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Special Article

Radiation therapy for glioblastoma: Executive summary of an American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

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Dr Kirkpatrick receives research funding, honoraria, and travel expenses from Varian; is a partner in ClearSight Radiotherapy Products; and received previous research funding from Genentech. Dr Fiveash receives honoraria, travel expenses, and research funding from Varian. Dr Shig serves on an advisory board for Genentech and received previous honoraria and travel expenses from Merck. Dr Koay receives research funding from Phillips and has a pending patent on quantitative pancreatic image analysis. Dr Lutz had previous stock in Tosk and Oculus. Dr Vogelbaum is a consultant for NeuralStem and has stock options, royalties, and patent licensing and copyright fees from Infuseon. Dr Reardon serves on advisory boards for Roche/Genentech, EMD Serono, Novartis, Amgen, Abbvie, Bristol-Myers Squibb, Cavion, Celldex, Juno Pharmaceuticals, Momenta Pharmaceuticals, Novocure, Oxigene, Regeneron, and Stemline; served on a previous advisory board for Apogenix; is on speaker bureaus for Merck/Scherin and Roche/Genentech; and receives research funding from Celldex, Inovio, and Midatech. Dr Wen is on advisory boards for Roche/Genentech, Novartis, Regeneron, Monteris, and Cavion; is a speaker for Merck; is steering committee chair for Vascular Biogenics trial; and was previously on advisory boards for Abbvie, Cubist, Foundation Medicine, Merck, and Midatech. Dr Chang receives honoraria from Abbvie BrainLab, and Elekta.

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Abstract

Purpose: To present evidence-based guidelines for radiation therapy in treating glioblastoma not arising from the brainstem.

Methods and materials: The American Society for Radiation Oncology (ASTRO) convened the Glioblastoma Guideline Panel to perform a systematic literature review investigating the following: (1) Is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects? (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? (3) What are ideal target volumes for curative-intent external beam radiation therapy of glioblastoma? (4) What is the role of reirradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy? Guideline recommendations were created using predefined consensus-building methodology supported by ASTRO-approved tools for grading evidence quality and recommendation strength.

Results: Following biopsy or resection, glioblastoma patients with reasonable performance status up to 70 years of age should receive conventionally fractionated radiation therapy (eg, 60 Gy in 2-Gy fractions) with concurrent and adjuvant temozolomide. Routine addition of bevacizumab to this regimen is not recommended. Elderly patients ($\geq$70 years of age) with reasonable performance status should receive hypofractionated radiation therapy (eg, 40 Gy in 2.66-Gy fractions); preliminary evidence may support adding concurrent and adjuvant temozolomide to this regimen. Partial brain irradiation is the standard paradigm for radiation delivery. A variety of acceptable strategies exist for target volume definition, generally involving 2 phases (primary and boost volumes) or 1 phase (single volume). For recurrent glioblastoma, focal reirradiation can be considered in younger patients with good performance status.

Conclusions: Radiation therapy occupies an integral role in treating glioblastoma. Whether and how radiation therapy should be applied depends on characteristics specific to tumor and patient, including age and performance status.

Introduction

Radiation therapy (RT) occupies an integral role in treating glioblastoma (GBM), given its proclivity for local recurrence. This clinical practice guideline systematically reviews the evidence for RT and the ways systemic therapies modify its effects. It also reviews the data for ideal dose-fractionation and target volume design. Recommendations account for tumor-specific and patient-specific factors. Attention is also paid to reirradiation for recurrent GBM. This guideline is endorsed by the European Society for Radiotherapy & Oncology and the Society for Neuro-Oncology.

Methods and materials

Process and literature review

See full-text version for details of panel selection and review (available as supplementary material online only at www.practicalradonc.org).

A systematic literature review was performed in early 2014. A PubMed search identified studies published between January 1966 and February 2014. Population included adults ($\geq$18 years) with biopsy-proven GBM treated with RT. Outcomes included overall and progression-free survival, recurrence rates, toxicity, and quality of life (QOL). Overall, 3059 abstracts were retrieved. Exclusion criteria included: preclinical or nonhuman studies, case reports/series, non-English language, abstract only, absence of reported clinical outcomes, and poor relevance to key clinical questions. Ultimately, 157 full-text articles were abstracted.

Grading of evidence, recommendations, and consensus methodology

When available, high-quality evidence formed the basis of guideline statements in accordance with Institute of Medicine standards. Consensus was evaluated through a modified Delphi approach. Panelists independently rated agreement with recommendations on a 5-point Likert scale and a prespecified threshold of $\geq$75% indicated when consensus was achieved.

