Brain Oligometastases

Effective Date: July, 2017

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Brain metastases are the most common intracranial tumours in adults, accounting for more than one half of all brain tumours and occurring up to 10 times more frequently than primary brain tumours.\(^1,2\) Approximately 30% of adults with cancer develop brain metastases, and the incidence is rising as patients live longer due to advances in diagnosis of metastases and treatment of systemic disease.\(^3\) Although brain metastases can arise from most types of primary cancer, the most common source for brain metastases are primary lung cancers (40-50%), followed by breast cancer (15-25%), and melanoma (5-20%).\(^4\) The most common presenting symptoms for brain metastases are headaches (40-50%), focal neurological deficits (30-40%), and seizures (15-20%).\(^5\) Generally, when neurological symptoms develop in a patient with known systemic cancer, brain metastases should be suspected.\(^5\) The prognosis for patients with oligometastatic disease (limited intracranial metastases; usually defined as 1-3 lesions) appears to better than that for patients with >3 lesions.\(^3\) Currently, therapeutic approaches to oligometastases include surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and less frequently, systemic therapy.\(^2\) Often patients will receive some combination of treatment. Decisions are based on a variety of factors including the number of intracranial tumours, patient age, prior treatment, functional status, primary tumour type, available treatment options, and extent of extracranial disease.\(^1,6\) With appropriate treatment, many patients with brain metastases can see a reduction in symptoms and extension of life. The present guideline is intended to provide treatment recommendations for patients with 1-4 brain metastases.

GUIDELINE QUESTIONS

- What prognostic factors are important for assessing and managing patients with oligometastatic disease?
- What is the role of surgery in the management of oligometastatic disease?
- What is the role of radiotherapy in the management of oligometastatic disease?
- What is the appropriate follow-up and surveillance strategy for patients with oligometastatic disease?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Central Nervous System (CNS) Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a Knowledge Management Specialist from the Guideline Resource Unit and a working group comprised of members from the Alberta Provincial CNS Tumour Team. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

SEARCH STRATEGY

Peer-reviewed journal articles were searched using the MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: ‘brain metastasis’, ‘oligometastases’, ‘surgery’, and ‘radiation oncology’. Articles were limited to clinical trials, retrospective reviews, and systematic reviews. Articles were excluded from the review if they: had a non-English abstract, were case studies involving less than five patients, or were published prior to the year 2000.
A review of the relevant existing practice guidelines for brain metastases was also conducted by accessing the clinical practice guidelines on the websites of the National Comprehensive Cancer Network (NCCN), British Columbia Cancer Agency (BCCA), Cancer Care Ontario (CCA), American Society for Radiation Oncology (ASTRO), and American College of Radiology (ACR). The National Guideline Clearinghouse was also searched for relevant clinical practice guidelines. Guidelines published prior to 2010 were excluded.

**TARGET POPULATION**

The recommendations outlined in this guideline apply to adults age 18 and older with 4 or fewer brain metastases.

**RECOMMENDATIONS**

**Prognosis:**
1. Prognostic scoring systems, such as the recursive partitioning analysis (RPA) classification for brain metastases, can aid in decision making between more and less aggressive therapies.

2. A favorable prognostic group includes patients with a Karnofsky performance status (KPS) score >70, 4 or fewer cerebral metastases, and controlled or controllable systematic disease.

**Treatment:**
3. Patients with a favorable prognosis can be treated with multiple modalities, including: surgery, SRS, and/or WBRT. Patients with a poor prognosis should be treated according to recommendations outlined in the AHS guideline *Palliative Radiotherapy: Brain Metastases*.

4. For patients with a large or symptomatic single metastasis that is surgically accessible, total resection is recommended. SRS to the tumour bed and/or WBRT can be used to decrease the post-operative risk of recurrence. Patients with limited metastases with gross total resection of one or more metastases can be treated with post-operative SRS to the tumour bed of the resected section, plus SRS to the remaining unresected lesions.

5. SRS is an effective alternative to surgery if the metastasis is less than or equal to 4 cm in diameter and/or is in a surgically inaccessible location, or if the patient is not a surgical candidate.
   - For lesions <2 cm, a single-fraction dose of 20-24 Gy is recommended
   - For lesions 2-3 cm, a single-fraction dose of 18-20 Gy is recommended
   - For lesions >3 cm, a single-fraction dose of 15-16 Gy is recommended

6. For metastases greater than 4 cm, consider fractionated SRS (30-35 Gy in 5 daily fractions).

7. WBRT can be combined with surgery to increase local and regional disease control. It is generally not recommended that adjuvant WBRT is added to SRS as it can increase the likelihood of cognitive side effects without increasing overall survival. In the recurrent setting, WBRT may be considered in patients previously treated with SRS.

