



## Complete Summary

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### GUIDELINE TITLE

Radiotherapy for newly diagnosed malignant glioma in adults: a clinical practice guideline.

### BIBLIOGRAPHIC SOURCE(S)

Laperriere N, Perry J, Zuraw L, Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Nov 2. 32 p. (Evidence-based series; no. 9-3). [87 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Newly diagnosed malignant glioma

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Neurology  
Oncology  
Radiation Oncology

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

- To evaluate the role of radiotherapy in adult patients with newly diagnosed malignant glioma
- To evaluate the optimal radiotherapy characteristics, if it is to be offered

### **TARGET POPULATION**

Newly diagnosed adults with histologic confirmation of the following diagnoses:

- Glioblastoma multiforme
- Malignant astrocytoma
- Malignant astrocytoma grade 3
- Malignant astrocytoma grade 4
- Malignant glioma
- Gliosarcoma

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Postoperative external beam radiotherapy plus temozolamide

**Note:** Radiation dose intensification and radiation sensitizer approaches are considered but not recommended as standard care.

### **MAJOR OUTCOMES CONSIDERED**

- Survival
- 1-year mortality rates
- Toxicity

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

MEDLINE (1966 to April 2005), CANCERLIT (1983 to October 2002), and the Cochrane Library (2005, Issue 4) databases were searched with no language restrictions. "Glioma" (Medical subject heading [MeSH]) was combined with "radiotherapy" (MeSH), "radiotherapy dosage" (MeSH), "dose fractionation" (MeSH), "brachytherapy" (MeSH), "radiation-sensitizing agents" (MeSH), "radiosurgery" (MeSH), and each of the following phrases used as text words: "hypofraction:", "hyperfraction:", "accelerated", "particle". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. To identify non-randomized studies when no randomized trials were available, the search was repeated using all search terms except the study design terms described above. A search of the proceedings of the 1997 through 2005 meetings of the American Society of Clinical Oncology (ASCO) and the 1998 to 2004 meetings of American Society for Therapeutic Radiology and Oncology (ASTRO) was also conducted. Relevant articles and abstracts were reviewed and the reference lists from these sources were searched for additional trials.

### **Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- They were meta-analyses and randomized trials comparing various aspects of radiotherapy in patients with malignant glioma.
- Where no randomized trials were available, non-randomized studies were reviewed.
- Abstracts of trials were also considered.
- The outcome of interest was survival.

## **NUMBER OF SOURCE DOCUMENTS**

Forty-seven randomized trials were identified

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

One-year mortality data from the trials of postoperative radiotherapy versus no postoperative radiotherapy, and the trials of hyperfractionated radiotherapy versus conventional fractionation radiotherapy, were pooled in separate meta-analyses using the software package Metaanalyst<sup>0.998</sup> (J. Lau, Boston, MA, USA). Reported figures or estimates obtained from tables or graphs were used. For the calculation of survival, the total randomized population was included in the denominator, based on intention-to-treat, unless the only available data were for the evaluable patients. The random effects method was used as the more conservative estimate of effect. The pooled results were examined for statistically significant heterogeneity ( $p < 0.10$ ). Results were expressed as risk ratios (RR), where an RR less than 1.0 favours the experimental group, and an RR greater than 1.0 favours the control group.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

### **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The Neuro-Oncology Disease Site Group (DSG) reviewed the evidence and developed recommendations to address the following clinical questions: 1) What is the role of radiotherapy in adult patients with newly diagnosed malignant glioma? 2) If radiotherapy is offered, what are the optimal radiotherapy characteristics? This practice guideline report has been reviewed and discussed by the Neuro-Oncology DSG on several occasions and it was approved with the addition of the following general comments.

Many of the studies discussed in this systematic review were performed over the last two to three decades. There have been major technological advances in both the delivery of radiotherapy and in diagnostic imaging in the last five to ten years, such that results and recommendations based on these older data may no longer be pertinent. Until new evidence emerges revisiting many of the issues raised in this guideline, the DSG agreed that the current recommendations apply. However, the most recent literature search update provided sufficient evidence to recommend the addition of concurrent temozolomide (TMZ) to conventional radiotherapy regimens.

Additionally, most of these older studies did not address toxicity or quality of life. This is particularly pertinent for studies where higher intensities of therapy were being investigated. It is very possible that higher intensity therapies may prolong life but at a significant cost in terms of quality of life, such that patients and physicians should have this information available to be able to make informed choices among the therapeutic options. It is strongly recommended that future studies in patients with brain tumours include measures of toxicity and quality of life.

Postoperative radiotherapy as an appropriate recommendation for patients is well supported by randomized studies and remains standard therapy. With regard to the dose issue, only the Medical Research Council (UK) study of 60 Gy in 30 fractions compared with 45 Gy in 20 fractions showed a small statistically significant benefit for the higher dose. No other randomized studies of dose

escalation have shown any benefit compared with conventional doses in the range of 50 to 60 Gy. For this reason, the DSG felt that doses of 60 Gy with conventional fraction sizes were acceptable, particularly in view of the fact that higher doses are likely associated with higher toxicity and increased costs and inconvenience for the patient, in a disease which remains incurable.

