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Investigation of the efficacy and safety of CyberKnife hypofractionated stereotactic radiotherapy for brainstem metastases using a new evaluation criterion: 'symptomatic control'

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ABSTRACT

The treatment of brainstem metastases remains a challenge as the brainstem itself is considered a neurological organ at risk. We aimed to investigate the efficacy and safety of CyberKnife hypofractionated stereotactic radiotherapy (HFSRT) for brainstem metastases, and to examine the balance between efficacy and safety for the management of neurological symptoms. A total of 26 lesions [pons ($n = 18$), medulla ($n = 4$) and midbrain ($n = 4$)] in 20 patients treated with CyberKnife hypofractionated stereotactic radiotherapy were retrospectively analyzed. The total radiation doses (18–30 Gy) were delivered in 3 or 5 equal fractions. The median follow-up was 6.5 (range, 0.5–38.0) months. The 6- and 12-month local control rates were 100% and 90%, respectively. Symptomatic failures, defined as the worsening and appearance of neurological symptoms due to the brainstem lesion after CyberKnife HFSRT, were observed in 6 patients [local failure ($n = 1$) and adverse events ($n = 5$). The symptomatic control and overall survival rates were 90% and 72% (after 6 months), respectively, and 76% and 53% (after 12 months), respectively. Longer symptomatic control was associated with site of lesion origin, and longer overall survival was associated with a graded prognostic assessment score of >2. To our knowledge, this is the second study to investigate the efficacy and safety of CyberKnife HFSRT for brainstem metastases. The local control rate was comparable with that of prior stereotactic radiosurgery studies. We propose a new evaluation criterion—'symptomatic control'—to evaluate the efficacy and safety of brainstem radiotherapy.

KEYWORDS: brainstem metastasis, CyberKnife, stereotactic radiotherapy, symptomatic control

INTRODUCTION

Brainstem metastases (BSMs) are relatively rare in patients with metastatic brain lesions [1, 2]. However, the treatment of BSMs remains a challenge as the brainstem itself is considered a neurological organ at risk [3–5]. Specifically, in the brainstem, both uncontrolled tumor growth and stereotactic radiotherapy have the potential to cause significant neurological deficits. Brainstem toxicities have been discussed previously [6, 7]. There have also been several studies regarding the efficacy and safety of stereotactic radiosurgery (SRS) for BSMs. To reduce the rates of toxicity, dose reduction or hypofractionated stereotactic radiotherapy (HFSRT) has been proposed [8, 9]. In the treatment of large BSMs, multifractionated therapy improved local control (LC) and reduced the risk of radiation necrosis compared with single-fractionated therapy [10, 11]. However, there are very few studies on HFSRT for BSMs. In theory, the CyberKnife image-guided frameless radiosurgery

system should be able to deliver a highly conformal, uniform dose with steep dose gradients because >100 beams are delivered via circular collimators. In addition, this system can perform fractionated irradiation, unlike Gamma Knife radiosurgery. The purpose of this study was to investigate the efficacy and safety of CyberKnife HFSRT for BSMs and to examine the balance between efficacy and safety for the management of neurological symptoms.

MATERIALS AND METHODS

Patients

A total of 26 lesions in 20 patients treated with CyberKnife HFSRT at our institute between April 2013 and March 2016 were retrospectively analyzed. The patient characteristics are summarized in Table 1. The median age was 69 (range, 43–86) years. Twelve patients (60%) were male and 8 patients (40%) were female. The median Karnofsky performance status score was 90 (range, 50–100). Recursive partitioning analysis (RPA) classification and graded prognostic assessment (GPA) scores were determined for all patients. Of the 26 lesions treated with CyberKnife HFSRT, 18 (70%) were located in the pons, 4 (15%) in the medulla, and 4 (15%) in the midbrain. Primary pathologies included lung ($n = 12$ patients; 60%), kidney ($n = 3$ patients; 15%), breast ($n = 3$ patients; 15%) and thyroid cancer ($n = 1$ patient; 5%), and melanoma ($n = 1$ patient; 5%). Five lesions (19%) were treated with whole-brain radiotherapy prior to CyberKnife HFSRT. At the time of CyberKnife HFSRT consultation, 8 patients (40%) were symptomatic with neurological complaints, including weakness, ataxia and diplopia. This study was approved by our institution's review board (reference number: 2017-[kenkyu03]-17). Informed consent was obtained from all individuals involved in the study.

