

CADTH Health Technology Review

Bevacizumab for the Treatment of Patients With Brain Radionecrosis

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Abbreviations

CI	confidence interval
FLAIR	fluid attention inversion recovery
Gd	gadolinium
HIT-6	Headache Impact Test-6
KPS	Karnofsky Performance Status
MIDAS	Migraine Disability Assessment Test
RCT	randomized controlled trial
SR	systematic review

Key Messages

- This review identified limited evidence regarding the clinical effectiveness and safety of bevacizumab for patients with symptomatic brain radionecrosis after radiosurgery. These identified studies had several limitations, most notably due to the limited number of studies with control groups; therefore, the findings related to the effectiveness and safety in this population are uncertain.
- For adult patients with symptomatic brain radionecrosis, treatment with bevacizumab may be associated with radiographic responses, a reduction in volumetric outcomes, an improvement in overall clinical and neurologic symptoms, an improvement in functional outcomes, and a reduction in corticosteroid use.
- Limited evidence from 1 study suggests that treatment with bevacizumab may be associated with greater radiographic response, a reduction in volumetric outcomes, and clinical symptom improvement compared to treatment with corticosteroids. The recurrence of brain radionecrosis for patients who received bevacizumab compared to corticosteroids was similar between groups.
- Commonly reported adverse events after patients with symptomatic brain radionecrosis were treated with bevacizumab included hypertension, proteinuria, edema, pulmonary embolism, and various thromboembolic events.

Context and Policy Issues

Brain radiation necrosis (hereafter referred to as radionecrosis) is a severe complication characterized by tissue death caused by radiation that may impact all or part of the brain tissue.¹ Radionecrosis is most commonly associated with high-dose radiation treatment for primary or secondary brain tumours, but may also develop following radiotherapy to noncentral nervous system tumours that are in close proximity to brain tissues.¹ It is estimated that the incidence of systematic brain radionecrosis is increasing due to the growing use of stereotactic radiosurgery and higher doses of radiation during initial therapy.¹ In patients with brain metastases, the incidence of radionecrosis is between 5% and 25%.² Risk factors associated with the occurrence of brain radionecrosis may include tumour volume, prescribed radiotherapy dose, fraction size, volume of normal brain irradiated, previous radiation exposure, and the use of concurrent therapy.² Brain radionecrosis is largely diagnosed based on clinical symptoms and radiological presentation.¹ Clinical symptoms may include neurologic deterioration and functional loss, which may progress to death.¹ Conventional radiological imaging has limitations in differentiating between tumour progression and radionecrosis, but efforts have been made to improve imaging through MRI, magnetic resonance spectroscopy, and PET imaging.^{1,2}

Symptomatic brain radionecrosis is typically treated with high-dose corticosteroids, such as dexamethasone.^{1,2} Corticosteroids help reduce inflammation signals and cytokines produced by the necrotic tissues, and may reduce potential blood brain barrier leaks.² Because corticosteroids help reduce edema, most patients experience rapid clinical symptom improvements once steroids are initiated.² Corticosteroid dosing varies depending on the type of corticosteroid and indication, but typically is prescribed at 4 mg to 8 mg per day.² In some severe cases, surgical resection may be considered if treatment with corticosteroids proves unresponsive.^{1,2}

Bevacizumab is an alternative treatment option for brain radionecrosis that has been used for colorectal, lung, brain, ovarian, cervical, and kidney cancers.^{3,4} Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes human vascular endothelial growth factor.⁵ Bevacizumab prevents human vascular endothelial growth factor from binding to endothelial cell surface receptors, and therefore regulates vascular permeability, which reduces edema caused by brain radionecrosis.³ Bevacizumab treatment is also an accessible option because it allows for relatively long dosing intervals due to its prolonged half-life and does not require continuous use.³

A Health Canada Notice of Compliance does not exist for bevacizumab for brain radionecrosis,⁵ and CADTH's reimbursement review process does not typically review biosimilar drugs. The purpose of this report is to summarize and critically appraise the evidence related to the clinical effectiveness and safety of bevacizumab, to support decisions involved in the treatment of patients with symptomatic brain radionecrosis after radiosurgery.

Research Questions

1. What is the clinical effectiveness and safety of bevacizumab for patients with symptomatic brain radionecrosis after radiosurgery?
2. What is the comparative clinical effectiveness and safety of bevacizumab versus corticosteroids for patients with symptomatic brain radionecrosis after radiosurgery?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, 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 bevacizumab and radionecrosis. No filters were applied to limit the retrieval by study type. Conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was completed on October 24, 2022, and limited to English-language documents published since January 01, 2012.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), they were duplicate publications, or were published before 2012. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)⁶ for SR, and the Downs and Black checklist⁷ for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 423 citations were identified in the literature search. Following screening of titles and abstracts, 371 citations were excluded and 52 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 46 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised 4 SRs and 6 non-randomized studies. [Appendix 1](#) presents the PRISMA⁸ flow chart of the study selection.

Summary of Study Characteristics

Four SRs⁹⁻¹² including 1 with meta-analysis⁹ and 6 non-randomized studies¹³⁻¹⁸ were included in this report.

Table 1: Selection Criteria

Criteria	Description
Population	Q1 and Q2: Adult patients diagnosed with symptomatic brain radionecrosis after receiving radiosurgery for brain metastases
Intervention	Q1 and Q2: Bevacizumab (any dose)
Comparator	Q1: Placebo, no treatment, or no comparator Q2: Corticosteroids (e.g., dexamethasone)
Outcomes	Q1 and Q2: Clinical effectiveness (e.g., progression-free survival, overall survival, response rate, duration of response, radionecrosis volume, symptom management and/or relief, quality of life) and safety (e.g., adverse events of grade 3 and grade 4, serious adverse events, mortality)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Additional details regarding the characteristics of included publications are provided in [Appendix 2](#). There was a large degree of overlap between the studies included in the SRs. The degree of overlap between SRs is presented in [Appendix 5](#).

Study Design

Two SRs were published in 2021,^{9,10} 1 SR was published in 2017,¹¹ and 1 SR was published in 2013.¹² The authors of 1 SR and meta-analysis included 12 non-randomized studies published up to August 2020.⁹ The authors of 1 SR included 12 primary studies comprised of 2 randomized controlled trials (RCT) and 10 non-randomized studies published up to March 2020.¹⁰ The authors of 1 SR included 21 primary studies comprised of 1 RCT and 20 non-randomized study published up to September 2016.¹¹ The authors of 1 SR included 7 primary studies comprised of 1 RCT and 6 non-randomized studies published up to September 2012.¹² The primary study overlap between these SRs is summarized in [Appendix 5](#). Fourteen of the 31 primary studies were included in 2 or more SRs.

Two non-randomized studies were published in 2022,^{13,14} 2 non-randomized studies were published in 2021,^{15,16} 1 non-randomized study was published in 2017,¹⁷ and 1 non-randomized study was published in 2016.¹⁸ Four of the non-randomized studies were single-arm retrospective cohort studies that used historical patient data to compare the change in outcomes before and after treatment.^{13,15-17} Two of the non-randomized studies were single-arm prospective cohort studies that collected patient data prospectively to compare the change in outcomes before and after treatment.^{14,18} When reported, patient follow-up times varied across each study, but ranged from 6 months to 14.2 months.

Country of Origin

The included SRs were conducted in China,^{9,10} Italy,¹¹ and the US.¹²

The included non-randomized studies were conducted in Canada,¹³ the US,¹⁴ China,¹⁵⁻¹⁷ and Japan.¹⁸

Patient Population

All 4 SRs included primary studies of patients with brain radionecrosis due to radiosurgery for brain metastases.⁹⁻¹² The total number of patients included in the SRs ranged from 30 to 236, and the sample size of each included primary study ranged from 1 to 58.⁹⁻¹²

Each non-randomized study included patients who had undergone radiosurgery, were diagnosed with brain radionecrosis, and were subsequently treated with bevacizumab.¹³⁻¹⁸ The number of patients included in each non-randomized study ranged from 10 to 40, and the mean or median age of patients ranged from 35.1 years to 64 years.¹³⁻¹⁸

Interventions and Comparators

Consistent with the inclusion criteria for the current report, the identified SRs included primary studies that assessed the effectiveness of bevacizumab for the treatment of patients with brain radionecrosis due to radiosurgery for brain metastases.⁹⁻¹² The dose and regimen of bevacizumab treatment varied across the studies, from 1 mg/kg to 15 mg/kg for up to 8 weeks.⁹⁻¹² The comparators for the identified SRs included single-arm before and after treatment studies,⁹⁻¹² corticosteroids,¹⁰ and placebo.¹⁰⁻¹²

Similarly, the identified non-randomized studies assessed the effectiveness of bevacizumab for the treatment of patients with brain radionecrosis due to radiosurgery for brain

metastases.¹³⁻¹⁸ The dose and regimen of bevacizumab treatment varied across the studies, and ranged from 2.5 mg/kg to 10 mg/kg every 2 to 4 weeks for a maximum of 6 cycles.¹³⁻¹⁸ Each included non-randomized study was a single-arm before and after treatment study.¹³⁻¹⁸

Outcomes

The identified SRs reported outcomes related to the clinical effectiveness and safety of bevacizumab for the treatment of patients with brain radionecrosis after radiosurgery. Three SRs reported the number of patients that experienced a radiographic response to treatment.⁹⁻¹¹ Each SR reported MRI findings related to volumetric changes associated with brain radionecrosis, measured through MRI T1 gadolinium (Gd) or T2 fluid attention inversion recovery (FLAIR) enhancement.⁹⁻¹² Three SRs reported outcomes associated with neurologic symptom progression,⁹⁻¹¹ while 1 SR reported unspecified clinical symptom progression.¹² Two SRs reported outcomes associated with the Karnofsky Performance Status (KPS) score,^{9,10} which is a tool used to measure the functionality of patients with cancer, as well as their ability to perform ordinary tasks.¹⁹ Each SR reported outcomes related to corticosteroid use,⁹⁻¹² specifically dexamethasone, for 3 of the identified SRs.^{9,10,12} Three SRs reported outcomes related to safety and adverse events, which included occurrence and symptoms of adverse events,⁹⁻¹¹ as well as radionecrosis recurrence in 1 SR.¹⁰

Similarly, the identified non-randomized studies assess the clinical effectiveness and safety of bevacizumab for the treatment of patients with brain radionecrosis after radiosurgery. One single-arm retrospective cohort study reported outcomes related to the number of patients who experience a radiographic response to treatment.¹³ Five non-randomized studies reported MRI findings related to volumetric changes measured through MRI T1 Gd enhancement,¹³⁻¹⁷ while 4 non-randomized studies reported volumetric changes measured through MRI T2 FLAIR enhancement.¹³⁻¹⁶ One single-arm prospective cohort study reported MRI findings related to the efficacy of treatment specifically for perilesional edema remission.¹⁸ One single-arm prospective cohort study reported outcomes associated with neurologic symptom progression,¹⁴ while 1 single-arm retrospective cohort study reported unspecified clinical symptom progression.¹⁵ Four non-randomized studies reported outcomes associated with KPS score.^{14-16,18} Five non-randomized studies reported outcomes related to corticosteroid use,^{13-16,18} with 2 non-randomized studies reporting outcomes specifically for dexamethasone use.^{13,18} Five non-randomized studies reported outcomes related to safety and adverse events, which included occurrence and symptoms of adverse events,^{13-15,18} radionecrosis recurrence,^{14,17} overall survival,¹³ progression-free survival,¹³ and mortality.^{14,18}

Summary of Critical Appraisal

An overview of the critical appraisal of the included studies is summarized in the following. Additional details regarding the strengths and limitations of the included publications are provided in [Appendix 3](#).