Recommendation strength and evidence quality were rated using the *American College of Physicians Process for Assigning Strength of Recommendation and Grading of Quality of Evidence* (Appendix E1).[1] Table 1 shows the 5 key questions (KQs) and guideline statements.

Results

KQ1: When is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?

KQ1A. Benefits of adjuvant radiation therapy

Randomized controlled trials (RCTs) established the efficacy of RT following biopsy or resection over chemotherapy alone or best supportive care.[2–5] Brain Tumor Cooperative Group 6901 randomized 303 anaplastic glioma patients to whole brain radiation therapy (WBRT), WBRT with carmustine, carmustine alone, or best supportive care.[2] Patients in the radiation arms had improved survival compared with best supportive care or carmustine alone. Multiple RCTs demonstrated this survival benefit.[3,5,6] A Canadian meta-analysis pooling 6 randomized trials confirmed a significant survival benefit from postoperative RT compared with no RT (risk ratio confidence interval, 0.74-0.88).[7]

Many of these studies used older radiation techniques and included grade III gliomas in addition to GBM. A modern RCT that used magnetic resonance imaging (MRI) to create focal radiation plans for 81 elderly GBM patients (≥70 years of age) confirmed the survival benefit of conformal RT versus best supportive care.[8] This trial demonstrated no severe radiation-related toxicity, and no adverse effects on QOL or cognition.

KQ1B. Benefits of concurrent and adjuvant temozolomide

The European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted EORTC/NCIC 26981–22981, a phase 3 trial that randomized 573 patients (18–70 years old, World Health Organization performance status [PS] 0–2) to partial brain RT (60 Gy) versus RT with concomitant and adjuvant temozolomide (TMZ). TMZ increased median survival from 12.1 to 14.6 months, and improved 5-year survival from 1.9% to 9.8% ($P < .0001$).[9] The investigators detected more grade 3-4 hematologic toxicity with TMZ (7% vs 0%), but no impact on QOL.[10]

Three other RCTs interrogated adding TMZ to radiation, with 2 demonstrating a significant survival advantage.[11,12] The third did not, but was stopped early and severely underpowered.[13] A meta-analysis confirmed adding concomitant and adjuvant TMZ to RT improves survival following biopsy or resection in initial treatment of GBM.[14]

KQ1C. Adding bevacizumab to standard therapy

Two large phase 3 trials, Radiation Therapy Oncology Group (RTOG) 0825 and AVAglio failed to show improved overall survival with addition of bevacizumab to standard chemoradiation with TMZ.[15,16] Both trials suggested prolonged progression-free survival with bevacizumab, although a prespecified level of significance was not met in RTOG 0825.[16] Patients on RTOG 0825 receiving bevacizumab experienced worse QOL, more symptoms, and more frequent neurocognitive decline.[16] In contrast, patients receiving bevacizumab on AVAglio demonstrated longer maintenance of baseline QOL and PS, and lower glucocorticoid requirements. Concordant with RTOG 0825, bevacizumab patients on AVAglio experienced more grade 3+ toxicities.[11]

KQ1D. Other systemic therapies

Addition of other systemic agents has not been proven to improve survival over standard chemoradiation.

Biomarkers of response

Silencing of O-6-methylguanine-DNA methyltransferase (MGMT) by promoter methylation has been associated with improved survival.[17] In EORTC/NCIC 26981–22981, MGMT methylation status was prognostic, though not necessarily predictive.[9] Adding TMZ to radiation improved survival regardless of MGMT methylation, but survival differences were more pronounced among those with methylated promoters.

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?

KQ2A. Dose-fractionation for patients under age 70 with good performance status

Prospective studies have demonstrated improved survival with dose escalation at standard fractionation (1.8-2 Gy daily) up to 60 Gy.[4,18] A pooled analysis of 3 Brain Tumor Study Group protocols in which patients received WBRT doses from 0 to 60 Gy showed that survival correlated with dose.[4] Randomizing high-grade glioma patients (18–70 years old) to 45 Gy in 20 fractions versus 60 Gy in 30 fractions, the Medical Research Council showed that 60 Gy improved survival.[18]

Studies interrogating dose escalation beyond 60 Gy using standard fractionation have not demonstrated any survival benefit. One RTOG/ECOG RCT, for example, found no survival difference between 60 Gy (WBRT) and 70 Gy using a partial brain boost volume.[19]

