Table 2 Survival analyses

Variables	High-risk group	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, y	<60	1.32 (0.64-2.60)	.441		
Sex	Male	1.51 (0.75-3.29)	.261		
KPS (%)	<70	1.42 (0.74-2.75)	.291		
Extent of resection	<95%	1.44 (0.71-2.82)	.303		
RPA class (III/IV vs (V/VI)	V/VI	1.52 (0.79-3.05)	.215		
MGMT	UnMet	2.42 (1.10-6.08)	.026	1.57 (0.68-4.11)	.305
Necrosis (regional)	No	1.94 (0.91-4.61)	.089	1.70 (0.76-4.33)	.205
Necrosis (paraventricular)	No	4.08 (1.97-9.10)	.007	4.71 (2.08-11.55)	.0002

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; MGMT = *O-6-methylguanine-DNA methyltransferase* gene; RPA = recursive partitioning analysis; UnMet = unmethlylated.

(14) reported on their hypofractionated IMRT with 60 Gy in 3.0-Gy fractions. IMRT with 50 Gy in 5.0-Gy fractions was also reported by Floyd et al (15). In the above 2 trials, hypofractionation contributed to a shortened treatment period, but the biologically effective doses (BEDs) calculated based on the LQ model (alpha/beta = 10; 78 Gy in the trial by Sultanem et al [14], 75 Gy in the trial by Floyd et al [15]) were equivalent to that of conventional irradiation (72 Gy), and failed to improve patient survival. In contrast to these reports, we previously reported the benefits of dose escalation using hypofractionated IMRT (16). In that report, the dose for the central lesion was escalated from 48 Gy (BED, 77 Gy) to 68 Gy (BED, 126 Gy), and we demonstrated a favorable effect on local control without severe early toxicities. From these results, we fixed the dose at 68 Gy and used the same fractionation scheme: 8 fractions during 10 treatment days.

More recently, trials of dose escalation using hypofractionated IMRT with concurrent and adjuvant TMZ have been reported. In a study by Chen et al (17), all patients received a total dose of 60 Gy, but the dose per fraction was escalated from 3.0 to 6.0 Gy in 1.0-Gy increments. Their median patient survival was 16.2 months, and acute toxicity secondary to irradiation was extremely rare. A recent report by Tsien et al (18) also demonstrated the safety of hypofractionated IMRT. In our current series, we experienced no acute toxicity related to irradiation. In contrast to previous reports, our hypofractionated high-dose IMRT altered the dominant failure pattern from local to disseminated. A decreased incidence of local failure after high-dose irradiation has also been reported by several investigators. In addition to the report by Nakagawa et al (5) noted earlier, Tsien et al (18) reported a decreased probability of central failure with increased radiation doses. Intensive IMRT targeting regional tumors prolonged the time to local failure, but not to dissemination, resulting in earlier appearance of dissemination rather than local progression and alteration of the dominant failure pattern. Although our treatment still had limitations, the median patient survival was 20.0 months, and the 2- and 3-year survival rates were 42.8% and 26.5%, respectively. These survival results indicate the potential benefit of hypofractionated high-dose IMRT.

Late toxicities after our treatment were more frequent than early toxicities, and careful observation was required. Radiation necrosis was the most frequent late toxicity, and symptomatic necrosis requiring necrotomy developed in 5 patients. Surprisingly, these necroses progressed more frequently and much earlier in the SVZ than at the original tumor site, although SVZ was not included in the high-dose field. The irradiated doses to the SVZ were equivalent to 50 to 60 Gy of conventional radiation (alpha/beta = 3). Hypofractionated radiation might have a higher risk of SVZ injury than expected by the LQ model.

Table 3 Subgroup analyses of patient survival

	Median, mo (95% CI)	2 y (%)	3 y (%)	4 y (%)	5 years (%)
Overall (46)	20.0 (13.3-27.6)	42.8	26.5	13.3	6.6
Extent of surgery					
Complete resection (29)	20.0 (13.6-30.4)	46.1	26.3	13.2	8.8
Partial resection (17)	11.4 (5.9-38.3)	39.2	29.4	14.7	0.0
Age, y					
<50 (3)	20.4 (11.4-49.9)	33.3	33.3	33.3	0.0
50-60 (11)	20.0 (11.6-25.1)	31.8	0.0	0.0	0.0
>60 (32)	17.2 (9.8-36.2)	47.5	35.9	15.4	10.3
RPA					
Class IV (17)	25.1 (11.4-59.6)	51.3	36.7	24.5	12.2
Class V (16)	21.4 (7.9-36.2)	43.8	29.2	7.3	7.3
MGMT methylation					
Unmethylated (34)	14.8 (11.4-22.8)	29.9	15.0	7.5	3.7
Methlyated (11)	36.2 (9.8-not reached)	72.7	52.0	17.3	17.3

Abbreviations: CI = confidence interval; MGMT = *O-6-methylguanine-DNA methyltransferase* gene; RPA = recursive partitioning analysis.

On the other hand, the SVZ is believed to harbor cancer stem cells (CSCs) in patients with GBM (19, 20). Increased dose delivery to the SVZ (≥59.4 Gy) has recently been reported to correlate with better tumor control (21-23). However, CSCs may reportedly be resistant to radiation therapy because of preferential activation of the DNA damage checkpoint and DNA repair response (24). It is difficult to believe that conventional radiation may directly control CSCs in the SVZ, but impairment of CSC niches may sterilize the function of CSCs and decrease the supply of mature glioblastoma cells. In our current series, SVZ injury was strongly associated with patient survival. Hypofractionated radiation had a higher risk of SVZ injury, but it also had a stronger effect on impairment of CSC niches, which resulted in better patient outcomes. However, the SVZ also harbors neural stem cells, and injury to this area may increase the risk of neurocognitive sequelae. Several studies have recently reported a positive correlation between the radiation dose to the hippocampus and cognitive function in series of pediatric brain tumors (25-27). In our series, hippocampus injury was observed in only 1 patient, and the majority of necroses were observed in the SVZ of the anterior horn (6 patients), body (7 patients), and occipital horn of the lateral ventricle (1 patient). However, SVZ necrosis progressed after irradiation, and the performance status of the patients was impaired as necrosis progressed. Although it progressed very slowly, SVZ injury was the major cause of deterioration in the performance status of long-term survivors. Whether we should escalate the irradiation dose to the SVZ to control CSCs or spare this area to protect neural stem cells remains controversial.

Recent reports have indicated the usefulness of Met-PET to distinguish tumor recurrence from necrosis with excellent sensitivity (75%-100%) and specificity (60%-100%), although different T/N cutoff ratios (1.58-1.90) have been used (28-31). In this study, Met-PET was available in 22 cases; 16 lesions were diagnosed as necrosis, and the remaining 6 were diagnosed as tumor recurrence with a T/N threshold of 1.8. Among these lesions, the pathologic diagnosis was confirmed in 9 cases: 3 SVZ necroses, 1 regional necrosis, 2 local recurrences, and 3 disseminated diseases. No discrepancies in diagnosis were observed between Met-PET and pathologic analysis. However, another patient experienced regrowth of the lesion even though it had been diagnosed as necrosis by Met-PET 8 months before progression. We should be aware of the limitation of tracer imaging in that it reflects only the dominant features of lesions.

This single-institution prospective study demonstrated a satisfactory effect of hypofractionated high-dose IMRT on local control and survival in patients with GBM in the TMZ era. Despite the significant effect on control of GBM, this method still has some limitations. First, our IMRT contributed to local tumor control but not to prevention of dissemination. Second, our treatment increased the risk of radiation injury to the SVZ. The SVZ injury was associated with better patient survival but with impairment of patients' performance status. Third, this was a single-institution, small, nonrandomized study. Larger multiinstitutional randomized trials are required to validate our results and to confirm the efficacy of hypofractionated high-dose IMRT on control of GBM.

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Clinical Benefit of ^{11}C Methionine PET Imaging as a Planning Modality for Radiosurgery of Previously Irradiated Recurrent Brain Metastases

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Object: Stereotactic radiosurgery with gamma knife (GK-SRS) generally improves the focal control of brain metastases. Yet in cases of focal recurrence at a previous radiation site, MRI is often imperfect in differentiating between active tumor and radiation injury. We have examined whether the use of ^{11}C methionine (MET) with PET will facilitate this differentiation and improve the outcome of GK-SRS for focally recurrent brain metastases after prior treatment.

Methods: Eighty-eight patients underwent GK-SRS for postirradiation recurrent brain metastases. Thirty-four patients received radiation in areas manifesting high MET uptake (PET group) in a dose-planning procedure using MET-PET/MRI fusion images. Fifty-four patients referred from other institutes received radiation based on dose planning information obtained from MRI (MRI group).

Results: Sex, age, and the ratio of breast cancer differed significantly between the MRI and PET groups. The total irradiation volume was significantly smaller in the PET group, and the minimal irradiation dose was significantly higher. In a multivariable statistical analysis, the use of MET-PET ($P = 0.02$) was independently associated with prolonged overall survival after treatment, Karnofsky performance status ($P = 0.002$), the number of lesions ($P = 0.03$), and patient's sex ($P = 0.02$). The median survival time was significantly longer in the PET group (18.1 months) than in the MRI group (8.6 months) ($P = 0.01$).

Conclusion: ^{11}C methionine-PET/MRI fusion images for dose planning lengthened survival in patients undergoing GK-SRS for focally recurrent brain metastases.

