Received: 20 November 2023 | Revised: 6 February 2024 | Accepted: 20 February 2024

DOI: 10.1002/ijc.34980

IJC INTERNATIONAL JOURNAL of CANCER | UICC

RESEARCH ARTICLE

Cancer Therapy and Prevention

Stereotactic radiosurgery and radiotherapy for brainstem metastases: An international multicenter analysis

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Abstract

Brainstem metastases (BSM) present a significant neuro-oncological challenge, resulting in profound neurological deficits and poor survival outcomes. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) offer promising therapeutic avenues for BSM despite their precarious location. This international multicenter study investigates the efficacy and safety of SRS and FSRT in 136 patients with 144 BSM treated at nine institutions from 2005 to 2022. The median radiographic and clinical follow-up periods were 6.8 and 9.4 months, respectively. Predominantly, patients with BSM were managed with SRS (69.4%). The median prescription dose and isodose line for SRS were 18 Gy and 65%, respectively, while for FSRT, the median prescription dose was 21 Gy with a median isodose line of 70%. The 12-, 24-, and 36-month local control (LC) rates were 82.9%, 71.4%, and 61.2%, respectively. Corresponding overall survival rates at these time points were 61.1%, 34.7%, and 19.3%. In the multivariable Cox regression analysis for LC, only the minimum biologically effective dose was significantly associated with LC, favoring higher doses for improved control (in Gy, hazard ratio [HR]: 0.86, $p < .01$). Regarding overall survival, good performance status (Karnofsky performance status, ≥90%; HR: 0.43, $p < .01$) and prior whole brain radiotherapy (HR: 2.52, $p < .01$) emerged as associated factors. In 14 BSM (9.7%), treatment-related adverse events were noted, with a total of five (3.4%) radiation necrosis. SRS and FSRT for BSM exhibit efficacy and safety, making them suitable treatment options for affected patients.

KEYWORDS

brain metastasis, brainstem, fractionated stereotactic radiotherapy, radiosurgery, stereotactic radiosurgery

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What's New?

This international multicenter study investigates the impact of stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) on brainstem metastases (BSM). Our results, analyzing 136 patients with 144 BSM from nine institutions, underscore the long-term benefits in local control and the robust safety profile despite the delicate location of the treated metastases. Based on this analysis and review of other studies, the use of stereotactic radiotherapy for BSM in prospective SRS and FSRT trials appears justified.

1 | INTRODUCTION

Brain metastases represent a common and substantial neuro-oncological challenge, affecting 20%–40% of all cancer patients.[1] Brainstem metastases (BSM), constituting approximately up to 11% of all brain metastases, often lead to severe neurological deficits and particularly poor survival, with a median survival of only several months.[1–8] The brainstem houses crucial structures, including sensory and motor pathways, as well as multiple nuclei responsible for reflexes and cranial nerves.[9] Due to the intricate intracranial anatomy and its concealed central location, brainstem surgery is notably challenging.[10] Given the high risk of morbidity and mortality, resection for BSM is seldom considered.[2,6,7]

Historically, whole brain radiotherapy (WBRT) or fractionated radiotherapy, rather than stereotactic radiosurgery (SRS), were chosen as the preferred approaches due to the presumed lower radiation tolerance of the brainstem to high single doses.[1,7,11] In fact, earlier studies suggest a radiation brainstem tolerance of 12.5 Gray (Gy) in a single fraction, with other reports proposing max point doses of 15 Gy.[4,12–15] Consequently, BSM have often been excluded from radiosurgical studies for brain metastases due to concerns about inducing high-grade toxicity and potentially life-threatening brain injury.[16–20] However, with the improvement of focal and systemic therapies, patients may live longer to experience neurological deficits induced by WBRT, as well as local recurrences, and the recent literature suggests that radiosurgery is a reliable and presumably safe treatment option for BSM.[1–3,7,21,22]

Given the scarcity of comprehensive, multicenter analyses of stereotactic treatments for BSM, further exploration of the efficacy and safety of SRS and fractionated stereotactic radiotherapy (FSRT) is indicated. This international multicenter study aims to provide further evidence in the radiosurgical treatment of BSM and compares the results with the available literature.

2 | MATERIALS AND METHODS

This international retrospective multicenter analysis included patients treated with SRS or FSRT with up to five fractions for BSM. Included metastases had to be located in the pons, mesencephalon, or medulla oblongata, excluding surface metastases or those with presumed brainstem invasion from outside. All patients underwent SRS or FSRT utilizing robotic radiosurgery (CyberKnife, Accuray Inc., Sunnyvale, CA, USA). The prescription dose and the number of fractions were prescribed at the discretion of the managing physicians across the nine participating centers.

