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Review Article

Stereotactic radiosurgery versus whole-brain radiotherapy for intracranial metastases: A systematic review and meta-analysis

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ABSTRACT

Background: Brain metastasis has a negative influence on the morbidity and mortality of cancer patients. Conventionally, whole-brain radiotherapy (WBRT) was favored as the standard treatment for brain metastases. However, it has been linked to a significant decline in neuro-cognitive function and poor quality of life. Stereotactic radiosurgery (SRS) has recently gained prominence as an alternative modality, considering that it provides targeted high-dose radiation while minimizing adverse effects. This study evaluates the efficacy and safety of SRS versus WBRT in patients with intracranial metastases.

Methods: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, through July 2024, we searched PubMed, Scopus, and Web of Science for articles comparing WBRT and SRS in patients with intracranial metastases. Outcomes included local and distant recurrence, leptomeningeal disease (LMD), and survival. We also used a random-effect model to perform a meta-analysis.

Results: The findings revealed no significant differences in local (risk ratio [RR] = 0.70, 95% confidence interval [CI] [0.46, 1.06]) or distant recurrence rates (RR = 0.83, 95% CI [0.54, 1.28], $P = 0.41$) between WBRT and SRS. However, SRS was associated with a greater risk of post-radiation LMD (hazard ratio [HR] = 3.09, 95% CI [1.47, 6.49], $P = 0.003$). Survival rates at 1 year (RR = 1.03, 95% CI [0.83, 1.29], $P = 0.76$) and 5 years (RR = 0.89, 95% CI [0.39, 2.04], $P = 0.78$) demonstrated no significant differences.

Conclusion: SRS and WBRT exhibited similar recurrence rates and overall survival (OS) at 1 and 5 years, with WBRT being more effective in managing post-radiation LMD. SRS patients, on the other hand, had longer OS when measured in months.

Keywords: Brain, Metastases, Stereotactic radiosurgery, Whole-brain radiotherapy

INTRODUCTION

Brain metastases are a growing consequence of systemic malignancies and are a significant cause of illness and death in cancer patients.[14,20,36] Around 20–40% of cancer patients with initial extracranial malignancy will experience the development of brain metastases at some

point throughout their illness. There are between 98,000 and 170,000 new diagnoses in the United States each year.[19,31] The predicted median survival without treatment is 1 month, and this duration can be extended to 3–12 months with the use of cranial radiation therapy.[25]

Hematogenous dissemination is the most frequent method of metastatic spread leading to brain metastases; this implies that the entire brain is likely affected by micrometastatic illness, even if just one intracranial lesion is seen.[2] Recently, doubt has been cast on this premise, leading to the emergence of a contrarian philosophy suggesting that in certain patients, the disease within the skull is restricted to a small number of metastases, a state referred to as oligometastases.[2] The two main approaches that are commonly used in the management of brain metastases are symptomatic and therapeutic interventions. Symptomatic management frequently involves the use of corticosteroids to reduce swelling around the tumor and anticonvulsants to prevent seizures from reoccurring. Treatment options for brain metastases encompass surgical intervention, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy. Multiple patients receive a combination of these options, and treatment decisions must be based on various aspects, such as the patient's age and functional ability, the type of initial tumor, the extent of disease outside the brain, previous therapies, and the number of lesions within the brain.[6]

Until the early 2000s, WBRT was the sole radiation-based treatment available for brain metastases. However, SRS was then offered as an alternative option for brain metastases of a restricted number, typically defined as 1–3. Evidence from prospective trials has demonstrated that postoperative adjuvant WBRT decreases the likelihood of recurrence in the surgical site and lowers the occurrence of new metastases.[17,28] While adjuvant WBRT enhances control over intracranial tumors, it does not provide any proven advantage in terms of longevity and instead negatively impacts the quality of life and cognitive function.[5] To prevent the harmful consequences of WBRT, there is an increasing trend to use SRS to treat the area where surgery was performed. SRS involves delivering concentrated and accurate doses of radiation, and it is a well-established and successful treatment for brain metastases. However, its effectiveness compared to WBRT after surgery has not been proven.[32] This systematic review and meta-analysis aimed to compare SRS and WBRT in terms of their safety and efficacy in patients with intracranial metastases.

