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ASCO SPECIAL ARTICLE

Radiation Therapy for Glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline

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E.P.S and S.M.C. are co-chairs.

Clinical Practice Guideline Committee Approved: September 22, 2016.

Editor's note: This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/glioblastoma-radiotherapy-endorsement and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose
The American Society for Radiation Oncology (ASTRO) produced an evidence-based guideline on radiation therapy for glioblastoma. Because of its relevance to the ASCO membership, ASCO reviewed the guideline and applied a set of procedures and policies used to critically examine guidelines developed by other organizations.

Methods
The ASTRO guideline on radiation therapy for glioblastoma was reviewed for developmental rigor by methodologists. An ASCO endorsement panel updated the literature search and reviewed the content and recommendations.

Results
The ASCO endorsement panel determined that the recommendations from the ASTRO guideline, published in 2016, are clear, thorough, and based on current scientific evidence. ASCO endorsed the ASTRO guideline on radiation therapy for glioblastoma and added qualifying statements.

Recommendations
Partial-brain fractionated radiotherapy with concurrent and adjuvant temozolomide is the standard of care after biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age. Hypofractionated radiotherapy for elderly patients with fair to good performance status is appropriate. The addition of concurrent and adjuvant temozolomide to hypofractionated radiotherapy seems to be safe and efficacious without impairing quality of life for elderly patients with good performance status. Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care. Focal reirradiation represents an option for select patients with recurrent glioblastoma, although this is not supported by prospective randomized evidence. Additional information is available at www.asco.org/glioblastoma-radiotherapy-endorsement and www.asco.org/guidelineswiki.

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INTRODUCTION

In all of oncology, the treatment of patients with glioblastoma continues to be one of the greatest challenges. Although a rare tumor with an average annual incidence in the United States of approximately 11,000, glioblastoma is the most common primary brain malignancy in adults and one of the most lethal.[1] Because of its infiltrative nature, surgical resection alone leads to median survivals of only 3 to 6 months.[2-4] Since the 1960s, this duration of survival improved significantly with the addition of adjuvant radiation, which has been extensively reported in trials from the Brain Tumor Study Group (later called the Brain Tumor Cooperative Group).[5-7] In the modern era, radiation alone leads to median survivals of approximately 1 year, and the addition of the oral alkylating agent temozolomide to radiation extends survival to 14 to 16 months.[8-10]

Approaches to radiation therapy have evolved substantially over the decades since its early use for treatment of glioblastoma. Initially used to treat the whole brain,[11,12] radiation volumes have decreased, and inverse planning and dose modulation with intensity-modulated radiation therapy have allowed for more-precise targeting and

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Radiation Therapy for Glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline

Guideline Questions

1. When 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 on the basis of pretreatment characteristics such as age or performance status?
3. What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?
4. What is the role of reirradiation among patients with glioblastoma whose disease recurs after completion of standard first-line therapy?

Target Population

Patients with glioblastoma.

Target Audience

Primary care providers, radiation oncologists, neuro-oncologists, medical oncologists, neurosurgeons, and other providers.

Methods

An ASCO expert panel was convened to consider an endorsement of the American Society for Radiation Oncology (ASTRO) guideline on radiation therapy for glioblastoma recommendations, which were based on a systematic review of the medical literature. The ASCO panel considered the methodology used in the ASTRO guideline by reviewing the results through the Appraisal of Guidelines for Research and Evaluation II instrument. The ASCO panel carefully reviewed the ASTRO guideline content to determine appropriateness for ASCO endorsement.

ASCO Key Recommendations for Radiation Therapy for Glioblastoma

Additional ASCO panel statements are presented in boldface.

- Fractionated radiotherapy improves overall survival compared with chemotherapy or best supportive care alone after biopsy or resection of newly diagnosed glioblastoma (high-quality evidence [HQE]). Whether radiotherapy is indicated in a particular individual may depend on patient characteristics, such as performance status (see key question [KQ] 2; Strong recommendation).
- **Radiation should be initiated as soon as it is safely permissible. Clinical trials have typically initiated treatment 3 to 6 weeks after surgery.**
- The addition of concurrent and adjuvant temozolomide to fractionated radiotherapy improves overall survival and progression-free survival compared with 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 after biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age (see KQ2 for recommendations about patients older than 70 years; Strong recommendation).
- The addition of bevacizumab to standard therapy for newly diagnosed glioblastoma (ie, 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 (moderate-quality evidence [MQE]). The panel does not recommend the routine addition of bevacizumab to standard therapy for newly diagnosed glioblastoma outside a clinical trial (Strong recommendation).
- **The impact of bevacizumab to standard therapy on health-related quality of life requires further validation.**
- The addition of other systemic therapies to conventional radiotherapy with or without temozolomide remains investigational (Strong recommendation).