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 radiation therapy improves overall survival compared with chemotherapy or best supportive care alone following biopsy or resection of newly diagnosed glioblastoma (HQE). Whether radiation therapy 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 radiation therapy improves overall survival and progression free survival compared to fractionated radiation therapy alone, with a reasonably low incidence of early adverse events and without impairing quality of life (HQE). The guideline panel endorses fractionated radiation therapy 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 [a]	Strong
C. Adding bevacizumab to standard therapy for newly diagnosed glioblastoma (ie, fractionated radiation therapy 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 [b]	Strong
D. The addition of other systemic therapies to conventional radiation therapy with or without temozolomide remains investigational.	100 [a]	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 younger than age 70 with good performance status (KPS $\geq$60), the optimal dose-fractionation schedule for external beam radiation therapy following resection or biopsy is 60 Gy in 2-Gy fractions delivered over 6 weeks (HQE). Numerous other dose schedules have been explored without definitive benefit. Care should be taken to keep dose to critical structures (eg, brainstem, optic chiasm/nerves) within acceptable limits.	93	Strong
B. Older age and poor performance status are associated with shorter survival in GBM patients (MQE). Prognostic considerations should help guide treatment recommendations for individual patients.	100	Strong
C. Among elderly patients ($\geq$ 70 years of age) with fair-good performance status (KPS $\geq$ 50), the panel recommends external beam radiation therapy following biopsy or resection because radiation therapy (compared with 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).	100 [a]	Strong
D. Among elderly patients, there is no evidence that conventionally fractionated radiation therapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiation therapy (eg, 40 Gy in 15 fractions over 3 weeks) (HQE). Compared with conventionally fractionated radiation therapy, hypofractionated radiation therapy has been associated with superior survival and less corticosteroid requirement (MQE).	100	Strong
E. Given the absence of proven superiority for conventionally fractionated radiation therapy, the panel recommends hypofractionated radiation therapy 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 radiation therapy, particularly with respect to hematologic toxicity, nausea, and vomiting (MQE).	100 [a]	Strong
F. Among elderly patients with good performance status, adding concurrent and adjuvant temozolomide to hypofractionated radiation therapy appears to be safe and efficacious without impairing quality of life (LQE). In such patients, the panel	100 [a]	Strong

(Continued)

Table 1 (*continued*)

Guideline statement	Percent agreement with guideline statement	Strength of recommendation
recommends consideration of concurrent and adjuvant temozolomide. The combination of hypofractionated radiation therapy and temozolomide may be particularly efficacious in those with a methylated MGMT promoter (LQE).		
G. Reasonable options for patients with poor performance status include hypofractionated radiation therapy alone, temozolomide alone, or best supportive care (LQE).	100 [a]	Strong
KQ3. What are the ideal target volumes for curative-intent external beam radiation therapy 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 progression (MQE). Acceptable strategies include but are not limited to the following:	93	Strong
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 reirradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?		
In younger patients with good performance status, focal reirradiation (eg, stereotactic radiosurgery, hypofractionated stereotactic radiation therapy, brachytherapy) for recurrent glioblastoma may improve outcomes compared with supportive care or systemic therapy alone (LQE). Tumor size and location should be taken into account when deciding whether reirradiation would be safe (LQE).	93	Weak

HQE, high-quality evidence; KPS, Karnofsky performance status; LQE, low-quality evidence; MQE, moderate-quality evidence.
[a] Patrick Wen, Helen Shih, and David Reardon were recused from consensus voting on this recommendation.
[b] Patrick Wen, Helen Shih, David Reardon, and John Kirkpatrick were recused from consensus voting on this recommendation.

Other attempts at dose intensification have involved hyperfractionation, accelerated fractionation, hypofractionation, hypofractionated boost, and/or stereotactic radiosurgery (SRS) boost. None of these approaches has demonstrated convincing benefit in the general GBM population (< 70 years old with good PS). One RCT found no difference between conventional fractionation (59.4 Gy) and accelerated, dose-escalated hyperfractionation (1.6 Gy twice daily to 70.4 Gy).[20] RTOG 9305, a phase 3 RCT, found no survival benefit from adding SRS boost (15–24 Gy × 1) to conventionally fractionated 60 Gy.[21]

Dose intensification may come with a cost. The Quantitative Analysis of Normal Tissue Effects in the Clinic paper modeling radiation dose-volume effects found that, for conventionally fractionated partial brain RT, a 5% and 10% risk of symptomatic radionecrosis is predicted at doses of 72 Gy and 90 Gy, respectively.[22] Most hypofractionation studies demonstrate acceptable tolerance, but a few small series using particularly high doses (eg, 5-6 Gy per fraction to 50-60 Gy) suggest increased toxicity.[23,24]

See Table 5 in the supplementary material for a more comprehensive review.