Biologically effective dose (BED) and the equivalent dose in 2 Gy fractions (EQD2) were calculated as previously described, assuming an α/β ratio of 10 Gy.[23] Patient follow-up encompassed both radiological and clinical assessments. Local control (LC) was defined as an unchanged or decreased tumor volume on follow-up imaging, while local failure (LF) was defined as an increased tumor volume during follow-up assessed by managing physicians and radiologists. Patients were censored on the last day of available imaging for radiographic follow-up and on the last clinical contact for clinical follow-up. Overall survival (OS) and progression-free survival (PFS) were calculated from the day of SRS or the first fraction of FSRT until death from any cause (OS and PFS) or disease progression at any site (LF, new intracranial, or extracranial disease). Patient data, including medical history, previous treatments, and follow-up, were collected from institutional databases and medical records. The diagnosis of radiation necrosis was based on imaging alone and included assessments by the managing physicians as well as neuroradiologists. Multivariable Cox proportional hazards models were used to evaluate the influence of relevant clinical variables on LC, PFS, and OS. Variable selection was done a priori based on the most relevant risk factors. In the case of the minimum, mean, and maximum BED, a moderate degree of collinearity of variables was tolerated for the investigation. The proportional hazards assumptions were tested using global tests based on Schoenfeld residuals and visual assessment of log–log plots. The goodness of fit was determined by plotting the Cox-Snell residuals against the Nelson-Aalen cumulative hazard.

Comparable studies on the use of SRS or FSRT for BSM were identified through a non-systematic search utilizing Medline/PubMed with various keyword combinations, including "brain metastasis," "brainstem metastasis," "stereotactic radiosurgery," "fractionated stereotactic radiotherapy," "SRS," and "FSRT." Data analysis was performed with STATA MP 17.0 (StataCorp, College Station, TX, USA). *P*-values equal to or less than .05 were considered significant. The graphical abstract was created with BioRender.com.

3 | RESULTS

A total of 136 patients with 144 BSM were analyzed. All treatments were conducted between 2005 and 2022. A total of 86 lesions were

located in the pons, 42 and 16 in the mesencephalon and the medulla oblongata, respectively. The most common primary tumor histologies were non-small cell lung cancer (NSCLC) ($n = 43$), breast cancer ($n = 43$), followed by malignant melanoma ($n = 12$), renal cell carcinoma ($n = 12$), and small cell lung cancer (SCLC) ($n = 12$). At the time of SRS or FSRT, 79 patients (58.0%) were diagnosed with additional brain metastases. A total of 35 patients (25.7%) underwent WBRT prior to BSM treatment, with a median time of 13.2 months until SRS or FSRT. One BSM was treated surgically before radiation (subtotal resection). The median time between cancer diagnosis and radiotherapy of the BSM was 28.0 months. The median Karnofsky performance status (KPS) before stereotactic radiotherapy was 90%, and the median age at the time of SRS and FSRT was 59.5 years. The median radiographic and clinical follow-up periods were 6.8 and 9.4 months, respectively. One hundred BSM received SRS, and the remaining 44 received FSRT. The median prescription dose and isodose line for SRS were 18 Gy and 65%, respectively, and 21 Gy and 70% for FSRT. The median overall BED and EQD2 were 43.2 and 36.0 Gy. Treated metastases were larger in FSRT cases (median 1.17 cc vs. 0.30 cc for SRS) and received lower BED (median prescription BED 36.6 vs. 50.4 Gy for SRS). The patient and treatment characteristics are summarized in Table 1.

During the available follow-up, 17 local failures, 97 tumor progressions (excluding LF and deaths), and 83 deaths were observed. Conversely, 119 patients (87.5%) have been censored for LC, 18 for PFS (13.2%), and 53 for OS (38.9%). The 1, 2, and 3-year LC rates were 82.9%, 71.4%, and 61.2%, respectively (Figure 1, Supplementary File 1). The median time of LC was not reached. The 1, 2, and 3-year PFS rates were 21.9%, 4.2%, and 2.1%, respectively, and the 1, 2, and 3-year OS rates were 61.1%, 34.7%, and 19.3%, respectively (Figures 2 and 3, Supplementary File 1). The median PFS and OS times were 5.5 (95% confidence interval [CI]: 4.4–6.7) and 15.7 months (95% CI: 12.2–18.5). In the multivariable Cox regression analysis for LC, only minimum BED was significantly associated with LC, favoring higher doses for improved control (in Gy, hazard ratio [HR]: 0.86, $p < .01$) (Figure 4). The applied margin was also a variable of the regression model, but due to a lack of LF for the 9 cases with a 1 mm total planning target volume margin, the hazard ratio could not be calculated. For PFS, only age at the time of BSM treatment was significantly associated (in years, HR: 0.97, $p = .04$) (Figure 4). The multivariable analysis for overall survival revealed a good performance status (KPS, ≥90%; HR: 0.43, $p < .01$) and previous WBRT (HR: 2.52, $p < .01$) as significant prognostic factors (Figures 3 and 4). The results stratified by location of the BSM can be found in the Supplementary Files 2, 3, 4, and 5. The proportional hazards assumptions were fulfilled for all variables and investigated endpoints.

