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Original Article

Stereotactic radiosurgery versus whole-brain radiotherapy in patients with 4–10 brain metastases: A nonrandomized controlled trial

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ABSTRACT

Background and Purpose: There is no randomized evidence comparing whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) in the treatment of multiple brain metastases. This prospective non-randomized controlled single arm trial attempts to reduce the gap until prospective randomized controlled trial results are available.

Material and Methods: We included patients with 4–10 brain metastases and ECOG performance status ≤ 2 from all histologies except small-cell lung cancer, germ cell tumors, and lymphoma. The retrospective WBRT-cohort was selected 2:1 from consecutive patients treated within 2012–2017. Propensity-score matching was performed to adjust for confounding factors such as sex, age, primary tumor histology, dsGPA score, and systemic therapy. SRS was performed using a LINAC-based single-isocenter technique employing prescription doses from 15-20Gyx1 at the 80% isodose line. The historical control consisted of equivalent WBRT dose regimens of either 3Gyx10 or 2.5Gyx14.

Results: Patients were recruited from 2017–2020, end of follow-up was July 1st, 2021. 40 patients were recruited to the SRS-cohort and 70 patients were eligible as controls in the WBRT-cohort. Median OS, and iPFS were 10.4 months (95%-CI 9.3-NA) and 7.1 months (95%-CI 3.9–14.2) for the SRS-cohort, and 6.5 months (95%-CI 4.9–10.4), and 5.9 months (95%-CI 4.1–8.8) for the WBRT-cohort, respectively. Differences were non-significant for OS (HR: 0.65; 95%-CI 0.40–1.05; P =.074) and iPFS (P =.28). No grade III toxicities were observed in the SRS-cohort.

Conclusion: This trial did not meet its primary endpoint as the OS-improvement of SRS compared to WBRT was non-significant and thus superiority could not be proven. Prospective randomized trials in the era of immunotherapy and targeted therapies are warranted.

Whole-brain radiotherapy (WBRT) was the only radiation-based treatment option for brain metastases (BM) until the early 2000s, when stereotactic radiosurgery (SRS) was introduced as an alternative intervention for a limited number of BM (mostly defined as 1–3). Three randomized trials established this paradigm shift. Aoyama et al. showed that an additional WBRT treatment did not improve overall survival (OS) compared to SRS alone [1,2]. Two subsequent studies by Chang and Brown et al. reported similar results, but also demonstrated that neurocognitive outcome worsened significantly for patients treated with additional WBRT. As these studies showed similar OS but fewer neuro-cognitive adverse

Abbreviations: AE, adverse events; BM, brain metastases; CSH, cause-specific hazard; CTCAE, common terminology criteria for adverse events; CT, computed tomography; ECOG, eastern cooperative oncology group; iPFS, intracranial progression free survival; IPW, propensity score-based inverse weighting; MRI, magnetic resonance imaging; OAR, organs at risk; OS, overall survival; PTV, planning target volume; SRS, stereotactic radiosurgery; SH, subdistribution hazard; WBRT, whole-brain radiotherapy.

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events (AEs), SRS alone is currently recommended for patients with a limited number of BM [3–5].

In 2014, Yamamoto et al. published a prospective cohort analysis in which they examined the impact of the total number of BM treated with SRS. They compared patients treated with 5–10 BM to those treated with < 5 BM [6]; while patients with a singular/solitary BM had the most favorable median OS (13.9 months), the cohort with 5–10 BM was comparable to the group with 2–4 BM in terms of median OS (both 10.8 months) [6]. Furthermore, non-inferiority of AEs for patients treated with 5–10 BM was seen in their 2017 follow-up analysis [7].

Since their pioneering publication, no randomized trials comparing SRS to WBRT for multiple BM have been published. According to clinicaltrials.gov a few randomized trials are underway (NCT04891471, NCT03775330, NCT04277403, NCT03550391, NCT01592968), but will not be completed until 2023. A Dutch group attempted to conduct a phase III trial but the study was terminated early due to poor recruitment (29 of 230 required patients) as patients and/or their clinicians favored SRS over WBRT [8].

At ASTRO 2020, Li et al. presented some results of their multicenter US phase III trial comparing SRS and WBRT in patients with 5–15 BM, which also closed prematurely after recruiting 72 patients. However, they showed that the 36 patients in the SRS cohort had significantly superior neurocognitive performance with comparable median OS [9].