Key Words: methionine, PET, recurrent brain metastases, radiosurgery

(*Clin Nucl Med* 2014;39: 939–943)

Gamma knife stereotactic radiosurgery (GK-SRS) is widely acknowledged to be effective for the treatment of newly diagnosed metastatic brain tumors.[1–3] Gamma knife stereotactic radiosurgery may also be helpful when tumors recur focally at or within previous radiation sites or when patients otherwise require additional treatment.[4–7] Yet it can be difficult to differentiate between a recurrent tumor and radiation injury caused by the initial SRS, as necrotic inflammation and recurrent active tumors are both similarly enhanced in gadolinium (Gd) contrast MRI.[8–11]

The authors have long been using ^{11}C methionine (MET) images with PET for the treatment of gliomas.[12] In more recent years, PET-MRI fusion images for surgical navigation have proven to be useful for achieving maximal resection of gliomas and prolonging patients' survival.[12–14] This trend, together with the established use of MET-PET for differentiating active metastatic brain tumor and radiation necrosis, suggests that the same type of approach (ie, MET-PET/MRI fusion images) may facilitate the GK-SRS procedure for locally recurrent brain metastases.[15,16] Our group started using PET-MRI fusion images in GK-SRS interventions for patients treated under our PET program in 2005. In this study, we retrospectively compared the posttreatment survival of these patients with that of patients treated in the same GK center using MRI information alone.

PATIENTS AND METHODS

Patient Population

This was an institutional review board–approved retrospective cohort study (Tokyo Women's Medical University and Tokyo Medical and Dental University). The subjects were selected from among 2502 patients with brain metastases who underwent GK-SRS at Katsuta Hospital Mito Gamma House (our GK center) from 1998 to 2011. Local recurrence at the previously irradiated site, with or without new lesions, was detected in 134 (5.4%) of the patients. Patients with a low Karnofsky performance status (KPS) score due to systemic disease, impaired neurocognitive function (resulting in a noncooperative state), meningeal dissemination, and/or an expected survival period of 3 months or less were excluded from re-treatment (n = 46). The other 88 patients underwent a second GK-SRS. The patients referred from Tokyo Medical and Dental University were enrolled in a PET program and treated using PET-MRI fusion images (n = 34, PET group). The patients referred from the other institutes were treated with MRI information alone (n = 54, MRI group). The patients' characteristics and the overall survival of the 2 groups were statistically compared.

PET Measurements

The PET images were obtained at the PET Center in the Tokyo Metropolitan Institute of Gerontology. The equilibrated radioactivity was measured with a PET scanner (SET 2400 W; Shimadzu, Kyoto, Japan) 20 minutes after administering an intravenous injection of MET (250–300 MBq). Transmission data were acquired in each patient using a rotating 68Ge rod source for attenuation correction. The regional MET uptake was expressed as a standardized uptake value. The PET images were transferred to our GK center in digital format.

GK-SRS Planning for the 2 Groups

The patients in the MRI group were judged to have recurrent lesions when the maximum diameter of the gadolinium-enhanced

Received for publication February 25, 2014; revision accepted July 2, 2014.

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Conflicts of interest and sources of funding: Supported by JSPS KAKENHI Grant No. 23390334.

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ISSN: 0363-9762/14/3911–0939

lesions was increased by more than 10% on T1-weighted MRI. Most of the patients in the MRI group were also examined by magnetic resonance spectroscopy to help distinguish recurrence from radiation injury. The patients in the PET group were judged to have recurrent lesions when the MET uptake exceeded the previously reported threshold (lesion and control ratio of more than 1.4).[15,16] The former received radiation only in areas with enhancement. The latter received radiation only in areas with elevated MET uptake, regardless of the lesions enhanced on MRI. Over the first years of the study period, the PET-MR fusion images were produced with Dr. View (Infocom Co, Ltd, Tokyo, Japan), a medical image analysis program for personal computers (n = 25). The fusion images were transferred into the Leksell Gamma Plan System (Elekta, AB, Stockholm). From 2009 onward, when Gamma Plan version 8.0 became available, the image fusion was conducted using an automated program capable of fusing MET-PET and MRI data (n = 9). The re-SRS was performed within 2 weeks or less from diagnosis in most of the patients in the 2 groups and within 6 weeks from diagnosis at the longest. Representative planning of PET-based GK treatment was demonstrated in Figure 1.

Statistical Analysis

The data were analyzed statistically using JMP (Japanese version 10.0, SAS Institute Inc, Cary, NC) running on personal computers. The overall survival period was defined as the interval between the day of GK treatment and either the last day of follow-up or the day of death by any cause. An analysis of time-to-event outcomes was performed using the Kaplan-Meier method with the log-rank test or regression analysis with the proportional hazard model. The odds ratios (OR) and 95% confidence intervals (CI) were estimated using the Cox proportional hazards model. Comparisons between groups were performed using the Wilcoxon rank sum test and the Fisher exact tests. $P < 0.05$ was considered to indicate statistically significant differences.

RESULTS

Table 1 shows the results of a statistical comparison of various clinical parameters between the 2 groups of patients treated using different modalities for planning, one with PET-MRI fusion imaging (PET group) and the other with MRI imaging (MRI group). The factors compared were sex, age, type and status of the primary lesion, KPS, recursive partitioning analysis class,[17] metastases to extracranial lesion, number of brain lesions, and dose and volume in GK radiation planning. The MRI and PET groups differed significantly in sex, age, and the ratio of breast cancer. The total irradiation volume was significantly smaller in the PET group than in the MRI group (6.87 vs 10.9 cc; $P = 0.0497$), and the minimal irradiation dose in the PET group was significantly higher (21 vs 19 Gy; $P = 0.04$). No statistically significant differences were found between the 2 groups in the other factors compared.

Figure 2 shows a statistical comparison between the 2 groups in overall survival. Follow-up visits in person and follow-up inquiries by telephone confirmed that 8 patients in the PET group and 2 patients in the MR group survived throughout the whole study period. The median survival time after the final GK was significantly longer in the PET group than in the MRI group (18.1 vs 8.6 months; $P = 0.01$). Table 2 shows the results of a multivariable analysis with a Cox proportional hazards model to examine if the use of PET-MRI fusion images independently contributed to a longer patient survival. The use of MET-PET (OR = 0.54; CI, 0.33–0.90; $P = 0.02$) was independently associated with a prolonged posttreatment survival time, the KPS (by 10% increase, OR, 0.71; CI, 0.57–0.88; $P = 0.002$), the

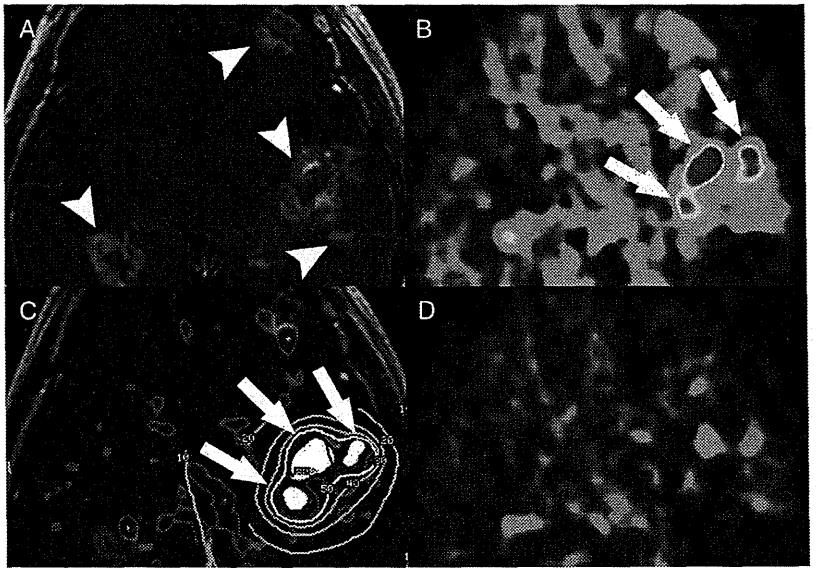

FIGURE 1. Representative plan for GK surgery for locally recurring brain metastases with guidance from MET-PET/MRI fusion imaging. The patient was a 42-year-old woman with brain metastases from breast cancer who had received 4 previous treatments with GK. A big discrepancy was clearly seen between the area with Gd contrast enhancement on the T1-weighted MR image (**A**, indicated by arrowheads) and the area with elevated MET uptake (**B**, indicated by arrows). **C**, The PET-MRI fusion image was rendered after constructing a binary image (shown in white) indicating areas with MET uptake 1.4 times higher than that in the contralateral brain.[15,16] **D**, The GK strategy was to administer a higher radiation dose to areas with higher MET uptake. ^{11}C methionine uptake was markedly reduced in a MET-PET image obtained 6 months after the GK (ie, good control of active cancer).

TABLE 1. Preradiosurgical Clinical Factors Between Patients Treated Only With Enhanced MRI (MRI Group) and With ^{11}C Methionine PET (PET Group)

	PET Group (n = 34)	MRI Group (n = 54)	*P*
Sex, n			0.005
Male	12	36	
Female	22	18	
Age, mean (range), y	58 (37–80)	63 (38–80)	0.03
Origin			0.07
Lung	18	34	
Breast	12	7	
Gastrointestinal	0	9	
Others	4	4	
Ratio of breast cancer	12/34 (35.3%)	7/54 (13.0%)	0.02
RPA class			0.36
Class 1	8	11	
Class 2	26	40	
Class 3	0	3	
KPS, median (range), %	90 (70–100)	90 (60–100)	0.41
State of original cancer			0.18
Good control	23	28	
Poor control	11	26	
Extracerebral metastases, n	13	16	0.49
No. lesions, median (range)	2 (1–35)	1 (1–25)	0.44
Radiosurgical characteristics			
Total tumor volume, mean (range), cc	6.87 (0.28–38.5)	10.9 (0.03–41.1)	0.0497
Maximum dose, mean (range), Gy	32 (20–48)	32 (20–50)	0.78
Minimum Dose, mean (range), Gy	21 (12–25)	19 (12–25)	0.04

Wilcoxon rank sum test or Fisher exact test was used for comparison.
RPA, Recursive partitioning analysis.

