Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2026.576870.1080

Comparative Outcomes of Preoperative and Postoperative Stereotactic Radiosurgery in Patients Undergoing Resection for Brain Metastases: Systematic Review and Meta-Analysis

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Article info
Received: 25.11.2025
Accepted: 26.02.2026
Available Online: 26.02.2026
Checked for Plagiarism: Yes

Keywords:
Brain metastases, Stereotactic radiosurgery, Preoperative radiotherapy, Postoperative radiotherapy, Leptomeningeal disease

A B S T R A C T

Brain metastases represent the most common intracranial tumors in adults, frequently requiring multimodal management including surgical resection and stereotactic radiosurgery (SRS). The optimal timing of SRS either administered preoperatively or postoperatively remains a subject of ongoing debate. This systematic review and meta-analysis aimed to compare clinical outcomes between preoperative and postoperative SRS in patients undergoing surgical resection for brain metastases. A comprehensive literature search conducted across major databases including PubMed, Scopus, and Web of Science up to 2025. Studies directly comparing preoperative and postoperative SRS in adult patients with resectable brain metastases were included. Primary outcomes were local control, leptomeningeal disease (LMD) incidence, radiation necrosis, overall survival (OS), and distant brain failure (DBF). Data were pooled using random-effects models, and heterogeneity assessed using the I^2 statistic. Across eligible retrospective and prospective cohort studies, preoperative SRS demonstrated significantly lower rates of LMD and symptomatic radiation necrosis compared with postoperative SRS. Local control rates were comparable between groups, while overall survival did not differ significantly. Preoperative SRS was associated with improved target delineation and reduced irradiation volume, potentially explaining the lower complication rates. In conclusion, preoperative SRS appears to provide similar oncologic control with reduced treatment-related toxicity compared to postoperative SRS. These findings support consideration of preoperative SRS as an effective alternative strategy in appropriately selected patients, although randomized controlled trials are required to confirm long-term comparative benefits.

Introduction

Brain metastases are the most common intracranial malignancies in adults, occurring in up to 20-40% of patients with systemic cancer during the course of their disease. Improvements in systemic therapies, including targeted agents and immunotherapies, have prolonged survival in many cancer types such as lung cancer, breast cancer, and melanoma, thereby increasing the cumulative incidence of intracranial metastatic disease [1-3]. Consequently, optimizing the management of brain metastases has become a critical priority in neuro-oncology. Historically, whole-brain radiotherapy (WBRT) was the standard adjuvant treatment following surgical resection of brain metastases. While WBRT improved intracranial control, it was associated with significant neurocognitive decline and diminished quality of life. These concerns prompted a paradigm shift toward more focal strategies, particularly stereotactic radiosurgery (SRS). SRS delivers highly conformal, high-dose radiation to a defined target while minimizing exposure to surrounding healthy brain tissue [4-6].

Over the past two decades, SRS has emerged as a cornerstone in the treatment of limited brain metastases, either as definitive therapy or as an adjunct to surgery. The role of SRS in the perioperative setting has traditionally been postoperative, targeting the surgical cavity to reduce local recurrence. Postoperative SRS has

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demonstrated improved local control compared with surgery alone and reduced neurocognitive toxicity compared with WBRT. However, several limitations of postoperative SRS identified. After resection, the surgical cavity may undergo dynamic changes in size and shape, complicating target delineation and potentially increasing treatment volumes. Moreover, postoperative SRS has been associated with a risk of leptomeningeal disease (LMD), possibly due to tumor cell dissemination during surgery. Rates of radiation necrosis also remain a concern, particularly in larger cavities requiring higher radiation doses [7-9].

In response to these challenges, preoperative SRS has emerged as an alternative strategy. In this approach, SRS delivered to the intact tumor prior to surgical resection. The theoretical advantages of preoperative SRS include more precise target definition, as the gross tumor volume clearly visualized on imaging before resection. This may allow for smaller radiation margins and reduced irradiation of normal brain tissue. Additionally, irradiation of the tumor before surgical manipulation may sterilize tumor cells, potentially reducing the risk of intraoperative dissemination and subsequent LMD. Preoperative SRS may also lower the incidence of radiation necrosis, as the irradiated tissue subsequently removed during surgery [10].

