Table 1. Patient characteristics (41 patients)

Characteristics	Value
Age (years)	
Median	66
Range	30–82
Gender (*n*)	
Male	22
Female	19
Primary cancer (*n*)	
Lung	25
Head and neck	6
Breast	3
Colorectal	2
Liver	1
Renal	1
Renal pelvic	1
Thymic	1
Apocrine gland	1
Primary histology (*n*)	
Adenocarcinoma	23
Squamous cell carcinoma	6
Thyroid cancer	2
Large cell carcinoma	2
Others	8
Treatment for primary cancer (*n*)	
Resection	23
SBRT	10
Conventional radiation therapy	8
Sites involved with oligometastatic disease (no. of tumors)	
Brain	33
Lung	22
Adrenal gland	5
Number of oligometastatic tumors (*n*)	
1	27
2	11
3	2
4	0
5	1
Number of oligometastatic involved organs (*n*)	
1	37
2	4

SBRT, stereotactic body radiotherapy.

margin was added to the GTV to create the planning target volume (PTV). Treatment was prescribed to the 100% isodose line, with the 80–90% isodose line covering the PTV. A total dose of 15–25 Gy was administered in one fraction for SCRS, and a total dose of 20–40 Gy was administered in four fractions for SCRT. A total dose of 30 Gy was administered in 10 fractions for WBRT.

SBRT Technique

All patients with lung metastases and 10 patients with primary lung cancer received SBRT as the definitive radiotherapy. They received real-time tumor-tracking radiotherapy (RTRT). The RTRT system has been described in detail elsewhere (24,25). In brief, 1.5–2.0-mm gold markers were implanted near the tumor by means of image-guided procedures. CT scans were taken with the patients holding their breath at the end of normal expiration. The GTV was contoured in axial CT images. The clinical target volume (CTV) was defined three dimensionally as the GTV on CT with a 6–8-mm margin for primary lung cancers and was considered to be equal to the internal target volume. We treated adrenal gland metastases using the RTRT system. The CTV was defined as the GTV on CT with a 3-mm margin for adrenal gland metastases and with a 5-mm margin for lung metastases. The PTV was three dimensionally defined as the CTV plus a 5-mm margin with optimal reduction near the organ at risk.

Treatment was prescribed to the 100% isodose line covering the PTV within the 80% isodose line. Patients were treated with 4-, 6- or 10-MV photons. SBRT was delivered by using multiple non-coplanar static ports. A total dose of 48 Gy was administered in eight fractions in patients with adrenal gland metastases. A total dose of 35–60 Gy was administered in four or eight fractions in patients with lung metastases or primary lung cancer, respectively.

Statistical Analysis

LC was defined as no progression of the tumor in the CTV, and marginal recurrence was counted as local failure in this study. Follow-up of the patients was based on clinical examination in the outpatient clinic and/or periodic radiological examination. In principle, radiological examinations such as chest X-ray, whole-body CT and brain MRI were performed once every 3–4 months, but the frequency strongly depended on the clinical situation. The overall survival (OS) and progression-free survival (PFS) rates were calculated from the day of SBRT and/or SCRT/SCRS to oligometastatic sites using the Kaplan–Meier method.

Possible prognostic factors were as follows: age, gender, primary cancer, primary histology, treatment for primary cancer, sites involved with oligometastatic disease, number of oligometastatic tumors and the treatment interval time from primary sites to oligometastatic sites (defined as interval to recurrence). The log-rank test was used to calculate the statistically significant differences. A value of $P < 0.05$ was considered to be statistically significant. Significant variables on univariate analysis (UVA) were tested with

multivariate analyses (MVA). MVA was performed using a Cox proportional hazards regression model.

RESULTS

Local Tumor Response and Distant Metastases

The median follow-up period was 20 months (range 1–111 months). The 3- and 5-year LC rates were each 80%, and the 3- and 5-year distant control (DC) rates were each 35% (Fig. 1).

Survival

The 3-year OS and PFS rates were 39% and 20%, respectively; and the respective 5-year rates were 28% and 20% (Fig. 2). The median survival time (MST) was 24 months. Patients with adrenal gland metastasis had an MST of 15 months.

Age, primary histology and the number of oligometastatic tumors were not found to be statistically significant prognostic factors for the OS rate; however, gender, primary cancer, treatment for primary cancer, oligometastatic lung disease and interval to recurrence were statistically significant prognostic factors for the OS rate in the UVA shown in Table 2.

The OS of female patients was significantly longer than that of male patients ($P = 0.01$), and the OS of patients who had undergone resection for primary cancer was significantly longer than those of others ($P = 0.0006$). For patients with primary cancer from favorable primary sites ($n = 8$), the 3- and 5-year OS rates were both 86%, compared with 27% and 17%, respectively, for patients with primary cancer from other primary sites ($n = 33$, $P = 0.02$). We separated the patients into two groups according to interval to recurrence of <12 or ≥ 12 months ($n = 18$, 23, respectively). The 3- and 5-year OS rates were 19% and 10%, respectively, for those with an interval to recurrence of <12 months, compared with 53% and 40%, respectively, for those with an interval to recurrence of ≥ 12 months (Fig. 3; $P = 0.006$). For patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$), the 3- and 5-year OS rates were both 63%, compared with 22% and 14%, respectively, for patients with only brain/adrenal metastases ($n = 25$) (Fig. 4; $P = 0.009$). MVA showed no statistically significant prognostic factors for the OS rate.

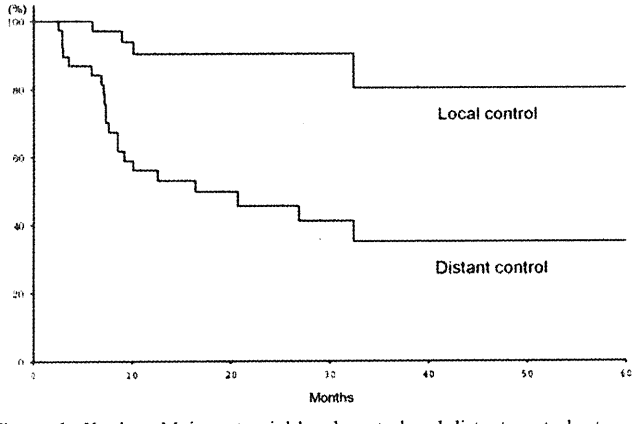

Figure 1. Kaplan–Meier actuarial local control and distant control rate.

