Gamma Knife surgery for patients with brainstem metastases

Clinical article

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Object. Because brainstem metastases are not deemed resectable, stereotactic radiosurgery (SRS) is the only treatment modality expected to achieve a radical cure. The authors describe their treatment results, focusing particularly on how long patients can survive without neurological deterioration following SRS for brainstem metastases.

Methods. This was an institutional review board–approved, retrospective cohort study in which the authors pulled from their database information on 2553 consecutive patients with brain metastases who underwent Gamma Knife surgery (GKS) at the Mito GammaHouse between July 1998 and July 2011. Among the 2553 patients, excluding cases in which there was meningeal dissemination, 200 cases of brainstem metastases (78 women and 122 men with a mean age of 64 years [range 36–86 years]) were identified and analyzed. The most common primary site was the lung (137 patients) followed by the gastrointestinal tract (24 patients), breast (17 patients), kidney (12 patients), and others (10 patients). Among the 200 patients, 15 patients (7.5%) harbored at least 2 tumors in the brainstem: 11 patients had 2 tumors, 2 patients had 3 tumors, and 1 patient each had 4 or 5 tumors. Therefore, a total of 222 tumors were irradiated. These 222 tumors were located in the pons (121 lesions), the midbrain (65 lesions), and the medulla oblongata (36 lesions). The mean and median tumor volumes were 1.3 and 0.2 cm³ (range 0.005–10.7 cm³), and the median peripheral radiation dose was 18.0 Gy (range 12.0–25.0 Gy).

Results. The overall median survival time (MST) was 6.0 months. Distribution of MSTs across Recursive Partitioning Analysis (RPA) classes showed that the MSTs were 9.4 months in Class I (20 patients), 6.0 months in Class II (171 patients), and 1.9 months in Class III (9 patients). Better Karnofsky Performance Scale score, single metastasis, and well-controlled primary tumor were significant predictive factors for longer survival. The neurological and qualitative survival rates were 90.8% and 89.2%, respectively, at 24 months post-GKS. Better KPS score and smaller tumor volume tended to be associated with prolonged qualitative survival. Follow-up imaging studies were available for 129 patients (64.5%). The tumor control rate was 81.8% at 24 months post-GKS. Smaller tumor volume tended to contribute to tumor control.

Conclusions. The present results indicate that GKS is effective in the treatment of brainstem metastases, particularly from the viewpoint of maintaining a good neurological condition in the patient. (<http://thejns.org/doi/abs/10.3171/2012.7.GKS12977>)

KEY WORDS • Gamma Knife surgery • stereotactic radiosurgery • brainstem • metastasis

BRAIN metastases are a common, life-threatening neurological problem in the absence of effective treatment for patients with cancer. In particular, metastatic lesions located in the brainstem, although uncommon (1.5%–11% of all brain metastases), are clinically the most crucial lesions because of the brainstem's anatomical location and critical functions.^{4,8–10,13} Historically, WBRT has played the dominant role in manage-

ment recommendations, because brainstem metastases have not been deemed resectable, even when the most recent advances in microsurgical techniques have been used. Recently, SRS plus WBRT has been recommended as the first treatment for patients with brain metastases.¹ However, a debate persists as to whether WBRT is necessary for all patients with brain metastasis. The primary argument against WBRT stems from the risk of deterioration of neurocognitive function, which cannot be ignored in long-surviving patients.^{2,3,19}

More than 10 authors recently reported the clinical efficacy of using SRS alone to treat brainstem metastases; their findings were based on relatively small patient populations—22 to 60 patients per study.^{4,7,8,10,13–16,18,22,25,28,33,34} Although patients' overall survival, factors impacting survival, and/or local tumor control rates were described

Abbreviations used in this paper: BSBM = Basic Score for Brain Metastases; GKS = Gamma Knife surgery; GPA = Graded Prognostic Assessment; HR = hazard ratio; KPS = Karnofsky Performance Scale; LINAC = linear accelerator; MET-PET = L-[methyl-¹¹C] methionine positron emission tomography; MST = mean survival time; RPA = recursive partitioning analysis; SIR = Score Index for Radiosurgery; SRS = stereotactic radiosurgery; WBRT = whole brain radiation treatment.

in these reports, functional survival has not yet been analyzed. Approximately 90% of patients died of extracerebral diseases in a subset in which SRS was performed.^{30,31} Thus, treatments for brain metastasis are crucial for maintaining the patient's good neurological state as long as possible. In this report, based on a relatively large patient population, we describe our treatment results, focusing particularly on this issue.

