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Stereotactic radiosurgery in brain metastasis: treatment outcomes and patterns of failure

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Original Article

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Abstract

Introduction: Stereotactic radiosurgery (SRS) has become a preferred treatment in the initial management of brain metastases (BM). This study reported treatment outcomes and identified the patient, tumour, and treatment-related factors that predict failure, survival, and brain necrosis (BN).

Methods: We retrospectively reviewed the electronic medical records of all BM patients treated with SRS. Patient, tumour characteristics and treatment details data were collected. All recurrences and BN were defined in the neurooncological tumour board.

Results: From December 2016 to April 2020, 148 patients were analysed. The median follow-up was 14·8 months (range 6–51). At the time of analyses, 72·3% of the patients were alive. Presence of initial neurological deficit (HR; 2·71 (1·07–6·9); $p = 0·036$) and prior RT (HR; 2·55 (1·28–5·09); $p = 0·008$) is associated with worse overall survival. The local recurrence rate was 11·5 %. The distant brain metastasis rate was 53·4 %. Leptomeningeal metastasis was seen in 11 patients (7·4%). Symptomatic BN was seen in 19 patients (12·8 %). Bigger lesions (13 versus 23 mm diameter; $p = 0·034$) and cavity radiosurgery are associated with more BN (63·2 % versus 36·8%; p: 0·004).

Conclusions: Distant BM is the leading cause of CNS recurrences and, salvage SRS is possible. Due to the increasing risk of developing BN routine metastasectomy should be made with caution.

Introduction

Brain metastases (BM) are the most common intracranial malignancy in adult patients with systematic cancer and a significant cause of morbidity and mortality.[1,2] With increasing incidence, BM occur in 20–40 % of patients suffering from primary solid extracerebral tumours.[3] Management options depend on patients and tumour characteristics such as performance status, neurological deficits, tumour size, life expectancy and extracranial disease activity.

Radiotherapy is almost always the most common treatment of brain metastasis. In recent years, stereotactic radiosurgery (SRS) has become a preferred treatment option in the initial management of patients with limited BM.[4] Randomised trials have demonstrated that SRS provides equivalent survival and better neurocognitive function (NCF) compared to whole-brain radiotherapy (WBRT) in both initial management (stand-alone) and postoperative adjuvant setting.[5–7]

In this single-institution retrospective study, we investigated local control (LC), distant brain metastasis (DBM), leptomeningeal control, overall survival (OS) and radiation necrosis rate in patients undergoing SRS for BM. We also aimed to identify the patient, tumour, and treatment-related factors that predict failure, survival, and brain necrosis (BN) after SRS in patients with BM.

Methods

We conducted an IRB-approved retrospective cohort study including all patients with BM with treated SRS. In addition, we retrospectively reviewed the electronic medical records of all consecutive patients with BM. The study cohort included all patients with prior surgery or radiotherapy [WBRT or prophylactic cranial irradiation (PCI)]. Data for his study were collected from December 2019 to March 2021.

In general, the institutional philosophy for salvage SRS versus WBRT was to postpone the use of WBRT for as long as possible and treat with salvage SRS when feasible. No further treatment was reserved for patients with poor life expectancy and who were not expected to benefit from salvage treatment.

We have two different platforms, robotic (Cyberknife M6) and linac-based (Varian EDGE), for SRS delivery. For planning purposes, high-resolution computed tomography (CT) slices

Table 1. Patient and tumour characteristics

Primary diagnosis	*Number*	*%*
Lung	95	64·2
Breast	29	19·6
Melanoma	9	6·1
Other	15	10·1
Lesion number		
1	70	47·3
2–4	50	33·7
≥ 5	28	19·0
Brain metastasis presentation		
Synchronous	52	35·1
Metachronous	96	64·9
Tumour location (patient)		
Frontal	119	80·4
Parietal	34	23·0
Temporal	29	19·6
Occipital	20	13·5
Cerebellum	38	25·7
Basal ganglion	10	6·8
Brain stem	6	4·1
Widespread*	24	16·2
Other	4	2·7
Neurological deficit		
Absent	51	34·4
Present	42	28·4
Unknown	55	37·2
Extracranial metastasis		
Absent	65	43·9
Present	83	56·1
Extracranial metastasis site		
Lung	37	25
Liver	21	14·2
Bone	36	24·3
Lymph node	21	14·2
Adrenal gland	8	5·4
Other	11	7·4
Unknown	5	3·3
Any type of systemic treatment		
Yes	111	75·0
No	19	12·8
Unknown	18	12·2
Type of systemic treatment		
Chemotherapy	60	40·5
Targeted therapy	32	21·6
Immunotherapy	10	6·7
Hormonotherapy	2	1·3
Other	4	2·7
Unknown	25	16·8,0

* More than three different supratentorial regions.

