# 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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In all of oncology, the treatment of patients with glioblastoma (GBM) continues to be one of the greatest challenges. Although GBM is a rare tumor, with an average annual incidence in the United States of approximately 11,000, it is the most common primary brain malignancy in adults and one of the most lethal.[1] Due to its infiltrative nature, surgical resection alone leads to median survivals of only 3 to 6 months.[2-4] Beginning in the 1960s, this duration of survival improved significantly with the addition of adjuvant radiation, 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 further to longer than 14 to 16 months.[8-10]

Approaches to radiation therapy have evolved substantially over the decades since its early use for treatment of GBM. Initially, the whole brain was treated,[11,12] but radiation volumes have decreased, and inverse planning and dose modulation with intensity-modulated radiation therapy have allowed for more precise targeting and sparing of critical, 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 or carbon ion.[15-17]

In addition to the modality of radiation delivery, alterations in the dose have been explored. Initial studies sought to identify the optimal dose that could be safely delivered with maximum benefit.[7,18,19] These questions, 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 GBM. Recognizing the complex challenge and the effort undertaken by ASTRO, the ASCO guideline serves to review and endorse the ASTRO guidelines, while adding clarifying statements, to aid in the treatment of patients with GBM.

Additional information is available at www.asco.org/glioblastoma-radiotherapy-endorsement. Patient information is available at www.cancer.net. JOP

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# THE BOTTOM LINE

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### *Guideline Questions*

1. When is radiation therapy indicated after biopsy/resection of glioblastoma (GBM) 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 GBM and how might treatment vary based on pretreatment characteristics such as age or performance status?
3. What are the ideal target volumes for curative-intent external beam radiotherapy of GBM?
4. What is the role of reirradiation among patients with GBM whose disease recurs following completion of standard first-line therapy?

### *Target Population*

Patients with GBM.

### *Target Audience*

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

### *Methods*

An ASCO Expert Panel was convened to consider endorsing the ASTRO guideline on radiation therapy for GBM recommendations that were based on a systematic review of the medical literature. The ASCO Expert Panel considered the methodology used in the ASTRO guideline by considering the results from the AGREE (Appraisal of Guidelines for Research and Evaluation) II review instrument. The ASCO Expert Panel carefully reviewed the ASTRO guideline content to determine appropriateness for ASCO endorsement.

### *ASCO Key Recommendations for Radiation Therapy for Glioblastoma*

Additional ASCO Expert Panel Statements *in* ***bold italics***.

- 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 KQ2). (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.***

- Adding 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 GBM in patients up to 70 years of age (see KQ2 for recommendations regarding patients older than 70 years). (Strong recommendation)

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- Adding bevacizumab to standard therapy for newly diagnosed GBM (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, however, may prolong progression-free survival (moderate-quality evidence [MQE]). The panel does not recommend the routine addition of bevacizumab to standard therapy for newly diagnosed GBM outside of 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)
- For patients younger than 70 years with good performance status (Karnofsky performance status $\geq$ 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)
- Older age and poor performance status are associated with shorter survival in patients with GBM (MQE). Prognostic considerations should help guide treatment recommendations for individual patients. (Strong recommendation)
- Among elderly patients ($\geq$ 70 years old) with fair to good performance status (Karnofsky performance status $\geq$ 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 (low-quality evidence [LQE]; see KQ2F). (Strong recommendation)
- 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 (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 results of recent randomized trials suggest shorter regimens may be equivalent to longer treatment duration.***

- 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 O-6-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, 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)

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- Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (LQE). (Strong recommendation)
- Although GBM 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 GBM. (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.
- 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)
- In younger patients with good performance status, focal reirradiation (eg, stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, brachytherapy) for recurrent GBM 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).

***There is no prospective evidence supporting reirradiation in any patient subgroup.***

### Additional Resources

Additional 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 GBM can be found at https://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.**

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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