**Follow up and recurrence:**
8. Follow up and surveillance imaging should be individualized taking into consideration likely prognosis, extent of initial disease and treatment, options available for salvage and status of systemic disease. Patients are encouraged to participate in clinical trials.
DISCUSSION

Prognostic Indices in Brain Metastases

Patients with brain metastases (BM) are a heterogeneous group in terms of response to treatment and survival. Prognostic indices are important tools for tailoring treatment based on expected survival and are also necessary for stratifying patients in clinical trials. Gasper et al. established the first prognostic index in 1997 after evaluating 1200 BM patients treated with WBRT from three consecutive RTOG trials (79-16, 85-28, and 89-05). Overall, Karnofsky performance status (KPS), age, control of primary tumour, and the status of extracranial disease were found to impact survival. Recursive partitioning analysis (RPA) was used to create a three class staging system for treatment decisions. The best survival (Class I; median 7.1 months) was seen in patients less than 65 years of age, KPS score > 70, and a controlled primary tumour with brain as the only site of metastases. The worst survival (Class III; median 2.3 months) was seen in patients with a KPS less than 70. All other patients fell into Class II and had intermediate survival (median 4.2 months). The RPA classification has since been validated with other clinical trials. Other prognostic scoring systems that have been developed include the Graded Prognostic Assessment (GPA), the Score Index for Radiosurgery (SIR), the Basic Score for Brain Metastases (BSBM), the Rotterdam System (ROTTERDAM), the Golden Grading System (GGS), 2 Rades Classification (RDES), and the disease specific Graded Prognostic Assessment (ds-GPA).

The multicenter randomized control trial RTOG 9508 compared WBRT and SRS with WBRT alone in patients with 1-3 brain metastases. One of the findings from this study was that the number of brain metastases was significant for prognosis. To reflect this discovery, Sperduto et al. developed the Graded Prognostic Assessment (GPA), which incorporates number of metastases (one, 2-3, more than three) into the prognostic score, along with age, KPS, and extracranial metastases (none vs present). This scoring system was further stratified based on primary diagnosis with the development of the disease specific GPA (ds-GPA). A multicenter analysis of 11 institutions and 5,067 patients found that prognostic factors for brain metastatic patients varied by diagnosis: for non-small cell lung cancer and small cell lung cancer, significant prognostic factors were KPS, age, presence of extra-cranial metastases, and number of BMs; for melanoma and renal cell cancer, significant prognostic factors were KPS and number of BMs; and for breast and gastrointestinal cancer the only significant prognostic factor was KPS. Separate indices were created and statistical separation between the groups has been confirmed.

This guideline defines a favorable prognostic group to include patients with a KPS > 70, 4 or fewer cerebral metastases, and no progressive systematic disease. For patients who do not fall into this category, please see recommendations outlined in the AHS guideline Palliative Radiotherapy: Brain Metastases.

Surgery and Postoperative Radiation

In patients with a single large metastasis (>4 cm) who are suffering from significant mass effect (>1 cm midline shift) or have no pathologic confirmation of the primary disease, surgical resection is warranted. Patients who are relatively asymptomatic may benefit from additional therapy. In patients with a newly diagnosed single brain metastasis, Class I evidence supports surgical resection followed by post-operative WBRT over surgical resection alone. Several randomized control trials (RCTs) have found improved brain metastasis control and overall brain control in surgery and WBRT patients in comparison to surgical resection alone. Similarly, several RCTs have found that surgical resection followed by post-operative WBRT is associated with better survival and quality of life over WBRT alone.
SRS to the tumour bed is a radiotherapy option following the resection of a single metastasis. SRS uses stereotaxis, multiple vantage points, and imaging technology to converge a high dose of radiation on a precisely defined target volume while minimizing irradiation to surrounding tissue. Retrospective studies published within the last 5 years have reported 1-year local control rates of 73-100% using tumour bed SRS. While most of the evidence to date has been retrospective in nature, preliminary results from several prospective RCTs have been presented in abstract form. A randomized trial comparing tumour bed SRS to observation alone in 131 patients with resected brain metastases showed improved local control (LC) at 12 months with SRS to the surgical cavity (72% vs 45%; HR 0.46 95% CI 0.25-0.85; p=0.011). A multivariate Cox regression analysis found that larger preoperative tumour size (>3 cm) was associated with poorer LC (HR 2.4, 95% CI 1.2-4.9). Median survival was 17 months in both arms. This study is the first to confirm the LC benefit of SRS to the tumour bed following resection in patients with 1-3 brain metastases. The preliminary results of N107/CEC.3, a phase III, multicenter RCT comparing post-operative SRS with WBRT, have also been released. One-hundred ninety four patients with 1-4 brain metastases were randomized to receive either SRS or WBRT after surgical resection of one lesion. Both arms received SRS to unresected metastases. No difference in overall survival was observed; however, worse cognitive function was observed in the WBRT group. The study concluded post-operative SRS to the tumour bed should be a standard of care due to equivalent survival, better preservation of cognitive function and quality of life (QOL), and less toxicity than WBRT. Risk factors and optimal dosing schedules are not well established; however, a phase II study looking at local failure after postoperative SRS found tumours that are ≥3 cm with superficial dural/pial involvement were associated with higher risk of local failure.