Table 1. Patient characteristics

Characteristic	Patients ($n = 20$)
Sex, *n* (%)	
M	12 (60)
F	8 (40)
Age (y), median (range)	69 (43–86)
Primary pathology, *n* (%)	
Lung	12 (60)
Breast	3 (15)
Kidney	3 (15)
Melanoma	1 (5)
Thyroid	1 (5)
Number of lesions, *n*	26
KPS, median (range)	90 (50−100)
RPA class, *n* (%)	
1	1 (4)
2	23 (88)
3	2 (8)
GPA score, median (range)	1.5 (0.5–3.0)
Prior WBRT, *n* (%)	
Y	5 (19)
N	21 (81)
Intracranial metastases, median (range)	4 (1–42)
Tumor location, *n* (%)	
Midbrain	4 (15)
Pons	18 (70)
Medulla	4 (15)

F = female, GPA = graded prognostic assessment, KPS = Karnofsky performance status, M = male, N = no, RPA = recursive partitioning analysis, WBRT = whole-brain radiotherapy, Y = yes.

Hypofractionated stereotactic radiotherapy

HFSRT was performed using the CyberKnife Robotic Radiosurgery System (Accuray Inc., Sunnyvale, CA, USA). All patients were immobilized using a relocatable thermoplastic mask. The gross tumor volume (GTV) and the organs at risk were contoured on fused non-contrast-enhanced computed tomography and contrast-enhanced T1-weighted magnetic resonance imaging (MRI) images with a 1.0-mm slice thickness. The planning target volume (PTV) was defined as the GTV expanded by 1.0 mm. Treatment planning was performed using the MultiPlan 4.6.0 treatment planning software (Accuracy Inc., Sunnyvale, CA, USA). Radiation doses were calculated using the ray-tracing algorithm. HFSRT consisted of a 6.0 MV radiation beam with one or two circular collimator cones. Total radiation doses (18–30 Gy) were delivered in 3 or 5 equal fractions. The radiation dose delivered to the PTV was prescribed to the 70–80% isodose line, covering ≥95% of the PTV. However, due to the constraints of the organs at risk, an underdosage of the PTV was permitted.

Follow-up

Patients underwent an initial follow-up MRI at 2–3 months following CyberKnife HFSRT. Most patients underwent serial MRI scans at 3-month intervals. Lesions were considered to have locally failed if there was evidence of tumor volume enlargement in ≥2 subsequent MRI scans. Differential diagnoses of tumor progression or radiation necrosis were performed by using MRI, with the agreement of the radiologist, radiation oncologist, and neurosurgeon. Symptomatic failure was defined as the worsening of neurological symptoms due to the brainstem lesion after CyberKnife HFSRT for patients with symptoms prior to HFSRT, or the appearance of new neurological symptoms due to the treated brainstem lesion. The appearance of new neurological symptoms included appearance of new symptoms for asymptomatic patients and also included new symptoms other than existing symptoms prior to HFSRT in symptomatic patients. The relationship between the brainstem lesions and neurological symptoms

was assessed anatomically. Symptoms derived from lesions outside the brainstem were excluded. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analyses

