Stereotactic radiosurgery versus whole-brain radiotherapy after resection of solitary brain metastasis: A systematic review and meta-analysis

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ABSTRACT

Objective: The standard of care in patients with solitary brain metastasis involves surgical resection and post-operative whole-brain radiotherapy (WBRT). However, WBRT is associated with adverse effects, mainly neuro-cognitive deterioration. Stereotactic radiosurgery (SRS) is a more targeted form of radiation therapy that could be as effective as WBRT without the detrimental neurocognitive decline.

Methods: We performed the first systematic review and meta-analysis comparing postoperative SRS versus post-operative WBRT in patients with one resected brain metastasis. PubMed, Scopus, and Cochrane library were systematically searched for studies comparing the efficacy of the two radiation modalities in terms of local and distant brain control, leptomeningeal disease control, and overall survival. Additionally, we extracted patients' neurocognitive function and quality of life after each postoperative radiation form.

Results: Four studies with 248 patients (128: WBRT, 120: SRS) were included in our analysis. There was no difference between SRS and WBRT in the risk of local recurrence (RR = 0.92, CI = 0.51–1.66, p = 0.78, I2 = 0%) and leptomeningeal disease (RR = 1.21, CI = 0.49–2.98, p = 0.67, I2 = 18%), neither in the patients' overall survival (HR = 1.06, CI = 0.61–1.85, p = 0.83, I2 = 63%). Nevertheless, SRS appeared to increase the risk of distant brain failure (RR = 2.03, CI = 0.94–4.40, p = 0.07, I2 = 61%). Neurocognitive function and quality of life in the SRS group were equal or superior to the WBRT group.

Conclusions: Although SRS may increase the risk of distant brain failure, it appears to be as effective as WBRT in terms of local control, risk of leptomeningeal disease, and overall survival while sparing the patients of the detrimental, WBRT-associated cognitive deterioration.

1. Introduction

The advent of adjuvant and neoadjuvant chemotherapy options, the continuous improvement of surgical techniques, and the application of sensitive patient monitoring protocols have significantly prolonged the life span of cancer patients, consequently increasing the frequency of detection of tumor metastases in the brain. Brain metastases are the most common type of intracranial tumor and the main neurologic complica-tion of primary cancers, with the most frequent being lung cancer, breast cancer, and melanoma.[1] As neurocognition and quality of life are shifting to becoming primary treatment endpoints in these types of patients, the

paramount importance of meaningful treatment and effective intracra-nial disease control is highlighted.[2] Treatment options consist of surgical removal, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and targeted agents, and there should be individualization ac-cording to the patients' Karnofsky Performance Status (KPS), the morphological structure of the malignant tumor, the feasibility of sys-temic therapy, as well as the number, size, and sites of metastatic lesions.[3]

The recommended approaches and treatment modalities for brain metastases have varied considerably over the past decades. In the 1990s, the first randomized trials indicated the benefits of surgical removal,

hitherto treated with pessimism,[4] but supplementary radiation is essential for local control.[5] After the landmark study by Patchell et al, surgical resection and postoperative whole-brain radiotherapy became the standard of care in patients with solitary brain metastasis, preceding the development of SRS.[6] However, the introduction of SRS transformed the clinical research, with trials testing it as companion radiation to WBRT[7] or as monotherapy instead of WBRT.[8] WBRT targets the whole brain, while SRS is a more precise form of radiotherapy delivering a radiation dose in a more restricted area, that of the surgical cavity. Although WBRT offers substantial intracranial disease control, its side effects, primarily in neurocognition, promote SRS as a potent favorable alternative.

This systematic review and meta-analysis aim to discover whether postoperative SRS can offer comparable results in local recurrence, distant recurrence, leptomeningeal disease, and overall survival compared to postoperative WBRT in patients with a solitary, previously resected brain metastasis. Additionally, information regarding patients' neurocognitive function and quality of life after each postoperative radiation treatment modality were also extracted from each study.

2. Material and methods

2.1. Search and selection

Medline, Scopus, and Cochrane library were systematically searched in January 2022 without time restriction for studies of any duration and design in English comparing SRS versus WBRT in patients with one previously resected brain metastasis. The search algorithm contained the following keywords: whole-brain radiotherapy, stereotactic radiosurgery, and brain metastasis with synonyms. The present systematic review and meta-analysis were conducted under the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[9]

All studies identified in our search were screened for eligibility by titles and abstracts from two independent investigators. Articles having the potential to fulfill our inclusion criteria underwent full-text evaluation. If concurrence on eligibility was not reached between the two investigators, a third investigator was involved to evaluate the article. Database searches were supplemented by using forward and backward citation analysis. The eligibility was defined by the PICO framework: Population (P): Patients with one resected brain metastasis; Intervention (I): Postoperative SRS; Comparison (C): Postoperative WBRT; Outcomes (O): Local recurrence, distant recurrence, leptomeningeal disease, and overall survival. Studies without an official postoperative histological report of brain metastasis or studies involving patients with more than one brain metastasis were excluded.

