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CADTH Reference List

Whole Brain Radiation Therapy for Patients With Limited Brain Metastases

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Summary of Abstracts

CADTH

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Key Messages

- No evidence was found about the comparative clinical effectiveness of whole brain radiation therapy versus stereotactic radiosurgery in patients with limited brain metastases.
- Thirteen evidence-based guidelines were identified about the treatment of patients with limited brain metastases.

Research Questions

1. What is the comparative clinical effectiveness of whole brain radiation therapy versus stereotactic radiosurgery in patients with limited brain metastases?
2. What are the evidence-based guidelines regarding the treatment of patients with limited brain metastases?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were whole brain radiation and brain metastases for research question 1. The main search concepts were brain metastases for research question 2. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons, and any types of randomized or non-randomized trials or studies for research question 1. CADTH-developed search filters were applied to limit retrieval to guidelines for research question 2. If possible, retrieval was limited to the human population. The search was completed on May 16, 2022, and limited to English-language documents published after January 1, 2017. Internet links were provided, if available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications. Open-access, full-text versions of evidence-based guidelines were reviewed when available, and relevant recommendations were summarized.

Table 1: Selection Criteria

Criteria	Description
Population	Patients with limited brain metastases (i.e., ≤ 4 brain lesions)
Intervention	Q1: Whole brain radiation therapy Q2: Whole brain radiation therapy, stereotactic radiosurgery
Comparator	Q1: Stereotactic radiosurgery Q2: Not applicable
Outcomes	Q1: Clinical benefits (e.g., overall survival, progression-free survival, intracranial control; health-related quality of life, neurocognitive function, functional status) and harms (e.g., memory impairments, radiation necrosis, toxic effects of radiation, neurologic toxicities, fatal toxicities, headaches, fatigue, seizures, vomiting) Q2: Recommendations regarding best practices (e.g., which treatment, appropriate indications, appropriate use)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Thirteen evidence-based guidelines were identified about the treatment of patients with limited brain metastases. No health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies were identified about the comparative clinical effectiveness of whole brain radiation therapy (WBRT) versus stereotactic radiosurgery (SRS) in patients with limited brain metastases.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Thirteen evidence-based guidelines were identified about the treatment of patients with limited brain metastases.[1-13] Consideration of factors that can impact treatment choice (e.g., prognosis, tumour size, location of metastases) vary across recommendations. See Table 2 for a detailed summary of recommendations with reported strength ratings and ratings of evidence quality when available.

Three guidelines recommended a suite of treatment options for patients with limited brain metastases.[4,10,11] One guideline recommended either surgery, SRS, or stereotactic radiotherapy for people with 1 brain metastasis.[4] Ramakrishna et al. recommended the same potential treatment options, but with the addition of fractioned stereotactic radiotherapy for individuals with 1 brain metastasis and favourable prognosis.[10] For patients with 2 to 4 brain metastases, Ramakrishna et al. recommended resection for large symptomatic lesions plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (without or without SRS), SRS (with or without WBRT), and fractionated stereotactic radiotherapy for metastases greater than 3 cm to 4 cm.[10] In addition to metastasis size, the same guideline advised that resectability and symptoms are important considerations when choosing treatment.[10] Alberta

Health Services stated that patients with limited brain metastases and a favourable prognosis can be treated with multiple modalities, including surgery, SRS, and/or WBRT.[11]

Seven evidence-based guidelines recommended SRS for patients with limited brain metastases, with varying conditions, evidence quality, and recommendation ratings.[1-3,7,9,12,13] Gasper et al. did not recommend WBRT for patients with 1 to 4 brain metastases when compared to surgical resection or radiosurgery alone.[6] Further, 3 evidence-based guidelines recommended against adjuvant WBRT or the addition of WBRT to varying treatments for patients with limited brain metastases.[1,4,6] Recommendations against adjuvant WBRT or the addition of WBRT to other therapies in patients with limited brain metastases also vary regarding conditions, strength, and evidence quality.[1,4,6] Gondi et al. specified that WBRT may be added to SRS in cases when salvage therapy is not feasible.[1] Additionally, Chao et al. recommended considering WBRT as a salvage treatment option for patients with 2 to 4 brain metastases.[12] Nahed et al. recommended surgery and WBRT as first-line treatment in patients with a single brain metastasis.[8]

No relevant literature was found regarding the comparative clinical effectiveness of WBRT versus SRS in patients with limited brain metastases; therefore, no summary can be provided.

Table 2: Summary of Recommendations in Included Guidelines

Summary of recommendations	Quality of evidence and/or strength of recommendations
Gondi et al. (2022)[1]	
For patients with an Eastern Cooperative Oncology Group performance status of 0 to 2 and up to 4 intact brain metastases, SRS is recommended.	**Strength of recommendation:** Strong **Quality of evidence:** High
For patients with favourable prognosis and limited brain metastases, routine adjuvant WBRT added to SRS is not recommended. Implementation remark: To maximize intracranial control and/or when close imaging surveillance with additional salvage therapy is not feasible, adjuvant WBRT may be offered in addition to SRS.	**Strength of recommendation:** Strong **Quality of evidence:** High
Vogelbaum et al. (2022)[2]	
SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with 1 to 4 unresected brain metastases, excluding small cell carcinoma. Qualifying statement: The inclusion criteria of the randomized trials that underly this recommendation were generally tumours of less than 3 cm or 4 cm in diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance.	**Strength of recommendation:** Moderate **Quality of evidence:** Intermediate
Le Rhun et al. (2021)[3]	
SRS is recommended for patients with a limited number (1 to 4) of brain metastases.	**Strength of recommendation** EANO: Level A; ESMO: Level A **Quality of evidence** EANO: Level 1; ESMO: Level 1