Methods

Patient Population

This study was approved by the Tokyo Women's Medical University's institutional review board. It is a retrospective cohort study in which we used a prospectively accumulated database that includes 2553 consecutive patients with brain metastases who underwent GKS alone, without WBRT, at the Katsuta Hospital Mito GammaHouse during the 13-year period, July 1998–July 2011. The treatment strategy was explained in detail to each patient and at least one adult relative by one of the authors (M.Y.) before GKS was performed. Written informed consent was obtained from all cases. From our database of 2553 patients with brain metastases, 200 (7.8%) with brainstem metastases were identified and included in our study population. Patients in whom there was meningeal dissemination and patients undergoing three-stage GKS were excluded from the study.

Table 1 summarizes the clinical characteristics in our patient population. There were 78 women (39%) and 122 men (61%). The mean age of the patients at the time of radiosurgery was 64 years (range 36–86 years). The most common primary site was the lung (137 patients; 68.5%) followed by the gastrointestinal tract (24 patients; 12%), breast (17 patients; 8.5%), kidney (12 patients; 6%), and other locations (10 patients; 5%, including 1 melanoma). Among the 200 patients, 15 (7.5%) had ≥ 2 tumors in the brainstem: 11 patients harbored 2 tumors; 2 patients harbored 3, 1 patient harbored 4, and 1 patient harbored 5. Thus, 222 tumors in all were irradiated. Among the 222 tumors, the location distribution was the pons for 121 lesions (54.5%), the midbrain for 65 lesions (29.3%), and the medulla oblongata for 36 lesions (16.2%). The brainstem was the only tumor location in 24 patients (12%), whereas the other 176 patients (88%) also harbored nonbrainstem tumors.

The median radiation dose directed at the tumor periphery was 18.0 Gy (range 12.0–25.0 Gy), and the median dose directed at the tumor center (maximum dose) was 30.0 Gy (range 20.0–40.0 Gy).

The primary cancer was reported by the referring primary physician to be well controlled in 61 patients (30.5%). A total of 88 patients (44%) had nonbrain metastases as well. The median KPS score¹² at the time of radiosurgery was 90% (range 50%–100%). The KPS was 80% or better in 156 patients (78%) and 70% or worse in 44 patients (22%). According to the Radiation Therapy Oncology Group's RPA classification system,⁵ 20 patients (10%) were in RPA Class I, 171 patients (85.5%) in RPA Class II, and 9 patients (4.5%) in RPA Class III. Fifty patients had various symptoms caused by brainstem lesions, such as hemiparesis (27 patients), diplopia (10 patients), head-

TABLE 1: Summary of clinical characteristics in 200 patients with 222 brainstem metastases

Characteristic	Value
sex—no. of patients (%)	
women	78 (39)
men	122 (61)
mean age in yrs (range)	64 (36–86)
location of primary cancer—no. of lesions (%)	
lung	137 (68.5)
gastrointestinal tract	24 (12)
breast	17 (8.5)
kidney	12 (6)
other	10 (5)
mean/median no. of tumors (range)	
whole brain	7/6 (1–19)
brainstem	1/1 (1–5)
location in brainstem location—no. of lesions (%)	
pons	121 (54.5)
midbrain	65 (29.3)
medulla oblongata	36 (16.2)
control of primary cancer—no. of patients (%)	
controlled	61 (30.5)
not controlled	139 (69.5)
extracerebral metastases—no. of patients (%)	
no	112 (56)
yes	88 (44)
KPS score—no. of patients (%)	
$\geq 80\%$	156 (78)
$\leq 70\%$	44 (22)
RPA class—no. of patients (%)	
I	20 (10)
II	171 (85.5)
III	9 (4.5)
brainstem symptom(s)—no. of patients (%)	
no	150 (75)
yes	50 (25)
prior surgery—no. of patients (%)	
no	198 (99)
yes	2 (1)
prior WBRT—no. of patients (%)	
no	187 (93.5)
yes	13 (6.5)
median tumor volume in cm ³ (range)	0.2 (0.005–10.7)
median peripheral dose in Gy (range)	18.0 (12.0–25.0)

