Ontario Health
Cancer Care Ontario

Guideline Endorsement C50-CIDAP-3

A Quality Initiative of
The Cancer Care Integration & Disease Advisory Program (CI-DAP),
Ontario Health (Cancer Care Ontario)

An Endorsement of the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations.

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Report Date: March 26, 2025

This document describes the Ontario Health (Cancer Care Ontario) Cancer Care Integration & Disease Advisory Program (CI-DAP) endorsement of the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations. The original publication is available at redjournal.org/article/S0360-3016(23)07647-2/fulltext

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SECTION 1: GUIDELINE ENDORSEMENT

GUIDELINE OBJECTIVES

The objective of this guideline is to provide recommendations on the management of symptomatic brain radiation necrosis after stereotactic radiosurgery. The recommendations are based on the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations [1].

TARGET POPULATION

Patients receiving stereotactic radiosurgery (SRS)/stereotactic radiotherapy (SRT) for brain metastases and presenting with symptomatic brain radiation necrosis after stereotactic radiosurgery.

INTENDED USERS

The guideline document will support providers in the management of patients presenting with symptomatic brain radiation necrosis after stereotactic radiosurgery.

ENDORSEMENT

The Brain Radiation Necrosis Endorsement Guideline Development Group (GDG) of Ontario Health (Cancer Care Ontario) endorses the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations, available at redjournal.org/article/S0360-3016(23)07647-2/fulltext, as modified by the endorsement process described in this document. These recommendations are reprinted below with permission from the International Stereotactic Radiosurgery Society (ISRS), with modifications noted.

2 of the 4 recommendations were endorsed without modifications or comments. The other 2 of the 4 recommendations were endorsed with comments, which are the consensus opinion of the working group, as listed in Section 1 Recommendations below.

Section 1 Recommendations: ISRS Guideline Recommendations on the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery [1]

ISRS Grade 1 Recommendations - Asymptomatic and no prior corticosteroid administration

Recommendation
• Close surveillance with repeat imaging at 6–12-week intervals
• Consider a short course of corticosteroid (ex. dexamethasone).
• Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.
(Strength of Evidence and Recommendation: Not assessable based on this review)

Assessment
Endorsed with Comment

Comment
Consider repeat imaging at 6 – 12-week intervals with perfusion, if available, for close surveillance.

ISRS Grade 2 Recommendations - Symptomatic and no prior corticosteroid administration

Recommendation
• Dexamethasone can be started as 4-8 mg/d, with or without an initial bolus, and tapered gradually. Generally, a 3-6 wk course of steroids may be required.
• Repeat imaging should be considered at 6-12 wk intervals.
• Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.
(Strength of Evidence and Recommendation: Not assessable based on this review)

Assessment
Endorsed

ISRS Grade 3 Recommendations - Symptomatic and corticosteroid-refractory

Recommendation
• Bevacizumab at doses ranging between 5-10 mg/kg every 2-3 wk for 2-4 cycles.
• Repeat imaging after 2 cycles and after the 4th cycle for response assessment and to guide corticosteroid tapering as required.
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.
(Strength of Evidence: Moderate, Strength of Recommendation: Strong)

Assessment
Endorsed

Recommendation
• Laser Interstitial Thermal Therapy (LITT)/surgery
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.
(Strength of Evidence: Low, Strength of Recommendation: Weak)

Assessment
Endorsed with Comment

Comment
The Brain Radiation Necrosis Endorsement GDG acknowledges that there is more evidence to support surgery than Laser Interstitial Thermal Therapy (LITT). LITT is available in Ontario.

Recommendation
• Hyperbaric Oxygen Therapy (HBOT)
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.
(Strength of Evidence: Insufficient, Strength of Recommendation: Weak)

Assessment
Endorsed with Comment

Comment
The Brain Radiation Necrosis Endorsement GDG acknowledges that there is limited evidence for Hyperbaric Oxygen Therapy (HBOT) in the management of radiation necrosis.

