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

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ABSTRACT

Background and Aim: Brain metastases pose a significant therapeutic challenge due to high rates of local recurrence and treatment complications. However, it is still unclear how preoperative stereotactic radiation (Pre-SRS) compares to postoperative radiation (Post-SRS) in terms of efficacy and safety. The aim of the present study was to compare the clinical outcomes of Pre-SRS and Post-SRS in patients with brain metastases.

Method: In the present study, PubMed, Embase, Cochrane Library, and Web of Science databases were searched between 2015 and 2025 with targeted keywords. Seven relevant studies, including randomized clinical trials and cohort studies, were included in the analysis. Meta-analysis was performed using stata.v17 software. To combine the results, a fixed-effect model with the Inverse-Variance method for the hazard ratio and Mantel Haenszel for the risk ratio was used, and heterogeneity between studies was assessed with the I^2 and H^2 indices.

Results: The hazard ratio for overall survival did not differ significantly between the Pre-SRS and Post-SRS groups (HR 0.891; 95% CI 0.55-1.23). Local failure at six months and one year was similar between the two groups. Pre-SRS reduced the risk of radiation necrosis (HR 0.689; 95% CI 0.352-1.026; $P < 0.05$) and leptomeningeal disease (HR 0.540; 95% CI 0.202–0.877; $P < 0.05$) compared with Post-SRS. Heterogeneity was minimal in all analyses (I^2=0–14%).

Conclusion: Based on the present meta-analysis, Pre-SRS had similar survival and recurrence rates to Post-SRS while reducing the risk of significant treatment complications. The present study suggests the use of Pre-SRS as a strategic intervention in patients with brain metastases.

Introduction

The most challenging issue in cancer patients is the occurrence of brain metastases(1); in these patients, the type of treatment, survival rate, disease control, and the incidence of complications are of great importance(2). Surgical removal of the lesion and focused stereotactic radiosurgery (SRS) are used for treatment(3). Studies have shown that local lesion control is possible after SRS without a significant increase in neurological complications(4, 5). However, there is evidence of local recurrence and a risk of leptomeningeal disease (LMD)(6); statistics have shown that 12% of patients develop tumor spread to the cerebrospinal fluid after treatment(3, 7).

In recent years, the introduction of preoperative or neoadjuvant SRS has provided more precise targeting of the healthy tumor(8). Preliminary studies suggest that this approach results in a reduced incidence of radiation necrosis and LMD(9). a study showed that pre-SRS compared with post-SRS had lower rates of two-year LMD (3.2% vs. 16.6%) and symptomatic radioactive necrosis (4.9% vs. 16.4%), while having no effect on overall survival(10). It was also reported in a study with a two-year follow-up period that pre-SRS was

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associated with only a 4.8% rate of symptomatic necrosis(11).

A meta-analysis of six pre-SRS and 33 post-SRS studies reported that the local recurrence rate in pre-SRS was 11% (95% CI:4.9-13.7) and in post-SRS was 17.5% (95% CI:15.1-19.9); the risk of leptomeningeal disease in pre-SRS was 4.4% (95% CI:2.6-6.2) compared with 12.3% (95% CI:8.9-15.7) in post-SRS; however, overall survival was not different(12). Another meta-analysis has shown that local control rates of over 89% and low rates of radiation complications are observed at one- and two-year follow-up periods. Maroufi et al., 2025 reported that the he preoperative group had lower risks of radiation necrosis and leptomeningeal disease in one-year follow-up(13).

Previous meta-analyses have examined one or two indicators, such as local control or overall survival. Whereas the current study considered overall survival, local control, local recurrence, leptospirosis, and radiation necrosis. Many previous meta-analyses have examined data from articles up to 2020, which is the most recent data in this study. Previous studies have mostly examined SRS without distinguishing preoperative vs postoperative. The innovation of the present study is the direct comparison of the effect of SRS timing on several important clinical indicators. By collecting comprehensive data and direct comparison, the present study can provide evidence-based guidance for choosing the best SRS timing, which has been less addressed in previous meta-analyses. Given the gap in evidence, particularly the lack of pooled data from different studies with adequate sample sizes and robust methodology, a systematic review and meta-analysis focused on a rigorous comparison of clinical outcomes between pre- and post-SRS is warranted. Present study can better determine the advantages and limitations of each approach and provide evidence-based guidance for clinical decision-making and the design of future studies, especially on the scale of randomized trials that are currently being planned. Therefore, the aim of the present study is Comparative Outcomes of Preoperative and Postoperative Stereotactic Radiosurgery in Patients with Brain Metastases.

Method

Information sources and Search strategy

The present study was conducted according to the PRISMA 2020 guidelines. A search was conducted in the PubMed, Embase, Web of Science, Scopus, and Cochrane Library databases over the last ten years (January 2015 to November 2025) to find emerging evidence.

