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Management of Brain Metastases

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Cancer Care Alberta

Clinical Practice Guideline CNS-014 – Version 2
www.ahs.ca/guru

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 malignant primary brain tumours[1-4]. More than 40% of adults with cancer develop brain metastases. More commonly they appear in patients with lung cancer (50%), breast cancer[3] (25%), and melanoma (20%) [5]. The most common presenting symptoms for brain metastases are headaches (40-50%), focal neurological deficits (30-40%), and seizures (15-20%)[6]

The treatment of brain metastases has evolved in recent years with the introduction of new surgical and radio surgical techniques. The therapeutic approach depends on several demographic and clinical variables, performance status (PS), tumor location, tumor size, number of tumors, amenability for surgery, and patient preference. Currently, therapeutic approaches to brain metastases include surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and less frequently, systemic therapy[2]. This guideline is intended to provide treatment recommendations for patients with brain metastases.

Guideline Questions

1. What prognostic factors are important for assessing and managing patients with brain metastases?
2. What are the recommended strategies for the management and treatment of adults with newly diagnosed solitary brain metastasis, multiple brain metastases and progressive or recurrent brain metastases?
3. What is the role of surgery in the management of brain metastases?
4. What is the role of radiotherapy in the management of brain metastases?
5. What is the role of palliative radiotherapy in the management of brain metastases?
6. What is the appropriate follow-up and surveillance strategy for patients with brain metastases?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to March 2022. The specific search terms included brain metastasis, oligometastases, surgery, palliative therapy, SRS, WBRT and radiation oncology. Articles were limited to clinical trials, retrospective reviews, and systematic reviews. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology[1], Cancer Care Ontario[7] and National Comprehensive Cancer Network[2]. Some treatment recommendations are adapted from the ASCO 2021 clinical practice guidelines on “Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline” with modifications based on local context[1].

Target Population

The following recommendations apply to adult cancer patients with brain metastases.

Recommendations

Baseline Investigations:[1]

- MRI brain with and without contrast
- Consider contrast enhanced CT chest/abdomen/pelvis or PET/CT if no recent scan available
- Pathological confirmation of primary or metastatic disease

Prognosis

A favourable prognostic group includes patients with:[8, 9]

- ECOG performance score of 0-2
- Limited number of brain metastases (definition variable but often taken ≤ 15)
- Stable primary disease and extracranial metastases or reasonable systemic therapy options exist
- Disease-specific Graded Prognostic Assessment (DS-GPA) may be helpful in selecting patients with favourable prognosis (expectation of overall survival ≥ 4-6 months)

Treatment

General Recommendations

1. All cases should be reviewed at an interdisciplinary tumour board conference including a Radiation Oncologist, Neurosurgeon and Neuroradiologist when feasible to develop recommendations about management and treatment planning. Individuals with training and experience specific in the treatment of brain metastases should be included in the interdisciplinary discussion.
2. Dexamethasone should be considered for management in symptomatic patients.[10]
3. A tissue-based diagnosis should be sought for patients in whom the primary is unknown or imaging findings are not typical characteristic for brain metastases.
4. Clinical trial enrollment should be considered for all patients, when available.

Surgery:

Surgery can be beneficial for patients who are symptomatic, have a large mass effect or where pathology from resection can help with diagnosis or is required for clinical trial enrollment.[1, 11, 12] *(Level of Evidence: I Strength of Recommendation: A)*

- Resection for symptomatic management of mass effect
- Resection of large lesions
- Resection of local recurrence in previously treated brain metastases, particularly if previously treated with radiation therapy (RT)

- Consider biopsy or resection for newly diagnosed patients to establish diagnosis

Radiation Therapy: (*Level of Evidence: I Strength of Recommendation: A*)[1, 13-16]

- Favourable prognosis: SRS preferred for (a) patients with stable primary/extracranial disease or (b) patients with uncontrolled primary/extracranial disease who have reasonable treatment options for their extracranial disease.
    - Postoperative resection bed SRS or WBRT in patients with resected brain metastases
    - For patients with 1-4 brain metastases SRS is strongly recommended, especially if maximal tumor size for largest lesion is less than 3 to 4cm.
    - There is no upper limit for number of metastases to be eligible for SRS. Total brain metastases of volume < 30cc is associated with a lower risk of adverse events and can be used to help select patients for SRS.
- Radiation doses for SRS (*Level of Evidence: II Strength of Recommendations: C)*[13, 17]
    - 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 Gy, or fractionated stereotactic radiotherapy (FSRT), is recommended.
    - For lesions >3 cm, FSRT of 27 Gy in 3 fractions or 30-35 Gy in 5 daily fractions is recommended[18].