In five cases (3.4%), the development of radiation necrosis was noted; however, no histopathological information for confirmation and no detailed grading were available for all patients. Two of these patients had undergone prior WBRT with a latency of 10.6 and 13.2 months from WBRT to SRS and FSRT. Three patients received SRS, and two received FSRT, with prescription doses of 14, 15, and 18 Gy, as well as 24 Gy, respectively. The gross tumor volume (GTV) of these cases ranged from 0.11 to 8.1 cc. Only one patient received systemic therapy (chemotherapy) during treatment, after which the radiation necrosis developed. In 14 BSM (9.7%), treatment-related adverse events were observed, primarily related to increased perifocal edema based on T2-weighted magnetic resonance imaging (MRI) with subsequent neurological deficits. Moreover, six of these cases developed LF. Figure 5 illustrates a case example of a patient treated with SRS and LF. Results of comparable publications on the treatment of BSM with SRS and FSRT were collected and summarized in Supplementary File 6.

4 | DISCUSSION

In this analysis, we present the results of a large multicenter cohort involving patients treated with SRS or FSRT for BSM.[2,4,6] Given the intricate nature of the brainstem, the unfavorable prognosis associated with BSM, and the limited treatment options available, addressing the oncological challenges posed by these metastases is essential. Thus, the objective of this analysis was to evaluate the safety and efficacy of SRS and FSRT for BSM in the context of current literature. Our observed LC rates were mostly comparable to the available literature, which reported rates in the range of 93%–95.2% and 86%–90.4% after 6 and 12 months, respectively.[3–6,21,24] According to the study of Trifiletti et al., increasing margin dose and maximum doses were associated with an increased LC.[3] However, a recent systematic review and meta-analysis of 32 studies conducted by Chen et al. stated that SRS dose was not associated with improved LC. Chen et al. also suggested a dose reduction or fractionation for patients with BSM larger than 1 cc, or with prior or concomitant WBRT.[6] In this analysis, a higher prescription dose was not associated with favorable LC rates. However, in our multivariable analysis, only the minimum BED was significantly associated, favoring higher doses for LC. BSM that locally failed had a median minimum BED of nearly 20% less compared to non-recurring metastases (34.7 Gy vs. 41.6 Gy). Outcomes after SRS and FSRT were not differing as the BED was used to compare different single doses and number of fractions. However, it is important to highlight that BSM treated with FSRT were larger (median GTV 1.17 vs. 0.30 cc) and had a lower BED (median prescription BED 36.6 vs. 50.4 Gy) than patients treated with SRS highlighting the hesitation to treat larger metastases with SRS and high single doses in delicate locations. Nicosia et al. did not observe considerable differences in LC rates between SRS and FSRT.[4] However, given the relative scarcity of available data on FSRT for BSM in contrast to SRS and other brain metastases locations, the quality of evidence remains particularly limited. The issue of limited data also applies to the role of BSM volume for LC. With conflicting results reported thus far, our study aligns with those reporting no differences in LC based on the volume of treated metastases.[6,24] It is important to consider that observed differences in the available results may also be caused by varying definitions of LC in the reported studies as well as cohort heterogeneity. Despite the frequent exclusion of BSM from prospective clinical trials, our study and reports

TABLE 1 Patient and treatment characteristics.