Mesh keywords:

("Brain Neoplasms"[Mesh]) OR ("Brain Neoplasms/complications"[Mesh] OR "Brain Neoplasms/diagnosis"[Mesh] OR "Brain Neoplasms/mortality"[Mesh] OR "Brain Neoplasms/prevention and control"[Mesh] OR "Brain Neoplasms/surgery"[Mesh] OR "Brain Neoplasms/therapy"[Mesh]) AND "Radiosurgery"[Mesh]) OR ("Radiosurgery/adverse effects"[Mesh] OR "Radiosurgery/methods"[Mesh] OR "Radiosurgery/mortality"[Mesh] OR "Radiosurgery/statistics and numerical data"[Mesh]) AND "Preoperative Period"[Mesh]) AND "Neoadjuvant Therapy"[Mesh]) AND "Postoperative Period"[Mesh]) AND ("Chemotherapy, Adjuvant"[Mesh] OR "Radiotherapy, Adjuvant"[Mesh])) AND ("Survival"[Mesh] OR "Mortality"[Mesh] OR "Survival Rate"[Mesh])) AND "Diffuse Noxious Inhibitory Control"[Mesh]) AND ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh]) AND "Meningeal Neoplasms"[Mesh]) AND "Necrosis"[Mesh]) AND "Progression-Free Survival"[Mesh]) AND "Disease-Free Survival"[Mesh]) AND ("complications" [Subheading] OR "Postoperative Complications"[Mesh]).

Eligibility Criteria

The study inclusion strategy was determined based on the PICOS framework, as follows:

- ✓ Population (P): Adult patients (≥18 years) with brain metastases.
- ✓ Intervention (I): Preoperative SRS.
- ✓ Comparison (S): Postoperative SRS.
- ✓ Outcomes (O): Overall survival (OS), local lesion control, local recurrence, LMD, and radiation necrosis.
- ✓ Study type (S): Observational studies, randomized clinical trials (RCTs), cohort studies.

Exclusion criteria: Studies without quantitative data, single case reports, all types of review studies, animal studies, letters to the editor, conference and symposium abstracts, non-English language articles, articles without full text, sparse data, articles without a specified control group.

Study Selection and Data Extraction

All titles and abstracts were reviewed by two independent investigators. Studies that met the inclusion criteria were selected for full-text review. Disagreements were resolved by a third investigator. Two independent investigators extracted data using a pre-prepared form. The extracted data included study characteristics (year and study design), patient characteristics (number, age, gender, primary tumor type), intervention details, and clinical outcomes (overall survival, local control, local recurrence, LMD, radiation necrosis).

Risk of Bias Assessment

To ensure the validity and quality of the data, randomized controlled trials (RCTs) were assessed with the Cochrane Risk of Bias 2.0 (RoB 2.0) tool(14) and non-randomized interventional studies with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool(15). RoB 2.0 examines five key areas of bias including randomization process, deviation from planned intervention, incomplete outcome data, outcome measurement, and selective reporting of outcomes, and each area is categorized with three levels of risk: Low risk, Some concerns, and High risk.

Statistical Analysis

All analyses were performed with Stata/MP. v17 software, and the significance level was considered to be $P<0.05$. Hazard Ratio (HR) was used for binary data and risk Ratio (RR) was used for proportional data. The fixed effects model was used using the Mantel-Haenszel method and inverse variance. Study weighting was performed based on sampling variance and, in the random model, between-study variance, and heterogeneity was measured using I^2 and Cochran's Q. Sensitivity and publication bias were examined with Funnel plots and Egger's test.

Result

Literature Search, and Characteristics of included studies:

The search strategy was carried out according to the selected keywords and based on PRISMA 2020 protocol. Initially, 284 articles were found; After removing duplicates and screening titles, the abstracts of 853 articles were reviewed, and 714 articles unrelated to the inclusion criteria and in accordance with the exclusion criteria were eliminated at this stage. The full text of 139 articles was reviewed. Articles with scattered data, low quality in methodology, unclear sample size, lack of grouping of studies, lack of presentation of accurate results, lack of access to full text, contradictory data, and biased data were excluded from the research. Finally, ten articles that met the inclusion criteria for the present study were selected (Figure 1).

The total number of included patients in preset studies was 908, with approximately 356 in the Pre-SRS group and 552 in the Post-SRS group. Patients were between 56 and 64.5 years old. The male-female gender ratio was approximately balanced (49–55% male and 45–51% female). The primary tumor type was similar in both groups, and the most common included lung cancer, breast cancer, melanoma, gastrointestinal cancers, urogenital cancers, kidney cancer, gynecological cancers, head and neck tumors, sarcoma, and other rare tumors. The characteristics of the brain lesions were also similar between the two groups. Lesions were mainly located in the supraantrenal regions including the frontal, parietal, temporal, occipital, and cerebellar lobes. The number and location of lesions were similar between the Pre-SRS and Post-SRS groups (Table 1).

