



Complete Summary

GUIDELINE TITLE

Management of single brain metastases: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Mintz AP, Perry J, Laperriere N, Cairncross G, Chambers A, Spithoff K, Neuro-oncology Disease Site Group. Management of single brain metastases: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 15. 26 p. (Evidence-based series; no. 9-1). [29 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, 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)

Confirmed cancer and a single brain metastasis

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Neurological Surgery
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if patients with confirmed single brain metastases should have surgical resection
- To evaluate if patients with single brain metastases undergoing surgical resection should receive adjuvant whole brain radiation therapy (WBRT)
- To evaluate the role of stereotactic radiosurgery in the management of patients with single brain metastases

TARGET POPULATION

Adults with confirmed cancer and a single brain metastasis

Note: This practice guideline does not apply to patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma.

INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment

1. Whole brain radiation therapy (WBRT) versus WBRT plus surgery
2. Surgery plus WBRT versus surgery alone
3. WBRT with or without stereotactic radiosurgery (SRS)
4. SRS versus surgical resection
5. SRS with or without WBRT

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Local control of disease
- Adverse effects

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 through December 2005), EMBASE (1980 through week 52, 2005), CANCELIT (1983 through October 2002), and the Cochrane Library (2005, Issue 4) databases were searched, with no language restrictions. "Brain neoplasms" (Medical Subject Heading [MeSH]), "brain adj2 metastas#s" (text word), "cerebral adj2 metastas#s" (text word) or "metastatic brain" were combined with "single" or "solitary" used as text words. These search terms were then combined with "radiotherapy, adjuvant" (MeSH), "combined modality therapy" (MeSH), "radiosurgery" (MeSH), and the following phrases used as text words: "surgery", "radiation", "radiotherapy", and "radiosurgery". These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, randomized controlled trials, clinical trials, cohort studies, and retrospective studies. In addition, the proceedings of major conferences, including the annual meetings of the American Society of Clinical Oncology (1997 to 2005) and the American Society for Therapeutic Radiology and Oncology (1998 to 2004), were also searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review if they were fully published reports or published abstracts of:

1. Meta-analyses, systematic reviews and randomized controlled trials (RCTs) addressing specific guideline questions. If none of those study types were available, non-randomized prospective studies and retrospective reviews were eligible for inclusion.
2. Outcomes of interest were survival, local control of disease, quality of life, and adverse effects. Studies had to report data on at least one of these outcomes to be eligible for inclusion.

Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.
3. Articles regarding patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, and sarcoma were excluded.
4. Studies including patients with multiple brain metastases in which results for patients with single brain metastases were not reported separately were excluded.

NUMBER OF SOURCE DOCUMENTS

5 randomized controlled trials, 3 prospective case series, 7 retrospective reviews, and 1 meta-analysis were reviewed.

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

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Neuro-oncology Disease Site Group (DSG) of Cancer Care Ontario (CCO's) Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the management of single brain metastases developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The Disease Site Group (DSG) decided to limit the target population for the guideline to exclude patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma because these are radiosensitive primary tumours, which respond differently than other tumours to radiation therapy.

After reviewing the guideline report, the DSG members discussed the role of postoperative whole brain radiotherapy (WBRT) in terms of increasing survival. Other issues addressed in the discussion of the guideline included computed tomography (CT) versus magnetic resonance imaging (MRI) (including contrast dosage), evidence surrounding stereotactic biopsy, stereotactic radiosurgery (SRS), and chemotherapy. The Neuro-oncology DSG drafted recommendations based on the evidence. The DSG attempted to draft recommendations based on the perceived practice variations within Ontario.

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

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

Feedback was obtained through an electronic survey of 99 practitioners in Ontario (medical oncologists, radiation oncologists, neurologists, and neurosurgeons). The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was emailed on June 22, 2006. Follow-up reminders were sent on July 21 and August 4, 2006. The authors reviewed the results of the survey.

This report reflects the integration of feedback obtained from the Report Approval Panel of the Program in Evidence-based Care and through the external review process, with final approval given by the Neuro-oncology Disease Site Group (DSG).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision. Since treatment in this disease is considered palliative, invasive local treatments must be individualized. Patients with lesions requiring emergency decompression due to intracranial hypertension were excluded from the randomized control trials but should be considered to be surgical candidates.
- Postoperative whole brain radiotherapy (WBRT) should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis. The optimal dose and fractionation schedule for whole brain radiation therapy is 3,000 cGy in 10 fractions or 2,000 cGy in five fractions.