The Fisher's exact test and Wilcoxon signed-rank test were performed to evaluate predictive factors of local recurrence (LR) and adverse events (AEs). LC, overall survival (OS) and symptomatic control curves were estimated using the Kaplan–Meier method and compared by the univariate log-rank test. All statistical analyses were conducted using R software, version 3.2.4 (The R Foundation, Vienna, Austria). A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 26 lesions in 20 patients were treated with CyberKnife HFSRT. The median follow-up was 6.5 (range, 0.5–38.0) months. The median follow-up of surviving patients was 11.5 months. The median maximum tumor diameter was 8.0 (range, 3.0–17.8) mm. The median minimum GTV dose was 24.7 (range, 18.6–29.6) Gy. The mean GTV dose was 28.3 (range, 20.2–35.3) Gy. Nineteen lesions (73%) were treated with 3 fractions, and 7 lesions (27%) were treated with 5 fractions. Dose selection and fractionation were based on various factors, including tumor volume, location, and prior whole-brain radiotherapy. The treatment parameters are summarized in Table 2. Sixteen patients had other intracranial metastases at the time of brainstem radiotherapy and they underwent additional SRS/HFSRT later. Four patients had a single brainstem metastasis only, but three of them experienced new intracranial metastatic lesions and underwent additional SRS/HFSRT later.

Local control

Of the 23 lesions for which follow-up MRI data was available, only 1 lesion (4%) had locally failed within 8 months of CyberKnife HFSRT. The treatment parameters of this lesion are summarized as follows: maximum tumor diameter, 8.0 mm; dose fractionation, 30 Gy delivered in 5 fractions; mean GTV dose, 35.3 Gy; and minimum GTV dose, 29.0 Gy. Three patients died or were lost to follow-up after the first follow-up MRI scan. Tumor progression was not observed in their first follow-up MRI scan compared with their pretreatment MRI scan. The 6- and 12-month LC rates were 100% and 90%, respectively (Fig. 1a). However, with only 1 local failure, significant predictors of LC could not be ascertained.

Table 2. Treatment parameters

Parameter	Lesions ($n = 26$)
MTD (mm), median (range)	8.0 (3.0–17.8)
GTV (ml), median (range)	0.33 (0.03–3.20)
Dose/fraction, *n* (%)	
18 Gy/3 fx	1 (4)
24 Gy/3 fx	15 (57)
27 Gy/3 fx	2 (8)
30 Gy/3 fx	1 (4)
25 Gy/5 fx	1 (4)
30 Gy/5 fx	6 (23)
Mean GTV dose (Gy), median (range)	28.2 (20.2–35.3)
Minimum GTV dose (Gy), median (range)	24.6 (18.6–29.6)

fx = fraction, GTV = gross tumor volume, MTD = maximum tumor diameter.