ache and consciousness disturbance caused by obstructive hydrocephalus (7 patients), dysphagia (6 patients), and so on. Prior treatments performed at other facilities included surgical removal (including biopsy) of brainstem lesions in 2 patients and WBRT (30 Gy/10 fractions) in 13 patients.

Statistical Analysis

Neurological and neuroimaging evaluations were

performed every 2–3 months after the initial GKS. Overall survival time was defined as the interval between the first SRS for brainstem metastasis and death due to any cause or the day of the last follow-up. Neurological death was defined as death caused by all intracranial diseases: tumor recurrence, carcinomatous meningitis, cerebral dissemination, and progression of other untreated intracranial tumors. Neurological death-free survival time was defined as the interval between the first SRS for brainstem metastasis and the day of any brain disease-caused death or the day of the last follow-up.

Control of the GKS-treated lesion was defined as no remarkable increase, namely regression or unchanged, in tumor diameter. Generally, the local recurrence criteria were increased size ($> 10\%$ increase in maximum diameter) of an enhanced area on gadolinium-enhanced T1-weighted MR images and an enlarged tumor core on T2-weighted MR images.¹¹ However, in some cases, in which MR imaging alone was not sufficient to confirm recurrence, MET-PET was very useful for distinguishing tumor recurrence from necrotic lesions.^{20,27} Qualitative survival time was defined as the interval between the first GKS and the day that the KPS score decreased to below 70% (functionally dependent) due to neurological status.

All data were analyzed according to the intention-to-treat principle. For baseline variables, summary statistics were constructed that used frequencies and proportions for categorical data and means and standard deviations for continuous variables. We compared patient characteristics using the Fisher exact test for categorical outcomes and t-tests for continuous variables, as appropriate. For time-to-event outcomes, times elapsed until a first event were compared using the log-rank test. The Kaplan-Meier method¹¹ was used to estimate the absolute risk of each event for each group, and hazard ratios and 95% confidence intervals were estimated with the aid of the Cox proportional hazards model. In addition, the cumulative incidences of neurological death, impaired neurological status, and local tumor control failure were estimated by performing a competing risk analysis, because death is a competing risk for lost to follow-up.^{6,23}

All comparisons were planned, and the tests were two-sided. A p value less than 0.05 was determined to indicate a statistically significant difference. All statistical analyses were conducted using JMP (version 8.0.2, SAS Institute Inc.). Competing risk analyses were performed by one of the authors (Y.S.), who was not involved in either the GKS treatment or patient follow-up, by using SAS software (version 9.2, SAS Institute Inc.).

Results

Overall Survival

The median post-GKS follow-up time among censored observations (21 patients) was 5.8 months (range 0.2–120.2), and 179 patients (89.5%) had died as of the end of August 2011. The MST was 6.0 months (95% CI 5.2–7.3) after GKS was performed to treat brainstem metastases. The Kaplan-Meier plots of all 200 patients are shown in Fig. 1 upper. Kaplan-Meier estimated survival

rates were 50.6%, 31.0%, and 8.7% at 6, 12, and 24 months post-GKS, respectively. The MSTs according to the primary cancer sites were 6.0 months (95% CI 4.9–8.0), 5.1 months (95% CI 2.2–7.4), 6.0 months (95% CI 1.8–16.6), and 11.2 months (95% CI 2.6–19.0) in patients with lung, gastrointestinal tract, breast, and renal tumors, respectively. There were no statistically significant differences in survival times among the original cancers ($p = 0.427$). According to the RPA classification, the MSTs were 9.4 months (95% CI 5.5–16.6) for Class I, 6.0 months (95% CI 4.9–7.1) for Class II, and 1.9 months (95% CI 0.3–6.9) for Class III (Fig. 1 lower). Although there was a statistically significant difference with the three-group stratification ($p < 0.001$), Classes I and II did not differ significantly ($p = 0.175$).