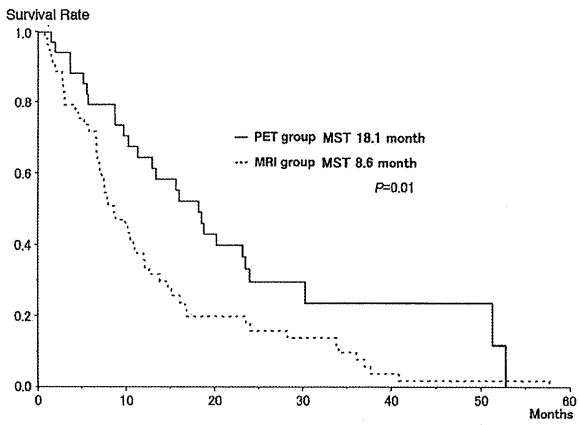

FIGURE 2. Graph depicting survival curves plotted by the Kaplan-Meier method for 2 groups of patients treated using different modalities for planning, one with PET-MRI fusion imaging (PET group, solid line) and the other with MRI imaging (MRI group, dotted line). The length of survival after GK treatment significantly differed between the 2 groups ($P = 0.01$, log-rank test). The difference in the median survival time between the 2 groups was close to 10 months (18.1 months in PET vs 8.6 months in MRI). Follow-up visits in person and follow-up inquiries by telephone confirmed that 8 patients in the PET group and 2 patients in the MR group survived throughout the whole study period.

number of lesions (OR, 1.06; CI, 1.007–1.11; $P = 0.03$), and sex (male to female, OR, 2.08; CI, 1.13–4.01; $P = 0.02$).

Improvements in various treatments against cancer over time may have contributed to the better survival of the PET group, as many of the PET patients were treated more recently (2005–2011) than the MRI group patients (1998–2011) overall. Yet according to an analysis of the post-GK survival time in the MRI group patients treated from 2005 to 2011 (n = 28), the median survival (7.8 months) was shorter than that of the patients in all MRI group patients (8.7 months) and significantly shorter than that of the PET group overall ($P = 0.01$).

TABLE 2. Preradiosurgical Clinical Factors Affecting Post–Re-Treatment Survival Period in Patients With Local Recurrence

	Odds Ratio	(95% CI)	*P*
Sex (Male to Female)	2.08	(1.13–4.01)	0.02
Age (continuous)	1.003	(0.98–1.03)	0.82
Origin (breast to others)	1.16	(0.48–2.81)	0.74
RPA class	1.56	(0.29–8.08)	0.60
KPS (by increase of 10%)	0.71	(0.57–0.88)	0.002
State of original cancer (good to poor)	0.75	(0.40–1.39)	0.37
Extracerebral metastases (yes to no)	1.54	(0.75–3.05)	0.23
Number of lesions (continuous)	1.06	(1.007–1.11)	0.03
Using MET-PET (yes to no)	0.54	(0.33–0.90)	0.02

Regression analysis with the proportional hazard model.

From this result, we concluded that the difference in the treatment period had little influence on the patients' survival.

DISCUSSION

The present report is the first to show the clinical benefit of PET-MRI fusion images for the planning of the GK-SRS intervention against metastatic brain tumors. Using MET as a suitable probe for PET brain tumor imaging, we statistically demonstrated that patients undergoing GK-SRS survived significantly longer after procedures performed using PET-MRI guidance versus those performed using MRI information alone.

Metastasis is a life-threatening process estimated to occur in 10% to 30% of all cancer patients.[18] The management of brain metastases is hence crucial for patients' prognosis. Whole-brain radiotherapy (WBRT) is being superseded by SRS without WBRT as a treatment of choice for brain metastases, even for patients with 5 or more lesions.[19] Whereas no clear consensus has been reached on the best approach to metastases,[20] WBRT poses grave problems: patients who achieve long-term survival may have decreased cognitive function or may be prohibited from receiving a second WBRT interventions even when metastases recur. Patients managed with SRS usually fare much better cognitively,[21] and any adverse events associated with the intervention tend to be manageable.[22] Patients may thus receive a second SRS safely and effectively when lesions recur.

Particular concern, however, is merited for patients who receive a second GK-SRS on the occurrence of radiation-induced necrosis. Conventional morphological MRI may be poor in differentiating tumor recurrence from radiation necrosis, as necrotic lesions without viable tumors are often well enhanced by Gd and occasionally grow in much the same way as recurrent tumors.[23] Magnetic resonance techniques such as the detection of T1 and T2 mismatch,[24] magnetic resonance spectroscopy,[25,26] and perfusion-weighted MRI[27–30] have been proposed as useful means for differentiating tumor recurrence from radiation necrosis. These maneuvers have high sensitivity and specificity for differentiation and thus may be sufficient for differentiation when an enhanced lesion is pure tumor or pure necrosis. Such instances may be rare, however, as tumors detected in formerly irradiated regions usually turn out to be a mixture of active tumor and necrotic tissue (Fig. 1). The MRI method may not work well in prospectively picking up active tumor tissue out of mixed tumors of this type.[31] Hence, PET metabolic imaging has considerable advantages over MRI as a source of guidance for GK treatment.

Among the various PET methods, ^{18}F-FDG has been considered useful for whole-body cancer imaging. Now, however, FDG is widely believed to be unsuitable for brain tumors. The physiological use of glucose in normal brain is generally higher than that of most metastatic tumors,[32] and high uptake of FDG into inflammatory tissues[33] may also hamper the detection of active tumors.

In contrast to glucose, amino acid uptake is lower in the brain than in most tumors. Amino acid imaging thus holds promise for the detection and focal treatment of malignant tumors of the brain. Our group previously reported the advantages of MET-PET imaging for the surgical resection of glial tumors.[13,14] When used for glioma surgery, MRI and MET-PET detect different tumor margins. ^{11}C methionine PET reportedly detect tumors invading far beyond the area with Gd enhancement,[34] and patients with remnant malignant gliomas in areas without Gd enhancement generally have worse outcome than patients without remnant tumor detectable by MET-PET.[12] Hence, the resection area determined with MET-PET is usually larger than that detected by enhanced MRI.

When GK-SRS is performed for focally recurrent brain metastases, the active tumor area detected with PET is smaller than that detected with Gd enhancement on MRI (Fig. 1). The same difference was manifested as a smaller total irradiation volume in the PET group versus the MRI group (Table 1). We suspect that the smaller irradiation volume in the PET group may have led to a significantly higher marginal dose in the PET group than in the MRI group (Table 1). We believe that the current results are quite reasonable, as a prior study has already demonstrated that a lower marginal dose leads to higher rate of local recurrence.[35]

The retrospective noncontrolled protocol of this study, however, made it difficult to wholly eliminate selection bias. With regard to sex difference, an analysis of the influence of breast and gynecologic cancers known to have a better prognosis than other cancers[36,37] indicated that the different rates of malignancy were not independently associated with prolonged overall survival. Next, with regard to a potential lead time bias (ie, improved survival in the PET group versus the MR group attributable to the earlier diagnosis of the former), no significant difference between the 2 groups was found at the time between the re-SRS and previous SRS (54.5 weeks in the PET group vs 37.9 weeks in the MR group; $P = 0.06$).

This retrospective study is the first to show the clinical benefit of PET-MRI fusion imaging as guidance for the GK-SRS intervention. We thus believe the study has value as an initial preliminary report on the use of a new technique. Our analysis, however, was performed under rather specific conditions. Although GK treatment was performed at a single institute and managed by a single specialist (M. Y.) with ample experience with GK treatment for metastatic brain tumors,[19,22,38,39] the patients were referred from multiple institutes. Most of the patients in the PET group were referred from the institute of the chief investigator, whereas all of the patients in the MRI group were referred from other institutes without available PET facilities. Hence, factors other than planning may have influenced the patient outcomes. Further, the number of focally recurrent patients who underwent repeated GK was small relative to the population of patients with brain metastases out of which they were selected (88 of 2502). In view of these limitations, we believe that our data constitute only preliminary evidence that MET-PET/MRI fusion imaging improves the outcome of GK-SRS for metastatic brain tumors. We propose a further prospective analysis with a larger population to confirm the usefulness of PET-based GK-SRS.

CONCLUSION

The results of our retrospective study indicated that MET-PET/MRI fusion images for dose planning prolong the survival of patients undergoing GK-SRS for locally recurring brain metastases compared with similar patients undergoing GK-SRS using MRI alone. A further prospective study on a larger number of patients will be necessary to clarify the real benefit of GK-SRS using MET-PET fusion images.

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J Neurosurg (Suppl 2) 121:16–25, 2014

Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2–9 versus 10 or more tumors

Clinical article

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Object. Although stereotactic radiosurgery (SRS) alone is not a standard treatment for patients with 4–5 tumors or more, a recent trend has been for patients with 5 or more, or even 10 or more, tumors to undergo SRS alone. The aim of this study was to reappraise whether the treatment results for SRS alone for patients with 10 or more tumors differ from those for patients with 2–9 tumors.