2.2. Data extraction

The data extraction was performed by three authors who filled in a pre-piloted extraction form independently. Any disagreement was resolved by consensus. Records of the same trial reporting at different follow-ups were considered a single trial. In the case of double reporting data, data from the most-informative publication and highest level of evidence were used. The data extraction sheet included: first author, year of publication, study design, number of patients with solitary brain metastasis (overall and by group), median age, radiation dose, the maximal extent of resection cavity, performance status, primary tumor sites, the extent of resection, survival, and progression (of any presentation) rates and hazard ratios.

2.3. Quality assessment

Study quality was assessed by Cochrane Risk of Bias Tool in the case of Randomized controlled trials, whereas in cohort studies, the Newcastle–Ottawa Scale was utilized. Study quality evaluation was performed independently by two authors (NV, MGL). Discrepancies were resolved by discussion.

2.4. Quantitative analysis

Randomized clinical trials and cohort studies were combined in a single meta-analysis. Regarding overall survival, we extracted the hazard ratio from each study, whereas local and distant recurrence as well as leptomeningeal disease were expressed in terms of Risk Ratio (RR) and 95% Confidence Intervals (CI). Statistical heterogeneity was assessed using the I^2 statistic. In cases of substantial heterogeneity ($I^2 > 50\%$), the DerSimonian and Laird inverse variance random-effect model was used. Conversely, in the presence of low heterogeneity ($< 25\%$), the Mantel-Haenszel (M−H) fixed effect model was utilized.

All statistical analyses were performed with Review Manager (RevMan) version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, Denmark; 2014).

3. Results

Medline, Scopus and Cochrane library yielded 3063 results. From them, 2380 duplicates were removed and from the remaining 683 studies we excluded 666 studies based on their title and abstract or because the text language was other than English. The remaining 17 relevant articles were evaluated in their full-text form for eligibility criteria. From the full-text assessment, 14 studies were rejected as they included patients with more than one brain metastasis. Finally, four (4) studies were incorporated in our systematic review and meta-analysis: Two (2) randomized controlled trials (RCTs)[10,11] and two (2) retrospective studies.[12,13] One-hundred twenty-eight (128) patients with a median age of 59 years received postoperative WBRT while 120 patients with median age 59 years were treated with postoperative SRS. The radiation dose of WBRT varied from 30 to 50 Gy whereas the SRS counterpart from 15 to 50 Gy. In all cases, the dose was fractionated. Fig. 1 presents the process of study selection in our systematic review and meta-analysis. Table 1 summarizes the main features of the included studies.

3.1. Principal findings

3.1.1. Local recurrence

All studies[10–13] provided information regarding the local recurrence rates. As shown in Fig. 2, there was no statistically significant difference in the pooled risk ratio comparing local recurrence incidence between WBRT and SRS groups (RR = 0.92, CI = 0.51–1.66, p = 0.78, $I^2 = 0\%$).

3.1.2. Distant recurrence

Three studies with 229 patients reported data in terms of distant recurrence incidence.[10–12] From those 229 patients, 114/229 received adjuvant WBRT while the remaining 115/229 adjuvant SRS. Using the fixed-effect model, the pooled result indicated that patients who underwent postoperative SRS had a 76% greater risk of distant recurrence compared to the WBRT group (RR = 1.76, CI = 1.20–2.56, p = 0.003). There was substantial heterogeneity between the included studies ($I^2 = 64\%$). Random-effect meta-analysis of the distant recurrence incidence failed to reach a statistically significant result, though showing a trend of increased risk for distant recurrence in patients treated with postoperative SRS in the brain metastasis resection cavity (RR = 2.03, CI = 0.94–4.40, p = 0.07, $I^2 = 61\%$) (Fig. 3).

