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RESEARCH

Short-term predictors of stereotactic radiosurgery outcome for untreated single non-small cell lung cancer brain metastases: a restrospective cohort study

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Abstract

Stereotactic radiosurgery (SRS) is an option for brain metastases (BM) not eligible for surgical resection, however, predictors of SRS outcomes are poorly known. The aim of this study is to investigate predictors of SRS outcome in patients with BM secondary to non-small cell lung cancer (NSCLC). The secondary objective is to analyze the value of volumetric criteria in identifying BM progression. This retrospective cohort study included patients >18 years of age with a single untreated BM secondary to NSCLC. Demographic, clinical, and radiological data were assessed. The primary outcome was treatment failure, defined as a BM volumetric increase 12 months after SRS. The unidimensional measurement of the BM at follow-up was also assessed. One hundred thirty-five patients were included, with a median BM volume at baseline of 1.1 cm^3 (IQR 0.4–2.3). Fifty-two (38.5%) patients had SRS failure at follow-up. Only right BM laterality was associated with SRS failure (p=0.039). Using the volumetric definition of SRS failure, the unidimensional criteria demonstrated a sensibility of 60.78% (46.11%–74.16%), specificity of 89.02% (80.18%–94.86%), positive LR of 5.54 (2.88–10.66) and negative LR of 0.44 (0.31–0.63). SRS demonstrated a 61.5% local control rate 12 months after treatment. Among the potential predictors of treatment outcome analyzed, only the right BM laterality had a significant association with SRS failure. The volumetric criteria were able to identify more subtle signs of BM increase than the unidimensional criteria, which may allow earlier diagnosis of disease progression and use of appropriate therapies.

Keywords Brain metastases · Radiosurgery · Non-small cell lung tumor

Introduction

Brain metastases (BM) account for more than 50% of all intracranial tumors and are responsible for significant morbidity and mortality in oncologic patients [1–3]. Lung tumors are common sources of BM, being the non-small cell lung cancer (NSCLC) the subtype that most frequently evolves with these lesions [4, 5]. Patients with BM have poor prognosis due to the neurological disability and limited survival – estimated in 1-7 months after BM diagnosis [6–8].

The current therapeutic options for BM include surgery resection, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), chemotherapy, immunotherapy, among others. SRS has become an important tool to treat BM, especially for lesions not eligible for surgical resection [9–11]. Previous studies have shown that the use of SRS in BM has a rate of local disease control of 70-90% in one year after the procedure [12–17] and, since it is able to high radiation dose in a target with elevated precision, SRS is associate with significant less neurocognitive side effects than WBRT [17]. However,

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there are still no objective criteria to choose one treatment over the other, being this decision subject to clinical judgment and multidisciplinary team debate.

There is a lack of evidence not only about the best treatment for patients with single BM, but also about the best radiological criteria for BM progression identification. Currently, the diagnosis of BM progression follows the determinations of the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group [9], which recommends using the unidimensional criteria for defining disease progression – meaning an increase of more than 20% in the maximum measured diameter of the brain metastasis. The use of volumetric criteria was also discussed by the RANO-BM working group, which concluded that the 3D analysis could be unfeasible in all treatment centers due to its cost and complexity and suggested that future trials should investigate the role of these criteria in assessing disease progression [9].

Therefore, given the need to demonstrate the subgroup of patients with BM that would benefit the most from SRS, the main objective of this study is to investigate potential predictors of treatment failure in patients with a single BM secondary to NSCLC [18–20]. Additionally, as the value of volumetric criteria in the identification of intracranial disease progression is still unclear, the secondary objective is to assess the value of volumetric criteria in assessing BM progression when compared to the unidimensional criteria.

Methods

This was a retrospective study of patients with NSCLC BMs who had a single metastasis treated using SRS, (Elekta Gamma Knife Perfexion System, Elekta Solutions AB, Stockholm, Sweden) between January 1, 2010, and December 31, 2015. Patients were followed for 12 months after SRS. Demographic, histopathological, and radiological data were obtained from the patients' records.

Study population

We included patients >18 years of age with a single lesion who had no previous treatment. Patients with (1) previous treatments, (2) incomplete radiological follow-up – defined as only CT scan evaluation, no magnetic resonance imaging (MRI) assessment 3 months after SRS, or < 2 MRI following the procedure, (3) metastases from other primary tumors, and (4) patients with leptomeningeal dissemination were excluded.

Clinical evaluation

Clinical data were collected at the moment of SRS (baseline) and included gender, age, clinical performance Karnofsky Performance Scale (KPS), Graded Prognostic Assessment (GPA), systemic cancer staging, BM genetic profile, immunotherapy, WBRT, steroid use, death, and last follow-up. Data about the use of immunotherapy or WBRT before or one year after SRS was also assessed.