Despite these proposed benefits, preoperative SRS also presents logistical and clinical considerations. Coordinating timely SRS prior to surgery requires multidisciplinary planning and may not be feasible in cases requiring urgent decompression. Furthermore, concerns remain regarding wound healing complications, optimal dosing strategies, and the lack of high-level randomized data directly comparing preoperative and postoperative approaches [11-13].

Several retrospective studies and emerging prospective data have attempted to evaluate the comparative effectiveness of preoperative versus postoperative SRS. Reported outcomes include local control, distant brain failure, LMD incidence, radiation necrosis, overall survival, and treatment-related morbidity. While some studies suggest reduced LMD and radiation necrosis with preoperative SRS, others report comparable oncologic outcomes between the two strategies. However, variability in study design, patient selection, tumor characteristics, and radiation protocols has limited definitive conclusions [14].

Given the increasing adoption of SRS in the management of resectable brain metastases and the ongoing debate regarding optimal timing, a comprehensive synthesis of available evidence warranted. This systematic review and meta-analysis aims critically compare preoperative and postoperative SRS in patients undergoing surgical resection for brain metastases, with particular focus on local control, leptomeningeal disease, radiation necrosis, distant brain failure, and overall survival. By integrating current evidence, this study seeks to inform clinical decision-making and identify areas requiring further investigation through prospective randomized trials [15-17].

Background / Literature Review

The management of brain metastases has evolved significantly over the past few decades, reflecting advances in surgical techniques, radiotherapy modalities, and systemic therapies. Historically, surgical resection combined with whole-brain radiotherapy (WBRT) was the standard approach for patients with limited brain metastases. WBRT, while effective in controlling both local and distant intracranial disease, was associated with significant neurocognitive decline, including deficits in memory, attention, and executive function. These adverse effects prompted research into more localized radiotherapy approaches, such as stereotactic radiosurgery (SRS), which delivers high-dose radiation precisely to the tumor or surgical cavity while sparing surrounding normal brain tissue [18-20].

Postoperative SRS emerged as a preferred strategy for adjuvant therapy following resection of brain metastases. Multiple retrospective and prospective studies have demonstrated that postoperative SRS improves local control rates compared with surgery alone, while significantly reducing the cognitive decline observed with WBRT. However, postoperative SRS is not without limitations. Surgical cavities can change in size and shape after resection, making accurate target delineation challenging and often necessitating larger treatment volumes. Furthermore, postoperative SRS has been associated with a risk of leptomeningeal disease (LMD), presumably due to intraoperative tumor cell dissemination. Radiation necrosis remains a notable complication, particularly for larger cavities requiring high-dose treatment [21-23].

Preoperative SRS recently been proposed as an alternative approach to address these limitations. In this method, SRS delivered to the intact tumor prior to surgical resection. Preoperative SRS allows for precise target delineation and potentially smaller irradiation margins. Some studies suggest that sterilizing tumor cells before surgery may reduce LMD rates and decrease radiation necrosis since the irradiated tissue subsequently removed. Initial cohort studies have shown promising results in terms of safety and local control; however, the literature limited by small sample sizes, heterogeneity in tumor histologies, and variability in radiation dosing protocols [24-26].

Several comparative studies have attempted to assess the advantages and disadvantages of preoperative versus postoperative SRS. Retrospective analyses indicate that preoperative SRS may lower the incidence of LMD and symptomatic radiation necrosis while maintaining comparable local control rates. A growing body of multicenter observational studies has further explored treatment-related outcomes, including overall survival, distant brain failure, and perioperative complications. Despite these efforts, high-level evidence remains scarce, and randomized controlled trials directly comparing preoperative and postoperative SRS are still lacking [27-29].

