CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Factors influencing the outcome of stereotactic radiosurgery in patients with five or more brain metastases

E. Hamel-Perreault MD,* D. Mathieu MD,* and L. Masson-Cote MD*

ABSTRACT

Background Stereotactic radiosurgery (SRS) for patients with 5 or more brain metastases (BMets) is a matter of debate. We report our results with that approach and the factors influencing outcome.

Methods In the 103 patients who underwent SRS for the treatment of 5 or more BMets, primary histology was non-small-cell lung cancer (57% of patients). All patients were grouped by Karnofsky performance status and recursive partitioning analysis (RPA) classification. In our cohort, 72% of patients had uncontrolled extracranial disease, and 28% had stable or responding systemic disease. Previous irradiation for 1–4 BMets had been given to 56 patients (54%). The mean number of treated BMets was 7 (range: 5–19), and the median cumulative BMets volume was 2 cm^3 (range: 0.06–28 cm^3).

Results Multivariate analyses showed that stable extracranial disease ($p < 0.001$) and RPA ($p = 0.022$) were independent prognostic factors for overall survival (OS). Moreover, a cumulative treated BMets volume of less than 6 cm^3 (adjusted hazard ratio: 2.54; $p = 0.006$; 95% confidence interval: 1.30 to 4.99) was associated with better OS. The total number of BMets had no effect on survival ($p = 0.206$). No variable was found to be predictive of local control. The RPA was significant ($p = 0.027$) in terms of distant recurrence.

Conclusions Our study suggests that SRS is a reasonable option for the management of patients with 5 or more BMets, especially with a cumulative treatment volume of less than 6 cm^3.

Key Words Brain metastasis, stereotactic radiosurgery, Gamma Knife, multiple brain metastases, central nervous system, radiation oncology

Curr Oncol. **2019 Feb;26(1):e64-e69** **www.current-oncology.com**

INTRODUCTION

Metastases are the most common intracranial tumours in adults, accounting for more than 50% of all cases. Brain metastases (BMets) occur in 20%–40% of patients with cancer and are commonly associated with poor prognosis[1]. Evolving systemic treatments have resulted in improved life expectancy for oncology patients, which has contributed to a significant increase in the incidence of BMets. Screening with brain magnetic resonance imaging (MRI) for early detection of BMets is also playing a role in the growing incidence.

The management of BMets has also become more complex and individualized as radiosurgical techniques have evolved. Randomized trials have shown that whole-brain radiotherapy (WBRT) improves the rate of intracranial disease control, but does not confer any improvement in overall survival (OS) and has detrimental neurocognitive effects negatively affecting quality of life[2]. Recently, multiple publications have supported the use of upfront stereotactic radiosurgery (SRS) as the initial management for patients with a limited number of BMets, mostly up to 4, when life expectancy is more than 6 months. In that selected population, SRS provides local control that is equally effective and has fewer neurologic sequelae than those seen with WBRT. However, SRS as the initial treatment for patients with 5 or more BMets is still a matter of debate by physicians. Some believe that, with a higher number of

Correspondence to: Laurence Masson-Cote, Centre hospitalier universitaire de Sherbrooke, 3001 12e avenue Nord, Sherbrooke (Québec) J1H 5N4.
E-mail: Laurence.Masson-Cote@Usherbrooke.ca **DOI:** https://doi.org/10.3747/co.25.4244

BMets, the risk of distant brain recurrence increases, and the consequences for neurologic decline could be worse than the neurocognitive effect of WBRT. However, there is a growing tendency to hold WBRT for salvage treatments, such as in leptomeningeal dissemination, and to prioritize early preservation of neurocognitive function and quality of life. Currently, no well-defined criteria for the selection of patients with multiple BMets (≥5) who would benefit from SRS as the initial approach have been established. Current guidelines consider several factors to guide clinicians, such as the number of metastases, active or stable extracranial disease, and performance status [recursive partitioning analysis (RPA) or Karnofsky performance status (KPS)][3,4]. The total volume of metastases being treated is not considered in any guideline; however, some recent publications show that volume could be an important predictor of treatment response and OS.