Radiological evaluation

Data on the SRS treatment included radiation dose (18-20 Gy) and BM measures at baseline – meaning in the moment of SRS. BM characteristics were assessed using T1-weighted MRI with 0.5 mm-thin slices and gadolinium contrast. BMs were characterized by maximum diameter, volume, topography, and contrast enhancement. Metastases were classified into one out of three categories, based on the proximity to the functional cortex: non-eloquent (grade I), near eloquent (grade II), and eloquent (grade III). BM with contrast enhancement within its total extension were defined as homogeneous, while lesions with partial contrast enhancement were defined as heterogeneous. Volumetric analyses were calculated through manual lesion segmentation using BrainLab Elements (BrainLAB, Munich, Germany) (Fig. 1). Measurements were performed by a neurosurgeon and reviewed by a neuroradiologist. BM dimensions were obtained when patients began SRS and during the follow-up after the procedure.

Follow-up

Participants were followed until 12 months post-SRS. The primary outcome assessed was treatment failure, defined as BM volume increase compared to the SRS moment. Treatment failure was also assessed using the unidimensional criteria, which defines failure as the ≥ 20% increase in the BM longest longitudinal diameter when compared to the initial assessment [21]. After the determination of SRS failure by the volumetric criteria, analyses were performed to study clinical, radiological, and molecular predictors of SRS failure.

Statistical analysis

Categorical data were described as frequencies (%). Continuous data were described as mean (standard

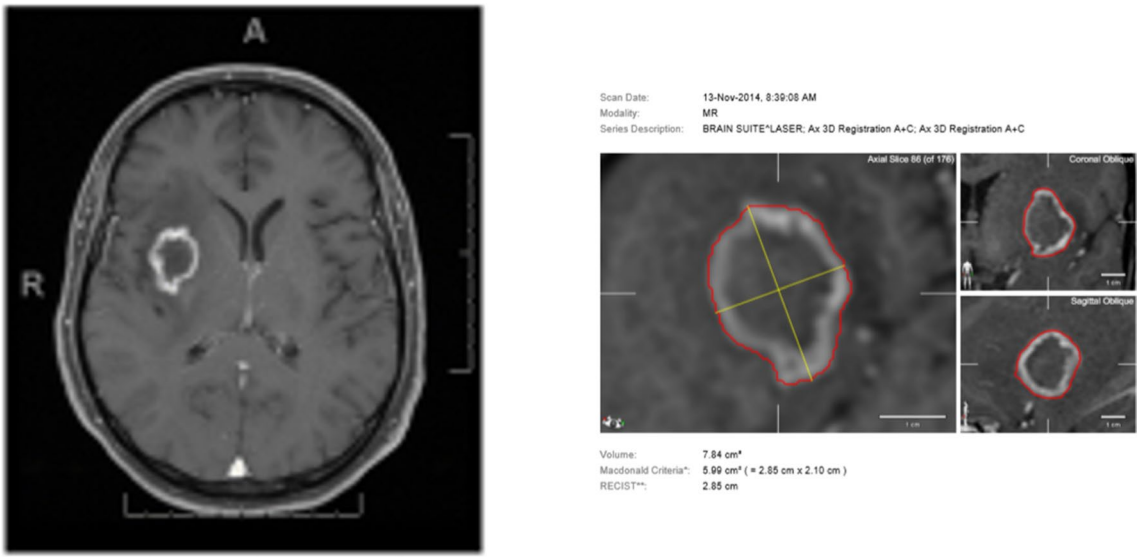

Fig. 1 Lesion dimensional measurement. Dimensional measurement using BrainLAB Elements software through definitions of lesion limits in axial, coronal, and sagittal incidences. *2 dimensional tumor criteria for gadolinium-enhancing T1-weighted lesions. **Response Evaluation Criteria in Solid Tumors (1 dimensional) for gadolinium-enhancing T1-weighted lesions. Algorithm gives the longest diameter of the object within original slices. RECIST: Response Evaluation Criteria in Solid Tumors

deviation) or median (interquartile range), as appropriate. Normality assumption was evaluated through distribution asymmetry, skewness, and kurtosis using graphical methods. For 1-year PFS results, potential categorical predictors were identified using the Kaplan Meier method and log-rank tests for comparison of survival curves.

Continuous variables were analyzed using univariate Cox regressions. Proportionality and linearity assumptions were verified using graphical methods and Schoenfeld and Martingale residuals, respectively. Preoperative KPS are included in the GPA scores, and therefore, were not considered for simultaneous inclusion in multivariable models. Both GPA and SRS doses were included in multivariable models due to biological plausibility. Optimal cut points for dichotomization of analyses were determined using receiver operating characteristic curves. All tests were two-tailed. Analyses were conducted using Statistical Package for Social Sciences (IBM, SPSS Statistics for Windows, 24.0, Armonk, New York, USA).

Results

Study population characterization at baseline

A total of 135 patients were included. Most participants were male (n=82; 60.7%) and the mean age was 61.8 ± 10.6 years (Fig. 2). At the time of SRS treatment, most patients had KPS ≥ 70 (n=131, 97%), 67 (50.4%) had extracranial metastasis, and 36 (27.1%) had estimated median survival of 14.8 months (GPA 3.5 – 4). Further study population characteristics are summarized in Table 1.

