CLINICAL STUDY

A matched-pair analysis comparing stereotactic radiosurgery with whole-brain radiotherapy for patients with multiple brain metastases

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Abstract

Introduction Stereotactic radiosurgery (SRS) is an emerging treatment for patients with multiple brain metastases (BM). The present work compares the SRS of multiple brain metastases with whole-brain radiotherapy (WBRT).

Methods We performed a matched-pair analysis for 128 patients with multiple BM treated with either SRS or WBRT over a 5-year period. Patients were matched pairwise for seven potential prognostic factors. A mixed Cox Proportional Hazards model with univariate and multivariate analysis was fitted for overall survival (OS). Distant intracranial progression-free survival (icPFS) and local control were assessed using a Fine and Gray subdistribution hazard model and considering death as competing event.

Results Patients undergoing SRS had a median of 4 BM (range 3–16). 1-year local control of individual BM following SRS was 91.7%. Median OS in the SRS subgroup was 15.7 months (IQR 9.7–36.4) versus 8.0 months (interquartile range, IQR 3.8–18.0) in the WBRT subgroup (HR 2.25, 95% CI [1.5; 3.5], p < 0.001). Median icPFS was 8.6 (IQR 3.4–18.0) versus 22.4 (IQR 5.6–28.6) months, respectively (HR for WBRT 0.41, 95% CI [0.24; 0.71], p = 0.001). Following SRS, synchronous BM diagnosis (HR 2.51, 95% CI [1.30; 4.70], p = 0.004), higher initial number of BM (HR 1.21, 95% CI [1.10; 1.40], p = 0.002) and lung cancer histology (HR 2.05, 95% CI [1.10; 3.80], p = 0.024) negatively impacted survival. Excellent clinical performance (KPI 90%) was a positive prognosticator (HR 0.38, 95% CI [0.20; 0.72], p = 0.003), as was extracerebral tumor control (HR 0.48, 95% CI [0.24; 0.97], p = 0.040). Higher initial (HR 1.19, 95% CI [1.00; 1.40], p < 0.013) and total number of BM (HR 1.23, 95% CI [1.10; 1.40], p < 0.001) were prognostic for shorter icPFS.

Conclusion This is the first matched-pair analysis to compare SRS alone versus WBRT alone for multiple BM. OS was prolonged in the SRS subgroup and generally favorable in the entire cohort. Our results suggest SRS as a feasible and effective treatment for patients with multiple BM.

Keywords Multiple brain metastases · Radiosurgery · Neurologic function · Palliative · Radiotherapy · Whole-brain radiotherapy · Stereotactic · Linear accelerator · CyberKnife · Robotic

Introduction

Stereotactic radiosurgery (SRS) is the recommended treatment for patients with limited brain metastases, according to current guidelines [1, 2]. For patients with multiple brain metastases (BM), whole-brain radiotherapy (WBRT) is recommended. Recently, however, a large prospective observational trial by Yamamoto et al. could demonstrate overall survival to be non-inferior for patients with 5–10 BM, compared to patients with 2–4 BM when all lesions are treated with SRS instead of WBRT. Furthermore, their

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study showed that for the majority of patients who developed distant intracerebral recurrences after SRS, repeated SRS of new lesions was adequate salvage treatment [3].

The significant neurotoxicity and negative impact on quality of life associated with WBRT have been conclusively demonstrated in several phase-3 trials [4–6]. Thus, a strong rationale exists for the use of SRS over WBRT, where feasible and indicated.

Recent technical developments have facilitated the stereotactic treatment of multiple BM. Today, several different systems exist that allow high-dose conformity and steep dose gradients, combined with relatively time-efficient treatment and precise treatment application: Robotic radiosurgery with continuous motion tracking is the approach employed by the CyberKnife system (Accuray Inc., Sunnyvale California), while the Gamma Knife (Elekta, Stockholm, Sweden) was first in employing rigid fixation of the head within a stereotactic frame [7, 8]. Both methods have been well established for more than two decades, while more recently introduced systems are based on the use of single-isocenter volumetric modulated arc therapy (VMAT). Those systems provide enhanced treatment efficiency and are more widely available, while making some compromises in terms of dose conformity [9–11].

At our center, patients with up to ten simultaneous brain metastases have been treated with robotic SRS or hypofractionated stereotactic radiotherapy (HFSRT) from the beginning of 2016. To date, no prospective randomized trial exists for the comparison of SRS and WBRT in this setting. Retrospective analyses are prone to selection bias and a matched-pair design is one methodology capable of decreasing this risk [12]. The present work is the first to compare the SRS of multiple brain metastases with WBRT, performing a matched-pair analysis for a total of 128 patients treated at our institution.