Methods. This was an institutional review board–approved, retrospective cohort study that gathered data from the Katsuta Hospital Mito GammaHouse prospectively accumulated database. Data were collected for 2553 patients who consecutively had undergone Gamma Knife SRS alone, without whole-brain radiotherapy (WBRT), for newly diagnosed (mostly) or recurrent (uncommonly) brain metastases during 1998–2011. Of these 2553 patients, 739 (28.9%) with a single tumor were excluded, leaving 1814 with multiple metastases in the study. These 1814 patients were divided into 2 groups: those with 2–9 tumors (Group A, 1254 patients) and those with 10 or more tumors (Group B, 560 patients). Because of considerable bias in pre-SRS clinical factors between groups A and B, a case-matched study, which used the propensity score matching method, was conducted for clinical factors (i.e., age, sex, primary tumor state, extracerebral metastases, Karnofsky Performance Status, neurological symptoms, prior procedures [surgery and WBRT], volume of the largest tumor, and peripheral doses). Ultimately, 720 patients (360 in each group) were selected. The standard Kaplan-Meier method was used to determine post-SRS survival times and post-SRS neurological death–free survival times. Competing risk analysis was applied to estimate cumulative incidence for local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-induced complications.

Results. Post-SRS median survival times did not differ significantly between the 2 groups (6.8 months for Group A vs 6.0 months for Group B; hazard ratio [HR] 1.133, 95% CI 0.974–1.319, p = 0.10). Furthermore, rates of neurological death were very similar: 10.0% for group A and 9.4% for group B (p = 0.89); neurological death–free survival times did not differ significantly between the 2 groups (HR 1.073, 95% CI 0.649–1.771, p = 0.78). The cumulative incidence of local recurrence (HR 0.425, 95% CI 0.0.181–0.990, p = 0.04) and repeat SRS for new lesions (HR 0.732, 95% CI 0.554–0.870, p = 0.03) were significantly lower for Group B than for Group A patients. No significant differences between the groups were found for cumulative incidence for neurological deterioration (HR 0.994, 95% CI 0.607–1.469, p = 0.80) or SRS-related complications (HR 0.541, 95% CI 0.138–2.112, p = 0.38).

Conclusions. Post-SRS treatment results (i.e., median survival time; neurological death–free survival times; and cumulative incidence for local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-related complications) were not inferior (neither less effective nor less safe) for patients in Group B than for those in Group A. We conclude that carefully selected patients with 10 or more tumors are not unfavorable candidates for SRS alone. A randomized controlled trial should be conducted to test this hypothesis.
(http://thejns.org/doi/abs/10.3171/2014.8.GKS141421)

Key Words • **brain metastases** • **radiation therapy** • **radiosurgery** • **Gamma Knife** • **tumor number** • **stereotactic radiosurgery**

Abbreviations used in this paper: HR = hazard ratio; KPS = Karnofsky Performance Status; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

Since Sturm et al. reported successful treatment of brain metastases with use of stereotactic radiosurgery (SRS),[25] evidence of the effectiveness of this treatment strategy has been accumulating, for both SRS

alone and SRS in combination with whole-brain radiotherapy (WBRT).[1,3,10,13,15,23,24] Among patients with brain metastases, numerous factors affect outcomes, such that a one-size-fits-all treatment paradigm is no longer appropriate. Nevertheless, a solid patient selection criterion is still necessary before SRS treatment of brain metastases. SRS alone for patients with 4 or more, or even 5 or more, metastatic tumors is not a standard treatment, and in most industrialized nations, WBRT is still strongly recommended.[17] However, by the early 21st century, a trend for patients with 5 or more tumors to be potential candidates for SRS alone had already become apparent.[3,8,13,15,16,20,23,24,26–30,32] Very recently, in a prospective observational study of 1194 brain metastasis patients, Yamamoto et al. showed that SRS without WBRT as the initial treatment was not inferior (in terms of overall survival as well as most secondary end points) for patients with 5–10 metastatic brain tumors compared with those with 2–4 metastatic tumors.[35] Considering the present lack of evidence supporting the superiority of WBRT over SRS alone for patients with 5–10 tumors, their results are considered to constitute the highest level of evidence to date, allowing SRS alone to be advocated for such patients. Existing treatment guidelines for managing brain metastasis patients need to be revised in the very near future.

The next step is to reappraise whether SRS alone is inferior for patients with 10 or more metastatic tumors compared to patients with fewer metastatic tumors. Very recently, 2 studies evaluating outcomes in patients with 10 or more metastatic brain tumors treated with SRS were published in the Journal of Neurosurgery.[8,20] Grandhi et al. studied 61 patients with 10 or more metastatic brain tumors (mean 13 tumors) treated with SRS and found median survival time after SRS to be 4 months; they concluded that SRS safely and effectively treats intracranial disease with a high rate of local control in patients with 10 or more metastatic brain tumors.[8] These authors stated that SRS might be one of the most effective treatment options available for patients with fewer tumors, a non-melanomatous primary lesion, controlled systemic disease, and assignment to a low recursive partitioning analysis (RPA) class. Grandhi et al. concluded that SRS can thus be regarded as a first-line treatment. Rava et al. studied 53 patients with 10 or more metastatic brain tumors treated with SRS (mean number of tumors = 11) and found that post-SRS median survival time exceeded 6 months; they concluded that aggressive local treatment remains an option, although rapid CNS failure is to be expected.[20] Patients with breast cancer represent a group of patients likely to benefit greatly from SRS alone; survival time and time to CNS recurrence are extended. Although these 2 articles discuss several important issues and present significant potential treatment advances, a common weakness is that sample sizes were relatively small (61 and 53 patients).[8,20]

Therefore, we conducted this retrospective cohort study, based on our SRS-treated brain metastasis patients, including 560 patients with 10 or more tumors, to reappraise whether treatment results were truly inferior for patients with 10 or more versus 2–9 tumors and to identify factors determining inferiority and/or noninferiority. We excluded patients with only 1 tumor because it is widely recognized that survival periods are much longer for patients with a single brain metastastic tumor than for those with multiple metastatic brain tumors.[13,23,24,30]

Methods

Patient Population

This retrospective cohort study used the prospectively accumulated Katsuta Hospital Mito GammaHouse database of 2553 patients who consecutively underwent SRS alone, without WBRT, for newly diagnosed (mostly) or recurrent (uncommonly) brain metastases during the 13-year-period July 1998 through June 2011. The study was approved by the institutional review board of Tokyo Women's Medical University. Because all patients had been referred to the Katsuta Hospital Mito GammaHouse for SRS, their primary physicians had made most of the patient selections. Patient selection criteria may thus have differed among referring physicians. Therefore, one author (M.Y.) decided whether to accept a patient. We did not perform SRS on patients with low Karnofsky Performance Status (KPS) scores[14] resulting from systemic diseases, a noncooperative state resulting from poor neurocognitive function, meningeal dissemination, or an anticipated survival period of 3 months or less. Therefore, only 173 (6.8%) patients were categorized into RPA Class III,[6] while 1189 (46.6%) were categorized into modified-RPA Class IIc+III.[33,34] Also, the primary physicians responsible for each patient decided the indications for both surgery and radiotherapy. Therefore, before undergoing SRS, 468 (18.3%) of the 2553 patients had undergone surgical removal of brain metastases and 125 (4.9%) had undergone WBRT.

Before SRS, the first author (M.Y.) explained the treatment strategy in detail to each patient and at least 1 adult relative of the patient. Written informed consent was obtained from all patients. Because our previous report[32,33] describes our radiosurgical techniques and dose selection for multiple brain metastases in detail, they are not repeated herein. In brief, before June 2003, standard SRS procedures were performed by using a Leksell Gamma Unit Model B and thereafter a Leksell Gamma Unit Model C (Elekta AB). For target coordinate determination and dose planning, until August 2002 stereotactic single-dose gadolinium-enhanced T1-weighted axial MR images with a slice thickness of 2 mm, multiple slices of which covered the entire brain, were obtained by using a Magnetom Impact Expert 1.0-T unit (Siemens); thereafter, a Magnetom Symphony 1.5-T unit (Siemens) was used.

After SRS, patients were usually managed by their referring physicians; clinical and neuroimaging examinations at approximately 2- to 3-month intervals were recommended. However, for 761 (29.8%) of the 2553 patients, neuroimaging follow-up could not be performed because of early post-SRS death or remarkable deterioration of general condition. Among the 2553 patients, follow-up information was obtained during periodic visits to our outpatient clinic (approximately 60%), from clinical and/or neuroimaging data that were mailed to us (about 25%),

or by phone call from the first author (M.Y.) to patients or their relatives (15%). For deceased patients, information about the day of death, cause of death, and detailed information on patient condition changes was obtained by telephone calls to relatives.

Study Design and Case Matching

Karlsson et al.[13] recently conducted a study of 1921 brain metastasis patients who underwent SRS. They reported that although patients with a single metastatic brain lesion survived longer than those with multiple brain metastases, median survival times did not significantly differ among patients with 2, 3–4, 5–8, or more than 8 metastatic tumors. Also, using our database and including the present cohort (of the 2553 patients, 2232 had 15 tumors or fewer), we used the Kaplan-Meier method[12] to compare 14 pairs of groups based on number of tumors (1 tumor vs 2 tumors, 2 vs 3, 3 vs 4, and so on through 14 vs 15). As shown in Table 1, among the 14 pairs, median survival times differed significantly only for patients with 1 versus 2 tumors ($p < 0.001$); no significant differences were detected for the other 13 pairs of groups based on number of tumors (Bonferroni threshold $0.05/14 = 0.0036$). Thus, we excluded 739 (28.9%) patients with a single metastatic brain lesion and studied the remaining 1814 patients with multiple metastatic brain tumors. These 1814 patients were divided into 2 groups; those with 2–9 tumors (Group A, 1254 patients) and those with 10 or more tumors (Group B, 560 patients).

