ORIGINAL ARTICLE

Stereotactic Radiosurgery for Metastases in Eloquent Central Brain Locations

Fred Hsu, Alan Nichol, Roy Ma, Para Kouhestani, Brian Toyota, Michael McKenzie

ABSTRACT: ***Background:*** To examine stereotactic radiosurgery (SRS) following whole brain radiotherapy for metastases in eloquent, central brain locations: brainstem, thalamus, and basal ganglia. ***Methods:*** We conducted a retrospective review of patients with metastases in eloquent, central brain locations who were treated with SRS between January 2000 and April 2012. All patients had whole brain radiotherapy. Patients eligible for SRS had one to three brain metastases, metastasis size ≤4 cm, and Karnofsky performance status ≥70. Local progression-free survival and overall survival were calculated using the Kaplan-Meier method. ***Results:*** For 24 patients, the median age was 50 years (range, 36-73). Metastases by location were: 11 brainstem, 9 thalamus, and 5 basal ganglia. The median metastasis size was 15 mm (range, 2-33) and the median SRS dose prescription was 15 Gy (range, 12-24). The median local progression-free survival was 13.7 months and median overall survival was 16.4 months. Compared with a cohort of 188 patients with noneloquent brain metastases receiving a median dose of 24 Gy, overall survival of 10.8 months was not significantly different ($p = 0.16$). The only symptomatic complication was grade 2 headache in 8.3%. Asymptomatic adverse radiologic events were radionecrosis in two (8.3%), peritumoural edema in four (16.7%), and hemorrhage in one patient (4.2%). ***Conclusions:*** Lower SRS marginal doses do not appear to compromise survival in patients with eloquently located brain metastases compared with higher doses for other brain metastases, with minimal symptomatic complications.

RÉSUMÉ: Radiochirurgie stéréotaxique comme traitement de métastases situées dans des aires éloquentes du cerveau. ***Contexte:*** Le but de l'étude était d'examiner la radiochirurgie stétéotaxique (RSS) administrée après la radiothérapie du cerveau entier pour des métastases situées dans des aires éloquentes du cerveau, soit le tronc cérébral, le thalamus et les noyaux de la base. ***Méthode:*** Nous avons effectué une revue rétrospective des dossiers de patients atteints de métastases situées dans des aires éloquentes du cerveau, qui ont été traités par RSS entre janvier 2000 et avril 2012. Tous les patients avaient été traités préalablement par radiothérapie du cerveau entier. Les patients éligibles à la RSS avaient de une à trois métastases cérébrales dont la taille était de 4 cm ou moins et un score à l'échelle de Karnofsky de 70 ou plus. La survie sans progression locale et la survie globale ont été calculées au moyen de la méthode de Kaplan-Meier. ***Résultats:*** Chez les 24 patients de l'étude, l'âge médian était de 50 ans (écart de 36 à 73 ans). La répartition des métastases selon leur localisation était la suivante: 11 au tronc cérébral, 9 au thalamus et 5 aux noyaux de la base. La taille médiane des métastases était de 15 mm (écart de 2 à 33 mm) et la dose médiane de RSS prescrite était de 15 Gy (écart de 12 à 24 Gy). La survie médiane sans progression locale était de 13,7 mois et la survie médiane globale était de 16,4 mois. La survie globale n'était pas significativement différente de celle d'une cohorte de 188 patients ayant des métastases cérébrales dans des aires non éloquentes du cerveau. Ces patients avaient reçu une dose médiane de 24 Gy ($p = 0,16$), et leur survie globale était de 10,8 mois. La seule complication symptomatique observée était une céphalée de grade 2 chez 8,3% des patients. Parmi les incidents radiologiques asymptomatiques observés, les plus fréquents étaient une radionécrose chez 2 patients (8,3%), un œdème péritumoral chez 4 patients (16,7%) et une hémorragie chez 1 patient (4,2%). ***Conclusions:*** Des doses marginales plus basses de RSS ne semblent pas compromettre la survie chez les patients ayant des métastases situées dans des aires cérébrales éloquentes par rapport à des doses plus élevées administrées pour traiter d'autres métastases cérébrales et entraînent des complications symptomatiques minimes.

Keywords: Radiation oncology, Radiosurgery, Stereotactic

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The benefits of whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) for the treatment of brain metastases have been reported in several randomized studies. For patients with one to three brain metastases, WBRT and SRS have demonstrated an improvement in local control.[1-3] In one randomized study, selected patients with single brain metastasis treated with WBRT and SRS boost had better survival.[2] Additionally, SRS-related grade ≥3 neurologic toxicities are uncommon.