Timing for Simulation: *(Level of Evidence: II Strength of Recommendations: C)*[7, 19, 20]

Simulation (MRI) to treatment should be performed as close as possible before the treatment delivery date and optimally no longer than 7 calendar days and certainly no more than 14 calendar days (including weekend days and statutory holidays).

- SRS to be completed within 4 weeks of post-op SRS cases and no later than 3 weeks after referral for intact brain metastases

Whole Brain Radiation Therapy:

- In patients with limited treatment options for uncontrolled primary/extracranial disease, or poor performance status, WBRT, SRS, or best support care are treatment options.[1, 21]
- Radiation doses for WBRT *(Level of Evidence: II Strength of Recommendations: C)*[2, 22, 23]
    - Doses of 20 Gy in 5 fractions or 30-37.5 Gy in 10-15 fractions may be used. In the uncommon scenario of re-irradiation with WBRT, consider 20-25 Gy in 10 fractions.
    - Hippocampal sparing WBRT can be considered in patients that have no hippocampal lesions and 4 months or more expected survival.[1, 23, 24]
    - Memantine is not currently Health Canada approved but is actively being investigated in clinical trials for the indication of brain metastases.

Systemic Therapy: *(Level of Evidence: II Strength of Recommendations: C)*[1, 2]

- For patients with numerous, small, asymptomatic metastases, systemic therapy upfront can be considered on a case-by-case basis if effective CNS response rate has been observed with administered agent.
- Treatment with RT and/or surgery with progression on close surveillance.

Recurrent Disease: *(Level of Evidence: I Strength of Recommendations: A)*[1, 2]

- Favourable prognosis[25-27]:
    - Repeat SRS or resection followed by post-operative SRS or WBRT (in patients who have not previously received WBRT) or upfront SRS are preferred
    - Stereotactic radiosurgery, which can be delivered safely with prior history of WBRT and with increased but still acceptable toxicity if prior history of SRS
    - Consider WBRT for large volume recurrence in patients who have not previously received it
    - Systemic therapy may be considered in this setting
    - For second recurrence, consider laser interstitial thermotherapy (LITT), which is available for selected cases in Alberta
- Unfavourable prognosis[1, 3]:
    - In patients who have not previously received WBRT, WBRT or best supportive care are preferred
    - In patients who have previously received WBRT, consider SRS or reirradiation with WBRT in selected patients with a limited number of unfavourable prognostic criteria or best supportive care.

Follow-up and Surveillance[1, 2]

- Follow up and surveillance imaging should be individualized taking into consideration of prognosis, extent of initial disease, treatment, and patient preference.
- Favourable prognosis: MRI Brain every 3-4 months for 1-2 years, then every 6 months.
- Unfavourable prognosis: Surveillance imaging only if clinically indicated/will alter patient management.
- Radiation necrosis:
    - Initial therapy of symptomatic radionecrosis is steroids.
    - Treatment of symptomatic radionecrosis refractory to steroid therapy with bevacuzimab is supported by randomized data and can be considered after discussion of potential adverse effects including bowel necrosis in selected patients[28].

Discussion: Summary

Patients with brain metastases 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. Overall, age, ECOG, number of brain metastases, status of extracranial disease and Graded Prognostic Assessment (GPA) are important prognostic factors[1]. Surgical resection is recommended in patients with a single large metastasis (>2 cm) who have neurological deficits, significant mass effect or have no pathologic confirmation of the primary disease. SRS alone has become the standard of care therapy for up to four brain metastases based on multiple RCTs that have demonstrated reduced toxicity with no change in survival compared to WBRT in this patient population[16, 29].

