Management of Single Brain Metastases

A.P. Mintz, J. Perry, N. Laperriere, G. Cairncross, A. Chambers, K. Spithoff, and the Neuro-Oncology Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Neuro-Oncology Disease Site Group

Report Date: August 15, 2006

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EBS 9-1 Version 2.2006 consists of:
Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review

and is available on the CCO website (http://www.cancercare.on.ca)
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Evidence-based Series 9-1 (Version 2.2006): Section 1

Management of Single Brain Metastases: A Clinical Practice Guideline

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Report Date: August 15, 2006
This Evidence-based Series report replaces an earlier version of the report that was completed in 2004.

Questions
1. Should patients with confirmed single brain metastases have surgical resection?
2. Should patients with single brain metastases undergoing surgical resection receive adjuvant whole brain radiation therapy (WBRT)?
3. What is the role of stereotactic radiosurgery (SRS) in the management of patients with single brain metastases?

Outcomes of interest were survival, local control of disease, quality of life, and adverse effects.

Target Population
These recommendations apply to adults with confirmed cancer and a single brain metastasis. This practice guideline does not apply to patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma.

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 controlled trials but should be considered to be surgical candidates.
• Postoperative 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.
• SRS boost should be considered following WBRT for patients with single metastases. There is insufficient evidence to recommend SRS alone as single modality therapy.
Qualifying Statements

• 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.

• 3,000cGy in 10 fractions is the standard 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 3,000cGy in 10 fractions over 2,000cGy in five fractions; however, there is a belief that fraction size is important and that 300cGy a day (3000/10) will be associated with less long-term neurocognitive effects than 400cGy a day (2000/5) in the few long-term survivors. For that reason, many radiation oncologists in Ontario prefer 3,000cGy in 10 fractions. There are no data to either support or refute this belief; therefore, there is no way to resolve this issue at present. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.

Key Evidence

• Two randomized controlled trials (RCTs) have shown that surgical excision followed by 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.

Related Guidelines

Practice Guideline Report #13-4: Management of Brain Metastases (developed by the Supportive Care DSG).
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Management of Single Brain Metastases: A Systematic Review

A.P. Mintz, J. Perry, N. Laperriere, G. Cairncross, A. Chambers, K. Spithoff, and the Neuro-Oncology Disease Site Group

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QUESTIONS
1. Should patients with confirmed single brain metastases have surgical resection?
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INTRODUCTION
Cerebral metastases occur in 15% to 30% of cancer patients during the course of their disease (1-3). Approximately half of these patients have single metastases as shown by computed tomography (CT) (2-4). Patients with single metastases tend to undergo more aggressive therapy than those with multiple metastases; therefore, general treatment guidelines should be specific to this patient group.

Since the distinction between intracranial primary and metastatic cancer and between single and multiple metastases frequently determines the choice of treatment, care must be taken in initial diagnosis of a suspected metastasis. Contrast-enhanced computerized tomography or magnetic resonance imaging (MRI) are the standard diagnostic tests for individuals suspected of intracranial primary or metastatic cancer. In those individuals in whom there appears to be a single metastasis and in whom the primary tumour site is controlled or unknown, high-dose contrast imaging studies are appropriate. This may be accomplished with iodinated contrast and a repeat computerized tomographic scan. Alternatively, high-dose contrast gadolinium-enhanced MRI may be used as it has demonstrated increased sensitivity in detecting smaller lesions; however, in several studies, between 2% and 11% of patients were misdiagnosed as having single brain metastases, using MRI (6,8). Surgical resection or stereotactic biopsy should be used if a solitary lesion with characteristics of a cancer is seen with no known primary to establish tissue diagnosis prior to other treatments.
Currently in Ontario, there is variation in the management of patients with suspected single brain metastases. An informal poll was conducted by the Neuro-oncology Disease Site Group (DSG), which represents nine regional cancer centres, to establish the current practice in Ontario for the treatment of patients with single metastases. The findings, summarized in Table 1, are categorized according to patient prognosis (good versus poor) based on the Karnofsky performance score (KPS) and status of the underlying primary disease. However, it should be noted that no formal criteria for prognosis have been established. Patients with a “good” prognosis would generally have resection via craniotomy followed by 3000 cGy in 10 fractions, although patients treated at two Regional Cancer Centres (RCCs) receive 2000 cGy in five fractions and the dose varied at two other RCCs. At some RCCs, patients receive boost radiation or SRS if the lesion is unresectable. At most RCCs, patients with a “poor” prognosis do not have a resection. Patients at seven RCCs receive 2000 cGy in five fractions, whereas the dose varied at the other two centers, depending on pathology. Patients were referred for surgical consideration based on both tumour-specific factors (location, size, or degree of mass effect) and patient-specific factors (age, co-morbid medical conditions, or extra-cranial disease). The decision to operate was also based on the above factors, with local physician referral patterns and individual patient judgments being the rule, rather than RCC-specific guidelines.