Patient and treatment characteristics						
Number of patients	136					
Number of BSM	144					
Sex (number of male/female)	57/79					
Location	Pons		Mesencephalon		Medulla oblongata	
Number of BSM	86		42		16	
	NSCLC	Breast	Melanoma	Renal cell	SCLC	Other
Tumor entity (number of patients)	43	43	12	12	12	14
			Median	Mean (SD)	IQR	Range
Age at SRS or FSRT (years)			59.5	60 (11.3)	52.3–68.4	34.3–84.4
KPS before SRS/FSRT[a] (%)			90	–	80–90	60–100
Number of brain metastases excluding BSM at time of SRS/FSRT			1	2 (3.4)	0–2	0–19
GTV[b] (cc)			0.42	1.48 (2.57)	0.14–1.75	0.01–19.7
Total CTV/PTV margin[a] (mm)			0	–	0–0	0–1
Prescription dose SRS (Gy)			18	–	16–18.5	12–21
Prescription dose FSRT (Gy)			21	–	21–24	15–32.5
Prescription isodose line SRS (%)			65	–	65–70	50–83
Prescription isodose line FSRT (%)			70	–	61.6–77.1	56–85
Number of fractions			1	–	1–3	1–5
Prescription BED (Gy)			43.2	44.8 (9.0)	37.5–50.4	19.5–65.1
Prescription EQD2 (Gy)			36.0	37.4 (7.4)	31.2–42.0	16.2–54.2
Max BED (Gy)			86.3	83.1 (24.6)	61.0–103.6	31.7–127.1
Mean BED[c] (Gy)			62.9	61.2 (14.8)	49.0–72.1	27.4–91.7
Minimum BED[a] (Gy)			40.9	42.3 (9.9)	35.2–49.9	14.1–78.7
Conformity index[d]			1.16	1.25 (0.31)	1.10–1.28	1.00–2.83
Homogeneity index[a]			1.47	1.46 (0.16)	1.45–1.54	1.05–2.00
Clinical follow-up (months)			9.4	13.0 (12.7)	4.3–16.3	1.0–83.5
Radiographic follow-up (months)			6.8	11.2 (12.3)	3.2–14.6	0.2–83.3
Time from first diagnosis to BSM SRS/FSRT (months)[a,e]			28.0	47.4 (51.7)	10.7–71.2	0.0–275.0
Time between prior WBRT and SRS/FSRT (months)			13.2	18.9 (16.8)	8.0–21.5	0.9–74.7
Total dose of prior WBRT[a] (Gy)			35	35.1 (4.4)	30–40	25–41.1

Abbreviations: BED, biologically effective dose; BSM, brainstem metastases; cc, cubic centimeters; CTV, clinical target volume; EQD2, equivalent dose in 2 Gy fractions; FSRT, fractionated stereotactic radiotherapy; GTV, gross tumor volume; Gy, Gray; IQR, interquartile range; KPS, Karnofsky performance status; NSLCL, non-small cell lung cancer; PTV, planning target volume; SCLC, small cell lung cancer; SD, standard deviation; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

[a]Data not available for one patient.

[b]Five diffuse BSM of one patient were contoured as one GTV.

[c]Data not available for three patients.

[d]Data not available for two patients.

[e]When the exact day was not available, the 15th of the respective month was used for calculation.

from other groups generally highlight that stereotactic treatment of BSM is feasible and should be offered to affected patients, who would have been offered SRS in the case of a different location of the metastasis.[6,24] Based on the prescription dose and BSM volume, our observed LC rates correspond well to other studies on stereotactic treatments for brain metastases in other locations.[25] While we acknowledge the potential impact of even small BSM on the performance status of patients, we encourage more future trials on SRS and FSRT to consider the inclusion of BSM.

Despite achieving solid LC rates with SRS and FSRT, the OS of affected patients remains limited. The 12-month OS rates reach around 33%, as reported in a recent systematic review and meta-analysis.[6] Notably, the OS rates within this time period exhibit a wide range from 8% to 71%, severely influenced by differences in the number of analyzed patients, performance status, systemic treatment, observation period, and tumor burden.[6] Herein, we report a favorable 12-month OS of 61.1% for patients treated between 2005 and 2022, potentially reflecting the underlying advances in cancer care of

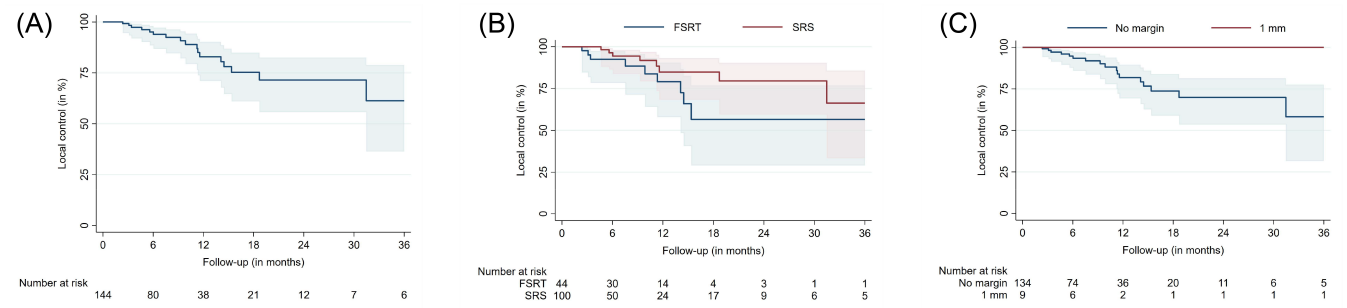

FIGURE 1 (A) Overall local control, (B) local control stratified for stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT), (C) local control stratified by total treatment margin. 95% confidence intervals represented by shaded areas.