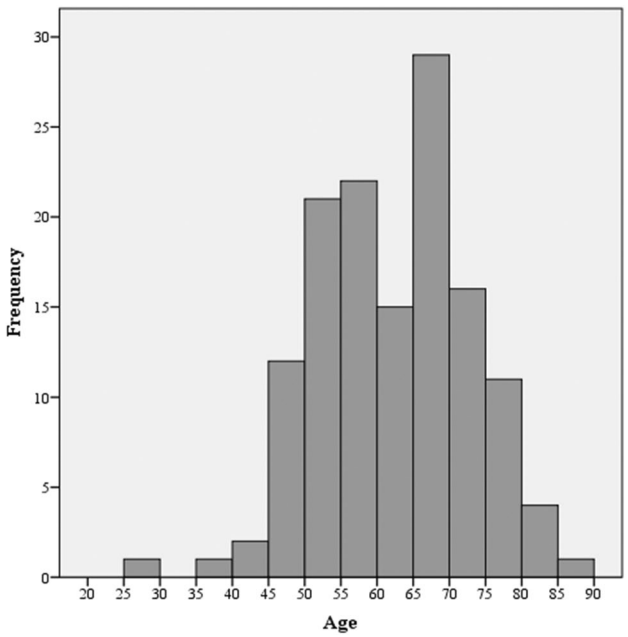

Fig. 2 Age distribution of the study population

Table 1 Study population baseline characteristics

	All patients (*n*=135)	Treatment failure		*p*-value *
		No (*n*=83)	Yes (*n*=52)	
Age (mean ± SD)	61.8 ± 10.6	61.8 ± 9.9	62.0 ± 11.6	0.867
Male n (%)	82 (60.7)	49 (59.0)	33 (63.5)	0.706
KPS median (IQR)	90 (80 – 90)	90 (80 – 100)	90 (80 – 90)	0.165
60	4 (3.0)	2 (2.4)	2 (3.8)	0.164
70	12 (8.9)	6 (7.2)	6 (11.5)	
80	28 (20.7)	18 (21.7)	10 (19.2)	
90	58 (43.0)	36 (43.4)	22 (42.3)	
100	33 (24.4)	21 (25.3)	12 (23.1)	
Extracranial metastases n (%)	67 (50.4)	42 (51.2)	25 (49.0)	0.725
GPA median (IQR)	2.5 (2.0-3.5)	2.5 (2.0 – 3.5)	2.5 (2.0 – 3.0)	0.767
0 – 1,0	2 (1.5)	0 (0.0)	2 (3.9)	0.457
1.5 – 2.0	37 (27.8)	25 (30.5)	12 (23.5)	
2.5 – 3.0	58 (43.6)	33 (40.2)	25 (49.0)	
3.5 – 4.0	36 (27.1)	24 (29.3)	12 (23.5)	
Lesion dimensions				
Volume median (IQR)	1.1 (0.4 – 2.3)	1.0 (0.4 – 2.3)	1.1 (0.4 - 2.5)	0.835
Diameter median (IQR)	12 (7.3 – 16.6)	12.2 (8.4 – 16.9)	9.9 (5.5 – 12.4)	0.722
DVR mean (SD)	19.1 ± 14.9	17.8 ± 14.2	24.0 ± 16.5	0.207
DVR ≥ 22.2 n (%)	26 (29.9)	17 (24.6)	9 (50.0)	0.099
BM topography n (%)				0.459
Frontal	47 (34.8)	31 (37.3)	16 (30.8)	
Temporal	16 (11.9)	7 (8.4)	9 (17.3)	
Parietal	22 (16.3)	14 (16.9)	8 (15.4)	
Occipital	16 (11.9)	11 (13.3)	5 (9.6)	
Cerebellum	24 (17.8)	14 (16.9)	10 (19.2)	
Brainstem	5 (3.7)	2 (2.4)	3 (5.8)	
Thalamus	2 (2.4)	1 (1.9)	3 (2.2)	
Other	2 (2.4)	0 (0.0)	2 (1.5)	
Laterality n (%)				0.039
Right	56 (41.5)	29 (34.9)	27 (51.9)	
Left	72 (53.3)	51 (61.4)	21 (40.4)	
Midline (Thalamus or Cerebellum)	7 (5.2)	3 (3.6)	4 (7.7)	
Infratentorial n (%)	26 (19.3)	15 (18.1)	11 (21.2)	0.744
Homogeneous BM n (%)	76 (56.3)	51 (61.4)	25 (48.1)	0.082
Eloquence n (%)				0.395
Non-Eloquent	69 (51.1)	46 (55.4)	23 (44.2)	
Near eloquent	16 (11.9)	8 (9.6)	8 (15.4)	
Eloquent	49 (36.3)	28 (33.7)	21 (40.4)	
Steroid use n (%)	98 (80.3)	61 (78.2)	38 (84.1)	0.201
Immunotherapy n (%)	39 (31.7)	25 (32.1)	14 (31.1)	0.394
SRS dose median (IQR)	20 (18 – 20)	20 (18 – 20)	20 (18 – 20)	0.549
WBRT n (%)				0.277
No	113 (84.3)	70 (85.4)	43 (82.7)	
Yes (before SRS)	13 (9.7)	8 (9.8)	5 (9.6)	
Yes (after, up to 1 year)	8 (6.0)	4 (4.9)	4 (7.7)	

*Survival analysis log-rank test or Cox regression, *SD* standard deviation, *IQR* interquartile range. *KPS* Karnofsky Performance Scale, *GPA* Graded Prognostic Assessment, *BM* brain metastasis, *SRS* stereotactic radiosurgery, *WBRT* Whole Brain Radiotherapy, *DVR* diameter/volume ratio.

