PALLIATIVE RADIOTHERAPY: BRAIN METASTASES

Effective Date: August, 2014

The recommendations contained in this guideline 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

Palliative radiotherapy plays an important role in the relief of suffering for patients with advanced cancer.\(^1\) Palliation of patient symptoms with radiotherapy (RT) can often be undertaken with the potential to alleviate symptoms. This document attempts to reduce practice variations in RT for brain metastases where the evidence exists to support a pattern of practice. Goals of treatment include maximizing outcomes such as survival, local control, distant in-brain control, duration of functional independence, and neurocognitive status.\(^2,3\) \textit{Whenever possible, participation in a clinical trial is strongly encouraged.}

Metastatic disease is the most common type of intracranial malignancy, occurring in approximately 10 to 30\% of all patients with cancer.\(^4-6\) In adults, lung cancer, breast cancer, and melanoma have the highest incidence of brain metastases; other common histologies include colorectal and renal cell carcinoma, and unknown primary site.\(^5,6\) The therapeutic approach depends on several demographic and clinical variables including estimated prognosis, performance status (PS), anatomic localization, lesion size, amenability for surgery, comorbidities, and patient preference. Factors predictive of better survival include: age younger than 65 years, good PS, successful control of the primary tumour, absence or stability of extracranial disease, and a single brain metastasis.\(^7\)

GUIDELINE QUESTIONS

What are the recommended strategies for the management and treatment of adults with:

- A newly diagnosed solitary brain metastasis?
- Newly diagnosed multiple brain metastases?
- Progressive or recurrent brain metastases?

DEVELOPMENT AND REVISION HISTORY

The original guideline was developed in 2008 by the clinical leaders of the Fast Track Palliative Radiotherapy Clinic for Bone Metastases in Calgary and the Palliative Radiation Oncology program (originally called the Rapid Access Palliative Radiotherapy Program) in Edmonton, with input from provincial radiation oncologists. For the 2010 updates, evidence was selected and reviewed by a working group comprised of radiation oncologists from Alberta Health Services – CancerControl Alberta and a Knowledge Management Specialist from the Guideline Resource Unit. In 2014 the larger guideline was converted into several smaller guidelines. A detailed description of the methodology followed during the guideline development process can be found in the \textit{Guideline Resource Unit Handbook}.

This guideline was originally developed in August, 2014.

SEARCH STRATEGY

For the 2014 update, the National Library of Medicine’s PubMed database was search (July, 2010 to January, 2014) using the following search terms: Palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields])). Articles were excluded if they: were not written or translated into English, were case studies involving less than 10 patients, or involved pediatric patients. The references cited in articles identified through the formal searches were also
scanned for additional sources. In total, 103 articles were identified, of which 19 were reviewed in detail based on a title/abstract screen.

A search for new or updated clinical practice guidelines published from July, 2010 to April, 2013 was also conducted, and yielded published guidelines by the following organizations: American Society for Radiation Oncology (ASTRO), National Cancer Institute, National Institute for Health and Clinical Excellence (NICE), and European Society for Medical Oncology.

TARGET POPULATION

Adult patients, with a single or multiple brain metastases, arising from cancer of any histology, excluding germ cell tumours and hematologic malignancies.

RECOMMENDATIONS

Summary of Recommendations:

Solitary:
- Neurosurgery should be consulted for patients with a solitary brain metastasis.
- For solitary brain metastasis, WBRT is recommended after surgery. If patients are ineligible for surgery, or complete excision was not achieved, SRS plus WBRT should be considered.

Multiple:
- For patients with up to four newly diagnosed brain metastases, WBRT can be considered with or without SRS boost.
- Consider best supportive care for those patients with multiple brain metastasis and poor prognosis.

Recurrent/Progressive:
- Status of extracranial disease burden, interval since initial treatment, initial treatment modalities, performance status, symptom burden, co-morbidities, prognosis and patient wishes should guide treatment decisions.