Factors Predicting Longer Survival Period

As shown in Table 2, among the 10 clinical factors an-

Fig. 1. Overall survival (upper) and survival stratified by RPA classes (lower), estimated using the standard Kaplan-Meier method. M = months. Numbers of patients at risk for each time point are indicated below each graph.

alyzed (patient age and sex, KPS score, number of tumors, tumor volume, peripheral dose, primary tumor status, nonbrain metastasis, neurological brainstem symptoms, and prior WBRT), univariate analyses showed that 4 of them significantly favored longer survival: 1) better KPS score ($p < 0.001$; HR = 4.966 [95% CI 2.666–9.134]); 2) single metastasis ($p = 0.005$; HR = 2.097 [95% CI 1.251–3.473]); 3) smaller tumor volume ($p = 0.041$; HR = 2.199 [95% CI 1.035–4.288]); and 4) well-controlled primary tumor ($p < 0.001$; HR = 1.762 [95% CI 1.278–2.465]). The multivariate analyses showed 3 clinical factors that significantly favored longer survival: 1) better KPS score ($p < 0.001$; HR = 5.416 [95% CI 2.507–11.479]); 2) single metastasis ($p = 0.012$; HR = 2.065 [95% CI 1.174–3.598]); and 3) well-controlled primary tumors ($p = 0.021$; HR = 1.494 [95% CI 1.061–2.128]).

Neurological Survival

Among the 180 deceased patients, the cause of death could not be determined in 5 but was confirmed in the remaining 175 patients: nonbrain disease in 156 patients (89.1%), progression of brain metastases in 15 patients (8.6%), and both in 4 patients (2.3%). In the 156 patients who died of their primary cancer or nonbrain metastases, good brain condition was maintained until 1 to several days before death. In the 19 patients who died of progression of brain metastases, only 4 died of progression of brainstem metastases. The neurological survival rate was 90.8% at 24 months post-GKS (Fig. 2A). Among the aforementioned 10 clinical factors, none were statistically significant, but the univariate analyses revealed that 1 of them, smaller tumor volume, tended to be associated with longer neurological survival ($p = 0.057$).

Qualitative Survival

We did not perform GKS in patients with low KPS scores due to systemic disease. Thus, only 9 patients with low KPS scores were treated with GKS for brainstem metastases: 1 patient with a KPS score of 50% and 8 patients with a KPS score of 60%. After treatment, a deterioration in performance occurred in 27 cases. The qualitative survival rate was 90.8% at 24 months post-GKS (Fig. 2B). Among the 10 clinical factors, the univariate analyses

showed 2 factors that significantly favored longer survival: 1) better KPS score ($p = 0.009$; HR = 8.394 [95% CI 1.717–39.654]); and 2) smaller tumor volume ($p = 0.026$; HR = 6.284 [95% CI 1.286–22.621]). However, according to the multivariate analyses, neither factor was statistically significant (better KPS score, $p = 0.172$; smaller tumor volume, $p = 0.222$).

Follow-Up MR Imaging and Local Tumor Control

In this series, follow-up MR images were available for 129 patients (65%). Local recurrence of treated brainstem lesions occurred in 22 patients (17.1%). Kaplan-Meier-estimated local control rates were 93.6%, 82.7%, and 81.8% at 6, 12, and 24 months post-GKS, respectively (Fig. 2C). Among the 22 patients in whom there was local control failure, 13 underwent repeated GKS. Among these 13 patients, MET-PET was used for GKS dose planning in 5 patients. At the second GKS, the median dose at the tumor periphery was 15.0 Gy (range 9.0–17.5 Gy). In the 8 patients (62%) in whom post-GKS follow-up MR images were available, the images demonstrated treated tumors to be well controlled in 5 patients and not well controlled in the other 3.