We designed the present retrospective study to identify factors influencing OS, local recurrence [LR (that is, recurrence of a BMet treated with SRS at the time of the studied intervention)] and distant recurrence [DR (that is, disease progression in the brain excluding LR)] with special emphasis on the cumulative volume of treated BMets. Ultimately, the goal was to precisely acknowledge a subpopulation of patients with multiple metastases who might benefit from an SRS approach.

METHODS

We reviewed the database of patients who underwent SRS for BMets between September 2005 and March 2016 at the Centre hospitalier universitaire de Sherbooke, identifying 103 patients who underwent SRS for 5 or more BMets. The charts of those patients and the Gamma Knife (Elekta Instruments, Stockholm, Sweden) SRS database, which is prospectively collected by neurosurgeons and radiation oncologists at the time of treatments, were reviewed. All data and statistical analyses are therefore presented based on patient characteristics at the time of the SRS treatment for 5 or more BMets and as they evolved after treatment. Local research ethics board approval was obtained for the study.

Data collected included baseline and post-SRS demographic, clinical (KPS, neurologic symptoms, side effects), and imaging characteristics (baseline and follow-up brain MRI every 2–3 months). Response to SRS treatment was assessed using the Response Assessment in Neuro-Oncology criteria[5]. Side effects of SRS were classified using the *Common Terminology Criteria for Adverse Events,* version 4.0.

Patient Characteristics

Table I presents details of the patient characteristics. The diagnosis of BMets was made by MRI. The use of SRS rather than conventional WBRT as management for 5 or more BMets was selected for patients with a limited cumulative volume of BMets and a life expectancy of more than 6 months, or for patients who had already been treated with WBRT. Radiation for 1–4 BMets had been given in 56 patients (54%, Table II). In selected patients (7%), SRS was performed not just on multiple unresected BMets, but also on the tumour bed after resection of a large BMet.

Median patient age was 58 years, and women constituted 70% of the cohort. Primary histology included non-small-cell lung cancer (57%), breast cancer (28%), melanoma (12%), and colorectal cancer (3%). Diagnosis of the primary cancer and the BMets was synchronous (defined

TABLE I Patient characteristics

Variable	Pts (*n*)	Value	*p* Value[a]
Age (years)	103		0.004
Median		58	
Range		26–88	
Age group [*n* (%)]	103		
<65 Years		71 (68)	
≥65 Years		32 (31)	
Sex [*n* (%)]	103		0.060
Men		31 (30)	
Women		72 (70)	
Primary cancer [*n* (%)]	103		0.011
NSCLC		59 (57)	
Adenocarcinoma		40 (40)	
Epidermoid		5 (5)	
Large cell		3 (3)	
Undifferentiated		11 (11)	
Primary cancer site [*n* (%)]	103		NA
Breast		29 (28)	
Melanoma		12 (12)	
Colorectal		3 (3)	
Combined TNM stage at initial Dx [*n* (%)]	89		NA
I		6 (7)	
II		9 (10)	
III		18 (20)	
IV		56 (63)	
Synchronicity [*n* (%)]	103		0.023
Synchronous		43 (42)	
Metachronous		60 (58)	
Antecedent <5 brain metastases [*n* (%)]	103		0.012
Yes		55 (53)	
No		48 (47)	
Previous irradiation treatment[b] [*n* (%)]	56		0.712
With WBRT		34 (61)	
Without WBRT		22 (39)	
Extracranial disease status at SRS [*n* (%)]	103		<0.001
Controlled		29 (28)	
Active		74 (72)	
Treatment of primary tumour at SRS [*n* (%)]	94		NA
Curative RT/CTx		13 (14)	
Palliative RT/CTx		66 (70)	
Supportive care only		15 (16)	

