



## Complete Summary

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### GUIDELINE TITLE

Management of brain metastases: role of radiotherapy alone or in combination with other treatment modalities.

### BIBLIOGRAPHIC SOURCE(S)

Supportive Care Guidelines Group, Neuro-oncology Disease Site Group. Tsao MN, Laetsch NS, Wong RKS, Laperriere N. Management of brain metastases: role of radiotherapy alone or in combination with other treatment modalities [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar. 35 p. (Practice guideline report; no. 13-4). [36 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)

Brain metastases

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Neurological Surgery  
Oncology  
Radiation Oncology

### **INTENDED USERS**

Physicians

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

- To evaluate the role of radiotherapy alone or in combination with other treatment regimens in adult patients with single or multiple brain metastases
- To evaluate the optimal radiotherapy regimen if radiotherapy is offered

### **TARGET POPULATION**

Adult patients with a clinical and radiographic diagnosis of brain metastases (single or multiple) arising from cancer of any histology (except for choriocarcinoma and other germ cell tumours, and hematologic malignancies).

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Whole brain radiotherapy plus surgery
2. Whole brain radiotherapy alone
3. Use of altered dose fractionation whole brain radiotherapy schedules
4. Use of radiosensitizers (not recommended)
5. Chemotherapy and whole brain radiotherapy
6. Supportive care and whole brain radiotherapy
7. Supportive care alone

### **MAJOR OUTCOMES CONSIDERED**

Outcomes of interest are survival, intracranial progression-free duration, tumour response, neurological function, quality of life, symptom control, and 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 January 2003), CANCERLIT (1975 to October 2002), CINAHL (1982 to February 2003), EMBASE (1980 to 2002), and the Cochrane Library (2002, Issue 4) databases were searched through Ovid. The terms "brain neoplasms" (Medical subject heading [MeSH]), "metastas#s" (text word), and "metastatic brain" were combined with "radiotherapy" (MeSH), "radiotherapy, adjuvant" (MeSH), "combined modality therapy" (MeSH), "chemotherapy" (MESH), "surgery" (MESH), and "radiosurgery" (MeSH). These 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 Physician Data Query (PDQ) clinical trials database ([http://www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/)) and the proceedings of the annual meetings of the American Society of Clinical Oncology (1997–2002), the American Society for Therapeutic Radiology and Oncology (1997–2002), and the European Society for Therapeutic Radiology and Oncology (1997–2002) 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 of the evidence if they met the following criteria:

1. Design: published randomized or quasi-randomized controlled studies including abstracts.
2. Population: adult patients with single or multiple brain metastases from cancer of any histology.
3. Interventions: external beam radiotherapy or radiosurgery in one study arm.
4. Outcomes: survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, toxicity.

### **Exclusion Criteria**

Studies were excluded if they were:

1. Studies that used prophylactic radiotherapy for brain metastases
2. Phase I or II because of the availability of randomized controlled trials
3. Published in languages other than English

### **NUMBER OF SOURCE DOCUMENTS**

Twenty-three studies and 4 abstracts 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**

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

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

Since the types of patients, prognosis, and treatment strategy are different between patients with a single brain metastasis compared to those with multiple brain metastases, studies addressing these two groups of patients were examined separately. The studies were further divided by study design, based on the question the trials were intended to address. The quality of the studies was assessed using the Jadad quality assessment tool.

Study characteristics, including inclusion criteria, intervention, number analysed, types of outcomes reported, and results, were extracted in duplicate. Specifically, data on outcomes of interest, including survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, and toxicity, were extracted.

The proportion of patients with brain response and progression is dependent on the imaging modality used (computed tomography [CT] or magnetic resonance imaging [MRI]). Similarly, neurological symptom response and quality of life are sensitive to the tool used for evaluation. These details were tabulated.

For the evaluation of dose response, many different dose fractionation schedules were compared. The most commonly employed "control" regimen was 3,000 cGy in 10 fractions. The concept of Biological Equivalent Dose (BED) was used to facilitate comparison among different dose fractionation regimens. BED can be calculated using the equation  $BED = nd (1 + d/\alpha/\beta)$  where  $n$  = number of fractions,  $d$  = dose per fraction, and  $\alpha/\beta = 10$  for tumour. For the purpose of assessing dose response, studies were divided into those comparing lower doses to 3,000 cGy in 10 fractions, and higher doses compared with 3,000 cGy in 10 fractions. As 2,000 cGy in five fractions is most commonly employed in Canada, and this is the second most commonly employed standard regimen, outcomes comparing 2,000 cGy in five fractions versus 3,000 cGy in 10 fractions are also presented.