3.1.3. Leptomeningeal disease

There were two studies with 170 patients (WBRT: 84, SRS: 86) which provided data regarding the development of leptomeningeal disease.[11,12] The combination of surgical resection and postoperative SRS was not associated with an increased risk of leptomeningeal disease development compared to the standard of care, resection and postoperative WBRT
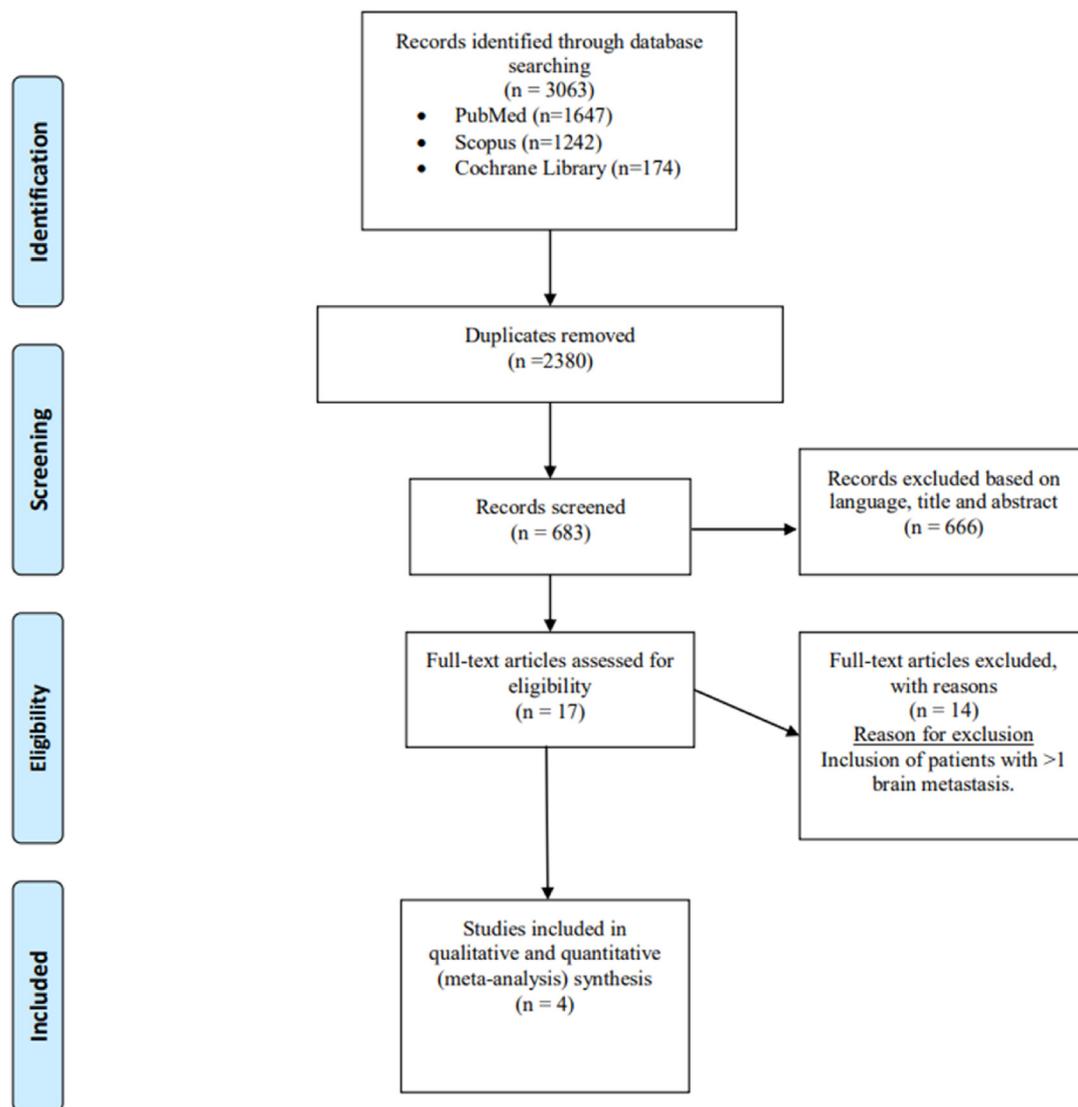
Fig. 1. Flowchart diagram presenting the selection of the eligible studies.

(RR = 1.21, CI = 0.49–2.98, p = 0.67). Heterogeneity between the two studies was low ($I^2 = 18\%$) (Fig. 4).

3.1.4. Overall survival

Information regarding the overall survival of patients was available in three studies with 229 patients (WBRT:114, SRS:115).[10–12] Pooled analysis using the random-effect model did not show any difference in the patients' overall survival between the two treatment groups (HR = 1.06, CI = 0.61–1.85, p = 0.83, $I^2 = 63\%$) (Fig. 5).