Because there was bias and a large discrepancy in the number of patients in groups A and B, a case-matched study was conducted by one of the authors (Y.S.), who did not participate in other aspects of this study and was blinded as to the final outcomes. Patient selection was performed by using the propensity score matching method with a Greedy 5-To-1 Digit-Matching algorithm[18] for clinical factors (i.e., age, sex, primary tumor status, extracerebral metastases, KPS score, neurological symptoms, prior procedures [surgery and WBRT], volume of the largest tumor, and peripheral doses).[4,21] After all the propensity score matches had been performed, we compared baseline covariates between the 2 groups. Ultimately, 720 patients were selected (360 with 2–9 tumors [Group A] and 360 with 10 or more tumors [Group B]) (Table 2).[33,34] The p values after matching exceeded 0.05 for all clinical factors.

Clinical Outcomes

The primary end point was overall survival, and the secondary end points were neurological death, neurological deterioration, local recurrence of the treated tumor, repeat SRS for new lesions, and SRS-induced major complications. For each end point, failures were regarded as events, and any others were regarded as censored. Because the criteria for each end point have been described,[32,33] they are not repeated herein.

Statistical Analyses

All data were analyzed according to the intention-to-treat principle. For the baseline variables, summary statistics were constructed by using frequencies and proportions for categorical data and using means and standard deviations for continuous variables. We compared patient characteristics by using the Fisher exact test for categorical outcomes and t-tests for continuous variables, as appropriate. The standard Kaplan-Meier method was used for overall and neurological death–free survival calculations.[12] Also, to determine pre-SRS clinical factors favoring longer survival time, we performed univariable analysis by using the Cox proportional hazard model.

For time-to-event outcomes, we estimated the cumulative incidence for local recurrence, repeat SRS, neuro-

TABLE 1: Median survival time differences between patient groups based on number of tumors*

No. of Tumors	No. of Patients	Median Survival Time (95% CI), Months	HR (95% CI)	Log–Rank p Value†
1	739	10.6 (9.4–11.8)		
2	390	7.4 (6.7–8.4)	0.730 (0.641–0.831)	<0.001 (vs 1)
3	235	8.0 (6.4–9.2)	1.046 (0.883–1.236)	0.60 (vs 2)
4	189	7.1 (5.9–8.5)	0.994 (0.815–1.216)	0.96 (vs 3)
5	118	6.2 (5.1–7.6)	0.953 (0.751–1.213)	0.69 (vs 4)
6	115	7.0 (4.8–9.1)	1.030 (0.789–1.345)	0.83 (vs 5)
7	69	8.1 (5.0–10.6)	1.042 (0.759–1.420)	0.79 (vs 6)
8	80	5.5 (3.2–6.5)	0.656 (0.468–0.916)	0.01 (vs 7)
9	57	5.1 (3.7–7.0)	0.888 (0.625–1.253)	0.50 (vs 8)
10	69	7.0 (4.3–9.3)	1.186 (0.824–1.700)	0.35 (vs 9)
11	46	6.3 (3.7–9.1)	0.980 (0.665–1.432)	0.92 (vs 10)
12	32	7.1 (3.5–10.7)	1.063 (0.676–1.694)	0.79 (vs 11)
13	35	6.1 (3.8–8.9)	0.971 (0.591–1.570)	0.96 (vs 12)
14	38	5.7 (2.6–10.0)	0.936 (0.580–1.504)	0.78 (vs 13)
15	20	8.5 (3.8–11.0)	1.038 (0.578–1.810)	0.90 (vs 14)

* Data exclude 4 patients who were lost to follow-up.

† Parentheses indicate number of tumors in comparison group.

TABLE 2: Summary of clinical characteristics of 720 patients with brain metastases*

Characteristic	Total	No. of Tumors		p Value†
		2–9 (Group A)	≥10 (Group B)	
no. of patients	720	360	360	
no. lost to follow-up	3	1 (0.3%)	2 (0.6%)	1.00
no. of tumors				
mean	11	4	17	
median	9, 10	4	14	
range	2–69	2–9	10–69	
age (yrs)				
mean	63	63	63	0.98
range	25–96	26–96	25–91	
sex: female	319 (44.3%)	154 (42.8%)	165 (45.8%)	0.45
primary cancer sites				
lung	498 (69.2%)	251 (69.7%)	247 (68.6%)	0.81‡
breast	101 (14.0%)	49 (13.6%)	52 (14.4%)	
alimentary tract	61 (8.5%)	36 (10.0%)	25 (6.9%)	
kidney	19 (2.6%)	7 (1.9%)	12 (3.3%)	
others	41 (5.7%)	17 (4.7%)	24 (6.7%)	
primary cancer status: controlled	195 (27.1%)	104 (28.9%)	91 (25.3%)	0.31
extracerebral METs: no.	342 (47.5%)	169 (46.9%)	173 (48.1%)	0.82
KPS score ≥80%	542 (75.3%)	269 (74.7%)	273 (75.8%)	0.80
modified-RPA class				
I+IIa	76 (10.6%)	42 (11.7%)	34 (9.4%)	
IIb	220 (30.6%)	106 (29.4%)	114 (31.7%)	0.35§
IIc+III	424 (58.9%)	212 (58.9%)	212 (58.9%)	0.68¶
neurological Sx: no	353 (49.0%)	176 (48.9%)	177 (49.2%)	1.00
prior surgery: yes	103 (14.3%)	54 (15.0%)	49 (13.6%)	0.67
prior WBRT: yes	36 (5.0%)	19 (5.3%)	17 (4.7%)	0.86
tumor volume (cm^3)				
cumulative				
mean	10.88	11.45	10.31	0.26
range	0.08–115.3	0.08–115.3	0.15–81.4	
largest tumor				
mean	6.14	6.51	5.77	0.24
range	0.03–94.2	0.04–94.2	0.03–65.0	
peripheral dose (Gy)				
mean	20.62	20.51	20.72	0.35
range	10.00–25.00	10.00–25.00	12.00–25.00	

* KPS = Karnofsky Performance Status; METs = metastases; Sx = symptoms.
† The Student t-test was used for continuous variables and the Fisher exact test for pairs of categorical variables.
‡ Lung vs not lung.
§ Modified RPA Class I+IIa vs IIb.
¶ Modified RPA Class IIb vs IIc+III.

logical deterioration, and major complications by using a competing risk analysis because death is a competing risk for loss to follow-up (i.e., patients who die can no longer become lost to follow-up).[9,12,22] Also, to identify baseline and clinical variables associated with the 4 above-mentioned outcomes, we performed competing risk analyses with the Fine-Gray generalization of the proportional hazards model accounting for death as a competing risk.[5,7] For modeling cumulative incidence, the Fine-Gray generalization uses the subdistribution hazard, thereby quantifying the overall benefit or harm of an exposure.[2]

All comparisons were planned, and the tests were 2-sided. A p value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed by one of the authors (Y.S.) who used SAS software, version 9.3 (SAS Institute), and the R statistical

program, version 3.0.0. Before statistical analyses, inaccurate records in the database were corrected (by Y.H.). These 2 authors were not involved in either SRS treatment or patient follow-up evaluations.

Results

Four patients were lost to follow-up and excluded from analysis, leaving a cohort of 2549 patients. Among these 2549 patients, the overall post-SRS median survival time was 7.4 (95% CI 7.1–7.9) months. In the subset of 720 patients (excluding 3 patients lost to follow-up [1 in Group A and 2 in Group B]), the median post-SRS follow-up time among censored observations (39 patients) was 16.7 (range 2.1–110.2) months, and 678 (94.2%) patients died. The post-SRS median survival time was 6.4 (95% CI 5.7–7.0) months. Actuarial survival rates after SRS were 51.9%, 27.7%, 10.5%, 4.3%, and 1.6% at 6, 12, 24, 36, and 60 months, respectively. For 40 patients who died, the cause of death could not be determined; but for the remaining 638, the cause of death was confirmed to be non-brain diseases for 576 (90.3%) and brain diseases for 62 (9.7%). Among the subset of 720 patients, salvage surgery was required for 4 patients and WBRT for 29 patients. There were no significant differences between the 2 groups in the incidences of salvage surgery (0.6% vs 0.6%, p = 1.00) and WBRT (3.1% vs 5.0%, p = 0.19) (Table 3).

Comparisons Between Groups A and B

The post-SRS median survival time was slightly longer for patients in Group A (6.8 months) than for those in Group B (6.0 months). However, the median survival time difference, 0.8 months, did not reach statistical significance, as shown in the graph on the left side of Fig. 1 (hazard ratio [HR] 1.133, 95% CI 0.975–1.320, p = 0.10). Incidence rates for death caused by brain disease progression were very similar: 10.0% for Group A and 9.4% for Group B (p = 0.89) (Table 3). Furthermore, neurological death–free survival intervals did not differ significantly between the 2 groups (HR 1.059, 95% CI 0.680–1.649, p = 0.80) (Fig. 1 right).