METHODS

Database search

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[26] we searched PubMed, Scopus, and Web of Science through July 2024 for articles comparing WBRT and SRS in patients with intracranial metastases using the following search strategy: (Stereotactic Radiosurgery OR SRS OR Stereotactic Radiation OR Stereotactic Radiotherapy OR Radiotherapy OR Radiosurgery OR Gamma Knife Radiosurgery OR Gamma Knife OR Linear Accelerator OR Linear Accelerator Radiosurgery OR LINAC Radiosurgery OR Stereotactic Body Radiotherapy OR CyberKnife Radiosurgery OR CyberKnife) AND (Whole-Brain Radiation Therapy OR Whole-Brain Radiotherapy OR WBRT) AND (Brain Metastasis OR Metastatic Brain Tumor OR Secondary Brain Tumor OR Intracranial Metastasis OR Intracranial Metastases). A prospective protocol was registered in the International Prospective Register of Systematic Reviews (registration number CRD42024558131).

Screening

Electronic database search results were uploaded to Rayyan Software for selection, screening, and duplicate removal. Potentially relevant papers found through the database searches were screened by title and abstract by four independent reviewers. The eligibility of articles that satisfy the inclusion criteria was assessed by four other independent reviewers based on the full text of the studies. A PRISMA flow diagram was used to record the search and screening process.

Eligibility criteria

Following the PICO framework, our inclusion criteria were as follows: Population (P): adults aged 18 and above diagnosed with single or multiple brain metastases; Intervention (I): Postoperative SRS targeting intracranial metastases, Comparison (C): Postoperative WBRT targeting intracranial metastases, and Outcomes (O): safety and effectiveness in terms of tumor control (local recurrence, distant recurrence, and leptomeningeal disease [LMD]) and survival rates (1-year survival, 5-year survival, and overall survival [OS]). Reviews, case reports, editorial letters, conference abstracts, and study protocols were excluded from the study.

Quality and risk of bias (Rob) assessment

Quality and Rob assessments were conducted using the Newcastle–Ottawa Scale tool for cohort studies,[33] the Cochrane Rob-2 tool for randomized controlled trials (RCTs),[23] and the Rob in non-randomized studies of interventions-1 tool for non-randomized clinical trials.[10] Two independent reviewers conducted the assessments, and conflicts were resolved through consultation with a third reviewer.

Data extraction

Two independent reviewers extracted the baseline data from the eligible articles, including the study design, sample size, age, and gender of patients. We also extracted the outcome data, including local recurrence, distant recurrence, LMD, OS, and 1- and 5-year OS rates. Any disagreements were resolved by consulting a third reviewer.

Statistical analysis

All the statistical procedures were conducted using Review Manager software (version 5.2) by applying the random effect model for heterogeneous outcomes and the fixed effect model for homogenous outcomes and 95% confidence intervals (CI). For the categorical data, we calculated the pooled risk ratio (RR) or hazard ratio (HR), while for continuous variables, we calculated the pooled mean difference between the two groups. Heterogeneity was assessed using I^2, and $P = 0.05$ was applied for all steps. Subgroup analysis according to study design (cohort and RCTs) was done. Sensitivity analysis by leave-one-out was done to resolve heterogeneity.

RESULTS

Database searching and screening

After searching the databases, a total of 388 articles were produced with 144 duplicates, so we conducted title and abstract screening for 244 studies. We excluded 229 studies and conducted full-text screening for the remaining 15 studies. A total of 11 studies were included in the final meta-analysis[3,4,7-9,11,13,15,16,20,29] [Figure 1].

Baseline characteristics of the included studies

Multiple studies with different study designs carried out between 2010 and 2023 were included in the study. Among these, seven were cohort studies, three RCTs, and a non-randomized trial. Sample sizes ranged from 26 to 194 participants, with varying male representation across the studies. The proportion of males receiving WBRT ranged from 31% to 72.2%, while those receiving SRS showed an almost similar representation. The mean ages of participants varied, with WBRT mean ages ranging from 53 to 65 years, while SRS patients' mean ages ranged from 53 to 66 years. These baseline characteristics indicate a diverse population across the studies. The baseline characteristics of the included studies are fully illustrated in Table 1.

Quality and Rob assessment

Five of the cohort studies were of high quality, and two were of moderate quality [Table 2]. Regarding RCTs, two had a low Rob, and one had some concerns [Figure 2], while the non-randomized clinical trial had a moderate Rob [Figure 3].

Local recurrence

Local recurrence is a crucial indicator of the effectiveness of treatment, reflecting the need for further therapeutic interventions. Data were extracted from seven included studies, and the meta-analysis revealed no statistically significant no statistically significant difference between WBRT and SRS groups, whether in the cohort studies or RCTs with a total effect size (RR = 0.78, 95% CI [0.52, 1.17]) as indicated by $P = 0.22$. Data were homogenous among studies ($P = 0.4$, $I^2 = 3\%$), as illustrated in Figure 4.

