study, demonstrated improved progression free and overall survival among recurrent GBM patients treated with bevacizumab plus lomustine compared to either agent alone.[168] These results are being further investigated in an ongoing phase III trial for recurrent GBM (EORTC 26101; NCT01290939). Various combinations of targeted agents and complementary chemotherapeutics have been explored.[169-175]

Systemic therapies carry unique risks. Bevacizumab, for example, may cause potentially severe adverse effects, including gastrointestinal perforation, wound healing complications, hemorrhage, and blood clots.[37,38,176-179]

Radiation Therapy

KQ4. Focal Re-irradiation

Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy

Since most recurrences occur within brain previously irradiated to a high dose, reirradiation with doses and margins used in the primary treatment of GBM could confer high toxicity risks. Thus, limited volume reirradiation using stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (HFSRT) is often employed. Both SRS and HFSRT deliver more than 2 Gy per fraction and typically have smaller margins and much shorter

durations than conventionally fractionated radiation courses. RTOG 90-05, a phase I dose escalation study, established maximum tolerated doses according to target size and demonstrated that single-fraction SRS could be performed in this setting with acceptable morbidity.[180] Moreover, a short course of radiation has logistic advantages over the much longer courses of radiation typically employed in primary treatment. In the rare event that disease recurs in a portion of brain not previously irradiated (e.g., new contralateral disease or a transformed malignant glioma), conventional radiotherapy with chemotherapy should be considered after maximal safe resection (or biopsy).

The concept of using SRS and HFSRT to treat recurrent GBM does present theoretical limitations. As GBM has an infiltrative component beyond well-demarcated tumor, it is uncertain why a highly focal treatment of radiographically apparent tumor should substantially alter outcome. Enthusiasm for SRS in the treatment of GBM also waned after RTOG 93-05 failed to demonstrate a benefit from adding SRS boost to chemoradiation in the primary treatment of this disease.[79]

Despite these limitations, SRS and HFSRT appear to provide promising outcomes compared to chemotherapy alone for the treatment of recurrent GBM, with median survival from the time of reirradiation ranging from 4 to 18 months (typically 8-12), as shown in Table 9. These studies were nearly all retrospective, however, lacking randomized control groups. Selection bias is a serious concern, as recurrent tumor is generally amenable to SRS or HFSRT only when small and discrete; diffuse, infiltrative recurrences would not have been represented in these series and may be associated with worse survival. Many of the patients, moreover, did not have pathologic confirmation of recurrent disease, so some of these “local recurrences” may have actually represented treatment-related changes, including radiation necrosis.

Radiation necrosis is a well-documented toxicity from upfront chemoradiation, and salvage reirradiation adds to the risk. Several of the early studies involving single-fraction SRS reported high rates of late complications requiring re-operation (20-40%).[177,178,191,192] Compared to SRS, the use of HFSRT may help mitigate the risk of adverse radiation events. One of the largest series examining HFSRT comes from Thomas Jefferson University, where 105 GBM patients treated with 35 Gy in 10 fractions had a median survival from salvage HFSRT of 11 months, with no reported clinically significant acute morbidity and only one grade 3 late CNS toxicity (severe headaches).[153] Again, however, no high level data are available comparing salvage SRS with HFSRT.

Defining target volumes for SRS and HFSRT is controversial and variable. Table 10 includes a selection of currently used strategies, but these approaches have not been directly compared.

Brachytherapy

Brachytherapy has also been evaluated for use in recurrent GBM. Typically performed after resection of recurrent disease, brachytherapy features a sharp dose gradient. Strategies include permanent iodine 125 (I-125) seeds and a silicone balloon catheter system containing I-125 solution (GliaSite, IsoRay, Richland, WA). Table 9 details some relevant studies. Retrospective studies on I-125 have demonstrated median survivals from the time of brachytherapy ranging from 11 to 15 months. One phase I/II study of 34 patients reported a median survival of 15.9 months, but also a 24% rate of radiation necrosis.[177] A multi-institutional retrospective study of 95 patients treated with GliaSite demonstrated a median survival of 8.3 months, with an 11% rate of RTOG grade 2-3 toxicities, including 3 cases of radionecrosis.[148]

These outcomes seem reasonable, though again based on low quality data from uncontrolled studies. As with the literature on SRS, selection bias confounds interpretation, as patients who receive brachytherapy have to be well enough to undergo surgery and generally have discrete rather than diffuse recurrences.

Conventionally fractionated radiation

Although most studies interrogating repeat external beam radiotherapy have focused on SRS or HFSRT, conventionally fractionated radiation may theoretically allow more generous target volumes. The University of Heidelberg published one of the largest retrospective series exploring this in a study of 172 recurrent glioma patients including 59 patients with GBM (Table 9).[181] The median dose was 36 Gy (15-62 Gy) given at 2 Gy per day, and radiation was delivered to the enhancing volume plus a 0.5-1 cm margin. Median survival was 8 months for GBM patients and only one patient developed radiation necrosis.

One strategy to improve the therapeutic index of re-irradiation is to take advantage of the inverse dose rate effect, a paradoxical increase in cell kill with decreasing dose rate thought to be related to a blockade of the cell cycle in radiosensitive G2/M. A retrospective study from the University of Wisconsin of 103 patients (86 GBM) with recurrent gliomas treated with pulsed reduced dose rate therapy (PRDR) to a median of 50 Gy (range, 20-60 Gy) in 1.8-2.0 Gy fractions showed a median survival for recurrent GBM patients of 5.1 months.[182] Compared to patients in SRS studies, these patients had larger volumes of disease and significantly larger target volumes, with 2-2.5 cm margins added to account for microscopic extension.

Not enough clinical data exist for the panel to endorse conventionally fractionated radiation therapy (with or without PRDR) for routine use in the recurrent setting. This does not

imply that the panel recommends against conventionally fractionated radiotherapy. Practitioners using large-volume reirradiation should take into account brain tolerance data to reduce the risk of radionecrosis.[58]

Particle therapy

Particle therapy includes proton, neutron, and carbon ion therapy. Two small retrospective studies of boron neutron capture therapy (BNCT) in recurrent malignant glioma patients demonstrated median survivals after BNCT of 9.6 and 8.7 months, respectively.[183,184] Carbon ion therapy is being assessed in a Phase I/II study named CINDERELLA.[185] Not enough clinical data exist for the panel to endorse particle therapy in the recurrent setting. Clinical data do not support the superiority of particle therapy to photon therapy.

Radiotherapy dose and target volume

A variety of dose fractionation regimens, target volumes, and stereotactic systems have been used in the treatment of recurrent GBM. These approaches have not been subjected to randomized comparison, so the optimum technique has yet to be established. Table 10 describes representative techniques, but not enough data exists for the panel to endorse any specific approach.