Among the 10 clinical factors, the univariate analyses showed that smaller tumor volume, as a continuous variable, tended to impact the local control rate, although the association did not reach the level of statistical significance ($p = 0.202$). However, if tumor volume was analyzed as a categorical variable, that is, $< 1.0 \text{ cm}^3$ versus $\geq 1.0 \text{ cm}^3$ or $< 3.0 \text{ cm}^3$ versus $\geq 3.0 \text{ cm}^3$, as reported,^{7,14} incidences of local recurrence were significantly lower in patients with smaller tumors than in patients with larger tumors: $< 1.0 \text{ cm}^3$ versus $\geq 1.0 \text{ cm}^3$ ($p = 0.020$) compared with $< 3.0 \text{ cm}^3$ versus $\geq 3.0 \text{ cm}^3$ ($p = 0.035$).

Illustrative Case With a Complication

Among the 200 patients, 1 patient experienced a severe GKS-related complication. The man, who was in his 70s and harbored a long-known lung adenocarcinoma, presented with ataxia. Magnetic resonance images showed an enhanced lesion at the pons. The tumor volume was 3.4 cm^3 . The tumor was covered with a 60% isodose gradient, and a central dose of 30.0 Gy was selected to obtain a peripheral dose of 18.0 Gy (Fig. 3A and B). With

TABLE 2: Univariate and multivariate analyses of prognostic factors for overall survival

Variables	Univariate Analysis		Multivariate Analysis	
	p Value	HR (95% CI)	p Value	HR (95% CI)
patient age	0.072			
patient sex	0.439			
KPS	<0.001	4.966 (2.666–9.134)	<0.001	5.416 (2.507–11.479)
tumor number	0.005	2.097 (1.251–3.473)	0.012	2.065 (1.174–3.598)
tumor volume	0.041	2.199 (1.035–4.288)	0.856	1.099 (0.382–2.956)
peripheral dose	0.542			
primary tumor status	<0.001	1.762 (1.278–2.465)	0.021	1.494 (1.061–2.128)
extracranial metastases	0.222			
neurological symptoms	0.296			
prior WBRT	0.572

FIG. 2. Neurological death (A), qualitative deterioration (B), and local recurrence (C) estimated using competing risk analysis.

this dose planning, the conformity and gradient indexes were estimated to be 0.86 and 2.87, respectively.²¹ The patient's condition gradually worsened for 9 months after treatment, and MR imaging demonstrated severe edema (Fig. 3C–E). Although steroid therapy was administered for several months, the man's condition continued to deteriorate. He eventually died of this treatment-related complication 16 months after GKS.

An additional 6 patients were administered oral steroids for 1–3 months after SRS because MR imaging demonstrated an increase in peritumoral edema. However, all 6 patients remained asymptomatic.

Discussion

To date, 14 series (a linear accelerator system was used in 5 series and a Gamma Knife in 9 series) have demonstrated the clinical efficacy of SRS for the treatment of brainstem metastases (Table 3).^{4,7,8,10,13–16,18,22,25,28,33,34} To the best of our knowledge, this is the first report based on a relatively large number of patients to describe GKS for brainstem metastases in which the focus was on neurological and qualitative survivals. These issues are crucial and should be given consideration in the management of patients with brain metastasis.

FIG. 3. Gadolinium-enhanced T1-weighted MR images obtained before (A) and 9 months after (C) GKS, and T2-weighted MR images obtained before (B) and 9 months after (D and E) GKS in a patient with a severe GKS-induced complication (see text for further description).