3.2. Secondary outcome

3.2.1. Neurocognitive function and quality of life

Kepka et al, in their randomized trial, failed to indicate non-inferiority of SRS radiation modality compared to WBRT regarding neurocognition. Neurocognitive failure was defined as the deterioration of neurological status ≥1 point on the MRC (Medical Research Council) scale or worsening of ≥3 points in the MMSE (Mini-Mental State Examination) test score or neurological death. While neurological/cognitive failure was detected in 21/29 patients (72%) in the SRS patients compared to 19/30 (63%) WBRT patients, when it comes to treatment-specific neurocognitive deterioration, 4/19 patients reported WBRT-
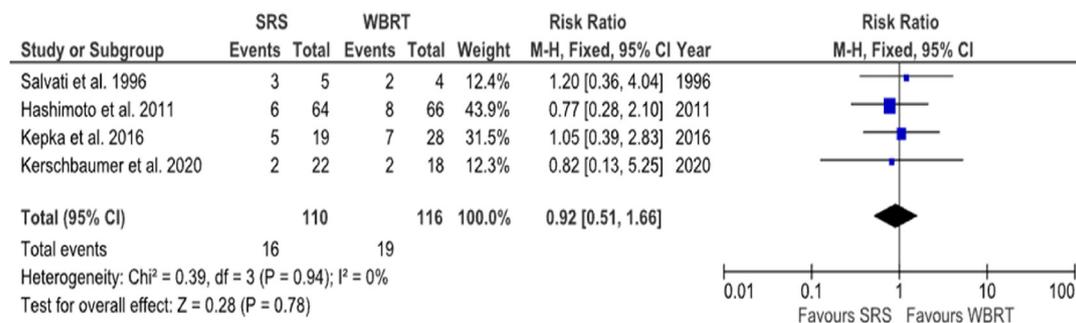
associated toxicity in contrast to the SRS group where no case of neurocognitive deterioration was attributed directly to the SRS treatment.[10] Hashimoto et al, despite failing to describe the detailed neurocognitive function as well as the quality of life of patients in both radiotherapy modality groups, reported that at 2-years follow-up, the KPS remained stable in both treatment groups.[12] Finally, in the study of Kerschbaumer et al, there were signs of a better quality of life in the SRS group compared to the WBRT group. Of note, at 6 and 18 months after radiotherapy, SRS patients experienced fewer compared communication impairments in comparison with their WBRT counterparts (p = 0.032 and p = 0.048, respectively). However, the global QLQ and the QLQ-C30 summary scores did not reach a statistically significant difference between the two treatment groups.[11]

4. Discussion

Our study represents the first systematic review and meta-analysis comparing postoperative SRS and WBRT exclusively in patients with solitary, previously resected brain metastasis. The results indicate that the efficacy of SRS in terms of local recurrence risk, leptomeningeal failure risk, and overall survival is comparable to that of WBRT. However, patients treated with adjuvant SRS appear to have an increased risk

Table 1
Summary of the main characteristics of the included studies.

Study	Type of study	N patients	Study arms	Median age (y)	Radiation dose	Resection cavity maximal extent	Performance status	Primary tumor site	Extent of resection
Kepka et al, 201,6[10]	*RCT*	*59*	*WBRT: 30/59*	*59,5*	• *30 Gy in 10 fractions*	*n/s*	*KPS>70%: 100%*	• *Lung (50%)<* • *CRC (6,5%)<* • *Breast (20%)<* • *Melanoma (10%)<* • *Other (13,5%)*	*GTR: 90%*
			SRS: 29/ 59	*59,5*	• *15 Gy in one fraction<* • *25 Gy in 5 fractions when surgical cavity > 5 cm*	*n/s*	*KPS>70%: 100%*	• *Lung (48%)<* • *CRC (24%)<* • *Breast (3,5%)<* • *Melanoma (3,5%)<* • *Kidney (7%)<* • *Other (14%)*	*GTR: 83%*
Kerschbaumer et al, 202,0[11]	*RCT*	*40*	*WBRT: 18/40*	*59*	• *40Gy on the 95%-Isodose, which means 20 fractions and a single dose of 2Gy*	*2,76 cm*	*KPS>70: 100%*	• *NSCLC (55,5%), <* • *Melanoma (11,1%), <* • *Breast (0%), <* • *Other (33,3%)*	*n/s*
			SRS: 22/ 40	*59*	• *30 Gy in five fractions*	*3,34 cm*	*KPS >70: 100%*	• *NSCLC (50%)<* • *Melanoma (18,1%)<* • *Breast (9%)* • *Other (22,7%)*	*n/s*
Hashimoto et al,201,1[12]	*Cohort*	*130*	*WBRT: 66/130*	*58*	• *30 Gy in 10 fractions <* • *37.5 Gy in 15 fractions*	*Median 3,8 cm (1,5–6,0)*	*Median KPS 70 (40–100)*	• *Lung (26%) <* • *Breast (9%) <* • *CRC (8%)<* • *Skin (3%)<* • *Other (20%)*	*GTR: 98%*
			SRS: 64/ 130	*58*	• *50 Gy in 25 fractions*	*Median 3,8 cm (1,0–6,5)*	*Median KPS 70 (40–100)*	• *Lung (29%) <* • *Breast (9%)<* • *CRC (6%)* • *Skin (3%)* • *Other (17%)*	*GTR: 92%*
Salvati et al,199,6[13]	*Cohort*	*19*	*WBRT: 14/19*	*n/s*	• *40–50 Gy*	*n/s*	*n/s*	*Melanoma*	*GTR: 100%*
			SRS: 5/19	*n/s*	*n/s*	*n/s*	*n/s*	*Melanoma*	*GTR: 100%*