Based on the available data, the EANO-ESMO guideline published in 2021 summarized that SRS for a higher number of BM (4–10) "may be considered" up to a total tumor volume of 15 ml [10]. To address this lack of evidence, randomized data are urgently needed.

On the other hand, WBRT is currently optimized in multiple ways including simultaneous or sequential boosts, hippocampal sparing, concomitant application of memantine, or reducing the WBRT dose while boosting metastases [11–13]. Nevertheless, as demonstrated by the failure of randomized studies, obtaining class I evidence is problematic because SRS is already routinely offered by many centers to patients with multiple BM.

At the Department of Radiation Oncology, University Hospital, LMU Munich, WBRT has been the treatment of choice in all patients with 4–10 BM until 2017. From 2017, all patients were treated with SRS. To identify a median shift in OS between the patients treated with SRS and our historical WBRT patients an, we designed a non-randomized prospective controlled trial with identical selection criteria.

Materials and methods

Study design and recruitment

This study has been designed as a prospective, monocentric, nonrandomized study with matched historical controls. The goal was to compare SRS to WBRT in patients with 4–10 BM. The patients receiving SRS were recruited prospectively, the patients receiving WBRT were retrospectively obtained from the department's database. The primary endpoint was OS and the secondary endpoint intracranial progression free survival (iPFS). Results were reported using the TREND-checklist (Transparent Reporting of Evaluations with Nonrandomized Designs).

Before study initiation, the protocol was approved by the LMU Munich ethics committee (Nr. 436–16). The study was registered at the German clinical trials registry (DRKS00014694). Recruitment of the prospective cohort started in October 2017 when we changed the departmental treatment guidelines for SRS in patients with > 3 BM, and ended in September 2020. Last follow-up was on July 1st, 2021. For the retrospective cohort, the clinical database was screened for patients treated between 2012 and 2017.

Radiation treatment planning and dose delivery

For treatment planning of SRS, both thin-sliced (1 mm) contrast-enhanced computed tomography (CT) simulation as well as magnetic resonance imaging (MRI) were performed. Patients were immobilized using dedicated thermoplastic mask systems. Metastases and organs at risk (OAR) were delineated using the Elements Multiple Brain Mets® SRS application (Brainlab, Munich, Germany), a 1 mm isotropic margin was used to generate the planning target volume (PTV). The dose was prescribed to each PTV separately depending on the respective size and proximity to OARs ranging from 15 Gy to 20 Gy/80%-isodose line and adapted according to the number of BM by 1 Gy [14]. Treatment planning was performed either with the same application for single isocenter dynamic conformal arc therapy plans (SIDCA) or Monaco® (ELEKTA, Stockholm, Sweden) for volumetric conformal arc therapy (VMAT) [15,16] based on sphericity of the BM [17]. SRS was administered on a VersaHD® (ELEKTA, Stockholm, Sweden) linear accelerator equipped with ExacTrac® (Brainlab, Munich, Germany) for Image Guidance. Positioning deviations were corrected using a robotic couch HexaPOD® evo RT (ELEKTA, Stockholm, Sweden) in 6 DOF [18]. The historical control consisted of WBRT dose regimens of either 3Gyx10 or 2.5Gyx14, all after CT simulation and 3D-conformal radiotherapy planning.

Eligibility criteria

In addition to general inclusion criteria (written informed consent; age $\geq$ 18; eastern cooperative oncology group (ECOG) performance scale of $\geq$ 2; mental and legal capacity to understand the trial), patients with 4–10 BM with a diameter of 0.3 to 2.5 cm as measured on contrast-enhanced MRI were eligible for the study.

Exclusion criteria included a histology of lymphoma, germ cell tumor, or small cell lung cancer, pregnancy, inability to undergo an MRI examination, leptomeningeal disease, or participation in conflicting clinical trials. The retrospective WBRT cohort was selected by applying the same inclusion/exclusion criteria.

Data collection and Follow-Up

After treatment, patients had follow-up visits every three months until death or end of study. Follow-up consisted of clinical and neurological examination, and thin-sliced (1 mm) contrast-enhanced MRI. Clinical AEs were documented using the common terminology criteria for adverse events (CTCAE) v4.0. MRI findings were documented according to the RANO criteria [19].