TABLE I Continued

Variable	Pts (*n*)	Value	*p* Value[a]
Symptoms at Dx of ≥5 brain metastases [*n* (%)]	103		NA
None		48 (47)	
Focal deficit		19 (18)	
Seizures		10 (10)	
Severe headaches		16 (16)	
Cerebellar disorders		9 (9)	
Amnesia		1 (1)	
Karnofsky PS at SRS [*n* (%)]	90		<0.001
90–100		56 (62)	
70–80		29 (32)	
<70		5 (6)	
RPA at SRS [*n* (%)]	90		<0.001
1		11 (12)	
2		74 (82)	
3		5 (6)	
Neurologic status at SRS [*n* (%)]	103		NA
Asymptomatic		67 (65)	
Symptomatic		36 (35)	
Brain metastases *(n)*	103		0.206
Mean		7	
Range		5–19	
5–9		81 (79)	
≥10		22 (21)	
Cumulative tumour volume	101		0.024
Median (cm^3)		2.0	
Range (cm^3)		0.06–28	
<6 cm^3 [*n* (%)]		80 (79)	
≥6 cm^3 [*n* (%)]		21 (21)	
Volume of the largest tumour (cm^3)	103		NA
Mean		1.1	
Range		0.02–16	
Corticosteroids [*n* (%)]	99		NA
At SRS		55 (55)	
At last follow-up		44 (44)	

[a] Log-rank test in univariate analysis.
[b] For 1–4 brain metastases.
Pts = patients; NSCLC = non-small-cell lung cancer; NA = not applicable; Dx = diagnosis; WBRT = whole-brain radiation therapy; SRS = stereotactic radiosurgery; RT = radiation therapy; CTx = chemotherapy; PS = performance status; RPA = recursive partitioning analysis.

as an interval of less than 6 weeks between diagnoses) in 42% of the patients; the remaining 58% of the patients had a metachronous diagnosis. In 72% of the patients, extracranial disease was uncontrolled; the remaining 28% had stable or responding systemic disease. In 70% of patients, chemotherapy or radiotherapy was given with palliative intent; 14% were receiving curative-intent treatment for their extracranial disease; and 16% were receiving only supportive care. When stratified by the Radiation Therapy Oncology Group RPA, 12% of patients were designated class I; 82%, class II; and 6%, class III. The mean number of treated BMets was 7 (range: 5–19), with 79% of patients having 5–10 BMets, and 21% having more than 10 BMets. Median volume of the largest BMet was 1.1 cm^3 (range: 0.02–16 cm^3), and the median cumulative BMet volume was 2.0 cm^3 (range: 0.06–28 cm^3). In 79% of patients, the total cumulative tumour volume was less than 6 cm^3.

TABLE II Previous irradiation in 56 patients for 1–4 brain metastases more than 6 months before stereotactic radiosurgery

Patient group	Value [*n* (%)]
With WBRT	34 (61)
WBRT only	11 (20)
WBRT, SRS	11 (20)
WBRT, surgery	6 (11)
WBRT, SRS, surgery	6 (11)
Without WBRT	22 (39)
SRS only	10 (18)
SRS, surgery	11 (20)
SRS, fractionated RT	1 (2)

WBRT = whole-brain radiation therapy; SRS = stereotactic radiosurgery; RT = radiation therapy.

Radiosurgery Procedures

Treatments were performed using a Leksell Gamma Knife (model 4C or Perfexion) under local anesthesia, with conscious sedation. A volumetric contrast-enhanced magnetization-prepared rapid gradient echo MRI sequence with 3-dimensional reconstruction was used for dose planning. Radiosurgical plans were devised using the Leksell GammaPlan software (Elekta Instruments). The median cumulative treatment volume was 3.2 cm^3 (range: 0.24–41 cm^3). The median margin dose prescribed was 20 Gy (range: 16–25 Gy), and the median maximum dose was 30 Gy (range: 20–44 Gy). The isodose line varied between 50% and 85%, and the number of isocentres varied between 1 and 15 (median: 1) depending on target coverage and conformity indices.