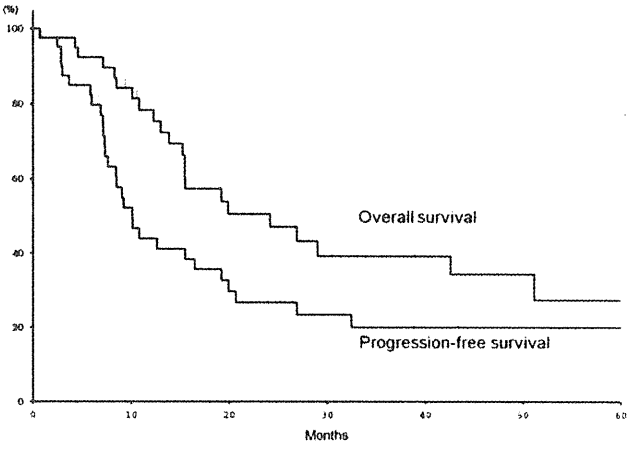

Figure 2. Kaplan–Meier actuarial overall survival (OS) and progression-free survival rate.

Table 2. UVA and MVA for OS rate

Variables	*P* value	
	UVA	MVA
Age		
<65 years	0.72	
Gender		
Female[a]	0.01*	0.72
Primary cancer		
Favorable[a]	0.02*	0.37
Primary histology		
Adenocarcinoma	0.84	
Treatment for primary cancer		
Resection[a]	0.0006*	0.26
Sites involved with oligometastatic disease		
Brain	0.09	
Lung	0.009*	0.47
Adrenal gland	0.09	
Number of oligometastatic tumors		
Single metastasis	0.47	
Interval to recurrence		
≥12 months[a]	0.006*	0.52

UVA, univariate analysis; MVA, multivariate analysis; OS, overall survival.
*Significant ($P < 0.05$).
[a]These variables were favorable predictors for overall survival rate on UVA.

Long Survivors

Four 5-year survivors consisted of two with lung adenocarcinoma, one with renal pelvic cancer and one with thymic cancer. One patient with lung adenocarcinoma had one brain metastasis treated by SCRT, whereas the other patient with lung adenocarcinoma had one brain metastasis treated by SCRS with WBRT and one lung metastasis treated by SBRT. The patient with renal pelvic cancer had two lung metastases treated by SBRT, and the patient with thymic cancer had one lung metastasis treated by SBRT.

Toxicities

Adverse effects were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0. Grade 2 complications occurred in four patients (9.8%), radiation necrosis of the brain occurred in three patients and intercostal neuralgia occurred in one patient. No other adverse effects of Grade 2 or more were observed.

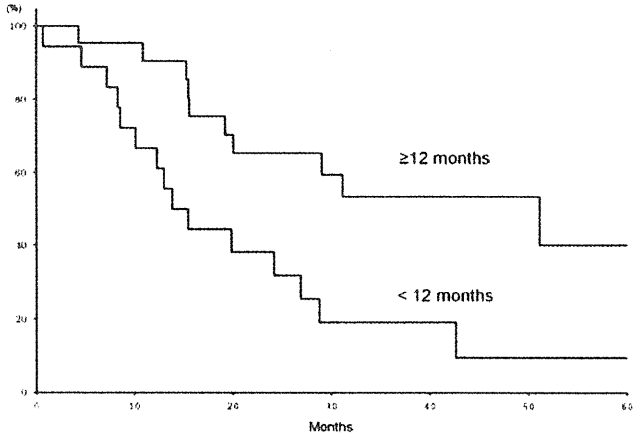

Figure 3. Kaplan–Meier curve of OS rates for patients with interval to recurrence of <12 months ($n = 18$) and ≥12 months ($n = 23$). Significant statistical difference was found ($P = 0.006$) between the two groups.

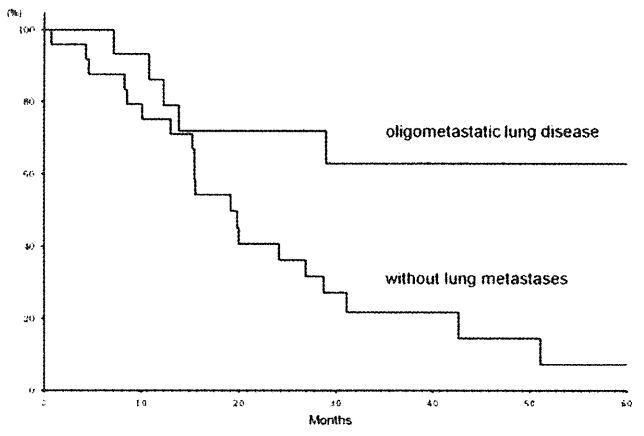

Figure 4. Kaplan–Meier curve of OS rates for patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$) and only brain/adrenal metastases ($n = 25$). Significant statistical difference was found ($P = 0.009$) between the two groups.

DISCUSSION

In this study, the OS rates at 3 and 5 years were 39% and 28%, respectively, and the MST was 24 months, which is equivalent to that in the study of oligometastases previously published, as follows. Milano et al. (22) reported the results of a Phase II trial using SBRT to a dose of 50 Gy in 10 fractions in the treatment of oligometastatic disease with 4-year OS, PFS, LC and DC rates of 28%, 20%, 60% and 25%, respectively. Patients with breast cancer fared significantly better with respect to OS, PFS, LC and DC rates (26), and those with adrenal metastases had significantly worse OS, LC and DC rates (13).