For the pooled analysis of brain tumour response, the number of patients with a complete or partial response was abstracted from the tables or text in published reports. Tumour response was determined by the proportion of patients achieving complete response (CR) or partial response (PR). Patients were considered to have responded (CR + PR) if there was a 50% or greater decrease in lesion size and they were on a stable or decreasing dose of corticosteroids. Intracranial progression-free duration was defined as the duration during which there was no intracranial tumour growth and no new brain metastases.

Mortality data were obtained by estimating, from the Kaplan-Meier probability curves presented in each report, the number of patients who died within six months after randomization.

The statistical package Revman 4.1 (Metaview © Update Software) provided by the Cochrane Collaboration was used for all analyses. Relative risk (RR) with 95% confidence intervals (CI) using the random effects model was reported as the more conservative estimate of effect. Analyses were primarily conducted on an intention-to-treat basis; however, when the number of patients randomized per study arm was not reported, the number of patients evaluable was analyzed. For tumour response, a RR >1.0 indicates that the patients in the experimental treatment group experienced better response compared with those in the control group. For mortality analyses, a RR <1.0 indicates that the patients in the experimental treatment group experienced fewer deaths compared with those in the control group.

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

Expert Consensus

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

A draft outline of this practice guideline report was discussed at the Neuro-oncology Disease Site Group (DSG) meeting in February 2002, with a view to submit the final form of these guidelines under the auspices of the Supportive Care Guidelines Group (SCGG). The Neuro-oncology DSG felt that the guideline should include sections on single brain metastasis and refer readers to Practice Guideline Report #9-1 for more detail on single brain metastases. The group also suggested including surgical options for patients with multiple brain metastases. As such, the title of the guideline was changed from *Radiotherapy for Brain Metastases* to *Management of Brain Metastases*.

At the next Neuro-oncology DSG meeting in September 2002, the Neuro-oncology DSG learned that the Protocol on this topic was accepted by the Cochrane Library. The guideline report was discussed at the SCGG meeting in November 2002, at which time some concerns about the methodology and interpretation of the studies were raised. A suggestion was made to include a statement that the numbers of patients in the studies that had 3,000 cGy in 10 fractions versus 2,000 cGy in five fractions was small. The authors included a qualifying statement in response to this comment. Further modifications to the draft report as a result of feedback from the SCGG included adding a bullet to the recommendations to state that there is no advantage of other altered-dose-fractionation whole brain radiotherapy (WBRT) schedules, adding subtitles to the recommendations relating to the intervention, and modifying the guideline question to include radiotherapy *alone or in combination with other treatment regimens*.

The Neuro-oncology DSG discussed the guideline again in May 2003, since much new information and tables had been added. The DSG questioned the relevance of having separate guidelines on similar topics by two different guideline groups. Dr. Tsao maintained that two guidelines were necessary as the SCGG's guideline has a greater palliative focus than does the one by the Neuro-oncology DSG. The

information in the two guidelines is consistent. The Neuro-oncology DSG suggested revising the recommendation under "Radiotherapy and Surgery for Single Brain Metastasis" from "postoperative WBRT is recommended..." to "postoperative WBRT *should be used...*", since the evidence is available to make a stronger statement. Modifications were made in response to the group's suggestion.

## **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**

Practitioner feedback was obtained through a mailed survey of 246 practitioners in Ontario (26 neurosurgeons, 137 medical oncologists, and 83 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 14, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Supportive Care Guidelines Group (SCGG) reviewed the results of the survey.

The practice guideline report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Four of eight members of the PGCC returned ballots. Three PGCC members approved the practice guideline report as written, while one member approved the guideline and provided a suggestion for consideration by the SCGG. The SCGG agreed and made the suggested revision.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Supportive Care Guidelines Group and by the PGCC.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

#### **Radiotherapy and Surgery for Single Brain Metastasis**

- 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.
- Postoperative whole brain radiotherapy should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis.