In case of suspected progressive disease, fluoroethyl-L-tyrosine positron emission tomography [20], stereotactic biopsy or, immediate resection were considered to differentiate between radiation induced effect or progressive disease. If new BM were found, salvage SRS was offered [21]. For the WBRT-cohort, the same data were assessed retrospectively from patient files and external reports.

Statistics

Data were analyzed using R (release 4.1.2). Fisher's exact and Mann-Whitney test were used to compare both groups with respect to categorical and quantitative covariates, respectively.

For OS and iPFS, the Kaplan-Meier method was used to provide estimates of survival probabilities and median (progression-free) survival times since study-RT. The median follow-up time was calculated with the reverse Kaplan-Meier method. Groups were com-

pared using the logrank test, the Wald test in a univariable Cox model and in a multivariable Cox model adjusting for sex, age, primary tumor, dsGPA score, and systemic therapy.

The initial sample size calculation was done with ADDPLAN® neo (Version 10.0.4, Berry Consultants, Austin, Texas, USA) and based on the primary OS endpoint. The historical WBRT-cohort was planned to be identically selected from consecutive patients. At a two-sided significance level of 5% and with a 1:2 group size ratio, a total number of 99 events (deaths) across the two groups allows to detect with a power of 80% an increase in median OS from 6 months (historical estimate) to 11 months (SRS) considered clinically relevant and to be expected by JLGK0901 results [6]. This increase corresponds to a hazard ratio of 0.55 under the assumption of exponential survival time distributions within groups. Due to expected censoring, the groups were intended to comprise 40 (SRS) and 80 (WBRT) patients.

Death without event was considered as competing risk for local recurrence of BM or intracranial distant failure to estimate their cumulative incidences (sub-distribution functions) and perform subdistribution hazard analyses with the package 'cmprsk' (version 2.2–11) and cause-specific hazard analyses.

As additional analyses, propensity scores (PS) were derived by fitting a logistic regression model with the following covariates: sex, age, primary tumor, dsGPA score, and systemic therapy. PS analyses were performed in four different ways: stratification, weighting, adjustment, and 1:1 matching (with the following matching algorithms successively: optimal, nearest neighbor or caliper) [22]; see Table S2 for details.

Results

In total, 40 patients (21 male (52.5%), 19 female (47.5%)) with overall 230 BM were included in the SRS-cohort and 70 patients (37 male (52.9%), 33 female (47.1%)) with 396 BM in the WBRT-cohort. For the WBRT-cohort, the case records of 599 patients treated between 2012 and 2017 were screened and 70 eligible cases identified (see Fig. 1).

Median age, median Karnofsky index, median dsGPA score and LungMolGPA score at study-RT were 66 years (range 33–84 years), 80% (range 50–100%), 1.5 (range 0–3.0) and 1.25 (range 0–2.5) (n = 24) for the SRS-cohort, and 62 years (range 47–94 years), 80% (range 60–100%), 1.5 (range 0–3.5) and 1.5 (range 0–3.5) (n = 41) for the WBRT-cohort, respectively. The most common primary diagnoses were lung cancer and melanoma, with 24/40 (60.0%) and 6/40 (15.0%) patients in the SRS-cohort, and 41/70 (58.6%) and 12/70 (17.1%) in the WBRT-cohort. All patients in the SRS-cohort received a cranial MRI before study-RT, whereas in the WBRT-cohort, 9/70 (12.9%) received no MRI but only a cranial contrast-enhanced CT. 34/40 (85%) SRS patients had extracranial metastases at time of RT and 54/70 (77.1%) in the WBRT-cohort. The tumor volume prior to RT was median 2.1 ml (range 0.1–9.6 ml) and 2.9 ml (range 0.2–12.9 ml) for the SRS and WBRT cohort, respectively. Concerning concurrent/sequential systemic