Rusthoven et al. (9,10) have recently reported the results of multi-institutional Phase I/II trials of SBRT for lung and liver metastases. The actual LC rate at 1 and 2 years after SBRT for oligometastatic lung tumors were 100% and 96%, respectively, and the MST was 19 months. The actual in-field LC rates at 1 and 2 years after SBRT for oligometastatic liver tumors were 95% and 92%, respectively, and the MST was 20.5 months. The primary tumor site was significantly predictive of survival. Primary tumors of the lung and ovary as well as non-colorectal gastrointestinal malignancies were found to be associated with poorer survival compared with breast, colorectal, renal, carcinoid and gastrointestinal stromal tumors as well as sarcoma.

Flannery et al. (23) have reported long-term survival in patients with synchronous solitary brain metastasis from NSCLC treated with radiosurgery. The MST was 18 months, and the 1-, 2- and 5-year actuarial OS rates were 71.3%, 34.1% and 21%, respectively. For patients who underwent definitive thoracic therapy, the 5-year actuarial OS rate was 34.6% compared with 0% for those who had non-definitive therapy. The Karnofsky performance status (KPS) also significantly impacted the OS rate.

SBRT and SCRT have been applied for the treatment of metastatic lesions recently; however, conventional radiotherapy remains a standard option for the treatment of metastatic lesions. Andrews et al. (4) reported the result of a Phase III study that compared WBRT with or without SCRS for brain metastases. This study showed WBRT with SCRS improved survival for patients with single brain metastasis or patients with tumors > 2.0 cm in diameter. To our knowledge, there has been no study that compared SBRT with conventional radiotherapy for extra-cranial metastases.

It is important to find prognostic factors related to long-term survival after definitive therapy such as SBRT and SCRT for oligometastatic lesions. According to the studies described above, KPS, the primary tumor site and the oligometastatic site can be predictive of survival. Low KPS, a primary tumor site such as the lung and adrenal metastasis were found to be associated with lower survival in the

previous study (9,10,13,22,23,26). However, our results have shown that some patients with lung cancer can survive >5 years after treatment for oligometastases and that some with adrenal metastatic tumors can expect an MST of 15 months. These findings are consistent with those of Khan et al. (27). It would therefore be useful to find prognostic factors that are independent of the primary and metastatic sites.

In this study, we identified another factor that can be used to predict long-term survival. The treatment interval time from primary sites to oligometastatic sites, defined as interval to recurrence, was found to be significantly associated with the OS rate in the UVA. A long interval to recurrence implies that the patient has a slowly growing tumor or is under good control with regard to primary and other sites except for the apparent metastatic lesions. In contrast, a short interval to recurrence indicates rapid tumor growth or poor control of the primary and other metastatic sites. Although it was difficult to distinguish between the natural course of the disease and the effects of treatment in this retrospective study, interval to recurrence was shown to be an independent parameter to predict prognosis for patients with oligometastases.

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum (18), but a clear definition for oligometastasis has not yet been established. Table 3 shows various definitions of oligometastasis reported previously in the literature. The number of oligometastases ranges from 1 to 6 tumors. Oligometastatic lesions are mainly in the lung, liver and brain, although oligometastases in the bone, adrenal gland, lymphatic nodes and soft tissue have also been reported. In the present study, we defined the number of oligometastases as ranging from 1 to 5 tumors, and oligometastatic lesions were found in the lung, brain and adrenal gland, which is consistent with several previous reports. A definitive definition of oligometastasis may not be possible, due to its diverse nature, but a clear definition is required for further investigation.

Table 3. Definition of oligometastasis

	Number of patients	Oligometastases	Oligometastatic lesions
Norihisa et al. (8)	34	1–2	Lung
Rusthoven et al. (9)	38	1–3	Lung
Rusthoven et al. (10)	47	1–3	Liver
Katz et al. (11)	69	1–6	Liver
Rades et al. (14)	521	1–3	Vertebrae
Salama et al. (17)	29	1–5	Lung, node, liver, bone, soft tissue, adrenal gland
Milano et al. (22)	121	1–5	Lung, node, liver, brain, adrenal gland, bone
Flannery et al. (23)	42	1	Brain
Khan et al. (27)	23	1–2	Lung, brain, soft tissue, adrenal gland, bone
Current study	41	1–5	Lung, brain, adrenal gland

One shortcoming of this paper is the retrospective nature of the analysis. Patients with sufficient medical conditions were probably selected beforehand to receive SBRT and SCRT. The large number of patients who died within a short period may have masked the possible progression of the disease and local failure. However, it is notable that there is a definite group of patients treated with SBRT and SCRT who experienced long survival even with distant metastasis. A large prospective trial is required to investigate the actual benefits of SBRT and SCRT for patients with oligometastases. Our findings suggest that interval to recurrence should be included in the stratification criteria in a prospective randomized trial comparing treatment with or without SBRT and SCRT.

In conclusion, precise SBRT and SCRT were effective in controlling oligometastatic lesions for patients with an MST of 24 months. Interval to recurrence may impact the OS rate and should be included in the stratification criteria of a prospective randomized trial to investigate the benefits of SBRT and SCRT for patients with oligometastases.

Conflict of interest statement

None declared.

References

1. Aoyama H, Shirato H, Onimaru R, Kagei K, Ikeda J, Ishii N, et al. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys* 2003;56:793–800.
2. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006;295:2483–91.
3. Sperduto PW, Berkey B, Gaspar LE, Mehta MCurran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008;70:510–4.
4. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;3:1665–72.
5. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94–100.
6. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;20:3290–6.
7. Okunieff P, Petersen AL, Philip A, Milano MT, Katz AW, Boros L, et al. Stereotactic body radiation therapy (SBRT) for lung metastases. *Acta Oncol* 2006;45:808–17.