Fig. 2. Local recurrence: Resection and postoperative SRS versus resection and postoperative WBRT. The I2 and P values for heterogeneity are also presented. CI=Confidence interval

of developing recurrence in other parts of their brain during their disease compared to those treated with postoperative WBRT, though there was no statistical significance in the pooling of distant failure risk ratios.

In 1998, Patchell et al published their landmark randomized trial in which patients diagnosed with solitary brain metastasis were randomly assigned to postoperative treatment with WBRT or observation. Patients in the latter group had statistically significant lower risk for local recurrence (10% vs 46%, p < 0.001), distant brain recurrence (14% vs 37%, p < 0.01) and neurologic death (14% vs 44%, p = 0.003). Nevertheless, median survival was not significantly increased (48 weeks versus
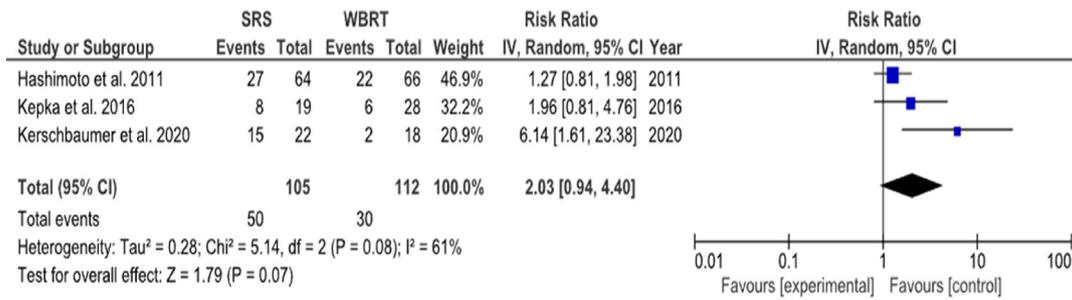
Fig. 3. Distant recurrence: Resection and postoperative SRS versus resection and postoperative WBRT. Since there was substantial heterogeneity using the fixed effect model (I2 = 64%), the inverse variance random effect model was considered the appropriate meta-analysis method. CI=Confidence interval
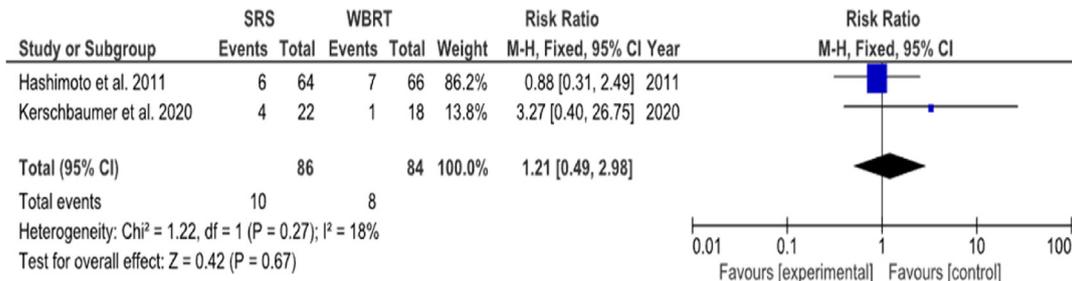