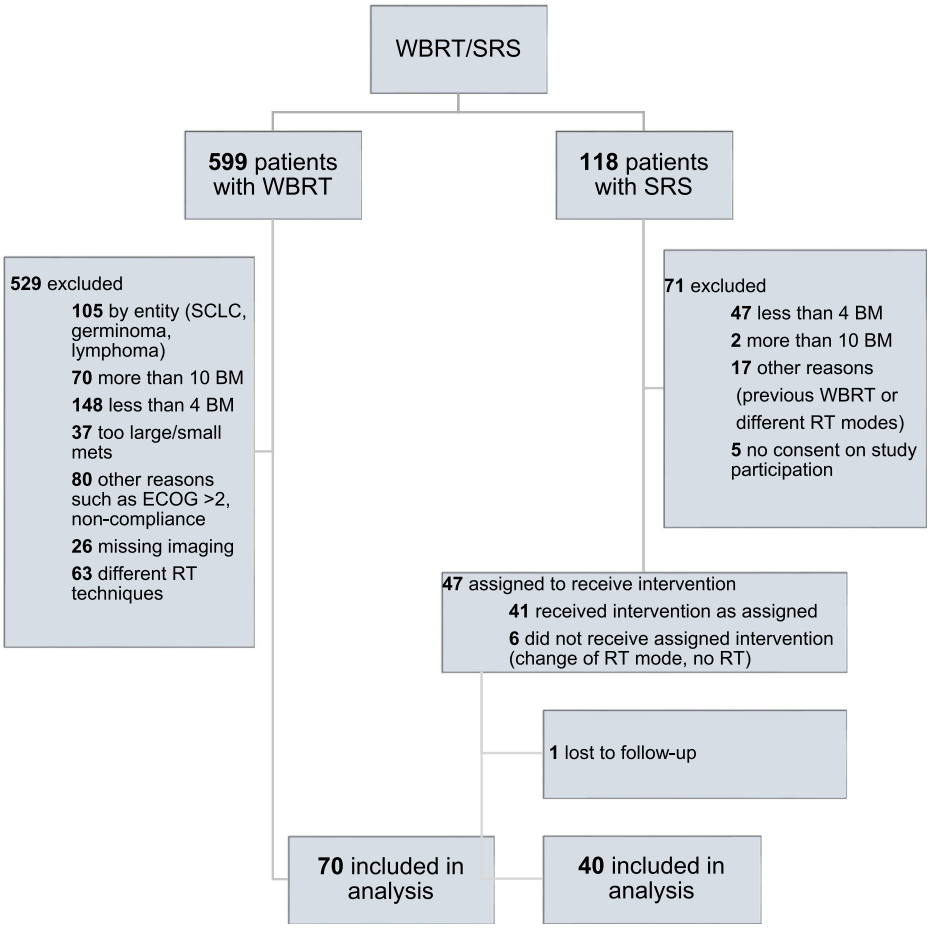

Fig. 1. Flow diagram of patient acquisition.

treatment, chemotherapy, targeted therapy, immunotherapy, or no systemic therapy were applied in 12/40 (30.0%), 4/40 (10.0%), 23/40 (57.5%), and 1/40 (2.5%) patients of the SRS-cohort, and 32/70 (45.7%), 9/70 (12.9%), 21/70 (30.0%), and 8/70 (11.4%) WBRT patients. Further patient characteristics can be found in Table 1.

Median follow-up was 21.6 months (95%-CI 19.8-NA) for the SRS-cohort and 61.4 months (95% 54.6-NA) for the WBRT-cohort. During follow-up, 25/40 (62.5%) SRS patients and 56/70 (80.0%) WBRT patients died. Six (8.6%) WBRT patients were lost to follow-up but none in the SRS-cohort.

Median OS was 10.4 months (95%-CI 9.3-NA) for the SRS-cohort and 6.5 months (95%-CI 4.9–10.4) for the WBRT-cohort. Local progression and new BM were diagnosed in 0/40 (0.0%) and 18/40 (45.0%) patients in the SRS-cohort and in 7/70 (10.0%) and 15/70 (21.4%) in the WBRT-cohort.

In the univariable Cox-model, the OS-comparison of SRS and WBRT was non-significant with a HR of 0.65 (95%-CI 0.40–1.05, P =.076). Similarly, the logrank test comparing OS of SRS versus WBRT missed statistical significance (P =.074). Median iPFS was comparable with 7.1 months (95%-CI 3.9–14.2) for the SRS-cohort and 5.9 months (95%-CI 4.1–8.8) for the WBRT-cohort (P =.28). Survival rates at 12 and 24 months were 48.2% and 33.4% in the SRS cohort versus 35.9% and 19.6% in the WBRT cohort. In the multivariable analysis, SRS turned out to be a significant predictor of OS with P <.001, HR 0.39 (95%-CI 0.22–0.68), as well as dsGPA with P <.001, HR 0.32 (95%-CI 0.21–0.48). The entire results using the multivariable Cox-model are shown in Supplementary Table S1.