Systematic Reviews

All 4 SRs provided clearly defined the research question, inclusion criteria, and provided adequate details of the included primary studies.⁹⁻¹² Only 1 SR stated that review methods were established before the review was conducted and provided the PROSPERO registration number.¹⁰ Because 3 SRs did not state that the review methods were established before the review was conducted, it is challenging to determine if there were any deviations in the methods used that may impact validity. Three SRs included multiple database searches in their search strategy,⁹⁻¹¹ while 1 SRs stated that only 1 database was used for the search

strategy.¹² Each included SR provided literature search terms and a search strategy, which may help determine reproducibility.⁹⁻¹² None of the SRs restricted the time frame of their search,⁹⁻¹² while 3 SRs did not restrict by study design, which may allow for reduced selection or publication bias;^{9,11,12} however, this may be impacted because each SR only included studies published in English.⁹⁻¹² Two SRs indicated that literature search screening and data collection were done in duplicate, thus minimizing potential errors in data collection and synthesis.^{10,11} Only 2 SRs assessed the risk of bias of the included primary studies using appropriate techniques;^{9,10} however, it was unclear if risk of bias between primary studies was accounted for when interpreting the results of the review for each SR.⁹⁻¹² It is unclear if risk of bias was assessed in 2 SRs, which may impact the ability to interpret the validity of findings for each study.^{11,12} Additionally, publication bias was not assessed in any of the SRs.⁹⁻¹² One SR with MA included appropriate methods of statistical combination and measurement of heterogeneity (e.g., I^2 statistics), and discussed heterogeneity in its findings when applicable.⁹ Three SRs did not provide adequate information related to the statistical analysis, presenting challenges in determining if appropriate statistical analyses were conducted for primary study outcomes.¹⁰⁻¹² None of the SRs reported sources of funding for the included primary studies.⁹⁻¹² Each SR disclosed any potential conflict of interest implications for the review,⁹⁻¹² while 2 SRs disclosed if any funding was received for the review.^{9,10}

Non-Randomized Studies

None of the included non-randomized studies had a separate control group, which creates a major challenge in determining the true measure of effect for the intervention; therefore, any findings from these studies should be interpreted with caution as uncontrolled factors may have influenced the findings.¹³⁻¹⁸ All 6 included non-randomized studies clearly defined the objective, outcomes, intervention, and characteristics of included patients.¹³⁻¹⁸ Each non-randomized study received ethical approval,¹³⁻¹⁸ while 1 study registered the protocol before conducting the study, which allows for greater confidence in determining if there were any deviations in the methods used.¹⁴ Five non-randomized studies clearly defined the patient inclusion criteria,^{13-15,17,18} while 1 non-randomized study did not define the patient inclusion or exclusion criteria, which may impact study reproducibility.¹⁶ Each non-randomized study clearly described the main findings,¹³⁻¹⁸ with 4 studies including appropriate measures of variability (range and 95% confidence intervals [CIs]).^{13-15,18} Four non-randomized studies used appropriate statistical tests to assess main outcomes and the outcomes measures used were valid and reliable.^{13-15,18} Two non-randomized studies did not provide adequate information related to the statistical tests used to assess the main outcomes, which may create challenges for accurately interpreting the findings and could impact internal validity.^{16,17} Patient data were collected from the same population over the same period of time in each non-randomized study, and patient data were likely representative of the population from which they were recruited, which may help determine generalizability in similar populations.¹³⁻¹⁸ No evidence was provided in any of the non-randomized studies that indicated that the staff, places, and facilities may have been representative of the treatment the majority of the patients received.¹³⁻¹⁸ None of the identified non-randomized studies adequately identified principal confounders or account for possible confounding factors in the analysis, which may impact the true measure of effect for the intervention.¹³⁻¹⁸ Compliance with the intervention was reliable for each non-randomized study due to the nature of the intervention.¹³⁻¹⁸ Two non-randomized studies clearly accounted for patients lost to follow-up, with 1 study indicating that no patients were lost to follow-up.^{14,18} Due to the retrospective cohort study design of 4 of the non-randomized studies, there may be limitations to the data available for follow-up analysis, as these studies are limited by information captured in the past.^{13,15-17} Three non-randomized studies provided information related to any funding received

for the study,^{14,15,18} while 5 non-randomized studies declared any potential conflict of interest implications.^{13,15-18}

Summary of Findings

Four SRs⁹⁻¹² (1 with an MA)⁹ and 6 non-randomized studies¹³⁻¹⁸ were identified regarding the clinical effectiveness and safety of bevacizumab for patients with symptomatic brain radionecrosis after radiosurgery. [Appendix 4](#) presents the main study findings by outcome, which include radiographic response after treatment, MRI change after treatment, change in clinical symptoms, KPS score, corticosteroid use, and safety and adverse events. One SR included 2 primary studies with direct comparison outcomes for bevacizumab treatment versus placebo or corticosteroids.¹⁰ The other findings in this review from the SRs⁹⁻¹² and non-randomized studies¹³⁻¹⁸ did not include a separate control group (i.e., relevant evidence was single-arm and uncontrolled). The findings from the controlled studies (i.e., versus placebo or versus corticosteroids) are presented separately from the findings, with no control group (i.e., no comparator), in the tables and text, when applicable.

There was some overlap in the primary studies that were included in the SRs. Findings from the SRs were reported using pooled estimates (either by MA or simple data pooling) or by individual primary study, based on how the data were presented in the SR. When feasible, to avoid duplication of the results, outcome data from an individual primary studies within SRs were only reported once; however, some of the pooled estimates from separate reviews may contain some of the same data. A citation matrix illustrating the degree of overlap is presented in [Appendix 5](#).

Clinical Effectiveness and Safety of Bevacizumab for Patients With Symptomatic Brain Radionecrosis After Radiosurgery

All 4 SRs and 6 non-randomized studies reported outcomes for patients who received bevacizumab treatment for symptomatic brain radionecrosis after radiosurgery from single-arm uncontrolled studies,⁹⁻¹⁸ while 1 SR included 1 RCT that reported findings for patients who received bevacizumab compared to patients who received placebo.¹⁰ Three SRs presented overall results from pooled findings of included primary studies.⁹⁻¹¹

Radiographic Response After Treatment

Bevacizumab Treatment Versus Placebo

One SR reported on 1 primary RCT that indicated that all patients who received bevacizumab treatment for brain radionecrosis experienced a radiographic response compared to none of the patients who received placebo.¹⁰ This finding was statistically significantly different ($P = 0.013$).¹⁰

Bevacizumab Treatment With No Control Group

Three SRs reported the number of patients who experienced a radiographic response for patients who received bevacizumab treatment.⁹⁻¹¹ One SR defined a radiographic response as any reduction observed in radionecrosis or edema volume on MRI images.⁹ Three SRs that combined uncontrolled findings from primary studies and reported that 93%,⁹ 84.7%,¹⁰ and 97.6%¹¹ of patients who received bevacizumab treatment for brain radionecrosis experienced a radiographic response.

One single-arm retrospective cohort study reported that among 15 patients who received bevacizumab treatment for brain radionecrosis, 60% reported no radiographic response, while 33% and 7% reported a minimal or definite radiographic response, respectively.¹³

MRI Change After Treatment

MRI T1 Gd Enhancement Volume Change for Bevacizumab Treatment Versus Placebo

One SR reported on 1 primary RCT that indicated that patients who received bevacizumab treatment for brain radionecrosis were shown to have a 63% reduction in MRI T1 Gd enhancement volume compared to a 17% increase for patients who were given a placebo.¹⁰ This finding was statistically significantly different ($P = 0.0058$).¹⁰

MRI T1 Gd Enhancement Volume Change From Bevacizumab Treatment With No Control Group

All 4 SRs reported uncontrolled findings from primary studies for MRI T1 Gd enhancement volume changes after treatment with bevacizumab for patients with brain radionecrosis.⁹⁻¹² Three SRs reported combined findings from primary studies and found that patients treated with bevacizumab showed a reduction in MRI T1 Gd enhancement volume, which ranged from a 26% to 100% reduction in volume.⁹⁻¹¹ One SR with MA reported the pooled uncontrolled MRI T1 Gd enhancement volume findings across 6 included primary studies and reported a statistically significant reduction rate after patients were treated with bevacizumab for brain radionecrosis (i.e., 48.58% reduction; 95% CI, 38.32% to 58.85%; $I^2 = 80\%$; $P < 0.001$).⁹ One SR reported on 1 primary study that was not captured in the other included SRs, and found that MRI T1 Gd enhancement volume was reduced but did not report any numeric value associated with the reduction.¹²

Five single-arm cohort studies reported on MRI T1 Gd enhancement volume changes after treatment with bevacizumab for patients with brain radionecrosis.¹³⁻¹⁷

Three single-arm cohort studies reported the number of patients who experienced an MRI T1 Gd enhancement volume reduction, and found that 80%,¹⁴ 95%,¹⁵ and 92.86%¹⁷ of included patients from each study experienced a volume reduction.

One single-arm retrospective cohort study reported a mean reduction of 3 cm³ (95% CI, 4.9 cm³ to 11.0 cm³) among patients after bevacizumab treatment, but no measure of statistical significance was reported.¹³ One single-arm retrospective cohort study¹⁴ reported that the median volume reduction difference after bevacizumab treatment was 12.1 cm³, with a 76% median reduction volume at 12 months, which was statistically significantly different ($P = 0.012$). One single-arm retrospective cohort study reported that the reduction in MRI T1 volume from baseline was statistically significant at 1 month (48.4%), 3 months (74%), and 6 months (75%).¹⁵ One single-arm retrospective cohort study reported the mean MRI T1 Gd volume reduction to be 45% after treatment, but no measure of statistical significance was reported.¹⁶

MRI T2 FLAIR Enhancement Volume Change From Bevacizumab Treatment Versus Placebo

One SR reported on 1 primary RCT that indicated that patients who received bevacizumab treatment for brain radionecrosis had a 59% reduction in MRI T2 FLAIR volume compared to an increase of 14% in patients who were given a placebo.¹⁰ This findings was statistically significant ($P = 0.0149$).¹⁰

MRI T2 FLAIR Enhancement Volume Change From Bevacizumab Treatment With No Control Group

All 4 SRs reported MRI T2 FLAIR enhancement volume changes after treatment with bevacizumab for patients with brain radionecrosis.⁹⁻¹² Three SRs reported combined findings from primary studies and found that patients treated with bevacizumab showed a reduction in MRI T2 FLAIR enhancement volume, which ranged from a 48% to 74% reduction in volume.⁹⁻¹¹ One SR with MA reported the pooled uncontrolled MRI T2 FLAIR volume findings across 6 included primary studies and reported a statistically significant reduction rate of 62.017% (95% CI, 52.23% to 71.79%; P = 0.01).⁹ One SR reported on 1 primary study that was not captured in the other included SRs, and found that MRI T2 FLAIR volume was reduced but did not report any numeric value associated with the reduction.¹²

Four single-arm cohort studies reported on outcomes found through MRI T2 FLAIR enhancement volume changes after treatment with bevacizumab for patients with brain radionecrosis.¹³⁻¹⁶ Two single-arm cohort studies reported the number of patients who experienced an MRI T2 FLAIR volume reduction, and found that 90%¹⁴ and 95%¹⁵ of included patients from each study experienced a volume reduction. One single-arm retrospective cohort study reported a mean volume reduction of 27.9 cm³ (95% CI, 12.0 cm³ to 67.7 cm³) among patients after bevacizumab treatment, but no measure of statistical significance was reported.¹³ One single-arm prospective cohort study reported that the median vasogenic edema reduction difference between before bevacizumab treatment and after, as measured by MRI T2 FLAIR images, was 27.61 cm³, with a 70% median reduction at 12 months; however, this was not statistically significant (P = 0.086).¹⁴ One single-arm retrospective cohort study reported that the reduction in MRI T2 edema volume from baseline was statistically significant at 1 month (47.6%), 3 months (76.2%), and 6 months (66.3%) after bevacizumab treatment.¹⁵ One single-arm retrospective cohort study reported that the mean MRI T2 FLAIR volume after treatment was 26.1 cm³ with a mean volume reduction of 74%, but no measure of statistical significance was reported.¹⁶ One single-arm prospective cohort study reported a statistically significant rate of perilesional edema remission for patients who received bevacizumab treatment compared to those who received baseline measurements (78.9%; 95% CI, 62.7% to 90.4%; P < 0.001).¹⁸ Additionally, the median time to remission was 3.03 months (95% CI, 2.86 months to 3.85 months), the mean reduction in perilesional edema volume from baseline to 1 month after treatment was 63%, and the mean reduction in contrast-enhanced lesions from baseline to last treatment was 92.8%.