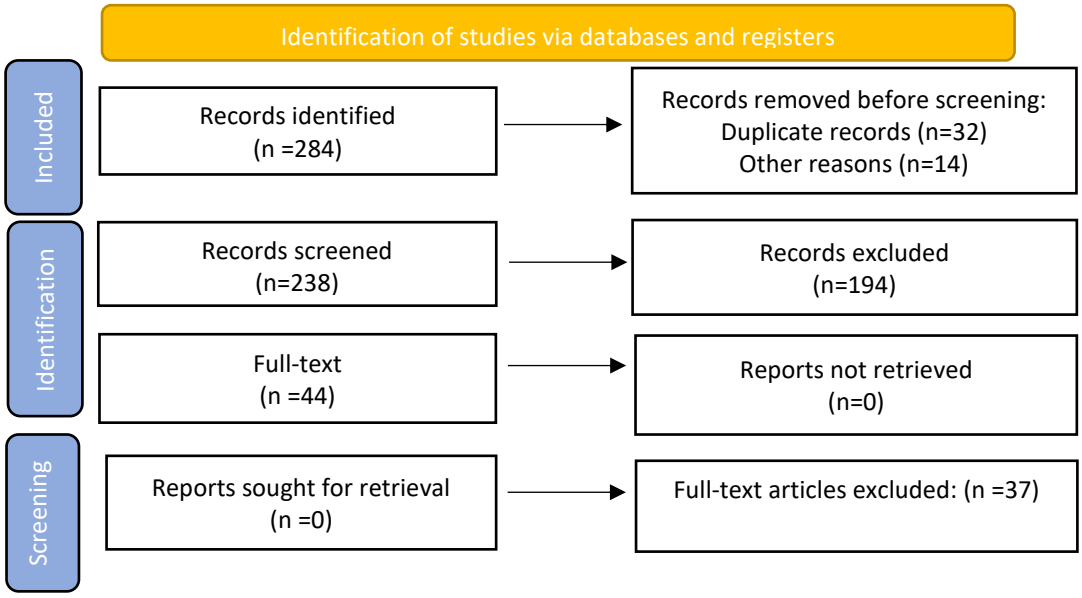

Figure 1. PRISMA 2020 Flow Diagram

Table 1. Characteristics of the included RCT and cohort studies.

Study. Years	Study type	Number of Patients				Mean age		Dose (Gy)		Number of Lesion (n)	
		Pre-SRS		Post-SRS		Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS
		Male	female	Male	female						
Yeboa et al., 2025 (16)	RCT	26	25	30	22	61	59			51	52
Kutuk et al., 2024 (17)	RCs	18	21	23	39	62.7	662.4	15	27	47	74
Mallela et al., 2024 (18)	RCs	13	13	12	18	64.5	62.5	8-27	14-21	NR	NR
Perlow et al., 2023 (19)	RCs	41	39	121	78	61.9	62.3	18-20	18-20	228	71
Cheok et al., 2023 (20)	RCs	23	22	23	22	59.6	59.6	12	12	45	45
Yeboa et al., 2023 (21)	RCs	27	22	25	25	58.4	57.1			49	50
Patel et al., 2016 (22)	RCs	32	34	50	64	58.2	56	14	18	71	118

- ✓ RCs: Retrospective Cohort.
- ✓ BC: Breast cancer.
- ✓ SRS: Radiosurgery.
- ✓ GKRS: Gamma Knife Radiosurgery.
- ✓ LINAC: Linear Accelerator.
- ✓ GU: Genitourinary.
- ✓ GI: Gastrointestinal.
- ✓ HNT: Head, Neck, Throat.
- ✓ GYN: Gynecologic.
- ✓ CRC: Colorectal.
- ✓ NR: Not Reported.
- ✓ Me: Melanoma.

Table 2. continued…

Study (Year)	Variable	primary cause of cancer											Lesion Location					
		BC	GI	GU	GYN	Lung	CRC	Renal	HNT	Melanoma	Sarcoma	Other	Frontal	Parietal	Temporal	Occipital	Cerebellar	Multi
Yeboa et al., 2025 (16)	Pre-SRS	6	-	-	-	30	-	8	-	14	-	16	43	44	-	-	-	-
	Post-SRS	6	-	-	-	13	-	7	-	8	-	16	8	8	-	-	-	-
Kutuk	Pre-SRS	8	1	4	4	17	-	-	2	2	-	3	18	6	5	7	10	1