Table 2. Treatment characteristics

Fraction number	*Number*	*%*
1	65	43·9
3	74	50·0
5	9	6·1
SRS platform		
Robotic	92	62·2
Linac-based	56	37·8
Previous brain radiation		
Absent	114	77·0
WBRT	26	17·6
PCI	8	5·4
Surgery before SRS		
(–)	126	85·1
(+)	22	14·9

with a 1·25 mm thickness were obtained and fused with magnetic resonance imaging (MRI) for tumour contouring. Planning target volume (PTV) was created by adding gross target volume (GTVs) 1 mm in each direction in intact tumours and clinical target volume (CTVs) in resection cavities. Treatment planning was performed using Precision (version 2.0.0.1, Accuray Inc.) and Eclipse (version 15.5, Varian Medical System) treatment planning system software. The prescription dose was normalised to the 70%–80% isodose line range to cover 95% of the PTV volume.

After undergoing SRS, patients underwent follow-up with clinical and radiographic surveillance per institutional standards. Patient and tumour-related factors, treatment details, time until first CNS progression after SRS, type of first central nervous system (CNS) progression (local, distant and leptomeningeal), cause of death and duration of follow-up data were recorded.

An experienced radiologist defined all local recurrences and radiation necrosis with a contrast-enhanced MRI and additional perfusion MRI in the neurooncological tumour board. DBM was defined as any new brain metastasis that developed outside the prior SRS treatment volume. MRI evidence of new nodular enhancement of the dura, diffuse leptomeningeal enhancement or positive cerebrospinal fluid cytology was considered a leptomeningeal failure. Overall survival (OS) was calculated from the completion of SRS to death.

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov–Smirnov test. Independent sample *t*-test and Mann–Whitney *u*-test

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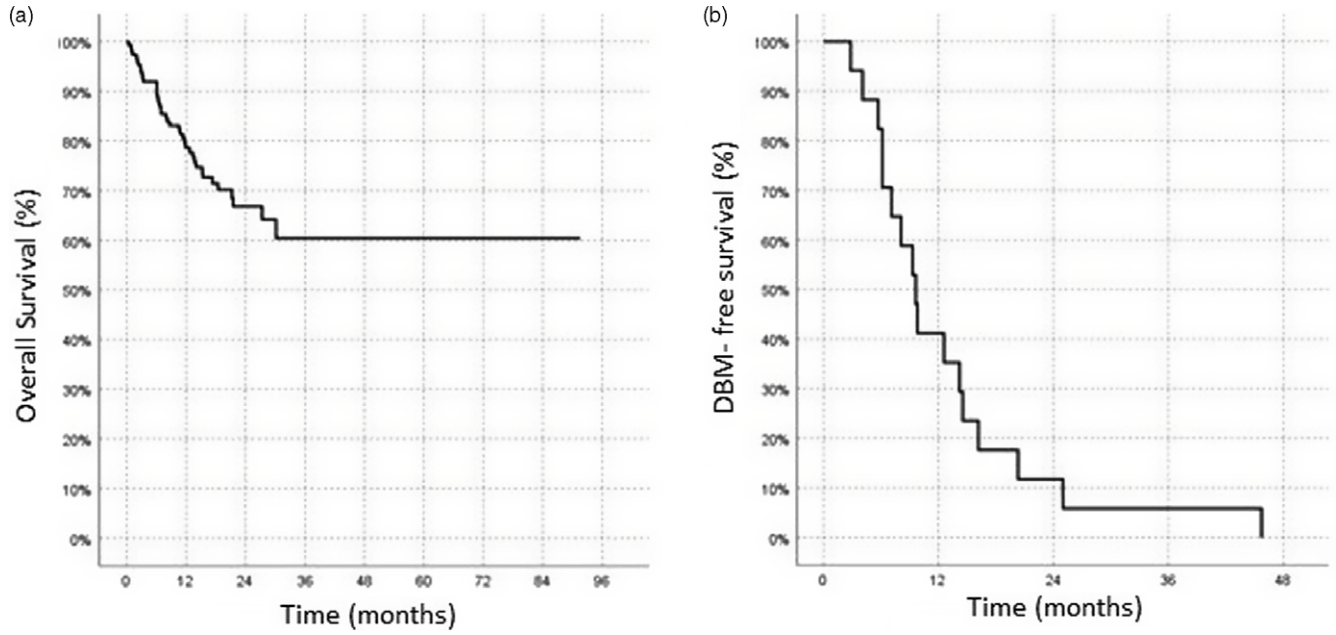