8. Norihisa Y, Nagata Y, Takayama K, Matsuo Y, Sakamoto T, Sakamoto M, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. *Int J Radiat Oncol Biol Phys* 2008;72:398–403.
9. Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009;27:1579–84.
10. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27:1572–8.
11. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys* 2007;67:793–8.
12. Katoh N, Onimaru R, Sakuhara Y, Abo D, Shimizu S, Taguchi H, et al. Real-time tumor-tracking radiotherapy for adrenal tumors. *Radiother Oncol* 2008;87:418–24.
13. Chawla S, Chen Y, Katz AW, Muhs AG, Philip A, Okunieff P, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys* 2009;75:71–5.
14. Rades D, Veninga T, Stalpers LJ, Basic H, Rudat V, Karstens JH, et al. Outcome after radiotherapy alone for metastatic spinal cord compression in patients with oligometastases. *J Clin Oncol* 2007;25:50–6.
15. Yamada Y, Bilsky MH, Lovelock DM, Venkatraman ES, Toner S, Johnson J, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008;71:484–90.
16. Sahgal A, Ames C, Chou D, Ma L, Huang K, Xu W, et al. Stereotactic body radiotherapy is effective salvage therapy for patients with prior radiation of spinal metastases. *Int J Radiat Oncol Biol Phys* 2009;74:723–31.
17. Salama JK, Chmura SJ, Mehta N, Yenice KM, Stadler WM, Vokes EE, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Can Res* 2008;14:5255–9.
18. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8–10.
19. Niibe Y, Kazumoto T, Toita T, Yamazaki H, Higuchi K, Ii N, et al. Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: a multi-institutional study. *Gynecol Oncol* 2006;103:435–8.
20. Niibe Y, Kenjo M, Kazumoto T, Michimoto K, Takayama M, Yamauchi C, et al. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5,000. *Int J Radiat Oncol Biol Phys* 2006;66:1366–9.
21. Niibe Y, Kuranami M, Matsunaga K, Takaya M, Kakita S, Hara T, et al. Value of high-dose radiation therapy for isolated osseous metastasis in breast cancer in terms of oligo-recurrence. *Anticancer Res* 2008;28:3929–31.
22. Milano MT, Katz AW, Muhs AG, Philip A, Buchholz DJ, Schell MC, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer* 2008;112:650–8.
23. Flannery TW, Suntharalingam M, Regine WF, Chin LS, Krasna MJ, Shehata MK, et al. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. *Int J Radiat Oncol Biol Phys* 2008;72:19–23.
24. Shirato H, Shimizu S, Kunieda T, Kitamura K, van Herk M, Kagei K, et al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1187–95.
25. Shirato H, Shimizu S, Kitamura K, Nishioka T, Kagei K, Hashimoto S, et al. Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor. *Int J Radiat Oncol Biol Phys* 2000;48:435–42.
26. Milano MT, Zhang H, Metcalfe SK, Muhs AG, Okunieff P. Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat* 2009;115:601–8.
27. Khan AJ, Mehta PS, Zusag TW, Bonomi PD, Penfield Faber L, Shott S, et al. Long term disease-free survival resulting from combined modality management of patients presenting with oligometastatic, non-small cell lung carcinoma (NSCLC). *Radiother Oncol* 2006;81:163–7.

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Radiosurgery alone for 5 or more brain metastases: expert opinion survey

Clinical article

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Object. Oligometastatic brain metastases may be treated with stereotactic radiosurgery (SRS) alone, but no consensus exists as to when SRS alone would be appropriate. A survey was conducted at 2 radiosurgery meetings to determine which factors SRS practitioners emphasize in recommending SRS alone, and what physician characteristics are associated with recommending SRS alone for ≥ 5 metastases.

Methods. All physicians attending the 8th Biennial Congress and Exhibition of the International Stereotactic Radiosurgery Society in June 2007 and the 18th Annual Meeting of the Japanese Society of Stereotactic Radiosurgery in July 2009 were asked to complete a questionnaire ranking 14 clinical factors on a 5-point Likert-type scale (ranging from 1 = not important to 5 = very important) to determine how much each factor might influence a decision to recommend SRS alone for brain metastases. Results were condensed into a single dichotomous outcome variable of "influential" (4–5) versus "not influential" (1–3). Respondents were also asked to complete the statement: "In general, a reasonable number of brain metastases treatable by SRS alone would be, at most, ___." The characteristics of physicians willing to recommend SRS alone for ≥ 5 metastases were assessed. Chi-square was used for univariate analysis, and logistic regression for multivariate analysis.

Results. The final study sample included 95 Gamma Knife and LINAC-using respondents (54% Gamma Knife users) in San Francisco and 54 in Sendai (48% Gamma Knife users). More than 70% at each meeting had ≥ 5 years experience with SRS. Sixty-five percent in San Francisco and 83% in Sendai treated ≥ 30 cases annually with SRS. The highest number of metastases considered reasonable to treat with SRS alone in both surveys was 50. In San Francisco, the mean and median numbers of metastases considered reasonable to treat with SRS alone were 6.7 and 5, while in Sendai they were 11 and 10. In the San Francisco sample, the clinical factors identified to be most influential in decision making were Karnofsky Performance Scale score (78%), presence/absence of mass effect (76%), and systemic disease control (63%). In Sendai, the most influential factors were the size of the metastases (78%), the Karnofsky Performance Scale score (70%), and metastasis location (68%). In San Francisco, 55% of respondents considered treating ≥ 5 metastases and 22% considered treating ≥ 10 metastases "reasonable." In Sendai, 83% of respondents considered treating ≥ 5 metastases and 57% considered treating ≥ 10 metastases "reasonable." In both groups, private practitioners, neurosurgeons, and Gamma Knife users were statistically significantly more likely to treat ≥ 5 metastases with SRS alone.