KQ2B-G. Management options for elderly patients and patients with poor performance status

Therapeutic decisions depend in part on prognosis, and the most important patient factors influencing survival are age and PS.[25] Analyses of prospective data have strongly associated older age and/or poor PS with shorter survival. Population-based studies demonstrate median survival of approximately 4 to 5 months for patients older than 65, and a similar life expectancy for poor PS (KQ2B).[25]

Although EORTC/NCIC 26981–22981 established 6 weeks of RT plus TMZ as standard of care for patients

younger than age 70 with good PS, patients older than 70 and those with poor PS were excluded from the study. Fortunately, a French RCT randomized patients 70 or older with a Karnofsky Performance Scale (KPS) score >60 to RT (50.4 Gy in 28 fractions) versus supportive care. RT increased median survival from 16.9 to 29.1 weeks without worsening QOL or cognition (KQ2C).[8]

The French study established the efficacy of RT in elderly patients with good PS,[8] but optimal dose-fractionation remained unclear. Two phase 3 RCTs compared conventionally fractionated RT (60 Gy in 30 fractions over 6 weeks) to hypofractionation (KQ2D).[26,27] A Canadian trial randomized patients ≥60 years old with KPS ≥50 to conventionally fractionated RT versus 40 Gy in 15 fractions. Results showed no difference in median survival (5.1 and 5.6 months, respectively), but patients receiving conventionally fractionation required more corticosteroids.[26] The Nordic trial randomized 342 patients aged ≥60 with World Health Organization PS 0–2 to conventionally fractionated RT versus 34 Gy in 10 fractions versus TMZ alone. This study showed no significant survival difference between the radiation groups as a whole or among patients aged 60 to 70, but in patients older than 70, hypofractionated RT resulted in better survival (hazard ratio 0.59, $P < .02$).[27]

Two RCTs evaluated TMZ monotherapy as an alternative to RT in elderly GBM patients (KQ2E). The Nordic trial demonstrated improved survival with TMZ compared with conventionally fractionated RT, but no difference between TMZ and hypofractionated RT.[27] NOA-08, a phase 3 noninferiority trial, randomized patients >65 years old (KPS >50) to TMZ versus conventionally fractionated RT. The investigators concluded TMZ was not inferior to conventionally fractionated RT.[28] Both RCTs demonstrated more adverse events with TMZ than RT, particularly with respect to nausea/vomiting and hematologic toxicities.

In both Nordic and NOA-08, on subgroup analysis, MGMT promoter methylation was associated with improved survival among patients receiving TMZ, but not among those receiving RT. In NOA-08, event-free survival was actually worse among patients with unmethylated MGMT promoters who received TMZ compared with RT. A nonrandomized ANOCEF phase 2 trial evaluated TMZ alone in patients aged ≥70 with poor PS (KPS <70), and associated TMZ with improved functional status in 33% (KQ2G).[25,29]

No RCTs have interrogated the efficacy of conventionally fractionated chemoradiation with TMZ in patients older than age 70. Nonrandomized data in this population suggest hypofractionated RT with TMZ is safe and efficacious (KQ2F). For example, a phase 2 multicenter trial combined 40 Gy in 15 fractions with concurrent and adjuvant TMZ in patients ≥70 years old and with KPS >50. Median survival was 12.4 months and QOL stable-improved. MGMT methylation status was the strongest prognostic factor.[30,31]

High-quality studies assessing RT in patients with poor PS are lacking. The poor prognosis of this patient group, combined with practical considerations, merits strong consideration of hypofractionated RT, TMZ monotherapy, or best supportive care alone (KQ2G).

KQ3: What are the ideal target volumes for curative-intent external beam radiation therapy of glioblastoma?

KQ3A. Rationale for partial brain irradiation

GBM is infiltrative. This understanding derives in part from the failure of extensive resection to control it.[32] Radiation, when initially applied, was delivered to the whole brain. Over the past several decades, practice evolved toward partial brain irradiation (PBI), treating only areas at highest risk. Patterns of failure studies demonstrated that approximately 80% to 90% of patients recur within 2 cm of the primary site.[33,34] Prospective RCTs also support the efficacy of PBI. Brain Tumor Cooperative Group 8001, which randomized patients to WBRT to 60.2 Gy versus WBRT to 40.3 Gy plus 17.2 Gy partial brain boost, showed coning down did not affect survival.[35] One small RCT found no survival difference between WBRT and PBI, but better PS following PBI.[36]

KQ3B. Target volume design

Variation in target volume design exists. North American cooperative groups generally treat patients in 2 phases, with an initial phase directed at edema (T2/fluid-attenuated inversion recovery [FLAIR] hyperintense), resection cavity and gross residual tumor (T1-enhancing) followed by a boost directed only at resection cavity and gross tumor. T2 hyperintense regions are targeted because T2 hyperintensity sometimes reflects infiltrative tumor.[37] Some institutions, however, use a 2-phase paradigm targeting resection cavity and gross tumor alone *without* specifically targeting edema, citing similar patterns of failure with this approach.[38] The EORTC has adopted a single-phase approach, targeting 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 margin size, with the American Brain Tumor Consortium using the smallest volumes. Table 8 in the supplementary material summarizes the cooperative group margins used in contemporary clinical trials.