As sensitivity analysis, the four widely used propensity score (PS) approaches (stratification, weighting, adjustment, matching) were implemented to mitigate the effect of confounding variables and enable a more balanced comparison between two groups (Supplement Table S2) [22]. The treatment continued to have a non-significant effect on OS in a stratified logrank test (P =.10) (Supplement Table S3). PS-based inverse weighting (IPW) yielded a non-significant result (P =.09) as well, whereas Cox regression using SRS as covariate while adjusting for PS yielded a significant benefit for SRS (P =.046) (Supplement Table S3) [23]. Optimal propensity matching was performed with adjustment for covariates displaying a standardized mean difference (SMD) > 0.1, resulting in multivariable Cox regression with a HR of 0.38 (95%-CI 0.21–0.68) and P =.001 (Supplement Table S4) [24]. The survival curves for the entire cohort and the pairwise matched data can be found in the top panels of Fig. 2. Supplementary Figs. S1a and S1b show the same survival curves when using other matching methods (nearest neighbor, caliper). The respective Table S5a + b lists the results of the corresponding multivariable Cox regression analyses.

As some patients of the WBRT-cohort did not receive cranial MRI before treatment, and therefore some important information (number of BM, leptomeningeal disease) might not have been adequately noticed on CT, a further sensitivity analysis was performed to detect the impact of these nine (12.9%) patients without MRI. When comparing the SRS-cohort with the reduced WBRT-cohort (N = 61) using the logrank test, the p-value changed to P =.037.

Subdistribution hazard (SH) and cause-specific hazard (CSH) analyses were performed considering local progression/new BM and death without local progression/new BM as competing risks (Fig. 3). SH analysis revealed that local progression was significantly less frequent for SRS than for WBRT ($\beta = -10.81$, HR = $2e^{-5}$, P <.0001). CSH analysis could not be performed for local progres-

Table 1
Patient characteristics in both cohorts and respective P values for group comparisons.

	SRS (n = 40)	WBRT (n = 70)	P-value
Sex			P = 1
Male (%)	21 (53)	37 (53)	
Female (%)	19 (48)	33 (47)	
Age at study-RT (median, range)	66 (33–84)	62 (47–94)	P =.21
Karnofsky Index (median, range)	80 (50–100)	80 (60–100)	P =.57
dsGPA score (median, range)	1.5 (0–3.0)	1.5 (0–3.5)	P =.41
LungMolGPA score (median, range)	1.25 (0–2.5) (n = 24)	1.5 (0–3.5) (n = 41)	P =.21
Primary diagnosis			P =.87
Lung cancer (%)	24 (60)	41 (59)	
Breast cancer (%)	1 (3)	4 (6)	
Melanoma (%)	6 (15)	12 (17)	
Gastrointestinal cancer (%)	2 (5)	5 (7)	
Other primary tumor (%)	7 (18)	8 (11)	
Time between primary diagnosis to BM in months (median, range)	9.3 (0.0–73.9)	6.3 (0.0–220)	P =.37
Time between diagnosis BM and RT in months (median, range)	0.9 (0.1–27.0)	0.9 (0.0–79.3)	P =.92
Treated BM			P =.79
4 (%)	11 (28)	23 (33)	
5 (%)	13 (33)	16 (23)	
6 (%)	3 (8)	10 (14)	
7 (%)	6 (15)	11 (16)	
8 (%)	4 (10)	4 (6)	
9 (%)	1 (3)	5 (7)	
10 (%)	2 (5)	1 (1)	
Tumor volume before RT (median, range, in ml)	2.1 (0.1–9.6)	2.9 (0.2–12.9)	P =.04
Extracranial metastases at time of RT			P =.46
Yes (%)	34 (85)	54 (77)	
No (%)	6 (15)	16 (23)	
Systemic therapy			P =.03
Chemotherapy (%)	12 (30)	32 (46)	
Targeted therapy (%)	4 (10)	9 (13)	
Immunotherapy (%)	23 (58)	21 (30)	
None (%)	1 (3)	8 (11)	

Abbreviations: WBRT, Whole-Brain Radiotherapy; SRS, Stereotactic Radiosurgery; BM, Brain metastases; RT, Radiotherapy; dsGPA, Disease-specific Graded Prognostic Assessment.

Table 2
Adverse events measured after SRS (N = 40).