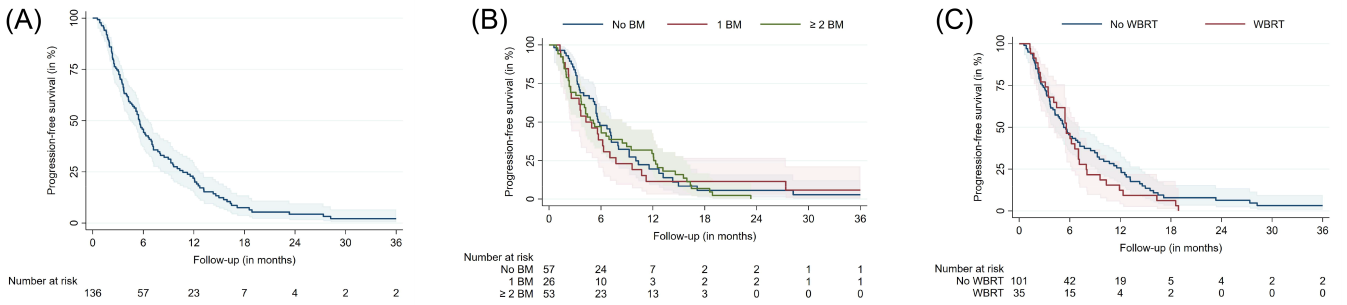

FIGURE 2 (A) Overall progression-free survival, (B) progression-free survival stratified by number of brain metastases (BM) at the time of brainstem metastases (BSM) treatment, (C) progression-free survival stratified by prior whole brain radiotherapy (WBRT). 95% confidence intervals represented by shaded areas.

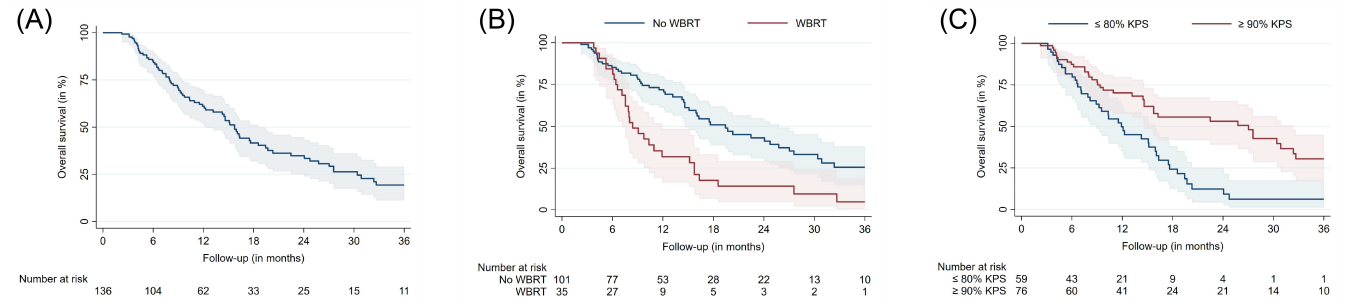

FIGURE 3 (A) Overall survival, (B) overall survival stratified by prior whole brain radiotherapy (WBRT), (C) overall survival stratified by Karnofsky performance status (KPS) at time of stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT). 95% confidence intervals represented by shaded areas.

metastatic tumor patients in the recent years and sampling, i.e., patient selection. With several studies demonstrating correlations between higher OS rates and better general health conditions, we also observed a favorable KPS to be positively associated with OS.[2,5,24] It is important to note that the analyzed patients herein mostly had an excellent performance status at the time of treatment (76 patients with KPS ≥80%). Remarkably, the presence and number of other brain metastases had no impact on OS. A finding which was not observed in the multicenter studies of Trifiletti et al. and Kawabe et al.[2,24] In our analysis, prior WBRT was found to negatively affect survival which is accordance with the multi-institutional report from Nicosia et al., reporting lower rates of cancer-specific survival and a higher chance of neurological death.[4] The varying findings underline the heterogeneity of analyzed cohorts reported thus far and limit further means to improve patient stratification.