The median BM volume at the time of SRS treatment was 1.1 cm^3 (IQR 0.4 – 2.3). The mean DVR was 19.1 ± 14.9, and 26 (29.9%) patients had DVR ≥ 22.2. Concerning the BM topography, the most common location was the frontal lobe (*n*=47; 34.8%), followed by the occipital lobe (*n*=16;11.9%), cerebellum (*n* = 24; 17.8%), and brainstem (*n* = 5; 3.7%). Most BM were on the left side (*n*=72; 53.3%), and 7 (5.2%) subjects had BM on the midline. Supratentorial BM accounted for 109 (80.7%) cases, including 59 (43.7%) patients with left-side lesions and 50 (37%) right-side lesions. Regarding the contrast enhancement pattern, most patients (*n*=76; 56.3%) had homogeneous lesions. Sixty-nine (51.1%) patients had grade I BM (lesion in non-eloquent areas), forty-nine (36.3%) had grade III BM (lesion in eloquent areas), and sixteen (11.9%) had grade II BM (lesion near eloquent areas) (Table 1).

Genetic assessment was performed in 41 (29.6%) patients (Table 2). The genetic mutations identified were EGFR (*n* = 10), KRAS, (*n* = 9), TP53 (*n* =21), and BRAF (*n* = 1). Ninety-eight (80.3%) patients received corticoid therapy with dexamethasone and thirty-nine (31.7%) underwent immunotherapy. Most participants (*n* = 113; 84.3%) did not receive WBRT, 13 (9.7%) underwent WBRT before SRS treatment, and 8 (6%) received WBRT up to 1 year after SRS treatment.

Table 2 Genetic evaluation

Mutation	Overall (*n*=83)	Treatment failure		*p*-value *
		No (*n*=52)	Yes (*n*=31)	
EGFR	10 (12.0)	6 (11.5)	4 (12.9)	0.712
KRAS	9 (10.8)	5 (9.6)	4 (12.9)	0.381
TP53	21 (25.3)	14 (26.9)	7 (22.6)	0.415
BRAF	1 (1.2)	1 (1.9)	0 (0.0)	0.665

*Survival analysis log-rank test or Cox regression. *BS* Brainstem, *SRS* stereotactic radiosurgery

Predictors of SRS failure

Fifty-two (38.5%) patients had SRS failure at 12 months follow-up. Among the several potential predictors of SRS failure, only BM on the right side was associated with BM volumetric increase in the follow-up (*p* = 0.039). The mean period free of failure was 285.6 ± 15.4 days for left-side lesions, and 234.7 ± 17.7 days for right-side lesions (Figs. 3 and 4). The group with SRS failure on follow-up had a median BM volume at baseline of 1.1 (IQR 0.4 – 2.5) cm^3, while the group without SRS failure had a median baseline lesion volume of 1.0 (IQR 0.4 – 2.3) cm^3 (*p*=0.835) (Fig. 5). The pattern of contrast enhancement at baseline was not associated with SRS failure (*p*=0.082) in the univariate analysis. Patients with homogeneous lesions demonstrated longer progression-free survival (279.7 ± 14.8 days) than patients with heterogeneous lesions (239.8 ± 18.5 days) (Fig. 6).

The median SRS dose was 20 Gy (IQR 18-20). Patients with older age and grade III BM received lower doses of SRS. Figure 7 depicts the association between SRS dose, age, and BM's grade. Immunotherapy (*p* =

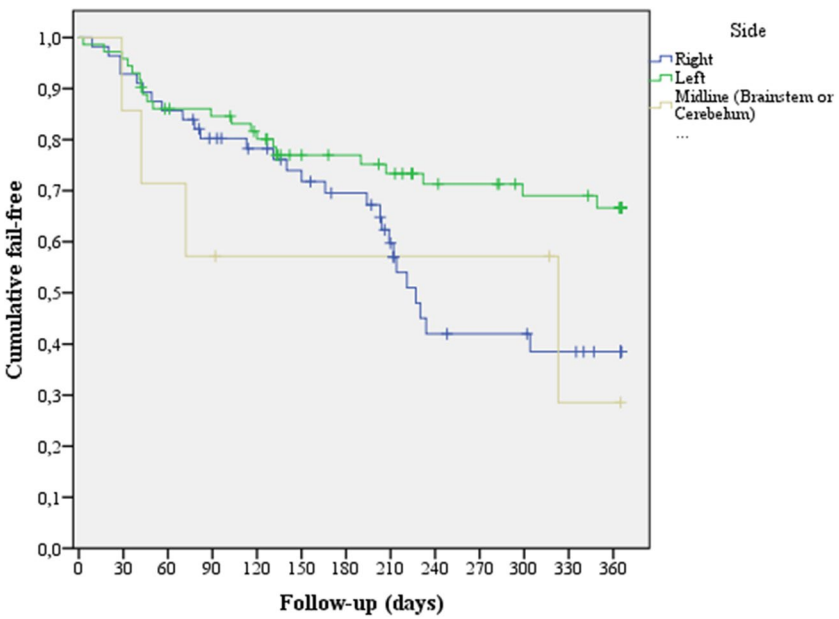

Fig. 3 Time free of failure according to the laterality (right, left, or midline)