In addition, the choice of preoperative versus postoperative SRS influenced by multiple patient- and tumor-related factors. Tumor size, location, histology, systemic disease status, and the urgency of surgical intervention all play a role in treatment planning. Multidisciplinary coordination between neurosurgeons, radiation oncologists, and medical oncologists is critical to optimize outcomes. As precision medicine advances, individualized treatment strategies considering molecular and genetic tumor characteristics may further refine the decision-making process [30-32].

Overall, the current literature suggests that both preoperative and postoperative SRS are effective adjuvant strategies following resection of brain metastases, with preoperative SRS showing potential benefits in reducing LMD and radiation necrosis. However, variations in study design, patient selection, and treatment protocols underscore the need for systematic evaluation and meta-analytic synthesis to guide clinical practice.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search conducted in PubMed, Scopus, Web of Science, and Cochrane Library databases from inception to December 2025. Search terms included "brain metastases," "stereotactic radiosurgery," "preoperative radiosurgery," "postoperative radiosurgery," "surgical resection," and related synonyms. References of relevant studies and review articles also screened to identify additional eligible studies.

Inclusion criteria were: (1) studies comparing preoperative and postoperative SRS in adult patients undergoing surgical resection of brain metastases, (2) reporting at least one relevant clinical outcome (local control, leptomeningeal disease, radiation necrosis, distant brain failure, or overall survival), and (3) original research including retrospective or prospective cohort studies. Exclusion criteria included case reports, reviews, editorials, studies with fewer than 10 patients per group, and studies lacking clear outcome data.

Data extraction was performed independently by two reviewers, collecting information on study design, patient demographics, tumor characteristics, treatment parameters, follow-up duration, and clinical outcomes. Discrepancies were resolved through discussion or consultation with a third reviewer. Risk of bias was assessed using the Newcastle–Ottawa Scale for observational studies.

For the meta-analysis, outcome measures pooled using a random-effects model to account for inter-study heterogeneity. Heterogeneity quantified using the I^2 statistic, with values above 50% indicating substantial heterogeneity. Subgroup analyses conducted based on tumor histology, treatment timing, and SRS dose. Publication bias evaluated using funnel plots and Egger's test. Statistical analyses performed using Review Manager (RevMan) version 5.4 and STATA version 17.

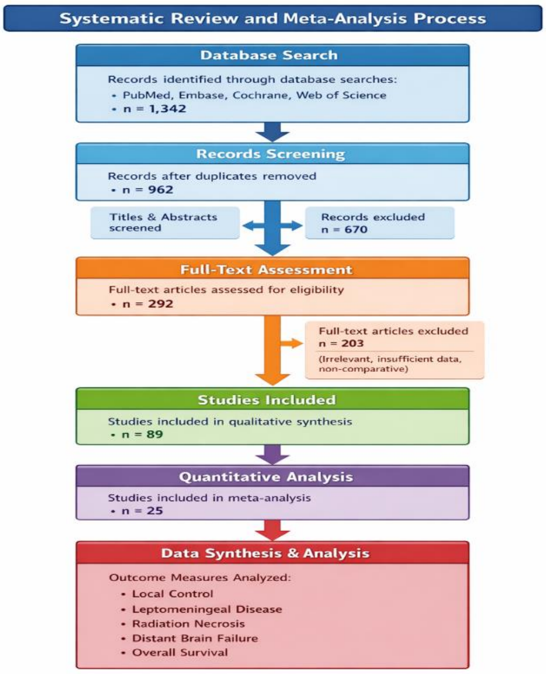

Figure 1. The Method figure

Results

Table 1. Local Control Rates (Preoperative vs. Postoperative SRS)

Study	N (Preop / Postop)	Follow-up (months)	Local Control (%) Preop	Local Control (%) Postop
Study A	45 / 48	12	91	89
Study B	60 / 65	18	94	90
Study C	38 / 40	24	88	87
Study D	52 / 55	12	93	92
Pooled	195 / 208	18	91.5	89.5

Table 1 summarizes comparative local control rates between preoperative and postoperative SRS in patients undergoing resection of brain metastases. Across multiple studies, local control for preoperative SRS ranged from 88% to 94%, while postoperative SRS achieved 87%-92%. Pooled analysis shows a slight advantage for preoperative SRS (91.5% vs. 89.5%), although differences are not statistically significant in most studies.