However, some brain regions may be more sensitive to radiation injury, particularly when using large single-fraction doses. In a

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study of arteriovenous malformations, Flickinger et al[4] reported that the risks of developing permanent symptomatic complications from radiosurgery vary significantly with lesion location and, to a lesser extent, volume. The locations at most risk were the medulla, thalamus, basal ganglia, and pons/midbrain. These eloquent, central brain regions are involved in important somatosensory, emotional, motivational, associative, and cognitive functions. Metastases to these brain regions are less common, but patients are at a potentially higher risk of treatment related morbidity and mortality. There are few studies examining SRS for metastases in these eloquent locations and treatment outcomes are less well-known. An important question is whether SRS for metastases in these eloquent brain locations is safe.

With institutional ethics approval, we conducted a population-based retrospective study to examine the outcomes of SRS following WBRT for metastases in eloquent, central brain regions: brainstem, thalamus, and basal ganglia.

Methods

Patients were identified from our institution's stereotactic database, capturing all patients treated with SRS in British Columbia, Canada. There were 212 consecutive patients treated with WBRT and SRS for brain metastases from January 2000 and April 2012. This patient population was divided into "eloquent" and "noneloquent" cohorts. The eloquent cohort comprised 24 patients with at least one metastasis in an eloquent, central brain location defined as the brainstem (pons, medulla, and midbrain), thalamus, or basal ganglia. A total of 188 patients without metastases in these brain locations composed the noneloquent cohort.

At our institution, patients are reviewed by radiation oncologists, neurosurgeons, and a neuroradiologist at a provincial stereotactic conference before SRS. All patients had WBRT. Lesions deemed unsuitable for resection are considered for SRS. The patients eligible for SRS had one to three metastases, metastasis size $\leq$4 cm, and Karnofsky performance status (KPS) $\geq$70. There was also evidence of stable extracranial disease. For treatment planning, patients had high-resolution contrast-enhanced CT and MRI. CT and MRI images were coregistered in the stereotactic planning software (Brainlab, Germany). The gross tumour volume was delineated as the contrast-enhancing tumour on the CT/MRI coregistered images. A 1-mm (when using a stereotactic head ring) or 1.5-mm (when using a frameless stereotactic mask) volumetric expansion of the gross tumour volume was used to construct a planning target volume, accounting for the accuracy of the immobilization and positioning system. Dose prescription was to the 80% isodose volume encompassing the planning target volume. For noneloquent metastases, the stereotactic group's dose prescription was: 15 Gy for 31- to 40-mm diameter metastases, 18 Gy for 21- to 30-mm metastases, and 24 Gy for $\leq$20-mm metastases. For metastases in the brainstem, thalamus, or basal ganglia, the group favoured more conservative dose prescriptions rather than the same size-based guideline. The dose prescription was at the discretion of the treating oncologist, and there was no size-based guideline. Metastases in these locations were considered unsuitable for resection. Single-fraction treatment was delivered using linear accelerator-based SRS with multiple static beams or multiple dynamic arcs using 3-mm multileaf collimation.

Patients had follow-up one to three months after SRS and every three to four months thereafter. The median follow-up in clinic was 12.1 months (range, 0-89.0). The patients' electronic health records were reviewed for neurologic symptoms to include ataxia/incoordination, motor/sensory deficits, other movement disorders, visual disturbances, dysphagia, seizures, and headaches. Radiosurgery-related neurologic symptoms were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. The median follow-up with brain imaging (using CT or MRI, at the discretion of the oncologist) was 12.1 months (range, 0-75.9). The patients' brain images were reviewed for lesion progression and SRS-related complications (as reported by a neuroradiologist): necrosis, hemorrhage, and edema. When lesion progression versus radionecrosis was unclear, subsequent brain imaging was reviewed for evolution of those changes. Radionecrosis imaging findings were defined as those that stabilized, whereas tumour progression imaging findings did not. The reporting of an adverse imaging event was back-dated to when the changes were first seen.