Fig. 4. Leptomeningeal disease: Resection and postoperative SRS versus resection and postoperative WBRT. The I2 and P values for heterogeneity are also presented. CI=Confidence interval
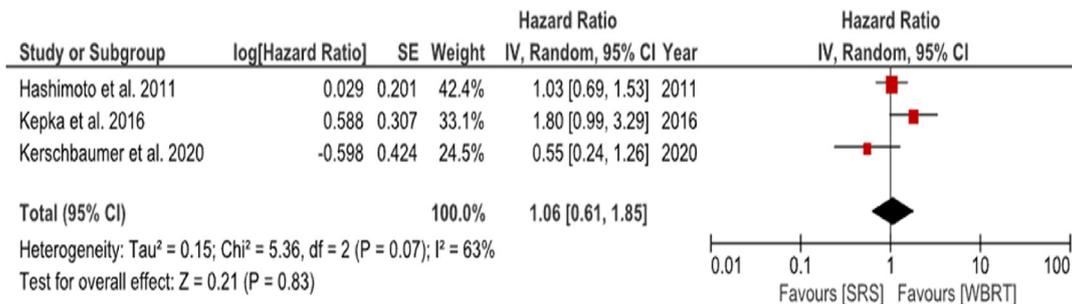

Fig. 5. Overall Survival: Resection and postoperative SRS versus resection and postoperative WBRT. There was substantial heterogeneity between the included studies (I2 = 63%). CI=Confidence interval.

43 weeks, p = 0.39), which, according to the authors, was due to insufficient control of the patients' systemic disease rather than a lack of WBRT's efficiency.[6] Based on the latter study, surgical excision with postoperative WBRT became the standard of care in patients with solitary brain metastasis.[6,14]

WBRT has been associated with both short-term adverse effects (weeks to months after treatment initiation) such as fatigue or somnolence as well as late toxicities (90 days after treatment commencement), most commonly neurocognitive deterioration, leukoencephalopathy, and radiation necrosis.[15] The neurocognitive decline represents the most notorious one, which can affect almost half of the patients with brain metastases treated with WBRT in 3 months, a percentage which can reach up to 90% in 1 year. Additionally, this irreversible, WBRT-related adverse effect may appear as late as 30 years after treatment.[16] As our molecular understanding of brain metastases is constantly increasing, eventually giving birth to novel therapies, including tyrosine-kinase inhibitors and immunotherapy, patients' life expectancy is prolonged, thus necessitating the preservation of their neurocognitive function and their overall quality of life.[17]

SRS constitutes a more localized radiation treatment modality whose efficacy was suggested in three RCTs comparing WBRT and SRS versus SRS alone in patients with 1–4 brain metastases.[8,18,19] Pooled analysis of those studies by Tsao et al revealed that even though the combination of radiation modalities confers superior local (HR = 2.61, p < 0.0001) and distant brain control (HR = 2.15, p < 0.00001), there is no difference in patient overall survival (0.98, p = 0.88).[20] On top of that, Chang et al, by using the Hopkins Verbal Learning Test-Revised test to assess neurocognition, reported that patients receiving WBRT + SRS experienced a significant deterioration of their cognitive abilities compared to patients undergoing SRS in 4 months (52% versus 24%, respectively) which was also documented in 6 months.[18] Similar results were also observed in the RCT of Brown et al, where patients with 1–3 brain metastases received either WBRT plus SRS or SRS alone. The latter group displayed significantly lower cognitive deficits (63,5% vs 91,7%, p < 0.001) and better overall quality of life (p = 0.001) in 3 months compared to patients in the former group while there was no statistically significant difference in the overall survival between the two treatment modality groups (10.4 months for SRS alone versus 7.4 months for WBRT plus SRS, HR = 1.02, 95% CI = 0.75–1.38, p = 0.92), highlighting once again the negative impact of WBRT on the cognitive function of the patients.[21] Consequently, SRS could provide an alternative option of postoperative administration of radiation in patients with one resected brain

metastasis-a treatment option that would have similar efficacy to WBRT while sparing the above-mentioned, detrimental, WBRT-associated toxicities.