Change in Clinical Symptoms

Unspecified Clinical Symptoms for Bevacizumab Versus Placebo

One SR reported the findings from 1 primary RCT and found that the proportion of patients who experienced clinical improvement after bevacizumab treatment was 100% compared to 0 patients who received a placebo (n = 7 in both groups), but no measure of statistical significance was reported.¹⁰

Unspecified Clinical Symptoms From Bevacizumab Treatment With No Control Group

One SR reported on 1 primary study that was not captured in the other included SRs, and found that there was an improvement in clinical symptoms for the patients who received bevacizumab treatment but no numeric value was provided for this finding.¹² One single-arm retrospective cohort study reported the overall change in symptomatic response for patients who received bevacizumab treatment.¹⁵ The authors reported that 2.5% of patients

experienced progressed symptoms, 30% of patients experience stable symptoms, and 67.5% of patients experienced improved symptoms.¹⁵

Neurologic Symptoms

Three SRs that reported combined uncontrolled findings from primary studies, reported on the overall number of patients who experience a change in neurologic symptoms after treatment with bevacizumab for brain radionecrosis.⁹⁻¹¹ Two SRs reported that 3.5%⁹ and 3.2%¹¹ of included patients showed no response or worsened neurologic symptoms. Three SRs reported that 10%,⁹ 9%,¹⁰ and 5.6%¹¹ of included patients showed stable neurologic symptoms. Three SRs reported that 46%,⁹ 79.7%,¹⁰ and 91.2%¹¹ of included patients showed improved symptoms. Two SRs reported that 40%⁹ and 6%¹⁰ of included patients showed complete symptom resolution.

One single-arm prospective cohort study reported on the change in the Migraine Disability Assessment Test (MIDAS)²⁰ and Headache Impact Test-6²¹ at 3 months after bevacizumab treatment for patients without radionecrosis recurrence.¹⁴ Overall, the MIDAS score statistically significantly decreased (median decrease = 92%; range, 58% to 100%; P = 0.022) and the total Headache Impact Test-6 score statistically significantly decreased (median decrease = 24.8%; range, -14.1% to 39%; P = 0.02).¹⁴ The total days of headache statistically significantly decreased (median = 77%; range, -11% to 95%; P = 0.019).¹⁴ The MIDAS pain score reported a statistical significant decrease by 36% (median = 33%; range, -43% to 100%; P < 0.001).¹⁴

Karnofsky Performance Status Score

Two SRs reported the overall number of patients who experienced a change in the KPS score after bevacizumab treatment for brain radionecrosis.^{9,10} Both SRs reported that KPS scores improved in 80%⁹ and 78%¹⁰ of patients, while 1 SR reported that 22% of patients experienced stable or decreased KPS scores.¹⁰ Four single-arm cohort studies reported on the change in KPS scores from baseline in patients who were treated with bevacizumab for brain radionecrosis.^{14-16,18} One single-arm cohort study reported a median score increase of 10 points,¹⁴ 1 single-arm cohort study reported a median post-treatment score of 70 points,¹⁵ and 1 single-arm cohort study reported a mean post-treatment score increase of 31.8 points overall.¹⁶ The study that reported an increase of 70 points was reported to be statistically significant,¹⁵ while the study that reported an increase of 10 points was reported as not statistically significant, and statistical significance for the increase in 31.8 points was not reported.^{14,16} One single-arm cohort study reported the number of patients who experienced an improvement in KPS score and found that overall, 42.1% of patients (95% CI, 21.8% to 54%) experienced an improvement, while 26.5% of those patients experience a score increase by 10%, and 15.8% experienced a score improvement by 20%.¹⁸ The number of patients who experienced a score improvement at last follow-up was 23.8% (95% CI, 8.2% to 47.2%).¹⁸ No measure of statistical significance was reported for these findings.

Corticosteroid Use

Dexamethasone

Three SRs reported uncontrolled findings related to the change in dexamethasone use after treatment with bevacizumab for brain radionecrosis.^{9,10,12} Two SRs reported that overall, 97%⁹ and 97.8%¹⁰ of patients reduced or discontinued dexamethasone after bevacizumab treatment. One SR reported a mean dexamethasone dose reduction of 9.08 mg,⁹ while another SR reported that the dexamethasone dose was reduced to 0 after bevacizumab

treatment; however, it is unclear what the initial dexamethasone dose was.¹² Two single-arm cohort studies reported on the change in dexamethasone use after treatment with bevacizumab. One single-arm retrospective cohort study reported that among the 9 patients who did receive dexamethasone treatment, 5 patients experienced a dose reduction after bevacizumab treatment, while 4 patients had no dose reduction.¹³ One single-arm prospective cohort study reported that 76.3% (95% CI, 59.8% to 88.6%) of patients experienced a reduction in dexamethasone after bevacizumab treatment.¹⁸ Additionally, the mean dexamethasone dose at 6 months post bevacizumab treatment was 0.6 mg per day and 0.8 mg per day at final follow-up compared to mean baseline measurements of 1.7 mg per day. No measure of statistical significance was presented for any of these findings.

Unspecified Corticosteroids

One SR reported that 97% of patients experienced a reduction of corticosteroid use, and the median decrease in corticosteroid dose was 8.6 mg (range = 0 mg to 24 mg)¹¹; this finding did not include a control group. One single-arm prospective cohort study reported that the median decrease of days of corticosteroid use was 13 (range, 0 to 355); however, this was not statistically significant (P = 0.374).¹⁴ One single-arm retrospective cohort study reported that the mean time for half reduction dose of corticosteroids was 7 days (range, 2 to 22 days), while the mean reduced dose was 7.6 mg (0 mg to 20 mg). No measure of statistical significance was reported for this finding. One single-arm retrospective cohort study reported that the proportion of patients who discontinued corticosteroid use after treatment was 100%.¹⁶

Safety and Adverse Events

Reported Adverse Events

Two SRs reported the occurrence of adverse events.^{9,10} One SR included adverse events from 5 included primary studies and found that adverse events occurred in 9.5% to 100% of patients from each study.⁹ One SR included adverse events from 5 included primary studies and found that adverse events occurred in 17% to 33% of patients in 3 primary studies, while 2 primary studies reported 41 and 6 events.¹⁰ The reported adverse events from 3 SRs included hypertension, proteinuria, edema, mild allergy, arthralgia, dysgeusia, fatigue, urinary tract infection, pulmonary embolism, infection, headache, rash, fever, blurred vision, hyperglycemia, ischemic stroke, anemia, leukopenia, neutropenia, lymphocytopenia, aspiration pneumonia, pneumonia with severe sepsis, deep vein thrombosis, superior sagittal sinus thrombosis, and ischemic changes due to small vessel thrombosis.⁹⁻¹¹ When reported, the severity of adverse events ranged from grade 1 to grade 3 or more.⁹⁻¹¹

Four single-arm cohort studies reported the occurrence of adverse events.^{13-15,18} One single-arm retrospective cohort study reported that of 15 included patients, 4 patients reported an adverse event.¹³ One single-arm prospective cohort study reported that 6 of 10 included patients experienced serious adverse events, while 9 of 10 included patients experienced a treatment-emergent adverse event.¹⁴ One single-arm retrospective cohort study reported 0 adverse events out of 40 included patients.¹⁵ One single-arm prospective cohort study reported that adverse events occurred in 87.8% of patients, while grade 3 or higher adverse events occurred in 24.4% of those patients who experienced adverse events.¹⁸ The reported adverse events from the 4 single-arm cohort studies included deep vein thrombosis, pulmonary embolism, stroke, wound dehiscence, transient monocular blurred vision, transient diplopia, headache, blurred vision, leg cramps, fall, neck pain, numbness, seizures, traumatic fall, vomiting, hypertension, elevated alanine aminotransferase, convulsion,

anemia, mucocutaneous hemorrhage, proteinuria, intracranial hemorrhage, and unexpected death.^{13-15,18} Only 1 single-arm cohort study reported that the severity of adverse events that was reported were grade 3 or higher.¹⁸

Radionecrosis Recurrence

One SR reported that 34% of patients who received bevacizumab for brain radionecrosis experienced radionecrosis recurrence.¹⁰ One primary RCT that compared patients who received bevacizumab to those who received a placebo for brain radionecrosis was included in the SR and reported that 3 of 7 patients treated with bevacizumab experienced radionecrosis recurrence; however, no comparison to the placebo group was carried out for this outcome because all patients in the placebo group experienced radionecrosis progression; therefore, patients were crossed over to the bevacizumab group.¹⁰ Two non-randomized studies reported that 20% and 84.6% of patients experienced radionecrosis recurrence after receiving bevacizumab.

Overall Survival and Progression-Free Survival

One single-arm prospective cohort study reported that the median overall survival from first treatment was 21.7 months, while the median overall survival from first MRI was 28.5 months in 15 patients who received bevacizumab for brain radionecrosis.¹³ In addition, the median progression-free survival from first treatment was 6.5 months in 15 patients who received bevacizumab for brain radionecrosis.¹³

Mortality

Two single-arm cohort studies reported the occurrence of all-cause mortality among patients who received bevacizumab for brain radionecrosis.^{14,18} One single-arm cohort study reported all-cause mortality in 0 of 10 included patients.¹⁴ One single-arm prospective cohort study reported that mortality occurred in 14.6% of included patients.¹⁸

Comparative Clinical Effectiveness and Safety of Bevacizumab Versus Corticosteroids for Patients With Symptomatic Brain Radionecrosis After Radiosurgery

One SR reported on 1 primary RCT that compared patients who received bevacizumab to patients who received unspecified corticosteroids for brain radionecrosis.¹⁰

Radiographic Response After Treatment

One RCT reported that a statistically significantly greater proportion of patients who received bevacizumab for brain radionecrosis experienced a radiographic response compared to patients who received corticosteroids (65.5% versus 31.5%; $P < 0.001$).¹⁰

MRI Change After Treatment

MRI T1 Gd Enhancement Volume Change

One RCT reported that patients who received bevacizumab for brain radionecrosis had a statistically significantly greater mean MRI T1 Gd enhancement volume reduction of 25.5%, compared to patients who received corticosteroids who had a mean reduction of 5% ($P = 0.027$).¹⁰

MRI T2 FLAIR Enhancement Volume Change

One RCT reported that patients who received bevacizumab for brain radionecrosis had a statistically significantly greater mean MRI T2 FLAIR enhancement volume reduction (i.e., 51.8%) compared to patients who received corticosteroids (i.e., 19.3%; $P < 0.001$).¹⁰

Change in Clinical Symptoms*Unspecified Clinical Symptoms*

One RCT reported that 62.1% of patients who received bevacizumab for brain radionecrosis had an improvement in clinical symptoms compared to 42.6% of patients who received corticosteroids, which was statistically significantly greater ($P = 0.039$).¹⁰

Radionecrosis Recurrence

One primary RCT reported that 24.1% of patients who received bevacizumab for brain radionecrosis experienced a recurrence, compared to 24% of patients who received corticosteroids. No statistical significance measure was reported for this finding.