Conclusions. Although there is no clear consensus for how many metastases are reasonable to treat with SRS alone, more than half of the radiosurgeons at 2 international meetings were willing to extend the use of SRS as an initial treatment for ≥ 5 brain metastases. Given the substantial variation in clinicians' approaches to SRS use, further research is required to identify patient characteristics associated with optimal SRS outcomes.
(DOI: 10.3171/2010.8.GKS10999)

Key Words • **brain metastasis** • **oligometastasis** • **stereotactic radiosurgery** • **survey**

It has been increasingly recognized over the last decade that patients with multiple brain metastases can be treated effectively with SRS alone with survival outcomes similar to WBRT.[7,9,19] The twin goals of SRS treatment—control of brain metastases and avoidance of normal tissue injury—have led to an increased use of initial SRS for brain metastases and a deferral of WBRT, even for patients whose anticipated survival is expected to be brief.

Since the landmark study by Patchell et al.[17] published 2 decades ago that documented the importance of focal treatments for patients with a single brain metastasis, SRS for brain metastases grew in popularity because this minimally invasive approach could be used to control or eradicate more than 1 metastasis in a single

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

session, and because it could also be used in conjunction with WBRT.[24] A randomized clinical trial sponsored by the National Cancer Institute (RTOG 95–08) enrolling patients with 1–3 brain metastases showed a survival advantage and improved local control for consolidative SRS in patients with a single brain metastasis as compared with WBRT alone.[1] Statistically significant improvements in functional autonomy at 6 months follow-up were documented in the cohort randomized to WBRT and SRS, no matter whether 1, 2, or 3 metastases were treated with consolidative SRS.

A clinical trial begun by the Japanese Radiation Oncology Study Group (JROSG 99–1) turned this management strategy on its head. Aoyama et al.[2] asked if the addition of WBRT to upfront SRS for patients with 1–4 brain metastases showed any benefit for survival or neurological function compared with SRS alone. No survival advantage was observed with the use of WBRT, and there was no difference in neurological outcomes after 1 year. Editorial commentaries and letters regarding this study highlighted divergent opinions among neurosurgeons, neurooncologists, and radiation oncologists about the appropriateness of deferring WBRT in patients with 1–4 brain metastases treated with SRS.[11,14,15,18]

The publication of these 2 important studies and the increasing interest in SRS for brain metastases as an initial, definitive treatment raises the question of whether practice patterns for patients with newly diagnosed brain metastases might be becoming divergent. No data-driven, universally accepted management standards for brain metastasis management exist today for patients with 1–4 metastases, and even less data exist for patients with ≥ 5 brain metastases managed with anything more than WBRT. Despite the absence of data, patients are seeking SRS alone, and physicians have started to provide SRS as an initial definitive therapy for patients with far more numerous brain metastases than is supported by published randomized, controlled clinical trials.

Because of the lack of guidance from clinical trials for the physicians who would be offering this novel treatment, we conducted a survey of radiosurgery practitioners to help determine what patient, physician, and equipment-related factors may be associated with offering SRS as the first management step for brain metastases. Furthermore, we assessed physician characteristics associated with recommending first-line SRS for ≥ 5 metastases.

Methods

Study Design

We conducted a cross-sectional survey of physicians attending the 8th Biennial Congress and Exhibition of the International Stereotactic Radiosurgery Society in San Francisco in June 2007. The Yale University Human Investigation Committee provided approval for the collection of data on this subject. A second survey using the same instrument (translated into Japanese) was conducted at the 18th Annual Meeting of the Japanese Society of Stereotactic Radiosurgery in Sendai in July 2009.

Survey Instrument

The survey instrument collected information on survey participant demographics, experience, and SRS equipment used and was distributed to all physician attendees at a single session in both meetings. The survey asked physicians to use a 5-point Likert-type scale to score 14 clinical factors that were believed to possibly be important in making a decision about offering SRS as an initial, definitive therapy to patients with multiple brain metastases (ranging from 1 = not important to 5 = very important).

Factors that physicians were asked to rank in the survey included patient age; sex; KPS score; social situation; the presence of metastases-related neurological symptoms; location, size, and radiographic characteristics of the brain metastases (cystic vs solid, nonhemorrhagic vs hemorrhagic); presence or absence of mass effect; histopathology of the brain metastases; status of the patients' systemic disease control; and the availability of additional useful chemotherapy for the malignancy undergoing treatment. Self-assessed physician workload was also to be scored. Respondents were also given an opportunity to write in any additional factors they might consider important. Lastly, physicians were asked to write in a number to answer the question: "In general, a reasonable number of brain metastases treatable by SRS alone would be, at most, _____."

Statistical Analysis

Results for each survey item addressing factors affecting the use of SRS were condensed into a single dichotomous outcome variable of "influential" (4–5) versus "not influential" (1–3). The characteristics of physicians willing to recommend SRS alone for ≥ 5 metastases were then assessed using bivariate chi-square tests, as well as multivariate logistic regression analysis (outcome: recommending SRS for ≥ 5 metastases). Statistical analyses were performed using STATA version 10.0.

Results

In San Francisco, 95 completed surveys were collected, and in Sendai, 54 were collected. The results of the demographic portions of these 2 surveys are summarized in Table 1. The response to the query about what would be a reasonable number of brain metastases to be treated with SRS alone ranged from 2–50 in San Francisco and 3–50 in Sendai. In San Francisco, the median number of metastases considered reasonable to treat with SRS alone was 5 and the mean was 6.7; in Sendai, the median was 10 and the mean was 11. In San Francisco, 55% of physicians considered treating ≥ 5 metastases with SRS alone reasonable, and 22% of physicians considered it reasonable to treat ≥ 10 metastases with SRS alone. In Sendai, 83% of the physicians surveyed believed that treating ≥ 5 metastases with SRS alone was reasonable, and 57% of physicians believed that treating ≥ 10 metastases with SRS alone was reasonable.