Figure 1. Kaplan–Meier curve of overall survival (a) and distant brain metastasis-free survival (b).

were used to analyse independent quantitative data. The chi-square test was used to analyse independent qualitative data, and the Fischer test was used when chi-square test conditions were not met. Cox regression (univariate–multivariate) was used for survival analysis. SPSS 27.0 (IBM SPSS Inc.) program was used in the analysis.

Results

From December 2016 to April 2020, 375 patients were treated with brain SRS. Two hundred twenty-seven patients were excluded because of missing data or less than 6 months of follow-up in surviving patients. The last follow-up was checked in March 2021. One hundred forty-eight consecutive patients, a total of 444 lesions, were analysed.

Patient, tumour and treatment characteristics are listed in Tables 1 and 2.

The median follow-up was 14·8 months (range 6–51), and the median age was 57 (26–85). The median Karnofsky Performance Scale (KPS) is 90 (50–90 range). Median 2 (1–16) lesions were treated. The medium maximum tumour diameter was 14·3 mm (1–65·3 mm). The prescription doses were 16–18 Gy in a single fraction, 24–27 Gy in three fractions and 30 Gy in five fractions depending on tumour size and the location. The median time between the initial prior RT (WBRT or PCI) and SRS was 7·7 months (1·8–34·1 months). The SRS is used as a salvage strategy in these patients.

Of the 148 analysed patients, 72·3% were alive, 41 were dead and 36 were alive without disease. One and three years OS survival rates are 80% and 60%, respectively (Figure 1a). Seventy-one patients were alive with disease progression. The presence of neurological deficit (OR 2·71,1·07–6·9, $p = 0·036$) and prior RT (WBRT and PCI) (OR 2·55, 1·28–5·09, 0·008) is associated with OS in multivariate analyses (Table 3).

The local recurrence rate was 11·5 % per patient. The median time to local recurrence was 9·6 months (between 2·8 and 45·7). No significant prognostic factors were associated with LC.

The distant brain recurrence rate was 53·4 % (Figure 1b). The median DBM number was 2 (1–50). The median time to DBM is 6·1 months (between 0·3 and 31). In multivariate analysis, brainstem located lesions (OR 7·97, 1·02–62·28, $p = 0·048$) and age (OR 1·02, 1–1·05, $p = 0·021$) were independent parameters for DBM (Table 4). A total of 68 SRS treatments in 53 patients with a median of 1 (1–4 times) and 28 WBRT were applied as a salvage strategy after DBM.

Leptomeningeal metastasis (LMD) was seen in 11 patients (7·4%). The median time to LMD was 14·8 months (between 1·5 and 27·4). No significant prognostic factors were associated with LMD.

Symptomatic radiation necrosis was seen in 19 patients (12·8 %). Median follow-up was longer in patients with BN than patients without BN. The duration of follow is 17·4 versus 13·4 months ($p = 0·015$). After SRS, the median time to BN development was 12·7 months (between 4·8 and 39·6). BN was more common in those without the extracranial disease (68·4 % versus 31·6%). If BN developed in patients with extracranial disease, it was more likely in patients with only bone metastases (83·3 % versus 40·3 %). The maximal tumour diameter was bigger in patients with BN 13 versus 23 mm ($p = 0·034$). Cavity radiosurgery is associated with more BN ($p = 0·004$). Seven out of 22 patients with prior surgery had BN.