Combined radiation therapy and systemic therapy

Several studies have explored adding systemic therapy to salvage reirradiation. A few studies have explored combining reirradiation with TMZ, given its efficacy at radiosensitization in the upfront treatment of GBM. Other studies have explored the addition of bevacizumab,

which offers theoretical benefits in conjunction with radiotherapy. Radiotherapy may upregulate hypoxia factor-mediated angiogenesis, a potentially counterproductive effect which could be blocked by anti-angiogenic agents.[186-188] Moreover, bevacizumab has been used to treat radionecrosis and may reduce the risk of radionecrosis following reirradiation.[189-191]

A few small studies have investigated adding concurrent TMZ to SRS or FSRT (Table 9). A prospective cohort study from Canada demonstrated a median survival of 9 months in 31 GBM patients treated with TMZ and SRS (25-35 Gy in 5 fractions).[192] Four patients (13%) exhibited acute grade 3-4 neurologic toxicity. A retrospective series from Italy demonstrated a median survival of 9.7 months in 36 GBM patients treated with concurrent TMZ and FSRT (37.5 Gy in 15 fractions), and reported neurologic deterioration secondary to radionecrosis in three (8%).[193]

Several studies have investigated adding bevacizumab to SRS.[147,178,194-197] A prospective trial from Memorial-Sloan Kettering investigating the safety of SRS and bevacizumab reported no radionecrosis among 25 recurrent malignant glioma patients at a median follow-up of 6.6 months, but three patients discontinued treatment because of grade 3 intratumoral hemorrhage, wound dehiscence, and bowel perforation while a fourth developed gastrointestinal bleeding shortly after coming off study for tumor progression. The study demonstrated a median survival of 12.5 months post SRS among GBM patients (secondary outcome).[178,198]

A prospective pilot study from Duke evaluating the safety of concurrent bevacizumab and SRS in 15 patients with recurrent malignant gliomas reported one grade 3 and zero grade 4-5 toxicities, while quality of life and neurocognition were well maintained.[194] Median survival (secondary outcome) from SRS was 14.4 months. A retrospective study from Duke in 63 recurrent malignant glioma patients found that median survival was longer for those who

received bevacizumab around the time of SRS than those who did not (11 vs 4 months for GBM patients, $p = .014$).[147] Most of these patients received a variety of chemotherapy drugs following SRS. A small case-control study from the University of Pittsburgh also suggested longer median survival (18 vs 12 months, $p = .005$) in patients treated with SRS followed by bevacizumab-containing regimens compared to controls who received SRS alone.[196] A small retrospective analysis from Henry Ford found that patients treated with SRS/HFSRT and bevacizumab had longer median survival than those receiving only bevacizumab (7.2 vs 3.3 months, p=0.03).[199]

Several studies have reported relatively low rates of adverse radiation events in patients treated with bevacizumab and SRS/HFSRT. In the retrospective study from Duke, 4 of 21 patients (19%) treated with SRS alone had symptomatic radionecrosis versus 2 of 42 (5%) receiving SRS and bevacizumab, though this difference was not statistically significant.[147] Patients receiving SRS and bevacizumab in the studies from Memorial-Sloan Kettering,[178] Ludwig-Maximilian,[179] and Cincinnati[200] exhibited similar rates of radionecrosis: 0%, 7%, and 9%, respectively.

The studies exploring the addition of systemic therapy to reirradiation are nonrandomized, so selection bias remains a serious concern and additional study is required. A phase III trial (RTOG 1205) randomizing patients to bevacizumab alone versus bevacizumab plus radiotherapy (35 Gy in 10 fractions) is ongoing.

Novel Therapies

Review of novel therapies for recurrent GBM, such as radioimmunotherapy and TTF, is beyond the scope of this guideline.

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Table 1. Grading of recommendations and consensus methodology

Guideline statement	Percent (%) agreement with guideline statement	Strength of recommendation
KQ1. When is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?		
A. Fractionated radiotherapy improves overall survival compared to chemotherapy or best supportive care alone following biopsy or resection of newly diagnosed glioblastoma (**HQE**). Whether radiotherapy is indicated in a particular individual may depend on patient characteristics such as performance status (see KQ2).	**100%**	**Strong**
B. Adding concurrent and adjuvant temozolomide to fractionated radiotherapy improves overall survival and progression free survival compared to fractionated radiotherapy alone, with a reasonably low incidence of early adverse events and without impairing quality of life (**HQE**). The guideline panel endorses fractionated radiotherapy with concurrent and adjuvant temozolomide as the standard of care following biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age (see KQ2 for recommendations regarding patients older than 70).	**100%***	**Strong**
C. Adding bevacizumab to standard therapy for newly diagnosed glioblastoma (i.e., fractionated radiotherapy with concomitant and adjuvant temozolomide) does not improve overall survival and is associated with a higher incidence of early adverse events (**HQE**). Bevacizumab may, however, prolong progression free survival (**MQE**). The panel does not recommend the routine addition of bevacizumab to standard therapy for newly diagnosed glioblastoma outside of a clinical trial.	**100%^**	**Strong**
D. The addition of other systemic therapies to conventional radiotherapy with or without temozolomide remains investigational.	**100%***	**Strong**
KQ2. What is the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma and how might treatment vary based on pretreatment characteristics such as age or performance status?		
A. For patients under 70 with good performance status (Karnofsky performance status [KPS] ≥ 60), the optimal dose-fractionation schedule for external beam radiation therapy following resection or biopsy is 60 Gy in 2-Gy fractions delivered over 6 weeks (**HQE**). Numerous other dose schedules have been explored without definitive benefit. Care should be taken to keep dose to critical structures (e.g., brainstem, optic chiasm/nerves) within acceptable limits.	**93%**	**Strong**
B. Older age and poor performance status are associated with shorter survival in GBM patients (**MQE**). Prognostic considerations should help guide treatment recommendations for individual patients.	**100%**	**Strong**
C. Among elderly patients (≥ 70 years old) with fair-good performance status (KPS ≥ 50), the panel recommends external beam	**100%***	**Strong**

Guideline statement	Percent (%) agreement with guideline statement	Strength of recommendation
radiation therapy following biopsy or resection, as radiotherapy (compared to supportive care alone) improves overall survival without impairing quality of life or cognition (**HQE**). The efficacy of concurrent and adjuvant temozolomide in this population has not been evaluated in a randomized trial, but may be considered for selected patients (**LQE**, see KQ2F).		
D. Among elderly patients, there is no evidence that conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiotherapy (e.g., 40 Gy in 15 fractions over 3 weeks) (**HQE**). Compared to conventionally fractionated radiotherapy, hypofractionated radiotherapy has been associated with superior survival and less corticosteroid requirement (**MQE**).	**100%**	**Strong**
E. Given the absence of proven superiority for conventionally fractionated radiotherapy, the panel recommends hypofractionated radiotherapy for elderly patients with fair-good performance status (**HQE**). Temozolomide monotherapy is an efficacious alternative for elderly patients with MGMT promoter methylation (**HQE**), but the panel does not recommend temozolomide monotherapy as first-line therapy for patients with unmethylated MGMT promoters (**MQE**). Temozolomide monotherapy confers a higher risk of adverse events than radiotherapy, particularly with respect to hematologic toxicity, nausea, and vomiting (**MQE**).	**100%***	**Strong**
F. Among elderly patients with good performance status, adding concurrent and adjuvant temozolomide to hypofractionated radiotherapy appears to be safe and efficacious without impairing quality of life (**LQE**). In such patients, the panel recommends consideration of concurrent and adjuvant temozolomide. The combination of hypofractionated radiotherapy and temozolomide may be particularly efficacious in those with a methylated MGMT promoter (**LQE**).	**100%***	**Strong**
G. Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (**LQE**).	**100%***	**Strong**
KQ3. What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?		
A. Although glioblastoma is thought to be diffusely infiltrative, partial brain radiation therapy leads to no worse survival than whole brain radiation therapy (**HQE**). The panel endorses partial brain radiation therapy as the standard treatment paradigm for glioblastoma.	**100%**	**Strong**
B. Several strategies for target volume definition produce similar outcomes (**LQE**). All confer a low risk of isolated marginal or distant failure, with a high risk of local failure as a component of disease	**93%**	**Strong**