Distant recurrence

Extracted data from five included studies were used to perform a meta-analysis. Pooled effect estimate calculation revealed no statistically significant difference between WBRT and SRS groups in the cohort and RCTs with (RR = 0.83, 95% CI [0.54, 1.28], $P = 0.41$) with marked heterogeneity detected ($P = 0.05$; $I^2 = 59\%$). Sensitivity analysis was conducted, leaving out Bodensohn *et al*.,[3] 2023, as it included patients with 4–10 brain metastases, which resolved that heterogeneity ($P = 0.36$; $I^2 = 6\%$). Figure 5 shows the forest plot of distant recurrence outcomes.

LMD

Results of the meta-analysis showed a statistically significant difference between WBRT and SRS, favoring WBRT as SRS is associated with higher hazards of post-radiation LMD (HR = 3.09, 95% CI [1.47, 6.49], $P = 0.003$) with no significant heterogeneity detected ($P = 0.28$; $I^2 = 15\%$), as shown in Figure 6.

One year survival

Survival rates after 1 year of treatment were calculated in 11 studies. A meta-analysis was conducted and showed no statistically significant difference between WBRT and SRS in 1-year survival rates (RR = 1.03, 95% CI [0.83, 1.29], $P = 0.76$), with moderate heterogeneity detected ($P = 0.0006$; $I^2 = 68\%$). This heterogeneity was observed in the RCTs subgroup and after the sensitivity analysis by leave-one-out with removal of Brown study, the heterogeneity was resolved. This heterogeneity was attributed to surgical bed control after SRS, which was reported to be worse than that reported in previous studies, as indicated by Brown *et al*.,[4] 2017 [Figure 7].

Five-year survival

The 5-year survival rate is a long-term indicator of the therapeutic effect of interventional groups; the meta-analysis

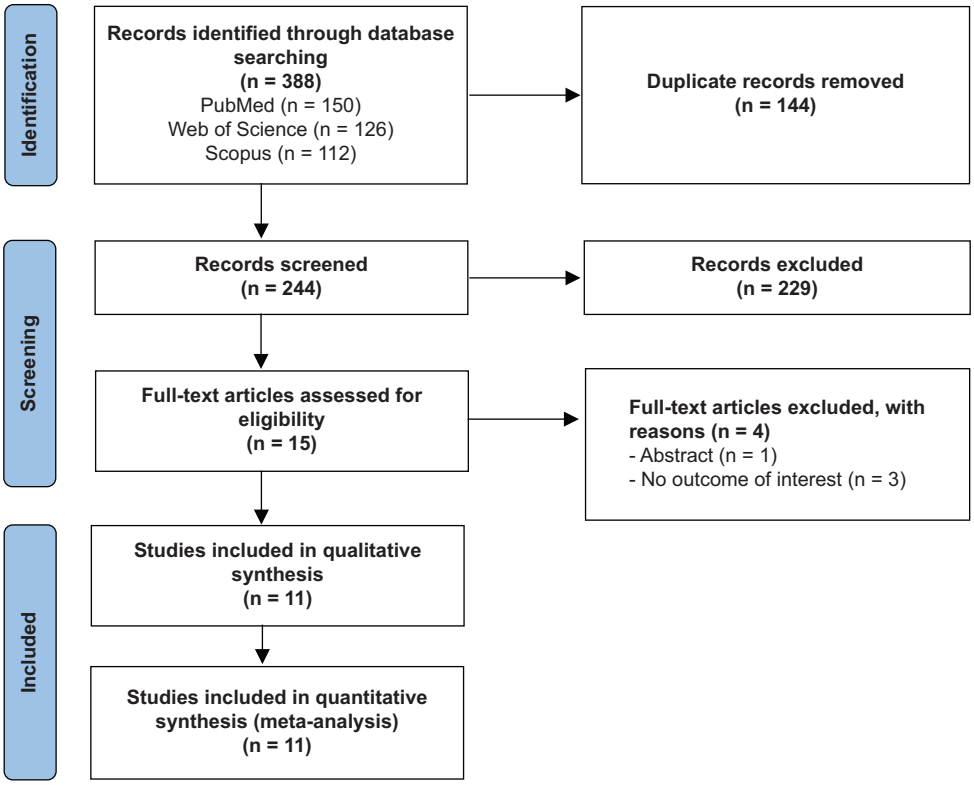

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the searching and screening processes.[3,4,7-9,11,13,15,16,20,29]

Table 1: Baseline characteristics of the included studies.