Table 1. Summary of the informal poll of the Neuro-oncology DSG to establish current practice in Ontario for the treatment of single brain metastases.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Yes, if the metastasis is resectable.</td>
<td>Generally not</td>
</tr>
<tr>
<td>Radiation</td>
<td>5 centers: 3000 cGy in 10 fractions</td>
<td>7 centers: 2000 cGy in 5</td>
</tr>
<tr>
<td></td>
<td>2 centers: 2000 cGy in 5 fractions</td>
<td>2 centers: Varied depending on pathology</td>
</tr>
<tr>
<td></td>
<td>2 centers: Variable doses</td>
<td></td>
</tr>
<tr>
<td>Boost Radiation or</td>
<td>Some would if unresectable</td>
<td>No</td>
</tr>
<tr>
<td>Radiosurgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>For control of primary disease; Experimental protocols</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Neuro-oncology DSG felt that a systematic review and practice guideline were warranted, based on three factors:

1. The conflicting results from the three randomized trials of surgery and radiation therapy compared with radiation therapy alone;
2. The increasing use of SRS;
3. The variation in treatment across RCCs in Ontario.

METHODS
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by members of the PEBC Neuro-oncology DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the management of single brain metastases. The body of evidence in this review is primarily comprised of mature RCT data. That evidence forms the basis of a clinical practice guideline developed by the Neuro-oncology Disease Site Group. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.
Literature Search Strategy
MEDLINE (1966 through December 2005), EMBASE (1980 through week 52, 2005), CANCERLIT (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), and “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 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.

RESULTS
Literature Search Results
Table 2 outlines the type and number of studies included in this practice guideline by question.
Table 2. Studies included in the systematic review

<table>
<thead>
<tr>
<th>Question</th>
<th>Type of study (reference)</th>
</tr>
</thead>
</table>
| 1. Should patients with confirmed single brain metastases have surgical resection? | 3 RCTs (6-8)  
1 meta-analysis (9)                                                      |
| 2. Should patients with single brain metastases undergoing surgical resection receive adjuvant WBRT? | 1 RCT (10)                                                      |
| 3. What is the role of SRS in the management of patients with single brain metastases? | 1 RCT (11)  
3 prospective case series (12-14)  
7 retrospective reviews (15-21)                                           |

Note: RCT, randomized controlled trial; SRS, stereotactic radiosurgery.

Outcomes

1. **Should patients with confirmed single brain metastases have surgical resection?**

Three RCTs have compared surgery plus WBRT to WBRT alone in the treatment of single brain metastases (6-8) (Table 3). All three trials required patients to have histologically verified extracranial cancer and radiographic evidence of a surgically resectable single brain metastasis. Patients with certain radiosensitive tumours, such as small cell lung cancer and lymphoma, were excluded from all trials. In the trial by Patchell et al (6), patients were stratified by tumour location, extent of disease, and type of primary tumour. Stratification in the trial by Vecht et al (7) was by centre, site of extracranial disease, and status of extracranial disease. Mintz et al (8) stratified patients by type of cancer, size of metastasis, and extent of primary cancer. The majority of patients in all trials had non-small cell lung cancer, while other primary tumour types included breast, gastrointestinal, genitourinary, and melanoma. All patients randomized to the surgery plus WBRT groups in the trials by Patchell et al (6) and Vecht et al (7) underwent surgical resection but treatment compliance with WBRT was not reported. In the Mintz trial (8), six patients in the surgery plus WBRT group did not receive WBRT and two patients did not undergo surgery. In the WBRT alone group, one patient did not receive WBRT and ten patients had a surgical procedure. Analyses for all three RCTs were by the intention-to-treat principle.

Table 3. Randomized trials of surgery plus radiation therapy compared with radiation therapy alone.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment</th>
<th># of patients</th>
<th>Eligibility criteria</th>
<th>Steroids</th>
<th>Median Survival (months)</th>
<th>Local Recurrence (%)</th>
<th>Median Functionally independent survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell, 1990 (6)</td>
<td>WBRT</td>
<td>23</td>
<td>KPS ≥70 Age ≥18</td>
<td>All</td>
<td>3.5</td>
<td>52</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>WBRT surgery</td>
<td>+</td>
<td>25</td>
<td></td>
<td>9.2 p&lt;0.01</td>
<td>20 p&lt;0.02</td>
<td>8.8 p&lt;0.005</td>
</tr>
<tr>
<td>Vecht, 1993 (7)</td>
<td>WBRT</td>
<td>31</td>
<td>WHO PS ≤2 Age ≥18</td>
<td>Most</td>
<td>6</td>
<td>NR</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>WBRT surgery</td>
<td>+</td>
<td>32</td>
<td></td>
<td>10 p=0.04</td>
<td>NR</td>
<td>7.5 p=0.06</td>
</tr>
<tr>
<td>Mintz, 1996 (8)</td>
<td>WBRT</td>
<td>43</td>
<td>KPS ≥50 Age &lt;80</td>
<td>All</td>
<td>6.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>WBRT surgery</td>
<td>+</td>
<td>41</td>
<td></td>
<td>5.6 p=0.24</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Notes: KPS, Karnofsky Performance Status; WBRT, whole brain radiation therapy; WHO PS, World Health Organization Performance Status.
**Survival**

Two randomized trials demonstrated a significant survival benefit for patients who received surgery with WBRT compared to those who received WBRT alone (6,7), while one randomized trial detected no significant survival difference between treatment groups (8). Median survival was 9.2 months for patients who received surgery compared to 3.5 months for patients who received WBRT alone (p<0.01) in the trial by Patchell et al (6) and 10 months compared to 6 months (p=0.04) in the trial by Vecht et al (7). In the trial by Vecht et al, the difference in survival was most robust in a subgroup of patients with stable or absent extracranial disease (median survival 12 months versus 7 months, p=0.02). No significant survival difference was observed in patients with active extracranial disease (median survival five months in both treatment groups, p=0.88). In Mintz et al's RCT (8), median survival was not statistically different between the surgery plus WBRT arm or WBRT-alone arm (5.6 months and 6.3 months, respectively, p=0.24). In addition, most patients died within the first year (69.8% in the WBRT arm, 87.8% in the surgery plus WBRT arm). The systemic extent of primary disease was identified as a major contributing factor and predictor of mortality, using a univariate Cox proportional hazard model (relative risk, 1.86; p=0.006). A Cochrane collaboration meta-analysis of the published survival data from those three trials indicated no significant difference in overall survival, with a hazard ratio of 0.74 (95% confidence interval [CI] 0.39 to 1.4, p=0.35) (9). A high degree of heterogeneity for survival was detected between trials.