et al., 2024	Post-SRS	8	3	4	4	27	-	-	2	13	-	1	22	12	17	10	12	1
Mallela et al., 2024	Pre-SRS	4	-	-	-	9	4	2		4	-	3	13	7	2	2	2	
	Post-SRS	3	1	-	-	11	1	3		4	-	8	11	4	3	6	6	
Perlow et al., 2023	Pre-SRS	6	3	14	1	45	-	-	1	1	2	1	33	10	7	13	14	1
	Post-SRS	20	13	31	5	81	-	-	14	14	4	2	69	41	19	22	32	2
Cheok et al., 2023	Pre-SRS	5	1	4	2	10	12	2	1	5	1	33	12	-	-	-	-	-
	Post-SRS	5	1	4	2	10	12	2	1	5	1	33	12	-	-	-	-	-
Yeboa et al., 2023	Pre-SRS	5	-	-	-	19	-	15	-	10	-	53	46	-	-	-	-	-
	Post-SRS	5	-	-	-	20	-	15	-	10	-	8	8	-	-	-	-	-
Patel et al., 2015	Pre-SRS	18	-	-	-	24	-	-	-	11	-	13	25	19	11	2	14	-
	Post-SRS	12	-	-	-	48	-	-	-	23	-	31	51	28	9	7	23	-

Overall survival

The overall survival between the Pre-SRS and Post-SRS groups was 0.891 with a 95% confidence interval of 0.554 to 1.228. This finding indicates that there was no statistically significant difference in overall survival between the two groups (Figure 2).

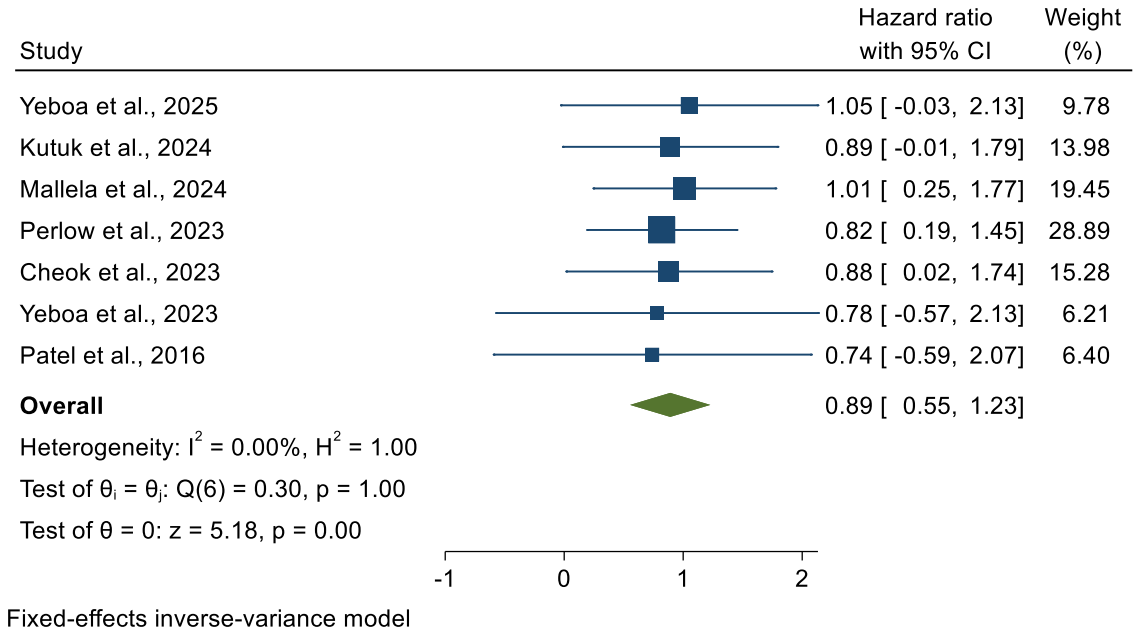

Figure 2. forest plot showed overall survival between the Pre-SRS and Post-SRS

local failure

The hazard ratio for local failure was 1.40 with a 95% confidence interval of 1.063 to 1.738. This finding indicates no significantly increased risk of local failure in the Post-SRS group compared to the c group (p>0.05) (Figure 3).

According to subgroup meta-analysis, At 6 months, the risk ratio for local failure was -0.83 with a 95% confidence interval of -1.51 to -0.15. This finding suggests that patients in the Post-SRS group have not a significantly higher risk of local failure than those in the Pre-SRS group (p>0.05). The risk ratio for the one-year period was -0.10 with a 95% confidence interval of -0.47 to 0.26, indicating that there is no statistically significant difference in local failure control between Pre-SRS and Post-SRS in the long term. The overall risk ratio of -0.30 and the 95% confidence interval of -0.62 to 0.02 confirmed that there was no significant difference between subgroups (p=0.06) (Figure 4).