Limitations

The SRs identified in this report have limitations that should be considered while interpreting the results. Most notably, the quality of evidence included in the SRs is limited by study design, specifically with case studies, case series, or single-arm non-randomized studies. Thus, the quality of evidence that informed many of the outcomes in this review is unclear and may be at high risk of bias and uncertainty. Additionally, 2 of the SRs presented information from primary studies based on individual case outcomes, which creates challenges in appropriately controlling for information overlap in this report; as such, some findings may overlap with other outcomes across the SRs included in this review. There was also a large degree of heterogeneity within and across primary studies included in the SR, specifically related to cancer type and treatment protocols. Because of this heterogeneity, it is challenging to accurately compare outcomes across primary studies.

Similarly, all 6 included primary clinical studies were observational single-arm cohort studies (i.e., uncontrolled studies). Because of this study design, the primary clinical studies included in this report may be at high risk of bias and any finding associated with these studies should be interpreted with caution. The measure of clinical effect of the intervention is uncertain due to a lack of randomization, lack of separate control group, limited statistical analysis, and high potential for confounding factors associated with any findings. Findings may also be limited by heterogeneity across primary clinical studies regarding type of cancer and treatment protocol. The heterogeneity across primary clinical studies may also impact the generalizability of the reported findings to specific patient groups.

There was a lack of comparative evidence from the controlled studies included in this report. Only 1 study was included regarding the clinical effectiveness and safety of bevacizumab for brain radionecrosis compared to corticosteroids, which was included as a primary study in 1 SR. Details related to baseline patient characteristics and information related to treatment protocols were not provided, which may impact the ability to interpret the findings related to this comparison. In addition, 1 study was included that compared bevacizumab treatment to

placebo, which was included as a primary study in 1 SR. This study included a small cohort and similarly lacked details related to baseline characteristics and treatment protocols, therefore impacting the ability to interpret findings related to this comparison. The other evidence included in this review was single arm (i.e., no control group), and either had no comparison (e.g., radiographic response to treatment) or reported the change from baseline within a single group. The limited evidence comparing outcomes in patients who received bevacizumab to a separate group of patients who did not receive bevacizumab highlights a potential gap in the evidence base and the overall ability to determine the measure of effects for bevacizumab treatment.

The generalizability of findings specifically from the primary studies included in the SRs may be challenging to determine because the time frame of included primary studies extends to 2007 and it is unknown if older findings may be applicable to the modern treatment landscape. Additionally, only 1 included non-randomized study was conducted in Canada.¹³ The majority of the included evidence related to the clinical effectiveness and safety of bevacizumab for brain radionecrosis was conducted in a variety of countries. Thus, it is unclear how generalizable the findings are to the Canadian context. This should be considered because management of cancer-related outcomes may vary between countries; therefore, may have different implications depending on the population and cultural context.

Conclusions and Implications for Decision- or Policy-Making

This report included 4 SRs (1 with an MA)⁹⁻¹² and 6 non-randomized studies¹³⁻¹⁸ related to the clinical effectiveness and safety of bevacizumab for patients with brain radionecrosis after radiosurgery. One of these SRs also reported findings from 1 primary RCT related to the clinical effectiveness and safety of bevacizumab for patients with brain radionecrosis after radiosurgery compared to corticosteroids.¹⁰ Each included study specified that the population of interest included adult patients who received bevacizumab treatment for brain radionecrosis after radiosurgery for related brain metastases.⁹⁻¹⁸ Each study indicated the treatment protocol for bevacizumab, but this varied among studies. The dose of bevacizumab treatment ranged from 1 mg/kg to 15 mg/kg for up to 8 weeks, which may have included multiple cycles.⁹⁻¹⁸ No information was available related to the treatment protocol for patients who received corticosteroids.¹⁰

Based on the evidence summarized within this report, the majority of patients included in the SRs who received bevacizumab treatment for brain radionecrosis reported a radiographic response after treatment (based on evidence from single-arm studies, or compared to placebo)⁹⁻¹¹ but findings from 1 single-arm cohort study showed that the majority of patients experienced no radiographic response.¹³ Evidence from all 4 SRs and 5 single-arm cohort studies reported that patients who received bevacizumab reported reductions in MRI T1 Gd enhancement volumes; the reductions ranged from 26% to 100% when compared to baseline measurements or placebo.⁹⁻¹⁷ Similarly, evidence from all 4 SRs and 4 single-arm cohort studies reported that patients who received bevacizumab reported reductions in MR1 T2 FLAIR enhancement volumes, which ranged from reductions of 11% to 96%, when compared to baseline measurements or placebo.⁹⁻¹⁶ The number of patients who experience

radionecrosis recurrence after treatment with bevacizumab ranged from 20% to 85%, as reported in 1 SR (with single-arm evidence) and 2 single-arm cohort studies.^{10,14,17}

Evidence from 2 SRs (that included single-arm studies or comparisons with placebo) and 1 single-arm cohort study reported that the majority of patients experienced clinical symptom improvement after receiving bevacizumab treatment.^{10,12,15} Single-arm evidence from 3 SRs reported that the majority of patients who received bevacizumab had an improvement in neurologic symptoms associated with brain radionecrosis (ranging from 85% to 96% of patients),⁹⁻¹¹ and 1 single-arm cohort study reported a decrease in symptoms measured by standardized migraine and headaches tests.¹⁴ Single-arm evidence from 2 SRs and 4 cohort studies reported that the majority of patients who received bevacizumab had improvements in KPS scores, with 3 single-arm cohort studies reporting score improvements of 10 to 90 points.¹⁴⁻¹⁶

Single-arm evidence from 4 SRs and 5 cohort studies reported on the reduction or discontinuation of dexamethasone and other corticosteroid use, and indicated that the majority of patients discontinued or reduced their use after bevacizumab treatment (ranging from 55.5% to 100% of patients).^{9-16,18} Three SRs and 4 single-arm cohort studies reported outcomes related to adverse events, and stated that the proportion of patients who experienced an adverse event following bevacizumab treatment ranged from 0% to 100% of patients (based on studies with sample sizes ranging from 4 to 112 patients).^{9-11,13-15,18} Commonly reported adverse events included hypertension, proteinuria, edema, pulmonary embolism, and various thromboembolic events. When reported, the severity of adverse events ranged from grade 1 to grade 3.^{9-11,18} One single-arm cohort study reported that the median overall survival after first treatment and first MRI was 21.7 and 28.5 months, respectively, while the median progression-free survival was 6.5 month for patients treated with bevacizumab.¹³ Similarly, 2 single-arm cohort studies reported that all-cause mortality occurred in none of the 10 patients from 1 study and in 14.6% of patients in the other study who received bevacizumab treatment.^{14,18}

When compared to patients who received corticosteroid treatment for brain radionecrosis, a statistically significantly larger proportion of patients who received bevacizumab experienced radiographic responses to treatment.¹⁰ In addition, patients who received bevacizumab had statistically significantly larger reductions in MRI T1 Gd and T2 FLAIR enhancement volumes, and a higher proportion of patients reported clinical improvements compared to those who received corticosteroids.¹⁰ The number of patients who experienced radionecrosis recurrence was similar in patients who received bevacizumab compared to corticosteroids.¹⁰ These findings are from 1 primary RCT included in 1 SR within this report.¹⁰

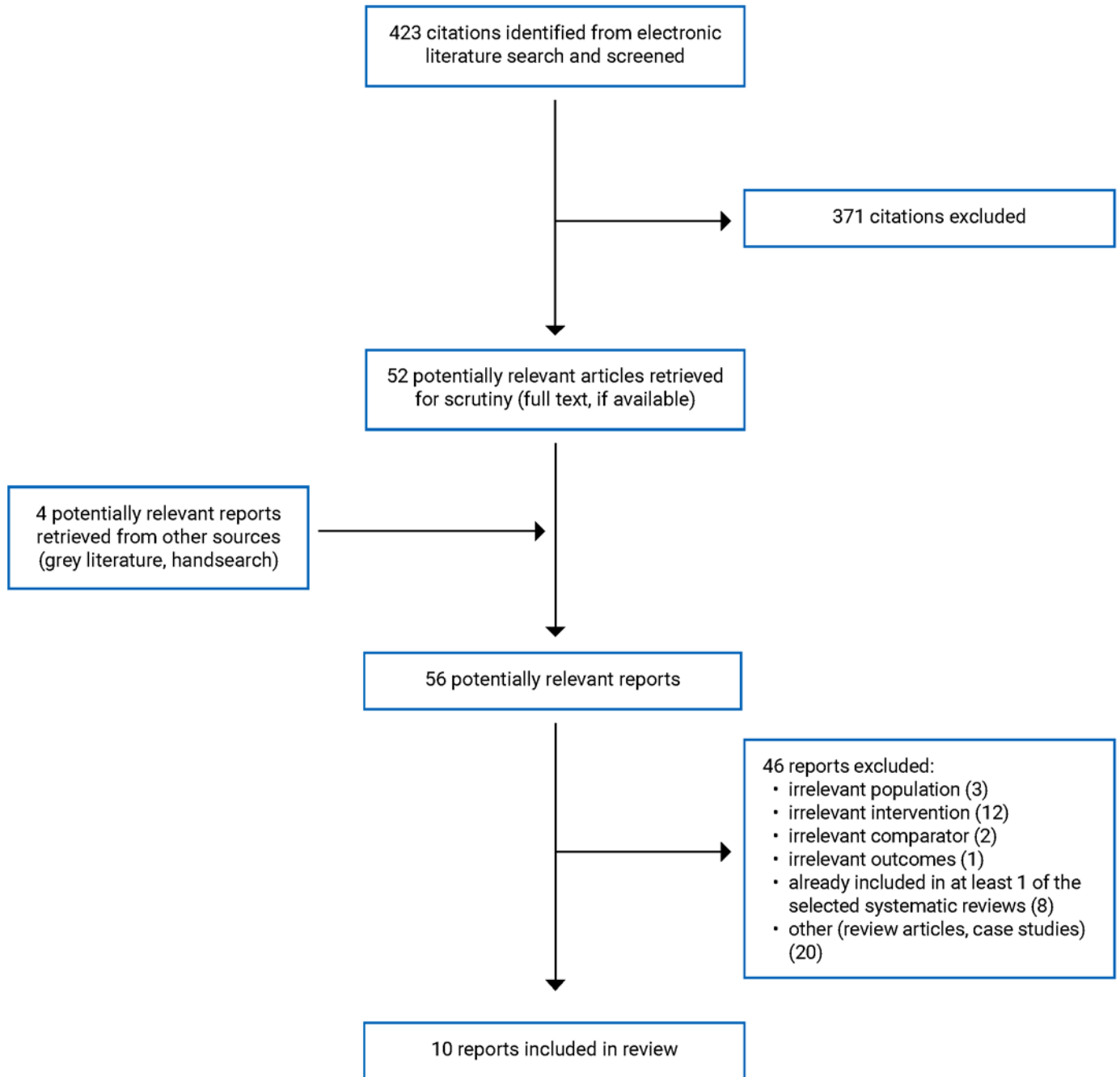
The limitations for the included literature (e.g., uncertain quality of primary studies included in the SRs, clinical heterogeneity of all included studies, the overall quality of included studies and potential high risk of bias, lack of statistical analyses, limited evidence from controlled studies, and limited Canadian context) should be considered when interpreting the findings of this report. The evidence from this report will help stakeholders in decision-making related to the use of bevacizumab for patients with brain radionecrosis. Further high-quality research that is specific to the Canadian context is needed to adequately assess the clinical effectiveness and safety of bevacizumab use in this patient population.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Khan et al. (2021)⁹ China Funding source: The Natural Science Foundation of Shenzhen (No. JCYJ20170307095828424); Shenzhen Health and Family Planning System Research Project (No.SZBC2017024)</p>	<p>Study design: SR with MA Last search date: August 2020 Number of included studies: 12 non-randomized studies</p>	<p>Eligibility criteria: Studies reporting the efficacy of bevacizumab for radionecrosis in patients with brain metastases after receiving radiotherapy for intracranial disease Total number of patients included: 89 Sample size (range): 1 to 21</p>	<p>Intervention (dose range): Bevacizumab (1 mg/kg to 15 mg/kg) up to 6 weeks Comparator: Single arm before and after treatment studies</p>	<p>Outcomes:</p> <ul style="list-style-type: none"> • Radiographic response • MRI volume reductions • Neurologic symptom improvement or resolution • KPS score • Change in dexamethasone use • Adverse events <p>Follow-up (range): 3.3 to 22.7 months</p>
<p>Liao et al. (2021)¹⁰ China Funding source: Natural Science Foundation of Shenzhen (No. JCYJ20170307095828424) and Shenzhen Health and Family Planning System Research Project (No. SZBC2017024)</p>	<p>Study design: SR Last search date: March 2020 Number of included studies: 12 (2 RCTs and 10 non-randomized studies)</p>	<p>Eligibility criteria: Published RCTs and non-randomized studies with more than 5 participants that investigated the efficacy and safety of bevacizumab for the treatment of radiation-induced brain necrosis Total number of patients included: 236 Sample size (range): 6 to 58</p>	<p>Intervention (dose range): Bevacizumab (1 mg/kg to 15 mg/kg) up to 6 weeks Comparators: Corticosteroids, placebo, and single arm before and after studies</p>	<p>Outcomes:</p> <ul style="list-style-type: none"> • Symptom improvement or resolution • KPS score • Edema volume change • Necrosis recurrence • Adverse events • Cognitive function <p>Follow-up (range): 8.1 to 22.7 months</p>
<p>Delishaj et al. (2017)¹¹ Italy Funding source: NR</p>	<p>Study design: SR Last search date: September 2016 Number of included studies: 21 (1 RCT and 20 non-randomized studies)</p>	<p>Eligibility criteria: Studies including patients with brain radionecrosis and treated with bevacizumab Total number of patients included: 125 Sample size (range): 1 to 24</p>	<p>Intervention (dose range): Bevacizumab (5 mg/kg to 15 mg/kg) up to 4 weeks Comparator: Placebo or single arm before and after treatment studies</p>	<p>Outcomes:</p> <ul style="list-style-type: none"> • Neurologic symptoms • Radiographic response • Adverse events <p>Follow-up (median): 8 months</p>