The hypofractionated dose utilized in the study by Glinski, given over three months, is an extremely unusual fractionation, and one that the DSG does not recommend.

All other studies of hyperfractionation, radiation sensitizers, or particle therapy have thus far failed to demonstrate a benefit, and these approaches remain within the domain of experimental therapy. In view of the poor results of conventional radiotherapy in this disease, the DSG recommends that patients be encouraged to participate in properly conducted experimental studies.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Neuro-oncology Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 65 practitioners in Ontario (13 medical oncologists, 15 radiation oncologists, 22 surgeons, 13 neurologists, one hematologist, and one pathologist). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-Oncology DSG reviewed the results of the survey.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. The guideline has been approved by the Neuro-Oncology DSG and the Practice Guidelines Coordinating Committee.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- Postoperative external beam radiotherapy is recommended as standard therapy.
- The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g., 2 cm) for the planning target volume, and the total dose delivered should be 60 Gy in 2 Gy fractions, with concurrent temozolomide at 75 mg/m<sup>2</sup>.
- Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Five of six randomized studies demonstrated that postoperative radiotherapy improves survival compared with no radiation in patients with malignant glioma.
- Seven of eight randomized studies of hyperfractionated versus conventionally fractionated radiotherapy demonstrated no significant survival benefit of hyperfractionated radiotherapy. No randomized trials have examined survival following doses in the 50-60 Gy range.
- A high-dose volume incorporating the enhancing tumour plus a limited margin (e.g., 2 cm) has achieved similar survival to volumes incorporating whole brain for part or all of the treatment in two randomized studies.
- Two randomized studies demonstrated that concurrent and adjuvant administration of temozolomide with radiotherapy improves survival compared to radiotherapy alone in patients with glioblastoma.

### POTENTIAL HARMS

- Radiotherapy has long been recognized to cause possible significant deleterious effects on normal brain tissue. Common acute effects include alopecia, scalp erythema, serous otitis media, nausea, and fatigue. Late effects include radiation necrosis, dementia, and effects on higher cognitive functioning. Many of these clinical late effects can be related to white matter changes noted on magnetic resonance imaging and computed tomography.

One study found that the severity and frequency of white matter injury was statistically associated with increasing radiation dose in a phase I/II dose-seeking trial of hyperfractionated cranial radiotherapy.

- In view of the high rate of recurrence at the original site in patients treated with malignant gliomas of the brain, many of the reviewed therapies in this guideline deal with strategies to increase the radiation dose either directly or through mechanisms of radiation sensitization. Inherent in these strategies is a possible increased risk of radiation damage to nearby normal brain structures, which would be associated with toxicity or even shortened survival. Radiation toxicity can sometimes be very difficult to ascertain in patients with glioblastoma multiforme for two reasons: the short median survival of less than one year is probably not long enough for late radiation toxicity to be expressed in many of these patients, and those tumours are associated with large zones of necrosis that may obscure radiation damage both on imaging studies and at autopsy.
- Patients with anaplastic-atypical astrocytoma have a median survival of approximately three years and represent a group of patients who are related to the more aggressive neoplasms discussed in this guideline and for whom the same types of experimental treatments have been attempted. One study compared three cohorts of patients treated on different Radiation Therapy Oncology Group (RTOG) protocols with photons alone, photons with chemotherapy, and photons with a neutron boost. The survival rates for these three cohorts were 3.0 years, 2.3 years, and 1.7 years, respectively. This suggests that more aggressive treatments were associated with a decrease in survival, and a warning that, in future studies, patients should be made aware of the possible increased risks of adverse events that may be associated with a decrease in survival over conventional therapy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- A randomized study has established the equivalence of 60 Gy in 30 fractions to 40 Gy in 15 fractions in older patients ( $\geq 60$  years).
- Since the outcome following conventional radiotherapy is so poor in older patients with a poor performance status, supportive care alone is a reasonable therapeutic option in these patients.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Laperriere N, Perry J, Zuraw L, Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Nov 2. 32 p. (Evidence-based series; no. 9-3). [87 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2000 Sep 19 (revised 2005 Nov 2)

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### SOURCE(S) OF FUNDING

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

### GUIDELINE COMMITTEE

Provincial Neuro-oncology Disease Site Group

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Not stated

## **GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following is available:

- Radiotherapy for newly diagnosed malignant glioma in adults. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Nov 2. Various p. (Practice guideline; no. 9-3). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004. This NGC summary was updated by ECRI on September 27, 2004. The updated information was verified by the guideline developer on October 20, 2004. This NGC summary was updated on June 8, 2006. The updated information was verified by the guideline developer on June 26, 2006.

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