Patients and methods

128 patients who received either SRS/HFSRT or WBRT for the initial treatment of multiple BM between 2015 and 2019 were included in this analysis. The SRS subgroup consisted of 64 patients with 3 to 16 BM per patient (maximum 10 BM per treatment session) and a total of 313 BM treated with CyberKnife SRS/HFSRT. The WBRT subgroup was identified from a cohort of 988 patients who received WBRT by individually matching patients 1:1 for seven potential prognostic factors. Patients were required to match for the following characteristics: age at radiotherapy, primary tumor, interval between initial diagnosis and diagnosis of BM, the presence of extracranial metastases, Karnofsky Performance Score index (KPI), initial number of BM and recursive partitioning analysis (RPA) class. Here, the seven

abovementioned characteristics, deemed to have the highest prognostic value, yielded the best compromise between exact matching, while maintaining an adequate sample size for analysis.

Patient and treatment data was extracted from a clinical database maintained at our institution and from medical and official records [13]. All reviews were performed following institutional guidelines and the Declaration of Helsinki of 1975 in its most recent version. Ethics approval for the study and a waiver of written informed consent was granted by the Heidelberg University ethics committee on April 12th, 2018 (#S-172/2018). Patient confidentiality was maintained by anonymizing patient data to remove any identifying information.

Patient and treatment characteristics

Median patient age at the beginning of radiotherapy (RT) was 60 years and the most common histology was nonsmall cell lung cancer (NSCLC), followed by breast cancer. Detailed patient characteristics are illustrated in Table 1 for the entire cohort and in Table 2 regarding the SRS and WBRT subgroups.

Treatment indication was discussed interdisciplinarily in the context of our institution's comprehensive cancer center. Regarding treatment allocation, it must be noted that the CyberKnife M6 was introduced to our center in early 2016, providing the necessary technical requirements for the SRS of multiple BM. An institutional paradigm shift followed, so that from that timepoint on, SRS was more frequently used instead of WBRT for the treatment of multiple BM. Whenever feasible, it was aspired to treat distant intracerebral recurrences after SRS with repeated SRS so that 50% of the patients in the SRS subgroup (n = 32) received more than one treatment course.

For all cranial RT, an individual thermoplastic head fixation mask was fitted for each patient. Treatment planning for SRS was based on high-resolution computed tomography (CT) and magnetic resonance imaging (MRI). Standardized imaging protocols were used for all patients, complying to the following specifications: CT scan was acquired with 1 mm slice thickness. MRI contained a contrast-enhanced, T1-weighted, three-dimensional sequence with multiplanar reconstruction and a slice thickness of ≤ 1 mm. The MRI was thoroughly co-registered and served as basis for target and organs at risk (OAR) delineation. Gross tumor volume (GTV) consisted of all contrasted tissue in the T1-weighted MRI. A safety margin of 1 mm was added to the GTV by isotropic expansion to create the planning target volume (PTV). Dose prescription was done according to metastasis size and in compliance with current guidelines [14, 15]. The most commonly prescribed margin doses were 20 or 18 Gy to the 70% isodose, covering at least 98% of the PTV

Table 1 Baseline characteristics of all patients in cohort (n = 128) and treatment/metastases characteristics in SRS subcohort (n = 64)

Patient characteristics	
Age at radiotherapy (years)	
Mean	59
Median	60
SD	10
Q1–Q3	52–66
Min.–max.	24–84
Gender	
Female	78 [60.9%]
Male	50 [39.1%]
Primary histology	
Lung cancer	52 [40.6%]
Breast cancer	24 [18.8%]
Melanoma	19 [14.8%]
Gynecologic	8 [6.3%]
Urologic	8 [6.3%]
Gastrointestinal	4 [3.1%]
Other	13 [10.2%]
Total number of BM	
3	64 [50.0%]
4–10	37 [28.9%]
> 10	27 [21.1%]
Diagnosis of BM	
Metachronous	86 [67.2%]
Synchronous	42 [32.8%]
Extracerebral tumor controlled	
No	77 [60.2%]
Yes	51 [39.9%]
Extracerebral metastases	
No	30 [23.4%]
Yes	98 [76.6%]
KPI at initial presentation for SRS (%)	
Median	80
Q1–Q3	80–90
Min.–max.	50–100
RPA class	
I	18 [14.1%]
II	102 [79.7%]
III	8 [6.3%]
GPA score	
2.5–4.0	10 [7.8%]
1.5–2.0	52 [40.6%]
0–1	66 [51.6%]
Treatment and metastases characteristics (SRS subgroup)	
Single BM volume (ccm)	
Mean	1.55
Median	0.29
SD	4.85
Q1–Q3	0.12–0.9

Table 1 (continued)

Min.–max.	0.01–38.77
Total summed volume of all BM per patient	
Mean	7.58
Median	3.33
SD	10.74
Q1–Q3	1.91–7.43
Min.–max.	0.32–56.65
Prescribed margin dose (Gy)	
18	17 [5.4%]
20	281 [89.8%]
30 (6 fractions)	13 [4.2%]
35 (7 fractions)	2 [0.6%]
Prescription isodose (%)	
70	284 [90.7%]
80–95	29 [9.3%]
Total number of BM per patient	
Mean	4.89
Median	4
SD	2.59
Q1–Q3	3–5
Min.–max.	3–16

KPI Karnofsky Performance Score Index, *RPA* recursive partitioning analysis, *GPA* graded prognostic assessment, *BM* brain metastases, *SRS* stereotactic radiosurgery

with a conformity index (CI) of < 1.1 as a planning objective. Lesions exceeding a maximum diameter of 3 cm were treated with HFSRT, most commonly 6 × 5 Gy to the 70% isodose. Treatment planning for CyberKnife was done in Accuray's Multiplan v5.3 and subsequent versions. Treatment was delivered using the CyberKnife M6 (Accuray Inc., Sunnyvale California). Details regarding SRS/HFSRT characteristics are illustrated in Table 1.