Guideline statement	Percent (%) agreement with guideline statement	Strength of recommendation
progression (**MQE**). Acceptable strategies include but are not limited to the following: 1. Two-phase: 1) primary target volume encompasses edema (hyperintense region on T2 or FLAIR on MRI) and gross residual tumor/resection cavity; 2) boost target volume encompasses gross residual tumor/resection cavity. A range of acceptable clinical target volume margins exists. 2. One-phase: single target volume includes gross residual tumor/resection cavity with wide margins, without specifically targeting edema.		
C. Reducing target volumes allows less radiation to be delivered to radiographically normal brain. Delivering less radiation to normal brain should result in less late toxicity (**LQE**), but this remains to be validated.	**93%**	**Weak**
KQ4. What is the role of re-irradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?		
In younger patients with good performance status, focal re-irradiation (e.g., stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, brachytherapy) for recurrent glioblastoma may improve outcomes compared to supportive care or systemic therapy alone (**LQE**). Tumor size and location should be taken into account when deciding whether re-irradiation would be safe (**LQE**).	**93%**	**Weak**

* Patrick Wen, Helen Shih, and David Reardon were recused from consensus voting on this recommendation.

^ Patrick Wen, Helen Shih, David Reardon, and John Kirkpatrick were recused from consensus voting on this recommendation.

LQE = low quality evidence, MQE = moderate quality evidence, HQE = high quality evidence

Table 2. Randomized studies evaluating radiation and chemoradiation (without temozolomide) in the upfront treatment of glioblastoma

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Shapiro, 1976[9] (Memorial Sloan-Kettering Cancer Center)	33	Resection of malignant glioma	- Carmustine and vincristine - Carmustine and vincristine + RT	45 Gy to whole brain, followed by 15 Gy to the side of the brain with tumor	- Chemotherapy: 30 weeks - ChemoRT: 44.5 weeks Not statistically significant.
Walker, 1978[5] (Brain Tumor Study Group)	303	Resection of anaplastic glioma	- BCNU alone - BCNU + RT - RT alone - Best supportive care	50 to 60 Gy to whole brain using opposed laterals	- Best supportive care: 14 weeks - BCNU: 18.5 weeks - Radiotherapy alone: 35 weeks - BCNU + RT: 34.5 weeks All interventions significantly improved survival compared to best supportive care.
Walker, 1979[7] (Brain Tumor Study Group)	621	Resection of malignant glioma Retrospective analysis of three successive BTSG protocols between 1966 and 1975	- No radiotherapy - Different radiation doses	- No radiotherapy - ≤45 Gy - 50 Gy - 55 Gy - 60 Gy Using opposed laterals	- No radiotherapy: 18.0 weeks - ≤45 Gy: 13.5 weeks - 50 Gy: 28 weeks - 55 Gy: 36.0 weeks - 60 Gy: 42.0 weeks All RT arms significantly improved survival compared to no RT. Clear dose-response relationship.
Walker, 1980[6] (Brain Tumor Study Group 7201)	467	Resection of malignant glioma	- MeCCNU - RT - BCNU + RT - MeCCNU + RT	60 Gy to whole brain using parallel opposed ports	- MeCCNU: 31 weeks - RT: 37 weeks - BCNU + RT: 49 weeks - MeCCNU + RT: 43 weeks Both RT and chemoRT suggested improvement over MeCCNU alone. Only the comparison with BCNU + RT was statistically significant.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Kristiansen, 1981[8] (Scandinavian Glioblastoma Study Group)	118	Resection of grade III/IV glioma	- RT - RT + bleomycin - Best supportive care	45 Gy to whole brain using opposed laterals	- RT: 10.8 months - RT + bleomycin: 10.8 months - Best supportive care: 5.2 months Both RT arms significantly improved survival compared to best supportive care.
Sandberg-Wollheim, 1991[10] (University Hospital Lund, Sweden)	171	Resection of grade III/IV glioma	- PCV - PCV + RT	58 Gy to the tumor-bearing hemisphere and 50 Gy to the contralateral hemisphere	Patients <50 years old: - PCV alone: 66 weeks - PCV + RT: 124 weeks (p=0.037) Patients >50 years: - PCV alone: 39 weeks - PCV + RT: 51 weeks RT significantly prolonged survival on multivariate analysis for patients <50 years.
Keime-Guibert, 2007[13] (Association of French-Speaking Neuro-Oncologists)	81	Resection of anaplastic glioma or glioblastoma, age ≥70 years, KPS ≥70	- Supportive care with focal radiation to 50.4 Gy at 1.8 Gy per fraction - Supportive care only	50.4 Gy to tumor bed using 3D conformal technique	- RT: 29 weeks - Supportive care only: 16.9 weeks (p=0.002) RT significantly improved survival in this elderly population.

BCNU = carmustine; MeCCNU = semustine, PVC = procarbazine, lomustine, and vincristine; KPS = Karnofsky performance status; chemo = chemotherapy; chemoRT = chemoradiotherapy; RT = radiation therapy

Table 3. Randomized trials evaluating chemoradiation with temozolomide in the upfront treatment of glioblastoma

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Athanassiou, 2005[30] (St. Savas Cancer Hospital, Metaxa Cancer Hospital, IASO Hospital, General Army Hospital, Papageorgiou Hospital, Greece)	131	Histologically confirmed glioblastoma	- RT - RT + concomitant and adjuvant TMZ	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal technique	- RT: 7.7 months - ChemoRT: 13.4 months ($p<0.0001$) ChemoRT significantly improved survival compared to radiotherapy alone.
Stupp, 2005[28] (EORTC 22981/ 26981and National Cancer Institute of Canada Clinical Trials Group CE.3)	573	Histologically confirmed glioblastoma	- RT - RT + concomitant and adjuvant TMZ	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal technique	- RT: 12.1 months - ChemoRT: 14.6 months ($p<0.001$) Chemoradiotherapy significantly improved survival compared to radiotherapy alone.
Kocher, 2008[31] (University of Cologne, Germany)	65	Macroscopic complete resection of glioblastoma	- RT - ChemoRT + TMZ	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal technique	- RT: 17 months - ChemoRT: 15 months ($p=0.67$) No significant survival difference, but the study was stopped early and severely underpowered.
Szczepanek, 2013[32] (University of Medicine Lublin, Warsaw University of Medicine, and Jagiellonian University, Poland)	58	Histologically confirmed glioblastoma	- RT - RT + TMZ before, during, and after RT	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal technique	- RT: 12.5 months - ChemoRT: 16.0 months ($p<0.05$) Chemoradiotherapy significantly improved survival over radiotherapy alone.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Gilbert, 2013[34] (RTOG 0525, EORTC 26052/22053, and North Central Cancer Therapy Group)	833	Histologically confirmed glioblastoma	- Standard adjuvant TMZ - Dose-dense adjuvant TMZ All patients received standard concomitant chemoRT + TMZ first.	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal technique	- Standard adjuvant temozolomide: 16.6 months - Dose-dense adjuvant temozolomide: 14.9 months (p=0.63) No significant difference in survival.