Local progression-free survival (LPFS) and overall survival (OS) were measured from the date of SRS and calculated using the Kaplan-Meier method. For patients still alive, the date of last follow-up was used to censor survival time. The date of last imaging was used to determine local control. For LPFS, patients lost to imaging follow-up before death were censored at the time of last imaging, not at the time of death. Survival between the two cohorts was compared using the log-rank test. Hazards ratios (HR) and confidence intervals were computed using Cox regression

Table 1: Patient characteristics for the eloquent and noneloquent cohorts

		Eloquent cohort	Noneloquent cohort
No. of patients		24	188
Gender	Male	6 (25%)	66 (35%)
	Female	18 (75%)	122 (65%)
Median age (years)		50	57
Primary site	Lung	8 (33%)	87 (46%)
	Breast	11 (46%)	42 (22%)
	Melanoma	1 (4%)	16 (9%)
	Colorectal	0 (0%)	9 (5%)
	Renal	0 (0%)	14 (7%)
	Other	4 (17%)	20 (11%)
Median KPS		80	80
No. of eloquent metastases		25	—
Total no. of metastases		40	300
Mean no. of metastases per patient		1.7	1.6
Median no. of metastases per patient		1	1
ECM	Yes	12 (50%)	104 (55%)
	No	12 (50%)	84 (45%)
RPA class	I	12 (50%)	60 (32%)
	II	11 (46%)	126 (67%)
	III	1 (4%)	2 (1%)

ECM = extracranial metastases.

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analysis. Univariate analysis was performed to investigate patient and disease characteristic differences between the eloquent and noneloquent cohorts. Comparisons were made using the t-test and Mann-Whitney-Wilcoxon test for continuous characteristics with normal and skewed distributions, respectively. The Pearson chi-square test was used for categorical characteristics, and the Fisher's exact test was used for categorical characteristics with small frequencies. The covariates used in the multivariate analysis were age, recursive partitioning analysis (RPA) class, presence of extracranial metastases (yes/no), number of brain metastases (1 versus >1), gender, and primary site. The variables were entered in the multivariate model using a backward selection to determine the final model.

Table 2: Dose prescription for metastases in eloquent brain locations

	Mean dose (Gy)	Median dose (Gy)	Dose range (Gy)
All eloquent metastases	16.2	15	12-24
Brainstem only	13.6	12	12-18
Thalamus only	19.0	18	15-24
Basal ganglia only	16.8	18	15-18

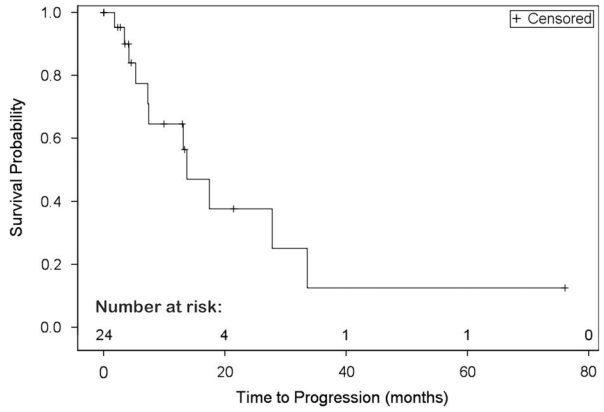

Figure 1: *Kaplan-Meier curve showing local progression free survival for patients in the eloquent cohort*

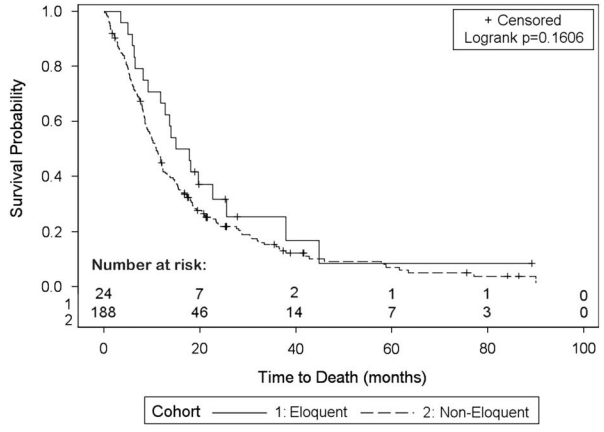

Figure 2: *Kaplan-Meier curves showing survival for eloquent and non-eloquent cohorts*

Results

For 24 patients, there were 25 metastases in eloquent, central brain locations: 11 in the brainstem, nine in the thalamus, and five in the basal ganglia. This eloquent cohort was composed of 14 patients with metastases limited to eloquent locations and 10 patients with metastases in both eloquent and noneloquent locations. The median age was 50 years (range, 36-73) and the median KPS was 80 (range, 70-100). Diagnosis by primary site was 11 breast, eight lung, and five other. At the time of analysis, five patients (21%) were alive and 19 (79%) had died. Compared with the noneloquent cohort of 188 patients, there was no significant difference in primary site ($p = 0.12$), KPS ($p = 0.36$), RPA class ($p = 0.08$), or number of brain metastases ($p = 0.92$). The median age was younger for the eloquent cohort (50 versus 57 years, $p = 0.04$). The patient characteristics for each cohort are presented in Table 1.