Treatment planning for WBRT was done in Oncentra External Beam v4.5 (Elekta, Stockholm Sweden) using a 3 mm computed tomography (CT). The prescribed dose for WBRT was 30 Gy in 10 fractions. In 6 selected cases (9.3%), an additional dose of 9 Gy in 3 fractions to large brain metastases was applied after three-dimensional conformal (3DCRT) treatment planning. Treatment was delivered at a linear accelerator using two laterally opposing fields for WBRT and multi-field technique for 3DCRT, as has been previously described [16, 17].

Statistical analysis

For baseline analyses, descriptive statistics are used, continuous variables are given as means (standard deviation, SD) and/or median (interquartile range (IQR) and range, as appropriate) and categorical variables as absolute and relative frequencies. The quantiles of the follow-up time were

Table 2 Distribution of patient characteristics between the two sub-cohorts after pair-matching

	WBRT sub-cohort		SRS subco-hort	
	n	%	n	%
Age at radiotherapy (years)				
< 65	44	[68.8%]	44	[68.8%]
≥ 65	20	[31.3%]	20	[31.3%]
Primary histology				
Lung cancer	26	[40.6%]	26	[40.6%]
Breast cancer	12	[18.8%]	12	[18.8%]
Other	26	[40.6%]	26	[40.6%]
Diagnosis of BM				
Metachronous	43	[67.2%]	43	[67.2%]
Synchronous	21	[32.8%]	21	[32.8%]
Extracerebral metastases				
No	15	[23.4%]	15	[23.4%]
Yes	49	[76.6%]	49	[76.6%]
KPI at initial presentation for SRS (%)				
≤ 70	12	[18.8%]	12	[18.8%]
80–100	52	[81.2%]	52	[81.2%]
Initial number of BM				
4	24	[37.5%]	24	[37.5%]
1–3	40	[62.5%]	40	[62.5%]
RPA class				
I	9	[14.1%]	9	[14.1%]
II	51	[79.7%]	51	[79.7%]
III	4	[6.3%]	4	[6.3%]

WBRT whole-brain radiotherapy, *SRS* stereotactic radiosurgery, *BM* brain metastases, *KPI* Karnofsky Performance Score Index, *RPA* recursive partitioning analysis

calculated using the reverse Kaplan–Meier method [18]. Overall survival was calculated from the beginning of RT to the date of death or last follow-up. Intracranial progression-free survival in the distant brain (icPFS) and local control (LC) were calculated from the beginning of RT to last imaging follow-up or confirmed progression. Overall survival was investigated using the method of Kaplan–Meier. To identify prognostic factors on overall survival, univariate and multivariate mixed Cox Proportional regression models were used. The matching ID was included as random effect to account for the matching procedure, the prognostic factors were included as fixed effects. To identify prognostic factors on LC and icPFS, Fine and Gray subdistribution hazard models with univariate and multivariate analysis were fitted for the cumulative incidence of progression, considering death as competing event. Variables with statistical significance in univariate analysis and those of special clinical interest were considered in multivariate regression. Since this was a retrospective exploratory data analysis, p-values

are of descriptive nature. A descriptive p-value of < 0.05 was considered as statistically significant. Statistical analyses were performed with the software *R Version 3.5.1*.

Results

Survival and prognostic factors

Median follow-up time for overall survival (OS), as estimated by the reverse Kaplan–Meier method (KM), was 35.8 months (IQR 24.6.7–41.3) for the entire cohort. At the time of this analysis, 120 patients had died, and 8 patients were still alive, corresponding to 0.49 (KM estimate; CI 0.41–0.59) survival probability at 12 months and 0.23 (KM estimate; CI 0.17–0.33) at 24 months. Survival significantly differed between the SRS and WBRT subgroups with a median OS of 15.7 months (IQR 9.7–36.4) in the SRS subgroup and 8.0 months (IQR 3.8–18.0) in the WBRT subgroup (hazard ratio (HR) for WBRT 2.25, 95% CI [1.5; 3.5], $p < 0.001$). Survival curves stratified by treatment modality are displayed in Fig. 1a.