Adverse event	Grade I (CTCAE) (n = 11)	Grade II (CTCAE) (n = 4)
	Number of patients (percent)	
Fatigue	10 (25)	1 (3)
Headache	5 (13)	-
Vertigo	8 (20)	-
Motor impairment	5 (13)	-
Sensory disturbances	1 (3)	-
Neurocognitive impairment	8 (20)	1 (3)
Seizure	1 (3)	1 (3)
Alopecia	2 (5)	1 (3)

sion as the SRS patients were all censored. For new BM, SH analysis revealed that the appearance of new BM in the follow-up was significantly more frequent in the SRS cohort than in the WBRT cohort (β = 1.03, HR = 2.79, P =.004). However, this effect was not significant in the corresponding CSH analysis (β = 0.67, HR = 1.96, P =.060) although in the same direction (more new BM in the SRS group), thus suggesting a possible moderate deleterious effect of SRS regarding the development of new BM. The reason for the higher frequency of new BM in the SRS group could be the therapeutic effect of WBRT.

Adverse events

Concerning toxicity, 15 (37.5%) patients reported mild to moderate AEs, 11 (27.5%) with CTCAE grade I, and four (10.0%) with CTCAE grade II AEs. The grade II events were all reported at the first follow-up, so they occurred within three months after SRS. The most notable grade II AEs were a seizure, and neurocognitive decline. The other two grade II AEs were severe fatigue and alopecia, of which the latter was caused by concurrent systemic therapy. Grade III toxicities were not reported in the SRS-cohort. More information on AEs can be found in Table 2.

Discussion

This study was designed to compare historical WBRT with SRS in patients with 4–10 BM. The primary endpoint of improved median OS for the SRS-cohort was not met, and adjustment for potential confounders through optimal propensity matching analysis or multivariable analysis revealed discordant results, which may be due to the limited sample size. As increasingly recommended in current literature on good statistical practice, we "conduct[ed] and report[ed] results for many analyses to determine whether results, as a whole, are consistent with the underlying hypothesis" [25]. The results were non-significant in the primary analysis, and only reached significance after optimal propensity matching. Med-