**Neurologic Control of Disease**

Local recurrence of disease was reported in only one randomized trial (6). Recurrence or progression at the site of the original metastasis in the trial by Patchell et al was less frequent in the combined surgery plus WBRT group than in the WBRT-alone group (20% versus 52%, respectively, p<0.02). The median length of time from treatment to recurrence of the brain metastasis was significantly longer in patients who underwent surgery compared to patients who received WBRT alone (>59 weeks versus 21 weeks; p<0.0001) (6).

No significant difference in the neurologic versus systemic cause of death was reported between treatment groups in the three randomized trials. Mintz et al (8) reported that the cause of death was systemic disease in 46% in the surgical group and 35% in the radiation group (p=0.42). Death due to neurologic cause alone was 15% in the surgical group and 28% in the radiation group (p=0.30). The remainder of patients died from a combination of neurologic and systemic causes or from an unknown cause. Vecht et al (7) reported no difference in systemic or neurological cause of death between treatment groups, with neurological death being approximately one third in both treatment groups. Patchell et al (6) reported that 71% of patients in the surgical group and 50% in the WBRT group died of systemic causes (p=0.26). The Cochrane meta-analysis indicated that patients who were treated by surgery were somewhat less likely to die from neurological causes (odds ratio [OR] 0.57 [95% CI 0.29 to 1.10], p=0.09); however, this trend was not statistically significant (9).

**Quality of Life and Performance Status**

Two randomized trials demonstrated a benefit in quality of life for patients who received surgery and WBRT compared to patients who received WBRT alone (6,7), and one randomized trial showed no significant difference between groups (8). In the trial by Patchell et al (6), the length of functional independence, defined as a KPS greater than or equal to 70, was significantly improved in the surgical group (8.8 months versus 1.8 months, p<0.005). Multivariate analysis showed that surgical treatment was the only factor associated with a better quality of life (p<0.007). In the trial by Vecht et al (7), median functionally independent survival, defined in that trial as a World Health Organization (WHO) performance status less than or equal to one, was somewhat longer in patients who received surgery compared to patients who received
WBRT alone (7.5 months versus 3.5 months, p=0.06). The analysis of patients with progressive extracranial disease demonstrated no difference in functionally independent survival between treatment groups (p=0.88), but the analysis of patients with stable extracranial disease demonstrated a significant benefit for patients who received surgery compared to patients who received WBRT alone (p=0.01). There were no statistically significant differences in the mean Spitzer quality-of-life scores or the Karnofsky performance scores between treatment groups in the trial by Mintz et al (8).

Adverse Effects
In the trials by Patchell et al (6) and Mintz et al (8), surgical mortality, defined as death within 30 days following surgery, did not differ significantly from 30-day mortality in the WBRT-alone groups. In the trial by Vecht et al (7), 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 (6) and did not differ between groups in another trial (8). Postoperative complications in the trial by Vecht et al (7) 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 (OR 1.25 [95% CI 0.68 to 2.66, p=0.39]) (9).

2. Should patients with single brain metastases undergoing surgical resection receive adjuvant WBRT?
Although all three RCTs examining the efficacy of surgery for single brain metastases also administered WBRT to the surgical treatment arm (6-8), the need for postoperative WBRT had not been established through randomized trials. Patchell et al (10) conducted a follow-up RCT comparing surgery plus WBRT to surgery alone to determine whether postoperative WBRT increased survival or the neurologic control of disease. Patchell et al randomly assigned 49 patients to postoperative WBRT and 46 patients to observation after complete resection of a single brain metastasis. Contrast-enhanced MRI was performed following resection to confirm complete resection and rule out additional lesions, and resected tissue was examined to confirm that all patients had metastatic tumours. Patients were required to have a KPS greater than or equal to 70. Patients with small cell lung cancer, germ-cell tumours, lymphoma, leukemia, or multiple myeloma were excluded and included patients were stratified by type and extent of extracranial disease.

The recurrence of a tumour at the site of the original metastasis (10% versus 46%, p<0.001) as well as anywhere in the brain (18% versus 70%, p<0.001) was less frequent in the WBRT group compared to the observation group (10). Patients in the radiation group were less likely to die of neurological causes than patients in the observation group (14% versus 44%, p=0.003); however, there was no significant difference in overall length of survival or the length of time that patients remained functionally independent.