Statistical Analyses

Median survival duration was determined using the Kaplan–Meier method. The Kaplan–Meier method with log-rank test was used in univariate analysis to determine the difference in OS between categories of independent variables. A log-rank test for trend was also used when appropriate. Significant variables in the univariate analysis were included in a multivariate Cox model to find predictors of OS. Multivariate analyses using Cox regression with the same independent factors were also performed to model local control and distant recurrence. All analyses were performed using the IBM SPSS Statistics software application (version 24: IBM, Armonk, NY, U.S.A.). Any *p* value less than 0.05 was considered significant.

RESULTS

Survival

The median OS duration after SRS was 6 months (range: 1–58 months). Median follow-up was 13 months (range: 1–35 months). Six patients were lost to follow-up. Median survival rates at 2, 6, and 12 months were 92%, 55%, and 34% respectively. The multivariate Cox regression revealed that stable extracranial disease status ($p < 0.001$) and RPA class I ($p = 0.022$) were independent prognostic factors for OS. Patients with a cumulative volume of treated BMets less than 6 cm^3 (adjusted hazard ratio: 2.54; $p = 0.006$; 95% confidence interval: 1.30 to 4.99; Figure 1) experienced improved survival. On multivariate analysis, metachronous diagnosis of the BMets ($p = 0.210$) did not significantly influence survival; neither did prior treatment for fewer than 5 BMets ($p = 0.848$). In the univariate log-rank tests, the total number of BMets ($p = 0.206$, Figure 2) and the absence of extracranial metastases ($p = 0.380$) had no effect on survival and were not considered in the multivariate analyses.

The exact cause of death was identified in only 36% of deceased patients. Neurologic progression or complications were determined to be the cause of 11 deaths, and 26 patients died from systemic progression. Leptomeningeal dissemination occurred in 9 patients.

Local and Remote Tumour Control

According to the last follow-up data, local tumour control, defined as the absence of any progression of the treated BMets according to the Response Assessment in Neuro-Oncology criteria, was achieved in 75% of patients (1% complete response, 8% partial response, and 66% stable disease). Tumour control was 96% at 2 months, and 79% at 6 months. In the multivariate Cox model, no variable predictive of local control was found, including primary cancer histology, age, synchronous diagnosis, primary cancer status, RPA, or total volume of treated BMets.

New remote BMets, or distant recurrence, were eventually observed in 72% of patients: 17% presented with 1–5 new BMets, 13% with 5–10 BMets, 26% with more than 10 BMets, and 12% with leptomeningeal dissemination. The distant recurrence rate was 41% at 2 months and 53% at 6 months. The only variable that, in multivariate Cox regression analysis, had a significant effect on remote brain control was RPA status ($p = 0.027$). Cancer histology, age, synchronous diagnosis, primary cancer status, and total volume of treated BMets were nonsignificant.

When LR or DR was diagnosed, patients either underwent repeat SRS, WBRT, or surgery with SRS; received palliative care; or were left under observation. Intra-arterial chemotherapy was given in 6 patients with breast cancer. Overall, patients had a mean of 2 SRS treatments in total (range: 1–10).

Toxicity

No patient presented with long-term side effects or complications of SRS. Radiation necrosis was suspected in 10 patients, but no patient presented a confirmed case of radionecrosis based on MRI assessment and surgery (surgery only confirmed cases of LR). One patient developed progressive headaches and seizures after treatment for a cumulative volume of 2.56 cm^3; brain computed tomography demonstrated increased cerebral edema. The patient had progressive systemic disease and declined any further treatment. He died within 2 weeks after deciding to pursue supportive care only.