Role of WBRT and SRS

WBRT and steroids have historically been the standard treatment for patients with brain metastases; however, due to high level evidence that WBRT in conjunction with SRS or surgery leads to better outcomes for select patients as well as concerns surrounding neurotoxicity, the role of WBRT has changed. WBRT is now primarily recommended when the patient is not a candidate for surgery or SRS, as adjunctive therapy to prevent recurrence, and as treatment for recurrent disease.

**WBRT + SRS vs WBRT alone:** Following the discovery that adding WBRT to surgical resection results in improved survival outcomes, several studies have explored whether adding SRS to WBRT improves outcomes for patients with brain metastases. Patil et al. conducted a systematic review comparing WBRT and SRS versus WBRT alone in adult patients with newly diagnosed BMs. Their meta-analysis of two RCTs (a total of 358 participants) found no statistical significant difference in overall survival between the two treatment options (HR 0.82; 95% CI 0.65-1.02). However, they did find that WBRT+SRS group had decreased local failure compared to the WBRT alone group (HR 0.27; 95% CI 0.14 – 0.52, p<0.0001). In addition, RTOG 9508 (n=333) conducted a subgroup analysis and found a survival advantage in the WBRT+SRS group for patients with one metastasis (median survival time 6.5 vs 4.9 months, p=0.0393) and patients with RPA Class I (overall survival 11.6 months WBRT+SRS vs. 9.6 months WBRT, p=0.045). WBRT in conjunction with surgery or SRS leads to better clinical outcomes than WBRT alone for good performance patients with solitary brain metastases.

**WBRT + SRS vs SRS alone:** To explore whether WBRT in conjunction with SRS results in better outcomes than SRS alone, multiple RCTs and several meta-analyses have been conducted. An individual patient data meta-analysis that included three RCTs evaluating SRS with or without WBRT found age to be a significant effect modifier (p=0.04) and favored SRS alone in patients ≤ 50 years of age. A meta-analysis by Tsao et al. determined additional WBRT improves distant and local brain control in
oligometastatic patients, however; they found no overall survival benefit for WBRT and an SRS boost compared to SRS alone.\(^6\) The reviewers concluded that SRS should be considered the routine treatment option due to negative neurocognitive outcomes associated with WBRT. A 2014 Cochrane systematic review compared the efficacy and safety of surgery or SRS plus WBRT with that of surgery or SRS alone for the treatment of BMs in patients with systemic cancer.\(^32\) The review identified 5 RCTs\(^{16,17,29,30,33}\) for a total of 663 patients with 1 to 4 brain metastases. While adding upfront WBRT decreased relative risk of intracranial disease progression at 1 year by 53% (RR 0.47; 95% CI 0.34-0.66, \(p<0.0001\)), there was no clear evidence of difference in overall survival (HR 1.11; 95% CI 0.83-1.48, \(p=0.47\)) or progression free survival (HR 0.76; 95% CI 0.53 1.10, \(p= 0.14\)). The review could not evaluate the impact of WBRT on neurocognitive function, HRQOL and neurological adverse events due to high risk of bias and inconsistencies across studies.\(^32\)

Primary SRS is a reasonable alternative to resection or WBRT for small tumours that are not surgically accessible. The choice between SRS and resection should be individualized for patients who are candidates for both procedures, as no RCTs comparing the two methods are available.