Post-SRS follow-up MR images were available for 485 (67.4%) patients: 249 (69.2%) in Group A and 236 (65.6%) in Group B (p = 0.34). The median survival time for patients in whom follow-up MRI examinations were not available was 2.3 (95% CI 1.8–2.6) months. Therefore, most patients in this group died or deteriorated remarkably because of extracerebral disease progression before post-SRS MRI examinations could be performed. Among these 485 patients, the incidence of local recurrence was significantly lower for those in Group B than in Group A (3.0% vs 8.4%, p = 0.01) (Table 3). Also, the cumulative incidence of local recurrence differed significantly between the 2 groups (HR 0.425, 95% CI 0.181–0.990, p = 0.04) (Fig. 2A). Our criteria for detecting local recurrence by using MRI and/or methionine positron emission tomography are detailed elsewhere.[31,32]

As shown in Table 3, among the 720 patients, the incidence of repeat SRS for new lesions was significantly lower among patients in Group B than in Group A (23.7% vs 32.3%, p = 0.01). Also, there was a significant difference between the 2 groups in the cumulative incidence of repeat SRS for new lesions (HR 0.732, 95% CI 0.554–0.970, p = 0.03) (Fig. 2B). There were no significant differences between the 2 groups in the incidence of neurological deterioration or SRS-related complications. Also, there were no significant differences between the 2 groups in the cumulative incidence of neurological deterioration (HR 0.994, 95% CI 0.607–1.469, p = 0.80) (Fig. 2C) or SRS-related complications (HR 0.541, 95% CI 0.138–2.112, p = 0.38) (Fig. 2D).

Factors Affecting Longer Survival for Patients With 10 or More Metastatic Brain Tumors

As shown in Table 4, univariable analysis demonstrated that among various pre-SRS clinical factors, significant predictors of a longer survival period for the 360 patients with 10 or more metastatic brain tumors were female sex, younger age, controlled primary cancer, no extracerebral metastases, better KPS score, better modified-RPA class, smaller tumor volume, and higher peripheral dose. Among these 8 factors, hazard ratios were higher for patients with a KPS score of 80% or higher versus

TABLE 3: Crude incidence of outcomes after SRS*

Outcome	Total	2–9 Tumors (Group A)	≥10 Tumors (Group B)	p Value
no. of patients	720	360	360	
neurological death†	62 (9.7)	32 (10.0)	30 (9.4)	0.89
salvage WBRT	29 (4.0)	11 (3.1)	18 (5.0)	0.19
salvage surgery	4 (0.6)	2 (0.6)	2 (0.6)	1.00
local recurrence‡	28 (5.8)	21 (8.4)	7 (3.0)	0.01
repeat SRS	201 (27.9)	116 (32.3)	85 (23.6)	0.01
neurological deterioration	81 (11.3)	45 (12.5)	36 (10.0)	0.35
SRS-related complications	12 (1.7)	9 (2.5)	3 (0.8)	0.14

* Values represent numbers of cases (%).

† Data are for 638 patients for whom cause of death could be determined (319 in Group A and 319 in Group B).

‡ Data are for 485 patients (249 in Group A and 236 in Group B); 235 patients were excluded because neuroimaging results were not available.

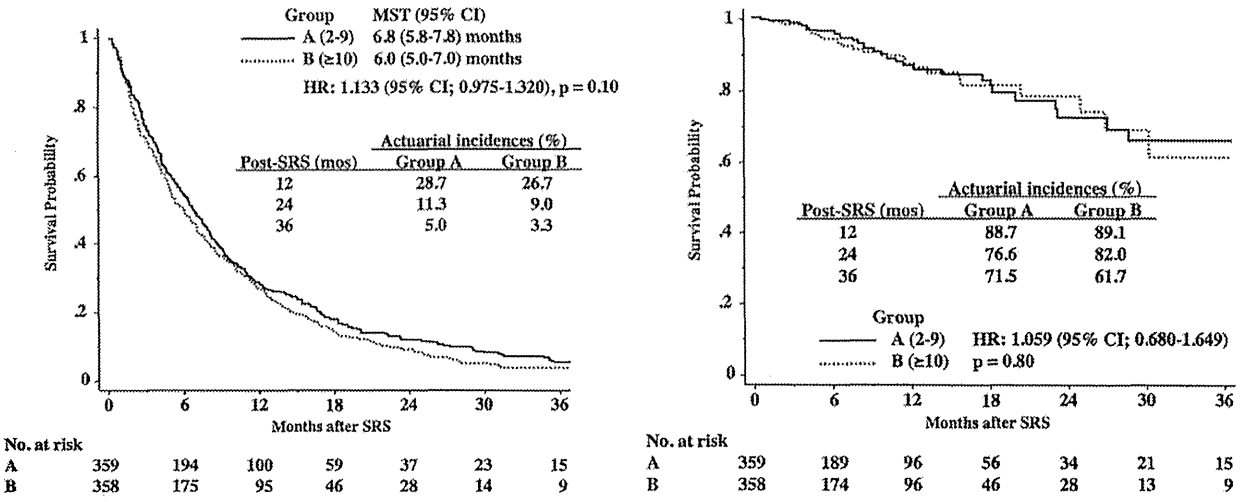

FIG. 1. Probabilities of overall survival (**left**) and neurological death–free survival (**right**) according to number of tumors (2–9 [Group A] and 10 or more [Group B]), estimated by using the Kaplan-Meier method.[12] Three cases lost to follow-up were excluded. MST = median survival time.

70% or lower, primary cancer controlled versus not controlled, no extracerebral metastases versus extracerebral metastases, and modified-RPA Class I+IIa versus IIb and Class IIb versus IIc+III. Also, as shown in Table 4, hazard ratios and 95% confidence intervals for these 4 clinical factors were nearly the same for patients in groups A and B. All of the above-mentioned results differed minimally between the 2 groups.

Discussion

In the study reported here, the post-SRS median survival time difference between the 2 groups, 0.8 months, was not statistically significant. Furthermore, approximately 90% of patients with brain metastases died of causes other than brain disease progression, regardless of the number of metastatic tumors. The results for Group B patients were not inferior to those for Group A patients in terms of neurological death, local recurrence, repeat SRS required for new tumors, maintenance of good neurological state, and SRS-related complications. Because approximately 90% of patients died of extracerebral diseases, it is clearly crucial that brain metastasis treatments contribute to maintenance of a good neurological state. We thus consider it to be very important that the herein-reported results of maintenance of a good neurological state for patients with 10 or more tumors were clearly not inferior to results for patients with 2–9 tumors. Cumulative incidence rates of local recurrence and repeat SRS for patients in Group A were rather high compared with those for patients in Group B; these differences reached statistical significance, although the reasons for their significance are unclear. However, considering our large patient numbers and the fact that the upper 95% CIs (0.990 and 0.970) were very close to 1.0, p values (0.04 and 0.03) were relatively high. Therefore, these differences are not considered to be particularly crucial.

Because we have extensively discussed the benefits of SRS alone versus WBRT with or without SRS for patients with multiple brain metastases in 2 previous articles,[32,35] we will not repeat them here. However, it is noteworthy that previously published studies show tumor numbers to not significantly affect post-SRS overall survival.[3,13,30,32] The central criticism of SRS alone for treatment of multiple brain metastases is the assumption that frequent microscopic tumors will soon require salvage SRS or other treatments. Thus, WBRT has generally been advocated. However, as reported by Aoyama et al., the longest time that WBRT can be expected to prevent new tumors from arising is 6–8 months.[1] We should remember that considerable numbers of patients with brain metastasis can survive more than 1 year, thereby outliving the effects of WBRT. Fortunately, we already live in an era when a metastatic brain lesion of 0.005 cm^3 or even slightly smaller can be detected with thin-slice, gadolinium-enhanced MR images.[11] Hanssens et al. recently reported that according to high-resolution MR imaging, SRS alone decreased the incidence of and lengthened the time to distant recurrences.[10] Although data on periods between SRS and the appearance of new lesions were not available in the study reported here, the rate of repeat SRS among Group B patients was not inferior to that among Group A patients. Therefore, the availability of an alternative treatment for multiple brain metastases enables reservation of WBRT for subsequent treatment attempts (i.e., for meningeal dissemination or miliary metastases treatable only with WBRT).

How Many Brain Metastases Make a Patient Ineligible for SRS?

Current evidence-based guidelines have supported the use of SRS for patients with 1–4 metastatic brain tumors.[17] However, such guidelines frequently lag behind contemporary clinical practice because at least several years are required for completion of rigorous prospective clinical trials. Particularly with use of SRS with a Gamma Knife, when targeting multiple tumors, each addition-