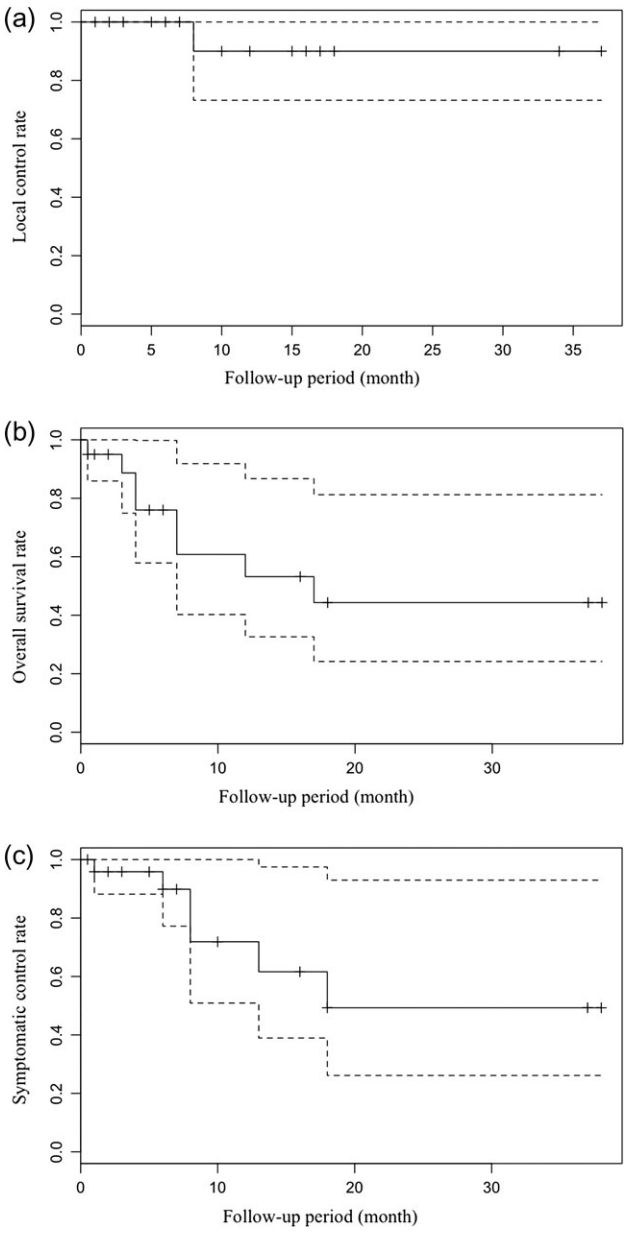

Fig. 1. Kaplan–Meier curves of (a) local control, (b) overall survival and (c) symptomatic control at 6 and 12 months.

Overall survival

Seven patients died during follow-up. Death was related to extracranial evolution in three patients and neurological complications due to brain metastases other than brainstem in two patients. The cause of death was unknown in the remaining two patients. The 6- and 12-month OS rates were 76% and 53%, respectively (Fig. 1b). Longer OS was associated with a GPA score of >2 ($P < 0.05$). Longer OS was also associated with the absence of extracranial metastases, although this difference in survival time was not significant ($P = 0.053$). The number of intracranial metastases was not a significant factor of OS ($P = 0.284$). Other factors evaluated are shown in Table 3.

Adverse events and symptomatic control

Grade 3 intracranial hemorrhage was observed in 1 patient. The primary histology of this lesion was melanoma, and hemorrhage occured within 18 months of CyberKnife HFSRT. High-density areas in the lesion were not detected on pre-radiotherapy computed tomography imaging. Grade 2 AEs [pyramidal tract syndrome ($n = 2$), radiation necrosis ($n = 1$) and abducens nerve disorder ($n = 1$)] were observed in 4 patients. All 4 patients were characterized by expansion of the edematous brain tissue surrounding the lesion. However, expansion of the contrast enhancement area was observed only in 1 patient with radiation necrosis. We judged the above 5 AEs were derived from treated brainstem lesions and included them in symptomatic failure. Therefore, symptomatic failure was observed in 6 patients (the above-mentioned 5 patients and 1 patient with LR). The 6- and 12-month symptomatic control rates were 90% and 72%, respectively (Fig. 1c). Longer symptomatic control was significantly associated with a favorable origin (lung or breast; $P < 0.05$). A GPA score of >2 was associated with a trend towards longer symptomatic control ($P = 0.058$). LR and fractionation number, however, were not significant factors associated with longer symptomatic control ($P > 0.05$). Grade 1 AEs [vomiting ($n = 2$) and headache ($n = 1$)] were observed in 3 patients. Because their symptoms weren't able to be distinguished from symptoms derived from treated brainstem lesions, we didn't count this as symptomatic failure. There were no AEs of Grade ≥4, and no significant predictors were associated with AEs of Grade >2.

Table 3. The univariate log-rank analysis of factors related to overall survival and symptomatic control

	Overall survival *P* value	Symptomatic control *P* value
RPA	0.186	0.186
GPA ≥2	0.035	0.058
Prior WBRT	0.137	0.315
Intracranial lesion ≥2	0.284	0.987
Extracranial metastasis	0.053	0.064
Tumor location	0.907	0.709
Favourable origin	0.81	0.015
MTD ≥10 mm	0.611	0.387
GTV ≥1 ml	0.489	0.102
Mean GTV dose ≥30 Gy	0.72	0.171
Minimum GTV dose ≥24 Gy	0.576	0.347
Fractionation number	0.568	0.225
Local recurrence	0.371	0.174
Neurological adverse event	0.903	<0.001

RPA = recursive partitioning analysis, GPA = graded prognostic assessment, WBRT = whole-brain radiotherapy, MTD = maximum tumor diameter, GTV = gross tumor volume.