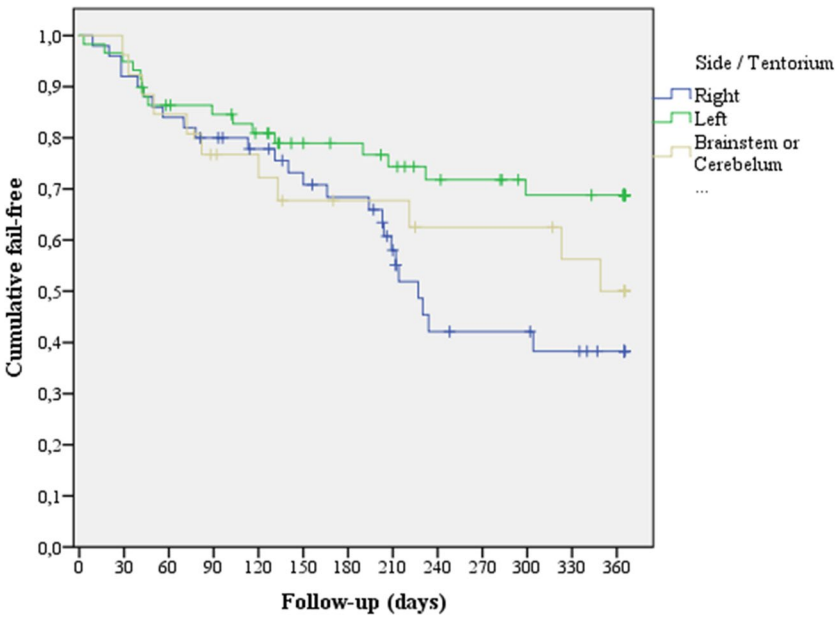

Fig. 4 Time free of failure according to the laterality and tentorium relative location (right supratentorial, left supratentorial and infratentorial)

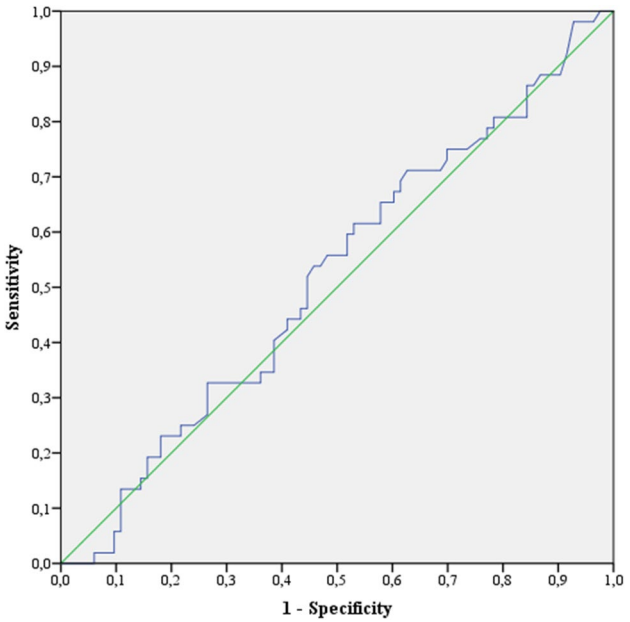

Fig. 5 AUC ROC representing the relationship between BM volume at baseline and SRS failure. AUR ROC 0.519 ± 0.051, 95% CI 0.420 – 0.619, $p = 0.706$

0.394), dexamethasone use ($p = 0.201$), and current or previous WBRT ($p = 0.277$) were not associated with SRS failure in the follow-up. The type of genetic mutation was also not associated with disease progression (Table 2).

To identify potential predictors of SRS failure, a multivariate analysis with a model including BM homogeneity and diameter ≤ 11.9 mm was performed. The analysis demonstrated that homogeneous BM had a coefficient of – 0.1 (SD 0.64), Wald test of 0.002, HR of 0.91 (CI95% 0.26 – 3.20; $p = 0.881$), while the diameter ≤ 11.9 mm had a coefficient of 1.08 ± 0.60), Wald test of 3.27, and HR of 2.94 (CI 95% 0.91 – 9.49; $p = 0.071$) (Table 3).