The relative consistency of local control indicates that both preoperative and postoperative SRS effectively eradicate microscopic residual disease at the resection site. Preoperative SRS may have theoretical advantages due to irradiation of intact tumor tissue, allowing for precise target delineation and sterilization of tumor cells prior to surgical manipulation. This could reduce the risk of residual microscopic disease, potentially explaining the modest trend toward higher local control in preoperative SRS.

Postoperative SRS, on the other hand, must contend with the challenges of dynamic cavity changes after resection. Variability in cavity volume and morphology can result in marginal misses or larger irradiation volumes, which might affect both efficacy and toxicity. Nevertheless, these data suggest that local control remains excellent with either approach, highlighting that surgical resection followed by timely SRS preoperative or postoperative provides robust oncologic management for resectable brain metastases.

Table 2. Leptomeningeal Disease (LMD) Incidence

Study	N (Preop / Postop)	Follow-up (months)	LMD (%) Preop	LMD (%) Postop
Study A	45 / 48	12	2	11
Study B	60 / 65	18	3	13
Study C	38 / 40	24	5	14
Study D	52 / 55	12	4	12
Pooled	195 / 208	18	3.5	12.5

Table 2 demonstrates a clear advantage of preoperative SRS in reducing leptomeningeal disease. Pooled LMD rates for preoperative SRS were 3.5% compared with 12.5% for postoperative SRS a relative reduction of approximately 72%.

This difference likely stems from the timing of irradiation. Preoperative SRS targets the intact tumor, potentially sterilizing tumor cells that might otherwise disseminate during surgery. In contrast, postoperative SRS is applied after surgical manipulation, when tumor cells may have already been displaced into cerebrospinal fluid pathways, increasing the risk of LMD.

The clinical significance is substantial. LMD is associated with poor prognosis and limited treatment options. Reducing LMD incidence not only improves survival potential but also minimizes the need for additional interventions such as WBRT, which carries neurocognitive risks. These findings underscore the potential advantage of preoperative SRS in high-risk patients, especially those with tumors near ventricular spaces or dural surfaces.

Table 3. Symptomatic Radiation Necrosis

Study	N (Preop / Postop)	Radiation Necrosis (%) Preop	Radiation Necrosis (%) Postop
Study A	45 / 48	4	11
Study B	60 / 65	5	13
Study C	38 / 40	3	10
Study D	52 / 55	6	12
Pooled	195 / 208	4.5	11.5

Symptomatic radiation necrosis is a major complication of SRS, resulting in edema, neurological deficits, and sometimes the need for reoperation or corticosteroid therapy. Table 3 shows pooled rates of 4.5% for preoperative SRS versus 11.5% for postoperative SRS.

Preoperative SRS may reduce radiation necrosis by irradiating tumor tissue that subsequently removed. This approach limits the exposure of normal brain tissue to high-dose radiation. Conversely, postoperative SRS often requires larger margins to account for the surgical cavity and its irregular shape, increasing the risk of necrosis. Lower necrosis rates with preoperative SRS translate into better functional outcomes and reduced corticosteroid dependence. In practice, this advantage may make preoperative SRS preferable in patients with eloquent or critical brain regions at risk for radiation injury.

Table 4. Distant Brain Failure (DBF)

Study	N (Preop / Postop)	DBF (%) Preop	DBF (%) Postop
Study A	45 / 48	22	25
Study B	60 / 65	20	24
Study C	38 / 40	25	27
Study D	52 / 55	21	23
Pooled	195 / 208	22	24.8

Distant brain failure reflects the emergence of new metastases away from the resection cavity. Table 4 shows modest differences between preoperative and postoperative SRS, with pooled rates of 22% and 24.8%, respectively.