DISCUSSION

The majority of studies have assessed the use of Gamma Knife SRS for the management of BSMs. In 2016, the findings of a multi-institutional joint research program were announced, and Trifiletti *et al.* [12] described the efficacy and safety of Gamma Knife SRS for BSMs. Recently, several reports [3, 4, 13–16] have described the efficacy and safety of linear accelerator–based SRS/HFSRT. However, few data are available regarding HFSRT. To our knowledge, ours is the second study to examine the use of HFSRT for the management of BSMs. We propose a new evaluation criterion—'symptomatic control'—to evaluate the efficacy and safety of brainstem radiotherapy.

A summary of previous studies examining the efficacy and safety of SRS/HFSRT for BSMs is provided in Table 4. Only a single study [13] included HFSRT. Leeman *et al.* [13] reported a 6- and 12-month LC rate of 93% in 36 patients treated with SRS/HFSRT (16 HFSRT-treated patients included). Our data demonstrate that HFSRT for BSMs provides effective LC (6- and 12-month LC rates: 100% and 90%, respectively), with failure documented in only 1 (4%) of 23 lesions with follow-up MRI data available. The LC rate was consistent with that of other reports concerning the use SRS/HFSRT for the treatment of BSMs. In our study, we could not find any predictor of LR, owing to the small number of events.

In our study, the 6- and 12-month OS rates were 76% and 53%, respectively. These rates were somewhat higher compared with those given in other reports. It is difficult to compare the findings of our study directly with those of other studies, owing to the referral and patient selection bias that exists at each institution. A GPA score of ≥2 was the only significant predictive factor of longer OS. There was no correlation between RPA classification and longer OS, because very few patients had an RPA classification of 1 or 3. This has already been documented in the literature [13, 17]. Our findings suggest that the GPA may represent a better scoring system than the RPA classification for evaluating OS in patients with BSMs.

In our study, only 1 patient (5%) developed an AE of Grade ≥3. This frequency is comparable to that given in other reports. Grade ≥2 AEs were observed in 5 patients (25%). This frequency was higher than that observed in other studies. This may be explained by how we counted AEs, including the worsening of neurological symptoms, as well as development of new neurological symptoms without LR. In our study, we analyzed symptomatic

Table 4. Literature review

Author(s)	Treatment modality	Patients/ lesions (*n*)	Dose (Gy)/fx	Prescription	LC (6/12 m) (%)	OS (6/12 m) (%)	MST (m)	AE (%)
Valery *et al.* [3]	LINAC	30/30	12–14/1	70% isodose	100/79	63/40	10	13
Kelly *et al.* [4]	LINAC	24/24	8–16/1	70–80% isodose	88/79	NA/29	5.3	8 (≥G3)
Trifiletti *et al.* [12]	GK	547/596	8–25/1	50% isodose (median)	NA/82	NA/33	5.6	7.4 (≥G3)
Leeman *et al.* [13]	GK + LINAC	36/38	12–24/1–5	NA	93/NA	27/8	3	8
Liu *et al.* [14]	CK	54	18 (median)/1	NA	80 (crude)	4 (crude)	5	NA
Lin *et al.* [15]	LINAC	45/48	10–17/1	90% isodose	92/88	NA	11.6	4.7
Hatiboglu *et al.* [16]	LINAC	60	8–18/1	90–95% isodose	NA/76	NA	4.2	20
Present study	CK	20/26	18–30/3 or 5	70–80% isodose	100/90	76/53	17	25 (5 ≥ G3)