**Neurocognitive Effect of WBRT**

Despite evidence supporting the use of WBRT after surgery or SRS in oligometastatic patients with favorable prognoses, the clinical significance is uncertain due to concerns surrounding the impact of WBRT on neurocognitive function. Increasingly, WBRT is being omitted from initial treatment strategies to avoid late radiation effects.\(^30\) Multiple RCTs have demonstrated improved intracranial tumour control with the addition of WBRT to SRS; however; none of these studies have observed an overall survival advantage, and all observed potential deterioration of cognitive function and QOL associated with WBRT.\(^17,29,30\) A multicenter RCT of 359 patients with 1-3 brain metastases found patients in the observation arms (surgery or SRS alone) reported better HRQOL scores overall in comparison those who received additional WBRT.\(^5\) A study by Chang et al. was stopped early due to high probability that the patients randomly assigned to SRS and WBRT were significantly more likely to show a decline in learning and memory function as assessed by the Hopkins Verbal Learning Test –Revised.\(^29\) The potential side effects of WBRT must be weighed against the likelihood of morbidity resulting from intracranial recurrence or progression if WBRT is omitted.

In a 2016 study, Brown et al. randomized 213 patients with 1-3 brain metastases to receive either SRS or SRS plus WBRT (N0574).\(^3\) The primary endpoint was cognitive deterioration (decline >1SD from baseline on at least one cognitive test at 3 months), with secondary of time to intracranial failure, QOL, functional independence, long-term cognitive status, and overall survival. The study found that patients receiving SRS alone had significantly less cognitive deterioration at 3 months in comparison to the patients receiving both SRS and WBRT (63.5% vs 91.7%, \(p<0.001\)). In long term survivors, the incidence of cognitive deterioration was also less in SRS patients (60% vs 94.4%, \(p = 0.04\)). As with previous RCTs, the time to intracranial failure was significantly shorter in the SRS alone group (HR 3.6; 95% CI 2.2-5.9, \(p<0.001\)). However, since there was no significant difference in OS between the two groups, the authors conclude that in oligometastatic patients who are candidates for radiosurgery, SRS alone is the preferred strategy.\(^3\)

In 2014, as part of the ‘Choosing Wisely’ initiative, the American Society for Radiation Oncology (ASTRO) released the following recommendation: ‘Don’t routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases’. In line with this recommendation and the supporting...
evidence, the Alberta CNS Tumour Team does not recommend adjuvant WBRT following SRS, except as an option for recurrent metastases previously treated with SRS.

**Surveillance and Follow Up**

An increasing number of patients are living long enough after initial treatment to experience recurrence in the brain, resulting in a greater need for appropriate follow up and retreatment. NCCN Guidelines recommend an MRI every 2-3 months for one year, and then as clinically indicated. For patients treated with SRS alone, closer follow-up (every two months) may be preferred as recurrence imaging can be confounded by treatment effects of SRS. When recurrence of brain metastases is confirmed, surgery and radiosurgery can be utilized to improve disease control. Additional therapy will be strongly influenced by initial treatment modality; for example, repeat WBRT is not often administered due to concerns of toxicity. Patients should only receive repeat WBRT if they had a positive response to first treatment. Patients are encouraged to participate in clinical trials when available.

**GLOSSARY OF ABBREVIATIONS**

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACR</td>
<td>American College of Radiology</td>
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<tr>
<td>AHS</td>
<td>Alberta Health Services</td>
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<td>ASTRO</td>
<td>American Society of Radiation Oncology</td>
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<td>BCCA</td>
<td>British Columbia Cancer Agency</td>
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<td>BM</td>
<td>brain metastases</td>
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<td>BSBM</td>
<td>Basic Score for Brain Metastases</td>
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<td>CCA</td>
<td>Cancer Care Ontario</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>ds-GPA</td>
<td>disease specific Graded Prognostic Assessment</td>
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<td>GGS</td>
<td>Golden Grading System</td>
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<td>GPA</td>
<td>Graded Prognostic Assessment</td>
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<td>HRQOL</td>
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<td>KPS</td>
<td>Karnofsky performance status</td>
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<td>LC</td>
<td>local control</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<td>QOL</td>
<td>quality of life</td>
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<td>RCT</td>
<td>randomized control trial</td>
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<td>RDES</td>
<td>2 Rades Classification</td>
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<td>RPA</td>
<td>recursive partitioning analysis</td>
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<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SIR</td>
<td>Score Index for Radiosurgery</td>
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<td>SRS</td>
<td>stereotactic radiosurgery</td>
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<td>WBRT</td>
<td>whole brain radiation therapy</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial CNS Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial CNS Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


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