Management of Single Brain Metastases  
Practice Guideline Report #9-1  

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Report Date: August 17, 2004  

SUMMARY  

Guideline Questions  

**Diagnosis**  
1. What is the optimal imaging modality for the diagnosis of single brain metastases?  
2. When should stereotactic biopsy be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments?  

**Management**  
3. What is the optimal dose of whole brain radiation therapy for patients with confirmed single brain metastases?  
4. Should patients with confirmed single brain metastases have surgical resection prior to radiation therapy?  
5. What is the role of stereotactic radiosurgery in the management of patients with single brain metastases?  
6. What is the role of chemotherapy in patients with single brain metastases?  

Outcomes of interest were survival, quality of life, morbidity of interventions, and local control of disease.  

**Target Population**  
These recommendations apply to adults with confirmed cancer and a suspected 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**  
- Contrast-enhanced computerized tomography is the standard diagnostic test for individuals suspected of intracranial primary or metastatic cancer. In those individuals in whom there appears to be a solitary 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 (100ml of current non-ionic contrast at 30mg I/ml) and a repeat computerized tomographic scan. Alternatively, high-dose contrast gadolinium enhanced magnetic resonance images may be used as they have been demonstrated to increase the sensitivity in detecting smaller lesions.
- Data from two randomized control trials report that the false positive rate for magnetic resonance imaging in determining the presence of brain metastases ranges from 2% to 11%.

- Stereotactic biopsies 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. Patients should be encouraged to participate in clinical trials of stereotactic biopsy.

- 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. 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.

- 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 and should be considered surgical candidates.

- There are insufficient data to recommend the use of stereotactic radiosurgery as an alternative to surgical excision.

- Insufficient data exist regarding chemotherapy alone to extrapolate these findings to patients with single brain metastases where alternate treatment modalities exist.

**Qualifying statements**

- 3,000cGy in 10 fractions is the standard 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, that 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 a day (3,000/10) will be associated with less long term neurocognitive effects than 400cGy a day (2,000/5) in the few long-term survivors, which is the reason that many radiation oncologists in Ontario prefer 3,000cGy in 10 fractions. There is no data to either support or refute this belief; hence, there is no way to resolve it at present. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.

- Age greater or less than 60 was used in the meta-analysis as a common variable that was statistically significant related to survival. Older age should be used as a guideline for survival with older patients responding less well to surgical intervention. A strict cut-off at 60 is not implied in the decision-making process. Other factors such as performance status and status of the primary disease were also variables that were statistically related to survival. All three of these factors should be considered in deciding which patients should be surgical candidates.

**Methods**

Entries to MEDLINE (1966 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1983 through October 2002), and Cochrane Library (2004, Issue 2) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2004) and the American Society for Therapeutic Radiology and Oncology (1998 to 2003) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative’s Neuro-oncology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Neuro-oncology Disease Site Group, which
comprises medical and radiation oncologists, neuro-oncologists, neurosurgeons, a neuroradiologist, a neuropathologist, an oncology nurse, and a patient representative.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

**Key Evidence**

- There are no randomized control trials comparing magnetic resonance imaging and computed tomography. Nine prospective trials were identified addressing the role of either magnetic resonance imaging or computed tomography. The studies consistently reported that high doses of contrast detected more metastases than standard doses of contrast, either immediately after contrast administration or within one hour of contrast administration.
- The false positive rate for magnetic resonance imaging in determining the presence of brain metastases ranges from 2% to 11%.
- Five randomized control trials compared radiation dosages. Radiation doses greater than 3,000 cGy in 10 fractions did not provide increased survival or palliation. In addition, neither misonidazole, boost irradiation, nor hyperfractionation influenced survival.
- Two randomized control trials have shown that surgical excision followed by radiation significantly improves survival compared with radiation alone. However, a third randomized control trial did not demonstrate any significant benefit for the addition of surgery compared with radiation alone. A combined analysis of individual patient data from the three trials showed no significant overall survival advantage for the surgery plus radiation therapy group. The subgroup analysis showed that age (<60) and extent of primary disease (limited primary disease or no known primary site) were statistically significant variables in the Cox model that predicted increased survival. Subgroup analysis suggested that there was marginal statistical significance for increased survival in patients with limited primary disease having surgical excision prior to radiation.
- A randomized trial of surgery plus whole brain radiation therapy compared with surgery alone demonstrated a significant reduction in the incidence of recurrent brain metastases favouring whole brain radiation therapy although an overall survival advantage or maintenance of functional independence was not detected.
- No randomized control trials were found that compared stereotactic radiosurgery and surgical resection. Preliminary evidence suggests that stereotactic radiosurgery provides similar median survivals to surgical resection in highly selected patients.

**Related Guidelines**

Practice Guidelines Initiative’s Practice Guideline Report #13-4: *Management of Brain Metastases (developed by the Supportive Care Disease Site Group).*

For further information about this practice guideline report, please contact Dr. James Perry, Chair, Neuro-oncology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Room A-442, Toronto, Ontario, M4N 3M5; TEL 416-480-4766; FAX 416-480-4563.

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The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

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FULL REPORT

I. QUESTIONS

Diagnosis
1. What is the optimal imaging modality for the diagnosis of single brain metastases?
2. When should stereotactic biopsy be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments?

Management
3. What is the optimal dose of whole brain radiation therapy (WBRT) for patients with confirmed single brain metastases?
4. Should patients with confirmed single brain metastases have surgical resection prior to radiation therapy?
5. What is the role of stereotactic radiosurgery (SRS) in the management of patients with single brain metastases?
6. What is the role of chemotherapy in patients with single brain metastases?

Outcomes of interest were survival, quality of life, morbidity of interventions, and local control of disease.

II. CHOICE OF TOPIC AND RATIONALE

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).

Currently in Ontario, there is variation in the management of patients with suspected single metastases. The diagnostic test of choice varies according to availability of magnetic resonance imaging (MRI) as well as differing regional protocols. There is also some question about the optimal dose to give in contrast-enhanced CT or MRI in patients with suspected brain metastases. In Ontario, many sites use 15g of iodine for routine contrast-enhanced CT, in part based on cost of the non-ionic iodine contrast used (about $80 per 100 ml) and in part because of the availability of contrast-enhanced MRI.