3. What is the role of SRS in the management of patients with single brain metastases?
WBRT with or without SRS
One RCT was identified that compared the use of WBRT with SRS boost to WBRT alone in patients with brain metastases (11). The RTOG 9508 RCT by Andrews et al randomized patients with one to three brain metastases, including 186 patients with single metastases, to receive either WBRT and SRS or WBRT alone. The target sample size was calculated to
provide sufficient statistical power to detect a survival difference between treatment arms in patients with single brain metastases. Patients with a KPS less than 70, lesions greater than 4 cm in diameter, or known active extracranial disease were excluded from the study. Patients randomized to SRS boost received SRS within one week following WBRT. Fourteen patients with single metastases (15%) randomized to SRS boost did not receive radiosurgery but were included in the analysis using an intention-to-treat approach. There was a significant improvement in median survival time in patients with single brain metastases receiving both WBRT and SRS compared to patients receiving WBRT alone (6.5 months versus 4.9 months, p=0.039). The cause of death and adverse effects did not differ between treatment groups. Local control and quality of life results were not reported separately for patients with single brain metastases.

SRS versus Surgical Resection
No randomized trials were found that compared SRS with traditional surgical resection; however, three retrospective reviews were identified that compared those treatment modalities (18,19,21).

The study by Muacevic et al (18) reviewed 108 patients with single metastases no larger than 3.5 cm in diameter and stable systemic disease who received SRS alone or surgery plus WBRT. Patients in the SRS group had significantly smaller tumour size than patients in the surgery plus WBRT group (mean 2.07 cm versus 2.7 cm, p<0.001) and a higher proportion of patients with melanoma. Although median survival was 15.7 months in the surgery plus WBRT group and 8.1 months in the SRS group, that survival difference was not statistically significant. No significant differences in local control or complications were observed between groups, but a higher incidence of distant recurrences was reported in the SRS group.

The review by Schoggl et al (19) retrospectively matched 133 patients who received WBRT and either gamma knife SRS or surgery for the treatment of single brain metastases under 3 cm in diameter. Median survival and one-year overall survival did not differ significantly between groups; however, the authors reported that SRS was superior for local control and morbidity.

In order to be included in the review by O'Neill et al (21), patients had to be candidates for both SRS and surgical resection. Tumour size had to be no larger than 3.5 cm in diameter, and patients with deep-seated tumours or ventricular obstruction were excluded. Twenty-three patients who had received SRS and 74 patients who had received surgery met the inclusion criteria, the majority of whom also received WBRT. Significantly fewer patients in the SRS group had a good performance score (p=0.0016). No significant differences in survival or cause of death were detected between groups, and the authors concluded that neither SRS nor surgical resection were superior in that study.

No conclusions can be drawn from the results of those studies because of the inherent limitations associated with comparisons using retrospective data. Those reviews were subject to selection bias, and patients differed between groups in important prognostic factors such as performance status and tumour size. In addition, small sample sizes limited the ability of those studies to detect significant differences between treatment groups for key outcomes.

SRS with or without WBRT
No randomized trials were identified that compared SRS plus WBRT to SRS alone; however, several retrospective reviews have addressed the efficacy of SRS with versus without WBRT. A subgroup analysis of the largest review by Sneed et al (20) compared 168 patients with single brain metastases who received SRS alone to 175 patients who received SRS with WBRT as their initial treatment. In order to be included in the SRS plus WBRT arm of the study, patients must have received radiosurgery (RS) and WBRT within one month of each other, although the order of treatment was not specified. Overall, patients who received SRS alone included a
higher percentage of patients with age over 65 and KPS less than 70, but it is unclear whether that imbalance was also present in patients with single metastases. A number of patients, particularly those who initially received SRS alone, underwent one or more salvage therapies for recurrence or new metastases. No significant survival difference was detected between groups (See Table 4). Tumour control results were not reported for patients with single brain metastases.

Flickinger et al (15) reviewed 116 patients with single metastases treated with linear accelerator (LINAC) SRS. Fifty-six percent of those patients also received fractionated radiation therapy. Forty-five (39%) patients had tumours that recurred after previous WBRT and 71 (61%) were treated with SRS as the initial management for their metastases. The median survival was 11 months, with local tumour control in 85% of patients. Recurrence was documented in 15% of the patients. In a multivariate analysis, local tumour control was significantly better in patients receiving both fractionated radiation therapy and SRS compared with SRS alone (p=0.011), but there was no effect on survival.

Two non-comparative retrospective reviews (16,17) and one single arm prospective case series (12) investigated the efficacy of SRS with WBRT. The study by Auchter et al (17) retrospectively reviewed 122 patients who matched the eligibility criteria for entry into the randomized trial by Patchell et al (6) and who had been treated with SRS followed by WBRT. None of those patients had received prior surgery or radiation therapy. The median survival time was 12.9 months, and the one- and two-year survival was 53% and 30%, respectively. Complete response was observed in 25% of patients and partial response in 34% of patients. One- and two-year local control was 85% and 77%, respectively. Twenty-two percent of patients experienced intracranial recurrence outside the SRS volume. The median duration of functionally independent survival, defined as a KPS greater than 70, was 10.2 months. A second retrospective review by Alexander et al (16) included 171 patients with single brain metastases. The majority of patients in that review received SRS to treat recurrent lesions. All patients received WBRT, either as part of their initial therapy or in combination with SRS. Median survival for patients with single brain metastases was 10.3 months. A small prospective case series of 24 patients who received SRS plus WBRT (12) reported a median survival of 10 months and tumour shrinkage in 58% of patients for whom data were available.

Two single-arm prospective studies (13,14) investigated the efficacy of SRS alone. The case series of 30 patients with inoperable single brain metastases by Sturm et al (13) reported a mean survival of 6.5 months, improvement of clinical symptoms in 18 of 27 patients, and tumour regression in 13 of 22 patients. A subgroup analysis of the study by Lutterbach et al (14) reported a median survival of 7.7 months for patients with single brain metastases.
Table 4. Studies investigating SRS.