DISCUSSION

In recent years, SRS has gained in popularity for the management of patients with multiple BMets. However, clear recommendations about which patients could benefit from that approach compared with conventional WBRT have not been established. We aimed to determine whether patients with 5 or more BMets could benefit from the SRS approach. We confirmed that the cumulative volume of treated BMets is an independent prognostic factor for OS, but that the total number of BMets is not statistically significant in

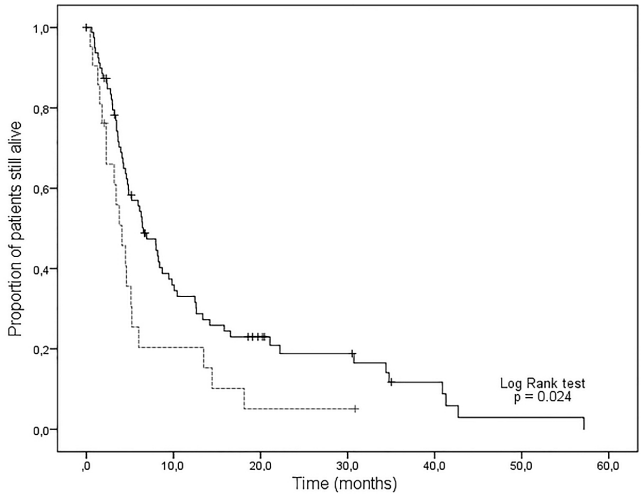

FIGURE 1 Kaplan–Meier plot depicting survival rates by the cumulative volume of treated brain metastases (solid line, <6 cm^3; dotted line, ≥6 cm^3), with log-rank test.

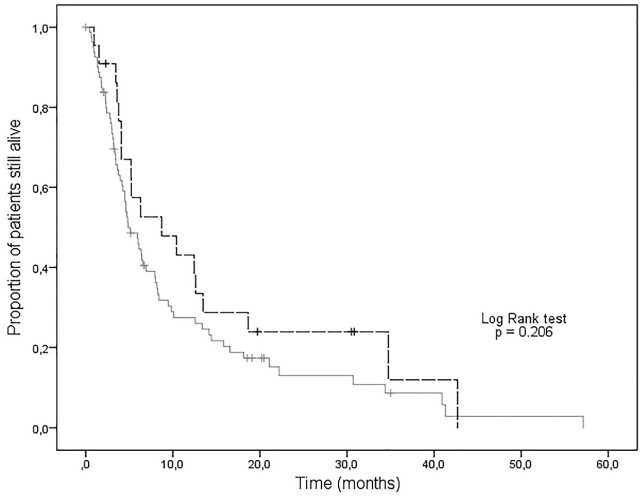

FIGURE 2 Kaplan–Meier plot depicting survival rates by the total number of treated brain metastases (solid line, 5–9; dashed line, ≥10), with log-rank test.

terms of OS, local control, or DR. More specifically, a total volume of treated BMets less than 6 cm^3 was associated with significantly better OS. Stable extracranial disease and RPA class I were also independent favourable prognostic factors for OS. In terms of local control, no factor was found to be significant. As for DR, RPA class I was identified on multivariate analysis as a statistically significant factor for better outcome.

Other studies corroborate our results, confirming that discrimination based on the total volume of BMets rather than the absolute number of BMets is more appropriate. A major prospective observational study from Japan, JLGK0901[6] (1194 patients enrolled), suggested that SRS without WBRT as the initial treatment for patients with 5–10 BMets is not inferior to SRS without WBRT in patients with 2–4 BMets in terms of OS (noninferiority $p < 0.0001$). In that study, patients eligible for standard SRS treatment had 1–10 newly diagnosed BMets and a KPS of 70 or greater. In multivariate analyses, longer survival was statistically associated with a KPS of 80 or greater ($p = 0.0001$), age less than 65 years ($p = 0.0001$), stable extracranial disease ($p = 0.0011$), and no neurologic symptoms ($p = 0.0013$). Cumulative tumour volume was found to be significant on univariate analysis, but not on multivariate analysis. The incidences of LR, distant new BMets, and use of salvage treatment was not higher in patients with 5–10 BMets than in those with 2–4 BMets.