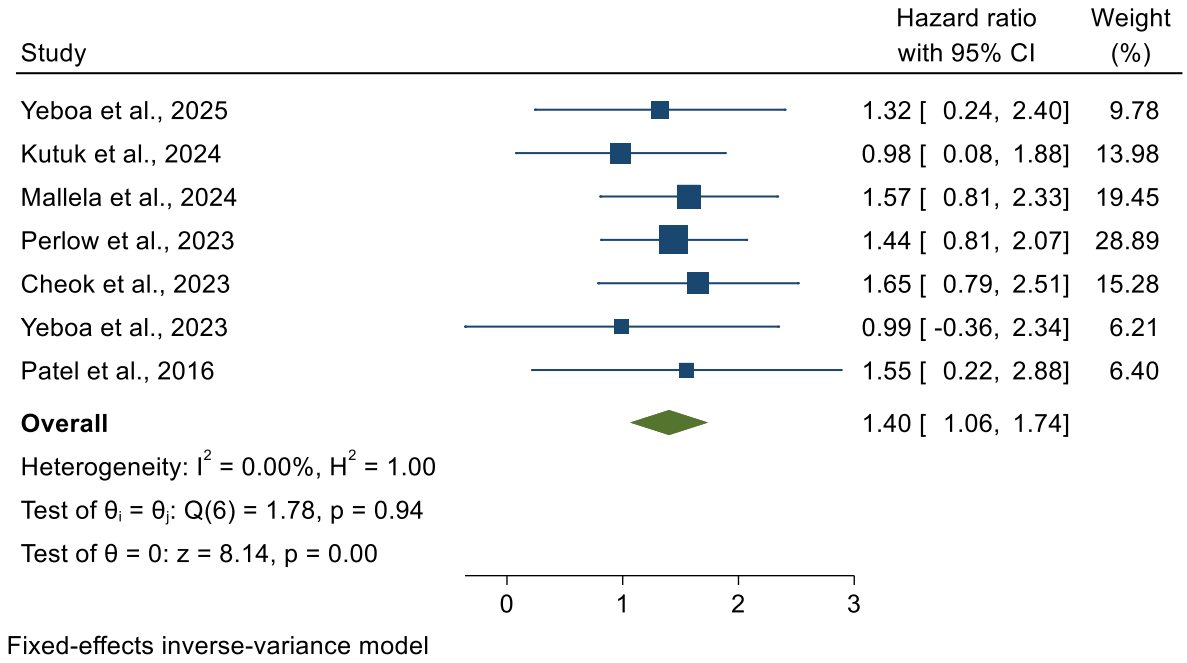

Figure 3. forest plot showed local failure between the Pre-SRS and Post-SRS

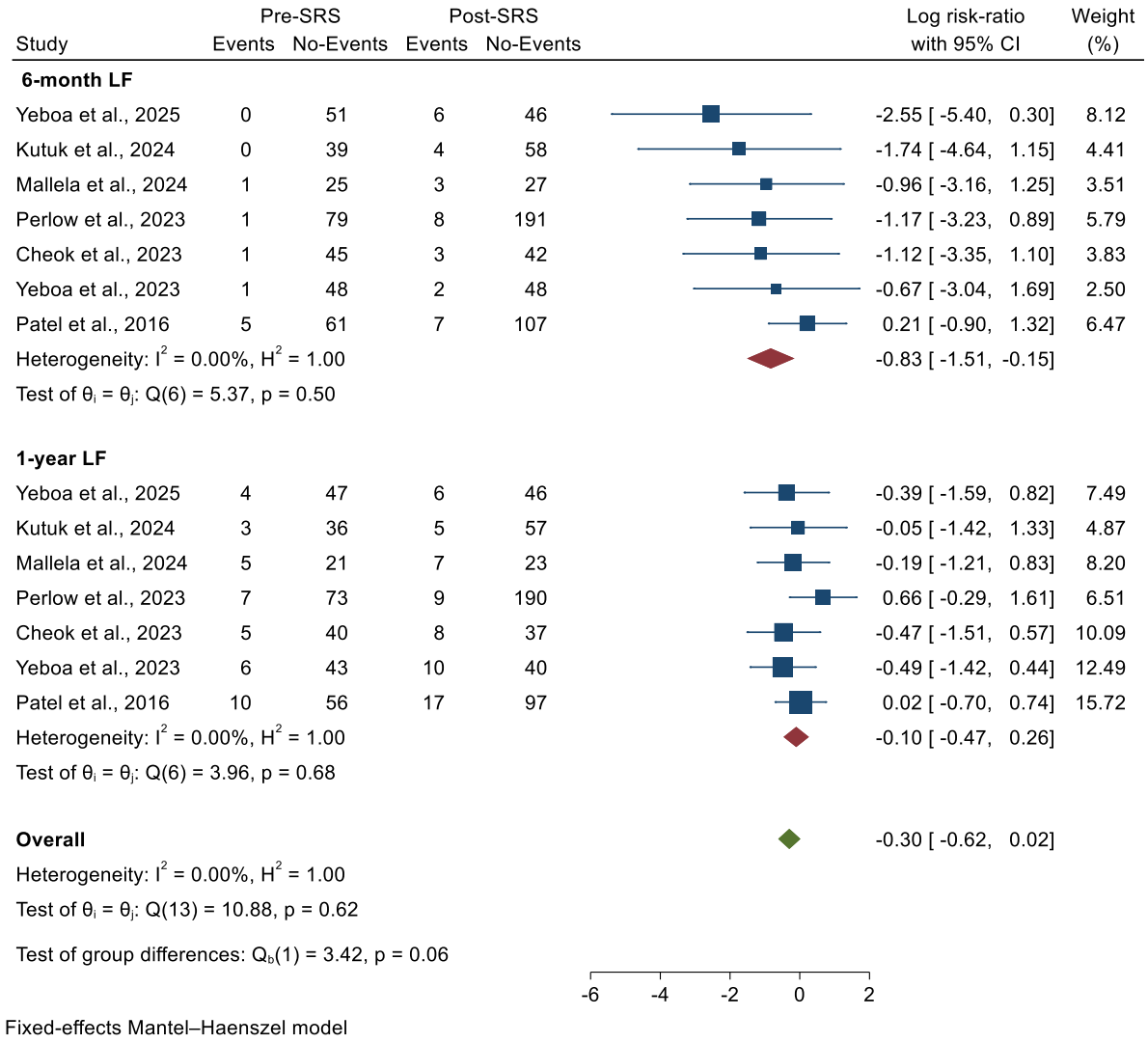

Figure 4. Forest plot showed subgroup meta-analysis of 6-month and one-years follow-up of local failure between the Pre-SRS and Post-SRS

Distant failure

According to subgroup meta-analysis, at six months, the risk ratio for distant failure was -0.155 with a 95% confidence interval of -0.416 to 0.106. This indicates that there was no statistically significant difference between Pre-SRS and Post-SRS in the incidence of distant failure of the lesion during this period. After one year, the risk ratio was -0.129 with a 95% confidence interval between -0.358 and 0.099, which, similar to the first interval, did not show a statistically significant difference between the groups (Figure 5).

The overall risk ratio was -0.140 and the 95% confidence interval was -0.312 to 0.032, indicating that SRS timing had no significant effect on the incidence of distant failure over the entire treatment period. The test for difference between groups (p = 0.89) confirmed this result, indicating that stratification of studies based on follow-up period had no significant effect (Figure 5).