Univariate and multivariate analysis were performed on both subgroups, as well as the entire cohort to assess potential prognostic factors. This was done independently for the endpoints of OS, as well as LC and icPFS. Covariates tested for prognostic significance were age, gender, timepoint of diagnosis of BM (within or later than three months after primary diagnosis), extracerebral tumor control, KPI, primary histology, initial number of BM, RPA class, and Graded Prognostic Assessment (GPA) score. In the SRS subgroup, where detailed information for every lesion was available, additionally the total number and volume of treated BM were included as covariates. Results of univariate analysis for the endpoint of OS are displayed in Table 3, showing hazard ratios and p-values only for significant covariates, and in Supplementary Tables 1–3, detailing all covariates. Prognosticators of OS differed between subgroups: In the SRS subgroup, synchronous BM diagnosis (HR 2.51, 95% CI [1.30; 4.70], $p = 0.004$), a higher initial number of BM (HR 1.21, 95% CI [1.10; 1.40], $p = 0.002$) and lung cancer histology (HR 2.05, 95% CI [1.10; 3.80], $p = 0.024$) negatively impacted survival, whereas excellent clinical performance (KPI 90%) was a positive prognosticator (HR 0.38, 95% CI [0.20; 0.72], $p = 0.003$), as was extracerebral tumor control (HR 0.48, 95% CI [0.24; 0.97], $p = 0.040$). In multivariate analysis, a higher initial number of BM stayed prognostic of inferior OS (HR 1.24, 95% CI [1.08; 1.42], $p = 0.002$). RPA score and GPA class showed no prognostic accuracy in this subgroup. For the WBRT subgroup, the univariate analysis yielded higher age (HR 1.03, 95% CI [1.00; 1.10], $p = 0.043$) and male gender (HR 2.01, 95% CI [1.20; 3.40], $p = 0.011$) as negative prognosticators for OS.
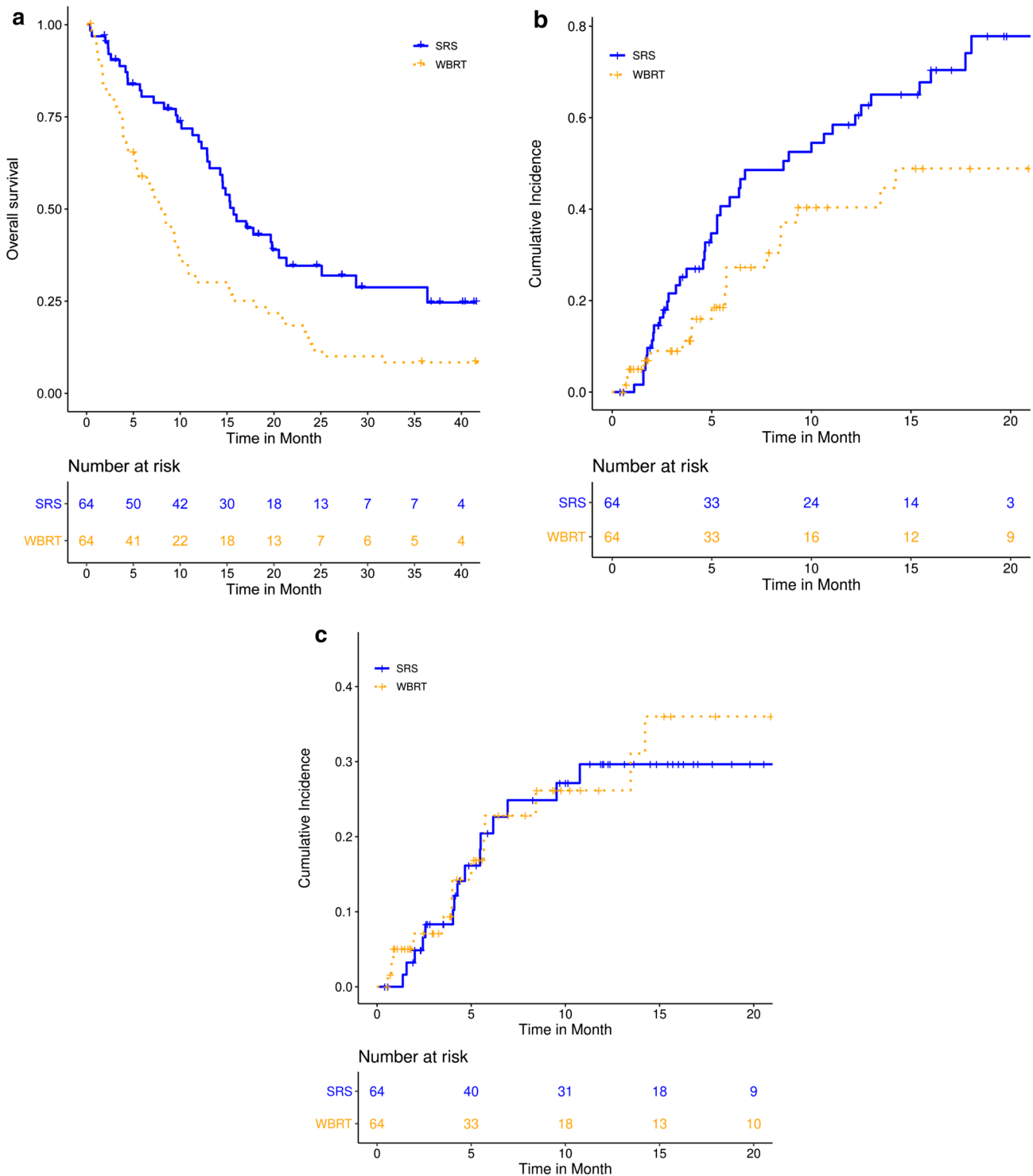
Fig. 1 Overall survival (**a**), distant intracranial progression-free survival (**b**) and local control (**c**) for 128 patients with multiple brain metastases treated with either stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT); overall survival was analyzed using the method of Kaplan–Meier, whereas for local and intracranial control, the cumulative incidence of failure is displayed, considering death as competing event