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THE BOTTOM LINE (CONTINUED)

- For patients younger than 70 years of age with good performance status (Karnofsky performance score ≥ 60), the optimal dose fractionation schedule for external beam radiation therapy after 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 (Strong recommendation).
- Older age and poor performance status are associated with shorter survival in patients with glioblastoma (MQE). Prognostic considerations should help to guide treatment recommendations for individual patients (Strong recommendation).
- Among elderly patients (≥ 70 years old) with fair to good performance status (Karnofsky performance score ≥ 50), the panel recommends external beam radiation therapy after biopsy or resection because radiotherapy (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 (low-quality evidence [LQE]; see KQ2F; Strong recommendation).
- Among elderly patients, no evidence shows that conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiotherapy (eg, 40 Gy in 15 fractions over 3 weeks; HQE). Compared with conventionally fractionated radiotherapy, hypofractionated radiotherapy has been associated with superior survival and less corticosteroid requirement (MQE; Strong recommendation).
- **The optimal dose fractionation schedule has not yet been determined for elderly patients, although recent randomized trials have suggested that shorter regimens may be equivalent to longer-duration treatment.**
- Given the absence of proven superiority for conventionally fractionated radiotherapy, the panel recommends hypofractionated radiotherapy for elderly patients with fair to good performance status (HQE). Temozolomide monotherapy is an efficacious alternative for elderly patients with O6-methylguanine DNA methyltransferase gene (*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).
- Among elderly patients with good performance status, the addition of concurrent and adjuvant temozolomide to hypofractionated radiotherapy seems 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).
- Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (LQE; Strong recommendation).
- Although glioblastoma is believed 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).
- 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):
  - Two phase: (1) Primary target volume encompasses edema (hyperintense region on T2 or fluid-attenuated inversion recovery on magnetic resonance imaging) and gross residual tumor/resection cavity, and (2) boost target volume encompasses gross residual tumor/resection cavity. A range of acceptable clinical target volume margins exists.
  - One phase: Single target volume includes gross residual tumor/resection cavity with wide margins, without specifically targeting edema.
- Reduction of target volumes allows less radiation to be delivered to radiographically normal brain. Delivery of less radiation to normal brain should result in less late toxicity (LQE), but this remains to be validated (Weak recommendation).

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THE BOTTOM LINE (CONTINUED)

- In younger patients with good performance status, focal reirradiation (eg, stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, 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; Weak recommendation).
- **No prospective evidence supports reirradiation in any patient subgroup.**

Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/glioblastoma-radiotherapy-endorsement and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

A link to the ASTRO guideline on radiation therapy for glioblastoma can be found at www.astro.org.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

sparing of critical and normal structures in the brain.[13] Image guidance during radiation delivery has further refined treatment,[14] and additional improvements are being explored with particle therapies, such as protons and carbon ion.[15-17]

In addition to the modality of radiation delivery, alterations in the dose have been explored. Initial studies identified the optimal dose that could be safely delivered with maximum benefit.[7,18,19] These questions, although explored decades ago, have been examined more recently in the context of modern radiation delivery techniques.[20] Particularly in elderly or poor performance status populations, hypofractionation has been used extensively.[21-25]

The American Society of Radiation Oncology (ASTRO) assembled a group of experts to develop guidelines for radiation treatment of patients with glioblastoma. In recognition of the complex challenge and effort undertaken by ASTRO, this ASCO guideline reviews and endorses the ASTRO guidelines and adds clarifying statements to aid in the treatment of patients with glioblastoma.

METHODS

Overview of the ASCO Guideline Endorsement Process

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodological quality by using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II instrument (Methodology Supplement).

Guideline Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, with regard to the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property that arises out of or is related to any use of this information or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy"; found at www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speakers bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the panel did not disclose any relationships that constitute a conflict under the Policy.