<table>
<thead>
<tr>
<th>Study, Year (ref)</th>
<th>Study Type</th>
<th>Treatment</th>
<th># of Pts</th>
<th>Metastasis diameter (cm)</th>
<th>Median Survival (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews, 2004 (11)</td>
<td>RCT</td>
<td>WBRT</td>
<td>94</td>
<td>≤4</td>
<td>4.9†</td>
<td>Pts with prior surgery not excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT + SRS</td>
<td>92</td>
<td></td>
<td>6.5† p=0.0393</td>
<td>Pts with active disease excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBRT 37.5 Gy/15 fractions SRS 15-24 Gy, LINAC or Gamma knife</td>
</tr>
<tr>
<td>Muacevic, 1999 (18)</td>
<td>RR</td>
<td>SRS</td>
<td>56</td>
<td>≤3.5</td>
<td>8.1</td>
<td>SRS group no surgery or WBRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery + WBRT</td>
<td>62</td>
<td></td>
<td>15.7</td>
<td>Surgical retreatment not excluded from surgery group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBRT 40 Gy + 10 Gy boost SRS 14-27 Gy, Gamma knife</td>
</tr>
<tr>
<td>Schöggel, 2000 (19)</td>
<td>RR</td>
<td>SRS + WBRT</td>
<td>67</td>
<td>&lt;3</td>
<td>12</td>
<td>Limited systemic disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery + WBRT</td>
<td>66</td>
<td></td>
<td>9 p=0.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBRT 30 Gy/10 fractions SRS median 17 Gy, Gamma knife</td>
</tr>
<tr>
<td>O’Neill, 2003 (21)</td>
<td>RR</td>
<td>SRS*</td>
<td>23</td>
<td>&lt;3.5</td>
<td>13</td>
<td>No prior treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery*</td>
<td>74</td>
<td></td>
<td>16</td>
<td>Pts candidates for SRS and surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pts with active systemic disease included</td>
</tr>
<tr>
<td>Sneed, 2002 (20)</td>
<td>RR</td>
<td>SRS</td>
<td>168</td>
<td>NR</td>
<td>8.3</td>
<td>No prior surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS + WBRT</td>
<td>175</td>
<td></td>
<td>8.4 p=0.94</td>
<td>SRS+WBRT within 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Some pts received salvage therapy &gt;1 month after initial treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS LINAC or Gamma knife</td>
</tr>
<tr>
<td>Coffey, 1991 (12)</td>
<td>CS</td>
<td>SRS + WBRT</td>
<td>24</td>
<td>≤3</td>
<td>10</td>
<td>3 pts received prior WBRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS margin 16-20 Gy, centre 18-40 Gy, Gamma knife</td>
</tr>
<tr>
<td>Auchter, 1996 (17)</td>
<td>RR</td>
<td>SRS + WBRT</td>
<td>122</td>
<td>NR</td>
<td>12.9</td>
<td>All metastases resectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No prior treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBRT 25-40 Gy, fractions 2-3 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS 10-27 Gy (median 17 Gy), LINAC</td>
</tr>
<tr>
<td>Flickinger, 1994 (15)</td>
<td>RR</td>
<td>SRS + some WBRT</td>
<td>116</td>
<td>≤3.6</td>
<td>11</td>
<td>39% of pts treated for recurrent tumours following prior WBRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56% of pts received SRS plus WBRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS mean min dose 17.9 Gy, mean max dose 34.8 Gy, Gamma knife</td>
</tr>
<tr>
<td>Alexander, 1995 (16)</td>
<td>RR</td>
<td>SRS + WBRT</td>
<td>171</td>
<td>NR</td>
<td>10.3</td>
<td>SRS min dose 9-25 Gy, max dose 14-31.23 Gy</td>
</tr>
<tr>
<td>Sturm, 1991 (13)</td>
<td>CS</td>
<td>SRS</td>
<td>30</td>
<td>NR</td>
<td>6.5†</td>
<td>All pts inoperable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS 20-30 Gy, LINAC</td>
</tr>
<tr>
<td>Lutterbach, 2003 (14)</td>
<td>CS</td>
<td>SRS</td>
<td>55</td>
<td>≤3</td>
<td>7.7</td>
<td>No prior treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SRS 18 Gy, LINAC</td>
</tr>
</tbody>
</table>

Note: f/u, follow up; LINAC, linear accelerator; MST, median survival time; NR, not reported; Pts, patients; RCT, randomized controlled trial; RR, retrospective review; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy

* Most patients also received WBRT (82% of surgery group and 96% of SRS group).
† Mean survival time.
DISCUSSION

1. Should patients with confirmed single brain metastases have surgical resection prior to radiation therapy?

Definitive conclusions are difficult to reach, based on the results of the three RCTs comparing WBRT with surgery to WBRT alone. Those trials were relatively small and differed with respect to important baseline patient characteristics. The largest trial by Mintz et al (8) was calculated to have only 50% statistical power to detect a 50% difference in the median survivals between treatment arms (22). The two major differences between the results of the three RCTs are the reduced survival time for the surgery plus WBRT group in Mintz et al’s RCT (8) and the diminished survival time for the WBRT-alone group reported by Patchell et al (6).