### **Radiotherapy for Multiple Brain Metastases**

- It is recommended that the whole brain be irradiated for multiple brain metastases. Commonly used dose fractionation schedules are 3,000 cGy in 10 fractions or 2,000 cGy in five fractions.
- Altered dose fractionation whole brain radiotherapy schedules have not demonstrated any advantages in terms of overall survival or neurologic function relative to more commonly used fractionation schedules.
- The use of radiosensitizers is not recommended outside research studies.
- The optimal use of radiosurgery in the treatment of brain metastases remains to be defined. In patients with one to three brain metastases (less than 3 cm in size) and limited or controlled extracranial disease, radiosurgery may be considered to improve local tumour control either as boost therapy with whole brain radiation or at the time of relapse after whole brain radiotherapy.

### **Chemotherapy and Whole Brain Radiotherapy**

The use of chemotherapy as primary therapy for brain metastases (with whole brain radiotherapy used for those whose intracranial metastases fail to respond) or the use of chemotherapy with whole brain radiotherapy to treat brain metastases remains experimental.

### **Supportive Care and Whole Brain Radiotherapy**

Supportive care alone without whole brain radiotherapy is an option (for example, in patients with poor performance status and progressive extracranial disease). However, there is a lack of Level 1 evidence to guide practitioners as to which subsets of patients with brain metastases should be managed with supportive care alone without whole brain radiotherapy.

### **CLINICAL ALGORITHM(S)**

None provided

## **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The recommendations are supported by randomized clinical trials.

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

- Two randomized controlled trials examined patients with good performance status (Karnofsky Performance Status 70-90 or World Health Organization 0, 1) and a surgically accessible single brain metastasis. Surgical excision combined with whole brain radiotherapy were found to improve duration of functional independence and overall survival compared to radiotherapy alone (mortality at six months 33% versus 61%, respectively, relative risk 0.54 (95% confidence interval 0.31, 0.93). Perioperative mortality (30 days) ranged from 4 to 10%.
- One randomized study of postoperative whole brain radiotherapy following excision of a single brain metastasis detected a significant reduction in intracranial tumour recurrence rates, but no difference in overall survival as compared to surgery alone was detected.
- Nine randomized controlled trials showed no benefit of altered dose-fractionation schedules as compared to a standard control fractionation schedule (3,000 cGy in 10 fractions) of whole brain radiotherapy for probability of survival at six months and neurological improvement. Two trials showed no difference between 3,000 cGy in 10 fractions and 2,000 cGy in five fractions. Both fractionation schemes are commonly used in Canada.
- For conventional external beam radiotherapy, the volume of radiotherapy studied in randomized controlled trials has been whole brain radiotherapy. There have been no randomized trials investigating the use of radiotherapy to the whole brain versus conventional external beam radiotherapy to only part of the brain volume.
- The addition of radiosensitizers, as assessed in five fully published randomized controlled trials, did not confer additional benefit to whole brain radiotherapy in terms of overall survival or the frequency of response to radiotherapy of the tumour metastases.
- One randomized trial detected a benefit in terms of local control of brain metastases with the addition of radiosurgery to whole brain radiotherapy for two to four brain metastases all less than 25 mm in maximum diameter. However, overall survival was not improved. Fully published results of two further randomized trials examining the use of radiosurgery for brain metastases are pending. The optimal timing of radiosurgery (e.g., boost after whole brain radiotherapy, as salvage after whole brain radiotherapy relapse, or as primary treatment followed by whole brain radiotherapy at the time of relapse of brain metastases) remains to be defined.
- One older randomized trial examined the use of whole brain radiotherapy versus supportive care alone (via the use of oral prednisone). Results were not conclusive. Further randomized controlled trials are needed to assess the benefit of whole brain radiotherapy versus supportive care alone particularly in patients with brain metastases who have poor performance status or uncontrolled extracranial malignant disease.

## **POTENTIAL HARMS**

### **Whole Brain Radiotherapy (WBRT) with or without Surgery**

Toxicities reported in three studies of surgery and WBRT included surgical mortality, postoperative morbidity (including serious morbidity), headache, nausea, and vomiting. With WBRT alone, toxicities included undefined morbidity and headache, nausea, and vomiting (see Table 10 in the original guideline document for details).