An informal poll was conducted by the Neuro-oncology Disease Site Group (DSG), which represents nine regional cancer centres, to establish current practice in Ontario for the treatment of patients with single brain metastases. Findings, summarized in Table 1, are categorized according to patients’ prognoses (good versus poor) based on the Karnofsky performance score 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 3,000 cGy in 10 fractions, although patients treated at two Regional Cancer Centres (RCCs) receive 2,000 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 resection. Patients at seven RCCs receive 2,000 cGy in five fractions, whereas the dose varied at the other two centres, depending on pathology. Patients were referred for surgical consideration based on both tumour-specific factors (location, size, and degree of mass effect) and patient-specific factors (age, co-morbid medical conditions, and extracranial 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></td>
<td>Resectable</td>
<td>Non-resectable</td>
</tr>
<tr>
<td>Surgery</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 centres – 3,000 cGy in 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 centres – 2,000 cGy in 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 centres - variable doses</td>
<td></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>
</tbody>
</table>

The Neuro-oncology DSG felt that a practice guideline was 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. Variations in treatment across RCCs in Ontario.

III. METHODS
Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of 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 PGI’s Neuro-oncology DSG and methodologists. Members of the Neuro-oncology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the management of single brain metastases, developed through systematic reviews and evidence synthesis. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care. External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1983 through October 2002), and the Cochrane Library (2004, Issue 2) 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), “chemotherapy, adjuvant” (MeSH), “tomography, x-ray computed” (MeSH), “magnetic resonance imaging” (MeSH), “diagnostic imaging” (MeSH), and
the following phrases used as text words: “surgery”, “radiation”, “radiotherapy”, “chemotherapy”, “computed tomography”, “contrast dose”, and “contrast enhancement”. 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 2004) and the American Society for Therapeutic Radiology and Oncology (1998 to 2003), 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 practice guideline if they were fully published reports or published abstracts of:
1. Meta-analyses, systematic reviews, and randomized trials addressing specific guideline questions. If none of these study types were available, retrospective reviews and prospective case series were eligible for inclusion.
2. Outcomes of interest were survival, quality of life, morbidity of interventions, and local control of disease. 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.

Synthesizing the Evidence
An analysis of individual patient data from the three RCTs (6-8) that compared surgery plus radiation therapy to radiation therapy alone was conducted. The patient mortality data had four common and comparable variables: treatment allocation (surgery plus radiation versus radiation alone), age (≤60 versus >60), primary site of cancer (lung versus other), extent of disease (limited versus extensive). Mortality data was converted to days to allow for the production of Kaplan-Meier survival curves. The survival curves were generated and compared using a modified Gehan-Wilcoxon test. Overall median survival was calculated. Main effects Cox modeling was utilized to generate hazard ratios on the above four variables, which were chosen a priori to the analysis.

IV. 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 practice guideline

<table>
<thead>
<tr>
<th>Question</th>
<th>Type of study (reference)</th>
</tr>
</thead>
</table>
| 1. What is the optimal imaging modality for the diagnosis of single brain metastases? | 4 case series (9-12)  
5 prospective phase II studies (13-17) |
| 2. When should stereotactic biopsy be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments? | 2 RCTs\(^a\) (6,8)  
3 retrospective reviews (18-20) |
| 3. What is the optimal dose of whole brain radiation therapy (WBRT) for patients with confirmed single brain metastases? | 5 RCTs\(^b\) (21-24)  
1 retrospective review (25)  
1 prospective phase II (26) |
| 4. Should patients with confirmed single brain metastases have surgical resection prior to radiation therapy? | 4 RCTs (6-8,27) |
| 5. What is the role of stereotactic radiosurgery (SRS) in the management of patients with single brain metastases? | 2 RCTs (28) (abstract (29))  
5 case series (30-34)  
7 retrospective reviews (35-41) |
| 6. What is the role of chemotherapy in patients with single brain metastases? | 2 prospective cohorts (42,43)  
1 prospective phase II (44) |

Note: RCT, randomized controlled trial.
\(^a\) Neither RCT was designed to address the role of stereotactic biopsy; however, both studies comment on the use of biopsy.
\(^b\) 2 RCTs reported in (21).

Diagnosis

1. What is the optimal imaging modality for the diagnosis of single brain metastases?

Two case series formally evaluated the additional yield of contrast-enhanced MRI in patients with an apparently single metastasis diagnosed by CT (9,13). In Kuhn et al’s (9) prospective case series, standard-dose MRI did not detect any additional metastases compared with CT in three out of four patients. However, high-dose MRI identified two additional metastases in each of those patients. In the fourth patient, standard-dose MRI detected five metastases, and high-dose MRI showed 12 enhancing lesions. Similarly, Mastronardi et al (13) studied 35 patients with CT confirmation of single lesions, and 28.6% of those patients showed two to six metastases with MRI.

Three case series assessed contrast agents in CT in a total of 45 patients with metastatic brain tumours (10-12). All patients underwent both high- (51-80g iodine) and standard-dose (around 30g iodine) scans. High-dose scan showed additional lesions in 16 of 45 patients compared with standard-dose scans. The remaining 29 patients showed no additional lesions with high-dose scans compared to standard-dose scans. The diagnosis of extracranial malignancy was confirmed by biopsy in 25 patients.

Four prospective phase II studies involving a total of 160 patients assessed contrast agents in MRI (14-17). They compared standard-dose gadolinium (0.1mmol/kg) with high-dose gadolinium (either 0.2 or 0.3 mmol/kg). High-dose contrast-enhanced MRI showed more lesions than standard-dose MRI (919 versus 515). In addition, 0.2 mmol/kg showed fewer enhancing lesions (n=142) compared with 0.3 mmol/kg (n=176) (16). Van Dijk et al (16) also reported that eight out of sixteen patients showed a diagnostically important increase in the number of metastases (i.e., from zero to more, from one to more, or from two to more) detected with high-dose gadolinium.