RTOG = Radiation Therapy Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; chemoRT = chemoradiotherapy; RT = radiation therapy; TMZ = temozolomide

Table 4. Randomized trials evaluating bevacizumab in the upfront treatment of glioblastoma

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Chinot, 2014[37] (Multi-institutional)	921	Histologically confirmed glioblastoma	- Standard chemoRT* + placebo - Standard chemoRT + bevacizumab	Focal irradiation to 60 Gy at 2 Gy per fraction using conformal technique	- Placebo: 16.7 months - Bevacizumab: 16.8 months (p=0.10) No significant difference in survival.
Gilbert, 2014[38] (RTOG 0825, ECOG, and North Central Cancer Treatment Group)	637	Histologically confirmed glioblastoma	- Standard chemoRT* + placebo - Standard chemoRT + bevacizumab	Focal irradiation to 60 Gy at 2 Gy per fraction using 3D conformal or IMRT	- Placebo: 16.1 months - Bevacizumab: 15.7 months (p=0.21) No significant difference in survival.

* Radiation with concurrent and adjuvant temozolomide.

RTOG = Radiation Therapy Oncology Group; ECOG = Eastern Cooperative Oncology Group; IMRT = intensity-modulated radiotherapy; chemo = chemotherapy; chemoRT = chemoradiotherapy; RT = radiation therapy

Table 5. Studies evaluating different dose fractionation schemes in patients under 70 with good performance status

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Standard fractionation dose escalation					
Chang, 1983[52] (RTOG 7401 and ECOG 1374)	626	Grade III or IV malignant glioma, age <70 years	- RT - RT + boost - RT + BCNU - RT + methyl-CCNU + dacarbazine	- 60 Gy at 1.7-2 Gy QD - 60 Gy at 1.7-2 Gy QD + 10 Gy boost at 1.5-2 Gy QD	- RT: 9.9 months - RT + boost: 8.4 months - RT + BCNU: 10.0 months - RT + methyl-CCNU + dacarbazine: 9.8 months No significant differences between arms
Bleehen, 1991[51] (Medical Research Council Brain Tumour Working Party)	474	Grade III or IV malignant glioma, age 18 to 70 years	Two RT dose levels	- 45 Gy at 2.25 Gy QD - 60 Gy at 2 Gy QD with conedown after 40 Gy	- 45 Gy: 9 months - 60 Gy: 12 months (p=0.007) Median survival was significantly longer in the 60 Gy arm.
Nakagawa, 1998[57] (University of Tokyo)	38	Grade IV malignant glioma	Low or high-dose RT Stratified into CTV groups: - Tumor - Tumor + 2 cm margin - Tumor and edema + 2 cm margin	For respective CTV groups, doses at center of PTV: - Low-dose: 59.5-80 Gy, 48-60 Gy, and 26-40 Gy - High-dose: 90 Gy, 70 Gy, and 50 Gy	3-year overall survival: - Low-dose: 40% - High-dose: 22% No significant difference in overall survival but a trend toward better survival for the low dose arm.
Chan, 2002[56] (University of Michigan)	34	Grade III or IV malignant glioma, age ≥18 years	IMRT	90 Gy in 2 Gy fractions	11.7 months No survival advantage was seen with use of 90 Gy.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Tsien, 2009[54] (RTOG 9803)	209	Grade IV malignant glioma, age ≥18 years	RT + BCNU Stratified by PTV2 <75 cc vs. PTV2 ≥75 cc	46 Gy at 2 Gy QD + boost to 66 Gy, 72 Gy, 78 Gy, or 84 Gy	PTV2 <75 cc: - 66 Gy: 11.6 months - 72 Gy: 11.8 months - 78 Gy: 11.8 months - 84 Gy: 19.3 months PTV2 ≥75 cc: - 66 Gy: 8.2 months - 72 Gy: 12.3 months - 78 Gy: 10.0 months - 84 Gy: 13.9 months No p-values were reported.
Standard fractionation with hypofractionation or SRS boost					
Souhami, 2004[79] (RTOG 9305)	203	Grade IV malignant glioma, age ≥18 years	- RT and BCNU - RT and BCNU + upfront SRS	- 60 Gy at 2 Gy QD - 60 Gy at 2 Gy QD + 24 Gy x 1 fx (tumors ≤20 mm), 18 Gy x 1 fx, (tumors 21-30 mm), or 15 Gy x 1 fx (tumors 31-40 mm)	- RT and BCNU: 13.6 months - RT and BCNU + upfront SRS: 13.5 months (p=0.5711) There was no significant difference in survival between arms.
Cardinale, 2006[78] (RTOG 0023)	76	Grade IV malignant glioma, age ≥18 years	Accelerated RT + fractionated SRT boost + BCNU	50 Gy at 2 Gy QD + 20 or 28 Gy in 4 fx	12.5 months No significant improvement in survival compared to RTOG historical data.
Baumert, 2008[77] (EORTC 22972-2699)	25	Grade III or IV malignant glioma, age 18-65 years	- RT - RT + FSRT boost	- 60 Gy at 2 Gy QD - 60 Gy at 2 Gy QD + 20 Gy boost at 5 Gy QD	- RT: Not reported - RT + FSRT boost: 21.4 months The trial was closed early due to low accrual. It was not possible to reach a