There are several factors that may have contributed to the reduced survival time for the WBRT-alone group in the trial by Patchell et al (6). Macdonald and Cairncross (23) suggest that this trial may have had a referral bias. Patients in the Patchell trial were recruited from a cohort of patients referred to the neurosurgical service; thus, they represent a pre-selected group of patients thought to benefit from surgery or who required more urgent surgery. That referral bias was minimized in the trial by Mintz et al (8) by having eligible patients identified by oncologists, neurologists, or surgeons instead of considering only patients referred to the neurosurgical service. Differences in the proportions of primary tumour histologies are another explanation for the lower survival for the radiation-alone group in the trial by Patchell et al (6). That trial had a large proportion of patients with non-small cell lung cancer (77.0%) compared to the trials by Vecht et al (52.3%) (7) and Mintz et al (53.6%) (8). Since non-small cell lung cancer is a relatively radioresistant tumour, a higher proportion of that tumour type may have biased the results in Patchell et al against WBRT alone. Patchell et al reported that lung cancer was not found to be a significant variable in a multivariate analysis of survival, but their small sample size may have had low statistical power to detect that difference.

The benefit for surgery may be lost in patients with poor prognostic factors such as advanced extracranial disease or lower performance status. Decreased median survival was reported in two randomized trials (7,8) in patients with a greater systemic involvement of their primary malignancy. Forty-five percent of the patients in the study by Mintz et al (8) had extracranial metastases compared with only 37.5% in the trial by Patchell et al (6) and 31.7% in the trial by Vecht et al (7). The univariate Cox regression model identified extent of disease as the most significant variable in the report by Mintz et al, with a relative risk of 1.86 (p=0.006). Vecht et al reported no difference in median survival time between groups for patients with progressive extracranial disease; however, a significant survival advantage was reported for patients with stable disease who received surgery compared to patients who received WBRT alone. In the trial by Mintz et al (8), 21% of patients had a KPS of less than 70, while patients in the trials by Patchell et al (6) and Vecht et al (7) had a performance score equivalent to a KPS of 70 or greater. In addition, while patients in the trials by Patchell et al and Vecht et al were required to have a minimum life expectancy of six months, that specification was not required in the trial by Mintz et al (8). The increased proportions of patients in Mintz et al with poor prognoses and the fact that ten patients in the WBRT alone arm underwent a surgical procedure may have made it more difficult to detect a survival advantage for surgery.

A pooled analysis of the three trials showed no significant overall survival advantage for the surgical group compared to the WBRT-alone group (9). However, the key differences in patient baseline characteristics between studies and wide confidence intervals around the pooled estimate of effect allow for the possibility that surgery may have a beneficial effect on survival in selected groups of patients and provide no survival benefit for others. The pooled results suggest that surgery may reduce mortality from neurological causes; however, this difference was not statistically significant in those studies. There is limited evidence to determine whether surgical resection has a benefit on quality of life compared to treatment with WBRT alone. However, two RCTs (6,7) have reported that WBRT with surgery significantly
prolonged functionally independent survival compared to WBRT alone. The published meta-
analysis reported no significant increase in adverse effects for patients who underwent surgical resection compared to those who received WBRT alone.

Surgical excision should be considered for patients with prognostic factors that would increase the potential benefit of such aggressive treatment, as randomized trials have demonstrated a benefit in those patients. Those prognostic factors include 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.

2. Should patients with single brain metastases undergoing surgical resection receive adjuvant WBRT?
The one randomized trial examining surgery and WBRT versus surgery alone (10) supports the use of postoperative WBRT in addition to surgery. Tumour recurrence was significantly reduced both at the original and distant sites, and patients were less likely to die of neurological causes if radiation therapy was used postoperatively. However, there were no significant differences in overall survival or maintenance of functional independence between the two groups. Thus, the use of postoperative radiation is supported by that trial in order to prevent central nervous system relapse and neurological death rather than to increase survival time or maintain functional independence.

Although the trial by Patchell et al (10) used 5,040cGy in 28 fractions, the current standard management of patients with single brain metastases in the United States is 3,000cGy in 10 fractions. That dosage is usually the standard arm in randomized studies of radiation in patients with brain metastases. Based solely on evidence, there is no reason to choose 3,000cGy in 10 fractions over 2,000cGy in five fractions, but there is a belief that fraction size is important and that 300cGy per day (3000/10) will be associated with less long term neurocognitive effects than 400cGy per day (2000/5) in the few long-term survivors, which is the reason that many radiation oncologists in Ontario prefer 3,000cGy in 10 fractions. Since there are no data to either support or refute this belief, there is no way to resolve the question at present. More randomized trials examining various dosages of radiation therapy for patients with single brain metastases are necessary to determine the optimal dose of radiation therapy to maximize survival and minimize toxicity. The Neuro-oncology DSG will update the recommendations as new evidence becomes available.

3. What is the role of SRS in the management of patients with single brain metastases?
The randomized trial by Andrews et al (11) demonstrated a significant survival benefit for patients with single brain metastases who received WBRT with SRS boost compared to patients who received WBRT alone. With that evidence, it is reasonable to conclude that SRS should be considered for patients with small single brain metastases who have good performance status and controlled extracranial disease and meet additional eligibility criteria for SRS.