The incidence of treatment-associated toxicity following SRS and FSRT for BSM appears to be low, with grade 3 or higher toxicities observed in approximately 2.4% of cases, ranging from 0% to 12%.[6,26] Correspondingly to the dose-volume relation in the radiation of brain metastases, higher toxicity in the treatment of BSM is more likely in larger tumor volumes and higher margin doses.[6,24,27] Moreover, the risk of toxicity after BSM radiation might increase with malignant

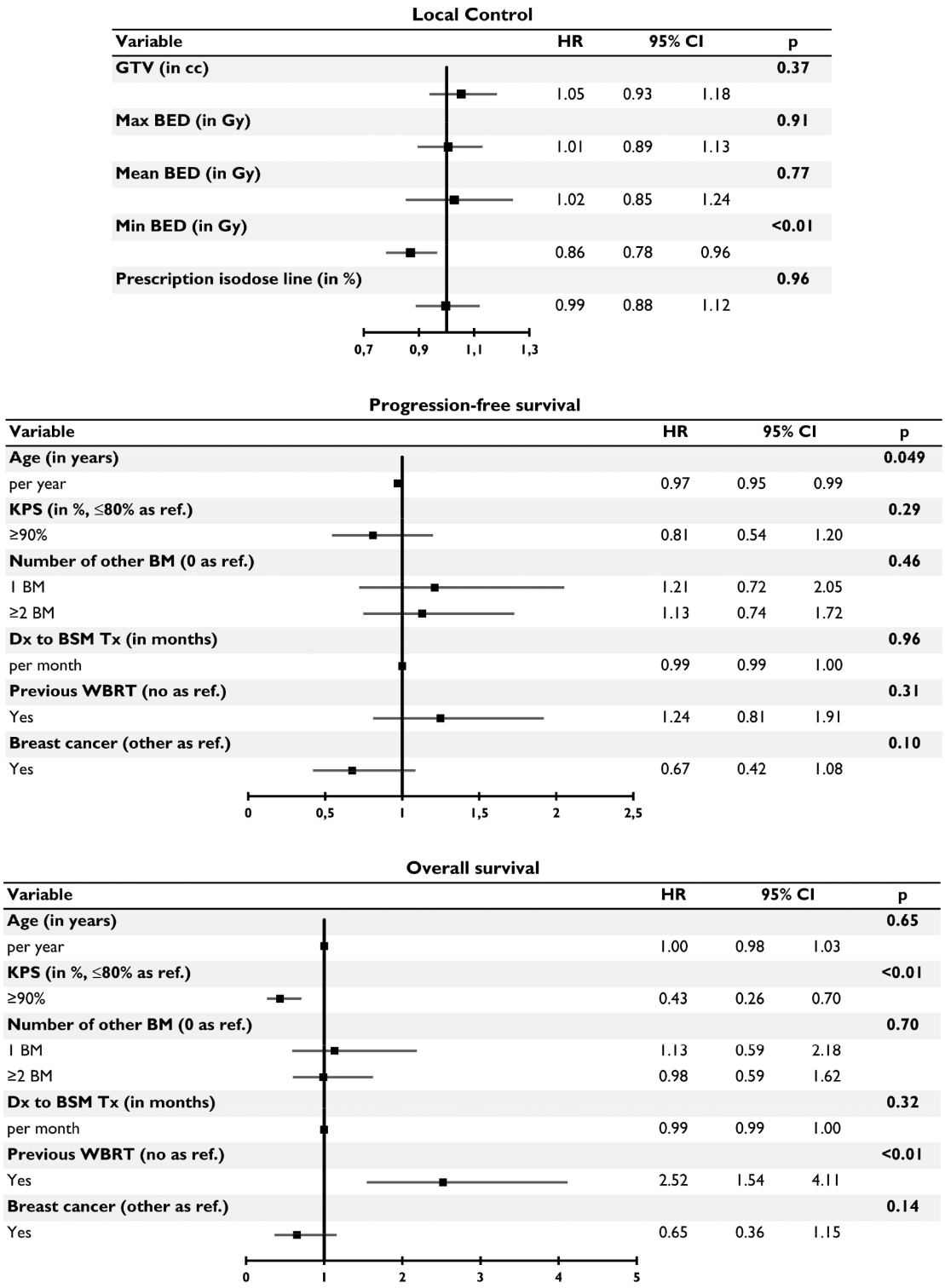

FIGURE 4 Multivariable Cox proportional hazards models for local control, progression-free survival, and overall survival. BED, biologically effective dose; BM, brain metastasis; BSM, brainstem metastases; cc, cubic centimeters; CI, confidence interval; Dx, diagnosis; GTV, gross tumor volume; Gy, Gray; HR, hazard ratio; KPS, Karnofsky performance status; Tx, treatment; WBRT, whole brain radiotherapy.

melanoma as a primary histology and after WBRT.[6] However, the risk decreases with longer time intervals between WBRT and SRS of the BSM in the case of previously irradiated patients.[6,24] Trifiletti et al. found no toxicity after SRS of BSM at all if the BSM volume was smaller than 0.1 cc or with a margin dose of less than 12 Gy.[24] In our cohort, treatment-related toxicity was observed in 14 cases (9.7%), which appears higher than recently reported in the systematic review (5.6%).[6] It is important to note that adequate assessment of