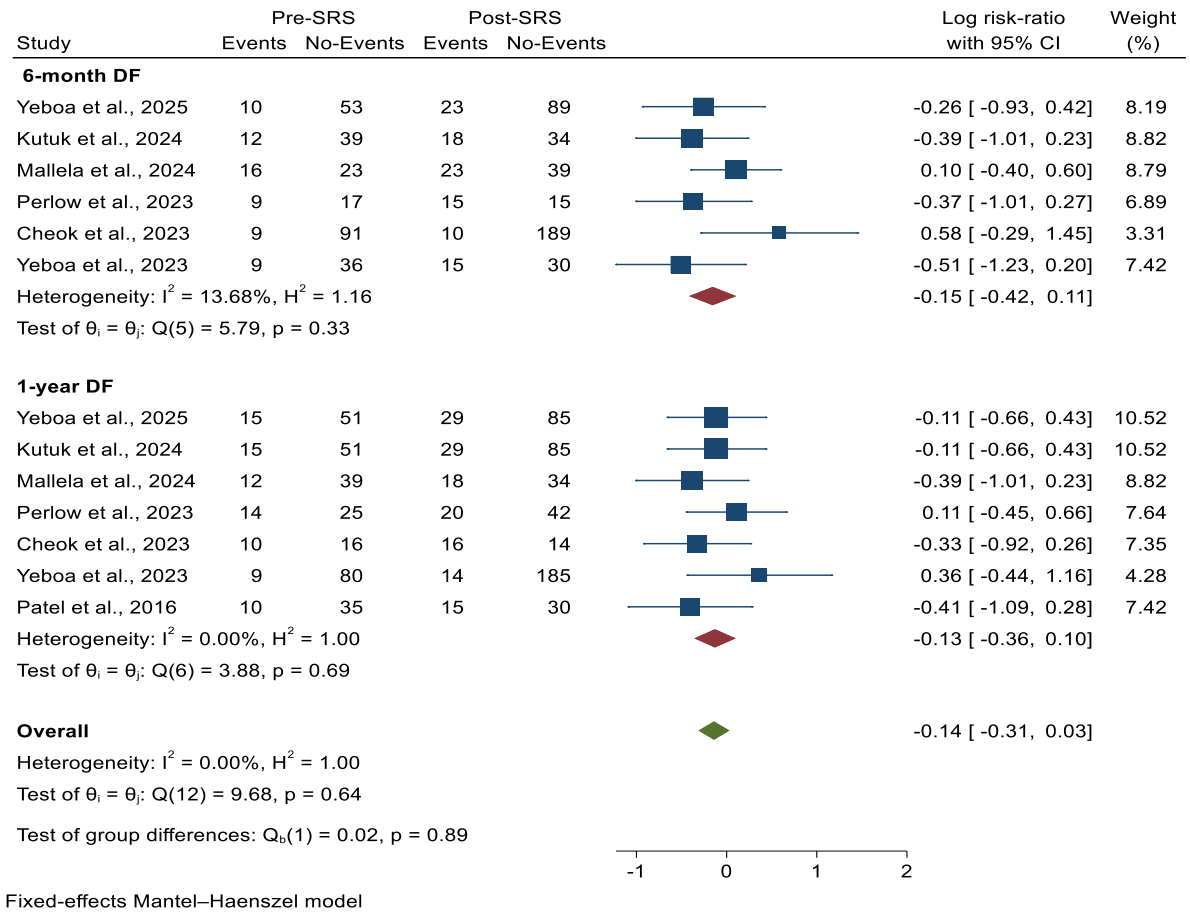

Figure 5. Forest plot showed subgroup meta-analysis of 6-month and one-years follow-up of distant failure between the Pre-SRS and Post-SRS

Radiation necrosis

The hazard ratio for the occurrence of radiation necrosis was 0.689 with a 95% confidence interval of 0.352 to 1.026. This finding suggests that patients in the Pre-SRS group are less likely to develop radiation necrosis compared with the Post-SRS group, and that preoperative SRS timing may reduce the risk of this important complication ($p<0.05$) (Figure 6).

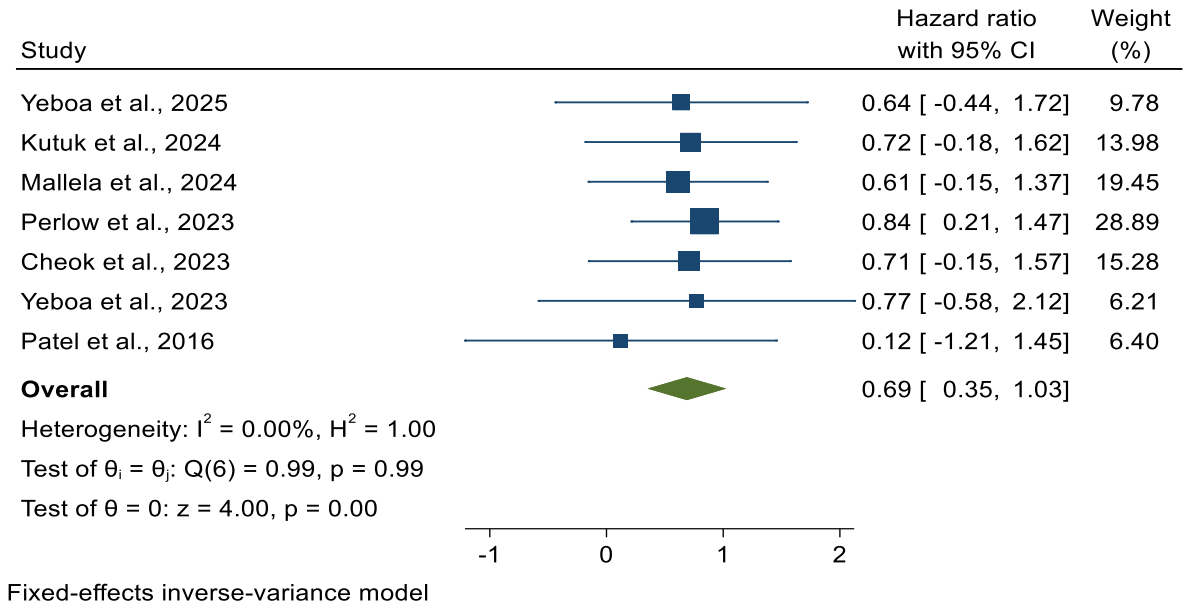

Figure 6. Forest plot showed radiation necrosis between the Pre-SRS and Post-SRS

leptomeningeal disease (LMD)

The hazard ratio for LMD was 0.540 with a 95% confidence interval of 0.202 to 0.877. This finding suggests that preoperative SRS is associated with a significant reduction in the risk of LMD compared with postoperative SRS (Figure 6).