Both eloquent and noneloquent cohorts were treated with the same median WBRT dose, 30 Gy in 3-Gy fractions. Brain metastasis size was measured using the largest linear dimension in any plane. For metastases in eloquent brain locations, the median lesion size was 15 mm (range, 2-33) and the median SRS dose prescription was 15 Gy (range, 12-24). The size of metastases were not significantly different than those in noneloquent brain locations, median = 13 mm ($p = 0.23$). However, the SRS prescription dose was lower compared with a median of 24 Gy for non-eloquent metastases ($p < 0.0001$). The dose prescriptions for metastases in eloquent brain locations are presented in Table 2.

Local progression-free survival for metastases in eloquent brain locations was 13.7 months. The Kaplan-Meier curve showing LPFS is presented in Figure 1. The 6- and 12-month LPFS were 78% and 65%, respectively. The median OS for the eloquent cohort was 16.4 months. Overall survival was not statistically different compared with the noneloquent cohort, median of 10.8 months ($p = 0.16$). Kaplan-Meier survival curves for both cohorts are presented in Figure 2.

For the eloquent cohort, 15 patients had neurologic symptoms before treatment and nine were asymptomatic. On clinical follow-up, the incidence of SRS-related symptoms was 8.3%. Twenty-two patients (91.7%) had unchanged (n = 5, 21%), improved (n = 5, 21%), or no (n = 12, 50%) neurologic symptoms. Two patients (8.3%) who had new-onset grade 2 headaches were effectively managed with prolonged courses of corticosteroids. On radiographic follow-up, the incidence of SRS-related adverse changes was 29.2%. None of the adverse radiographic events resulted in clinical symptoms. Two patients (8.3%) had suspected radionecrosis. Both cases were in the basal ganglia, and neither patient developed new or progressive neurologic problems. The median time to radionecrosis was 16.0 months. One patient (4.2%) had hemorrhage in a thalamic metastasis, which was self-limiting and resolved by the subsequent follow-up scan. Four patients (16.7%) had new or progressive edema in the setting of lesion stability or improvement (two brainstem and two thalamic), which we considered SRS-related. One patient had worsening edema in the setting of lesion progression, which we considered tumour-related.

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On multivariate analysis for the eloquent cohort, only number of brain metastases (1 vs. >1) was a significant factor for survival (HR, 3.8; 95% confidence interval, 1.4-10.5; p = 0.01). Age, RPA class (1 versus 2/3), presence of extracranial metastases (yes/no), gender (male versus female), and primary site (breast versus lung versus other) were not statistically significant for this cohort. Karnofsky performance status and control of primary disease were not included in the analysis because they were largely controlled for by the stereotactic group's eligibility criteria. In subset analysis comparing brainstem versus thalamus/basal ganglia metastases, LPFS (13.1 versus 13.7 months, p = 0.68) and OS (15.7 versus 16.5 months, p = 0.51) were not significantly different.

Discussion

To minimize the risk of radionecrosis in eloquent brain locations and serious complications from SRS, our stereotactic group used a reduced dose prescription compared with that used for other brain metastases. A primary concern when doing so is a compromise in local tumour control and survival. In this study, we report that, despite a lower median prescription dose, survival for patients with brain metastases in eloquent brain locations was comparable to other brain metastases patients. The 5.6-month longer survival in the eloquent cohort, although not statistically significant, was likely a result of patient selection. For the eloquent cohort, patients were younger and there was a trend toward more patients with a breast primary and RPA class I. These characteristics have been associated with longer survival in other studies of brain metastases.[5-7]