Another model including BM homogeneity, diameter ≤ 11.9 mm, GPA, and SRS dose was analyzed. BM homogeneous contrast enhancement demonstrated a coefficient of – 0.09 ± 0.67, Wald test of 0.02, and HR of 1.09 (CI 95% 0.30 – 4.03; $p = 0.89$); diameter had a coefficient of 0.97 (SD 0.64), Wald test of 2.31, and HR of 2.63 (CI 95% 0.76 – 9.12; $p = 0.129$); GPA had a coefficient of – 0.36 (SD 0.39), Wald test of 0.85, and HR of 0.70 (CI 95% 0.33 – 1.50; $p = 0.358$); and SRS dose had a coefficient of – 0.01 (SD 0.15), Wald test of 0.002, and HR 0.99 (CI 95% 0.74 – 1.34; $p = 0.965$) (Table 4) (Figs. 8 and 9).

Volumetric vs. unidimensional criteria for SRS failure

At the follow-up, fifty-two (38.5%) patients had a volumetric increase in BM, while 40 (30.1%) had a ≥ 20% increase in the BM longitudinal diameter. Among the 52 cases with volumetric SRS failure, 20 (15%) did not have treatment failure according to the unidimensional criteria. Among the 83 patients without volumetric SRS failure, 9 (6.8) had unidimensional criteria for failure (Table x). The Cohen's Kappa correlation between volumetric and unidimensional criteria for SRS failure was 0.519 (CI 95% 0.368 – 0.670, $p < 0.001$) (Table 5).

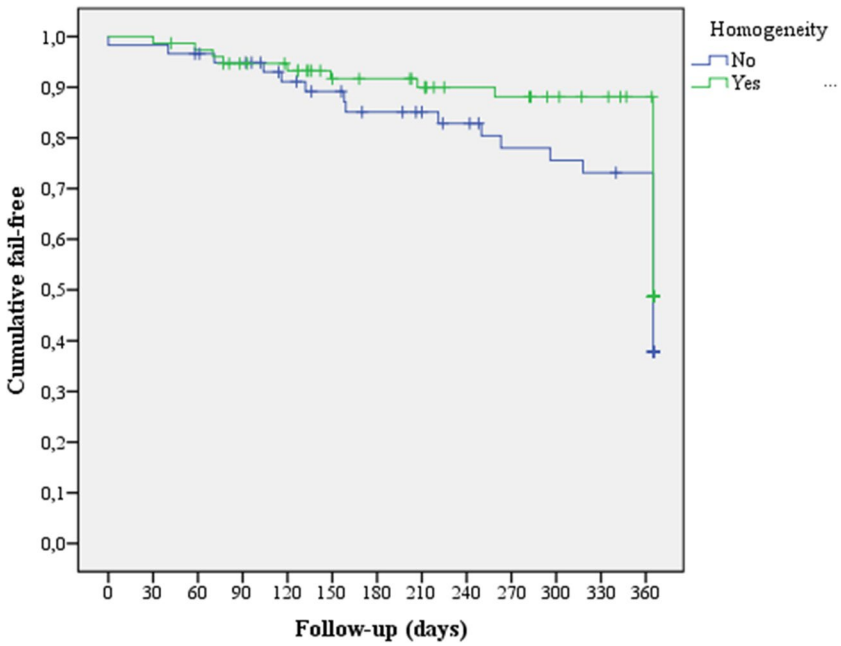

Fig. 6 Time free of failure according to brain metastasis homogeneity on imaging

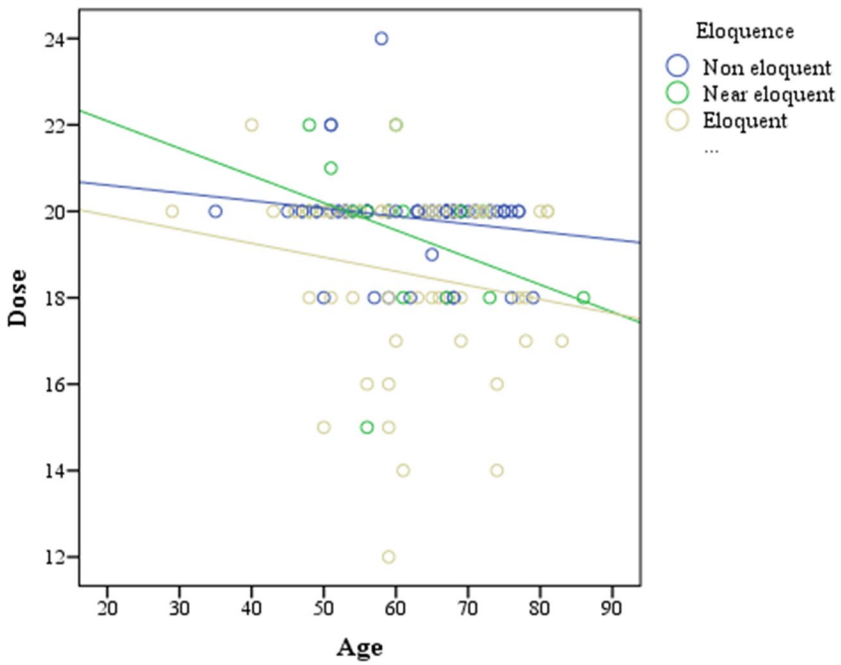

Fig. 7 Stereotactic Radiosurgery dose according to age and BM grade (relationship with eloquent areas)

Table 3 Multivariable analysis for the predictors of 1-year failure free survival

Variables	Coef. ± SE	Wald	HR	95% CI	*p* value
Homogeneous lesion	-0.10 ± 0.64	0.02	0.91	0.26 – 3.20	0.881
Diameter ≤ 11.9	1.08 ± 0.60	3.27	2.94	0.91 – 9.49	0.071

Coef: Coefficient. *SE* Standard error, *HR* Hazard Ratio, *CI* Confidence interval.