The evidence comparing the efficacy of SRS to the efficacy of surgery in the treatment of single brain metastases is limited to retrospective reviews. Radiosurgery has been used increasingly in recent years due to minimal invasiveness, low risk, and the ability to treat metastases considered surgically unresectable. No significant difference in survival was detected for patients receiving SRS versus surgery in the three studies included in this review (18,19,21); however, one study suggested a benefit for SRS in local control and morbidity (19). Those studies were limited by small sample size and differences in key prognostic factors, such as tumour size and performance status, between treatment cohorts. Patients in those studies represent a highly selected study population, and the results of those retrospective comparisons need to be interpreted cautiously. While preliminary evidence suggests a similar efficacy for SRS compared to surgical trials, direct comparisons between surgery and SRS, using random
patient allocation, are needed to determine which treatment should be administered to patients who are candidates for both modalities.

The evidence comparing SRS with WBRT to SRS alone in patients with single brain metastases is of poor quality and should be viewed as hypothesis generating. The addition of WBRT to SRS remains to be clarified through randomized trials. The rationale for using WBRT in addition to SRS rather than SRS alone is similar to the reasons presented for the use of radiation therapy following surgery. WBRT allows for the irradiation of any microscopic intracranial tumour deposits not revealed by neuroimaging studies (24) and metastases that have infiltrated into the brain beyond the SRS margins. An additional theoretical consideration for using combined SRS and WBRT relates to tumour shrinkage, which may occur following initial treatment with fractionated WBRT. The smaller radiosurgical target may provide better local control and decreased complication rates. While the addition of WBRT to SRS appears to increase local and distant intracranial control, WBRT may be associated with adverse effects such as radiation-induced dementia, particularly in long-term survivors. There is no quality data to determine whether WBRT should be given before or after SRS or whether selected patients should receive WBRT only at recurrence or progression.

A recent RCT by Aoyama et al (25) comparing SRS plus WBRT to SRS alone in patients with one to four brain metastases did not meet the inclusion criteria for this systematic review because it did not report results for patients with single metastases separately; however, 64 out of 132 patients had single brain metastases. This study did not detect a significant difference in overall survival between treatment groups but one-year rates of brain tumour recurrence (46.8% vs 76.4%, p<0.001) and development of new brain metastases (41.5% vs 63.7%, p=0.003) were lower in patients who received SRS plus WBRT compared to those who received SRS alone. Salvage treatment for brain tumour progression was required more frequently in patients who received SRS alone that those who received SRS plus WBRT (p<0.001).

The maximum size of lesions treatable with SRS is not well established, although it seems that larger tumour volumes are associated with poorer response and local control with higher complication rates. Radiosurgical treatment of larger metastases may increase the risk for the development of necrotic lesions. The majority of studies included in this review set limits for maximum lesion diameter up to three or four centimetres.

**ONGOING TRIALS**
The Physician Data Query (PDQ) clinical trials database (www.cancer.gov/clinical_trials) was searched for reports of new or ongoing trials.

**Table 5. Ongoing trials of treatment for single brain metastases.**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC 01-546</td>
<td>Whole brain radiation following surgical resection in patients with newly-diagnosed single brain metastases: A phase III prospective randomized trial.</td>
</tr>
<tr>
<td>MDACC 00-377</td>
<td>A phase III prospective randomized trial comparing radiosurgery with versus without whole brain radiotherapy for 1-3 newly diagnosed brain metastases.</td>
</tr>
<tr>
<td>EORTC 22952</td>
<td>Phase III randomized study of adjuvant whole brain radiotherapy versus no adjuvant radiotherapy for 1 to 3 brain metastases from solid tumour after prior surgical resection or radiosurgery</td>
</tr>
<tr>
<td>EORTC 26001</td>
<td></td>
</tr>
<tr>
<td>NCT00002899</td>
<td></td>
</tr>
<tr>
<td>RTOG 0320</td>
<td>Phase III randomized study of whole brain radiotherapy and stereotactic radiosurgery with versus without Temozolomide or Erlotinib in patients with non-small cell lung cancer and brain metastases</td>
</tr>
<tr>
<td>NCT0096265</td>
<td></td>
</tr>
<tr>
<td>021108</td>
<td>Phase III trial comparing radiosurgery with surgery for solitary brain metastases</td>
</tr>
<tr>
<td>NCT00124761</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS
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 controlled trials but should be considered to be surgical candidates. Postoperative WBRT should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis.

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

CONFLICT OF INTEREST
Members of the Neuro-oncology DSG involved in the development of this Evidence-Based Series were polled for potential conflicts of interest. No conflicts were declared.

JOURNAL REFERENCE

ACKNOWLEDGEMENTS
The Neuro-oncology DSG would like to thank Dr. Arlan Mintz, Dr. James Perry, Dr. Normand Laperriere, Ms. Alexandra Chambers, and Ms. Karen Spithoff for taking the lead in drafting and revising this systematic review.

For a complete list of the Neuro-oncology Disease Site Group members, please visit the CCO Web site at http://www.cancercare.on.ca/
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Phone: 905-525-9140, ext. 22055     Fax: 905-522-7681
REFERENCES


Evidence-based Series 9-1 (Version 2.2006): Section 3

Management of Single Brain Metastases: Guideline Development and External Review - Methods and Results

A.P. Mintz, J. Perry, N. Laperriere, G. Cairncross, A. Chambers, K. Spithoff, and the Neuro-Oncology Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Developed by the Neuro-Oncology Disease Site Group

Report Date: August 15, 2006

This Evidence-based Series report replaces an earlier version of the report that was completed in 2004.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series:

Each Evidence-based Series is comprised of three sections:

- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
• **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

• **Section 3: Guideline Development and External Review: Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Development and Internal Review**

This evidence-based series was developed by the Neuro-oncology DSG of CCO’s 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 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 in terms of increasing survival. Other issues addressed in the discussion of the guideline included CT versus MRI (including contrast dosage), evidence surrounding stereotactic biopsy, stereotactic radiosurgery, 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.