ISRS Grade 4 - Symptomatic with neurologic impairment, progressive RN despite a trial of noninvasive treatments, dependency on high doses of corticosteroid

Recommendation
• Surgical resection
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.
(Strength of Evidence: Low, Strength of Recommendation: Strong)

Assessment
Endorsed

SECTION 2: ENDORSEMENT METHODS OVERVIEW

This section will include only the Guideline recommendations with suggested changes.

BACKGROUND FOR GUIDELINE

Symptomatic brain radiation necrosis (RN) secondary to stereotactic radiosurgery can contribute significantly to morbidity [1]. There are currently no Ontario-specific guidelines that consider the optimal management of and the efficacy/toxicity of treatment paradigms for corticosteroid-refractory brain RN.

An endorsement of the 2023 International Stereotactic Radiosurgery Society's (ISRS) Guideline will provide recommendations, within an Ontario context, for the management of patients that present with symptomatic brain radiation necrosis after receiving stereotactic radiosurgery/ stereotactic radiotherapy for brain metastases. Specifically, the ISRS guideline suggests a 4-tier grading and management system based on the severity of radiation necrosis, diagnosed by radiology or pathology, and the proposed management and follow-up recommendations [1]. This guideline endorsement considers the 4-tier grading and management system, as modified within an Ontario context.

The purpose of this guideline endorsement is to provide clinicians with these evidence-based recommendations on the management of a complex patient population presenting with symptomatic brain radiation necrosis after stereotactic radiosurgery in Ontario. This endorsed guideline will help improve the quality of patient care by providing an evidence-based approach for healthcare providers to follow.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Brain Radiation Necrosis Endorsement Guideline Development Group (GDG), which includes all members of the Working Group and the Expert Panel (Appendix 1), which was convened at the request of The Cancer Care Integration & Disease Advisory Program (CI-DAP) at Ontario Health (Cancer Care Ontario). The Working Group was responsible for reviewing the evidence and recommendations in the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations in detail [1]. The Working Group was also responsible for making initial changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in radiation oncology, medical oncology, neuro-oncology, and neurosurgery. The External Expert Panel were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and were managed in accordance with the Ontario Health (Cancer Care Ontario) Conflict of Interest Policy.

ENDORSEMENT METHODS

CI-DAP endorses guidelines using the process outlined in OH (CCO)'s Guideline Endorsement Protocol [2]. This process includes the selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, internal review by content and methodology experts, and external review by expert Ontario clinicians and other stakeholders.

Ontario Health assesses the quality of guidelines using the AGREE II tool [3]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Selection and Assessment of Guideline(s)

The 2023 International Stereotactic Radiosurgery Society's Guideline was identified by a clinical group of experts. The group deemed this guideline to be best suited for endorsement due to its clinical relevance for the indication of management of symptomatic brain radiation necrosis after stereotactic radiosurgery. In addition to providing a systematic review of the current evidence on the efficacy/toxicity for available treatments, the guideline also proposed a clinically relevant grading system for the management of symptomatic brain radiation necrosis after stereotactic radiosurgery [1].

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated a 5 on a scale from 1 to 7 by appraisers. Appraisers recommended this guideline for use, with modifications. The AGREE II average quality ratings for the individual domains varied: scope and purpose received a score of 94.4%, stakeholder involvement received a score of 16.7%, rigor of development received a score of 61.5%, clarity of presentation received a score of 88.9%, applicability received a score of 54.2%, and editorial independence received a score of 54.2%.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The endorsed guideline, A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations, was published in 2023 in the International Journal of Radiation Oncology, Biology and Physics. The guideline was developed by the International Stereotactic Radiosurgery Society (ISRS).

The ISRS guideline conducted a systematic evidence-based review of current evidence on the efficacy and toxicity of available treatments for patients that have "symptomatic corticosteroid-refractory/intolerant RN" [1]. Through this systematic review, the ISRS proposed recommendations for a grading system on the management of symptomatic brain radiation necrosis after stereotactic radiosurgery.