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
					conclusion regarding the impact on survival of FSRT boost.
Balducci, 2010[80] (Catholic University of the Sacred Heart, University Hospital Maggiore della Carita, Italy)	41	Grade III or IV malignant glioma, age >18 years	RT + FSRT boost and TMZ	50.4 or 59.4 Gy at 1.8 Gy QD + 10 Gy (at 2.5 Gy QD) or 19 Gy (9 Gy at 0.9 Gy every other day + 10 Gy at 2.5 Gy QD) boost	28 months The study was small and lacked a control group without FSRT boost.
Hyperfractionation without drug therapy					
Bese, 1998[68] (University of Istanbul, Turkey)	36	Grade III or IV malignant glioma, age 18-75 years	Accelerated hyperfractionated RT	59.8 Gy to whole brain (morning and evening) and 39.9 Gy to target volume in 1.05 Gy TID	58 weeks Hyperfractionated accelerated radiotherapy showed survival comparable with conventional fractionation.
Brada, 1999[61] (Royal Marsden Hospital)	211	Grade III or IV malignant glioma	Accelerated RT	55 Gy at 1.5-1.7 Gy BID	10 months Survival was comparable to conventional radiotherapy.
Fitzek, 1999[59] (Massachusetts General Hospital)	23	Grade IV malignant glioma, age 18-70 years	Accelerated RT using protons and photons	81.6-94.2 Gy (RBE) at 1.8 Gy photon qAM and 1.92 Gy (RBE) proton qPM	20 months In analysis by RTOG prognostic criteria or Medical Research Council indices, median survival improved compared to conventional fractionation.
Genc, 2000[66] (University of Hacettepe, Turkey)	75	Grade III or IV malignant glioma	Accelerated hyperfractionated RT	60 Gy at 2 Gy BID	10 months (GBM patients) No significant improvement in survival was observed.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Beauchesne, 2010[67] (Centres hospitalier universitaire of Nancy, Bordeaux, and Clermont-Ferrand; centres hospitalier of Metz and Thionville; Centers G Le Conquerant, A Vautrin, and Val d'Aurelle-P Lamarque, France)	31	Grade IV malignant glioma, age ≥18 years	Ultrafractionated focal RT Survival compared with EORTC/NCIC trial 26981-22981/ CE.3 of RT alone versus RT + TMZ	67.5 Gy at 0.75 Gy TID with fractions at least 4 hours apart	9.5 months EORTC/NCIC 26981-22981/CE: - RT: 7.9 months - ChemoRT: 9.4 months Improved survival compared to radiotherapy alone patients in EORTC/ NCIC 26981-22981/CE. No difference was seen compared to patients receiving radiotherapy and TMZ in the same trial.
Hyperfractionation with drug therapy					
Payne, 1982[69] (Princess Margaret Hospital, Canada)	157	Grade III or IV malignant glioma, age 26-70 years	- Daily RT + CCNU and hydroxyurea - Every 3 hours RT + CCNU and hydroxyurea	- 50 Gy at 2 Gy QD - 36-40 Gy at 1 Gy QID	- Daily: 306 days - Every 3 hours: 320 days No significant differences between two RT regimens.
Fulton, 1984[71] (Cross Cancer Institute and Tom Baker Cancer Centre, Canada)	128	Grade III or IV malignant glioma, age 18-70 years	- Conventionally fractionated RT (until January 1983) - MDF RT - MDF RT + misonidazole - High-dose MDF RT (from January 1983)	- 58.0 Gy in 30 fractions - 61.41-71.2 Gy at 0.89 Gy TID fractions over 5.5 weeks	- Conventional RT: 29 weeks - MDF RT: 45 weeks - MDF RT + misonidazole: 50 weeks - High-dose MDF RT: Not reported Median survival was significantly improved for MDF and MDF + misondazole compared to conventionally fractionated RT.
Curran, 1992[62] (RTOG 8302)	304	Grade III or IV malignant glioma, age 18-70 years	Two dose regimens of accelerated hyperfractionated RT + BCNU	- 48.0 Gy at 1.6 Gy BID - 54.4 Gy at 1.6 Gy BID	- 48.0 Gy: 11.7 months - 54.4 Gy: 10.8 months No significant difference overall or in subgroup analyses by age and histology.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Goffman, 1992[63] (Radiation Oncology Branch, National Cancer Institute)	45	Grade IV malignant glioma, age >18 years	HF RT + intravenous iododeoxyuridine	45 Gy followed by conedown to 70-75 Gy, most at 1.5 Gy BID	11 months No benefit from addition of iododeoxyuridine to RT.
Werner-Wasik, 1996[70] (RTOG 8302)	786	Grade III or IV malignant glioma, age 18-70 years	- HF RT + BCNU - AHF RT + BCNU	- 64.8 Gy, 72 Gy, 76.8 Gy, or 81.6 Gy at 1.2 Gy BID - 48 Gy or 54.4 Gy at 1.6 Gy BID	GBM patients: -HF: - 64.8 Gy: 9.6 months - 72 Gy: 11 months - 76.8 Gy: 10.9 months - 81.6 Gy: 10.2 months -AHF - 48 Gy: 10.2 months - 54.4 Gy: 10.4 months No significant differences between HF and AHF arms or between different dose levels.
Coughlin, 2000[64] (RTOG 9411)	108	Grade IV malignant glioma, age ≥18 years	AHF RT + BCNU	- 64 Gy for patients with cross-sectional tumor mass >20 cm^2 - 70.4 Gy for ≤20 cm^2 at 1.6 Gy BID	- 64 Gy: 9.1 months - 70.4 Gy: 11.0 months, (p=0.068) No significant difference in survival between arms.
Prados, 2001[65] (University of California San Francisco)	231	Grade IV malignant glioma, age ≥18 years	- AHF RT - AHF RT + DFMO - Standard fractionation RT - Standard fractionation RT + DFMO	- 70.4 Gy at 1.6 Gy BID - 59.4 Gy at 1.8 Gy QD	- AHF: 40 weeks - AHF + DFMO: 42 weeks - Standard fractionation: 37 weeks - Standard fractionation + DFMO: 44 weeks No significant difference between AHF and standard fractionation RT or between arms with and without DFMO.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival
Mizumoto, 2010[72] (University Hospital of Tsukuba)	20	Grade IV malignant glioma, age 20-80 years	RT + hyper-fractionated proton boost and nimustine hydrochloride	50.4 Gy at 1.8 Gy photons qAM + 46.2 Gy (RBE) at 1.65 Gy (RBE) protons qPM	21.6 months Hyperfractionated concomitant boost proton RT showed favorable survival, but the study was small and lacked a control group.
Hypofractionation without drug therapy					
Glinski, 1993[75] (Maria Sklodowska-Curie Memorial Center, Poland)	108	Grade III or IV malignant glioma	- Conventionally fractionated RT - Hypofractionated RT	- 50 Gy [20 Gy at 4 Gy QD WBRT, 4 week break, repeat 20 Gy at 4 Gy QD WBRT, 4 week break, then 10 Gy at 2 Gy QD conedown] - 60 Gy [50 Gy at 3 Gy QD WBRT then 10 Gy at 2 Gy QD conedown]	2-year overall survival: - Conventionally fractionated RT: 23% - Hypofractionated RT: 10% Difference was statistically significant.
Hypofractionation with drug therapy					
Chen, 2011[73] (University of Colorado)	16	Grade IV malignant glioma, age ≥18 years	Fractional dose escalated IMRT + TMZ	60 Gy in fractions of 3 Gy, 4 Gy, 5 Gy, 6 Gy	16.2 months Maximal tolerated fraction size was not reached.
Reddy, 2012[74] (University Of Colorado)	24	Grade IV malignant glioma, age ≥18 years	Hypofractionated IMRT + TMZ	60 Gy at 6 Gy QD over 2 weeks	16.6 months Hypofractionated IMRT showed survival comparable to current standard of care.
Yoon, 2013[76] (University of Ulsan, South Korea)	39	Grade IV malignant glioma	Hypofractionated IMRT + TMZ	50, 40, or 30 Gy at 10 Gy QD	16.8 months Hypofractionated IMRT showed survival comparable to current standard of care.

EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group; ECOG = Eastern Cooperative Oncology Group; NCIC = National Cancer Institute of Canada; RT = radiation therapy; IMRT = intensity-modulated radiotherapy; HF = hyperfractionated; AHF = accelerated hyperfractionated RT; MDF = multiple daily fractionated; FSRT = fractionated stereotactic radiotherapy; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy; TMZ = temozolomide; BCNU = carmustine; CCNU = lomustine; DFMO = difluoromethylornithine; PTV = planning target volume; CTV = clinical target volume; MGMT = O-6-methylguanine-DNA methyltransferase; QD = once a day; BID = twice a day; TID = three times a day; QID = four times a day; qAM = each morning; qPM = each evening

Table 6. Studies evaluating radiotherapy options according to age and performance status

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival and Tolerability
Thomas, 1994[96] (The Royal Marsden Hospital and Institute of Cancer Research, United Kingdom)	38	Grade III or IV malignant glioma, KPS ≤ 50 or age 55-70 years with KPS 50-70 or >70 years old with any KPS	Hypofractionated RT	30 Gy in 6 fractions over 2 weeks	6 months Hypofractionation is well tolerated in patients who have poor performance status and/or are elderly.
Jeremic, 1999[99] (University Hospital Kragujevac, Yugoslavia)	44	Grade IV malignant glioma, age ≥60, KPS 50-70	Hypofractionated RT	45 Gy in 15 fractions over 3 weeks	9 months Hypofractionation appears safe and effective in elderly and frail patients.
Roa, 2004[101] (Cross Cancer Institute, Tom Baker Cancer Center, London Regional Cancer Center, Northwestern Ontario Regional Cancer Center, Canada)	100	Grade IV malignant glioma, age ≥60 years	- Conventionally fractionated RT - Hypofractionated RT	- 60 Gy in 30 fractions over 6 weeks - 40 Gy in 15 fractions over 3 weeks	- Conventionally fractionated RT: 5.1 months - Hypofractionated RT: 5.6 months No difference in overall survival. Greater corticosteroid requirements in 60 Gy arm.

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival and Tolerability
Keime-Guibert, 2007[13] (Association of French-Speaking Neuro-Oncologists)	85	Grade III or IV malignant glioma, age ≥70 years	- RT + supportive care - Supportive care alone	50.4 Gy at 1.8 Gy per fraction	- RT + supportive care: 29.1 weeks - Supportive care alone: 16.9 weeks RT improved overall survival without reducing quality of life or cognition
Gallego Perez-Larraya, 2011[104] (Association of French-Speaking Neuro-Oncologists)	77	Grade IV malignant glioma, age ≥70 years, postoperative KPS <70	TMZ alone	None	25 weeks Temozolomide is tolerated well in the elderly and resulted in favorable survival, particularly in patients with methylated MGMT promoter.
Scott, 2011[90] (H. Lee Moffit Cancer Center)	2836	Grade IV malignant glioma, age >70 years old From Surveillance, Epidemiology, and End Results cancer registry	- Surgery - RT only - Surgery + RT - Neither	Various	- Surgery: 3 months - RT only: 4 months - Surgery + RT: 8 months - Neither: 2 months (p<0.001) Elderly patients who received RT had improved overall survival compared to those who did not.
Malmstrom, 2012[102] (Multi-institutional)	342	Grade IV malignant glioma, age ≥60 years	- Conventionally fractionated RT - Hypofractionated RT - TMZ alone	- 60 Gy in 30 fractions over 6 weeks - 34 Gy in 10 fractions over two weeks	- Conventionally fractionated RT: 6.0 months - Hypofractionated RT: 7.5 months (p=0.24) - TMZ alone: 8.3 months (p=0.01) In patients age >70 years, better survival with hypofractionated RT than with conventionally fractionated.
Minniti, 2012[105]	71	Grade IV malignant glioma, age ≥70 years, KPS ≥ 60	Hypofractionated EBRT + TMZ	40 Gy in 15 fractions over 3 weeks	12.4 months

Author (Institution/ Cooperative Group)	Number of Patients	Eligibility	Intervention	Radiation dose and technique	Median Survival and Tolerability
(Sant' Andrea Hospital, University Sapienza, Italy)					Temozolomide + hypofractionated EBRT was well tolerated.
Wick, 2012[103] (NOA-08 Study Group of the Neuro-oncology Working Group of the German Cancer Society)	412	Grade III or IV malignant glioma, age >65 years, KPS ≥ 60	- TMZ - RT	59.4-60 Gy at 1.8-2.0 Gy over 6-7 weeks	- TMZ: 8.6 months - RT: 9.6 months (p=0.033) Temozolomide associated with more grade 3-4 toxicity.
Minniti, 2013[106] (Sant' Andrea Hospital, University Sapienza and Neuromed Institute, Italy)	65	Grade IV malignant glioma, age ≥70 years, KPS ≥ 60	Hypofractionated RT + TMZ	40 Gy in 15 fractions over 3 weeks	12.4 months Quality of life stable to improved until time of disease progression

EBRT=external beam radiation therapy; KPS = Karnofsky performance status; MGMT = O(6)-methylguanine-DNA methyltransferase

Table 7. Patterns of failure following radiation therapy with MR-based planning and concurrent temozolomide for glioblastoma**.**

Author (Institution/ Cooperative Group)	Number of Progressing Patients	CTV Margin	% Central or in-field	Comment
Brandes, 2009[123] (Bellaria-Maggiore Hospital, Bellaria Hospital, Istituto Oncologico Veneto, Azienda Ospedale-Universita, Santa Maria della Misericordia, Italy)	79	20-30 mm	72%	One-phase
Milano, 2010[201] (University of Rochester)	39	20-25 mm	80%	Two-phase
McDonald, 2011[122] (Emory University)	43	5 mm	93%	Two-phase
Petrecca, 2013[202] (McGill University, Canada)	20	25 mm	90%	One-phase
Sheriff, 2013[203] (Queen Elizabeth Hospital, UK)	71	15-20 mm	77%	One-phase
Gebhardt, 2014[121] (University of Alabama at Birmingham)	95	5 mm	81%	Two-phase
Paulsson, 2014[120] (Wake Forest University)	29 78 38	5 mm 10 mm >10-20 mm	79% 77% 87%	Two-phase

MGMT = O(6)-methylguanine-DNA methyltransferase
Reports of mixed histologies or of patients that were treated in the pre-temozolomide or pre-MR era were not included in table 7.

Table 8. Target volume definitions utilized by cooperative groups in the United States and Europe

Cooperative Group	One or Two Phase	CTV (initial)	CTV(boost)	PTV
ABTC	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 5 mm	Cavity + T1E + 5 mm	Institution specific but generally 3-5 mm
EORTC	One-phase	Cavity + T1E + 2-3 cm	-	Institution specific but generally 5-7 mm
NCCTG/Alliance	Two-phase: 50 + 10 = 60 Gy	T2 + T1E + cavity + 20 mm to block edge	Cavity + T1E + 20 mm to block edge	PTV addressed in CTV expansions
RTOG/NRG	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 20 mm	Cavity + T1E + 20 mm	3-5 mm

T1E=residual T1-enhancing abnormality. RTOG (Radiation Therapy Oncology Group) is now part of NRG. The listed RTOG margins from RTOG derive from RTOG 0825. New Approaches to Brain Tumor Therapy (NABTT) and the North American Brain Tumor Consortium (NABTC) were combined to form the American Brain Tumor Consortium (ABTC). Mayo/North Central Cancer Treatment Group (NCCTG) is now part of the Alliance for Oncology Trials consortium (described in table as Alliance). In most cases, editing of the CTV along anatomic barriers (e.g. bone) is allowed. The panel emphasizes that these cooperative group target volume definitions continue to evolve as data on outcomes and patterns of failure accrue.