**Report Approval Panel**

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

- For the first question on surgical resection, three small RCTs were included. Analyses done both by intention to treat and by actual treatment received would be helpful. The DSG should indicate compliance with the assigned therapy and expand the interpretations in the Discussion section if the data demonstrate compliance problems.
- The section on Quality of Life cites only data regarding performance status. If these are the only data available, the DSG should consider renaming the section and address the topic as a performance-status outcome evaluation rather than an assessment of quality of life.
- The DSG should consider a more definitive recommendation stating that there are insufficient data to recommend stereotactic radiosurgery alone as a single-modality therapy.

**Modifications/Actions**

In response to feedback received from the Report Approval Panel, the DSG made the following modifications to the document:

- Information regarding treatment compliance was added to the Results section and the Discussion of the systematic review. The three RCTs did not perform analyses according to treatment received.
- The authors changed the title of the Quality of Life section to Quality of Life and Performance Status to reflect that most of the data are for performance status.
- The DSG added a statement to the recommendations to emphasize that there is insufficient evidence to recommend stereotactic radiosurgery alone as single modality therapy.
External Review by Ontario Clinicians
Following review and discussion of sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Neuro-oncology DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 1, 2006)

**Target Population**
These recommendations apply to adults with confirmed cancer and a single brain metastasis. This practice guideline does not apply to patients with metastatic lymphoma, small cell lung cancer, germ cell tumour, leukemia, or sarcoma.

**Recommendation**
- 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 controlled trials but should be considered to be surgical candidates.
- Postoperative 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.
- SRS boost should be considered following WBRT for patients with single metastases. There is insufficient evidence to recommend SRS alone as single modality therapy.

**Qualifying Statements**
- 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.
- 3,000cGy in 10 fractions is the standard 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 3,000cGy in 10 fractions over 2,000cGy in five fractions; however, there is a belief that fraction size is important and that 300cGy a day (3000/10) will be associated with less long-term neurocognitive effects than 400cGy a day (2000/5) in the few long-term survivors. For that reason, many radiation oncologists in Ontario prefer 3,000cGy in 10 fractions. There are no data to either support or refute this belief; therefore, there is no way to resolve this issue at present. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.
Methods
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.

Results
Fifteen responses were received out of the 99 surveys sent (15% response rate). Two of the 15 responses were received via fax and 13 practitioners filled out the electronic survey. Key results of the practitioner feedback survey are summarized in Table 6.

Table 6. Responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.</td>
<td>15 (100)</td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>14 (93)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>12 (80)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>13 (87)</td>
</tr>
<tr>
<td>The draft recommendations in the report are clear.</td>
<td>12 (80)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>11 (73)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>11 (73)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely 3 (20) Unsure Strongly disagree or unlikely 1 (7)</td>
</tr>
</tbody>
</table>

Summary of Written Comments
Six respondents (40%) provided written comments. The main points contained in the written comments are summarized below.
- One respondent commented that this was a very good draft.
- One respondent stated that the recommendations were as clear as possible given the vagueness of the literature. The respondent felt that the data regarding surgical excision and adjuvant radiation were clear enough and agreed fully with this aspect of the report.
- One respondent commented that implementation of SRS would require significant resource allocation.
- Two respondents stated that the RCT by Aoyama et al (3) comparing SRS plus WBRT to SRS should be included in the systematic review. Although the full publication was outside the range of the literature review, results were available in the abstracts of the 2004 ASCO annual meeting.
- One respondent suggested that the study by Auchter et al (4) would be more appropriately included and discussed under the section “SRS versus Surgical Resection” as it describes a patient population that would have been eligible for surgery but were treated with radiosurgery.
- One respondent commented that there are few high quality data to support the statements made in the report and the data comparing SRS to surgery are as good as any of these. The little evidence suggests that SRS and surgery are roughly equivalent and SRS (with or
without WBRT) should be strongly considered for single lesions that are not amenable to surgery. The report should mention this.

• One respondent found it difficult to comment on the draft recommendations as they were not clear and no definitive recommendation was made for each of the questions. The respondent suggested that a summary of the recommendations would be helpful.

**Modifications/Actions**
The following modifications were made to the document in response to the results of the practitioner feedback survey:

• The issues of cost of treatment and resource allocation are beyond the scope of this evidence-based guideline.
• The RCT by Aoyama et al (3) was not included in the systematic review because it did not report results for patients with single brain metastases separately. A statement regarding this RCT was added to the Discussion section of the systematic review.
• The study by Auchter et al (4) was a single-arm study of SRS plus WBRT for patients whose tumours were considered resectable. This study was not included in the surgery versus SRS section of the systematic review because it was not a comparative study and patients did not undergo surgical resection.
• The recommendations state that SRS following WBRT should be considered for any patients whose tumour size and location are suitable for SRS. The authors did not feel that a separate recommendation for SRS specifically in patients with single lesions not amenable to surgery was necessary.
• The authors added a summary of the recommendations to the Conclusions section of the systematic review.

**ONGOING DEVELOPMENT AND MAINTENANCE**
This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Neuro-oncology DSG. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681
REFERENCES