References

1. Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *J Clin Oncol*. 02 10 2022;40(5):492-516.
2. NCCN Clinical Practice Guidelines in Oncology Central Nervous System Cancers. https://www.nccn.org/guidelines/guidelines-detail; June2, 2022.
3. J.S L. Overview of the treatment of brain metastases. UpToDate; 2022.
4. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin*. 1999;49(1):8-31, 1.
5. Fidler IJ. The Biology of Brain Metastasis: Challenges for Therapy. *Cancer J*. 2015 Jul-Aug 2015;21(4):284-93.
6. Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, et al. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. *Eur J Neurol*. Jul 2006;13(7):674-81.
7. Sahgal A, Kellett S, Ruschin M, Greenspoon J, Follwell M, Sinclair J, et al. A Cancer Care Ontario Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario, Canada. *Pract Radiat Oncol*. 2020 Jul - Aug 2020;10(4):243-254.
8. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. Jun 07 2006;295(21):2483-91.
9. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA*. Jul 26 2016;316(4):401-409.
10. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. Oct 22 2016;388(10055):2004-2014.
11. Akanda ZZ, Hong W, Nahavandi S, Haghighi N, Phillips C, Kok DL. Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. *Radiother Oncol*. 01 2020;142:27-35.
12. Kayama T, Sato S, Sakurada K, Mizusawa J, Nishikawa R, Narita Y, et al. Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. *J Clin Oncol*. Jun 20 2018:JCO2018786186.
13. Bowden GN, Kim JO, Faramand A, Fallon K, Flickinger J, Lunsford LD. Clinical dose profile of Gamma Knife stereotactic radiosurgery for extensive brain metastases. *J Neurosurg*. May 08 2020;134(5):1430-1434.
14. Hughes RT, Masters AH, McTyre ER, Farris MK, Chung C, Page BR, et al. Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience. *Int J Radiat Oncol Biol Phys*. 08 01 2019;104(5):1091-1098.
15. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 08 2017;18(8):1040-1048.
16. Yamamoto M, Sato Y, Higuchi Y, Kasuya H, Barfod BE. A Cohort Study of Stereotactic Radiosurgery Results for Patients With 5 to 15 Versus 2 to 4 Brain Metastatic Tumors. *Adv Radiat Oncol*. 2020 May-Jun 2020;5(3):358-368.
17. Serizawa T, Yamamoto M, Higuchi Y, Sato Y, Shuto T, Akabane A, et al. Local tumor progression treated with Gamma Knife radiosurgery: differences between patients with 2-4 versus 5-10 brain metastases based on an update of a multi-institutional prospective observational study (JLGK0901). *J Neurosurg*. Apr 26 2019;132(5):1480-1489.
18. Kim PH, Suh CH, Kim HS, Kim KW, Kim DY, Lee EQ, et al. Immune Checkpoint Inhibitor with or without Radiotherapy in Melanoma Patients with Brain Metastases: A Systematic Review and Meta-Analysis. *Korean J Radiol*. 04 2021;22(4):584-595.
19. Seymour J, Rietjens J, Bruinsma S, Deliens L, Sterckx S, Mortier F, et al. Seymour et al. Palliative sedation: Improvement of guidelines necessary, but not sufficient: A reply. *Palliat Med*. May 2015;29(5):481.
20. Salkeld AL, Hau EKC, Nahar N, Sykes JR, Wang W, Thwaites DI. Changes in Brain Metastasis During Radiosurgical Planning. *Int J Radiat Oncol Biol Phys*. 11 15 2018;102(4):727-733.
21. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. *Radiat Oncol*. Jul 12 2014;9:155.
22. Trifiletti DM, Ballman KV, Brown PD, Anderson SK, Carrero XW, Cerhan JH, et al. Optimizing Whole Brain Radiation Therapy Dose and Fractionation: Results From a Prospective Phase 3 Trial (NCCTG N107C [Alliance]/CEC.3). *Int J Radiat Oncol Biol Phys*. 02 01 2020;106(2):255-260.

23. Grosu AL, Frings L, Bentsalo I, Oehlke O, Brenner F, Bilger A, et al. Whole-brain irradiation with hippocampal sparing and dose escalation on metastases: neurocognitive testing and biological imaging (HIPPORAD) - a phase II prospective randomized multicenter trial (NOA-14, ARO 2015-3, DKTK-ROG). *BMC Cancer*. Jun 08 2020;20(1):532.
24. Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. *J Clin Oncol*. 04 01 2020;38(10):1019-1029.
25. Minniti G, Scaringi C, Paolini S, Clarke E, Cicone F, Esposito V, et al. Repeated stereotactic radiosurgery for patients with progressive brain metastases. *J Neurooncol*. Jan 2016;126(1):91-97.
26. Kurtz G, Zadeh G, Gingras-Hill G, Millar BA, Laperriere NJ, Bernstein M, et al. Salvage radiosurgery for brain metastases: prognostic factors to consider in patient selection. *Int J Radiat Oncol Biol Phys*. Jan 01 2014;88(1):137-42.
27. Chao ST, Barnett GH, Vogelbaum MA, Angelov L, Weil RJ, Neyman G, et al. Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy. *Cancer*. Oct 15 2008;113(8):2198-204.
28. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. Apr 01 2011;79(5):1487-95.
29. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. Jan 10 2011;29(2):134-41.

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial CNS Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial CNS Tumour Team who were not involved in the guideline's development, including [neurosurgeons, radiation oncologists, medical oncologists, nurses, pathologists and pharmacists]. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2023.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2023 If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

BM: Brain Metastases; DS-GPA: Disease-specific Graded Prognostic Assessment; FSRT: Fractionated Stereotactic Radiotherapy; PS: Performance Status; RT: Radiation Therapy; SRS: Stereotactic Radiosurgery; WBRT: Whole Brain Radiation Therapy;

Disclaimer

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.

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Conflict of Interest Statements

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