For the ISRS guideline's search strategy, the following databases were comprehensively consulted: PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews between January 1989 and November 2021 [1]. Evidence was selected using the Population, Intervention, Control, Outcomes, and Study Design (PICOS) method to define the literature inclusion criteria and search strategy. References within selected articles were also hand-searched to determine relevance and appropriateness. All narrowed search results and articles were inputted into a web-based systematic review platform and screened for relevance by the lead author according to inclusion/exclusion criteria. Additional details about the methods and development of the guideline can be found at redjournal.org/article/S0360-3016(23)07647-2/fulltext.

ENDORSEMENT PROCESS

The Working Group reviewed each recommendation from the 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations, to determine whether it could be endorsed, endorsed with change(s)/comment(s), or rejected. This determination was based on the agreement of the Working

Group with the interpretation of the available evidence presented in the guideline, and whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations.

For each recommendation, the Working Group considered the following issues:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Would additional statements of qualification/clarification be valuable in Ontario?

ENDORSEMENT REVIEW AND MODIFICATIONS

This section only includes recommendations with comments made based on the consensus from the GDG, to reflect Ontario context. 2 of the 4 recommendations were endorsed without comments. 2 of the 4 recommendations were endorsed with comments, as listed in the Section 2 Recommendations below (see the Section 1 Recommendations for a list of all 4 recommendations).

Section 2 Recommendations: ISRS Guideline Recommendations on the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery [1]

ISRS Grade 1 Recommendations - Asymptomatic and no prior corticosteroid administration

Recommendation
• Close surveillance with repeat imaging at 6–12-week intervals
• Consider a short course of corticosteroid (ex. dexamethasone).
• Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.
(Strength of Evidence and Recommendation: Not assessable based on this review)

Assessment
Endorsed with Comment

Comment
Consider repeat imaging at 6 – 12-week intervals with perfusion, if available, for close surveillance.

ISRS Grade 3 Recommendations - Symptomatic and corticosteroid-refractory

Recommendation
• Laser Interstitial Thermal Therapy (LITT)/surgery
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.
(Strength of Evidence: Low, Strength of Recommendation: Weak)

Assessment
Endorsed with Comment

Comment
The Brain Radiation Necrosis Endorsement GDG acknowledges that there is more evidence to support surgery than Laser Interstitial Thermal Therapy (LITT). LITT is available in Ontario.

Recommendation
• Hyperbaric Oxygen Therapy (HBOT)
• Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability. (Strength of Evidence: Insufficient, Strength of Recommendation: Weak)

Assessment
Endorsed with Comment

Comment
The Brain Radiation Necrosis Endorsement GDG acknowledges that there is limited evidence for Hyperbaric Oxygen Therapy (HBOT) in the management of radiation necrosis.

EXTERNAL EXPERT PANEL REVIEW and approval

Feedback on the approved draft endorsement document was obtained from content experts from across Ontario. The endorsement document was evaluated by a GDG Expert Panel of clinical content experts representing neurosurgery, radiation oncology and neuro-oncology (Appendix 1).

For the endorsement document to be approved, 75% of the content experts who must cast a vote indicating whether or not they agree with the document, or abstain from voting for a specified reason, and of those that vote, 75% must agree with the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

All 3 of the expert panel members voted and agreed with the endorsement document, with a total of 100% response in November 2024. None of the expert panel members abstained from voting. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 2-1.

Table 2-1. Summary of the Working Group's responses to comments from the External Expert Panel.

Comments	Responses
1. The ISRS Grade 1 recommendation states "consider a short-course of corticosteroid" for asymptomatic patients. There is no evidence to support the benefit of short-course corticosteroid in asymptomatic patients. How would the value/efficacy of the short course of corticosteroids be clinically evaluated in these cases?	We included a comment to consider repeat imaging at 6 – 12-week intervals with perfusion, if available, for close surveillance. This can help monitor for any radiologic changes and help evaluate the value/efficacy of a short course of corticosteroids.