Study ID	Design	Sample size		Males, *n* (%)		Age, mean (SD)	
		WBRT	SRS	WBRT	SRS	WBRT	SRS
Lee *et al.*, 2013[20]	Cohort	157		82 (52.2)		53.7 (9.12)	
Elaimy *et al.*, 2011[7]	Cohort	11	15	NR	NR	60.5 (10.97)	53.75 (12.55)
Gu *et al.*, 2015[8]	Cohort	93		57 (61.3)		NR	NR
Hwang *et al.*, 2010[13]	Cohort	18	25	13 (72.2)	7 (28)	52.8 (11.52)	59.47 (11.5)
Hsieh *et al.*, 2015[11]	Cohort	156	37	62 (69)	17 (46)	58 (8.83)	60 (9.25)
Patel *et al.*, 2014[29]	Cohort	36	96	11 (31)	42 (44)	65 (10.5)	54.6 (13.625)
Hashimito *et al.*, 2011[9]	Cohort	66	64	NR	NR	58 (12.25)	58 (13.75)
Kępka *et al.*, 2016[15]	RCT	30	29	15 (50)	11 (38)	59.5 (8.75)	59.5 (11.75)
Kerschbaumer *et al.*, 2020[16]	RCT	18	22	10 (55)	13 (59)	NR	NR
Bodensohn *et al.*, 2023[3]	Non-randomized clinical trial	70	40	37 (53)	21 (53)	62 (11.75)	66 (12.75)
Brown *et al.*, 2017[4]	RCT	96	98	50 (52)	46 (47)	61.33 (10.54)	60.33 (9)

WBRT: Whole-brain radiotherapy, SRS: Stereotactic radiosurgery, RCT: Randomized controlled trial, SD: Standard deviation, NR: Not reported

showed no statistically significant difference between WBRT and SRS in the RCTs and cohort subgroups (RR = 0.87, 95% CI [0.55, 1.38], P = 0.55) with no heterogeneity detected in cohort subgroup and RCTs subgroup was only one study [Figure 8].

OS (in months)

OS period data were extracted from five studies. Meta-analysis was conducted and showed a higher OS period in the SRS group compared to WBRT in the cohort subgroup

Table 2: Quality assessment of the included cohort studies using the Newcastle–Ottawa Scale.

Study name	Representativeness of the exposed cohort (★)	Selection of the non-exposed cohort (★)	Ascertainment of exposure (★)	Demonstration that outcome of interest was not present at the start of the study (★)	Comparability of cohorts on the basis of the design or analysis (max★★)	Assessment of outcome (★)	Was follow-up long enough for outcomes to occur? (★)	Adequacy of follow up of cohorts (★)	Quality level
Lee *et al.*, 2013[20]	★	-	★	★	★	★	★	-	Moderate
Elaimy *et al.*, 2011[7]	★	★	★	★	★	★	★	★	High
Gu *et al.*, 2015[8]	★	★	★	★	★	★	★	-	High
Hwang *et al.*, 2010[13]	★	★	★	★	★★	★	★	★	High
Hsieh *et al.*, 2015[11]	-	★	★	★	★	★	★	-	Moderate
Patel *et al.*, 2014[29]	★	★	★	★	★★	★	★	★	High
Hashimito *et al.*, 2011[9]	★	★	★	★	★★	★	★	★	High

★: Indicates a degree for each question if the study aligned with the question, ★★: Two points.

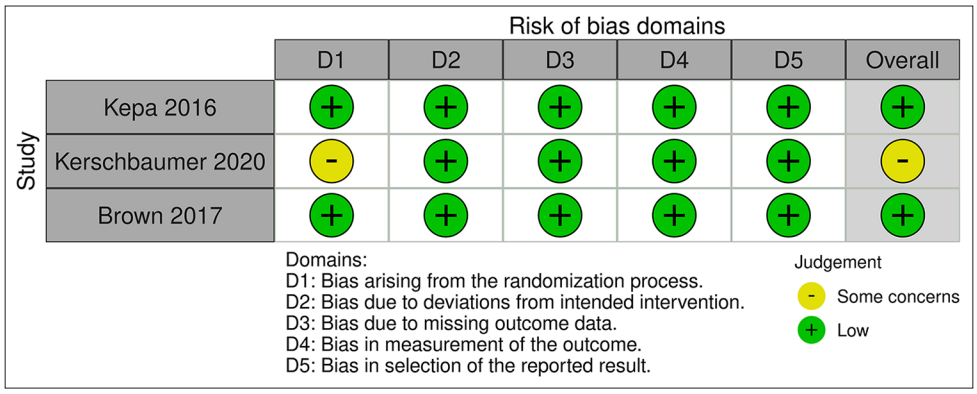

Figure 2: Risk of bias assessment of the included randomized controlled trials using the risk of bias 2 tool.