AE = adverse event, CK = CyberKnife, fx = fraction, FG = grade, GK = GammaKnife, LC = local control, LINAC = linear accelerator, MST = median survival time, NA = not available, OS = overall survival.

control as a new evaluation criterion. The purpose of brainstem radiotherapy is palliative. In the treatment of BSMs, both local failure and AEs directly cause neurological symptoms. Therefore, the balance between the efficacy and the safety of brainstem radiotherapy is of utmost importance. Liu *et al.* [14] described the importance of symptomatic control after brainstem radiotherapy. In our study, symptomatic failure was observed in 6 patients. The 6- and 12-month symptomatic control rates were 90% and 72%, respectively. Neurological AEs are influenced more by shorter symptomatic control than LR. Fuentes *et al.* [18] and Lorenzoni *et al.* [19] used higher mean prescribed doses, although there was no significant difference in terms of the LC and OS rates compared with those given in other reports. Valery *et al.* [3] described lower doses achieving the same LC rate with minimal side effects in linear accelerator–based SRS. The main advantage of dose reduction is to limit severe adverse effects involving normal tissue included in the prescription isodose. Currently, no guidelines exist concerning the appropriate therapeutic dose and fractionation of HFSRT for BSMs. Dose minimization is associated with a risk of LR. However, the OS of patients with brain metastases is inferior after a metastatic lesion has developed within the brainstem, despite favorable LC rates with brainstem SRS [20]. Therefore, dose minimization should also be considered in HFSRT. However, the actual dose delivered to the lesion varies considerably by the prescription isodose, even if the prescription dose is the same. The isodose values are given as a percentage of the maximum dose within the PTV. Generally, as the isodose value decreases, the dose to the central portion of the PTV increases. These conditions were not always stated in previous reports concerning BSMs. The prescription isodose should be discussed at the same time as the prescription dose. Several studies [10, 11] have shown that multifractionated therapy improved LC and reduced the risk of radiation necrosis compared with single-fractionated therapy in the treatment of large BSMs. Multifractionated therapy may make it possible to reduce the frequency of AEs while maintaining the LC rate in brainstem radiotherapy. In our study, favorable tumor origin was significantly associated with longer symptomatic control. Symptomatic control represents the balance between the efficacy and safety of brainstem radiotherapy. Therefore, future studies should evaluate this new criterion to determine the most appropriate prescription dose, isodose value, and fractionation of HFSRT for BSMs.

We proposed symptomatic control as a new evaluation criterion of HFSRT for BSMs, but there are some negative aspects. First, the reduction in treatment intensity will improve symptomatic control in the short term because AEs tend to appear earlier than LR. Therefore, dose minimization should be done carefully, considering the longer-term result. Second, AEs have the possibility to restore by medication in contrast to LR, and symptomatic control is not able to take this discrepancy into account. It is uncertain whether symptoms controlled by medication should be included as 'symptomatic control' or not. Third, the coexistence of non-BSM brain metastasis (such as cerebral or cerebellar metastases) may complicate accurate assessment of symptomatic control. Derivation of neurological symptoms should be carefully judged by the neurosurgeon, the neurologist and the radiation oncologist.

Our study has several limitations. First, its retrospective design that means it is prone to selection bias. Second, there was a limited number of patients and lesions in our cohort. Third, the short follow-up period may have resulted in better LC.

CONCLUSIONS

The efficacy and safety of HFSRT for BSMs had not previously been investigated fully. This is only the second study to investigate

the efficacy and safety of HFSRT for BSMs. The LC rate of HFSRT for BSMs was comparable with that reported in a prior study of SRS for BSMs. A GPA score of >2 was the only significant predictive factor of longer OS. We propose a new evaluation criterion—'symptomatic control'—that represents the balance between the efficacy and safety of brainstem radiotherapy. In the future, appropriate doses and fractionations should be determined to reduce the frequency of neurological AEs.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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