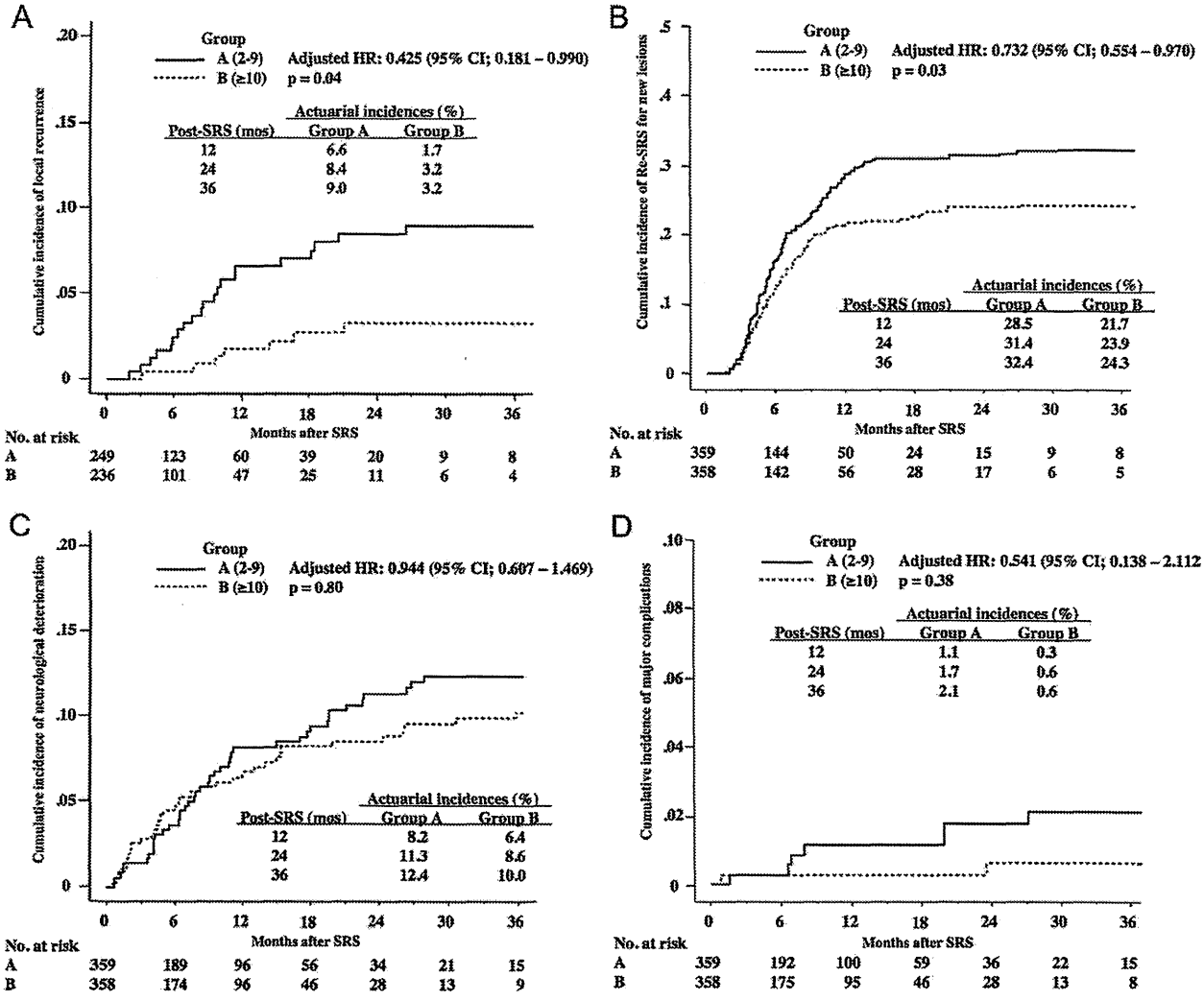

FIG. 2. Cumulative incidence of local recurrence **(A)**, repeat SRS (Re-SRS) for new lesions **(B)**, neurological deterioration **(C)**, and major complications **(D)** according to number of tumors (2–9 [Group A] and 10 or more [Group B]), estimated by using competing risk analysis. Three cases lost to follow-up were excluded. The estimated cumulative incidence of local recurrence was based on 485 (249 in Group A and 236 in Group B) patients (235 patients were excluded because neuroimaging results were not available).

al tumor adds approximately 10 minutes to the treatment time if the tumors are relatively small and a newly loaded unit is used. Therefore, for the past 1.5 decades, challenges have been encountered when using SRS for patients with 5 or more, or even 10 or more, metastatic brain tumors.[3,8,13,15,20,23,24,26,28–30,32] For our cohort of 560 patients with 10 or more tumors, the post-SRS median survival time of 5.6 (95% CI 4.9–6.4) months was slightly longer than the 4 months reported by Rava et al.[20] but similar to the 6 months reported by Grandhi et al.[8]

The North American Gamma Knife Consortium is currently conducting a prospective randomized study entitled "A Randomized Controlled Study Of Neurocognitive Outcomes In Patients With Five Or More Brain Metastases Treated With Radiosurgery Or Whole-Brain Radiotherapy" (http://www.clinicaltrials.gov/, identifier NCT01731704). The primary aim of that study is to compare the changes in neurocognitive function outcomes between baseline and 6 months among patients who undergo WBRT versus SRS. Patients with more than 4 metastatic brain tumors are eligible for this study. The results are expected to clarify the role of SRS alone versus WBRT.

Is SRS Alone for Multiple Brain Metastases Safe?

In 2002, the first author (M.Y.) and colleagues reported that in a series of 80 patients with 10 or more metastatic brain tumors (median 17, maximum 43) undergoing SRS, the estimated absorbed doses to the whole brain ranged from 2.16 to 8.51 (median 4.71) Gy.[29] It was thus assumed that these doses had not exceeded the threshold level of radiation-induced injury to the whole brain. Kawabe et al. presented evidence, based on 1246 SRS procedures for

TABLE 4: Univariable analysis of survival after SRS among 720 matched patients with brain metastases

Factor	No. of Tumors			
	2–9 (Group A)		≥10 (Group B)	
	HR (95% CI)	p Value	HR (95% CI)	p Value
no. of patients	360		360	
sex: M vs F	1.309 (1.054–1.630)	0.01	1.351 (1.090–1.677)	0.006
age				
continuous	1.007 (0.996–1.017)	0.20	1.015 (1.005–1.025)	0.002
>65 vs ≤65 yrs	1.213 (0.976–1.504)	0.08	1.278 (1.032–1.584)	0.02
no. of tumors				
continuous	1.069 (1.018–1.121)	0.007	1.009 (0.995–1.022)	0.22
≤13 vs ≥14			1.141 (0.920–1.417)	0.23
primary cancer: lung vs not lung	1.024 (0.808–1.289)	0.84	1.125 (0.890–1.413)	0.32
extracerebral METs				
controlled vs not controlled	2.726 (2.112–3.550)	<0.001	2.402 (1.856–3.108)	<0.001
present vs absent	1.443 (1.163–1.791)	<0.001	1.347 (1.088–1.670)	0.006
KPS score: ≥80% vs ≤70%	2.140 (1.666–1.725)	<0.001	3.206 (2.467–4.168)	<0.001
modified-RPA class				
I+IIa vs IIb	1.894 (1.298–2.826)	<0.001	1.447 (0.975–2.211)	0.07
IIb vs IIc+III	2.211 (1.728–2.849)	<0.001	2.451 (1.926–3.136)	<0.001
neurological Sx: yes vs no	1.412 (1.139–1.750)	0.002	1.201 (0.970–1.487)	0.09
prior surgery: yes vs no	0.921 (0.671–1.237)	0.59	0.795 (0.579–1.092)	0.15
prior WBRT: yes vs no	0.888 (0.540–1.371)	0.61	1.061 (0.631–1.783)	0.82
tumor volume				
cumulative	1.016 (1.008–1.023)	<0.001	1.023 (1.014–1.032)	<0.001
largest tumor	1.028 (1.014–1.041)	<0.001	1.032 (1.018–1.045)	<0.001
peripheral dose	0.954 (0.921–0.987)	0.007	0.938 (0.901–0.978)	0.003

900 patients with 5 or more metastatic brain tumors, that total absorbed energy for the whole skull of 15 Joules is clearly safe but that total absorbed energy exceeding 20 Joules carries an unacceptably high risk of causing radiation-induced brain injury; the zone between lower and higher risk may thus exist somewhere between 15 and 20 Joules (Kawabe T, Yamamoto M, Barfod BE, Urakawa Y: Gamma knife radiosurgery for multiple brain metastases: what is a safe integral dose for the whole skull? Paper presented at the 10th Congress of International Stereotactic Radiosurgery Society; Paris, France; May 9, 2011). Furthermore, we also recently reported that among 167 brain metastasis patients who survived more than 3 years after SRS, the number of tumors did not affect the incidence of SRS-induced complications (HR 1.066, 95% CI 0.968–1.131, p = 0.1567).[31] Our herein-reported results show no apparent increased risk for complications with SRS for patients with 5 or more metastatic brain tumors compared with 4 or more metastatic brain tumors. Post-SRS MR imaging confirmed the absence of leukoencephalopathy in patients who had undergone SRS alone. Also, in the study reported here, the cumulative incidence of SRS-induced complications among Group B patients was very similar to that among Group A patients. However, only patients with Radiation Therapy Oncology Group neurotoxicity Grade II or worse were counted in this study.[19] Usually, physicians who manage individual cases do not report minor problems like neurotoxicity Grade 0 or 1 to us. Therefore, the weakness of this study is that all patients who experienced minor complications were not surveyed.

How Should Good Candidates for SRS Alone Be Selected From Among Patients With 10 or More Brain Metastases?

Grandhi et al.[8] very recently reported that both univariable and multivariable analyses demonstrated that significant predictors of longer survival were tumor numbers of 13 or fewer versus 14 or more, melanoma versus other primary tumor types, better systemic disease status, and higher RPA class. Our database included only 2 melanoma patients. Thus, we could not test validity for melanoma versus other primary tumor types. In our study, we did not find the number of tumors, either as continuous or categorical variables (13 or fewer vs 14 or more), to be a significant predictor of survival duration (Table 4). Rather, our data indicate the following to favor a longer survival period: controlled primary cancer, no extracerebral metastases, better KPS scores, and higher RPA class. These factors were regarded as the 4 major prognostic factors for selecting good candidates.

Study Weaknesses

The major weakness of this study might be that be-

cause our cohort included all treated patients, clinical factors are obviously heterogeneous. Greater patient group homogeneity makes a study more scientific. However, heterogeneity actually reflects clinical settings rather closely as we physicians often deal with clinical factors that are not homogeneous. Particularly, our database included some patients whose brain metastases were not newly diagnosed. However, proportions of such patients in the 2 groups were very small and did not differ significantly (Table 2). Thus, this heterogeneity had only a minimal effect on our results, as we have reported elsewhere.[33]

Treatment selection is considered to be largely influenced by the characteristics of patients receiving a particular therapeutic regimen. This issue is important when estimating the effect of treatments or exposures on outcomes by using observational data. One approach for reducing or eliminating the effect of treatment selection bias and confounding effects is to use propensity score matching, which enables one to design and analyze an observational (nonrandomized) study that mimics some of the characteristics of a randomized controlled trial.[4] Original tumor phenotypes are now known to affect patient survival. Because these data were lacking for most patients who underwent SRS in the earlier years of our study period, we could not include them as a clinical factor for case matching.