Mean difference (MD) = 4.05 months, 95% CI [2.18, 5.91], $P < 0.0001$) with no heterogeneity detected ($P = 0.54$; $I^2 = 0\%$); however, no significant difference was obtained between the two groups in the RCTs subgroup [Figure 9].

DISCUSSION

In the present study, we observed that both treatment modalities were comparable regarding local and distant tumor recurrence. Moreover, both treatment strategies were similar in the OS for 1 and 5 years. However, the OS measured in months was higher in the SRS group than in WBRT. On the other hand, WBRT was superior regarding post-radiation LMD.

Consistent with the latest research conducted by Lamba *et al.*[19] that aimed to assess the effectiveness of different types of radiation treatment (WBRT and SRS) in terms of tumor recurrence and survival rates after surgery; our study demonstrated similar patterns in recurrence

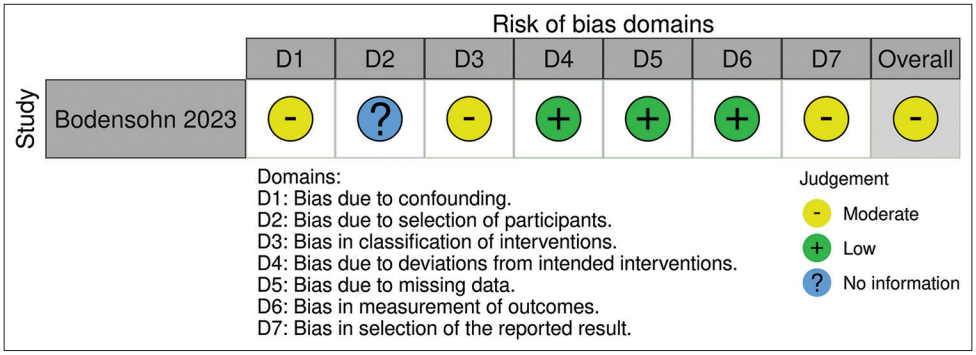

Figure 3: Risk of bias assessment of the included non-randomized clinical trial using the risk of bias in non-randomized studies of interventions-1 tool.

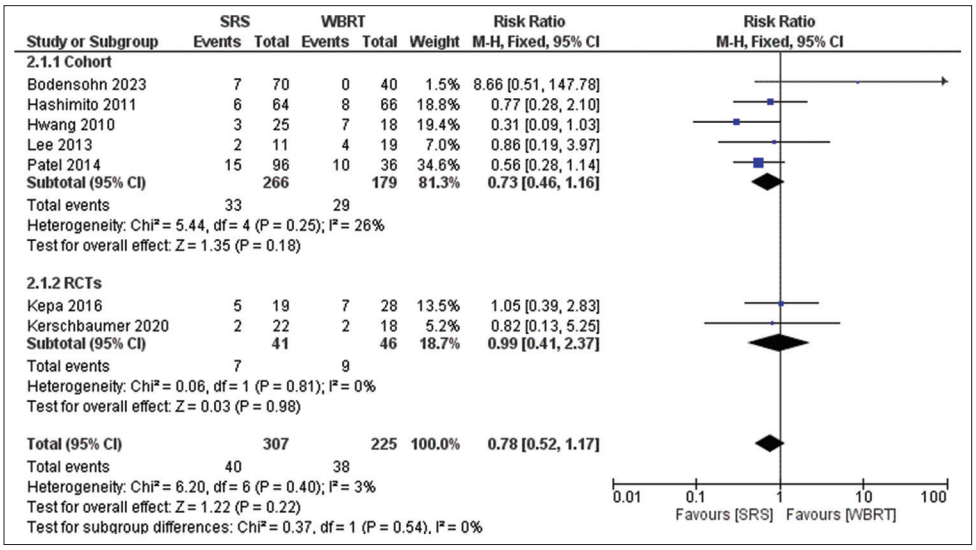

Figure 4: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding local recurrence. CI: Confidence interval, M-H: Mantel-Haenszel.