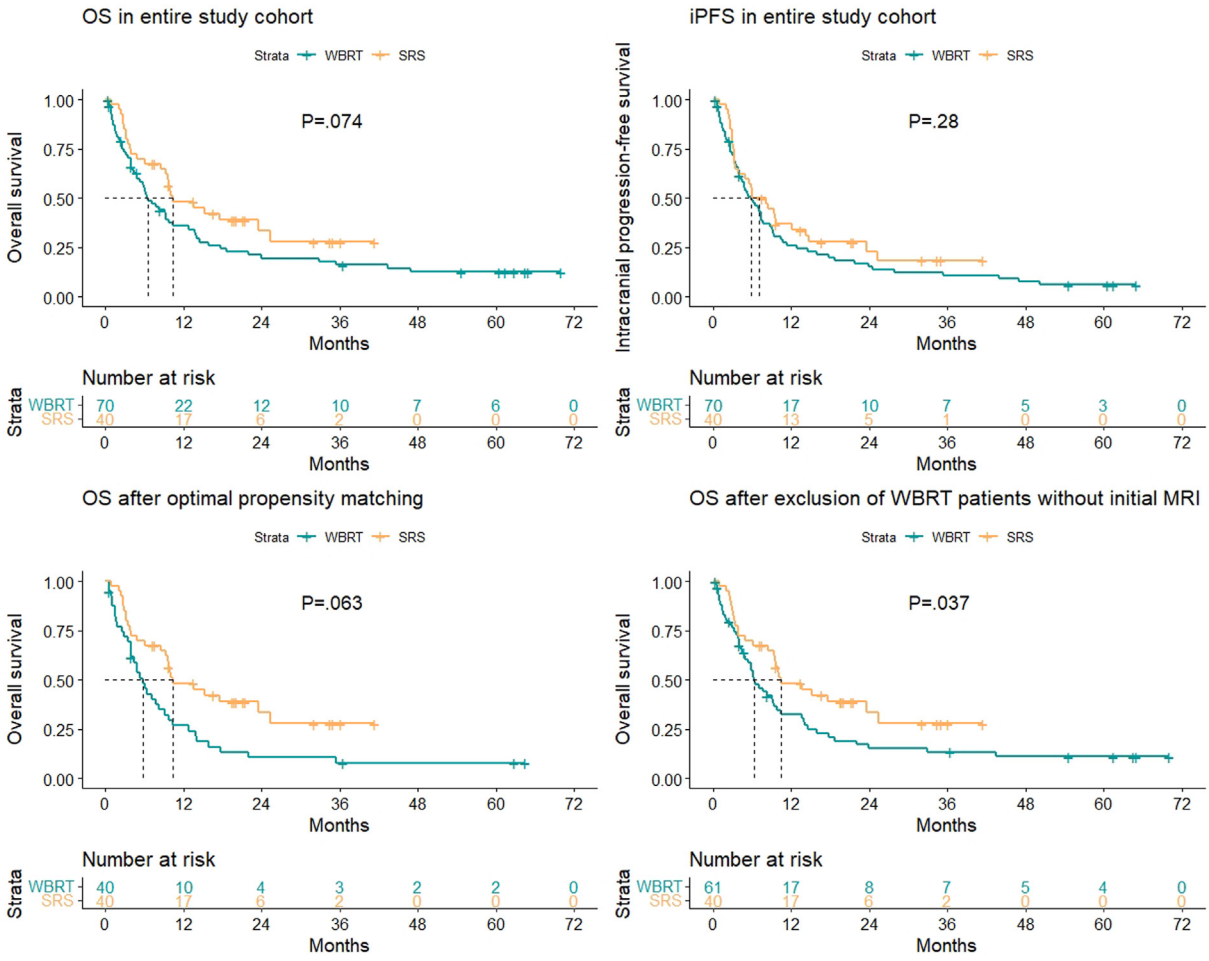

Fig. 2. Kaplan-Meier curves. Left upper panel: OS in the entire study cohort, right upper panel: intracranial progression-free survival in both cohorts, left lower panel: results after optimal propensity score matching, right lower panel: sensitivity analysis only focusing on patients with MRI.

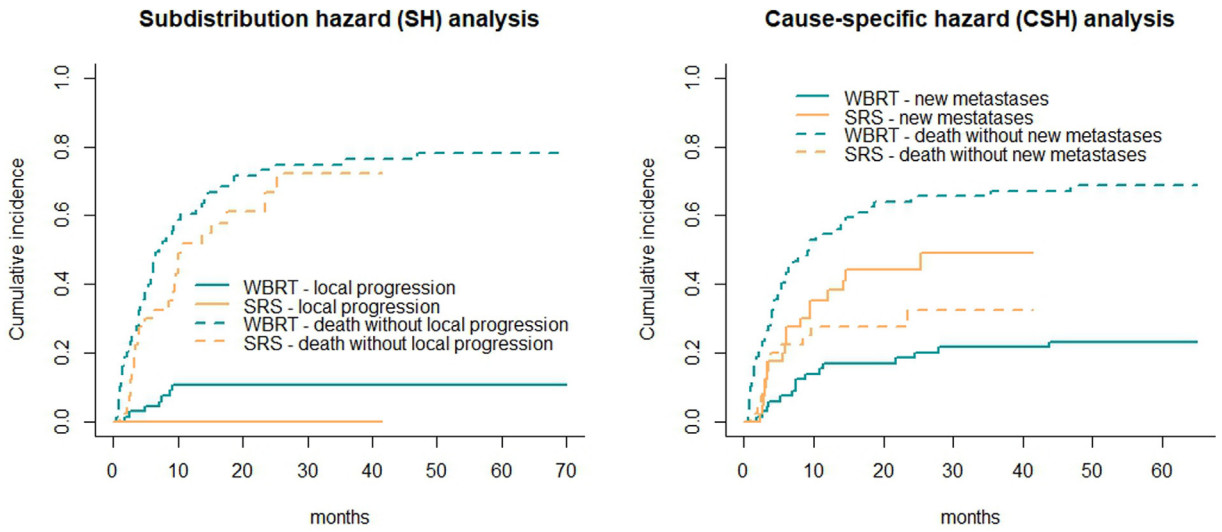

Fig. 3. Cumulative incidences for local progression (left) and new BM (right) in the SRS and WBRT cohorts. SH analysis revealed that local progression was significantly less frequent for SRS than for WBRT (HR = $2e^{-5}$, P <.0001). CSH analysis showed a near-significant effect for more new BM in the SRS group (HR = 1.96, P =.060).

ian survival differed hereby by four months. At the same time, the rate of new BM was increased within the SRS-cohort, which was probably due to increased survival rate and use of focal therapy. As recurrences can be adequately salvaged, this did not translate into a detrimental effect in terms of decreased survival rates. Toxicity was minimal while maintaining high local control rates. Furthermore, this trial can give guidance on linear accelerator based single isocenter SRS, target volume definition, need for non-coplanar imaging [18], as well as selection criteria according to number/size of lesions to be treated.