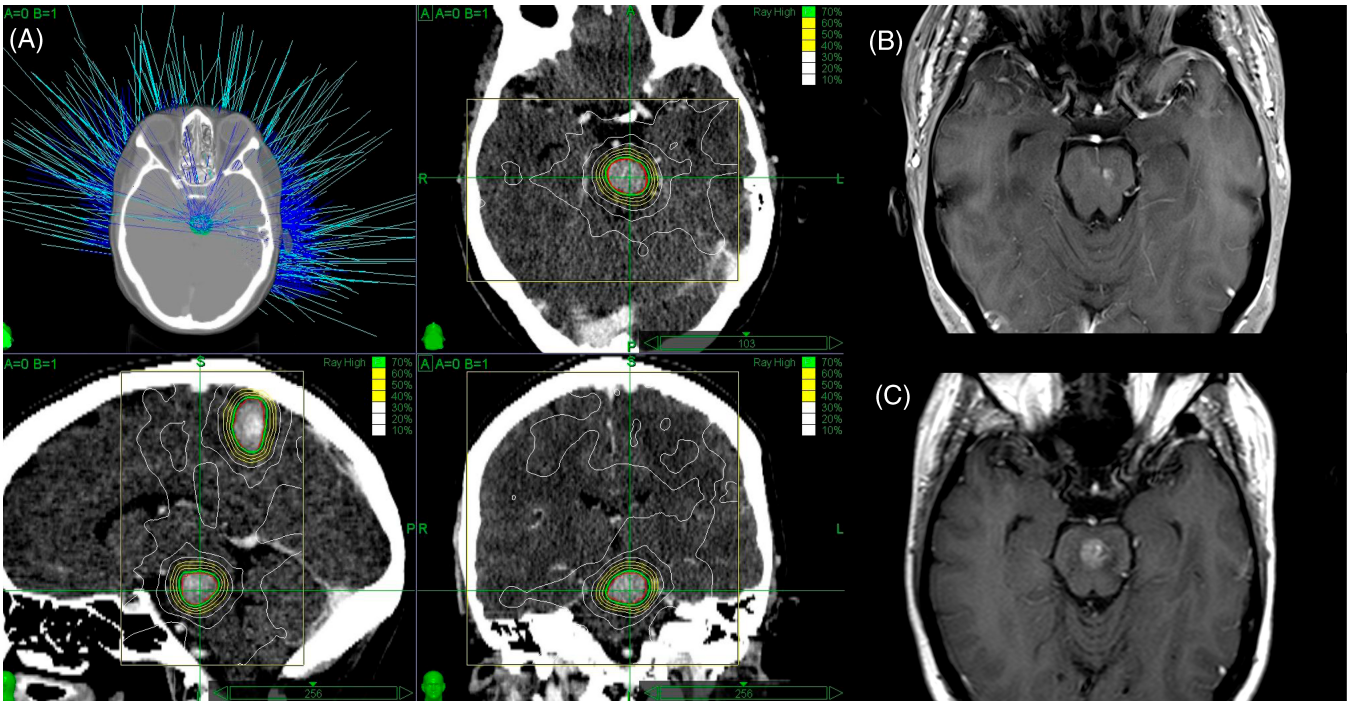

FIGURE 5 (A) Treatment plan of a 43-year-old patient with metastatic breast cancer and a brainstem metastasis with an additional metastasis in the parietal lobe. The patient received stereotactic radiosurgery (SRS) with a dose of 19 Gy, prescribed to the 70% prescription isodose line. (B) Axial view, contrast-enhanced T1-weighted magnetic resonance imaging. The brainstem metastasis showed a good treatment response, peaking a near complete regression 13 months after treatment. (C) Axial view, contrast-enhanced T1-weighted magnetic resonance imaging. Follow-up imaging nearly 19 months after SRS revealed local failure with new tumor growth.

treatment-related toxicity might be negatively affected by further brain metastasis, their progression, and treatment, as well as the retrospective nature of the analyses. Nevertheless, stereotactic treatments of BSM seem to be relatively well tolerated when managed at experienced treatment centers.[6,26] Among the treatment-related toxicities of SRS and FSRT, radiation necrosis ranks among the most important yet challenging ones, especially concerning BSM and in patients with prior WBRT. The overall radiation necrosis rate for BSM after SRS is approximately 1.5%, according to the review of Chen et al.[6] Herein, the presumed rate was again higher at 3.4%. While this difference appears significant at first sight, the remaining issues concerning the diagnosis of radiation necrosis and the lack of reporting and method of diagnosis in comparable studies profoundly limit meaningful comparisons. The gold standard of diagnosis, histopathological confirmation, appears inadequate in patients suffering from BSM. While advanced imaging techniques, such as perfusion MRI or functional imaging, have shown potential for differentiation between tumor progression and radiation necrosis, the lack of standardized and reliable non-invasive diagnostics remains.[28]