- Stereotactic radiosurgery (SRS) boost should be considered following WBRT for patients with single metastases. There is insufficient evidence to recommend SRS alone as single modality therapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials, prospective case series, retrospective reviews, and 1 meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Two randomized controlled trials (RCTs) have shown that surgical excision followed by whole brain radiotherapy (WBRT) significantly improves survival compared with radiation alone. In one RCT, that survival benefit was greatest in patients with controlled extracranial disease. A third RCT, which included patients with poorer prognostic characteristics, did not demonstrate any significant benefit for the addition of surgery compared with radiation alone. A pooled analysis of reported data from the three trials showed no significant overall survival advantage for the surgery plus radiation therapy group; however, significant heterogeneity was detected between study results.
- One RCT of surgery plus WBRT compared with surgery alone demonstrated a significant reduction in the incidence of recurrent brain metastases favouring WBRT, although an overall survival advantage or prolonged maintenance of functional independence was not detected.
- One RCT comparing WBRT with SRS to WBRT alone reported a significant survival benefit for patients with single brain metastases who received WBRT with SRS boost.
- No RCTs were found that compared SRS to surgical resection. Preliminary evidence suggests that stereotactic radiosurgery provides similar median survivals to surgical resection in highly selected patients.

POTENTIAL HARMS

In the trials by Patchell et al and Mintz et al, surgical mortality, defined as death within 30 days following surgery, did not differ significantly from 30-day mortality in the whole brain radiotherapy (WBRT)-alone groups. In the trial by Vecht et al, 30-day mortality was nine percent in the combined treatment group and zero percent in the WBRT-alone group; however, death within two months did not differ between groups. Thirty-day morbidity was eight percent in the surgery plus WBRT group and 17 percent in the WBRT-alone group in one trial and did not differ between groups in another trial. Postoperative complications in the trial by Vecht et al included respiratory problems in four patients, intracerebral

hemorrhage in one patient, infectious disease in three patients, and other complications in nine patients. Postoperative morbidity affected 13 patients, and those complications were serious in four patients. Complications of radiotherapy, including nausea, vomiting, and headache, did not differ between treatment groups (10 patients in the surgery plus WBRT group versus 9 patients in the WBRT-alone group). No significant difference in adverse effects was detected between groups in the Cochrane meta-analysis (overall risk [OR] 1.25 [95% confidence interval [CI] 0.68 to 2.66, $p=0.39$]).

QUALIFYING STATEMENTS

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- There are no high-quality data regarding the choice of surgery versus radiosurgery for single brain metastases. In general, size and location of the metastasis determine the optimal approach.
- 3,000 cGy in 10 fractions is the standard whole brain radiotherapy (WBRT) regimen for the management of patients with single brain metastases in the United States and is usually the standard arm in randomized studies of radiation in patients with brain metastases. It is correct that, based solely on evidence, there is no reason to choose 3,000 cGy in 10 fractions over 2,000 cGy in five fractions; however, there is a belief that fraction size is important and that 300 cGy a day (3,000/10) will be associated with less long-term neurocognitive effects than 400 cGy a day (2,000/5) in the few long-term survivors. For that reason many radiation oncologists in Ontario prefer 3,000 cGy in 10 fractions. There are no data to either support or refute this belief; therefore, there is no way to resolve it at present. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.
- 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 warranties 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)

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ADAPTATION

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

DATE RELEASED

2004 Aug 17 (revised 2006 Aug 15)

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

Members of the Neuro-oncology Disease Site Group (DSG) involved in the development of this Evidence-Based Series were polled for potential conflicts of interest. No conflicts were declared.

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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 are available:

- Management of single brain metastases: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Aug. Various p. (Practice guideline; no. 9-1). 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 summary was completed by ECRI on October 6, 2004. The information was verified by the guideline developer on October 20, 2004. This NGC summary was updated by ECRI Institute on June 5, 2007. The information was verified by the guideline developer on June 13, 2007.

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