Table 3 Factors significant in univariate and multivariate cox regression for the endpoint of overall survival with corresponding hazard ratios and p-values

	HR	95% CI for HR	p
Univariate analysis			
SRS subcohort			
Synchronous BM diagnosis	2.51	1.30–4.70	**0.004**
Extracerebral tumor controlled	0.48	0.24–0.97	**0.040**
KPI ≥ 90%	0.38	0.20–0.72	**0.003**
Lung cancer	2.05	1.10–3.80	**0.024**
Initial number of metastases	1.21	1.10–1.40	**0.002**
WBRT subcohort			
Age at radiotherapy	1.03	1.00–1.10	**0.043**
Gender	2.01	1.20–3.40	**0.011**
RPA class 1	0.41	0.17–0.96	**0.040**
Boost	0.36	0.13–1.00	**0.053**
Combined cohort			
Age at radiotherapy	1.02	1.00–1.02	**0.047**
KPI ≥ 90%	0.57	0.37–0.88	**0.010**
RT modality	2.25	1.50–3.50	**< 0.001**
RPA class 3	2.43	1.10–5.50	**0.033**
Multivariate analysis			
SRS subcohort			
Synchronous BM diagnosis	2.00	0.83–4.80	0.123
Extracerebral tumor controlled	0.71	0.30–1.70	0.425
KPI ≥ 90%	0.51	0.25–1.00	0.061
Lung cancer histology	1.25	0.58–2.70	0.563
Initial number of metastases	1.24	1.10–1.40	**0.002**
WBRT subcohort			
Age at RT	1.02	0.99–1.10	0.172
Male gender	1.75	0.97–3.20	0.064
RPA class 1	0.55	0.20–1.50	0.225
Boost	0.51	0.16–1.60	0.261
Combined cohort			
KPI ≥ 90%	0.81	0.48–1.40	0.436
RT modality (WBRT)	2.16	1.30–3.50	**0.001**
RPA class 3	2.75	1.10–6.80	0.028

WBRT whole-brain radiotherapy, *SRS* stereotactic radiosurgery, *BM* brain metastases, *KPI* Karnofsky Performance Score Index, *RPA* recursive partitioning analysis

RPA class 1 was a positive prognosticator for OS (HR 0.41, 95% CI [0.17; 0.96], p = 0.040. Delivery of a boost to the largest metastases seemed to be a positive prognostic factor in univariate (HR 0.36, 95% CI [0.13; 1.00], p = 0.053), though not in multivariate analysis. Analyzing the entire combined cohort, treatment modality (SRS vs. WBRT) was the strongest prognosticator for OS with inferior outcome for WBRT (HR 2.25, 95% CI [1.5; 3.5], p < 0.001). Additional prognosticators for inferior OS were higher age at radiotherapy (HR 1.02, 95% CI [1.00; 1.02], p < 0.047) and RPA class 3 (HR 2.43, 95% CI [1.10; 5.50], p < 0.033). Excellent

clinical performance with a KPI of ≥ 90% was prognostic of superior OS (HR 0.57, 95% CI [0.37; 0.88], p < 0.010). In multivariate analysis, RT modality (HR 2.16, 95% CI [1.30; 3.50], p < 0.033) and RPA class 3 (HR 2.75, 95% CI [1.10; 6.80], p < 0.028) stayed prognostic of inferior OS. The time-point of first RT, which was included into analysis as a surrogate for differences in systemic treatment over time, did not relevantly influence OS in the SRS and WBRT subgroups or in the combined cohort.