To mitigate treatment-associated toxicity, particularly the risk of radiation necrosis, dose constraints play a pivotal role in the treatment planning process of SRS and FSRT, especially when the brainstem is involved. Various dose constraints have been recommended based on previous research, reports, and studies. For SRS, the following recommendations were put forth: The quantitative analysis of normal tissue effects in the clinic (QUANTEC) summary advises a maximum dose of 12.5 Gy.[29] The American Association of Physicists in Medicine Task Group 101 report recommends a threshold dose of 10 Gy, with a maximum dose of 15 Gy at 0.035 cc.[14] The Timmerman table also proposes a maximum point dose of 15 Gy.[13] Herein, we do not formally report the maximum brainstem doses as the applied margin and prescription doses can be considered equivalent. These reported doses should be considered when interpreting the reported treatment-associated toxicity.

Notably, some studies reporting on SRS for BSM recommend margin doses, depending on tumor volume, up to 24 Gy in small metastases.[24] Nevertheless, most of the existing literature supports the administration of lower doses, particularly for larger tumor volumes or in cases with prior or concurrent WBRT.[2,3,6,24] Despite this, the overall treatment experience suggests that metastases in the brainstem do not generally preclude stereotactic treatments as our understanding of the brainstem tolerance to high radiation doses evolves.[6,26] However, the possibility exists that the low rates of adverse effects in BSM patients may go undocumented due to their short survival time, given the latency until the development of radiation necrosis. Finally, the interplay of new targeted therapies and immunotherapy with SRS and FSRT merits further exploration. Potential concerns and risks of increased treatment-associated toxicity persist. Prospective, high-quality data on the safety of stereotactic treatments with such treatments remain scarce but are crucial to advance the field and ensure patient safety.[30]

This study possesses several limitations primarily stemming from its retrospective design and inherent sampling biases. The treatment

decision for stereotactic irradiation of the BSM in favor of WBRT, the radiation dose, and the number of fractions were not standardized between the centers. Furthermore, accurately distinguishing between radiation necrosis and local tumor progression was and is not always feasible in the absence of histopathological examination. The consideration of biopsy and histopathological confirmation was excluded for all patients due to the evident and unjustifiable risk–benefit ratio. Moreover, it is essential to recognize the potential impact of systemic therapy on the observed outcomes and toxicity. However, due to the absence of comprehensive data, i.e., number of cycles, dates of administration, and administered doses, on systemic therapies, such as immunotherapy, chemotherapy, and targeted therapy, and heterogeneity of used drugs, a thorough assessment of their influence could not be adequately conducted in this study.

5 | CONCLUSION

Given the scarcity of comprehensive prospective data, larger studies, and remaining uncertainties concerning the normal tissue tolerance of the brainstem, this international multicenter analysis suggests that SRS and FSRT for BSM are effective and time-saving treatment options with an acceptable risk profile. Stereotactic treatment with a sufficient dose should be offered to patients with small to medium-sized BSM, given the favorable LC rates. The inclusion of BSM in prospective trials on SRS and FSRT appears justified.

AUTHOR CONTRIBUTIONS

Conceptualization: FE, AM; Methodology: FE, AM; Formal analysis: FE; Investigation: All authors; Writing–original draft: FE; Writing–review & editing: All authors; Visualization: FE; Supervision: AM. The work reported in the article has been performed by the authors unless clearly specified in the text.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Felix Ehret reports honoraria and travel support from ZAP Surgical Systems, Inc. David Krug has received honoraria from Merck Sharp & Dome, med update, onkowissen, best practice onkologie, ESO, ESMO, Gilead, Astra Zeneca and Pfizer as well as research funding from Merck KGaA, all outside the submitted work. Christoph Fürweger reports honoraria from ZAP Surgical Systems, Inc., and Accuray, Inc, and is the current Vice Chair of the Physics Committee of The Radiosurgery Society. Alexander Muacevic reports honoraria and travel support from ZAP Surgical Systems, Inc. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was reviewed and approved by the Institutional Review Board (EA4/038/22, Charité – Universitätsmedizin Berlin). Informed consent was waived due to the nature of the work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ehret F, Rueß D, Blanck O, et al. Stereotactic radiosurgery and radiotherapy for brainstem metastases: An international multicenter analysis. *Int J Cancer*. 2024;1-9. doi:10.1002/ijc.34980