Mastronardi et al (13) reported that the median survival for 25 patients who had CT diagnosis of single metastases was 40 weeks, and the median survival for 25 patients who had MRI diagnosis of single metastases was 36 weeks (p-value not reported). Mastronardi et al (13) concluded that those differences were not statistically different and the use of standard-dose MRI may not offer survival advantages compared to CT.
2. **When should stereotactic biopsy be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments?**

Two randomized trials were identified that addressed the utility of stereotactic biopsy; however, neither of those studies were designed to determine the utility of stereotactic biopsy prior to treatment (6,8). Patchell et al (6) used MRI to identify all 54 patients with single metastases who were enrolled in their randomized study comparing radiation therapy with or without prior surgical resection. Six patients (11%) were excluded from the study because stereotactic biopsies indicated that those six patients had primary brain tumours or treatable inflammatory or infectious processes, not single brain metastases. Since 11% of the patients in their study were misdiagnosed using MRI, Patchell et al argued that all patients should undergo biopsy prior to non-surgical therapy. However, Mintz et al’s (8) RCT, which compared surgery plus radiation therapy to radiation therapy alone, did not require patients to undergo stereotactic biopsy prior to treatment. Mintz et al reported that only one in 43 patients (2.3%) assigned to the surgical group was misdiagnosed (glioblastoma was found during a craniotomy).

Patchell et al (6) reported that there was no morbidity or mortality associated with stereotactic biopsy in their RCT, other than one patient who had a transient hemiparesis. A retrospective review by Kondziolka and Lunsford (19) reported no permanent morbidity or mortality in a ten-year period involving 35 patients with brain metastases undergoing biopsy.

**Management**

3. **What is the optimal dose of whole brain radiation therapy (WBRT) for patients with confirmed single brain metastases?**

The optimal dose and fractionation schedule for radiation therapy for brain metastases have not been determined. The best available data are reported by the Radiation Therapy Oncology Group (RTOG) (21-24) (Table 3). Borgelt et al (21) reported the results of two randomized RTOG studies. Over 1,800 patients with brain metastases were randomized to five schedules of whole brain irradiation ranging from 2,000 cGy in one week to 4,000 cGy over four weeks. Borgelt et al (21) detected that all treatment schedules were comparable with respect to frequency of improvement, time to progression, and survival. The use of steroids was not controlled in those studies. Patients with controlled primary disease or patients with brain metastases as the only tumour site other than the primary site were found to be a prognostically favourable group.

In the third RTOG trial, investigators attempted to select a group of patients with a relatively good prognosis to test if increasing the total dose of radiation would improve outcome (24). The investigators randomized 255 patients with single metastases. They found that 3,000 cGy (300 cGy in 10 fractions) over two weeks was as effective as 5,000 cGy in four weeks (250 cGy in 20 fractions) in terms of palliation of symptoms, neurological improvement rate, median survival, cause of death, and time to progression.

A fourth RTOG trial involved 779 patients who were randomized to either 30 Gy over ten fractions or 50 Gy over six fractions (23). Patients were also randomized to receive the radiation treatments with or without misonidazole (a radiation sensitizer). Neither misonidazole nor fractionation regimen influenced survival.
Table 3. Summary of data from the Radiation Therapy Oncology Group (RTOG).

<table>
<thead>
<tr>
<th>Study</th>
<th>Radiation Schedules</th>
<th>Sample Size</th>
<th>Median Survival (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borgelt, 1980 (21)</td>
<td>3,000/10 &lt;br&gt; 3,000/15 &lt;br&gt; 4,000/15 &lt;br&gt; 4,000/20</td>
<td>233 &lt;br&gt; 217 &lt;br&gt; 233 &lt;br&gt; 227</td>
<td>18* &lt;br&gt; 15† &lt;br&gt; 18 &lt;br&gt; 17</td>
</tr>
<tr>
<td>Borgelt, 1980 (21)</td>
<td>2,000/5 &lt;br&gt; 3,000/10 &lt;br&gt; 4,000/15</td>
<td>447 &lt;br&gt; 228 &lt;br&gt; 227</td>
<td>15†</td>
</tr>
<tr>
<td>Kurtz, 1981 (24)</td>
<td>3,000/10 &lt;br&gt; 5,000/20</td>
<td>130 &lt;br&gt; 125</td>
<td>18 &lt;br&gt; 17</td>
</tr>
<tr>
<td>Komarnicky, 1991 (23)</td>
<td>3,000/10 &lt;br&gt; 5,000/6 &lt;br&gt; 3,000/10‡</td>
<td>193 &lt;br&gt; 200 &lt;br&gt; 190</td>
<td>18 &lt;br&gt; 16 &lt;br&gt; 16</td>
</tr>
<tr>
<td>Murray, 1997 (22)</td>
<td>3,000/10 &lt;br&gt; 1.6 Gy b.i.d. to 5,400</td>
<td>213 &lt;br&gt; 216</td>
<td>18 &lt;br&gt; 18</td>
</tr>
</tbody>
</table>

*Overall median survival, with no significant differences among treatment schedules, ranging from 16 to 20 weeks.  †Overall median survival, with no significant differences among treatment schedules, ranging from 14 to 15 weeks.  ‡Misonidazole.

None of the treatment arms showed any statistically significant difference in survival.

To investigate whether increased local radiation to the tumour site in addition to whole brain irradiation increases survival or neurological improvement, Hoskin et al (25) reviewed 164 patients, 50 of whom had a boost irradiation of 15 Gy in eight fractions to the site of the metastasis following whole brain irradiation; the other 114 patients had whole brain radiation. No difference in overall survival was found between the two groups.

More recently, attention has been focused on alternative methods to deliver radiation. Hyperfractionation is a regimen of multiple daily fractions each smaller in dose than typical fractions. The theoretical rationale for the lower dose per fraction is that the toxicity of radiation will be less and an overall higher total tumourcidal dose may be delivered (26). The RTOG conducted a randomized trial of 1.6 Gy twice daily (b.i.d.) to a total dose of 54.4 Gy compared with standard therapy of 30 Gy in 10 daily fractions in 429 patients with single or multiple unresected brain metastases (22). Median survival in both groups was 4.5 months, which demonstrated that accelerated hyperfractionation provided no survival benefit compared with standard therapy.