Recommendations for a Solitary Brain Metastasis:

1. A neurosurgical opinion is strongly recommended for excision of a single brain metastasis, especially if it is larger than 3-4cm, if patients have a good PS and minimal, no, or controlled extra-cranial disease, especially in the absence of pathologic confirmation of malignancy. Surgical resection followed by post-operative whole brain radiotherapy (WBRT) is associated with a survival benefit over WBRT alone. Post-operative WBRT reduces the risk of local and in-brain recurrence, increases the duration of functional independence, and decreases the likelihood of death secondary to neurological causes. In a recently reported phase III trial in patients with one to three brain metastases from solid tumors, 199 patients post-stereotactic radiosurgery (SRS) and 160 post-resection were randomized between observation and WBRT. There were no significant differences in overall survival (OS) or time to deterioration of PS, but WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities.

2. In those not eligible for surgery or after incomplete excision, SRS should be considered in patients with one brain metastasis smaller than 4cm in an appropriate location, good PS, and minimal, no or controlled extra-cranial disease. The combination of SRS and WBRT improves local control over WBRT alone and may improve survival in patients with a solitary brain lesion. SRS may be delivered either up front or subsequent to WBRT as a boost. A phase III trial of 199 patients post-SRS
and 160 post-resection of 1 to 3 metastases from solid tumors randomized participants between observation and WBRT. There were no significant differences in overall survival (OS) or time to deterioration of PS. WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities.17

3. An alternative treatment option is surgery followed by SRS or RT directed to the resection cavity alone; however, supporting data is limited.2 There is no convincing evidence that use of SRS in this setting improves outcomes in comparison to conventional external beam RT.23

4. For a single metastasis <3-4cm, SRS alone may be delivered2 but is not considered standard of care. However, in certain clinical situations where surveillance and salvage therapy are readily accessible, this may be an option.20,22

5. In patients not eligible for surgery or SRS, WBRT alone is associated with an improvement in median survival compared to no treatment or best supportive care (BSC) with steroids.24,25

6. No strong evidence supports a specific WBRT dose fractionation schedule, with generally equivalent symptomatic improvement, median time to progression, and median survival for all regimens.26-28 A meta-analysis of 27 publications reported no significant differences in mortality, symptom control, or neurological improvement with altered-dose compared to standard fractionation schedules.8 Partial brain dose escalation has not proved clinically useful to date.8,14,29

7. In terms of toxicity, a WBRT dose of 30Gy/10 may be associated with less late neuromorbidity in select long-term survivors and should be considered in patients with good PS and/or in the setting of planned SRS boost.16 Prospective and retrospective studies have suggested moderate deterioration in global quality of life, physical/motor function, and communication ability three months after WBRT24,25,30. Adding WBRT to SRS may be associated with a decline in learning and memory by four months compared to patients receiving SRS alone.31 However, potential side effects of WBRT must be weighed against the likelihood of morbidity resulting from in-brain recurrence/progression if WBRT is not administered. Potential benefits and side effects of WBRT should be discussed with patients.

8. Although studies investigating chemotherapy following WBRT suggest improved intracranial response, they also generally report increased toxicity and no statistically significant survival benefit, and are therefore not currently recommended outside of a clinical trial setting.32

9. The use of radiosensitizers is not recommended outside of a clinical trial setting. The RTOG 7916 trial utilizing misonidazole and two subsequent systematic reviews have reported no survival benefit from the addition of radiosensitizers to WBRT.8,33,34

10. Patients with an expected very poor prognosis should be considered for BSC alone.2

**Recommendations for Multiple Brain Metastases:**

11. For patients with up to four newly diagnosed brain metastases each smaller than 4cm, there is strong evidence from two large randomized controlled trials and several systematic reviews and meta-analyses that SRS boost after WBRT significantly improves local control and PS compared with WBRT alone.2,3,18,20,22,35 There may also be a survival advantage for certain subgroups of patients, although
the evidence is limited. In a recently reported phase III trial, 199 post-SRS and 160 post-resection patients who had one to three brain metastases from solid tumours were randomized between observation and WBRT. There were no significant differences in OS or time to deterioration of PS, but WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities.

12. WBRT alone is associated with an improvement in median survival compared to steroids alone.

13. Following resection of one or more brain metastases causing significant mass effect, postoperative WBRT may be considered.