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
Lubelski et al. (2013) ¹² US Funding source: NR	Study design: SR Last search date: September 2012 Number of included studies: 7 (1 RCT and 6 non-randomized studies)	Eligibility criteria: Clinical studies of patients with radionecrosis following radiation therapy for high-grade glioma and were treated with bevacizumab Total number of patients included: 30 Sample size (range): 1 to 8	Intervention (dose range): Bevacizumab (5 mg/kg to 10 mg/kg) up to 8 weeks Comparator: Placebo or single arm before and after treatment studies	Outcomes: • Change in dexamethasone use • Radiographic response • Change in symptoms • Adverse events Follow-up: NR

KPS = Karnofsky Performance Status; NR = not reported; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design and objective	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
Climans et al. (2022) ¹³ Canada Funding source: NR	Study design: Single-arm retrospective cohort study Objective: To understand the use of bevacizumab for cerebral radionecrosis regarding the magnitude of clinical benefits and toxicities	Eligibility criteria: Data from neuro-oncology patients diagnosed with radionecrosis and treated with bevacizumab between January 2017 and March 2021 were included Number of participants: 15 Median age: 55 Number of females (%): 10 (67%) Cancer type, n (%): • Meningioma = 6 (40%) • Metastatic breast = 1 (7%) • Metastatic colon = 1 (7%) • Metastatic esophagus = 1 (7%) • Metastatic melanoma = 3 (20%) • Metastatic non-small	Intervention (dose): Bevacizumab (7.5 mg/kg) every 3 weeks for up to 4 total doses Comparator: Single arm before and after treatment study	Outcomes: • Change in symptoms • Change in steroid use • Change in performance status • Time to tumour progression • Time to death Follow-up (median): 14.2 months

Study citation, country, funding source	Study design and objective	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
		cell lung = 2 (13%) • Nasopharyngeal carcinoma = 1 (7%)		
Dashti et al. (2022) ¹⁴ US Funding source: Norton Health care Foundation and UK Health care	Study design: Single-arm prospective cohort study Objective: To evaluate the safety and efficacy of a single targeted low-dose bevacizumab infusion in patients diagnosed with brain radionecrosis	Eligibility criteria: Adults with a KPS score of $\geq 70\%$ and life expectancy of ≥ 3 months with at least 1 radionecrosis symptom Number of participants: 10 Mean age (SD): 35.1 (14.8) Number of females (%): 8 (80%) Cancer type, n (%): NR	Intervention (dose): Bevacizumab (2.5 mg/kg) Comparator: Single arm before and after treatment study	Outcomes: • Safety and adverse events • MRI efficacy • Changes in headache score • Changes in steroid use • Functional status Follow-up: 12 months
Li et al. (2021) ¹⁵ China Funding source: National Natural Science Foundation of China (NSFC) (No. 81703166), Natural Science Foundation of Guangdong Province (No. 2019A1515011943), China Postdoctoral Science Foundation (No. 2019M662974) and Science and Technology Program of Guangzhou (No. 202002030445), and Medical Scientific Research Foundation of Guangdong Province (A2020505 and A2020499).	Study design: Single-arm retrospective cohort study Objective: Evaluate the effects of bevacizumab as a treatment for brain radionecrosis following radiosurgery for brain metastases	Eligibility criteria: Patients diagnosed with brain metastases and radiographic radionecrosis who received bevacizumab for up to 6 months Number of participants: 40 Mean age (range): 55.5 (29 to 72) Number of females (%): 14 (35%) Cancer type, n (%): • Lung cancer = 34 (85%) • Malignant melanoma = 2 (5%) • Endometrial cancer = 2 (5%) • Breast cancer = 2 (5%)	Intervention (dose): Bevacizumab (5 mg/kg) every 2 weeks or 10 mg/kg every 3 weeks Comparator: Single arm before and after treatment study	Outcomes: • KPS score • Change in corticosteroid use • Radiographic response Follow-up: 6 months
Weng et al. (2021) ¹⁶ China Funding source: NR	Study design: Single-arm retrospective cohort study Objective: To evaluate the efficacy of low-dose bevacizumab	Eligibility criteria: Patients treated with bevacizumab for cerebral radionecrosis caused by Gamma Knife surgery between January 2013 and	Intervention: Bevacizumab (3 mg/kg) every 2 weeks for 2 to 4 courses Comparator: Single arm before and after treatment study	Outcomes: • Change in MRI findings • Radiographic response • Change in neurologic symptoms • Change in

Study citation, country, funding source	Study design and objective	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
	treatment for brain radionecrosis following Gamma Knife surgery in patients with brain metastases	December 2017 Number of participants: 22 Median age (range): 64 (48 to 79) Number of males (%): 11 (50%) Cancer type, n (%): <ul style="list-style-type: none"> • Lung cancer = 16 (72.7%) • Breast cancer = 2 (9.1%) • Renal clear cell carcinoma = 1 (4.5%) • Maxillary sinus carcinoma = 1 (4.5%) • Esophageal cancer = 1 (4.5%) • Ovarian cancer = 1 (4.5%) 		corticosteroid dosage • KPS score Follow-up: 6 months
Zhuang et al. (2017) ¹⁷ China Funding source: NR	Study design: Single-arm retrospective cohort study Objective: To evaluate clinical data of patients with cerebral radionecrosis who received bevacizumab treatment	Eligibility criteria: Patients with primary or metastatic lesions with a history of radiotherapy and diagnosis of radionecrosis who underwent bevacizumab treatment from June 2011 to December 2014 Number of participants: 14 Median age (range): 56 (31 to 70) Number of females (%): 8 (57%) Cancer type, n (%): <ul style="list-style-type: none"> • Lung cancer = 11 (78.6%) • Breast cancer = 1 (7.1%) • Lymphoma = 1 (7.1%) • Gastric cancer = 1 (7.1%) 	Intervention (dose): Bevacizumab (5 mg/kg) every 3 to 4 weeks for at least 3 cycles Comparator: Single arm before and after treatment study	Outcomes: <ul style="list-style-type: none"> • Changes in MRI findings • Adverse events Follow-up: NA (chart review)

Study citation, country, funding source	Study design and objective	Population characteristics	Relevant intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Furuse et al. (2016)¹⁸ Japan</p> <p>Funding source: Health and Labour Sciences Research Grant administered by Japan's Ministry of Health, Labour and Welfare (Clinical Trial on Development of New Drugs and Medical Devices, H24 to 006)</p>	<p>Study design: Single-arm prospective cohort study</p> <p>Objective: To evaluate the safety and efficacy of bevacizumab in patients with symptomatic brain radionecrosis</p>	<p>Eligibility criteria: Patients treated with radiotherapy for a tumour with perilesional edema caused by radionecrosis and a KPS score of ≥ 60</p> <p>Number of participants: 38</p> <p>Median age (range): 54.5 (17 to 73)</p> <p>Number of females (%): 16 (42.1%)</p> <p>Cancer type, n (%): Not specified</p>	<p>Intervention: Bevacizumab (5 mg/kg) every 2 weeks for up to 6 cycles</p> <p>Comparator: Single arm before and after treatment study</p>	<p>Outcomes:</p> <ul style="list-style-type: none"> • Changes in MRI findings (edema and lesion volume) • Changes in corticosteroid use • KPS score • Radionecrosis progression • Adverse events <p>Follow-up: 12 months</p>

KPS = Karnofsky Performance Status; NA = not applicable; NR = not reported; SD = standard deviation.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2⁶