This is the first study to examine eloquent and noneloquent brain metastases treated with SRS using similar patient cohorts selected using the same treatment criteria. Our study examined lesions in the brainstem, thalamus, and basal ganglia based on previously reported elevated risks of radionecrosis in these locations when using large single-fraction doses.[4] Only brainstem metastases have been examined in comparable studies. Survival with brainstem metastases varies widely from 4 to 12 months in published literature, with mean marginal doses range of 13-20 Gy. In a study of 28 patients with brainstem metastases treated with Gamma Knife, Fuentes et al[8] reported a median survival of 12.0 months with a mean marginal dose of 19.6 Gy. Other studies using a mean dose ≥16 Gy report a median survival between 8.5 and 11.1 months.[9-13] In five studies using a mean dose <16 Gy, the median survival range was 4.2-10.0 months.[14-18] Using a mean peripheral dose of 13.6 Gy, OS in our brainstem subset was 15.7 months. One reason for the wide differences in survival between studies is likely patient heterogeneity. This includes patient KPS, RPA, number of brain metastases, metastases size, and status of extracranial disease, which have been associated with survival.[5,7] Patients in our cohort had KPS ≥70, median number brain metastasis = 1, younger median age = 50 years, and control of extracranial disease. The highly selective eligibility criteria used by our stereotactic group likely explains our better survival. Higher SRS doses have also been suggested for better local control and survival.[19] However, we found that lower SRS doses achieved comparable survival for patients with eloquently located metastases as higher doses for other brain metastases. This finding is similar to that reported by Valery et al,[15] who examined reduced doses for brainstem metastases. This outcome is also supported by Hatiboglu et al,[18] who reported no difference in survival comparing published studies that used higher doses with those that used lower doses for brainstem metastases.

Symptomatic complications following SRS for brainstem metastases are variable between studies. Some published series report no complications,[8,9,12] whereas others report acute headache, hemiparesis, cranial nerve deficits, confusion, ataxia, or seizures.[13,15,16,18] In our study, only two patients had grade 2 toxicity and none had neurologic impairment. On the other hand, asymptomatic adverse radiographic events occurred in 29.2%. This was mostly in the form of asymptomatic peritumoural edema. The incidence of suspected radionecrosis was 8.3%, but no occurrences were in the brainstem where the lowest doses were used. Most studies of brainstem metastases fail to report on radionecrosis. This is partly because of the challenges in diagnosis as well as short patient survival for this late injury. Published literature for brain metastases would suggest the rate of SRS-related radionecrosis is in the range of 7-24%.[20-22] Our incidence of suspected radionecrosis is in keeping with these reports. We find that radiosurgery for metastases in eloquent brain locations to be safe, which is in keeping with a larger study by Dea et al using Gamma Knife.[23] They report that new neurologic deficits occurred in 5.7% and seizures in 5.7% of patients. Similar to our study, deficits were transient and patients recovered after a course of corticosteroids. Dea et al reported lower rates of edema (8.6%) and radionecrosis (1.4%). This may reflect differences in technique (SRS versus Gamma Knife), lesion size, or planning target volume margin.

We also looked at factors associated with survival, and the final model indicates that patients with single brain metastasis have significantly better survival compared with those with more than one. The other factors analysed were not significant in this cohort. The analysis is limited by the small size of the cohort and subpopulations because of the low frequency of brainstem, thalamic, and basal ganglia metastases. In addition, as with all retrospective analyses, interpretation of these results is limited by selection bias. Patients selected for SRS have better survival prognosis, which is reflected in the selection criteria of our stereotactic group.

Whole brain radiotherapy as a prerequisite to radiosurgery has been standard practice at our institution. However, the potential deleterious effects of WBRT on neurocognitive function remain an ongoing concern. In a randomized study by Chang et al,[24] WBRT + SRS resulted in a greater risk of a significant decline in memory and learning compared with SRS alone. This study suggests a strategy of SRS alone and close clinical monitoring in patients with a limited number of brain metastases, which is a strategy that has gained traction at many centres. Further support comes from a meta-analysis by Tsao et al,[25] who reported that patients with SRS alone had more favorable neurocognitive outcomes and less risk of late side effects, with no difference in OS. Conversely, however, patients with WBRT and SRS had better intracranial control, which might make WBRT a better strategy for patients not suitable for close follow-up. Although WBRT versus SRS alone remain under debate, SRS alone is worth further examination at our institution as a future direction where neurotoxicity is a concern.

Conclusions

The management of brain metastases, particularly those in sensitive brain regions, using SRS remains a balance between

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benefits and risks. In this study, we showed that use of a lower dose for metastases in eloquent brain regions gives good local control and OS, with an acceptable risk of clinical complications. Lower SRS doses did not appear to compromise survival in our cohort of patients with eloquently located brain metastases. This study should serve as a basis for larger studies comparing dose, outcomes, and toxicity for brain metastases in eloquent locations.

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