Nevertheless, only recently has postoperative SRS been directly compared with postoperative WBRT in patients with brain metastases in RCTs, cohorts, and meta-analysis of retrospective studies. Lamba et al, in their meta-analysis of eight retrospective with 646 patients with 1–3 brain metastases, concluded no difference in the local (RR = 0.59, 95% CI = 0.32–1.09, p = 0.36) and distant recurrence incidence (RR = 1.09, 95% CI = 0.74–1.60, p = 0.13) as well as in the overall survival (RR = 0.63, 95% CI = 0.40–1.00, random-effect model) between the two treatment strategies. However, postoperative SRS was associated with a three-fold risk for leptomeningeal disease development (RR = 2.99, 95% CI = 1.55–5.76).[22] Within the last 5 years, two RCTs comparing postoperative SRS with postoperative WBRT in patients with 1–4 brain metastases were published. Brown et al, in their study with 194 patients (SRS:98, WBRT:96), reported that despite the inferiority of SRS in securing local control (80,4% vs 87,1% WBRT at 6 months, p = 0.00068) and distant brain control (72,1% vs 94,6%, p = 0.00045), there was no statistically significant difference in the median overall survival (SRS:12.2 months vs WBRT: 11.6 months, HR = 1.07, 95% = 0.76–1.50, p = 0.70). Additionally, patients treated with adjuvant SRS experienced significantly less cognitive deficits at 6 months (41% vs 52% WBRT, p < 0.00031) and significantly higher median cognitive-deterioration-free survival (3.7 months vs 3.0 months WBRT, HR = 0.47, 95% CI = 0.35–0.63, p < 0.0001).[23] Similarly, in the non-inferiority RCT of Kayama et al in patients with 1–4 resected brain metastases, although SRS was associated with lower median intracranial progression-free survival (4.0 months vs 10.4 months WBRT, HR = 1.91, 95% CI = 1.46–2.51), no inferiority of SRS was detected in terms of median overall survival (15.6 months in both groups, HR = 1.05, 90% CI = 0.83–1.33, one-sided p for noninferiority = 0.027). Interestingly, regarding the cognitive and performance status of the patients, SRS failed to show superiority at 12 months (nonworsening MMSE score at 12 months: 42.5% SRS vs 45.3% WBRT; nonworsening performance status score at 12 months: 46.3% SRS vs 46.0% WBRT), which was attributed to the short follow-up period for detecting cognitive deterioration.[24]

The findings of our study, which is the first of its kind focusing solely on patients with one brain metastasis, are in line with the results of the above-mentioned clinical trials. Even though SRS may not be as effective as WBRT in terms of distant brain control, it does not appear to compromise patients' overall survival; At the same time, it protects them from the WBRT-related long-term cognitive deterioration. The increased risk of distant recurrence underlines the necessity of a close follow-up with regular MRI scans every 2–3 months, which has been recommended previously.[25]

5. Limitations and strengths

One major limitation of our systematic review and meta-analysis is the different types of the included studies: two are RCTs and two are retrospective studies. This may account for the substantial heterogeneity we encountered during the synthesis of our results. Moreover, the studies we incorporated comprised patients with different primary tumor sites-lung being the most common. Since it is well-established that some distinct subtypes, including melanoma and colon cancer, are notoriously radioresistant for WBRT,[26] this might have impacted our results. Regarding the extent of the resection cavity, the median extent was 3, 57 cm, while two studies[10,13] did not provide any information on this. This is probably of importance as larger tumor volume has been associated with an increased risk of local recurrence[27] and distant brain failure.[28] Additionally, the type of surgical resection ("en bloc" resection versus piecemeal) is not reported, although piecemeal excision of brain metastasis appears to increase the risk of leptomeningeal disease [29,30]. In terms of neurocognition, none of the included studies mentioned whether they implemented any preventive measures of WBRT-associated

neurocognitive decline, such as hippocampal sparing or usage of memantine. Finally, all studies focused on patients with a relatively good preoperative performance status, as indicated by their Eastern Cooperative Oncology Group or Karnofsky performance status scores (ECOG = 0–1 or Karnofsky≥70).

Notwithstanding the aforementioned limitations, our study represents the first of its kind to focus exclusively on patients with a single brain metastasis. Additionally, the implementation of both fixed and random effect models in our quantitative analysis aided to correct heterogeneity when appropriate, making our results even more reliable. Although there was no statistical difference between the two radiation modalities in the assessed outcomes (local and distant recurrence, leptomeningeal disease, overall survival and neurocognition), some tendencies were observed; These tendencies could be confirmed or dismissed in future, large-scale prospective studies.

6. Conclusion

The results of our study indicate that SRS may be a viable alternative postoperative radiation modality to the classical WBRT in patients diagnosed with solitary brain metastasis who have a good preoperative performance. Although SRS may increase the risk of distant brain failure compared to WBRT, it appears to be as effective as WBRT in terms of local control, risk of leptomeningeal disease, and overall survival while sparing the patients of the detrimental, WBRT-associated cognitive deterioration.

Authors contributions

N.V., M.G.L. and P.F. equally participated in the database search and data collection and extraction. All authors co-wrote the manuscript. S.V. and G.A.A. conceived and supervised the study and gave the final approval.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012; 14(1):48–54. https://doi.org/10.1007/s11912-011-0203-y.
2. Wu A, Colón GR, Lim M. Quality of life and role of palliative and supportive care for patients with brain metastases and caregivers: a review. *Front Neurol*. 2022;13, 806344. https://doi.org/10.3389/fneur.2022.806344. Published 2022 Feb 17.
3. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline [published correction appears in J clin oncol. 2022 apr 20;40(12):1392]. *J Clin Oncol*. 2022;40(5):492–516. https://doi.org/10.1200/JCO.21.02314.
4. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322(8):494–500. https://doi.org/10.1056/NEJM199002223220802.
5. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040–1048.
6. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17): 1485–1489. https://doi.org/10.1001/jama.280.17.1485.
7. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004; 363(9422):1665–1672. https://doi.org/10.1016/S0140-6736(04)16250-8.
8. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483–2491. https://doi.org/10.1001/jama.295.21.2483.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009; 6(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.