Using the volumetric criteria as definition of SRS failure, the unidimensional criteria demonstrated a sensibility of 60.78% (46.11% – 74.16%), specificity of 89.02% (80.18% – 94.86%), positive likelihood ratio of 5.54 (2.88 – 10.66) and negative likelihood ratio of 0.44 (0.31 – 0.63). The positive predictive number for the unidimensional criteria was 77.50% (61.55% – 89.16%), and the negative predictive number was 78.49% (68.76% – 86.34%).

Table 4 Multivariable analysis for the predictors of 1-year failure free survival

Variables	Coef. ± SE	Wald	HR	95% CI	*p* value
Homogeneous lesion	-0.09 ± 0.67	0.02	1.09	0.30 – 4.03	0.893
Diameter ≤ 11.9	0.97 ± 0.64	2.31	2.63	0.76 – 9.12	0.129
GPA (each unit)	-0.36 ± 0.39	0.85	0.70	0.33 – 1.50	0.358
SRS dose (each unit)	-0.01 ± 0.15	0.002	0.99	0.74 – 1.34	0.965

Coef: Coefficient. *SE* Standard error, *HR* Hazard ratio, *CI* Confidence interval, *GPA* Graded Prognostic Assessment, *SRS* stereotactic radiosurgery.

Discussion

In the present study, we found that patients with single BM secondary to NSCLC who underwent SRS had a 38.5% rate of treatment failure in 12 months. Among the several potential predictors of treatment failure analyzed, only the right BM laterality was associated with an increased risk of SRS failure. The pattern of contrast enhancement was not associated with treatment failure in 12 months, however, subjects with homogeneous lesions demonstrated longer progression-free survival. Concerning the performance of volumetric and unidimensional criteria for SRS failure, the methods demonstrated significant correlation, being the volumetric criteria able to identify more subtle signs of BM increase.

SRS is considered an efficient treatment option for patients with BM, with a local control rate of 70-90% in 12 months [12–16]. In this study, the local control rate at 1 year was 61.5% based on a definition of failure as a volumetric increase in brain metastasis above the value measured at the time of SRS. The local control rate using the bidimensional criteria was similar to the literature (69.1%). Nowadays, the value of the volumetric criteria for assessment of BM response is subject to debate, being recommended by the RANO-BM working groups for the evaluation of this method of measurement in further studies. Such verification was carried out in the present work and the discrepancy between the SRS failure rate by our study compared to the literature may indicate that volumetric measurement is able to identify more subtle signs of intracranial disease progression associated or not with pseudoprogression and radionecrosis, which might allow earlier use of appropriate therapies to improve quality of life and survival of patients.

Pseudoprogression and radionecrosis are post-radiation treatment effects that can mimic tumor recurrence. Pseudoprogression occurs up to 3 months after radiation exposure and is associated with the transient interruption of myelin synthesis of oligodendrocytes [22–24]. Studies suggests that pseudoprogression is a transient condition with spontaneous resolution [25, 26]. Radionecrosis, on