Conclusions

Post-SRS treatment results (i.e., median survival time; neurological death–free survival time; and cumulative incidence of local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-related complications were not inferior among Group B patients when compared with those among Group A patients. We conclude that carefully selected patients with 10 or more metastatic brain tumors are not unfavorable candidates for SRS alone. However, a randomized controlled trial is necessary, in the near future, to clarify the most appropriate role for SRS alone in patients with 10 or more metastatic brain tumors.

Acknowledgment

We are very grateful to Bierta E. Barfod, Katsuta Hospital Mito GammaHouse, for her help in preparing this English manuscript.

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: Yamamoto. Acquisition of data: Yamamoto, Kawabe, Watanabe. Analysis and interpretation of data: Yamamoto, Kawabe, Nariai. Critically revising the article: Yamamoto. Reviewed submitted version of manuscript: Yamamoto, Kawabe, Sato, Higuchi, Nariai, Kasuya. Approved the final version of the manuscript on behalf of all authors: Yamamoto. Statistical analysis: Sato, Higuchi. Study supervision: Yamamoto, Kasuya.

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Manuscript submitted June 24, 2014.
Accepted August 4, 2014.
Please include this information when citing this paper: DOI: 10.3171/2014.8.GKS141421.

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J Neurosurg 121:387–389, 2014

Intractable yawning associated with mature teratoma of the supramedial cerebellum

Case report

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Yawning occurs in various conditions such as hypoxia, epilepsy, and sleep disorders including sleep apnea. Intractable yawning associated with a brain tumor has been rarely reported. A 19-year-old woman presented with intractable yawning. Magnetic resonance imaging showed a tumor in the supramedial cerebellum that compressed the dorsal side of the midbrain and upper pons. After subtotal removal of the tumor, the yawning completely disappeared. Postoperative MRI showed resolution of compression of the brainstem. The tumor was histologically diagnosed as a mature teratoma. The present case suggested that the intractable yawning resulted from the tumor compressing the dorsal side of the junction between the midbrain and pons.
(http://thejns.org/doi/abs/10.3171/2014.4.JNS132243)

KEY WORDS • **yawning** • **paraventricular nucleus** • **parabrachial nucleus** • **oncology**

YAWNING occurs in various conditions such as hypoxia, epilepsy, and sleep disorders, including sleep apnea. Neural networks among the pons, hypothalamus, limbic system, and autonomic nervous system may be associated with yawning.[3,6,8,9] However, intractable yawning associated with a brain tumor has rarely been reported.[1]

We report a rare case involving a patient who had a mature teratoma in the supramedial cerebellum and suffered from intractable yawning. After subtotal removal of the tumor, the yawning completely disappeared.

Case Report

History and Examination. A 19-year-old woman with recurrent yawning visited a local hospital, and an intracranial mass was detected on MRI. The patient visited our institution 4 weeks after symptom onset. The yawning occurred 20 times per minute and continued for approximately 60–90 minutes. Such yawning attacks occurred 2 or 3 times per week. Neurological examination demonstrated no abnormal findings. Magnetic resonance imaging depicted a high-intensity mass in the supramedial cerebellum on T1- and T2-weighted images (Fig. 1). The tumor compressed the dorsal midbrain and upper pons.

Blood gas analysis findings, including partial oxygen pressure, were within normal limits during yawning. Blood counts and biochemical data were also within normal limits. Although the patient's score was 20/24 on the Epworth Sleepiness Scale for detection of sleep disorders (normal score < 11), polysomnography showed no abnormality. Electroencephalography also demonstrated no abnormality. After improving her daily living environment according to our advice, the patient's Epworth Sleepi-

Abbreviations used in this paper: PBN = parabrachial nucleus; PVN = paraventricular nucleus.

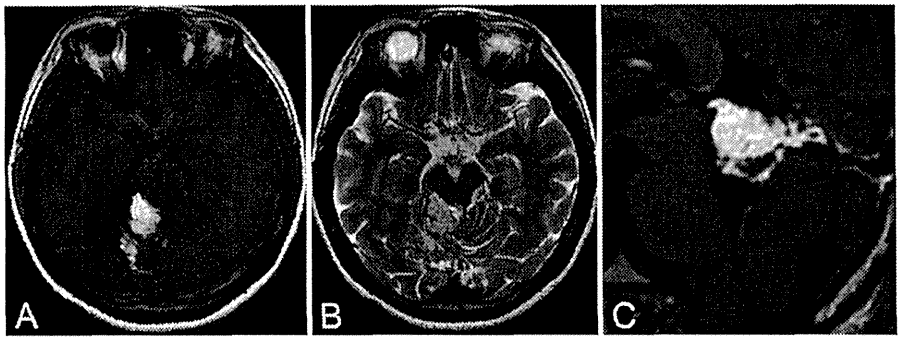

FIG. 1. Axial T1-weighted (A), axial T2-weighted (B), and sagittal Gd-enhanced T1-weighted MR images (C) obtained when the patient presented to our institution, showing a high-intensity mass in the supramedial cerebellum that compresses the dorsal midbrain and the upper pons.

ness Scale score declined to 9/24. However, the yawning continued for 2 years after the decrease in the Epworth Sleepiness Scale score, and then diplopia developed. Neurological examination demonstrated a right trochlear nerve palsy. Magnetic resonance imaging showed no change in the tumor.

Operation and Postoperative Course. The patient underwent removal of the tumor through an occipital transtentorial approach performed under general anesthesia. The tumor was hard and contained yellowish fat tissue and calcified components. During surgery, we found that the tumor adhered to the dorsal side of the midbrain and upper pons and involved the right trochlear nerve and the right superior cerebellar artery. Therefore, the tumor except the part adhering to the dorsal midbrain was removed. The surgical specimen was histologically diagnosed as a mature teratoma composed of fat, muscle, and nerve cells with poor heteromorphism. The yawning completely disappeared immediately after surgery and has not recurred 7 months after surgery. Postoperative MRI showed a residual tumor at the dorsal midbrain and resolution of the brainstem compression (Fig. 2).

Discussion

Based on blood gas analysis, the Epworth Sleepiness Scale score, and findings on polysomnography and electroencephalography, intractable yawning in this patient was likely not caused by hypoxia, epilepsy, or a sleep disorder such as sleep apnea. Furthermore, the yawning disappeared immediately after surgery and did not recur after surgery. These findings suggested that the yawning was associated with a tumor in the supramedial cerebellum that compressed the dorsal midbrain and upper pons.

The parabrachial area is located on the dorsal side of the junction of the midbrain and pons and plays a role in unifying the autonomic nervous system.[4,5,7] In the human brain, the parabrachial area is a horseshoe-shaped band of gray matter composed of the lateral parabrachial nucleus (PBN), the Kölliker-Fuse nucleus, and the medial PBN (Fig. 3 upper). These nuclei receive important afferent fibers from the cardiovascular, respiratory, and gustatory systems and project efferent fibers toward superior centers.[5] On the other hand, the paraventricular nucleus (PVN), which is located in the medial hypothalamus, is a center of the autonomic nervous system and neuroendocrine system, and it is closely associated with yawning (Fig. 3 lower).[4,6] An experimental study in rats demonstrated the occurrence of yawning upon electrical or chemical stimulation of the PVN.[8] Furthermore, the PVN has reciprocal connections with brainstem autonomic centers including the PBN.[2] In particular, the PVN transmits signals mainly from the lateral PBN.[7] In the present case, any extraordinary stimulation from the lateral PBN in the brainstem to the PVN in the hypothalamus may have led to the development of pathological yawning.

In this case, MRI showed that the tumor preoperatively compressed the dorsal side of the midbrain and up-

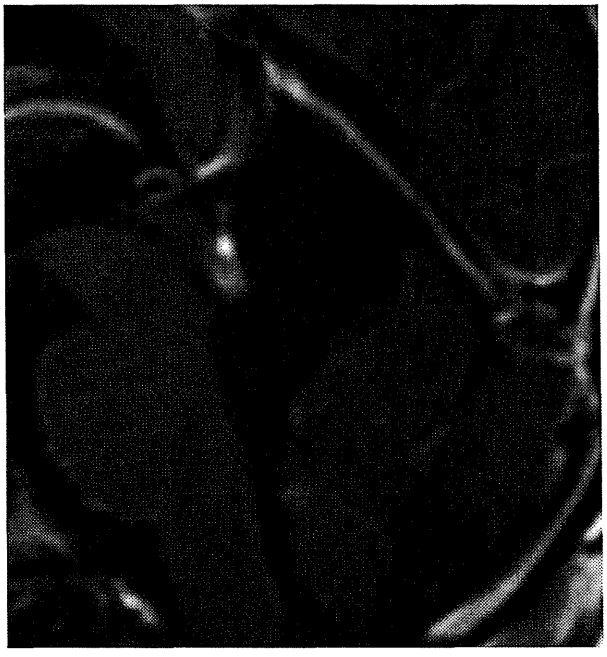

FIG. 2. Postoperative sagittal Gd-enhanced T1-weighted MR image revealing a residual tumor at the dorsal midbrain and resolution of compression of the brainstem.