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

Three randomized trials have compared surgery plus radiation therapy to radiation alone in the treatment of brain metastases (6-8) (Table 4), and one randomized trial compared surgery and radiation therapy to surgery alone (27). Patchell et al (6) randomized 48 patients with single metastases to receive surgery and radiation therapy or radiation therapy alone. Median survival (10 months versus 3.75 months, p<0.01) and length of functional independence (9.5 months versus 2 months, p<0.005) were significantly improved in the surgical group. Recurrence at the site of the original metastasis was less frequent in the combined surgery plus radiation therapy group than in the radiation alone group (20% versus 52%, respectively, p<0.02). Vecht et al (7) randomized 63 patients with single metastases and found that surgical excision in addition to radiation therapy led to a longer median survival (10.0 versus 6.28 months, p=0.04) and somewhat longer median functionally independent survival (7.5 months versus 3.5 months, p=0.06) (7). 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).
In Mintz et al’s (8) RCT, 84 patients were randomized to radiation therapy alone (43 patients) or surgery plus radiation therapy (41 patients). Median survival was not statistically different between the radiation therapy alone arm or surgery plus radiation therapy arm (6.3 months and 5.6 months, respectively, \(p=0.24\)). In addition, most patients died within the first year (69.8% in the radiation therapy arm, 87.8% in the surgery plus radiation therapy arm). There were also no significant differences in 30-day mortality, morbidity, or causes of death (neurologic, systemic, or combined) between the two groups at baseline. Patients were stratified according to the systemic extent of their primary disease: i) brain metastases only with no evidence of primary; ii) brain metastases and local primary disease only; and iii) extracranial metastases of primary disease. 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; \(p=0.006\)). However, the survival analysis demonstrated no significant treatment effect when patients were divided into baseline extent of disease. There were also no statistically significant differences in the mean Spitzer quality-of-life scores or the Karnofsky performance scores between treatment groups.

Table 4. Median survival reported in the randomized trials of surgery plus radiation therapy compared with radiation therapy alone.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Steroids</th>
<th>Median Survival (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell, 1990 (6)</td>
<td>48</td>
<td>All</td>
<td>3.75</td>
<td>10.0</td>
</tr>
<tr>
<td>Vecht, 1993 (7)</td>
<td>63</td>
<td>Most</td>
<td>6.28</td>
<td>10.0</td>
</tr>
<tr>
<td>Mintz, 1996 (8)</td>
<td>84</td>
<td>All</td>
<td>6.28</td>
<td>5.62</td>
</tr>
</tbody>
</table>

Results of the Meta-analysis Comparing Surgery and Radiation to Radiation Alone

The Neuro-oncology DSG was able to obtain patient-specific data from the three RCTs that compared surgery plus radiation therapy to radiation therapy alone (6-8). There were four variables common to all trials: treatment allocation (surgery plus radiation versus radiation alone); age (\(\leq 60\) versus >60); primary site of cancer (lung versus other), and extent of primary disease (limited versus extensive). The distribution of patients within each variable, across all three trials is listed in Table 5.

Table 5. Summary of variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Radiation Alone (N=97)</th>
<th>Surgery + Radiation (N=98)</th>
<th>Total (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>52%</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>Site</td>
<td>Lung</td>
<td>59%</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>Extent of Disease*</td>
<td>Limited</td>
<td>59%</td>
<td>63%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>Extensive</td>
<td>41%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>Treatment Allocation</td>
<td>Patchell, 1990 (6)</td>
<td>24%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Vecht, 1993 (7)</td>
<td>32%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>Mintz 1996 (8)</td>
<td>44%</td>
<td>42%</td>
<td>43%</td>
</tr>
</tbody>
</table>

*Limited disease – no evidence of primary disease or local primary and intracranial metastasis only. Extensive disease – extracranial metastases.

Survival was described by the Kaplan-Meier life table method and compared by a modified Gehan-Wilcoxon test (Figure 1). The overall median survival time for the radiation group was 160 days and 218 days for the surgery and radiation group. There was no significant difference in survival between the treatment groups (\(p=0.13\)).
The main effects Cox modeling revealed that only age and extent of disease were significantly associated with mortality. There were also no significant interactions. The Cox modeling is summarized in Table 6 and plotted as survival curves in Figures 2-4.

Table 6. Cox model summary.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: (surgery + radiation)</td>
<td>0.83</td>
<td>0.65-1.16</td>
<td>0.35</td>
</tr>
<tr>
<td>Site: (lung)</td>
<td>0.98</td>
<td>0.78-1.42</td>
<td>0.72</td>
</tr>
<tr>
<td>Age: (&gt;60)</td>
<td>1.77</td>
<td>1.24-2.26</td>
<td>0.00082</td>
</tr>
<tr>
<td>Extent: (extensive)</td>
<td>1.60</td>
<td>1.17-2.17</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

Figure 2 estimates survival based on age. Patients less than 60 years old have significantly improved survival compared with patients older than 60 years. Figure 3 graphs the Kaplan-Meier survival curve comparing treatment allocation and age. Patients younger than 60 years appear to have increased survival irrespective of treatment allocation compared to patients older than 60. However, that difference was not statistically significant.
Figure 2. Kaplan-Meier estimate of survival by age.

Kaplan-Meier Estimate of Survival by Age

Figure 3. Kaplan-Meier estimate of survival by treatment and age.

Kaplan-Meier Estimate of Survival by Treatment and Age

P = 0.000472

P = 0.00338
Subgroup analysis also compared patients with extensive primary disease to patients with limited disease. Extent of disease was shown to have a statistically significant survival benefit for those patients having limited disease (Figure 4). Lastly, the extent of disease by treatment was analyzed (Figure 5). That analysis demonstrated a marginal treatment effect favouring the surgery plus radiation treatment arm in patients with limited disease (mortality hazard ratio: 0.70, 95% confidence interval: 0.48 to 1.03, p=0.0007).