The most relevant data for defining targets relate to patterns of failure in patients who received concurrent TMZ with radiation plans designed using contemporary, MRI-based planning. These studies comprise secondary analyses of prospective cooperative group trials and single

institution retrospective studies. Nearly all demonstrate that ≥80% to 90% of recurrences have a component of failure within the high-dose volume (see Table 7 in the supplementary material). Central failure predominates regardless of target volume design.[39] Several institutions in the American Brain Tumor Consortium have published retrospective studies evaluating smaller clinical target volume margins, which suggest margins as low as 5 mm may not increase the risk of marginal recurrence; most of these plans incorporated additional planning target volume margin (3–5 mm).[40]

KQ3C. Potential significance of smaller target volumes

Reducing target volumes may decrease radiation to normal brain, but the clinical significance of this has not been well-studied.[38] EORTC 22844 randomized patients with low-grade gliomas to 45 Gy versus 59.4 Gy and found that higher radiation doses resulted in lower levels of functioning.[41] A phase 2 trial of hippocampal-sparing, intensity modulated WBRT for brain metastases demonstrated less memory decline compared with historical controls receiving conventional WBRT.[42] Given the absence of data for hippocampal sparing in GBM patients, the Panel does not recommend compromising target coverage for hippocampus protection.

KQ4: What is the role of reirradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

Prognostic factors in recurrent GBM

See the supplementary material for discussion of treatment response assessment.

When tumor recurs, options include supportive care, reoperation, reirradiation, systemic therapies, and combined-modality therapy. The appropriate strategy depends in part on prognosis. The most consistently demonstrated prognostic factor is favorable PS (KPS ≥70), which correlates with improved survival following salvage.[43] Younger age is the second most frequently reported positive prognostic factor.[43] Factors less strongly correlated with improved survival include smaller tumor size, non-eloquent location, longer interval from initial therapy to recurrence, and lack of steroid dependence.

Focal reirradiation

Stereotactic radiosurgery and hypofractionated stereotactic RT. Because most recurrences occur within previously irradiated brain, reirradiation with wide margins could confer high toxicity risks. Thus, limited volume reirradiation using SRS or short-course hypofractionated stereotactic RT (HFSRT) is often used. RTOG 90–05, a phase 1 study, demonstrated SRS could be performed with acceptable morbidity.[44]

SRS and HFSRT appear to provide promising outcomes compared with chemotherapy, with median survival from reirradiation typically 8 to 12 months (see Table 9 in the supplementary material). Relevant studies were nearly all retrospective, however, and selection bias a serious concern, because recurrent tumor is generally amenable to SRS or HFSRT only when small and discrete. Diffuse recurrences were not represented in these series and may be associated with worse survival.

Salvage reirradiation can result in radionecrosis. Several early SRS studies reported high rates of late complications requiring re-operation (20%-40%). Compared with SRS, HFSRT may offer lower risk, though no randomized comparisons are available.

Brachytherapy. Brachytherapy has also been evaluated for recurrent GBM. Table 9 in the supplementary material details relevant studies. Retrospective series have demonstrated median survivals from 8 to 15 months, and radionecrosis remains a risk. Available evidence is uncontrolled, and selection bias limits interpretation.

RT dose and target volume. Various dose fractionation regimens and target volumes are used for recurrent GBM. Table 10 in the supplementary material describes representative techniques, but not enough data exist for the panel to endorse any specific approach.

Reirradiation with systemic therapy. Several studies have investigated adding bevacizumab to salvage SRS or HFSRT (see Table 9). Two prospective, nonrandomized studies reported no radionecrosis, but 3 of 25 in 1 study and 1 of 15 in the other developed grade 3 toxicities. Median survivals post-SRS were 12.5 and 14.4 months, respectively.[45,46] Retrospective studies have reported radionecrosis rates of 5% to 9% and median survivals of 7 to 18 months. These studies were nonrandomized. Selection bias is a concern.

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ultimate judgment regarding any specific therapy in light of all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials.

This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

Supplementary material

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.prro.2016.03.007.

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