10. Kępka L, Tyc-Szczepaniak D, Bujko K, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: results from a randomized trial. *Radiother Oncol.* 2016;121(2):217–224. https://doi.org/10.1016/j.radonc.2016.10.005.

11. Kerschbaumer J, Pinggera D, Holzner B, et al. Sector irradiation vs. Whole brain irradiation after resection of singular brain metastasis-A prospective randomized monocentric trial. *Front Oncol.* 2020;10, 591884. https://doi.org/10.3389/fonc.2020.591884. Published 2020 Nov 24.

12. Hashimoto K, Narita Y, Miyakita Y, et al. Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e475–e480. https://doi.org/10.1016/j.ijrobp.2011.02.016.

13. Salvati M, Cervoni L, Caruso R, Gagliardi FM. Solitary cerebral metastasis from melanoma: value of the 'en bloc' resection. *Clin Neurol Neurosurg.* 1996;98(1):12–14. https://doi.org/10.1016/0303-8467(95)00077-1.

14. Patchell RA. The management of brain metastases. *Cancer Treat Rev.* 2003;29(6): 533–540. https://doi.org/10.1016/s0305-7372(03)00105-1.

15. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. *Surg Neurol Int.* 2013;4(Suppl 4):S236–S244. https://doi.org/10.4103/2152-7806.111301. Published 2013 May 2.

16. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. *Radiat Oncol.* 2012;7:77. https://doi.org/10.1186/1748-717X-7-77. Published 2012 May 28.

17. Liu Q, Tong X, Wang J. Management of brain metastases: history and the present. *Chin Neurosurg J.* 2019;5:1. https://doi.org/10.1186/s41016-018-0149-0. Published 2019 Jan 18.

18. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037–1044. https://doi.org/10.1016/S1470-2045(09)70263-3.

19. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* 2011;29(2): 134–141. https://doi.org/10.1200/JCO.2010.30.1655.

20. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer.* 2012;118(9):2486–2493. https://doi.org/10.1002/cncr.26515.

21. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA.* 2016;316(4):401–409. https://doi.org/10.1001/jama.2016.9839 [published correction appears in JAMA. 2018 Aug 7;320(5):510].

22. Lamba N, Muskens IS, DiRisio AC, et al. Stereotactic radiosurgery versus whole-brain radiotherapy after intracranial metastasis resection: a systematic review and meta-analysis. *Radiat Oncol.* 2017 Jun 24;12(1):106. https://doi.org/10.1186/s13014-017-0840-x.

23. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017;18(8):1049–1060. https://doi.org/10.1016/S1470-2045(17)30441-2.

24. Kayama T, Sato S, Sakurada K, et al. Effects of surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JCOG0504): a phase III, noninferiority, randomized controlled trial [published online ahead of print, 2018 jun 20]. *J Clin Oncol.* 2018, JCO2018786186. https://doi.org/10.1200/JCO.2018.78.6186.

25. Minniti G, Niyazi M, Andratschke N, et al. Current status and recent advances in resection cavity irradiation of brain metastases. *Radiat Oncol.* 2021;16(1):73. https://doi.org/10.1186/s13014-021-01802-9. Published 2021 Apr 15.

26. Khan M, Arooj S, Li R, et al. Tumor primary site and histology subtypes role in radiotherapeutic management of brain metastases. *Front Oncol.* 2020;10:781. https://doi.org/10.3389/fonc.2020.00781. Published h2020 Jul 7.

27. Patel AJ, Suki D, Hatiboglu MA, et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg.* 2010;113(2):181–189. https://doi.org/10.3171/2009.11.JNS09659.

28. Yu C, Chen JC, Apuzzo ML, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. *Int J Radiat Oncol Biol Phys.* 2002;52(5): 1277–1287. https://doi.org/10.1016/s0360-3016(01)02772-9.

29. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg.* 2008;108(2):248–257. https://doi.org/10.3171/JNS/2008/108/2/0248.

30. Suki D, Hatiboglu MA, Patel AJ, et al. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. *Neurosurgery.* 2009;64(4):664–676. https://doi.org/10.1227/01.NEU.0000341535.53720.3E.