Strengths	Limitations
Khan (2021)⁹	
<ul style="list-style-type: none"> • The research question and inclusion criteria were clearly described • Eligible study designs and search time frame were not restricted • Review authors did screen multiple databases and references of relevant review articles • Search terms and strategy were provided • Adequate detail of included studies was provided • Risk of bias was assessed using the Reporting Checklist for Authors by the Meta-analysis of Observational studies in Epidemiology Group • Descriptive statistics, including frequency, percentage, mean, median, range, and standard deviation were assessed using appropriate statistical analysis • Heterogeneity was assessed using I^2 statistics and heterogeneity was discussed where appropriate • Review authors did disclose funding and reported no potential conflicts of interest 	<ul style="list-style-type: none"> • Unclear if review protocol was registered in advance • Justification for publication restrictions were not provided (English studies only) • Unclear if literature search screening and selection was done in duplicate • Unclear if data extraction was done in duplicate • A list excluded studies was not provided • Source of funding was not provided for included studies • Potential impact of risk of bias for individual studies on the results on the meta-analysis was not assessed • Risk of bias for individual studies were not accounted for when interpreting the results of the review • Publication bias was not assessed
Liao (2021)¹⁰	
<ul style="list-style-type: none"> • The research question and inclusion criteria were clearly described • Review methods were established before review was conducted (PROSPERO: CRD42019134033) • Search time frame was not restricted • Review authors did screen multiple databases and references of relevant review articles • Search terms and strategy were provided • Literature search screening and selection was done in duplicate • Data extraction was done in duplicate • Adequate detail of included studies was provided • Risk of bias was assessed using the Reporting Checklist for Authors by the Meta-analysis of Observational studies in Epidemiology Group and Cochrane tools for RCTs • Review authors did disclose funding and reported no potential conflicts of interest 	<ul style="list-style-type: none"> • Justification for publication restrictions were not provided (Study designs, number of participants, English studies only) • A list excluded studies and justification for exclusion was not provided • Source of funding was not provided for included studies • Risk of bias for individual studies were not accounted for when interpreting the results of the review • Publication bias was not adequately assessed

Strengths	Limitations
Delishaj (2017)¹¹	
<ul style="list-style-type: none"> • The research question and inclusion criteria were clearly described • Eligible study designs and search time frame were not restricted • Review authors did screen multiple databases • Search terms and strategy were provided • Literature search screening and selection was done in duplicate • Data extraction was done in duplicate • Adequate detail of included studies was provided • Review authors reported no potential conflicts of interest 	<ul style="list-style-type: none"> • Unclear if review protocol was registered in advance • Unclear if any attempt was made for additional reference screening • A list excluded studies was not provided • Unclear if additional restrictions were used for publication inclusion criteria • Source of funding was not provided for included studies • Unclear if risk of bias among individual studies was assessed • Risk of bias for individual studies were not accounted for when interpreting the results of the review • Publication bias was not adequately assessed • Review authors did not report if they received any funding
Lubelski (2013)¹²	
<ul style="list-style-type: none"> • The research question and inclusion criteria were clearly described • Eligible study designs and search time frame were not restricted • Search terms and strategy were provided • Adequate detail of included studies was provided • Review authors reported no potential conflicts of interest 	<ul style="list-style-type: none"> • Unclear if review protocol was registered in advance • Justification for publication restrictions were not provided (English studies only) • Only 1 database was assessed, and unclear if any attempt was made for additional reference screening • Unclear if literature search screening and selection was done in duplicate • Unclear if data extraction was done in duplicate • Source of funding was not provided for included studies • Unclear if risk of bias among individual studies was assessed • Risk of bias for individual studies were not accounted for when interpreting the results of the review • Publication bias was not adequately assessed • Review authors did not report if they received any funding

AMSTAR 2 = A Measurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist⁷

Strengths	Limitations
Climans (2022)¹³	
<ul style="list-style-type: none"> • The objective, outcomes, inclusion and exclusion criteria, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described with appropriate estimates of variability for some findings (95% CI) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited 	<ul style="list-style-type: none"> • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may

Strengths	Limitations
<ul style="list-style-type: none"> • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data were from the same population over the same period of time • Authors declared potential conflicts of interest 	<ul style="list-style-type: none"> • impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not report study funding sources
Dashti (2022)¹⁴	
<ul style="list-style-type: none"> • The objective, outcomes, inclusion and exclusion criteria, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval and the trial protocol was registered (NCT02819479) • The main findings are clearly described with appropriate estimates of variability for some findings (95% CI) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited • No patients appear to have been lost to follow-up and length of follow-up was the same for each patient • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data were from the same population over the same period of time • Power calculations were used to determine adequate sample size • Authors declared study funding sources 	<ul style="list-style-type: none"> • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • Authors did not declare any potential conflicts of interest
Li (2021)¹⁵	
<ul style="list-style-type: none"> • The objective, outcomes, inclusion criteria, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described with appropriate estimates of variability for some findings (range and 95% CI) • Patient data used may have been representative of the entire population from which they were recruited • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Compliance with intervention was reliable • Patient data were from the same population over the same period of time 	<ul style="list-style-type: none"> • Exclusion criteria was not clearly described • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • Exact P values were not provided (P > 0.05, P < 0.05, or P < 0.001) • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis

Strengths	Limitations
<ul style="list-style-type: none"> • Authors declared funding and potential conflicts of interest 	<ul style="list-style-type: none"> • It is unclear if sufficient power calculations were used to determine adequate sample size
Weng (2021)¹⁶	
<ul style="list-style-type: none"> • The objective, outcomes, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described • Patient data used may have been representative of the entire population from which they were recruited • Compliance with intervention was reliable • Patient data were from the same population over the same period of time • Authors declared potential conflicts of interest 	<ul style="list-style-type: none"> • The inclusion and exclusion criteria were not clearly described • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • Appropriate estimates of variability were not provided • Exact P values were not provided • It is unclear if appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not report study funding sources
Zhuang (2017)¹⁷	
<ul style="list-style-type: none"> • The objective, outcomes, inclusion criteria, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • The main findings are clearly described and exact P values were provided for some findings • Patient data used may have been representative of the entire population from which they were recruited • Compliance with intervention was reliable • Patient data were from the same population over the same period of time • Authors declared potential conflicts of interest 	<ul style="list-style-type: none"> • Exclusion criteria was not clearly described • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • Appropriate estimates of variability were not provided • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • Patient loss to follow-up was likely not captured due to study design (retrospective cohort study) • It is unclear if appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size • Authors did not report study funding sources

Strengths	Limitations
Furuse (2016)¹⁸	
<ul style="list-style-type: none"> • The objective, outcomes, inclusion and exclusion criteria, intervention, and patient characteristics were clearly defined in the introduction and methods • The study received ethical approval • Patient loss to follow-up was clearly outlined and difference in length of follow-up was assessed appropriately • The main findings are clearly described with appropriate estimates of variability for some findings (95% CI) and exact P values unless < 0.001 • Patient data used may have been representative of the entire population from which they were recruited • Compliance with intervention was reliable • Patient data were from the same population over the same period of time • Appropriate statistical tests were used to assess main outcomes and main outcome measures used were valid and reliable • Authors declared funding and potential conflicts of interest 	<ul style="list-style-type: none"> • Study design did not include a control group • It is unclear if all important adverse events were reported • Principal confounders within study group were not clearly outlined • It is unclear if the staff, places, and facilities may have been representative of the treatment majority of the patients received • As this is a non-randomized study, there was no blinding or randomization and therefore confounding factors may impact findings • It is unclear if confounding factors were accounted for in analysis • It is unclear if sufficient power calculations were used to determine adequate sample size

CI = confidence interval.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Comparative Findings by Outcome – Radiographic Responses After Treatment

Outcome	Liao et al. (2021), ¹⁰ SR			
	Bevacizumab vs. corticosteroids ^a		Bevacizumab vs. placebo ^b	
	Bevacizumab treatment	Corticosteroid treatment	Bevacizumab treatment	Placebo group
Sample size	58	54	7	7
Proportion of patients with radiographic response	65.5%	31.5%	100%	0
P value	< 0.001		0.0013	

SR = systematic review

^aOutcomes based on 1 RCT (Xu et al. 2018)

^bOutcomes based on 1 RCT (Levin et al. 2011)

Table 7: Summary of Uncontrolled Findings by Outcome – Radiographic Responses After Treatment

Outcome	Khan et al. (2021), ⁹ SR with MA	Liao et al. (2021), ¹⁰ SR	Delishaj et al. (2017), ¹¹ SR	Climans et al. (2022), ¹³ Single-arm retrospective cohort study
Sample size	89	236	125	15
Overall number of patients with radiographic response, n (%)	83 (93%)	200 (84.7%)	122 (97.6%)	–
No response, n (%)	–	–	–	9 (60%)
Minimal response, n (%)	–	–	–	5 (33%)
Definite response, n (%)	–	–	–	1 (7%)

CI = confidence interval; MA = meta-analysis; RCT = randomized controlled study; SD = standard deviation; SR = systematic review.

Table 8: Summary of Comparative Findings by Outcome – MRI Change After Treatment

Outcome	Liao et al. (2021), ¹⁰ SR			
	Bevacizumab vs. corticosteroids ^a		Bevacizumab vs. placebo ^b	
	Bevacizumab treatment	Corticosteroid treatment	Bevacizumab treatment	Placebo group
MRI T1 Gd Enhancement volume Change				
Sample size	58	54	7	7
Mean volume change	25.5% (reduction)	5% (reduction)	63% (reduction)	17% (increase)
P value	0.027		0.0058	
MRI T2 FLAIR Enhancement volume Change				
Sample size	58	54	7	7
Mean volume change	51.8% (reduction)	19.3% (reduction)	59% (reduction)	14% (increase)
P value	< 0.001		0.0149	

SR = systematic review

^aOutcomes based on 1 RCT (Xu et al. 2018)

^bOutcomes based on 1 RCT (Levin et al. 2011)

Table 9: Summary of Uncontrolled Findings by Outcome – MRI Change After Treatment

Study citation and design	Sample size	Outcome	Result	P value	Notes
MRI T1 Gd Enhancement volume Change					
Khan et al. (2021) ⁹ SR with MA	89	Mean volume reduction (SD)	47.03% (24.4%) (reduction)	—	Mean volume reduction outcome was based on 12 included studies Pooled analysis was based on 6 included studies (n = NR)
	—	Pooled volume reduction rate (95% CI)	48.58% (38.32% to 58.85%); I ² = 80% (reduction)	P < 0.001	Pooled analysis was based on 6 included studies (n = NR)
Liao et al. (2021) ¹⁰ SR	236	Median volume reduction (range)	50% (26% to 80%) (reduction)	—	Median volume reduction outcome was based on 12 included studies
Delishaj et al. (2017) ¹¹ SR	94	Median volume reduction	64% (reduction)	—	Median volume reduction outcome was based on 9 included studies
		Range of mean volume reduction	48.1% to 100% (reduction)	—	Range of mean volume reduction was based on 10 included studies

Study citation and design	Sample size	Outcome	Result	P value	Notes
Lubelski et al. (2013) ¹² SR	1	Change in volume	Reduction	—	Change in volume outcomes is based on 1 included study with 1 patient No numeric value was provided in the change in volume outcome
Climans et al. (2022) ¹³ Single-arm retrospective cohort study	15	Mean volume reduction (95% CI)	3.0 cm ³ (4.9 cm ³ to 11.0 cm ³) (reduction)	—	—
Dashti et al. (2022) ¹⁴ Single-arm prospective cohort study	10	> 25% volume reduction at 3 month follow-up, n (%; 95% CI)	8 (80%; 44% to 98%)	—	Volume reduction was measured by MRI T1 images
		Median volume reduction at 12 months (range)	76% (53% to 96%) (reduction)	—	
		Median volume reduction difference (range)	12.1 cm ³ (-1.0 cm ³ to 27.3 cm ³) (reduction)	P = 0.012	
Li et al. (2022) ¹⁵ Single-arm retrospective cohort study	40	Number of patients with volume reduction, n (%)	38 (95%)	—	—
		Reduction in volume at 1 month post treatment (range)	48.4% (-18% to 92%) (reduction)	P < 0.001	
		Reduction in volume at 3 months post treatment (range)	74% (8% to 95%) (reduction)	P < 0.001	
		Reduction in volume at 6 months post treatment (range)	75% (-213% to 98.7%) (reduction)	P < 0.001	
Weng et al. (2021) ¹⁶ Single-arm retrospective cohort study	22	Mean volume after treatment (range)	6.99 cm ³ (0.7 cm ³ to 20.6 cm ³)	—	—
		Mean reduction after treatment	45% (reduction)	—	
Zhuang et al. (2017) ¹⁷ Single-arm retrospective cohort study	14	Volume reductions after treatment, n (%)	13 (92.86%)	—	—