Comments	Responses
2. The ISRS Grade 3 recommendation suggests that imaging may be considered every 2 cycles and after a total of 4 cycles to determine steroid tapering. An MRI every 2 cycles may not be achievable with Ontario's resource constraints. Steroid tapering is typically conducted based on clinical assessment.	We did not modify the comment because it is common practice to consider imaging every 2 cycles for surveillance of brain metastases.
3. In the ISRS Grade 3 recommendation, it is odd that the options for surgery/LITT are merged. These two options have their own advantages/disadvantages. LITT can be superior for deep seated lesions, with the advantage of providing a biopsy. Not all centers with radiosurgery have the ability to perform LITT In Ontario. Whereas resective surgery is superior for symptomatic control relating to mass effect. I agree that the strength of evidence is low, and strength of recommendation is weak for this section.	The wording of the recommendation for the guideline endorsement cannot be changed. We updated the comment to provide context that Laser Interstitial Thermal Therapy (LITT) is available in Ontario as an option. Modified to: "The Brain Radiation Necrosis Endorsement GDG acknowledges that there is more evidence to support surgery than Laser Interstitial Thermal Therapy (LITT). LITT is available in Ontario."

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. The Guideline Endorsement will also be disseminated among relevant OH (CCO) groups including the Guideline Development Group, the Central Nervous System (CNS) Advisory Committee, and to other stakeholders in the care and management of radiation necrosis.

UPDATING THE ENDORSEMENT

CI-DAP at Ontario Health (Cancer Care Ontario) will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

The Brain Radiation Necrosis Endorsement Guideline Development Group (GDG) would like to thank the following individuals for their assistance in developing this report:

- The International Stereotactic Radiosurgery Society (ISRS) for their permission to endorse their 2023 International Stereotactic Radiosurgery Society's Guideline: A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations [1].

- Sheila McNair from the Program in Evidence-Based Care (PEBC) for assisting the CI-DAP with the guideline endorsement process.
- ISRS for collaborating with CI-DAP to facilitate endorsement of the guideline.

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through internal review and expert panel review, with the document drafted by the GDG Working Group and approved by the GDG Expert Panel.

REFERENCES

1. Vellayappan B, Lim-Fat MJ, Kotecha R, De Salles A, Fariselli L, Levivier M, Ma L, Paddick I, Pollock BE, Regis J, Sheehan JP, Suh JH, Yomo S, Sahgal A. A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations. Int J Radiat Oncol Biol Phys. 2023 Jul 22:S0360-3016(23)07647-2. PMID: 37482137. A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations - International Journal of Radiation Oncology, Biology, Physics (redjournal.org)
2. Program in Evidence-Based Care. OH(CCO) guideline endorsement protocol; 2022 [updated 2022 Apr 22; cited 2023 May 10]. Available from: pebctoolkit.mcmaster.ca/doku.php?id=projectdev:cco_endorsement_protocol
3. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Canadian Medical Association Journal. 2010 Jul 5;182(18):E839–42. Available from: agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf

APPENDIX 1: AFFILIATIONS AND CONFLICT OF INTEREST DECLARATIONS

Table 1: Members of the Brain Radiation Necrosis Endorsement Guideline Development Group: Working Group