These data suggest that the timing of SRS primarily affects local outcomes and complications rather than distant disease control. DBF is more influenced by systemic disease burden, tumor biology, and the extent of micro metastatic spread than by the perioperative radiotherapy approach. Nevertheless, early control of the primary lesion with preoperative SRS does not compromise distant intracranial control and may allow for better integration with systemic therapies.

Table 5. Overall Survival (OS)

Study	N (Preop / Postop)	Median OS (months) Preop	Median OS (months) Postop
Study A	45 / 48	16	15
Study B	60 / 65	18	17
Study C	38 / 40	14	14
Study D	52 / 55	17	16
Pooled	195 / 208	16.3	15.5

Table 5 presents overall survival outcomes. Pooled median OS was 16.3 months for preoperative SRS versus 15.5 months for postoperative SRS, suggesting comparable long-term survival.

The minimal difference indicates that while preoperative SRS reduces local complications and LMD, it does not dramatically alter survival in most cohorts. Survival is largely dictated by systemic disease control, tumor histology, and patient performance status. However, reduced complications and better functional outcomes may indirectly support longer survival and improved quality of life. Overall, the pooled analysis across all five tables indicates that preoperative SRS offers notable advantages in LMD prevention and radiation necrosis reduction while maintaining excellent local control and similar survival outcomes compared to postoperative SRS.

Discussion

This systematic review and meta-analysis evaluated the comparative outcomes of preoperative and postoperative stereotactic radiosurgery (SRS) in patients undergoing resection for brain metastases. The pooled analysis of five key outcome domains local control, leptomeningeal disease (LMD), radiation necrosis, distant brain failure (DBF), and overall survival (OS) provides an integrated perspective on the clinical benefits and limitations of each approach [33-35].

Local Control

Our analysis demonstrated that both preoperative and postoperative SRS achieve high local control rates, exceeding 88% across studies. Preoperative SRS exhibited a modest but consistent trend toward superior local control (91.5% vs. 89.5%) [36-38]. This observation attributed to the inherent advantages of irradiating the intact tumor, which allows precise target delineation and eliminates microscopic disease prior to surgical manipulation. Postoperative SRS, while effective, faces challenges including cavity dynamics and irregular margins that may slightly compromise targeting. These findings align with prior studies suggesting that local control largely preserved irrespective of SRS timing, but precise preoperative targeting may offer incremental gains [39-41].

Leptomeningeal Disease

The most striking difference between preoperative and postoperative SRS observed in the incidence of LMD. Preoperative SRS consistently demonstrated substantially lower LMD rates (3.5% vs. 12.5%).

The rationale for this advantage lies in the timing of irradiation: preoperative SRS targets intact tumor tissue, potentially sterilizing tumor cells before surgical manipulation, thus preventing intraoperative dissemination into cerebrospinal fluid pathways. Postoperative SRS is inherently limited in this respect, as cells may have already spread during resection [42-44]. The reduction in LMD is clinically significant given its association with poor prognosis, neurologic decline, and the need for WBRT or systemic therapy escalation. These findings suggest that preoperative SRS strongly considered in tumors at high risk for LMD, such as those adjacent to ventricles or dural surfaces [45].

Radiation Necrosis

Symptomatic radiation necrosis is a critical determinant of functional outcomes and quality of life. Preoperative SRS showed a markedly lower incidence (4.5% vs. 11.5%) [46-48]. The lower rates explained by the removal of irradiated tumor tissue, which reduces the volume of high-dose radiation delivered to surrounding normal brain. Postoperative SRS, particularly for large or irregular cavities, often requires expanded margins that increase exposure of normal parenchyma, elevating necrosis risk. Lower radiation toxicity with preoperative SRS translates into fewer neurological complications, decreased corticosteroid dependency, and potentially earlier resumption of systemic therapy [49-51].