The recent progress made in terms of available efficient systemic therapies is also a major game-changer. New drugs, including immunotherapy agents[7–9] and novel targeted therapies (BRAF or MEK inhibitors[10] and selective cyclin-dependent kinase 4–6 inhibitors[11], among others), have shown increased efficacy to control systemic extracranial disease. Some selected molecules can cross the blood–brain barrier and might affect the outcome of BMets, such as dabrafenib–trametinib in patients with $BRAF^{V600E}$–mutant melanoma BMets[12]. Many investigators are currently studying the optimal combinations of SRS with those new drugs in patients presenting BMets of varying histology.

Our results also highlight the importance of establishing more accurate guidelines that include total tumour volume. The prognostic indexes currently used in clinical practice are the Radiation Therapy Oncology Group RPA[13], which does not consider the number or volume of BMets, and the diagnosis-specific graded prognostic assessment score[14], which pays attention exclusively to the total number of BMets. The current U.S. National Comprehensive Cancer Network guideline[15] suggests SRS as primary treatment for more than 3 BMets in patients with good performance status and a low overall BMets volume. The American Society for Radiation Oncology[3] cites level 1 evidence supporting SRS without concurrent WBRT only for patients with up to 4 BMets. Cut-off values in the literature are very variable. Indeed, in a retrospective study of 250 patients with multiple BMets, Baschnagel *et al.*[16] concluded, after adjusting for other factors (age, KPS, and extracranial disease), that patients presenting a total BMets volume of more than 2 cm^3 experienced statistically significant worse OS ($p = 0.008$), poor local control ($p < 0.001$), and a higher rate of DR ($p = 0.028$). The number of lesions was not a predictor of survival in univariate analysis ($p = 0.082$). Researchers at the Virginia Hospital Center[17] concluded in their retrospective study that a cumulative tumour volume of more than 7 cm^3 ($p < 0.05$) correlated with worse morbidity and mortality. In a retrospective study of patients ($n = 720$) with metastases from non-small-cell lung cancer, Bowden *et al.*[18] observed that the volume of BMets was inversely related to OS ($p < 0.001$): median survival duration was 10.3 months when the BMets volume was less than 5 cm^3 and 6.4 months when the BMets volume was 5 cm^3 or greater. Those studies, like ours, might have included patients who had already undergone irradiation. However, Ojerholm *et al.*[19] studied patients presenting with 4 or more BMets treated with SRS alone and observed that, when the total tumour volume was 3 cm^3 or greater, OS worsened ($p = 0.04$) and the rate of DR increased ($p = 0.042$). Even if studies are equivocal about the precise threshold for the BMets volume, data support treatment with SRS for selected patients having 5 or more BMets as an appropriate and reasonable strategy. The definitive volume cut-off for predicting OS and local control will need further studies—such as large prospective controlled trials.

One limitation of our study is the fact that more than half the patients (54%) had already undergone irradiation. However, we included only patients who were treated for fewer than 5 BMets more than 6 months before the SRS procedure that was the focus of the study, which we believe mitigates any effect on our results. Other limitations include the retrospective nature of the study, a possible treatment selection bias, and the relatively limited number of patients ($n = 103$). Evaluation of radionecrosis as an adverse side effect was also limited by the short survival of patients. Patient mobility also limited follow-up data collection and, in some cases, led to lack of information about the cause of death. However, the strength of our study is that the results are applicable to daily clinical oncology practice, given that patient characteristics and the choice of SRS compared with WBRT was not limited by strict predetermined criteria.

CONCLUSIONS

Stereotactic radiosurgery is a reasonable option for the management of patients with 5 or more BMets, especially when the cumulative treatment volume is less than 6 cm^3. Given earlier publications that similarly support that therapeutic approach, a large prospective trial and a revision of the current practice guidelines are needed to improve the management of patients with multiple BMets. With more targeted treatment, clinicians will be able to minimize the long-term toxicity of brain irradiation, because those side effects are a serious concern in the contemporary setting of new and effective systemic treatments and prolonged survival in this population.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Centre hospitalier universitaire de Sherbrooke, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, QC.

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