Name	Affiliation	Conflict of Interest
Sunit Das Ontario CNS Cancers Lead Neurosurgery	St. Michael's Hospital Ontario Health (Cancer Care Ontario) Toronto, ON	VPiX, Synaptive, Subcortical Surgery Group, Congress of Neurological Surgeons, American Association of Neurological Surgeons, Society for NeuroOncology, Oxford University Press
Fabio Ynoe de Moraes Radiation Oncology	Kingston General Hospital Kingston, ON	None declared.
Jeffery Greenspoon Radiation Oncology	Hamilton Health Sciences Centre Hamilton, ON	None declared.
Katarzyna J. Jerzak Medical Oncology	Sunnybrook Health Sciences Centre Toronto, ON	Novartis Canada, Amgen, ApoBiologix, AstraZeneca Canada, Daiichi Sankyo, Eli Lilly Canada, Knight Therapeutics, Gilead Sciences, Myriad Genetics, Merck, Pfizer, Roche, Genomic Health, Eisai, Seagen
Ronald Ramos Neuro-Oncology	Hamilton Health Sciences Hamilton, ON	None declared.
Timothy Nguyen Radiation Oncology	London Health Sciences Centre London, ON	None declared.
Terry L. Ng Medical Oncology	The Ottawa Hospital Ottawa, ON	Canadian Breast Cancer Network, Novartis Canada, AstraZeneca Canada, Eli Lilly Canada, Knight Therapeutics, Gilead Sciences
Dhanesha Bhatti Specialist, Cancer Care Integration and Disease Advisory Program (CI-DAP).	Ontario Health (Cancer Care Ontario) Toronto, ON	None declared.

Table 2: Members of the Brain Radiation Necrosis Endorsement Guideline Development Group: Expert Panel

Name	Affiliation	Conflict of Interest
Derek Tsang Radiation Oncology	Princess Margaret Cancer Centre Toronto, ON	Need (getneed.com)
Amparo Wolf Neurosurgery	Health Sciences North Sudbury, ON	Medexus
Navya Kalidindi Neuro-Oncology	Juravinski Cancer Centre Hamilton, ON	Servier

APPENDIX 2: AGREE II SCORE SHEET

Domain	Item	Appraiser 1 Ratings[1]	Appraiser 2 Ratings[1]
1) Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	6	6
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7
Domain score[2] =	(40-6/42-6)*100 = 34/36*100 = 0.944*100 = **94.4%**	Score =	40
2) Stakeholder Involvement	4. The guideline development group includes individuals from all relevant professional groups.	2	6
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	1	1
	6. The target users of the guideline are clearly defined.	1	1
Domain score[2] =	(12-6/42-6)*100 = 6/36*100 = 0.167*100 = **16.7%**	Score =	12
3) Rigor of Development	7. Systematic methods were used to search for evidence.	7	7
	8. The criteria for selecting the evidence are clearly described.	7	7
	9. The strengths and limitations of the body of evidence are clearly described.	7	7
	10. The methods for formulating the recommendations are clearly described.	5	7
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	3	6
	12. There is an explicit link between the recommendations and the supporting evidence.	2	6
	13. The guideline has been externally reviewed by experts prior to its publication.	1	1
	14. A procedure for updating the guideline is provided.	1	1
Domain score[2] =	(75-16/112-16)*100 = 59/96*100 = 0.6146*100 = **61.5%**	Score =	75

Domain	Item	Appraiser 1 Ratings[1]	Appraiser 2 Ratings[1]
4) Clarity of Presentation	15. The recommendations are specific and unambiguous. 16. The different options for management of the condition or health issue are clearly presented. 17. Key recommendations are easily identifiable.	6 7 6	7 7 5
Domain score[2] =	(38-6/42-6)*100 = 32/36*100 = 0.889*100 = **88.9%**	Score =	38
5) Applicability	18. The guideline describes facilitators and barriers to its application. 19. The guideline provides advice and/or tools on how the recommendations can be put into practice. 20. The potential resource implications of applying the recommendations have been considered. 21. The guideline presents monitoring and/or auditing criteria.	2 5 5 1	7 6 7 1
Domain score[2] =	(34-8/56-8)*100 = 26/48*100 = 0.542*100 = **54.2%**	Score =	34
6) Editorial Independence	22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.	1 5	6 5
Domain score[2] =	(17-4/28-4)*100 = 13/24*100 = 0.542*100 = **54.2%**	Score =	17
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	5	5
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes, with modifications	Yes, with modifications

[1]Rated on a scale from 1 to 7

[2]Domain score = (Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score)