Intracranial progression-free survival

Median follow-up time for icPFS in the distant brain, as estimated by the reverse Kaplan–Meier method, was 13.8 months (IQR 8.4–19.6) for the entire cohort. icPFS differed significantly between the SRS and WBRT subgroups with a median icPFS of 8.6 (IQR 3.4–18.0) months in the SRS subcohort and 22.4 (IQR 5.6–28.6) months in the WBRT subcohort (HR for WBRT 0.41, 95% CI [0.24; 0.71], p = 0.001). Results of the univariate and multivariate Fine and Gray subdistribution hazard model (death as competing event) for the endpoint of icPFS are displayed in Table 4 and Supplementary Tables 4–6, as well as Fig. 1b. In univariate analysis of the SRS subcohort, a higher total number of metastases was significantly associated with shorter icPFS (HR 1.24, 95% CI [1.10; 1.40], p < 0.001). A higher initial number (HR 3.02, 95% CI [1.40; 6.70], p = 0.007) and total number of metastases (HR 1.38, 95% CI [1.20; 1.60], p < 0.001) were independently prognostic for shorter icPFS in multivariate analysis. The effect of a higher number of metastases on shorter icPFS was similarly observed in the WBRT cohort (HR 3.48, 95% CI [1.30; 9.00], p = 0.010), as well as in the analysis of the combined cohort (HR 2.05, 95% CI [1.10; 3.70], p = 0.016) (detailed results displayed in Table 4). 6 patients (9.3%) in the WBRT subgroup received SRS as salvage therapy for newly occurring BM. 32 patients (50%) in the SRS subgroup received repeated radiosurgery for new BM; four patients from the SRS subgroup (6.3%) ultimately received salvage WBRT. The delivery of salvage therapy for new BM showed no statistically significant effect on OS in either subgroup, nor in the combined cohort (Supplementary Tables 1–3).

Local control

Local control was defined as stable or regressive contrast enhancement for all lesions visible prior to SRS or WBRT. Multivariate analysis revealed urologic histology to be associated with inferior LC in the SRS subgroup (HR 4.76, 95% CI [1.20; 18.00], p = 0.024). A higher initial number of BM was associated with inferior LC in the WBRT subgroup (HR 8.45, 95% CI [1.70; 43.00], p = 0.010) and in the analysis of the combined cohort (HR 4.21, 95% CI [1.50; 12.00],

Table 4 Factors significant in univariate and multivariate Fine and Gray subdistribution hazard model (death as competing event) for the endpoint of intracranial progression-free survival with corresponding hazard ratios and p-values

	HR	95% CI for HR	p
Univariate analysis			
SRS subcohort			
Total number of metastases	1.24	1.10–1.40	**< 0.001**
WBRT subcohort			
Initial number of metastases	3.27	1.20–9.20	**0.025**
Age at RT	0.96	0.92–1.00	**0.048**
Combined cohort			
Initial number of metastases	2.15	1.20–3.80	**0.010**
Melanoma histology	1.99	1.10–3.70	**0.032**
RT modality (WBRT)	0.41	0.24–0.71	**0.001**
Later RT date	1.77	1.10–3.00	**0.029**
Multivariate analysis			
SRS subcohort			
Synchronous BM diagnosis	1.14	0.47–2.80	0.770
Lung cancer histology	0.60	0.27–1.30	0.200
Initial number of metastases	3.02	1.40–6.70	**0.007**
Total number of metastases	1.38	1.20–1.60	**< 0.001**
WBRT subcohort			
Age at RT	0.95	0.91–1.00	**0.034**
Total number of BM	3.48	1.30–9.00	**0.010**
Combined cohort			
Initial number of metastases	2.05	1.10–3.70	**0.016**
RT modality (WBRT)	0.43	0.22–0.85	**0.016**
Later RT date	1.01	0.54–1.90	0.980

WBRT whole-brain radiotherapy, *SRS* stereotactic radiosurgery, *BM* brain metastases, *KPI* Karnofsky Performance Score Index, *RPA* recursive partitioning analysis

Table 5 Factors significant in univariate and multivariate Fine and Gray subdistribution hazard model (death as competing event) for the endpoint of local control with corresponding hazard ratios and p-values

	HR	95% CI for HR	p
Univariate analysis			
SRS subcohort			
Urologic histology	3.94	0.98–16.00	0.054
WBRT subcohort			
Age at RT	0.94	0.90–1.00	**0.049**
Initial number of BM	10.20	1.40–73.00	**0.020**
Combined cohort			
Initial number of BM	4.30	1.50–12.00	**0.006**
Multivariate analysis			
SRS subcohort			
Synchronous BM diagnosis	0.65	0.20–2.10	0.460
KPI ≥ 90%	0.35	0.10–1.20	0.097
Urologic histology	4.76	1.20–18.00	**0.024**
Total number of metastases	0.93	0.86–1.00	0.065
Initial number of metastases	3.05	0.96–9.70	0.058
WBRT subcohort			
Age at RT	0.95	0.88–1.00	0.082
Extracranial metastases	4.00	0.71–22.00	0.120
Lung cancer histology	0.44	0.10–1.90	0.270
Initial number of metastases	8.45	1.70–43.00	**0.010**
Combined cohort			
Age at RT	0.97	0.94–1.00	0.086
Extracranial metastases	2.41	0.83–7.00	0.110
Initial number of metastases	4.21	1.50–12.00	**0.007**

WBRT whole-brain radiotherapy, *SRS* stereotactic radiosurgery, *BM* brain metastases, *KPI* Karnofsky Performance Score Index, *RPA* recursive partitioning analysis

p = 0.007). Detailed results of the univariate and multivariate Fine and Gray subdistribution hazard model (death as competing risk) for the endpoint of LC are displayed in Table 5 and Supplementary Tables 7–9, as well as Fig. 1c.