Bivariate analysis (Table 2) showed that private practitioners were significantly more likely than academic

TABLE 1: Stereotactic radiosurgery survey demographic data

Variable	San Francisco	Sendai
no. of completed surveys	95	54
academicians	61%	31%
private practice physicians	39%	69%
neurosurgeons	54%	80%
radiation oncologists	46%	21%
>5 years experience performing SRS	75%	70%
treat >30 patients w/ brain metastases w/ SRS annually	65%	83%
use Gamma Knife	54%	48%
use LINAC	46%	52%

physicians to consider SRS alone an appropriate initial definitive therapy for ≥ 5 brain metastases (77% vs 44%, respectively, in San Francisco, p = 0.002; 88% vs 69%, respectively, in Sendai, p = 0.017). Neurosurgeons were significantly more likely to recommend SRS for patients with ≥ 5 metastases than radiation oncologists (69% vs 39%, respectively, in San Francisco, p = 0.003; 93% vs 54%, respectively, in Sendai, p = 0.004), and physicians who use a Gamma Knife to perform SRS were also significantly more likely to recommend SRS alone than LINAC users (72% vs 35%, respectively, in San Francisco, p = 0.002; 100% vs 68%, respectively, in Sendai, p = 0.005).

A multivariate analysis performed on data collected in San Francisco confirmed that neurosurgeons (p = 0.033) and Gamma Knife users (p = 0.002) were independently significantly more likely to treat ≥ 5 metastases with SRS alone, whereas the impact of private practice versus academic practice was no longer significant. The OR of recommending treating ≥ 5 metastases with SRS alone was 4.2 for Gamma Knife users versus LINAC users (p = 0.002). The OR of recommending SRS alone for patients with ≥ 5 metastases was 2.7 for neurosurgeons compared with radiation oncologists (p = 0.033).

Neurosurgeons participating in the Japanese survey were more likely to be in community practice, and this factor correlated strongly with the opinion that SRS alone for ≥ 5 metastases was reasonable. Because 100% of Gamma Knife users at the Japanese meeting indicated that they would treat ≥ 5 metastases, a multivariate analysis was unable to provide stable parameter estimates (Gamma Knife use predicted the treatment recommendation for ≥ 5 metastases perfectly).

From the survey in San Francisco (Table 3), the most influential decision-making factors were KPS score (78%), presence/absence of mass effect (76%), and systemic disease control (63%). Less important were metastases-related neurological symptoms (56%) or unrelated neurological disease (51%), metastases location (55%), patient age (50%), size of the metastases (45%), tumor histopathology (40%), and availability of additional potentially effective chemotherapy (38%). Radiographic appearance (20%), social situation (21%), and physician workload (5%) were mostly believed to not be influential factors. Nobody considered patient sex to be an influential factor.

At the Sendai meeting (Table 3), the most influential factors were the size of the metastases (78%), KPS score (70%), and metastasis location (68%). Although less influential, the presence or absence of neurological symptoms from the metastases (57%), mass effect (57%), other neurological disease (48%), systemic diseases control (44%), stability of the patient's social situation (40%), patient age (35%), and tumor histopathology (39%) were all considered more important than the availability of additional potentially effective chemotherapy (26%) or the radiographic appearance of the metastatic disease (25%). As in San Francisco, only a small percentage (6%) of the physicians considered their own workload a significant factor when advising patients about SRS alone for brain metastases, and again, no one considered patient sex an influential factor.

Discussion

The key finding of this study is the previously undocumented willingness of more than half of the surveyed physicians who are experienced in radiosurgical treatment of brain metastases to offer and recommend SRS alone to patients with numerous brain metastases. The range of number of metastases considered reasonable to treat with first-line SRS was essentially the same at both survey locations (2–50 and 3–50). While the median and the mean number of metastases considered reasonable to treat with SRS alone were significantly different between San Francisco (mean 6.7, median 5) and Sendai (mean 11, median 10), both medians and means fall outside the 1–4

TABLE 2: Bivariate analysis of physician and equipment characteristics associated with recommending SRS for ≥ 5 metastases

Variable	San Francisco		Sendai	
	No. of Patients (%)	p Value	No. of Patients (%)	p Value
no. recommending SRS for ≥5 metastases	52/95 (55)		45/54 (83)	
private practice physicians	27/35 (77)	0.002	23/26 (88)	0.017
academic physicians	24/54 (44)		11/16 (69)	
neurosurgeons	35/51 (69)	0.003	38/41 (93)	0.004
radiation oncologists	17/44 (39)		7/13 (54)	
Gamma Knife users	36/50 (72)	0.002	26/26 (100)	0.005
LINAC users	15/43 (35)		19/28 (68)	

TABLE 3: Percentage of respondents who scored each factor as influential (score 4 or 5) in deciding to perform or not perform SRS alone for oligometastatic brain metastases

Assessed Factors	Percentage of Respondents Considering This Factor Important	
	San Francisco	Sendai
KPS score	78	71
presence/absence of mass effect	76	57
systemic disease control	63	44
neurological symptoms from metastases	56	57
other neurological disease	51	48
metastases location	55	68
metastases size	45	78
metastases histopathology	40	39
radiographic appearance	20	25
patient age	50	35
patient social situation	21	40
availability of additional potentially effective chemotherapy	38	26
patient sex	0	0
physician workload	5	6

range set by the randomized controlled clinical trial data supported by the literature.[2] Stated conversely, the majority (55%) of physicians were willing to offer SRS alone to patients with ≥ 5 brain metastases at the 2007 meeting in San Francisco, and the vast majority (83%) were willing at a 2009 meeting in Sendai.

Although a minority (22%) of the clinicians surveyed at the 2007 meeting in San Francisco believed treating > 10 metastases was reasonable, a majority (57%) of those surveyed in Sendai in 2009 believed that using SRS alone for > 10 metastases was reasonable. It should be clearly recognized that this survey's overall response rate is unknown and that there is no knowledge about whether respondents differed from nonrespondents with regard to professional characteristics or inclination to use SRS, and that the generalizability of any analysis must be regarded as limited.

Based on the current literature, clinicians who strive to practice evidence-based medicine might not consider referring a patient with > 4 brain metastases for a consultative opinion regarding definitive SRS. Historical practice would certainly deem this acceptable, and such a patient might be offered WBRT without a discussion of SRS alone as a possible therapeutic option.