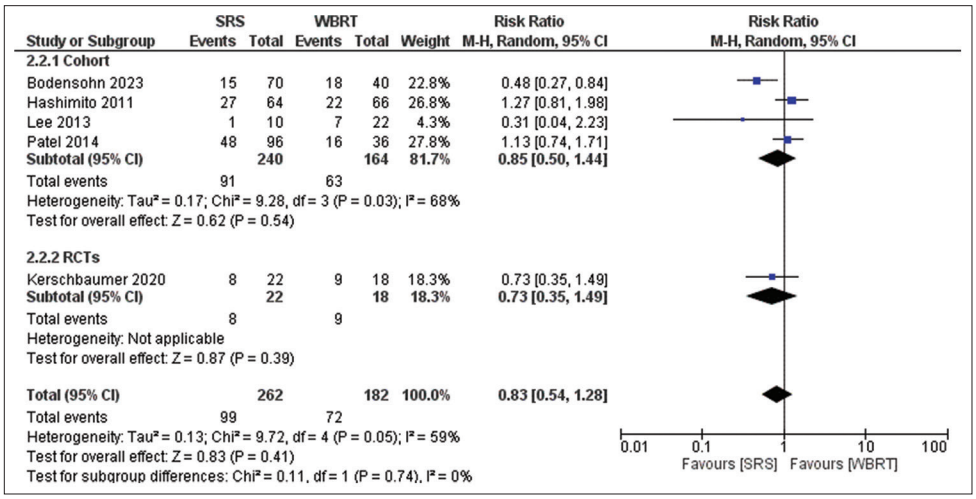

Figure 5: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding distant recurrence. CI: Confidence interval, M-H: Mantel-Haenszel.

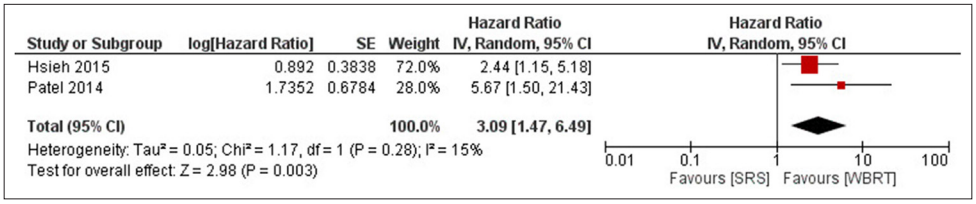

Figure 6: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding leptomeningeal disease. CI: Confidence interval, SE: Standard error.

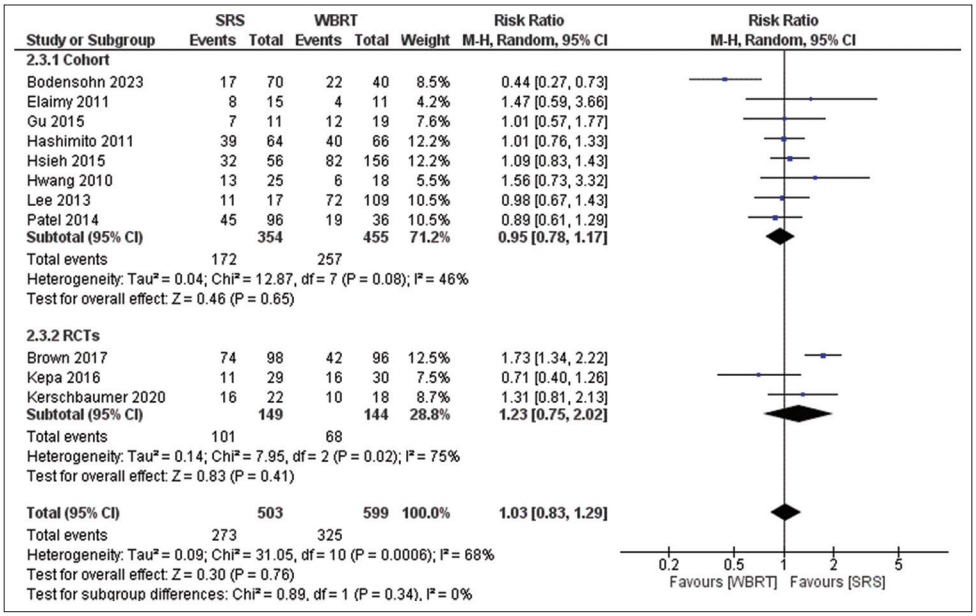

Figure 7: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding 1-year survival. CI: Confidence interval, M-H: Mantel-Haenszel.