Study citation and design	Sample size	Outcome	Result	P value	Notes
MRI T2 FLAIR Enhancement volume Change					
Khan et al. (2021) ⁹ SR with MA	89	Mean volume reduction (SD)	61.78% (23.2%) (reduction)	—	Mean volume reduction outcome was based on 12 included studies (n = 89) Pooled analysis was based on 6 included studies (n = NR)
	—	Pooled volume reduction rate (95% CI)	62.017% (52.235% to 71.799%); I ² = 66.9% (reduction)	P = 0.01	Pooled analysis was based on 6 included studies (n = NR)
Liao et al. (2021) ¹⁰ SR	236	Median volume reduction (range)	59% (48% to 74%) (reduction)	—	Median volume reduction outcome was based on 12 included studies
Delishaj et al. (2017) ¹¹ SR	84	Median volume reduction	60% (reduction)	—	Median volume reduction outcome was based on 9 included studies
		Range of mean volume reduction	48.4% to 66% (reduction)	—	Range of mean volume reduction was based on 8 included studies
Lubelski et al. (2013) ¹² SR	1	Change in volume	Reduction	—	Change in volume outcomes is based on 1 included study with 1 patient No numeric value was provided in the change in volume outcome
Climans et al. (2022) ¹³ Single-arm retrospective cohort study	15	Mean volume reduction (95% CI)	27.9 cm ³ (12.0 cm ³ to 67.7 cm ³) (reduction)	—	—
Dashti et al. (2022) ¹⁴ Single-arm prospective cohort study	10	> 25% vasogenic edema reduction at 3 month follow-up, n (%; 95% CI)	9 (90%; 56% to 100%)	—	Vasogenic edema reduction was measured by MRI T2 FLAIR images
		Median vasogenic edema reduction at 12 months (range)	70% (11% to 83%) (reduction)	—	
		Median vasogenic edema reduction difference (range)	27.61 cm ³ (0.6 cm ³ to -216.1 cm ³) (reduction)	P = 0.086	

Study citation and design	Sample size	Outcome	Result	P value	Notes
Li et al. (2022) ¹⁵ Single-arm retrospective cohort study	40	Number of patients with T2 edema volume reduction, n (%)	38 (95%)	—	—
		Reduction in edema volume at 1 month post treatment (range)	47.6% (-14% to 92.2%) (reduction)	P < 0.001	
		Reduction in edema volume at 3 months post treatment (range)	76.2% (-40% to 96%) (reduction)	P < 0.001	
		Reduction in edema volume at 6 months post treatment (range)	66.3% (-39% to 92%) (reduction)	P < 0.001	
Weng et al. (2021) ¹⁶ Single-arm retrospective cohort study	22	Mean volume after treatment (range)	26.1 cm ³ (5.6 cm ³ to 60.8 cm ³)	—	—
		Mean volume reduction after treatment	74% (reduction)	—	
Furuse et al. (2016) ¹⁸ Single-arm prospective cohort study	38	Rate of perilesional edema remission (95% CI)	78.9% (62.7% to 90.4%)	P < 0.001	Compared to baseline measurements
		Median time to remission from enrolment (95% CI)	3.03 months (2.86 to 3.85 months)	—	
		Mean reduction in perilesional edema volume from baseline to 1 month after treatment	63% (reduction)	—	
		Mean reduction in contrast-enhanced lesions from baseline to last treatment	92.8% (reduction)	—	

CI = confidence interval; FLAIR = Fluid attention inversion recovery; Gd = gadolinium; MA = meta-analysis; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review.

Table 10: Summary of Comparative Findings by Outcome – Clinical Symptoms

Outcome	Liao et al. (2021), ¹⁰ SR			
	Bevacizumab vs. corticosteroids ^a		Bevacizumab vs. placebo ^b	
	Bevacizumab treatment	Corticosteroid treatment	Bevacizumab treatment	Placebo group
Sample size	58	54	7	7
Clinical symptom improvement, n (%)	36 (62.1%)	23 (42.6%)	7 (100%)	0
P value	0.039		–	

SR = systematic review.

^aOutcomes based on 1 RCT (Xu et al. 2018)

^bOutcomes based on 1 RCT (Levin et al. 2011)

Table 11: Summary of Uncontrolled Findings by Outcome – Clinical Symptoms

Outcome	Khan et al. (2021), ⁹ SR with MA	Liao et al. (2021), ¹⁰ SR	Delishaj et al. (2017), ¹¹ SR	Lubelski et al. (2013), ¹² SR ^a	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Li et al. (2022), ¹⁵ Single-arm retrospective cohort study
Sample size	85	133	125	1	8	40
Change in Unspecified Clinical Symptoms						
Change in overall clinical symptoms	–	–	–	Improvement	–	–
Progressed symptoms, n (%)	–	–	–	–	–	1 (2.5%)
Stable symptoms, n (%)	–	–	–	–	–	12 (30%)
Improved symptoms, n (%)	–	–	–	–	–	27 (67.5%)
Change in Neurologic Symptoms						
No response or worsened symptoms, n (%)	3 (3.5%)	–	4 (3.2%)	–	–	–
Stable symptoms, n (%)	9 (10%)	13 (9%)	7 (5.6%)	–	–	–
Improved symptoms, n (%)	39 (46%)	106 (79.7%)	114 (91.2%)	–	–	–
Complete symptom resolution, n (%)	34 (40%)	8 (6%)	–	–	–	–
Total MIDAS score decrease	–	–	–	–	84%	–
Median (range); P value	–	–	–	–	92% (58% to 100%); P = 0.022	–
Total MIDAS pain score decrease	–	–	–	–	61%	–

Outcome	Khan et al. (2021), ⁹ SR with MA	Liao et al. (2021), ¹⁰ SR	Delishaj et al. (2017), ¹¹ SR	Lubelski et al. (2013), ¹² SR ^a	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Li et al. (2022), ¹⁵ Single-arm retrospective cohort study
Median (range); P value	—	—	—	—	33% (-43% to 100%); P < 0.001	—
Total decrease in days of headache	—	—	—	—	61%	—
Median (range); P value	—	—	—	—	77% (-11% to 95%); P = 0.019	—
Total HIT-6 score decrease	—	—	—	—	18.3%	—
Median (range); P value	—	—	—	—	24.8% (-14.1% to 39%); P value = 0.02	—

HIT-6 = Headache Impact Test – 6; MA = meta-analysis; MIDAS = Migraine Disability Assessment Test; SR = systematic review.

^aChange in clinical symptom outcome is based on 1 included study with 1 patient. No numeric value was provided for this outcome.

Table 12: Summary of Findings by Outcome – Karnofsky Performance Status Score

Outcomes	Khan et al. (2021), ⁹ SR with MA	Liao et al. (2021), ¹⁰ SR	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Li et al. (2021), ¹⁵ Single-arm prospective cohort study	Weng et al. (2021), ¹⁶ Single-arm retrospective cohort study	Furuse et al. (2016), ¹⁸ Single-arm prospective cohort study
Sample Size	10	37	10	40	22	38
KPS score improvement						
n (%)	8 (80%)	29 (78%)	—	—	—	16 (42.1%; 95% CI 21.8% to 54%)
Improvement by 10%, n (%)	—	—	—	—	—	10 (26.3%)
Improvement by 20%, n (%)	—	—	—	—	—	6 (15.8%)
Improvement at last follow-up, n (%)	—	—	—	—	—	5 (23.8%; 95% CI 8.2% to 47.2%)
Median (range)	—	—	10 points (-10 to 10); P = 0.232	—	—	—
Mean	—	—	—	31.8	—	—
KPS score stable or decreased, n (%)	—	8 (22%)	—	—	—	—

Outcomes	Khan et al. (2021), ⁹ SR with MA	Liao et al. (2021), ¹⁰ SR	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Li et al. (2021), ¹⁵ Single-arm prospective cohort study	Weng et al. (2021), ¹⁶ Single-arm retrospective cohort study	Furuse et al. (2016), ¹⁸ Single-arm prospective cohort study
KPS score post treatment, median (range)	—	—	—	70 (60 to 90); P < 0.001	—	—

CI = confidence interval; KPS = Karnofsky Performance Status.

Notes: KPS score outcomes for Dashti et al. (2022), Li et al. (2021), Weng et al. (2021), and Furuse et al. (2016) were compared to pre-treatment or baseline measurements.

Table 13: Summary of Findings by Outcome – Corticosteroid Use

Study citation and design	Sample size	Outcome	Result	Notes
Dexamethasone				
Khan et al. (2021) ⁹ SR with MA	31	Dose discontinuation or reduction, n (%)	30 (97%)	Among patients who recorded dexamethasone dosage before and after bevacizumab treatment
		Mean dexamethasone dose reduction	9.08 mg	
Liao et al. (2021) ¹⁰ SR	47	Dose reduction, n (%)	46 (97.8%)	Dexamethasone dose reduction outcome was based on 5 included studies
Lubleksi et al. (2013) ¹² SR	1	Change in dose of dexamethasone after treatment ^a	0 mg	Change in volume outcomes is based on 1 included study with 1 patient
Climans et al. (2022) ¹³ Single-arm retrospective cohort study	15	Dose reduction, n (%)	5 (33%)	Not applicable refers to patients who did not receive any dexamethasone treatment
		No dose reduction, n (%)	4 (27%)	
		Not applicable, n (%)	6 (40%)	
Furuse et al. (2016) ¹⁸ Single-arm prospective cohort study	35	Dose reduction, n (%; 95% CI)	29 (76.3%; 59.8% to 88.6%)	Compared to baseline measures (mean = 1.7 mg/day)
		Mean dexamethasone dose at 6 months post treatment	0.6 mg/day	
		Mean dexamethasone dose at final follow-up	0.8 mg/day	

Study citation and design	Sample size	Outcome	Result	Notes
Unspecified Corticosteroid				
Delishaj et al. (2017) ¹¹ SR	NR	Proportion of patient that had a reduction of corticosteroid use	97%	Corticosteroid use outcomes were based on 17 included studies
		Median decrease in corticosteroid dose (range)	8.6 mg (0 to 24 mg)	
Dashti et al. (2022) ¹⁴ Single-arm prospective cohort study	10	Median decrease of days of corticosteroid use (range); P value	13 (0 to 355); P = 0.374	During the 12 months follow-up after treatment
Li et al. (2021) ¹⁵ Single-arm retrospective cohort study	40	Mean time for half reduction dose, days (range)	7 (2 to 22)	—
		Mean reduced dose (range)	7.6 mg (0 to 20 mg)	
Weng et al. (2021) ¹⁶ Single-arm retrospective cohort study	22	Discontinuation of corticosteroid use after treatment, n (%)	22 (100%)	—

CI = confidence interval; NR = not reported.

^aBaseline dexamethasone dose was NR.