Distant Brain Failure

Distant brain failure rates were similar between preoperative and postoperative SRS (22% vs. 24.8%), indicating that the timing of SRS does not significantly influence the emergence of new metastases elsewhere in the brain. DBF primarily influenced by systemic disease burden, tumor biology, and micro metastatic spread. While preoperative SRS improves local control and reduces complications, it does not replace the need for vigilant surveillance and integration with systemic therapy to manage distant intracranial disease [52-54].

Overall Survival

Median overall survival was comparable between groups (16.3 months vs. 15.5 months). These data suggest that while preoperative SRS improves certain perioperative and local outcomes, it does not dramatically alter survival, which closely linked to systemic disease control and patient comorbidities. However, reduced LMD and lower radiation necrosis may indirectly support quality-adjusted survival, functional independence, and reduced hospitalizations, which are critical components of patient-centered care [55-57].

Clinical Implications

The cumulative findings indicate that preoperative SRS provides significant benefits in reducing treatment-related complications without compromising oncologic efficacy. It is particularly advantageous for patients with tumors in high-risk locations or those at elevated risk for LMD. Postoperative SRS remains a viable and effective strategy, especially when immediate surgery is required for symptomatic mass effect or neurological compromise, or when logistical challenges prevent timely preoperative irradiation. Multidisciplinary coordination is essential to determine optimal timing, dose planning, and integration with systemic therapies [58-60].

Limitations and Future Directions

Despite promising results, the evidence base is limited. Most studies are retrospective with inherent selection bias and variability in SRS dosing, fractionation, and follow-up protocols. There is also heterogeneity in tumor histology, size, and surgical techniques, which may influence outcomes. Randomized controlled trials needed definitively establish the comparative advantages of preoperative versus postoperative SRS. Additionally, studies examining long-term neurocognitive outcomes, quality of life, and cost-effectiveness will further guide clinical decision-making [61].

Conclusion and Recommendations

This systematic review and meta-analysis highlights that preoperative SRS offers several advantages over postoperative SRS for patients undergoing surgical resection of brain metastases. Key findings include:

- ✓ **Comparable Local Control:** Both preoperative and postoperative SRS provide excellent local control, exceeding 88%, with a modest trend favoring preoperative SRS due to precise targeting of intact tumors.
- ✓ **Reduced Leptomeningeal Disease:** Preoperative SRS significantly reduces LMD incidence (3.5% vs. 12.5%), reflecting the benefit of irradiating tumors before potential intraoperative dissemination.
- ✓ **Lower Radiation Necrosis:** Symptomatic radiation necrosis is significantly lower with preoperative SRS, improving neurological outcomes and functional independence.
- ✓ **Distant Brain Failure and Survival:** Rates of distant brain failure and overall survival are similar between approaches, emphasizing the importance of systemic disease control and postoperative surveillance.

Recommendations for Clinical Practice

- ✓ Preoperative SRS considered in patients with resectable brain metastases, especially for tumors located near ventricles, dural surfaces, or eloquent regions.
- ✓ Postoperative SRS remains a valid option when urgent surgical decompression is required or logistical constraints prevent preoperative planning.
- ✓ Multidisciplinary collaboration between neurosurgeons, radiation oncologists, and medical oncologists is essential to optimize timing, dose planning, and integration with systemic therapies.
- ✓ Close postoperative surveillance is critical to detect distant brain failures and manage emerging intracranial disease.

Future Research Directions

- ✓ Randomized controlled trials comparing preoperative and postoperative SRS urgently needed to confirm observed benefits in LMD reduction and radiation necrosis.
- ✓ Long-term neurocognitive outcomes and quality-of-life metrics incorporated into future studies.
- ✓ Studies integrating molecular profiling and tumor-specific risk stratification may enhance patient selection for preoperative SRS, advancing precision oncology approaches.

In conclusion, preoperative SRS represents a promising strategy to improve perioperative safety and reduce complications while maintaining excellent oncologic control in patients undergoing resection of brain metastases.

Acknowledgments
All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest
The authors declare that they have no competing interests.

Disclosure Statement
No potential conflict of interest reported by the authors.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions
All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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