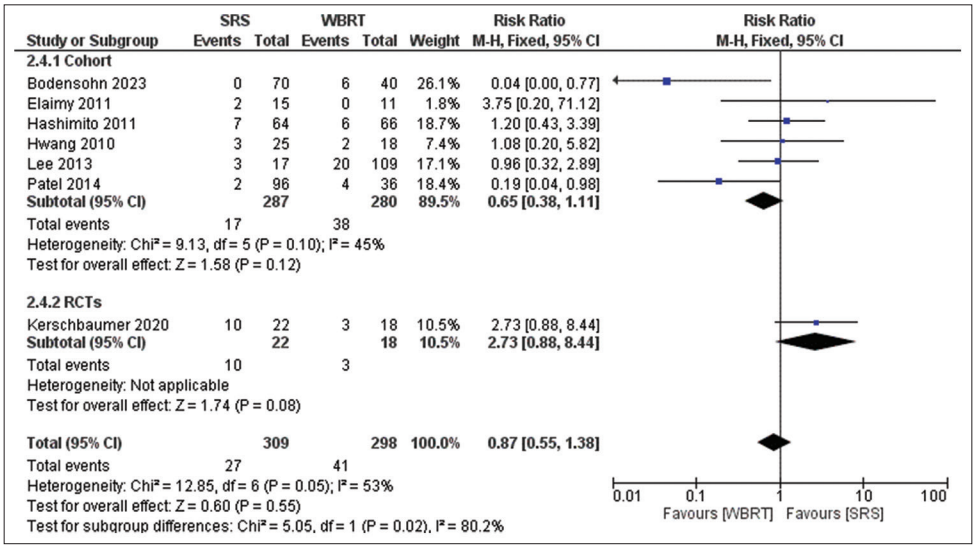

Figure 8: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding 5-year survival. CI: Confidence interval, M-H: Mantel-Haenszel.

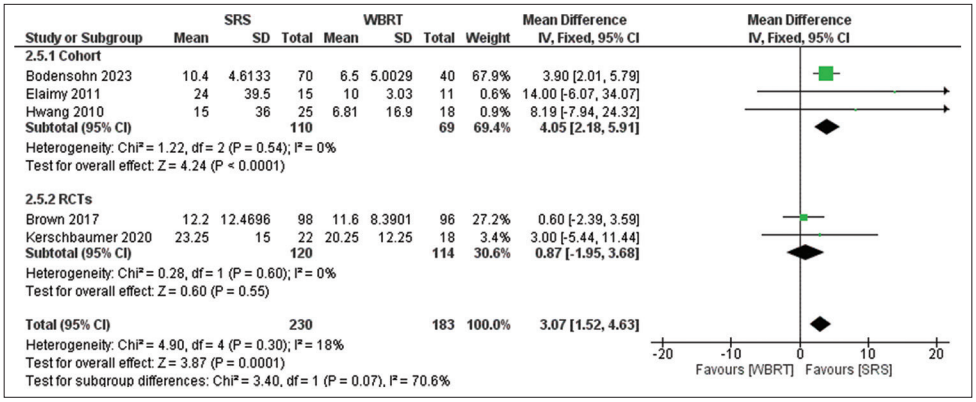

Figure 9: Comparison between stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) regarding overall survival. CI: Confidence interval, M-H: Mantel-Haenszel.

rates and LMD. Nevertheless, this study was exclusively comprised of retrospective cohort studies. Consequently, the present study offers a greater number of studies and a larger sample size, resulting in a more comprehensive assessment of the 1 and 5-year survival outcomes. Although Vlachos *et al*.[35] reported comparable results to ours in terms of local recurrence and OS, their results showed no discernible disparities between the two modalities in terms of LMD. In addition, they stated that SRS was linked to increased rates of distant failure compared to WBRT. This discrepancy can be ascribed to their limited inclusion of merely four studies and the utilization of smaller sample sizes in the analyses.

In 1998, Patchell *et al*. conducted a significant randomized experiment in which patients diagnosed with solitary brain metastasis were randomly allocated to receive either WBRT after surgery or to be observed without any additional treatment. Patients in the first group had a significantly decreased chance for local recurrence (10% vs. 46%, $P < 0.001$), distant brain recurrence (14% vs. 37%, $P < 0.01$), and neurologic mortality (14% vs. 44%, $P = 0.003$). However, the authors found no significant increase in median survival (48 weeks vs. 43 weeks, $P = 0.39$). They attributed this lack of improvement to inadequate treatment of the patient's systemic disease rather than a lack of effectiveness in WBRT.[28] According to the second study, the conventional treatment for individuals with a single brain metastasis is surgical removal followed by WBRT.[27,28] WBRT has been linked to both immediate adverse effects (occurring within weeks to months after starting treatment), such as fatigue or drowsiness, as well as delayed toxicities (occurring 90 days after beginning treatment), most typically including decline in cognitive function, leukoencephalopathy, and radiation necrosis.[22] The most prominent consequence is neurocognitive deterioration, which can impact over 50% of patients with brain metastases undergoing WBRT within 3 months. This percentage can escalate to as high as 90% within a year. Furthermore, this permanent harmful effect associated with WBRT might manifest as late as 30 years after the treatment.[34] With the advancement of our knowledge about brain metastases at the molecular level, new treatments such as tyrosine-kinase inhibitors and immunotherapy have emerged. These therapies have extended the life expectancy of patients, as it is important to maintain their neurocognitive function and overall quality of life.[21]