Discussion

We present our brain metastasis SRS results in modern technology and systemic treatment area. The survival of metastatic patients has increased since recent imaging and systemic therapy improvements. So LC and side effects related to RT have become increasingly important. The ASTRO guidelines recommend using estimated prognosis and guide treatment decisions.[1]

Survival is a complex end point in patients with BM and is influenced by multiple factors. WBRT does not provide survival benefits compared to SRS.[5–7] In our study, previous whole-brain radiation is associated with decreased survival. These patients

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Table 3. Univariate and multivariate competing risk regression analyses of overall survival

	Univariate					Multivariate				
	OR	(95% CI)			***p*-Value**	OR	(95% CI)			***p*-Value**
Age	1·02	0·99	–	1·05	0·153					
KPS	0·97	0·94	–	1·00	0·081					
Maximum dimension	0·99	0·96	–	1·02	0·551					
Tumour location										
Frontal	0·22	0·11	–	0·42	***0·000***					
Parietal	0·80	0·53	–	1·21	0·291					
Temporal	0·84	0·63	–	1·13	0·252					
Occipital	1·11	0·91	–	1·35	0·295					
Cerebellum	1·01	0·87	–	1·16	0·911					
Basal ganglion	1·06	0·87	–	1·29	0·567					
Brain Stem	1·13	0·95	–	1·34	0·159					
Widespread*	1·01	0·92	–	1·10	0·904					
Other	1·17	0·98	–	1·40	0·091					
Primary diagnosis										
Lung	1·11	0·57	–	2·14	0·755					
Breast	0·54	0·21	–	1·39	0·201					
Colorectal	0·05	0·00	–	>200	0·774					
Melanoma	1·79	0·55	–	5·83	0·334					
Kidney	0·78	0·11	–	5·72	0·811					
Female urogenital	0·93	0·13	–	6·82	0·945					
Other	2·33	0·72	–	7·58	0·159					
Systemic treatment	1·36	0·69	–	2·67	0·371					
Neurological deficit	3·45	1·41	–	8·40	***0·006***	2·71	1·07	–	6·90	***0·036***
Extracranial disease	1·10	0·57	–	2·10	0·781					
Fractionation	0·96	0·52	–	1·77	0·887					
Previous cranial RT	1·89	1·17	–	3·05	***0·010***	2·55	1·28	–	5·09	***0·008***
Surgery	0·67	0·26	–	1·71	0·401					
LMD	1·25	0·44	–	3·50	0·675					
Symptomatic BN	0·26	0·06	–	1·08	0·064					
Distant brain metastasis	0·70	0·38	–	1·29	0·252					
Local recurrence	0·71	0·25	–	1·99	0·514					

* More than three different supratentorial regions.

probably have more metastasis in initial brain metastasis diagnosis, and after WBRT, residual more radioresistance colones or decreased NCFs may lead to decreased survival.

Intracranial disease progression or WBRT itself can cause neurocognitive decline. In addition, declining NCF increases the caregiver burden and impairs financial, work and social activities.[8] There are no published randomised trials for SRS versus WBRT for patients with five or more BM. This study did not define any correlation between lesion number and treatment outcomes. Yamamoto et al.[9,10] documented non-inferior OS rates for patients with 5–10 BM treated with SRS compared to 2–4 lesions. There is no scientific rationale for selecting a certain number of tumours as the cut-off number. Cumulative tumour volume may be more critical in prognostication than lesion number.[11,12] Brain SRS versus hippocampus avoidance WBRT with memantine in multiple BM is now evaluating in a prospective study.[13]

Distant brain recurrence is the main recurrence pattern after brain SRS, with a median 54% (range 35·5%–68%) similar to our study.[14] Compared to WBRT, patients treated with SRS are more likely to require salvage therapy following the development of new BM,[15] but no differences in OS were found.[16] We observed that SRS is a frequent salvage treatment strategy for managing intracranial relapses after SRS (SRS: 68 times in 53 patients versus WBRT: 28 patients). Close surveillance with MRI after SRS treatments is standard in our department for early detection and possible early salvage treatments of CNS relapses. However, no prospective trial analysed the impact of regular MRI follow-up.