Given that the treatment of brain metastases with SRS is a labor-intensive process that requires the meticulous identification of each metastasis to be treated and the development and subsequent delivery of individualized, highly customized treatment plans, the escalating threshold of the number of "oligo" metastases that may "reasonably" be considered for SRS alone by radiosurgery practitioners is a remarkable finding. The more metastases that are treated, the more work (and more time) is involved, but our study shows that only 5% of physicians in San Francisco and 6% in Sendai considered their workload important in making a recommendation for SRS alone.

Our study further shows that neurosurgeons are more willing than radiation oncologists both in San Francisco and in Sendai to declare this management practice reasonable. This likely reflects differences in professional training and experience. Neurosurgeons implement focal treatments for intracranial pathology for mass effect or diagnosis and rarely see the benefits of WBRT, but only deal with its focal failures. In comparison, for a radiation oncologist, the use of a regional treatment such as WBRT is common, easy to institute, can prevent the progression of subclinical disease into clinically evident metastases, and can help control larger metastases that receive a focal treatment such as resection or SRS.[1,2,5,16] For a patient with multiple metastases in which staged craniotomies and resection of multiple metastases are rarely employed, the noninvasive focal alternative of SRS can be an attractive alternative that continues to involve the neurosurgeon.

The equipment used for SRS was also identified to be a significant variable in assessing whether individual physicians would treat a patient with SRS. Gamma Knife users in both surveys were statistically much more likely than LINAC users to offer SRS to a patient with ≥ 5 brain metastases. Why might opinions vary with the technology used? Treatment recommendations are guided by individual experience. The Gamma Knife machine is solely dedicated to the treatment of intracranial lesions accompanied by its own dedicated staff and the several hours required to provide comprehensive radiosurgical treatment can be accomplished during regular working hours. However, because LINACs are commonly used for treating many patients daily with fractionated radiotherapy, single-fraction SRS may only be started when the full daily roster of patients receiving fractionated radiotherapy is completed. Radiosurgical treatment for patients with multiple brain metastases with such equipment might often extend into the evening hours, and perhaps could lead to a greater likelihood to decline to offer SRS to a patient with multiple brain metastases by a busy radiation oncologist, particularly because of the higher potential of requiring additional short-term salvage treatment if WBRT is not part of the management plan. The absence of Class I data supporting the use of SRS alone for patients with > 4 brain metastases for important outcomes such as neurocognitive function provides good justification for such a management practice.

The recently published Phase III study by Chang et al.,[5] however, may change this justification.[10] This study showed that short-term neurocognitive outcomes for patients who were treated with SRS alone for 1–3 metastases was significantly better than those receiving SRS and WBRT. A survival advantage was also observed for deferring WBRT. Because this study's primary end point was not survival, this observation may be due to an imbalance of treatment arms and asymmetrical use of aggressive salvage treatment rather than a true treatment effect. In addition to the 2 randomized controlled trials that have been published on the use of SRS with or without WBRT for up to 4 brain metastases, a third trial, also randomizing patients with 1–3 brain metastases between

SRS alone and SRS with WBRT, is underway under the aegis of the National Cancer Institute as an Intergroup study (NCCTG-N0574) and is powered to evaluate neurocognitive outcomes in the two arms.[20]

Controversy is almost certain concerning whether this new study's (NCCTG-N0574) results may be extrapolated to patients with 4 or more brain metastases. In addition, appropriate studies still need to be conducted to determine what other factors may be critical in determining which patients may be appropriate for initial, definitive SRS. Important factors might include age, comorbidities, tumor site of origin, and histology, and a host of other variables.[13] Rational patient management recommendations ideally derive from high quality studies performed on patient populations that appropriately reflect disease stage, severity, comorbidities, and available therapeutic options, but recommendations for populations in general often differ significantly from recommendations for individual patients. Treatment individualization is a hallmark of modern oncological and medical practice.

It is far from certain that even well-designed oncological clinical trials and meta-analyses will affect patient management patterns if their results run counter to the perceived benefit of the treatment. University of Toronto investigators surveyed American oncologists about management recommendations for 5 hypothetical patients with breast cancer.[4] One scenario—offering systemic chemotherapy to postmenopausal women with early stage, estrogen receptor–negative, axillary node–negative breast cancer—was noted by the authors as counter to both large randomized controlled trials and a meta-analysis of available trial data, as neither evaluation had shown a survival benefit for the use of adjuvant chemotherapy in that setting. It took additional trials and a meta-analysis with 10- and 15-year follow-up to document a survival advantage for women up to 70 years of age with early stage, node-negative breast cancer who received adjuvant systemic chemotherapy in Phase III trials testing the value of that intervention.[6] Expert opinion preceded confirmatory trial data in this oncological situation, but it is unlikely that clinical trials will ever adequately resolve all management questions regarding patients with brain metastases because of 2 major issues: the heterogeneity of patients presenting with brain metastases, and the short expected lifespan for patients with metastatic cancer.

Stereotactic radiosurgery as a single, definitive treatment for brain metastases has been used with increasing frequency in North America, Europe, Asia, and around the world.[2,3,5,8,12,21–24] This approach defers the use of WBRT to a supplementary or salvage role. Stereotactic radiosurgery has been documented to provide excellent control for targeted lesions, and the focal nature of SRS permits retreatment if additional oligometastatic brain metastases are identified on surveillance images after SRS. Whole brain radiation therapy can be used for salvaging of patients who develop metastatic involvement of the leptomeninges or miliary parenchymal metastases. This management approach represents a paradigm shift for the management of brain metastases. Whole brain radiation therapy has been the standard of care for approximately 50 years because of its ease of application and palliative benefit for patients with symptomatic metastases. Whole brain radiation therapy has also been proven to delay or prevent the growth of clinically inapparent metastases. Stereotactic radiosurgery is not ubiquitous, however, and not all radiation oncologists or neurosurgeons may offer this treatment to patients with brain metastases because of a lack of specialized equipment or of appropriate training.