For individual lesions treated with SRS, LC was 91.7% after 12 months. 26 of 313 treated lesions developed progressive contrast enhancement. In 8 cases, tumor progression was diagnosed on the basis of radiological workup and overall clinical evaluation; in the rest of the cases, radiation induced changes (RIC) were suspected. In 12 of the cases with suspected RIC, patients had received targeted systemic therapy with either pembrolizumab or afatinib during or following SRS. Neurosurgical resection was performed in two of those cases where diagnosis was uncertain, with pathology confirming the suspected radionecrosis and finding no vital tumor cells in the sample. Four additional cases were confirmed clinically, as contrast enhancement regressed again following treatment with dexamethasone and bevacizumab in analogy to the findings of Levin et al. [19].

Discussion

A growing body of literature has recently been published, reporting on patients with multiple BM treated with SRS. The largest cohort has been described by Yamamoto et al. in a prospective observational study (JLGK0901) and included 1194 patients with 1–10 BM [3, 20, 21]. Survival was found not to differ significantly between patients with 2–4 and 5–10 BM, yielding a median OS of 10.8 months for those patients. Survival rates of 7.5 to 10.5 months have been reported in other, mainly retrospective analyses [22–25]. Highly favorable survival rates exceeding 21 months (median OS not reached) have been reported in a carefully selected cohort of patients treated with repeated SRS [26]. At 15.7 months, the median OS found in the SRS subgroup of our analysis compares favorably to the figures reported in recent literature and surpasses the survival rates reported by Yamamoto et al. for the prognostically superior group with only one BM (median OS 13.9 months). Baseline characteristics in our analysis

were comparable to those in the JLGK0901 cohort, regarding cumulative BM volume per patient in particular, which was described as significant to OS [3, 27]. Other factors prognostic for OS included KPI, sex and especially extracerebral tumor control [3, 27]. The latter characteristics were confirmed as significant prognosticators in our analysis for the SRS subgroup and improved extracranial tumor control with the use of novel systemic agents probably contributing to the improved OS found in this analysis.

The OS rates reported in the four phase III trials comparing WBRT alone with WBRT + SRS for patients with 1–3 BM ranged between 6.5 and 10.4 months with a notable trend towards improved OS in the more recent trials [4, 5, 28, 29]. Since OS in those trials did not significantly differ between WBRT and WBRT + SRS, survival in the WBRT subcohort of the present analysis at 8.0 months falls within the expected range based on available data.

We found OS to be significantly longer for patients receiving SRS compared to WBRT. Although patients in this analysis were matched pairwise for seven potential prognostic factors, a residual selection bias cannot be eliminated as one possible reason for this difference. Typically, patients with a more favorable prognosis would be more likely selected to receive SRS instead of WBRT, whenever feasible. In clinical routine, this decision is based on the overall case constellation, considering established prognostic factors such as KPI and RPA / GPA scores, but also other aspects not herein represented, such as the extent of systemic tumor burden, comorbidities and the availability of systemic treatment options. The past years have seen notable improvements in OS for different histologies due to the advent of immunotherapy and similar targeted therapies [30–34]. Consequently, we hypothesized that an earlier timepoint of BM diagnosis could possibly have negatively influenced the systemic treatment patients received and indirectly overall prognosis. To better account for the influence of systemic treatment, on which comprehensive information was not available, we included the timepoint of treatment in our OS analysis as a surrogate parameter. Here, no relevant effect was observed, leading to the conclusion that in our analysis, the effect on OS of differing systemic therapies over time was less pronounced than originally assumed.

The factors chosen for pairwise matching have previously been prognostic for OS in prospective clinical trials and have been employed in several matched-pair analyses for patients with BM [12, 35–38]. However, those analyses have focused on patients receiving WBRT. It has been discussed that for patient collectives receiving SRS, established prognostic scores such as RPA and GPA might not be valid [39, 40]. Badakhshi et al. recently analyzed the validity of five established prognostic scores on a collective of 80 melanoma patients with BM treated with SRS and found that the prognostic accuracy was not ideal for this particular constellation [40]. Those results are plausible, particularly in the light of melanoma being among the entities for which overall prognosis was most decisively influenced by the introduction of immunotherapy [41]. Similarly promising early results have been shown regarding the CNS activity of Pembrolizumab in NSCLC with prolonged response of BM and improved OS and prospective trials on the subject are ongoing [42]. Melanoma and NSCLC patients made up for 65% of the patients in our analysis and in agreement with the data discussed above, we found low prognostic accuracy for the established RPA and GPA scores.