**Figure 4. Kaplan-Meier estimate of survival by extent of disease.**

Kaplan-Meier Estimate of Survival by Extent of Disease

- **Limited**
- **Extensive**

\[ P = 0.000784 \]
Evidence for local control

A large proportion of patients receiving radiation therapy for metastases succumb from progressive systemic cancer while having stable neurological disease. Evidence from three randomized trials of surgery and postoperative radiation therapy compared with radiation therapy alone in patients with single metastases supports the observations that radiation therapy alone is adequate for local control of the central nervous system (6-8). Mintz et al (8) reported that the cause of death was systemic disease in 40% of patients and that systemic disease was a contributing factor in an additional 33% of patients across both treatment groups. Vecht et al (7) reported that the cause of death was neurologically related in only one third of patients in both treatment groups. Patchell et al (6) reported that 71% of patients in the surgical group and 50% in the radiation group (p=0.26) died of systemic causes.

Surgery and Radiation Therapy Compared with Surgery Alone

There is one randomized trial comparing surgery plus radiation therapy to surgery alone. Patchell et al (27) randomly assigned 49 patients to postoperative WBRT and 46 patients to observation after complete resection of a single brain metastasis. Recurrence of tumour at the site of the original metastasis (10% versus 46%, respectively, p<0.001) as well as anywhere in the brain (18% versus 70%, p<0.001) was less frequent in the radiation group compared with the observation group. Patients in the radiation group were less likely to die of neurologic 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.
5. What is the role of stereotactic radiosurgery (SRS) in the management of patients with single brain metastases?

No randomized trials were found that compared SRS with traditional surgical resection. Reports concerning the role of SRS in the treatment of brain metastases are retrospective reviews or prospective case series, which involve relatively few patients and short follow-up periods (Table 7).

The two largest series are those by Auchter et al (41) and Alexander et al (40). Auchter et al 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 56 weeks and the one- and two-year survival was 53% and 30%, respectively. The median duration of functionally independent survival, defined as a Karnofsky performance score of greater than or equal to 70, was 44 weeks.

Alexander et al (40) retrospectively reviewed their seven-year experience using modified LINAC-based SRS. Their study consisted of 248 consecutive patients (421 lesions) with stable systemic disease in 70% of patients, KPS scores greater than 70 and tumour diameters less than four centimetres. Almost 70% of patients had single metastases and 76% were referred for SRS to treat specific lesions that recurred at the same site after initial treatments of WBRT with or without surgical resection. All patients received WBRT either as part of their initial treatment or at the time of SRS (15%). Median follow-up was 26.2 months, which is significantly longer than most other series. Using a median treatment dose of 15 Gy, the overall median survival was 9.4 months. Actuarial local control was approximately 85% at one year and 65% at two years. The median survival in patients with single metastases was 11.2 months. These results are consistent with those reported in two randomized trials of patients with single metastases that had surgical resection followed by radiation therapy (6,7). However, there are serious concerns when direct comparisons are made between retrospective reviews and randomized surgical trials. Specifically, the patients in the study by Alexander et al are a cohort with a bias towards increased survival based not only on their baseline characteristics but also due to the fact that they had survived their initial therapy long enough to have a recurrence (median time from initial treatment to SRS was approximately eight months). Alexander et al found that presence of systemic disease and age greater than 60 years contributed independently to decreased survival. Lesions greater than three centimetres were less likely to be controlled than smaller lesions and were associated with increased rates of local failure. Tumours classically reported to be “radioresistant” (melanoma, renal cell, and sarcoma) had local control equivalent to those seen with “radiosensitive” tumours, although the number of patients in those subgroups was small.

Similar results have been observed using the Gamma Knife (26,30,45). In a representative series, Flickinger et al (45) reviewed 116 consecutive patients with single metastases who underwent SRS. Forty-five (40%) patients had tumours that recurred after previous WBRT and 71 (60%) were treated with SRS as initial management for their metastases. The minimum mean tumour dose was 17.9 Gy (range 8-30 Gy). The median survival was 11 months, with local tumour control in 85%. Recurrence was documented in 15%.
Stereotactic radiosurgery with whole brain radiation therapy (WBRT)

The use of SRS alone or in conjunction with WBRT (boost SRS) has been reported in two RCTs (28)(abstract (29)) and several retrospective reviews (31-39). The rationale for using SRS as a boost in addition to WBRT is similar to the reasons presented for the use of radiation therapy following surgery. Specifically, the WBRT allows for the irradiation of any microscopic intracranial tumour deposits not revealed by neuroimaging studies (36,37). Additionally, certain metastases can infiltrate into the brain beyond the SRS margins. An additional theoretical consideration for using combined WBRT and SRS 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 (32).

The RTOG 9508 RCT randomized 333 patients with brain metastases to receive either WBRT and SRS or WBRT alone (28). Approximately 56% of the patients included in the trial had solitary brain metastases. There was a significant improvement in median survival time in patients with solitary brain metastases receiving both WBRT and SRS compared to patients with solitary metastases receiving WBRT alone (6.5 months versus 4.9 months, p=0.04).

The interim results of a RCT have been reported recently comparing SRS and WBRT to SRS alone (29) (abstract). One hundred and twenty patients with less than four brain...
metastases were randomized to the treatment arms (59 patients in the SRS and WBRT arm and 61 patients in the SRS-alone arm). The trial has set an accrual target of 170 patients (85 per arm). After a median follow-up of six months, the interim results suggest that patients receiving SRS and WBRT have improved survival compared to SRS alone. The actuarial one-year survival was 26% among the patients receiving SRS alone and 39% in the patients receiving SRS and WBRT. The data from that trial are still maturing, thus it should be interpreted cautiously.

Data from retrospective studies has suggested that the use of SRS in conjunction with standard WBRT is more effective. Those studies have reported increased tumour progression and decreased local control in patients receiving SRS alone in comparison with those receiving combined SRS and WBRT, although survival was not increased (39,40,45). For example, Flickinger et al (45) reviewed 116 patients with single metastases treated with LINAC SRS. In the 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.