14. No strong evidence supports a specific WBRT dose fractionation schedule, with generally equivalent symptomatic improvement, median time to progression, and median OS reported for all regimens. Partial brain dose escalation and altered fractionation have not proved clinically useful to date; a 2005 meta-analysis reported no significant differences in mortality, symptom control, or neurological improvement in nine trials of altered-dose fractionation schedules.

15. In terms of toxicity, a WBRT dose of 30Gy/10 fractions may be associated with less late neuromorbidity in select long term survivors, and should be considered in patients with good PS and/or in the setting of planned SRS boost.

16. SRS alone is not considered standard of care, but in certain clinical situations where surveillance and salvage therapy are readily accessible, treatment with SRS alone may be an option.

17. Patients with an expected very poor prognosis should be considered for BSC alone.

18. In the setting of one or more inoperable brain metastases from non-small cell lung cancer (NSCLC), there is some interim randomized phase III data which suggests that treatment with WBRT plus BSC may not offer a measurable improvement in quality adjusted life years over BSC alone in patients median age 67 years, with 50% of patients having a Karnofsky performance status <70.

19. WBRT plus chemotherapy is associated with increased toxicity and no significant survival benefit over WBRT alone. Therefore, WBRT in combination with chemotherapy cannot be recommended outside of a clinical trial setting. Nevertheless, some evidence has demonstrated promising results when chemotherapy is used in combination with WBRT, as it may lead to improved in-brain responses and increased time to neurological progression, particularly for patients with breast or non-small cell lung cancer brain metastases.

20. The RTOG 7916 trial reported no survival benefit associated with the addition of the radiosensitizer misonidazole to WBRT. Since that trial, limited evidence suggests that motexafin gadolinium may increased time to neurological progression for intent-to-treat patients with NSCLC-associated brain metastases treated with WBRT, however, this has not been confirmed by additional studies. Therefore, the use of radiosensitizers is not recommended outside of a clinical trial setting.

Recommendations for Recurrent or Progressive Brain Metastases:
21. No standard treatment has been established. The choice of therapeutic approach will depend on the status of any extracranial disease, interval since initial treatment, initial treatment modalities, PS, symptom burden, co-morbidities, prognosis and patient wishes.

22. Although there is a lack of evidence for the use of SRS in the salvage setting, this may be an option for select patients with one to four recurrent or progressive brain metastases, good PS, and minimal, no, or controlled extra-cranial disease. 

23. Resection of one or more brain metastases causing significant mass effect, or salvage partial brain external beam RT, may be considered on a case-by-case basis.

24. Repeat WBRT is an option in highly selected patients with minimal, no or controlled extracranial disease and should be considered on a case-by-case basis in the absence of other treatment options. Patients who may benefit most from re-irradiation include those with a survival greater than three to six months after initial WBRT, new neurological symptoms, and a good PS. Several small retrospective studies have examined the utility of repeat WBRT in recurrent brain metastases. Early data suggests improvement in OS if reirradiation dose is >20Gy but there is no standard dose-fractionation in use. Median survival after re-irradiation was 2.8-5.2 months, with up to 68% of patients experiencing symptomatic improvement.
GLOSSARY OF ABBREVIATIONS

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>BSC</td>
<td>best supportive care</td>
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<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
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<td>OS</td>
<td>overall survival</td>
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<td>PS</td>
<td>performance status</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>RT</td>
<td>radiotherapy</td>
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<td>SRS</td>
<td>stereotactic radiosurgery</td>
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<td>WBRT</td>
<td>whole brain radiotherapy</td>
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DISSEMINATION

- Present and review the guideline at relevant local and provincial tumour team meetings and weekly rounds.
- Include a link to the guideline in other relevant disease-specific clinical practice guidelines published by Alberta Health Services – CancerControl Alberta.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services – CancerControl Alberta.

MAINTENANCE

A formal review will be conducted in April 2015. 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 the Alberta Health Services – CancerControl Alberta radiation oncologists 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. Alberta Health Services – Cancer Care 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 of the individuals involved in the development of this guideline 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