For patients receiving WBRT, the CNS spread is typically decisive for overall prognosis [28, 43, 44]. One reason lies in the dose of WBRT, which is limited by normal tissue tolerance and generally insufficient for lasting tumor control [12, 28]. In the case of intracerebral failure, which frequently occurs, options for salvage therapy are limited. On the contrary, doses applied during SRS are locally ablative and provide excellent local control of the irradiated lesion of around 90% after 12 months, as confirmed in our analysis [14, 45]. Additionally, subsequent to SRS, patients included in our analysis were typically followed up rigorously, including high-resolution MRI. Accordingly, the occurrence of new BM would receive timely salvage therapy, if feasible by repeated SRS. The consequence is a reduction of the impact of CNS spread on survival for SRS patients, since this CNS spread can be controlled by a combination of locally ablative doses and an effective means of salvaging newly occurring BM.

Median distant intracranial progression-free survival in the current analysis was 8.6 months following SRS and 22.4 months following WBRT, differing significantly between those subgroups. This finding is in agreement with previously published studies that have found the addition of WBRT to SRS to significantly improve intracranial progression-free survival, compared to SRS alone, though not overall survival [4, 6, 12, 28]. However, a randomized comparison of WBRT alone vs. SRS alone for patients with multiple BM, has not yet been done. We found a higher number of BM to be associated with inferior icPFS in the SRS and WBRT subgroups, as well as in the analysis of the combined cohort. Recently, Farris et al. proposed the brain metastasis velocity score (BMV) as a new metric to quantify the relationship between early distant brain failure and survival and similarly found a higher number of BM to be associated with a shorter interval to distant intracranial failure [46]. The BMV was subsequently validated by Yamamoto et al. in a cohort of 833 patients treated with repeated SRS [47].

Intracerebral failure following WBRT was predominantly local in our analysis (progression of pre-existing BM) and not due to new BM, suggesting that the dose of WBRT is insufficient to lastingly control macroscopic BM. Previous trials attempted to deliver a more adequate dose by

combining SRS and WBRT or adding a stereotactic boost to minimize the risk of local failure, which was not done in the WBRT subgroup of the current analysis [4, 6, 12, 28]. To assess the effect of local dose escalation in the context of WBRT, we examined the patients who received a boost of 3 × 3 Gy to larger BM. We found that the delivery of a boost positively affected OS in the WBRT subgroup in univariate analysis, though not in multivariate analysis. An effect on LC or icPFS could not be detected, since here again the number of BM seemed to play a more dominant role, as discussed above.

When assessing LC following SRS on the basis of MR imaging, caution for diagnostic uncertainties has to be applied in the interpretation of results. Available literature suggests that in up to 70% of the cases where progressive contrast enhancement is detected in MRI, it is possibly rather due to radiation-induced changes/radionecrosis, than due to real tumor progression [48–50]. To date, no reliable radiologic or clinical criteria exist to differentiate between necrosis and tumor progression, although proposed methods include measuring the T1/T2 ratio on MRI, employing positron emission tomography (PET) or radiomics analyses [49, 51–53]. On the basis of individual risk–benefit assessment, neurosurgical resection—and thus pathologic confirmation—is only performed in a small minority of cases, usually not exceeding 30% [48, 54]. In our analysis, the majority of cases (70%) with progressive contrast enhancement were attributed to radiation-induced changes and in 2 cases pathologic confirmation was obtained. Four additional cases were confirmed clinically, as contrast enhancement regressed again following treatment with dexamethasone and bevacizumab in analogy to the findings of Levin et al. (19).

Limitations of this analysis include its retrospective design with inherent selection bias, as well as the relatively small number of patients. Though a matched-pair design was chosen to minimize selection bias, as well as imbalances between treatment groups, a residual bias possibly remains, as was discussed in detail. A further limitation is the unavailability of detailed information regarding systemic treatments received concurrent to and following radiotherapy. With modern substances rapidly gaining relevance to the prognosis of BM, future analyses will have to be adjusted for this potential confounder.

Our analysis is strengthened by its rigorous matching of patients for prognostic factors to minimize bias. The use of a matched-pair design allowed for the consideration of seven prognostic factors, resulting in a higher number of matching variables than would have been possible e.g. with the use of a propensity score with respect to underlying sample size. Due to the high overall mortality in patient collectives with BM, accuracy of the assessment of local control endpoints is often limited in comparable analyses in literature. By considering death as a competing event in our analysis,

we have adequately addressed this caveat. Lastly, separate assessment of local and distant intracranial control allowed us to recognize differences in the primary pattern of failure following SRS or WBRT, as discussed above.

Conclusion

To the best of our knowledge and in the absence of a randomized trial, this is the first analysis to systematically compare SRS alone versus WBRT alone for multiple BM with means of matched-pair analysis. Irrespective of a possible residual selection bias, patient survival was prolonged in the SRS subgroup and generally favorable in the entire cohort. Prognostic factors for OS included the initial number of metastases, clinical performance, extracerebral tumor control, age and RPA class. WBRT prolonged distant brain control, though not improving survival. Intracranial failure was seen predominantly in irradiated lesions following WBRT and in the distant brain following SRS. Our results suggest SRS to be a feasible and effective treatment for patients with multiple BM.

Compliance with ethical standards

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