TABLE 3: Summary of published reports of SRS for brainstem metastases*

Authors & Year	Treatment Modality	No. of Patients	Tumor Vol (cm ³)†	Prescribed Dose (Gy) ‡	MST (mos)	Local Control (%)
Huang et al., 1999	GKS	26	1.1	16	9	95
Shuto et al., 2003	GKS	25	2.1	13	4.9	77
Fuentes et al., 2006	GKS	28	2.1	19.6	12	92
Yen et al., 2006	GKS	53	2.8	17.6	11	87
Hussain et al., 2007	GKS	22	0.9	16	8.5	100
Kased et al., 2008	GKS	42	0.26	16	9	85
Lorenzoni et al., 2009	GKS	25	0.6	20	11.1	95
Samblás et al., 2009	LINAC	28	1.86	11	16.8	NA
Koyfman et al., 2010	GKS	43	0.37	15	5.8	85
Kelly et al., 2011	LINAC	24	0.2	13	5.3	79
Hatiboglu et al., 2011	LINAC	60	1.0	15	4	76
Valery et al., 2011	LINAC	30	2.8	13.4	10	79
Yoo et al., 2011	GKS	32	1.5	15.9	7.7	88
Lin et al., 2012	LINAC	48	0.4	14	11.6	91
present study	GKS	200	1.3	18	6.0	82

* NA = not available.

† Mean or median tumor volume.

‡ Mean or median peripheral dose.

Overall Survival

Among previous reports, overall MSTs varied from 4.0 to 16.8 months. Although brainstem metastases have generally been regarded as a poor prognostic factor, some authors reported MSTs of more than 12 months—longer than those usually expected in patients with brain metastases.^{4,22} Recent advances in cancer treatment, as well as in SRS, which allow radical treatment of brain metastases, may have contributed greatly to prolonged overall survival. Nowadays, approximately 90% of patients with brain metastasis die as a result of progression of the systemic disease. Thus, these MST differences among reported series may reflect a bias in patient selection.

An improved prognostic index may resolve some of the uncertainty in making treatment decisions, specifically whether SRS should be performed. To date, 4 grading indexes have been proposed: 1) the Radiation Therapy Oncology Group's RPA;⁵ 2) the Score Index for Radiosurgery (SIR);²⁹ 3) the Basic Score for Brain Metastases (BSBM);¹⁷ and 4) the Graded Prognostic Assessment (GPA).²⁶ Table 4 shows MSTs in 3 or 4 subgroups according to the 4 systems as well as our subclassification of RPA Class II patients into 3 subclasses.³² Kaplan-Meier plots of our patient series showed statistically significant survival differences among patients stratified into 3 or 4 groups based on the 4 systems ($p < 0.001$). However, the MST differences between some pairs of groups failed to reach statistical significance with the 3 traditional systems—RPA, BSBM, and GPA—as well as with our subgroups of RPA Class II.

Neurological and Qualitative Survivals

Patients with metastases generally have poor prognoses. Therefore, it is important to prolong neurological

and qualitative survival. There are several reports detailing causes of death.^{4,22,33,34} The rates of death caused by brain tumor progression range from 14% to 50%, and the rates of death from brainstem tumor progression range from 4% to 13%. In our series, the rate of death caused by brain tumor progression was 10.9% (19/175 patients), and the rate of brainstem tumor progression was 2.3% (4/175 patients)—rates somewhat lower than those in previous reports. There were no statistically significant prognostic factors favoring neurological survival, but smaller tumors tended to be associated with prolonged neurological survival. In fact, as described herein, the rate of death caused by brainstem tumor progression was relatively low. However, we consider occasional assessments using MR imaging to detect small, asymptomatic brainstem lesions to be crucial for maintaining a better neurological state.

There are no previous reports on brainstem metastases in which patients' quality of life was assessed. Based on their large series of patients with brain metastasis, Serizawa et al.²⁴ reported that pretreatment KPS score and carcinomatous meningitis were significant factors influencing qualitative survival. In the present study of brainstem metastases, we excluded cases with carcinomatous meningitis, but our results were similar to those of Serizawa et al. in terms of prognostic factors influencing qualitative survival.

Local Control

In previous reports, local control rates varied from 76% to 100%.^{4,7,8,10,13,16,18,25,28,33} The differences among these rates were considered to reflect uncertainty in the definition of local control.