Table 9. Selected studies of salvage radiation therapy for previously irradiated malignant gliomas

Author (Institution)	Study Type	Number of patients	Modality	Dose Regimen	MS (months)	Toxicity post RT
Hall, 1995[204] (University of Minnesota)	Retrospective	35 (26 GBM)	SRS	20 Gy	8	31% reoperation rate, 14% rate of RN post SRS
Shrieve, 1995[205] (Harvard University)	Retrospective	86	SRS	13 Gy	10	22% patients with re-operation for RN
Halligan, 1996[206] (University of Washington)	Retrospective	22 (18 GBM)	I-125 Seeds	150-200 Gy at 5 mm initially and ~230 Gy at 5 mm for later patients	14.9	1 patient with symptomatic adverse radiation event
Cho, 1999[207] (University of Minnesota)	Retrospective	71 (42 GBM)	SRS FSRT	17 Gy (median) 37.5 Gy in 15 fxns (median)	11 12	Late complications from RN in 30% in SRS group vs 8% in FSRT group
Patel, 2000[176] (University of Cincinnati)	Retrospective	40	I-125 Seeds	120-160 Gy to 5 mm	10.8	2 patients with wound dehiscence, 1 infarct, no RN
Larson, 2004[208] (University of California, San Francisco)	Retrospective	38	I-125 Seeds	>250 Gy to 5 mm	12.0	45% required steroids >2 months post implant
Chan, 2005[146] (Johns Hopkins University)	Retrospective	24	I-125 Solution	45-60 Gy to 0.5-1.0 cm	9.1	2 patients with symptomatic RN, 1 with expressive aphasia
Combs, 2005[209] (Heidelberg University, Germany)	Retrospective	32	SRS	15 Gy (median)	10	No acute toxicities >CTC Grade 2. No long-term toxicities (including RN)

Author (Institution)	Study Type	Number of patients	Modality	Dose Regimen	MS (months)	Toxicity post RT
Gabayan, 2006[148] (Multi-institutional)	Retrospective	95 (80 GBM)	I-125 Solution	60 Gy to 1 cm (median)	8.3	2 patients with Grade 3 CNS toxicity (RN), no Grade 4 or 5
Kong, 2008[210] (Sungkyunkwan University, South Korea)	Prospective cohort	114 (65 GBM)	SRS	16 Gy (median)	13	Radiographic RN in 22 patients, re-operation for mass effect in 4 patients
Darakchiev, 2008[177] (University of Cincinnati)	Phase I/II	34	I-125 Seeds	~120 Gy to 5 mm	15.9	8 patients with RN, 4 with wound complications
Pellettieri, 2008[184] (Nyköping Hospital, Sweden)	Retrospective	12	BNCT	20 Gy-Eq (median)	8.7	No WHO Grade 3-4 treatment-related adverse events
Patel, 2009[199] (Henry Ford Health System)	Retrospective	36	SRS or HFRST	12-20 Gy in 1 fxn 36 Gy in 6 fxns	8.5 (SRS) vs 7.4 (FSRT) (NS)	3 patients (2 SRS, FSRT) with biopsy-proven RN
Gutin, 2009[178] (Memorial Sloan-Kettering Cancer Center)	Prospective (pilot)	25 (20 GBM)	SRS + BVZ	30 Gy in 5 fxns	12.5	1 patient with Grade 3 CNS hemorrhage, 1 each with Grade 4 bowel perforation, wound dehiscence, GI bleed
Miyatake, 2009[183] (Osaka Medical College, Japan)	Retrospective	22 (AA and GBM)	BNCT	13 Gy-Eq	9.6	No adverse effects reported, but RN noted as cause of death in 3 patients
Fogh, 2010[153] (Thomas Jefferson University)	Retrospective	147 (105 GBM)	HFSRT	35 Gy in 10 fxns	10	No acute complications or re-operations, 1 Grade 3 late CNS toxicity attributable to HFSRT
Torcuator, 2010[197] (Henry Ford Health System)	Retrospective	23 (18 GBM)	SRS or HFSRT + BVZ	18-20 Gy in 1 fxn 36 Gy in 6 fxn	7.2 RT + BVZ vs 3.3 BVZ (p=0.03)	Not reported
Adkison, 2011[182] (University of Wisconsin)	Retrospective	103 (Grade II-IV, 86 GBM)	PRDR	50 Gy in 25 fxn	5.1 (GBM)	27% autopsy patients with RN. Toxicity not reported.

Author (Institution)	Study Type	Number of patients	Modality	Dose Regimen	MS (months)	Toxicity post RT
Minniti, 2011[193] (Sant' Andrea Hospital, University Sapienza, Italy)	Retrospective	36	FSRT + TMZ	37.5 Gy in 15 fxn	9.7	Neurologic deterioration in 8%
Cuneo, 2012[147] (Duke University)	Retrospective	63 (49 GBM)	SRS +/- BVZ	18 Gy in 1 fxn or 25 Gy in 5 fxn	4 (no BVZ) vs 11 (+ BVZ)	Grade 3 toxicity in 11%, RN in 10%
Niyazi, 2012[179] (Ludwig-Maximilian University, Germany)	Retrospective	30 (AA and GBM)	FSRT +/- BVZ	36 Gy in 18 fxn	5.8 (no BVZ) vs. not reached (+ BVZ)	1 Grade 3 (DVT), 1 Grade 4 (wound dehiscence) complication, 2 patients with RN
Park, 2012[196] (University of Pittsburgh)	Case-control	11	SRS + BVZ	16 Gy	18	1 patient with Grade 3 toxicity, 1 with adverse radiation event
Cabrera, 2013[194] (Duke University)	Prospective (pilot)	15 (9 GBM)	SRS + BVZ	18 or 24 Gy in 1 fxn or 25 Gy in 5 fxn	13	1 patient with Grade 3 CNS toxicity, no Grade 4 or 5 toxicities
Minniti, 2013[150] (Sant' Andrea Hospital, University Sapienza, Italy)	Retrospective	54 (38 GBM)	SRS	30 Gy in 5 fxn	12.4	Grade 3 neurologic deterioration in 7%
Greenspoon, 2014[192] (McMaster University, Canada)	Prospective	31	SRS + TMZ	25-35 Gy in 5 fxn	9	3 patients with Grade 3 RN, 1 with Grade 4 RN

MS = median overall survival; BVZ = bevacizumab; fxn = fraction; SRS = stereotactic radiosurgery; HFSRT = hypofractionated stereotactic radiotherapy (10 fractions or less); FSRT = fractionated stereotactic radiotherapy (>10 fractions); PRDR = pulsed-reduced-dose-rate radiotherapy; BNCT = boron neutron capture therapy; AA = anaplastic astrocytoma; NS = nonsignificant; NS = not significant

Table 10. Representative planning target volumes (PTV) and dose fractionation regimens for re-irradiation of recurrent GBM

Technique	PTV	Dose Regimen	BED (Gy10)
Memorial Sloan Kettering[178]	CE T1 MRI volume + 5mm	6 Gy/day x 5 days	48
Duke[194]	CE T1 MRI volume + 1mm	<2cm*: 24 Gy once	81.6
		2-3cm: 18 Gy once	50.4
		3-5cm: 5 Gy/day x 5days	37.5

Thomas Jefferson[153]	CE T1 MRI volume only	3.5 Gy/day x 10 days	47.3
PRDR/Wisconsin[182]	CE T1 MRI volume + 20-25 mm	1.8-2 Gy/day x 28-25 days	59.5-60
RTOG 1205	CTV: CE T1 MRI volume + 0-5 mm PTV: At least 3 mm	3.5 Gy/day x 10 days	47.3

*Maximum PTV dimension

BED = biologically equivalent dose based on LQ model and an alpha/beta ratio of 10 Gy; CE = contrast-enhancing; CTV = clinical target volume; MRI = magnetic resonance imaging; PRDR = pulsed-reduced-dose-rate radiotherapy; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group

Appendix 1: American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence

Grading of Strength of Recommendations:

Strong Recommendation
Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

Weak Recommendation
Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

Grading of Strength of Evidence:

High Quality Evidence
Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.