## **Altered WBRT Dose Fractionation Schedules**

Data on toxicity are presented in Tables 14a and 14b in the original guideline document. Toxicities included nausea, vomiting, headache, increased neurologic deficit or fall in level of consciousness, and cerebral hemorrhage.

## **WBRT Plus Radiosensitizer Versus WBRT Alone**

In the study by DeAngelis et al., the most common side effects from lonidamine were myalgia (68%), testicular pain (42% of men), anorexia (26%), and ototoxicity (26%), malaise/fatigue (26%), and nausea/vomiting (19%). No acute or subacute radiation-related neurotoxicity was observed in either treatment group. WBRT combined with metronidazole in the Eyre et al. study resulted in a 51% incidence of nausea/vomiting compared with 3.2 % in the WBRT-alone arm. In the study by Komarnicky et al., misonidazole administration was well tolerated and produced no grade 3 neuro- or ototoxicity. However, several grade 3 symptoms of nausea and vomiting (defined as occurring one to three times daily) were noted. There was no increased radiation skin reaction or central nervous system (CNS) injury in the bromodeoxyuridine (BrdUrd) arm in the study by Phillips et al. Three fatal toxicities with BrdUrd were noted. One was a severe Stevens-Johnson skin reaction, and two were due to neutropenia and infection.

## **Chemotherapy and WBRT**

Toxicities were said to be "mild" in the Postmus trial. The predominant form of toxicity was hematologic. There were 13 toxic deaths in the trial by Robinet et al.: seven with the early chemotherapy arm (8.2%) and six with the delayed chemotherapy arm (6.9%). Ten of these deaths were due to sepsis during severe neutropenia. One patient in each arm died of pneumonia without neutropenia after the second cycle of chemotherapy. Another patient died of renal failure in the delayed chemotherapy arm after the first cycle. Two patients died in the trial by Ushio et al. of probable side-effects from chemotherapy. Antonadou et al. did not report on toxicity.

## **WBRT Plus Radiosurgery Versus WBRT Alone**

In terms of toxicity, Kondziolka et al. found no neurologic or systemic morbidity related to stereotactic radiosurgery. The Radiation Therapy Oncology Group (RTOG) reported no grade 4 or 5 toxicities in either group. Four percent (3/69) of patients treated with WBRT and stereotactic boost had acute grade 3 toxicity compared with 0% (0/70) of patients treated with WBRT alone. Late grade 3 toxicity occurred in 5% (2/39) of patients treated with WBRT and stereotactic boost compared with 2% (1/51) treated with WBRT alone. All grade 3 toxicities were neurologic in origin.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

- The number of patients included in the two trials comparing 3,000 cGy in 10 fractions versus 2,000 cGy in five fractions for multiple brain metastases was small.
- In the trials examining the use of surgery and whole brain radiotherapy for single brain metastasis, the whole brain radiotherapy doses were 3,000 cGy in 10 fractions daily, 4,000 cGy in 20 fractions given twice daily, 3,600 cGy in 12 fractions daily, and 5,040 cGy in 28 fractions daily. As such, the use of 2,000 cGy in five fractions of whole brain radiotherapy has not been studied directly in this scenario.
- The results of the studies may not be generalizable to all tumour types. The majority of the patients in the studies (except the chemotherapy studies) had lung, breast, or colorectal cancer primaries.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines 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

End of Life Care  
Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Supportive Care Guidelines Group, Neuro-oncology Disease Site Group. Tsao MN, Laetsch NS, Wong RKS, Laperriere N. Management of brain metastases: role of radiotherapy alone or in combination with other treatment modalities [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar. 35 p. (Practice guideline report; no. 13-4). [36 references]

### ADAPTATION

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

**DATE RELEASED**

2004 Mar 30

**GUIDELINE DEVELOPER(S)**

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

**GUIDELINE DEVELOPER COMMENT**

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), 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**

Supportive Care Guidelines Group  
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 Supportive Care Guidelines Group (SCGG) disclosed potential conflict of interest information.

**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 are available:

- Management of brain metastases: role of radiotherapy alone or in combination with other treatment modalities. Summary. Toronto (ON): Cancer Care Ontario (CCO). 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 June 29, 2004. The information was verified by the guideline developer on July 19, 2004.

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