Clinical Questions and Target Population

The ASTRO guideline addressed four main questions. These questions were as follows: (1) When 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 on the basis of pretreatment characteristics such as age or performance status? (3) What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma? (4) What is the role of reirradiation among patients with glioblastoma whose disease recurs after completion of standard first-line therapy? The complete set of clinical questions and corresponding recommendations are listed in Table 1. The target population for the ASTRO guideline is patients with glioblastoma.

Summary of the ASTRO Guideline on Radiation Therapy for Glioblastoma Guideline Development Methodology

The ASTRO guideline was developed by an author expert panel and a scientific advisory panel that included experts in radiation oncology and neuro-oncology. The literature search of Medline PubMed spanned January 1966 to February 2014. The search included all levels of evidence (randomized controlled trials [RCTs] as well as observational studies) as long as they appeared in peer-reviewed publications. Details of the search strategies and the study inclusion criteria and outcomes of interest are available at www.astro.org/Clinical-Practice-Statements.aspx.

The searches identified 157 studies for inclusion in the guideline's qualitative synthesis of the literature. The ASTRO guideline panel reviewed data from RCTs as well as from observational studies.

RESULTS

Results of the ASCO Methodology Review

The methodology review of the ASTRO guideline was completed independently by two ASCO guideline staff members who used the Rigour of Development subscale from the Appraisal of Guidelines for Research and Evaluation II instrument. Detailed results of the scoring for this guideline are available upon request to guidelines@asco.org. Overall, the ASTRO guideline on radiation therapy for glioblastoma scored 98%. The preliminary ASCO content reviewers of the ASTRO guideline on radiation therapy for glioblastoma, as well as the ASCO expert panel (Appendix Table A1, online only), found the recommendations well supported in the original guideline. Each section, including an introduction, methods, results, and recommendations, was clear and well referenced from the systematic review.

This is the most recent information as of the publication date. For updates, the most recent information, and to submit new evidence, visit www.asco.org/glioblastoma-radiotherapy-endorsement and www.asco.org/guidelineswiki.

Methods and Results of the ASCO Updated Literature Review

ASCO guidelines staff updated the ASTRO guideline on radiation therapy for glioblastoma literature search. Medline was searched from February 2014 to June 2016. The search was restricted to articles published in English and to systematic reviews, meta-analyses, and RCTs. The updated search was guided by the signals approach that identifies only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO expert panel members to identify potential signals. The Methodology Supplement provides additional information about the signals approach.

The updated search yielded 96 records of which only four studies were considered relevant to this guideline.[25-28] A review of these results revealed no new evidence that would warrant substantive modification of the ASTRO guideline on radiation therapy for glioblastoma practice recommendations. Of note, one of the phase III trials reported in the ASTRO guideline as being in abstract form has now been published.[26]

Results of the ASCO Content Review

The ASCO expert panel reviewed the ASTRO guideline on radiation therapy for glioblastoma and concurs that the recommendations are clear, thorough, and based on the most relevant scientific evidence in this content area and presents options that will be acceptable to patients. Overall, the ASCO expert panel agrees with the recommendations as stated in the guideline, with some panel statements discussed next.

ENDORSEMENT RECOMMENDATION

ASCO endorses the ASTRO guideline on radiation therapy for glioblastoma, with minor ASCO expert panel statements.

Benefits of Adjuvant Radiotherapy

Overall consensus was reached that fractionated radiotherapy improves overall survival compared with chemotherapy or best supportive care alone after biopsy or resection of newly diagnosed glioblastoma, and patient characteristics (eg, performance status) may determine whether radiotherapy is indicated in a particular individual. In addition, radiotherapy should be initiated as soon as it is safely permissible. Clinical trials have typically initiated treatment 3 to 6 weeks after surgery.