Moderate-Quality Evidence
Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case– control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate.

Low Quality Evidence
Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Appendix 2: Literature Search Strategies

Guideline Topic:	Radiation Therapy for Glioblastoma

Key Question 1: When is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?

Population	Intervention	Comparison	Outcomes
Glioblastoma patients after initial biopsy/maximally safe resection. Pretreatment variables which could alter recommendations include patient characteristics such as age and performance status or tumor characteristics such as MGMT promoter methylation.	External beam radiation therapy (with or without systemic therapy).	No radiation therapy (with or without systemic therapy).	Primary endpoint: overall survival. Secondary endpoints: progression free survival, toxicity, quality of life (QOL).

Search Limits:

Age Range	19+ years of age
Language	Only in English
Publication Date	1966 / 01/ 01 - present

Pub Med Search Strategy:

Searches:

1. "glioblastoma"[MeSH] OR “glioblastoma” OR “malignant glioma” OR “high-grade glioma” OR “anaplastic glioma”
2. “radiotherapy” OR “radiation” OR “radiotherapy, conformal”[MeSH] OR “radiotherapy, intensity-modulated”[MeSH]
3. “systemic therapy” OR “chemotherapy” OR “chemoradiotherapy” OR “chemoradiation”
4. “angiogenesis inhibitors”[MeSH] OR “alkylating agents”[MeSH] OR “antineoplastic agents, alkylating”[MeSH] OR “radiosensitizers” OR “biological agents” OR “targeted agents”
5. #3 OR #4
6. #2 AND #5
7. #1 AND (#2 OR #6)

Rationale for Abstract Exclusion:

- **Pre-clinical data (i.e., non-human)**
- **Pediatric populations**
- **Low grade gliomas (e.g., grade I-II)**

Key Question 2: What is the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma and how might this vary based on pretreatment characteristics such as age or performance status?

Population	Intervention	Comparison	Outcomes
Glioblastoma patients after initial biopsy/maximally safe resection. Pretreatment variables which could alter recommendations include patient characteristics such as age and performance status or tumor characteristics such as MGMT promoter methylation.	External beam radiation therapy dose-fractionation schedules with higher biological equivalent dose. Techniques for dose escalation include conventionally fractionated external beam radiotherapy boost, hyperfractionation, stereotactic radiosurgery, and brachytherapy.	External beam radiation therapy dose-fractionation schedules with lower biological equivalent dose (e.g., conventionally fractionated schedules with a lower total dose, hypofractionated regimens).	Primary endpoint: overall survival. Secondary endpoints: progression free survival, toxicity, QOL.

Search Limits:

Age Range	19+ years of age
Language	Only in English
Publication Date	1966 / 01/ 01 - present

Pub Med Search Strategy:

Searches:

1. "glioblastoma"[MeSH] OR “glioblastoma” OR “malignant glioma” OR “high-grade glioma” OR “anaplastic glioma”
2. “radiotherapy” OR “radiation” OR “radiotherapy, conformal”[MeSH] OR “radiotherapy, intensity-modulated”[MeSH]
3. “Radiosurgery”[MeSH] OR “Brachytherapy”[MeSH]
4. “Dose fractionation” OR “Biological equivalent dose” OR “Hypofractionation” OR “Hyperfractionation”
5. “Aged”[MeSH] OR “elderly” OR “Quality of Life” OR “Karnofsky” OR “performance status” OR “Palliative” OR “Cytogenetics”[MeSH]
6. #2 OR #3
7. #1 AND #6

8. #4 OR #5
9. #7 AND #8

Rationale for Abstract Exclusion:

- **Pre-clinical data (i.e., non-human)**
- **Pediatric populations**
- **Low grade gliomas (e.g., grade I-II)**

Key Question 3: What are ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?

Population	Intervention	Comparison	Outcomes
Glioblastoma patients after initial biopsy/maximally safe resection.	External beam radiation therapy plans employing clinical target volume expansions smaller than those used in RTOG protocols (e.g., RTOG 0825).	External beam radiation therapy plans employing clinical target volume expansions used in RTOG protocols.	Primary endpoint: overall survival. Secondary endpoints: progression free survival, toxicity, QOL.

Search Limits:

Age Range	19+ years of age
Language	Only in English
Publication Date	1966 / 01/ 01 - present

Pub Med Search Strategy:

Searches:

1. "glioblastoma"[MeSH] OR “glioblastoma” OR “malignant glioma” OR “high-grade glioma” OR “anaplastic glioma”
2. “radiotherapy” OR “radiation” OR “radiotherapy, conformal”[MeSH] OR “radiotherapy, intensity-modulated”[MeSH]
3. “Target volume” OR “CTV” or “margin”
4. #1 AND #2 AND #3

Rationale for Abstract Exclusion:

- **Pre-clinical data (i.e., non-human)**
- **Pediatric populations**
- **Low grade gliomas (e.g., grade I-II)**

Key Question 4: What is the role of re-irradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

Population	Intervention	Comparison	Outcomes

Glioblastoma patients with recurrent disease, focal or multifocal.	Re-irradiation (e.g., stereotactic radiosurgery, hypofractionated external beam radiotherapy, with or without systemic therapy).	No re-irradiation (with or without systemic therapy).	Overall survival, progression free survival, toxicity, quality of life.

Search Limits:

Age Range	19+ years of age
Language	Only in English
Publication Date	1966 / 01/ 01 - present

Pub Med Search Strategy:

Searches:

1. "glioblastoma"[MeSH] OR "glioblastoma" OR "malignant glioma" OR "high-grade glioma" OR "anaplastic glioma"
2. "radiotherapy" OR "radiation" OR "radiotherapy, conformal"[MeSH] OR "radiotherapy, intensity-modulated"[MeSH] OR "radiosurgery" OR "gamma knife" OR "cyberknife" OR "tomotherapy"
3. "systemic therapy" OR "chemotherapy" OR "chemoradiotherapy" OR "chemoradiation"
4. "angiogenesis inhibitors"[MeSH] OR "alkylating agents"[MeSH] OR "antineoplastic agents, alkylating"[MeSH] OR "radiosensitizers" OR "biological agents" OR "targeted agents"
5. "reirradiation" OR "recurrent" OR "recurrence"[MeSH] OR "patterns of failure" or "retreatment"
6. #2 OR #3 OR #4
7. #1 AND #5 AND #6

Rationale for Abstract Exclusion:

- **Pre-clinical data (i.e., non-human)**
- **Pediatric populations**
- **Low grade gliomas (e.g., grade I-II)**