6. **What is the role of chemotherapy in patients with single brain metastases?**

The role of chemotherapy alone in the treatment of brain metastases of solid tumours has not been addressed in a randomized trial. However, two prospective cohorts (42)(abstract (43)) and one non-randomized phase II study (44) address the role of chemotherapy for several different primary tumours with brain metastases. In a cohort study with primary breast cancer that metastasized to the brain, Rosner et al (42) treated 100 consecutive patients with two different chemotherapy regimens: cyclophosphamide, fluorouracil and prednisone (CFP) or CFP with methotrexate and vincristine. Approximately 10% of patients had a complete response, and 40% had a partial response with corresponding mean duration of remissions of 10 and 7 months, respectively.

Kim et al have reported their abstract results of a prospective cohort study comparing WBRT and platinum-based chemotherapy to WBRT alone in 63 patients with newly diagnosed brain metastases (43). They reported that the overall median survival was significantly longer for the patients receiving WBRT and chemotherapy compared to those receiving WBRT alone (58.1 weeks versus 19.0 weeks, p<0.001). The toxicity in the chemotherapy arm was reported to be “tolerable”; however, no additional details were given. It is important to recognize that the data in this study are still emerging and that the treatment groups were not randomized, so the significant difference in survival needs to be interpreted cautiously.

A non-randomized prospective trial of breast cancer patients with brain metastases (44) reported that chemotherapy combined with radiation therapy induced a higher rate of neurologic response than radiation alone. Boogerd et al (44) concluded that their results warranted more high-quality research to confirm their results.

Until recently it was assumed that the blood-brain barrier prevented chemotherapeutic agents from passing into the central nervous system. Temozolomide is a novel chemotherapeutic agent that does cross the blood-brain barrier. Temozolomide has been addressed in an evidence summary developed by the Neuro-oncology DSG (46).

V. **INTERPRETIVE SUMMARY**

**Diagnosis**

1. **What is the optimal imaging modality for the diagnosis of single brain metastases?**

There is limited evidence from prospective trials that enhanced MRI has increased performance in detecting lesions compared with contrast-enhanced CT (even at high doses) (9,13). Also, some patients who have additional lesions detected by MRI are ineligible for surgery anyway. Additional lesions shown may in fact not be metastases (e.g., telangiectasias), and patients who might be eligible for surgery may be denied it based on a false positive (for
metastases) high-dose-enhanced study. Lastly, the benefit shown for surgery in patients with an apparently single metastasis by CT or MRI with standard dose presumably includes patients who may have additional lesions shown with high-dose enhancement.

The optimal dose of contrast in both CT and MRI is not clearly defined. Hayman et al (10) suggested higher doses for a better depiction of abnormalities. Higher doses of contrast (74-80g iodine) seem to detect metastases (11,12) better than standard doses of contrast, either immediately after contrast administration or within one hour of contrast administration. Studies suggest a higher dose of paramagnet contrast for MRI for detection of intracranial tumours (12,14-17).

2. When should stereotactic biopsy be used to establish tissue diagnosis of single brain metastases prior to the initiation of other treatments?

Evidence from two randomized trials presented conflicting conclusions regarding the need for stereotactic biopsy prior to treatment. Also, neither of those studies were designed to determine the utility of stereotactic biopsy prior to treatment (6,8). Patchell et al argued that all patients should undergo biopsy prior to surgery because 11% of the patients in their study were misdiagnosed by MRI. However, Mintz et al detected a false positive rate of only 1.9% in their study, thus disputing Patchell et al’s results. More studies are warranted to address the role of stereotactic biopsy in patients with brain metastases.

Management

3. What is the optimal dose of whole brain radiation therapy (WBRT) for patients with confirmed single brain metastases?

Five trials by the RTOG compared various dosages of radiation therapy for patients with brain metastases. They did not identify that one dosage was better than another in terms of overall survival. For most patients with brain metastases, when treated with radiation therapy alone, 3,000 cGy in two weeks was as effective as four weeks of higher-dose regimens (up to 5,000 Gy) (24). Currently the standard management of patients with single brain metastases in the United States is 3,000cGy in 10 fractions. This 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 a day (3,000/10) will be associated with less long-term neurocognitive effects than 400cGy a day (2,000/5) in the few long-term survivors, which is the reason that many radiation oncologists in Ontario prefer 3,000cGy in 10 fractions. There is no data to either support or refute this belief; hence, there is no way to resolve it at present. More randomized trials examining various dosages of radiation therapy for patients with solitary brain metastases are necessary to determine the optimal dose of radiation therapy to maximize survival and minimize toxicity. The Neuro-oncology Disease Site Group will update the recommendations as new evidence becomes available.

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

The two major differences between the three RCTs that compared surgery plus radiation therapy to radiation therapy alone are reflected in the reduced survival time for the surgery plus radiation therapy group in Mintz et al's (8) RCT and the diminished survival time for the radiation-alone group reported by Patchell et al (6). The trials differed with respect to important baseline patient characteristics, including systemic extent of primary disease.

Macdonald and Cairncross (47) suggest that the trial by Patchell et al may have had a referral bias. Patients in that 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 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 Patchell et al. Patchell et al had a large proportion of non-small cell lung cancer patients (77.0%) compared with Vecht et al (7) (52.3%) and Mintz et al (53.6%). Since lung cancer is a relatively radioresistant tumour, a higher proportion of this histology may bias the results in Patchell et al against radiation. Patchell et al reported that lung cancer was not found to be a significant variable in a multivariate analysis but their small sample size may have had low statistical power to detect this difference.

The benefit for surgery may be lost if patients with more advanced cancer who are likely to die early represent a greater proportion of the trial population. Decreased median survival was reported in two randomized trials (7,8) in patients with greater systemic involvement of their primary malignancy. Forty-five percent of the patients in the study by Mintz et al had extracranial metastases compared with only 37.5% in the trial by Patchell et al and 31.7% in the trial by Vecht et al. 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 (5 months in both groups, p=0.88). However, they did find a greater survival advantage for surgery in patients with stable disease (12 versus 7 months, p=0.02) than in the combined results for all patients (10 versus 6 months, p=0.04), for surgery plus radiation and radiation alone, respectively. The increased proportions of patients in Mintz et al with extracranial metastases may have made it more difficult to detect a survival advantage for surgery.