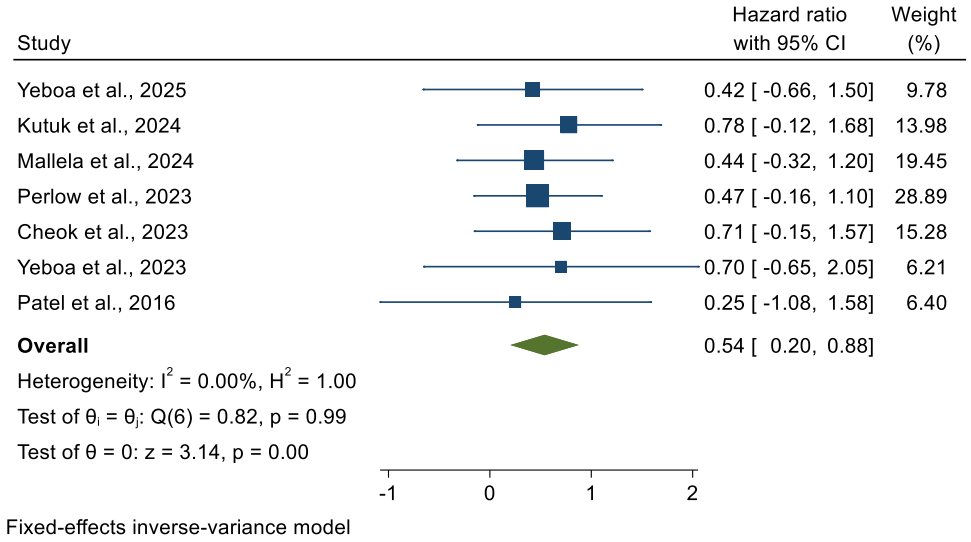

Figure 7. Forest plot showed LMD between the Pre-SRS and Post-SRS

Discussion

Brain metastasis has been one of the most challenging problems for cancer patients and is treated with SRS and systemic therapy(7, 23). Studies have shown that the timing of SRS versus surgery is of great importance for the success of treatment(24). In the present study, the effect of Pre-SRS and Post-SRS on survival, local lesion control, distant disease, radiation necrosis, and LMD was investigated during six months and one year of follow-up.

The present meta-analysis showed that there was no significant difference in overall survival between Pre-SRS and Post-SRS (HR=0.89; CI: 0.55–1.22). These findings are consistent with the results of the study by July et al., 2021 and Akanda, Xu et al., 2020 who showed that the type of fractionation does not affect survival and that tumor bio-factors such as systemic disease status, underlying disease severity, and genetic profile play a more decisive role in survival(25, 26).

The present meta-analysis showed that the risk of local failure was similar in both groups; previous studies have also reported these findings (27-29). More recent studies have also shown that local control in patients undergoing Pre-SRS is not significantly different from Post-SRS(13). Also, the results of Yeboa et al., 2023 and 2025 and Kutuk et al., 2024 have all emphasized the absence of a significant difference in LF between these two groups (16,17,21). The inclusion of these studies in the present meta-analysis has reduced heterogeneity and increased the accuracy of the effect estimate. Based on the findings, the similarity of local failure rates between the two groups indicates that SRS is an effective treatment independent of timing, and factors such as tumor histology, multiple lesions, patient physiological function, and receipt of systemic therapies before or after SRS have a greater impact on the probability of local failure.

The present meta-analysis showed that Pre-SRS had a better outcome in terms of radiation necrosis compared to Post-SRS. These findings confirm the results of previous studies and indicate that Pre-SRS can provide a protective effect against radiation necrosis and reduce the risk of this important complication(9, 13). Some older studies also found conflicting findings, which could be due to small sample sizes and study design limitations(26, 28). The final results of the studies can be influenced by the volume and number of lesions treated, the intensity of radiation and the resulting necrosis. Also, different radiation techniques and the number of fractions and doses of radiation can vary the results; biological factors of the lesion and surrounding tissue may also affect the sensitivity to radiation therapy.

According to the results of the present meta-analysis, the incidence of LMD in Pre-SRS was significantly lower than Post-SRS. In one study, Post-SRS was shown to be associated with a threefold risk of LMD(10). Other studies (13) have also emphasized the evidence that Pre-SRS is not only superior in terms of local control, but also has a clear advantage in terms of preventing a very challenging complication such as LMD. The advantage of the present study compared to other studies is that in the present study, data from studies over the last ten years have been examined; Improvements in dose delivery techniques in LINAC devices and reductions in postoperative cavity errors have improved the methodological quality of studies. Reduced heterogeneity between

studies has allowed the fixed-effects model to provide more reliable estimates.

The present study had limitations, such as not examining differences in radiation techniques and not considering quality of life or cognitive function indicators in interpreting the results. Tumor volume, lesion location, or precise timing of radiation can also affect results. Therefore, more articles should consider these variables to present findings with more definitive evidence.

Conclusion

The present study resolves uncertainty about the optimal timing of radiosurgery versus surgical resection in patients with brain metastases and provides strong evidence that preoperative intervention reduces clinical morbidity. From a clinical perspective, this evidence supports prioritizing preoperative radiosurgery in treatment planning to reduce morbidity from post-treatment necrosis and optimize patient outcomes in the multidisciplinary management of neuro-oncology. Future research should systematically evaluate patient and lesion-specific factors, including lesion volume and histologic radio sensitivity, to optimize individual scheduling strategies and integrate them into standard care protocols. These results establish preoperative radiosurgery as a superior strategic approach to reduce radiation-induced tissue damage while maintaining therapeutic efficacy.

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No potential conflict of interest reported by the authors.

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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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