Several authors have described factors favoring local tumor control, such as tumor volume, peripheral dose,

TABLE 4: Overall median survival times in patients classified according to 4 indexes*

Grade/Class	No. of Patients	MST in Mos (95% CI)	HR (95% CI), p Value
RPA class			
I	20	9.4 (5.5–16.6)	
II	171	5.9 (4.9–7.0)	1.41 (0.88–2.42), p = 0.159, vs RPA I
II-a	29	10.2 (5.5–18.3)	
II-b	53	9.1 (5.6–14.5)	1.51 (0.92–2.56), p = 0.104, vs RPA II-a
II-c	89	4.7 (3.5–5.8)	1.78 (1.24–2.58), p = 0.002, vs RPA II-b
III	9	1.9 (0.4–6.9)	2.94 (1.39–5.48), p = 0.007, vs RPA II
SIR			
8–10	25	16.5 (8.8–26.1)	
4–7	135	6.0 (4.9–7.1)	2.84 (1.72–5.02), p < 0.001, vs SIR 8–10
1–3	40	3.3 (2.1–5.2)	1.67 (1.14–2.38), p = 0.009, vs SIR 4–7
BSBM			
3	35	10.6 (6.9–16.5)	
2	72	6.9 (4.9–11.1)	1.40 (0.91–2.19), p = 0.129, vs BSBM 3
1	76	5.0 (3.8–6.0)	1.49 (1.06–2.11), p = 0.023, vs BSBM 2
0	17	2.3 (1.4–6.5)	1.40 (0.91–2.19), p = 0.129, vs BSBM 1
GPA			
3.5–4.0	10	10.4 (4.0–18.8)	
3.0	25	10.1 (5.6–17.7)	1.12 (0.52–2.70), p = 0.775, vs GPA 3.5–4.0
1.5–2.5	116	5.9 (4.7–7.1)	1.64 (1.04–2.68), p = 0.030, vs GPA 3.0
0–1.0	49	4.7 (2.7–6.5)	1.19 (0.84–1.69), p = 0.321, vs GPA 1.5–2.5

* See *Discussion* for references to indexes.

melanoma as the primary cancer, and so on. In Japan, a primary melanoma is very rare, and there has been only 1 case of brainstem metastases from a melanoma. A smaller tumor volume, such as between 1.0 and 3.0 cm³, was shown to favor local tumor control. Also, we found that a peripheral dose > 18.0 Gy contributed significantly to local tumor control.

A possible weakness in the present study is that neuroimaging follow-up was lacking in approximately 30% of patients. However, in most patients in this subset, MR imaging could not be performed due to early post-SRS death or remarkable deterioration in patients' general condition and not because the patients were lost to follow-up.

Complications

One of our patients experienced a fatal radiation-induced side effect. In this case, a peripheral dose of 18.0 Gy was delivered to a relatively large brainstem metastasis. Paddick and Lippitz²¹ reported that the gradient index may be a useful predictor of adverse effects. As described earlier in this paper, neither the conformity nor the gradient index was considered to have exceeded the safety range in this case. We compared the other 11 cases with brainstem metastases with tumor volumes > 3.0 cm³, in which follow-up MR images were available. The mean peripheral and central doses were 16.8 and 30.0 Gy, respectively, and the mean Paddick conformity and gradient indexes were 0.80 and 3.50, respectively. The patient in this case received a slightly higher peripheral dose than the control group (18 vs 16.8 Gy), but dose planning in

regard to the conformity and gradient indexes was actually better. Since this experience, we have been especially cautious not only about conformity but also about the optimal dose for brainstem metastases.

Our database included 6 asymptomatic patients in whom steroid treatment was required to prevent peritumoral edema progression. However, the primary physicians who managed our GKS cases may not have reported rather minor problems to us. Therefore, an additional weakness of this study is that all patients with minor complications were not surveyed.

Conclusions

Our present results indicate that GKS is an effective treatment for brainstem metastases. A better KPS score, a single metastasis, and a well-controlled primary tumor were significant predictive factors favoring survival.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kawabe, Yamamoto. Acquisition of data: Kawabe, Yamamoto. Analysis and interpretation of data: Kawabe. Drafting the article: Kawabe. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kawabe. Statistical analysis: Sato. Administrative/technical/material support: Urakawa, Kasuya. Study supervision: Yamamoto.

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