Table 14: Summary of Findings by Outcome – Safety and Adverse Events

Study citation and design	Primary study	Sample size	Number of adverse events reported, n (%)	Reported adverse event symptom; n (%)
Khan et al. (2021) ⁹ SR with MA	Tanigawa et al (2019)	4	4 (100%)	<ul style="list-style-type: none"> • Hypertension^a (3) • Proteinuria^a (3) • Edema^a (1)
	Zhuang et al. (2019)	21	2 (9.5%)	<ul style="list-style-type: none"> • Grade 1 mild allergy (1) • Grade 1 hypertension (1)
	Glitza et al. (2017)	7	1 (14%)	<ul style="list-style-type: none"> • Arthralgia^a (1) • Dysgeusia^a (1)
	Sadraei et al. (2015)	17	5 (29%)	<ul style="list-style-type: none"> • Grade 1 proteinuria (1) • Grade 2 hypertension (1) • Grade 2 fatigue (1) • Grade 2 UTI (1) • Grade 3 pulmonary embolism (1)
	Zhuang et al. (2015)	14	2 (14%)	<ul style="list-style-type: none"> • Grade 1 mild allergy (1) • Grade 1 hypertension (1)

Study citation and design	Primary study	Sample size	Number of adverse events reported, n (%)	Reported adverse event symptom; n (%)
Liao et al. (2021) ¹⁰ SR	Xu et a. (2018)	112	41 ^b	<ul style="list-style-type: none"> • Grade 1 or 2 hypertension (12) • Grade 1 or 2 fatigue (7) • Grade 1 or 2 infection (4) • Grade 1 or 2 hemorrhage (4) • Grade 1 or 2 insomnia (3) • Grade 1 or 2 headache (3) • Grade 1 or 2 rash (3) • Grade 1 or 2 fever (2) • Grade 1 or 2 blurred vision (1) • Grade 1 or 2 hyperglycemia (1) • Grade 3 ischemic stroke (1)
	Yonezawa et al. (2014)	9	3 (33%)	<ul style="list-style-type: none"> • Grade 1 or 2 anemia^c • Grade 1 or 2 leukopenia^c • Grade 1 or 2 neutropenia^c • Grade 1 or 2 lymphocytopenia^c
	Wang et al. (2012)	17	3 (18%)	<ul style="list-style-type: none"> • Grade 2 hypertension (1) • Grade 2 fatigue (1) • Grade 2 proteinuria (1)
	Levin et al. (2011)	11	6 ^b	<ul style="list-style-type: none"> • Aspiration pneumonia^a (1) • Pulmonary embolus secondary to DVT^a (1) • Superior sagittal sinus thrombosis^a (1) • Ischemic changes due to small vessel thrombosis^a (3)
	Torcuator et al. (2009)	6	1 (17%)	<ul style="list-style-type: none"> • Fatigue^a (1)
Delishaj et al. (2017) ¹¹ SR	Not specified	NR	—	<ul style="list-style-type: none"> • Grade 3 pulmonary embolus (3) • Pulmonary embolus^a (4) • Hypertension^a (6) • UTI^a (1) • Fatigue^a (1) • Proteinuria^a (1) • Sagittal sinus thrombosis^a (1) • Aspiration pneumonia^a (1) • Pneumonia with severe sepsis^a (1) • Small vessel thrombosis^a (3)
Climans et al. (2022) ¹³ Single-arm retrospective cohort study	—	15	—	<ul style="list-style-type: none"> • None = 11 (73%) • DVT^a = 1 (7%) • DVT, pulmonary embolism, and stroke^a = 1 (7%) • Sudden unexpected death = 1 (7%) • Wound dehiscence^a = 1 (7%)

Study citation and design	Primary study	Sample size	Number of adverse events reported, n (%)	Reported adverse event symptom; n (%)
Dashti et al. (2022) ¹⁴ Single-arm prospective cohort study	—	10	SAE, n (%) = 6 (60%)	<ul style="list-style-type: none"> • Transient monocular blurred vision^{a,d} = 1 (10%) • Transient diplopia^{a,d} = 1 (10%) • Headache^{a,d} = 5 (50%) • Blurred vision^{a,d} = 4 (40%) • Leg cramps^{a,d} = 2 (20%) • Fall^{a,d} = 2 (20%) • Neck pain^{a,d} = 2 (20%) • Numbness^{a,d} = 2 (20%) • Seizures^{a,d} = 2 (20%) • Traumatic fall^{a,d} = 2 (20%) • Vomiting^{a,d} = 2 (20%)
			Any treatment-emergent AE, n (%) = 9 (90%)	—
Li et al. (2021) ¹⁵ Single-arm retrospective cohort study	—	40	0	—
Furuse et al. (2016) ¹⁸ Single-arm prospective cohort study	—	41	AE, n (%) = 36 (87.8%)	<ul style="list-style-type: none"> • Any grade hypertension = 14 (34.1%) • Grade ≥ 3 hypertension = 2 (4.9%) • Any grade elevated ALT = 13 (31.7%) • Grade ≥ 3 elevated ALT = 2 (4.9%) • Any grade convulsion = 5 (12.2%) • Grade ≥ 3 convulsion = 2 (4.9%) • Any grade anemia = 12 (29.3%) • Grade ≥ 3 anemia = 1 (2.4%) • Any grade mucocutaneous hemorrhage = 7 (17.1%) • Any grade proteinuria = 5 (12.2%) • Any grade intracranial hemorrhage = 3 (7.3%) • Any grade venous thromboembolic event = 2 (4.9%)
			Occurrence of Grade ≥ 3 AE, n (%) = 10 (24.4%)	—

AE = adverse event; ALT = alanine aminotransferase; DVT = deep vein thrombosis; MA = meta-analysis; NR = not reported; OS = overall survival; SAE = serious adverse events; SR = systematic review; UTI = urinary tract infection.

^aGrade of adverse event was not specified.

^bReported as number of events and only based on patients that received bevacizumab, including those initially randomized to placebo who crossed over to bevacizumab.

^cThe number of patients experiencing the reported symptoms was NR.

^dReported as more than 10% frequency.

Table 15: Summary of Comparative Findings by Outcome – Radionecrosis Recurrence

Outcome	Liao et al. (2021), ¹⁰ SR			
	Bevacizumab vs. corticosteroids ^a		Bevacizumab vs. placebo ^b	
	Bevacizumab treatment	Corticosteroid treatment	Bevacizumab treatment	Placebo group
Sample size	58	54	7	NA
Number of radionecrosis recurrence, n (%)	14 (24.1%)	13 (24%)	3 (42.8%)	NA

NA = not applicable; SR = systematic review.

^aOutcomes based on 1 RCT (Xu et al. 2018)

^bOutcomes based on 1 RCT (Levin et al. 2011). Comparison with the placebo group is not applicable as all patients in the placebo group had disease progression and were crossed over to the bevacizumab group.

Table 16: Summary of Uncontrolled Findings by Outcome – Radionecrosis Recurrence

Outcome	Liao et al. (2021), ¹⁰ SR	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Zhuang et al. (2017), ¹⁷ Single-arm retrospective cohort study
Sample size	135	10	13
Number of radionecrosis recurrence, n (%)	46 (34%)	2 (20%)	11 (84.6%) ^a
95% CI	–	(3% to 56%)	–

CI = confidence interval; NR = not reported; SR = systematic review.

^aAmong patients who responded to first treatment.

Table 17: Summary of Findings by Outcome – Overall Survival and Progression-Free Survival

Outcome	Climans et al. (2022), ¹³ Single-arm retrospective cohort study	Notes
Sample size	15	–
Median OS from first treatment (months)	21.7	–
Median OS from first MRI (months)	28.5	–
Median PFS from first treatment (months)	6.5	PFS was defined as freedom from tumour progression but not radionecrosis progression

OS = overall survival; PFS = progression-free survival.

Table 18: Summary of Findings by Outcome – Mortality

Outcome	Dashti et al. (2022), ¹⁴ Single-arm prospective cohort study	Furuse et al. (2016), ¹⁸ Single-arm prospective cohort study
Sample size	10	41
Occurrence of all-cause mortality, n (%)	0	6 (14.6%)

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 19: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Khan (2021) ⁹	Liao (2021) ¹⁰	Delishaj (2017) ¹¹	Lubelski (2013) ¹²
Tanigawa et al. <i>Respirol Case Rep.</i> 2019; 7(7): e00454	Yes	–	–	–
Zhuang et al. <i>Onco Targets Ther.</i> 2019; 12: 8447 to 53	Yes	Yes	–	–
Li et al. <i>Int J Radiat Oncol Biol Physics.</i> 2018; 100(3): 621 to 9	–	Yes	–	–
Xu et al. <i>Int J Radiat Oncol Biol Physics.</i> 2018; 101(5): 1087 to 95	–	Yes	–	–
Glitza et al. <i>Melanoma Res.</i> 2017; 27(6): 580 to 4	Yes	–	–	–
Ma et al. <i>J Craniofac Surg.</i> 2017; 28(6): e569-e71	Yes	–	–	–
Zhuang et al. <i>Oncotarget.</i> 2016; 7(30): 48842 to 48849	–	–	Yes	–
Zhuang et al. <i>Sci Rep.</i> 2016; 6: 24364	Yes	Yes	–	–
Delishaj et al. <i>Rare Tumors.</i> 2015; 7(4): 6018	–	–	Yes	–
Sadraei et al. <i>Am J Clin Oncol.</i> 2015; 38(3): 304 to 10	Yes	Yes	Yes	–
Xian-Pan et al. <i>J Cancer Res Ther.</i> 2015; 11(2): 485 to 7	Yes	–	Yes	–
Bostrom et al. <i>Strahlenther Onkol.</i> 2014; 190(4): 416 to 421	–	–	Yes	–
Yonezawa et al. <i>J Neuro-Oncol.</i> 2014; 119(1): 101 to 9	Yes	Yes	–	–
Alessandretti et al. <i>Case Rep Oncol.</i> 2013; 6(3): 598 to 601	Yes	–	Yes	–
Boothe et al. <i>Neuro-Oncology.</i> 2013; 15(9): 127 to 63	Yes	Yes	Yes	–
Furuse et al. <i>Jpn J Clin Oncol.</i> 2013; 43(3): 337 to 41	Yes	Yes	Yes	–
DeSalvo et al. <i>J Radiol Case Rep.</i> 2012; 6(7): 9 to 16	–	–	Yes	–
Wang et al. <i>Eur J Med Res.</i> 2012; 17(1): 25	Yes	Yes	Yes	Yes
Arratibel-Echarren et al. <i>Neurologia.</i> 2011; 26(2): 74 to 80	–	–	Yes	Yes
Benoit et al. <i>J Neurol.</i> 2011; 258(2): 328 to 329	–	–	Yes	–
Furuse et al. <i>J Neurooncol.</i> 2011; 102(3): 471 to 475	–	–	–	Yes
Jeyaretna et al. <i>J Clin Oncol.</i> 2011; 29(7): e159 to 162	–	–	Yes	–
Levin et al. <i>Int J Radiat Oncol Biol Physics.</i> 2011; 79(5): 1487 to 95	–	Yes	Yes	Yes
Matuschek et al. <i>Strahlenther Onkol.</i> 2011; 187(2): 135 to 139	–	–	Yes	Yes
Nonoguchi et al. <i>J Neurooncol.</i> 2011; 105(2): 423 to 431	–	–	Yes	–

Primary study citation	Khan (2021) ⁹	Liao (2021) ¹⁰	Delishaj (2017) ¹¹	Lubelski (2013) ¹²
Sanborn et al. <i>Clin Neurol Neurosurg.</i> 2011; 113(9): 798 to 802	–	–	Yes	–
Liu et al. <i>Int J Radiat Oncol Biol Phys.</i> 2009; 75(4): 1148 to 1154	–	–	Yes	–
Torcuator et al. <i>J Neurooncol.</i> 2009; 94(1): 63 to 8	–	Yes	Yes	Yes
Wong et al. <i>J Clin Oncol.</i> 2008; 26(34): 5649 to 5650	–	–	Yes	–
Gonzalez et al. <i>Int J Radiat Oncol Biol Physics.</i> 2007; 67(2): 323 to 6	–	Yes	Yes	Yes