A final consideration regarding the differences between those trials is that they were all of relatively small sample size. The statistical power in Mintz et al based on the small sample size, was estimated to be quite low (Type II error). Specifically, that trial was calculated to only have a 50% power to detect a 50% increase in the median survivals between treatment arms (48). A pooled estimate of all patients, stratified according to baseline extent of disease would generate a more precise estimate of the true treatment effect by increasing the sample size.

An analysis of the three trials showed no significant overall survival advantage for the surgical group. Subgroup analysis showed that age (<60) and extent of primary disease (limited primary disease that included patients who presented with no known primary site) were statistically significant variables in the Cox model that predicted increased survival. There was marginal statistical significance for increased survival in patients with limited primary disease having surgical excision prior to radiation.

Surgery and Radiation Therapy Compared with Surgery Alone

The one randomized trial examining surgery and radiation versus surgery alone (27) supports the use of postoperative radiation therapy in addition to surgery. Tumour recurrence was significantly reduced both at the original and distant sites and patients were less likely to die of neurologic 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, it seems that the use of postoperative radiation is supported by that trial in order to prevent central nervous system relapse and neurological death rather than increasing survival time or maintaining functional independence.
5. **What is the role of stereotactic radiosurgery (SRS) in the management of patients with single brain metastases?**

The quality of the evidence concerning the role of SRS in the treatment of brain metastases is poor. Most series contain few patients; many report subjective outcomes such as neurologic improvement or local control and have short follow-up periods. The largest series, using a modified LINAC (40,41) and the Gamma Knife (45), reported median survivals, local control and functional performance scores similar to that reported in two randomized surgical trials (6,7). This data should be viewed as hypothesis generating rather than be considered as important clinical outcomes. Moreover, the patients in the SRS series are highly selected towards longer survival. In the surgical trials, the survival time was standardized (measured from the date of randomization to death), whereas there was no standardization in the SRS series (some investigators measured from the date of diagnosis and others from the date of recurrence). Direct comparisons between surgery and SRS are needed using random patient allocation and objective outcomes such as survival.

There is consistent but weak evidence that SRS should be used in conjunction with WBRT to optimize tumour control. This issue needs to be resolved in a randomized clinical trial. Several additional issues in the use of SRS for brain metastases need to be more clearly defined. For instance, the maximal size of treatable lesions is also not known although it seems that larger tumour volumes are associated with poorer response and local control with higher complication rates.

6. **What is the role of chemotherapy in patients with single brain metastases?**

There are no randomized trials investigating the role of chemotherapy alone in the treatment of brain metastases of solid tumours. The existing literature lists studies involving patients with multiple brain metastases or patients with single or multiple brain metastases. Insufficient data exists to extrapolate the findings to patients with single brain metastases where alternate treatment modalities exist.

VI. **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>
<thead>
<tr>
<th>Protocol ID(s)</th>
<th>Title and details of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson Cancer Center (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>RTOG 95-08</td>
<td>Phase III randomized study of fractionated external beam whole brain radiotherapy with or without a stereotactic radiosurgery boost in patients with one unresected brain metastasis. Projected accrual is 262 patients. The trial is now closed.</td>
</tr>
<tr>
<td>NCI-P02-0211</td>
<td>Phase III randomized study of methylphenidate to improve quality of life in patients receiving radiotherapy for primary or metastatic brain tumours.</td>
</tr>
</tbody>
</table>
VII. DISEASE SITE GROUP CONSENSUS PROCESS
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 WBRT in terms increasing survival. Other issues addressed in discussion of the guideline included CT versus MRI (including contrast dosage), evidence surrounding stereotactic biopsy, 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.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT
Based on the evidence reviewed, the Neuro-oncology DSG drafted the following recommendations:

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

Draft Recommendations
- Contrast-enhanced computerized tomography is adequate in the majority of cases for the diagnosis of clinically relevant brain metastases. The dosage of iodinated contrast should be at least 30g of iodine (100ml of current non-ionic contrast at 30mg I/ml). To increase the resolution, repeat the computerized tomography with 30g of iodine or gadolinium enhanced magnetic resonance imaging (gadolinium 0.1-0.3 mmol/kg). High dose contrast magnetic resonance images are preferable to standard dose due to increased sensitivity in detecting smaller lesions not seen on standard dose magnetic resonance images.
- There are insufficient data to recommend the use of stereotactic biopsy in all oncology patients presenting with lesions suspected to be metastases. However, histologic confirmation is recommended in cases of solitary lesions with unknown primaries to establish tissue diagnosis prior to other treatments. Patients should be encouraged to participate in clinical trials of stereotactic biopsy.
- The dose and fractionation schedule for WBRT should be 3,000 cGy in 10 fractions or 2,000 cGy in five fractions.
- Surgical excision should be considered for patients that are less than 60 years old with accessible lesions and limited primary disease. 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 and should be considered to be surgical candidates.
- There are insufficient data to recommend the use of stereotactic radiosurgery as an alternative to surgical excision. Patients should be encouraged to participate in clinical trials of stereotactic radiosurgery.
- Insufficient data exist regarding chemotherapy alone to extrapolate these findings to patients with single brain metastases where alternate treatment modalities exist.
Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Report #13-4: Management of Brain Metastases (Supportive Care DSG-in progress).

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 62 practitioners in Ontario (11 medical oncologists, 15 radiation oncologists, 26 surgeons, seven neurologists, one hematologist, and two pathologists). 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 June 4, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology DSG reviewed the results of the survey.

Results
Thirty-two responses were received out of the 62 surveys sent (52% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 29 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 8.

