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

• In all of oncology, the treatment of patients with glioblastoma (GBM) continues to be one of the greatest challenges.

• 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 American Society of Clinical Oncology (ASCO) guideline serves to review and endorse the ASTRO guidelines, while adding clarifying statements, in order to aid in the treatment of patients with GBM.
ASCO Endorsement Methodology

The ASCO Clinical Practice Guidelines Committee endorsement review process includes:

• a methodological review by ASCO guidelines staff
• a content review by an ad hoc expert panel
• final endorsement approval by ASCO CPGC.

The full ASCO Endorsement methodology supplement can be found at:
www.asco.org/glioblastoma-radiotherapy-endorsement

ASTRO Guideline Methodology can be found at:
Clinical Questions

The ASTRO guideline addressed four main 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 based on pre-treatment 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 re-irradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

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Target Population and Audience

Target Population
Patients with Glioblastoma

Target Audience
Primary care providers, radiation oncologists, neuro-oncologist, medical oncologist, neurosurgeons and other providers
Summary of Recommendations

ASTRO recommendations, with original language, are listed below with qualifying statements added by the ASCO Panel listed in **bold italics**

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

- 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. (Strong recommendation) *Radiation should be initiated as soon as it is safely permissible. Clinical trials have typically initiated treatment 3-6 weeks following surgery.*

- 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. (Strong recommendation)

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Summary of Recommendations

- 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) 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)
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?

• 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)

• 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)
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). (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 (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) The optimal dose fractionation schedule has not yet been determined for elderly patients, though recent randomized trials suggest shorter regimens may be equivalent to longer duration treatment.
Summary of Recommendations

• 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)

• 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)

• Reasonable options for patients with poor performance status include hypofractionated radiotherapy alone, temozolomide alone, or best supportive care (LQE). (Strong recommendation)
What are the ideal target volumes for curative-intent external beam radiotherapy of glioblastoma?

- 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)

- 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; 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.
Summary of Recommendations

• 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)

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). (Weak recommendation) There is no prospective evidence that supports re-irradiation in any patient subgroup.
Reprint Permission

Endorsement Recommendation

ASCO endorses the ASTRO guideline on radiation therapy for glioblastoma, with minor ASCO Expert Panel statements.
Additional Resources

More information, including a Data Supplement with a reprint of all (ORG) recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/glioblastoma-radiotherapy-endorsement

Link to original ASTRO guideline:

Patient information is available at www.cancer.net
## ASCO Endorsement Panel Members

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