SRS has emerged as the predominant treatment choice for patients with brain metastases. The effectiveness of SRS for brain metastases was initially documented in several retrospective investigations. In a study conducted by Sanghavi *et al*.,[30], they retrospectively analyzed 502 patients from many institutions. Patients were classified into recursive partitioning analysis classes I, II, and III. The study found that patients who had both WBRT and SRS had a significantly longer median survival period when compared to those who only received WBRT.

RTOG 9508 was a phase III trial that randomly assigned 333 patients with one to three brain metastases with a Karnofsky performance score (KPS) of 70 or above to receive either WBRT and SRS or WBRT alone.[1] Among patients with solitary brain metastasis, the use of both WBRT and SRS was found to be more effective than WBRT alone. This combined treatment approach led to a lower risk of local recurrence after 1 year and improved median survival periods. The combination treatment arm resulted in a considerable improvement in local control for patients with two or three brain metastases. However, there was no discernible difference in survival period between the two groups.

Patients who underwent both SRS and WBRT experienced extra benefits compared to those who only received WBRT in terms of maintaining or improving their KPS and reducing corticosteroid use. Subsequent studies

assessed the efficacy of SRS alone without the addition of WBRT. Aoyama *et al*.[2] conducted a prospective phase III trial called JROSG 99-1. In this trial, 132 patients, predominantly with lung cancer, were randomly assigned to receive either SRS alone or SRS combined with WBRT. The patients had a KPS score of 70 or higher and had four or fewer metastases. The results indicated that there was no significant difference in survival. However, it is important to note that the trial was not designed to detect a significant difference in OS. In terms of longer-term survival, there was a trend toward higher survival rates in the group treated with WBRT plus SRS compared to those treated with SRS alone. Specifically, the 1-year survival rates were 38.5% for the WBRT plus SRS group and 28.4% for the SRS alone group.[2] As expected, the study showed that the addition of WBRT to SRS increased local control rates. The 1-year failure rate was 23.6% for SRS + WBRT, compared to 53.2% for SRS alone. The EORTC 22952-26001 research randomly allocated 359 patients with one to three brain metastases to receive either 30 Gy of WBRT or to be observed after undergoing either surgery or SRS. Following either surgery or SRS, WBRT was linked to enhanced control of both local and distant brain recurrence.[17]

While SRS is commonly provided to individuals with four or fewer brain metastases, it is now being more frequently used for patients with five or more tumors. A retrospective analysis revealed that the median OS in individuals with five or more brain metastases was 7.5 months following treatment with SRS.[12] Surprisingly, the quantity of brain metastases did not have a significant impact on survival. However, a greater intracranial burden was associated with worse results.[24] A prospective and observational study was conducted at 23 hospitals in Japan to investigate the impact of the number of brain metastases on OS in patients treated with SRS alone. The study found no significant difference in OS between patients with two to four brain metastases and those with five or more.[37] The median OS following SRS was 13.9 months for patients with a solitary brain metastasis, 10.8 months for patients with two to four brain metastases, and 10.8 months for those with five to ten brain metastases. This indicates that SRS could be a suitable method for treating some individuals who have up to 10 brain metastases. This expands the potential applications of SRS in these patients and also provides evidence that the size, rather than the quantity, of metastases may be the determinant factor in the outcomes of brain metastases.[18]

The present study is limited by the inclusion of observational studies with RCTs in the analysis, which may cause a Rob. However, this should have been done due to the limited number of published RCTs and to gather comprehensive evidence. We recommend future large-scale RCTs to validate our present findings.

CONCLUSION

The rates of tumor recurrence, whether local or distant, were similar between SRS and WBRT. Furthermore, both treatment methods had comparable OS rates at 1 and 5 years. Nevertheless, WBRT demonstrated superior efficacy in treating post-radiation LMD. Conversely, the duration of the OS evaluated in months was greater in the SRS group when compared to WBRT.

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Declaration of patient consent: Patient's consent was not required as there are no patients in this study.
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Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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