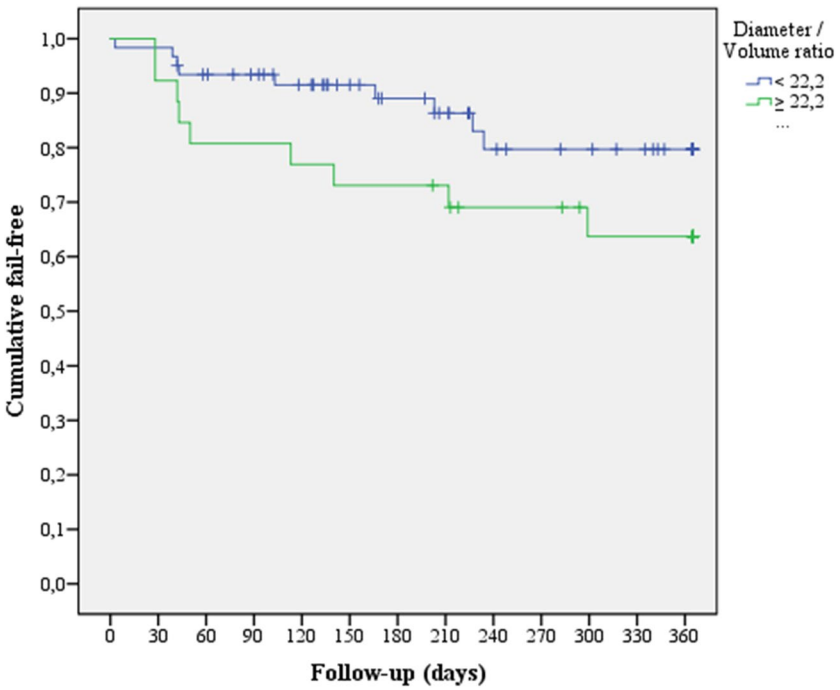

Fig. 8 Time free of failure according to the Diameter/Volume ratio

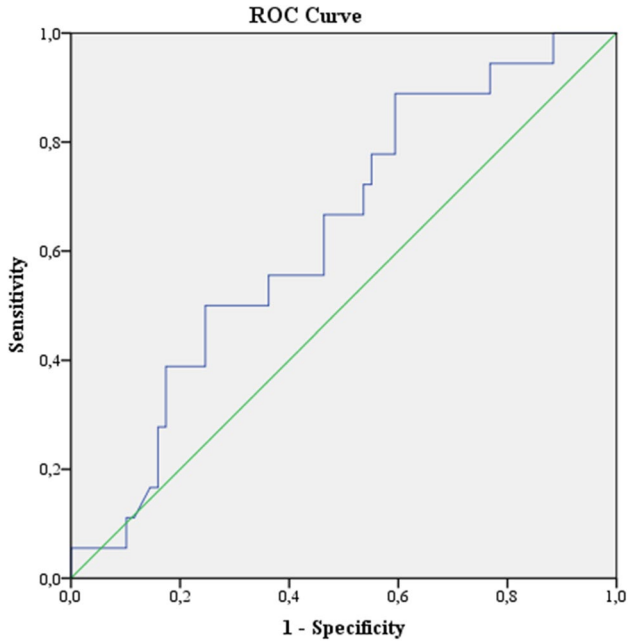

Fig. 9 AUC ROC representing the relationship between Diameter/Volume ratio and Treatment failure in 12 months: 0.633 ± 0.069, CI 95% 0.498 – 0.768, $p = 0.084$

Table 5 Correlation between radiological and volumetric criteria for SRS failure

Criteria		Volumetric		Total
		No failure	Failure	
Radiological	No failure	73 (54.9)	20 (15.0)	93 (69.9)
	Failure	9 (6.8)	31 (23.3)	40 (30.1)
Total		82 (61.7)	51 (38.3)	133 (100.0)

Data presented as n (%). Kappa: 0.519 (95% IC 0.369 – 0.670), $p < 0.001$.

the other hand, is a late and irreversible side effect of SRS that occurs months to several years after the treatment. Previous studies about radionecrosis following SRS in patients with BM from different types of cancers reported an incidence of around 25% [27, 28]. SRS dose, BM dimensions, and topography were identified as predictors of radionecrosis [29–31]. In our study, none of these were associated with treatment failure, suggesting that the increase in BM was more likely secondary to disease progression rather than radionecrosis. There is evidence that it is possible to differentiate BM progression from treatment effect (radionecrosis) using advanced imaging modalities – such as perfusion MRI, 18F-3′-fluoro-3′-deoxythymidine (FLT), F-18 fluorodeoxyglucose (FDG), PET or magnetic resonance spectroscopy [32, 33] – nonetheless, the literature is inconclusive about the best modality for that purpose [3, 32, 33].

The BM topography is an important factor not only to plan SRS, but also to manage expectations regarding the treatment outcomes [34–37]. In this study, the relationship of the BM to the tentorium and eloquent areas was not associated with treatment failure. However, lesions on the right side were associated with disease progression in 1 year. This is an interesting finding since a worse outcome would be expected for lesions in the left hemisphere due to a more conservative approach in dominant areas [38]. Therefore, we believe that this association most likely occurred by chance.

Concerning the homogeneity of the lesions, it was not associated with disease progression, even though patients with heterogeneous BM at baseline had shorter PFS when compared to patients with homogeneous lesions. In fact, there is evidence that heterogeneous BM from NSCLC are associated with significantly worse progression-free survival five years after SRS [39].

Limitations and strengths

The limitations of this study include (1) the very specific study population – patients with NSCLC with single BM – which impairs the generalizability of our results; (2) the small number of subjects in some groups – such as KPS 60, KPS 70, and GPS 0-1 – decreasing the power of our statistical analysis; (3) the absence of histopathological assessment of increased lesions to differentiate true SRS failure from pseudoprogression and radionecrosis; and (4) inherit limitations secondary to a retrospective design. On the other hand, our work presents a large number of patients from a very specific population and the homogeneity of the sample increases the internal validity of our findings.

Conclusion

SRS demonstrated a 61.5% rate of local control in patients with single BM secondary to NSCLC 12 months after treatment. Among the potential predictors of treatment outcome analyzed, only the right BM laterality had a significant association with SRS failure. Contrast enhancement pattern was not associated with treatment failure, however, subjects with homogeneous lesions demonstrated longer progression-free survival. The volumetric criteria were able to identify more

subtle signs of BM increase than the unidimensional criteria, which may allow earlier diagnosis of disease progression and use of appropriate therapies.

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Data availability Not applicable.

Declarations

Ethical approval The study was approved by the MD Anderson Cancer Center Ethics Review Board on April 4th, 2018.

Competing interests The authors declare no competing interests.

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