Addition of Bevacizumab to Standard Therapy

In two large randomized phase III trials that evaluated the impact of adding bevacizumab to standard therapy, the impact on health-related quality of life (HRQOL)[29-31] was evaluated, and in one of the studies, the impact on neurocognitive function and symptom burden was also assessed.[29] Over time, an increased symptom burden and a decline in neurocognitive function were more frequent with bevacizumab than with placebo.[29] The impact on HRQOL was mixed, with the RTOG 0825 study reporting declines in HRQOL over time in the specific domains of cognitive functioning, motor dysfunction, and communication,[29] whereas the Avastin in Glioblastoma (AVAglio) trials reported no between-arm differences in HRQOL on the basis of time to deterioration or changes over time in any domain but did note that in both arms, HRQOL declined at progression.[30,31] Because the patients who received bevacizumab had longer progression-free survival in this study, the median duration of stable or improved HRQOL was consistently longer in the bevacizumab arm than in the placebo arm.[30]

Despite the similarities between RTOG 0825[29] and the AVAglio trials,[30,31] numerous differences in study design, outcome measures, and statistical analyses make comparisons difficult. Most notably for the RTOG 0825 study, not all patients participated in the study, and no difference in characteristics between those who participated and those who did not were apparent. For the AVAglio study, participation was mandatory, but the completion rate was

Table 1. Original ASTRO Research Questions, Recommendations, and ASCO Expert Panel Statements

ASTRO Key Question	ASTRO Recommendation	ASCO Expert Panel Statement
KQ1: When is radiation therapy indicated after biopsy/resection of glioblastoma, and how does systemic therapy modify its effects?	Fractionated radiotherapy improves overall survival compared with chemotherapy or best supportive care alone after 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).	Radiation should be initiated as soon as it is safely permissible. Clinical trials have typically initiated treatment 3-6 weeks after surgery.
	The addition of concurrent and adjuvant temozolomide to fractionated radiotherapy improves overall survival and progression-free survival compared with 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 after biopsy or resection of newly diagnosed glioblastoma in patients up to 70 years of age (see KQ2 for recommendations about patients older than 70 years; Strong recommendation).	None
	The addition of bevacizumab to standard therapy for newly diagnosed glioblastoma (ie, 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 a clinical trial (Strong recommendation).	The impact of bevacizumab to standard therapy on health-related quality of life requires further validation.
	The addition of other systemic therapies to conventional radiotherapy with or without temozolomide remains investigational (Strong recommendation).	None
KQ2: What is the optimal dose fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma, and how might treatment vary on the basis of pretreatment characteristics such as age or performance status?	For patients younger than 70 years of age with good performance status (KPS $\geq$ 60), the optimal dose fractionation schedule for external beam radiation therapy after 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 (Strong recommendation).	None
	Older age and poor performance status are associated with shorter survival in patients with glioblastoma (MQE). Prognostic considerations should help to guide treatment recommendations for individual patients (Strong recommendation).	None
	Among elderly patients ($\geq$ 70 years old) with fair to good performance status (KPS $\geq$ 50), the panel recommends external beam radiation therapy after biopsy or resection because radiotherapy (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; Strong recommendation).	None
	Among elderly patients, no evidence shows that conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) is more efficacious than hypofractionated radiotherapy (eg, 40 Gy in 15 fractions over 3 weeks; HQE). Compared with conventionally fractionated radiotherapy, hypofractionated radiotherapy has been associated with superior survival and less corticosteroid requirement (MQE; Strong recommendation).	The optimal dose fractionation schedule has not been determined, although recent randomized trials have suggested that shorter regimens may be equivalent to longer-duration treatment.
	Given the absence of proven superiority for conventionally fractionated radiotherapy, the panel recommends hypofractionated radiotherapy for elderly patients with fair to 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).	

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Table 1. Original ASTRO Research Questions, Recommendations, and ASCO Expert Panel Statements (continued)

ASTRO Key Question	ASTRO Recommendation	ASCO Expert Panel Statement
	Among elderly patients with good performance status, the addition of concurrent and adjuvant temozolomide to hypofractionated radiotherapy seemss 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).	None
	Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (LQE; Strong recommendation).	None
KQ3: What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?	Although glioblastoma is believed 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).	None
	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): Two phase: (1) Primary target volume encompasses edema (hyperintense region on T2 or FLAIR on MRI) and gross residual tumor/resection cavity, and (2) boost target volume encompasses gross residual tumor/resection cavity. A range of acceptable clinical target-volume margins exists. One phase: single target volume includes gross residual tumor/resection cavity with wide margins, without specifically targeting edema.	None
	Reduction of target volumes allows less radiation to be delivered to radiographically normal brain. Delivery of less radiation to normal brain should result in less late toxicity (LQE), but this remains to be validated (Weak recommendation).	None
KQ4: What is the role of reirradiation among patients with glioblastoma whose disease recurs after completion of standard first-line therapy?	In younger patients with good performance status, focal reirradiation (eg, stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, 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; Weak recommendation).	No evidence supports reirradiation in any patient subgroup.