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Table 4. Univariate and multivariate competing risk regression analyses of distant brain metastasis

	Univariate					Multivariate				
	OR	(95% CI)			*p*-Value	OR	(95% CI)			*p*-Value
Age	1·02	1·00	–	1·04	***0·025***	1·02	1·00	–	1·05	***0·021***
KPS	0·99	0·97	–	1·02	0·611					
Maximum dimension	1·00	0·98	–	1·02	0·774					
Tumour location										
Frontal	1·35	0·70	–	2·61	0·376					
Parietal	0·69	0·49	–	0·97	***0·032***					
Temporal	1·03	0·84	–	1·26	0·767					
Occipital	0·94	0·78	–	1·13	0·519					
Cerebellum	1·03	0·94	–	1·14	0·495					
Basal ganglion	1·02	0·86	–	1·20	0·859					
Brain Stem	1·38	1·15	–	1·65	***0·001***	7·96	1·02	–	62·28	***0·048***
Widespread*	1·36	1·12	–	1·65	***0·002***					
Other	1·00	0·94	–	1·06	0·975					
Primary Diagnosis										
Lung	1·04	0·65	–	1·66	0·877					
Breast	0·80	0·46	–	1·39	0·424					
Colorectal	2·33	0·32	–	17·13	0·407					
Melanoma	0·98	0·42	–	2·28	0·968					
Kidney	6·49	0·84	–	50·25	0·073					
Female urogenital	0·66	0·09	–	4·78	0·682					
Other	5·10	1·18	–	22·10	***0·029***					
Systemic treatment	0·59	0·31	–	1·14	0·115					
Neurological deficit	1·14	0·61	–	2·16	0·678					
Extracranial disease	0·66	0·42	–	1·05	0·078					
Fractionation	0·91	0·58	–	1·44	0·696					
Previous cranial RT	1·40	0·89	–	2·20	0·141					
Surgery	0·73	0·41	–	1·31	0·287					
LMD	1·03	0·54	–	1·96	0·930					
Symptomatic BN	0·64	0·33	–	1·25	0·187					

* More than three different supratentorial regions.

Postoperative resection cavity radiosurgery is associated with symptomatic radiation necrosis. There are some uncertainties in defining postoperative treatment volume.[17] Normal brain tissue exposes to more radiation with additional PTV margins than primary intact brain SRS treatments.[18] Fractionated stereotactic radiotherapy should be preferred for these lesions.[19,20] Although we could not show it in this study, cavity SRS is associated with increased LMD rates in the literature.[21–23] Preoperative SRS can be a good treatment option for BM requiring surgical resection with lower BN and LMD rates.[18,24]

Melanoma, sarcoma and renal cell carcinoma BM have traditionally been considered radioresistant.[25] However, our analyses found no difference between LC rates comparing different histologies. This radioresistance probably exists in conventional radiotherapy settings, and high doses of radiation with SRS overcome this issue with some radiobiological advantages.[26] Nevertheless, there is a steep dose response in patients with small melanoma metastases, and dose escalation may benefit LC.[27]

Eloquent areas in the central nervous system have a potential higher toxicity risk than other brain regions.[20] We decreased the dose in the cerebellum, brainstem and eloquent areas by one gray per fraction and used multi-fractionated SRS. With this strategy, similar LC can be achieved compared to the other brain subregions without elevated symptomatic BN rates.

In our series, BN rate increased with longer follow-up and was more common in patients with extra- and intracranially controlled disease or only with bone metastases. As these patients live longer than with uncontrolled disease, the likelihood of side effects associated with oncological treatments may increase. In today's oncology era, where longer survivals can be achieved with better treatments, the importance of treatment-related toxicities such as BN is increasing, and stricter rules should be followed to prevent them.

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The present study has inherent limitations based on its retrospective nature, and the results may be somewhat influenced by clinical selection bias. Nevertheless, standardisation in treatment benefited from the fact that all imaging and treatment were done at a single institution.

Conclusion

SRS is an effective local treatment with a high LC rate in brain metastasis. Furthermore, distant brain recurrence is the main recurrence pattern after brain SRS and is generally salvageable with repeated brain SRS. Due to the increased risk of BN, routine metastasectomy should be made with caution.

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