Summary of recommendations	Quality of evidence and/or strength of recommendations
NICE (2021)[4]	
Consider maximal local therapy with either surgery, SRS, or stereotactic radiotherapy for people with a single brain metastasis.	**Quality of evidence:** Relevant evidence for the question on single brain metastasis (what is the most effective intracranial treatment for a single brain metastasis?) consisted of 5 studies, of which all but 1 outcome for 1 study was ranked as low-quality evidence.
Do not offer adjuvant WBRT to people with a single brain metastasis treated with SRS/radiotherapy or surgery.	**Quality of evidence:** Relevant evidence for the question on single brain metastasis (what is the most effective intracranial treatment for a single brain metastasis?) consisted of 5 studies, of which all but 1 outcome for 1 study was ranked as low-quality evidence.
Ammirati et al. (2019)[5]	
In patients with 2 to 3 brain metastases not amenable to surgery, the addition of SRS to WBRT is not recommended to improve survival beyond that obtained with WBRT alone.	**Strength of recommendation:** Level 1
Gasper et al. (2019)[6]	
Due to neurocognitive toxicity, local therapy (surgery or SRS) without WBRT is recommended for patients with ≤ 4 brain metastases amenable to local therapy in terms of size and location.	**Strength of recommendation:** Level 2
WBRT is not recommended in patients with WHO performance status 0 to 2 who have up to 4 brain metastases because, compared to surgical resection or radiosurgery alone, the addition of WBRT improves intracranial progression-free survival but not overall survival.	**Strength of recommendation:** Level 2
In patients with WHO performance status of 0 to 2 who have up to 4 brain metastases and the goal is minimizing neurocognitive toxicity versus maximizing progression-free survival and overall survival, local therapy (surgery or radiosurgery) without WBRT is recommended.	**Strength of recommendation:** Level 2
Graber et al. (2019)[7]	
For patients with solitary brain metastasis, SRS should be given to decrease the risk of local progression.	**Strength of recommendation:** Level 3
For patients with 2 to 4 brain metastases, SRS is recommended for local tumour control, instead of WBRT, when their cumulative volume is < 7 mL.	**Strength of recommendation:** Level 3
Nahed et al. (2019)[8]	
Surgery and WBRT is recommended as first-line treatment in patients with single brain metastases with favourable performance status and limited extracranial disease to extend overall survival, median survival, and local control.	**Strength of recommendation:** Level 1
Surgery and WBRT is recommended as superior treatment to WBRT alone in patients with single brain metastases.	**Strength of recommendation:** Level 1
Planchard et al. (2018)[9]	
In the case of a limited number of metastases and recursive partitioning analysis class I and II, SRS alone is recommended.	**Strength of recommendation:** B **Quality of evidence:** 3

Summary of recommendations	Quality of evidence and/or strength of recommendations
Ramakrishna et al. (2018)[10]	
For patients with a favourable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, SRS (± WBRT), WBRT (± SRS), and fractionated stereotactic radiotherapy depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 months to 4 months may be used to monitor for local and distant brain failure.	**Strength of recommendation:** Strong **Quality of evidence:** Intermediate
For patients with a favourable prognosis for survival and limited (2 to 4) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (± SRS), SRS (± WBRT), and FSRT for metastases > 3 cm to 4 cm. For metastases, < 3 cm to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.	**Strength of recommendation:** Weak **Quality of evidence:** Intermediate
Alberta Health Services (2017)[11]	
Patients with a favourable prognosis can be treated with multiple modalities, including surgery, SRS, and/or WBRT.	NA
Chao et al. (2017)[12]	
For a single brain metastasis: SRS alone should be offered for patients not requiring surgery, and WBRT reserved as 1 of many salvage therapies. WBRT on its own represents suboptimal treatment.	NA
For 2 to 4 brain metastases: SRS alone is the recommend upfront treatment, and WBRT reserved as 1 of many salvage treatment options.	NA
Marta et al. (2017)[13]	
Radiosurgery should preferably be performed in patients with up to 4 lesions and a maximum diameter of 4 cm.	Based on 4 studies rated as grade A evidence and recommendation

EANO = European Association of Neuro-Oncology; ESMO = European Society for Medical Oncology; FSRT = fractionated stereotactic radiotherapy; NA = not applicable; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

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References

Health Technology Assessments

No literature identified.

Systematic Reviews

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

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    Refer to Recommendations (p. 2805).
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Refer to What is the Maximum Number and Size of Metastatic Lesions in the Brain for Radiosurgery Treatment to Be Performed? (p. 560-561).

Appendix 1: References of Potential Interest

Previous CADTH Reports

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Systematic Reviews

Alternative Population — Not Specific to Patients With Limited Brain Metastases

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Randomized Controlled Trials

Mixed Population — Includes Patients With Greater Than 4 Brain Lesions Brain Lesions

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Non-Randomized Studies

Alternative Comparator — Resected Brain Oligometastases

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Unclear Population — Not Specific to Patients With Less Than or Equal to 4 Brain Lesions

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Alternative Comparator (Salvage SRS); Not Specific to Patients With Limited Brain Metastases

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Mixed Population — Includes Patients With More Than 4 Brain Lesions

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Guidelines and Recommendations

Unclear Methodology

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Mixed Population — CNS Tumours

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