Our sample size calculation was based on the initial JLGK0901 results [6]. Based on its results, SRS of multiple BM became a potential treatment option for well-selected patients (ECOG < 2). For example, the ESMO-EANO/ASTRO guideline [26,27] recommendations refer to JLGK0901 and the multi-institutional analysis by Hughes et al. favoring SRS for up to 15 BM [28]. This has not been without criticism – selection bias, potential molecular factors in lung cancer metastases (EGFR mutation), low metastatic tumor burden, retrospective design in the latter, and other arguments have been raised [29].

There is still lack of high-level evidence allowing for recommendations of SRS over WBRT. The current study tries to reduce this gap – specifically as WBRT without additional application of memantine or hippocampal sparing may lead to neurocognitive decline [12].

Nonetheless, this monocentric study has several important limitations that need to be discussed critically. Primarily, this trial was not randomized, and only has a retrospective historical cohort as comparison, which makes confounding likely. Secondly, the trial was underpowered and had low sample size as the target size was calculated for 80 historical controls, but only 70 could be included. The historical dropout rate was higher than expected and the inclusion interval for the control group could not be extended, as the earliest time point was chosen a priori to avoid imbalances regarding targeted therapeutics and checkpoint inhibitors. Additionally, for patients in the WBRT-cohort having been treated early on, fewer systemic agents were available, which could have caused worse OS. Although patients treated before 2012 were not included to make both groups reasonably comparable, a certain time bias is obvious. These limitations make a clear interpretation of the data challenging.

Over the past 10 years, there have been significant changes in systemic therapies, which is reflected in the patient characteristics showing a shift toward more targeted and immunotherapeutic treatments. We tried to adjust for this difference by using dsGPA and the type of systemic therapy at the time of radiotherapeutic intervention. The matching algorithm was able to minimize existing differences among both groups, although baseline differences were quite small due to the fact that the patient cohort did not change, but WBRT was replaced by SRS with the initiation of the STEREOBRAIN trial.

Finally, a sensitivity analysis was performed as some of the WBRT patients had an oligometastatic state diagnosed by contrast-enhanced CT only. Fortunately, this small sub-cohort did not influence the overall result; nevertheless, this clarifies that prospectively included patients underwent a more rigid imaging protocol which was not mandatory for formerly WBRT treated patients. Therefore, all results must be regarded as result of a novel single-isocentric SRS approach plus regular MRI follow-up to detect novel lesions at the earliest possible time point.

As mentioned above, the limitations of this trial make a conclusion difficult. Next to the retrospective design, the partly contradicting results also do not allow clear statements. Partially significant results were reached after propensity matching; however, the results are not robust enough to show clear superiority of SRS regarding OS. The study at most suggests that SRS is not substantially inferior to WBRT, as the upper bound of the 95% CI of HR (0.40–1.05) is close to 1 and significant superiority would have been obtained using one-sided instead of two-sided testing. The main advantage of SRS still is its short treatment time, which does not interrupt systemic therapy in a meaningful way, and its low toxicity rate compared to conventional WBRT.

In the light of more effective CNS-penetrating systemic agents, risk adapted multi-metastatic SRS may be a future option with high potential and favorable risk profile. WBRT could still be indicated in patients with a higher number of BM or frail patients although these indications are also being challenged by recent publications [30,31]. Future studies will focus on comparing SRS to WBRT with simultaneous integrated boost with hippocampal sparing, especially regarding intracranial control and neurocognitive outcome such as the CCTG CE.7 (NCT03550391) or DFCI trial (NCT03075072).

Conclusion

The primary endpoint of superior OS of SRS compared to WBRT was not met as statistical significance was missed: HR = 0.65 (95%-CI 0.40–1.05), P =.074. A clear statement concerning the benefits of SRS can therefore not be derived from this study and still needs evidence from prospective randomized trials in near future. Despite this, SRS was safe with no grade III toxicities reported.

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Role of the Funder/Sponsor

Brainlab had no influence on data collection, analysis, interpretation of the results, review, or approval of the manuscript.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109744.

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