Table 8. Practitioner 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 clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>28 (97%) 0 1 (3%)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>23 (79%) 5 (18%) 1 (3%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>28 (97%) 0 1 (3%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>28 (97%) 1 (3%) 0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>29 (100%) 0 0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>26 (90%) 2 (7%) 1 (3%)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>23 (82%) 2 (7%) 3 (11%)</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 Unsure Not at all likely or unlikely</td>
</tr>
<tr>
<td></td>
<td>20 (69%) 3 (10%) 6 (21%)</td>
</tr>
</tbody>
</table>
Summary of Written Comments
Seven respondents (22%) provided written comments. Three respondents indicated that they found the guideline to be well done with clear recommendations. Also, one respondent praised the individual patient meta-analysis. The main points of the other comments are:
1) Age should not be a strict parameter for deciding whether single brain metastases should be resected or not. Performance status of the patient and the status of the primary disease are very important as well and at times better judge of patient's survival post-treatment.
2) Not all cases of single metastases to the brain are palliative. Patients with surgically resectable primary lung cancer (usually advanced) presenting with single brain metastasis concurrently with the lung cancer have very good prognosis if treated radically.
3) MRI should be the recommended standard because CT is prone to missing small lesions. CT alone for centres with no access to MRI.
4) Surgical accessibility and the probability of achieving complete surgical resection should be considered a criterion.
5) RCTs not included in the guideline:
   • ASTRO 2002 stereotactic radiosurgery + whole brain radiotherapy versus whole brain radiotherapy.
   • Int J Rad Oncol Biol Phys, vol 45, p427-34.
6) Ongoing trials: MDACC is running a trial (in house) surgery versus SRS for single brain metastases.

Modifications/Actions
1) This recommendation is based on the statistical analysis. Age greater or less than 60 was used in the meta-analysis as a common variable among the three trials. It was a statistically significant variable that was related to survival. A qualifying statement was added to the recommendations for clarification.
2) While it is true that there are long-term survivors in a small proportion of patients with brain metastases, distant metastatic disease has an ominous prognosis as seen in the results of the three randomized trials.
3) As MRI becomes more widespread, MRI has become the standard in many centres. However, the Neuro-oncology DSG feels that treatment decisions can still be made on CT scans. If a contrast-enhanced CT scan detects only a single lesion and a treatment is then recommended (such as surgical resection), does the finding of a second very small lesion on MRI, not seen on CT, cause the patient to be treated differently? Imaging is only an estimate, thus the Neuro-oncology DSG decided that a CT is sufficient to make treatment decisions.
4) This criterion has been addressed in the fourth bullet in the recommendations.
5) The RCT abstract in ASTRO 2002 by Sperduto et al (49) has now been published in a full report, and so the full report was added to the guideline (28). The RCT in the International Journal of Radiation Oncology Biology and Physics by Kondziola et al (50) was not included because their RCT specifically excluded patients with single brain metastases.
6) The trial by MDACC was added to the list of ongoing trials.

Practice Guidelines Coordinating Committee Approval Process
The practice guideline report was circulated to members of the PGCC for review and approval. Eight of 12 members of the PGCC returned ballots. One member indicated that he was also a member of the Neuro-oncology DSG and as such was not eligible to review the practice guideline report. Four PGCC members approved the practice guideline report as
written, one member approved the guideline and provided suggestions for consideration by the Neuro-oncology DSG, and two members approved the guideline conditional on the Neuro-oncology DSG addressing specific concerns.

Both of the PGCC members who approved the guideline conditionally had concerns regarding the recommendations. One PGCC member thought that three of the bullets in the recommendations were unclear and offered some suggestions to clarify them. In particular, the PGCC member thought that the bullets regarding CT versus MRI, stereotactic biopsy, and surgical excision of brain metastases needed revisions. The other PGCC member wanted the Neuro-oncology DSG to reconsider its recommendation for the dosage and fractionation of WBRT. The PGCC member was concerned that the recommendation to use 3,000 cGy in 10 fractions was not evidence based, but that it was added to not “upset those who regard it as their standard practice”. Finally, one PGCC member offered a suggestion for the PGCC to consider: How should patients over 60 years be treated?

Modifications/Actions
The recommendations regarding the optimal imaging modality, stereotactic biopsy, and surgical excision of brain metastases were revised for clarity. A qualifying statement was added to further explain why the Neuro-oncology DSG chose to recommend either 30Gy in 10 fractions or 20Gy in 5 fractions. The second bullet of the qualifying statements describes the management for patients over 60 years.

IX. PRACTICE GUIDELINE
This practice guideline report reflects the integration of the draft recommendations with feedback obtained from the external review process. The report has been approved by the Neuro-oncology DSG and will be submitted for approval by the Practice Guidelines Coordinating Committee.

Target Population
These recommendations apply to adults with confirmed cancer and a suspected 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
• Contrast-enhanced computerized tomography is the standard diagnostic test for individuals suspected of intracranial primary or metastatic cancer. In those individuals in whom there appears to be a solitary 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 (100mL of current non-ionic contrast at 30mg I/ml) and a repeat computerized tomographic scan. Alternatively, high-dose contrast gadolinium enhanced magnetic resonance images may be used as they have been demonstrated to increase the sensitivity in detecting smaller lesions.
  − Data from two randomized control trials report that the false positive rate for MRI in determining the presence of brain metastases ranges from 2% to 11%.
• Stereotactic biopsies 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. Patients should be encouraged to participate in clinical trials of stereotactic biopsy.
• 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. The optimal dose and fractionation schedule for WBRT is 3,000 cGy in 10 fractions or 2,000 cGy in five fractions.
• 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 and should be considered surgical candidates.

• There are insufficient data to recommend the use of stereotactic radiosurgery as an alternative to surgical excision.

• Insufficient data exist regarding chemotherapy alone to extrapolate these findings to patients with single brain metastases where alternate treatment modalities exist.

Qualifying statements

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

• Age greater or less than 60 was used in the meta-analysis as a common variable that was statistically significant related to survival. Older age should be used as a guideline for survival with older patients responding less well to surgical intervention. A strict cut-off at 60 is not implied in the decision making process. Other factors such as performance status and status of the primary disease were also variables that were statistically related to survival. All three of these factors should be considered in deciding which patients should be surgical candidates.

Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Report # 13-4: Management of Brain Metastases (Supportive Care Practice Guideline).

X. JOURNAL REFERENCE
The Neuro-oncology DSG is in the process of developing a manuscript to be submitted to a peer-reviewed journal.

XI. ACKNOWLEDGMENTS
The Neuro-oncology Disease Site Group would like to thank Dr Arlan Mintz, Dr. James Perry, and Ms. Alexandra Chambers for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Neuro-oncology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: http://www.cancercare.on.ca/access_PEBC.htm.
REFERENCES