Abbreviations: FLAIR, fluid-attenuated inversion recovery; HQE, high-quality evidence; KPS, Karnofsky performance score; KQ, key question; LQE, low-quality evidence; *MGMT*, O^6-methylguanine DNA methyltransferase gene; MRI, magnetic resonance imaging; MQE, moderate-quality evidence.

only 50% at progression, which limited the assessment at this time point. Important differences in the tools used to measure patient-centered outcomes also existed. RTOG 0825 used three tests of cognitive function that measure memory, processing speed, and executive function as well as a multisymptom inventory (MD Anderson Symptom Inventory Brain Tumor); AVAglio had no such measure, and both RTOG 0825 and AVAglio used the European Organisation for Research and Treatment of Cancer QLQ-C30/BN20 HRQOL measures. In addition, differences in the statistical analysis, study entrance criteria, imaging criteria, and study design also make direct comparison not tenable. Hence, inconclusive evidence shows that the addition of bevacizumab to standard therapy improves HRQOL.

Hypofractionation for Elderly Patients

The term elderly has often been applied to patients between 65 and 70 years of age. In this population, which represents > 50% of the patients with glioblastoma, no optimal-dose regimen has been determined, and whether hypofractionation is superior to standard fractionation of 60 Gy in 30 fractions remains unclear. Several trials have investigated hypofractionation regimens.[24,25,32] The Nordic trial of patients 65 years of age and older compared standard fractionation without temozolomide to hypofractionation (34 Gy in 10 fractions) without temozolomide versus temozolomide alone.[24] Survival was worse in the standard radiation group, especially for patients older than 70 years, but this result is complicated by the poor completion rate of radiation in this group (72%) and the delayed time from surgery to the start of radiation (mean, 46 days). The Nordic trial included 22% with WHO performance status 2 to 3, equivalent to a Karnofsky performance score of 50 to 60. Conversely, the survival of elderly patients in the German Cancer Society Neuro-Oncology Working Group NOA-08 trial, which included a standard fractionation arm, was higher than that in the Nordic trial.[32] Patients in the NOA-08 trial had a Karnofsky performance score > 60, began radiation

sooner after surgery (mean, 30 days), had a higher completion rate (84%), but included cases of anaplastic astrocytoma as well as glioblastoma (although grade was not a significant prognostic factor in this trial). The International Atomic Energy Agency conducted a phase III trial of patients 65 years of age and older as well as patients 50 years and older with poor performance status and compared two hypofractionation schedules: 25 Gy in five fractions and 40 Gy in 15 fractions. No difference in survival was reported for the two fractionation schemes, although no stratification was performed for known prognostic factors, such as O^6-methylguanine DNA methyltransferase gene (*MGMT*) promoter methylation status.[25] From these data, the optimal dose and fractionation schedule remain unclear as does whether any deviation from standard fractionation with or without temozolomide is appropriate for patients with good performance status independent of age.

Focal Reirradiation

Data from several trials suggest benefits to reirradiation for recurrent glioblastoma. Salvage reirradiation has been offered as a potential treatment option.[33-36] Results obtained from > 300 patients with glioblastoma confirm a 6-month progression-free survival from 28% to 39% and a median 1-year overall survival of 26%.[37-39] Recent radiotherapy treatment advances, including proton therapy, intensity-modulated radiation therapy, and fractionated stereotactic radiotherapy, allow for highly conformal treatment and significantly reduce late CNS toxicity.[39] Several studies report an improvement in functional status and discontinuation of corticosteroid use.[34,35,38,40] Late CNS toxicity was uncommon, especially after fractionated stereotactic radiotherapy. The majority of studies have been retrospective and tended to select from smaller volumes of disease, although no standard volume or cross-sectional diameter has been determined as optimal for reirradiation. Thus, reirradiation at recurrence may be considered in select cases, although no phase III trial has yet been reported to inform detailed guidelines for optimal dose or volume.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Radiation Therapy for Glioblastoma ASCO Endorsement Expert Panel Members

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