The decision to survey physician attendees of the 8th Biennial Congress and Exhibition of the International Stereotactic Radiosurgery Society in San Francisco was undertaken to assess the factors that physicians (quite familiar with SRS) consider as significant when evaluating patients referred for an opinion regarding brain metastasis management. In the absence of guidelines derived strictly from evidence-based medicine, it was believed that value might be provided by determining what types of practices are common and what might be deemed acceptable in light of a changing paradigm for management of brain metastases. The survey instrument asked specific questions about the physician and the nature of their practice and equipment, and deliberately posed very general questions about patient and tumor-specific factors to avoid portraying clinical scenarios that might influence responses. A follow-up survey was performed at the 18th Annual Meeting of the Japanese Society for Stereotactic Radiosurgery in 2009 to try to confirm and extend the survey findings.

There are numerous limitations to interpretation of the survey responses obtained. No data were collected to allow an assessment of response rate of the physicians surveyed at the 2 meetings. The 2 surveys were conducted more than a year apart at radiosurgery meetings on 2 different continents. The San Francisco meeting was an international meeting, with physician attendance from around the globe, and the Sendai meeting was a national society's meeting. The different practice environments that these respondents practice in will confound simple comparisons over time or across practice environments. No data were collected about physician reimbursement schemes (single payer vs private health insurance, and others) or how reimbursement might affect recommendations for first-line SRS for multiple brain metastases. No data were collected about what LINAC platform or platforms might be associated with a greater willingness to perform SRS on ≥ 5 metastases. Finally, this analysis focused on the respondents' reported treatment patterns, rather than assessing actual patient care. Future work should explore actual patterns of patient care, as well as outcomes associated with different management options.

Conclusions

Stereotactic radiosurgery as a definitive initial management strategy for ≥ 5 brain metastases was considered reasonable by the majority of physicians attending radiosurgery conferences in 2007 and 2009, and at the second conference, the majority of physicians were willing to offer radiosurgery to patients with ≥ 10 metastases. Neurosurgeons and Gamma Knife users were more likely to recommend SRS alone for such patients. No clear consen-

sus exists for how many metastases are reasonable to treat with SRS alone or what factors should be used to assess candidate patients. Given the early neurocognitive results from Chang et al.,[5] there appears to be an advantage to a focal philosophy and the use of SRS alone for multiple brain metastases should be standard in first-line discussions regarding management of multiple metastases, even for patients with 5 or more metastases.

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: Knisely, Chiang. Acquisition of data: Knisely, Yamamoto, Castrucci, Jokura, Chiang. Analysis and interpretation of data: Knisely, Yamamoto, Gross, Castrucci, Chiang. Drafting the article: Knisely. Critically revising the article: Knisely, Castrucci, Jokura, Chiang. Reviewed final version of the manuscript and approved it for submission: Knisely, Yamamoto, Gross, Castrucci, Jokura. Statistical analysis: Gross. Administrative/technical/material support: Knisely. Study supervision: Knisely.

References

1. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. **Lancet 363:**1665–1672, 2004
2. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. **JAMA 295:**2483–2491, 2006
3. Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, et al: Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. **Int J Radiat Oncol Biol Phys 68:**1388–1395, 2007
4. Belanger D, Moore M, Tannock I: How American oncologists treat breast cancer: an assessment of the influence of clinical trials. **J Clin Oncol 9:**7–16, 1991
5. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. **Lancet Oncol 10:** 1037–1044, 2009
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Clarke M, Coates AS, Darby SC, Davies C, Gelber RD, et al: Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. **Lancet 371:**29–40, 2008
7. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. **Int J Radiat Oncol Biol Phys 28:**797–802, 1994
8. Fox J, Kleinberg L: Evolving management of newly diagnosed brain metastases: expanding role of radiosurgery in lieu of whole brain radiation. **Future Oncol 3:**285–293, 2007
9. Kihlström L, Karlsson B, Lindquist C: Gamma Knife surgery for cerebral metastases. Implications for survival based on 16 years experience. **Stereotact Funct Neurosurg 61 (Suppl 1):** 45–50, 1993
10. Knisely JP: Focused attention on brain metastases. **Lancet Oncol 10:**1024, 2009
11. Lunsford LD, Flickinger JC: Radiosurgery plus or minus whole brain radiation therapy for the treatment of brain metastases. An editorial comment. **Surg Neurol 66:**461–462, 2006
12. Lutterbach J, Cyron D, Henne K, Ostertag CB: Radiosurgery followed by planned observation in patients with one to three brain metastases. **Neurosurgery 52:**1066–1074, 2003
13. National Cancer Institute: **Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases.** (http://www.cancer.gov/clinicaltrials/NCCTG-N0574) [Accessed August 26, 2010]
14. Patchell RA, Regine WF, Loeffler JS, Sawaya R, Andrews DW, Chin LS: Radiosurgery plus whole-brain radiation therapy for brain metastases. **JAMA 296:**2089–2091, 2006
15. Patchell RA, Regine WF, Renschler M, Loeffler JS, Sawaya R, Chin LS, et al: Comments about the prospective randomized trial by Aoyama et al. **Surg Neurol 66:**459–460, 2006
16. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. **JAMA 280:**1485–1489, 1998
17. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al: A randomized trial of surgery in the treatment of single metastases to the brain. **N Engl J Med 322:** 494–500, 1990
18. Raizer J: Radiosurgery and whole-brain radiation therapy for brain metastases: either or both as the optimal treatment. **JAMA 295:**2535–2536, 2006
19. Shu HK, Sneed PK, Shiau CY, McDermott MW, Lamborn KR, Park E, et al: Factors influencing survival after gamma knife radiosurgery for patients with single and multiple brain metastases. **Cancer J Sci Am 2:**335–342, 1996
20. Sneed PK, Lamborn KR, Forstner JM, McDermott MW, Chang S, Park E, et al: Radiosurgery for brain metastases: is whole brain radiotherapy necessary? **Int J Radiat Oncol Biol Phys 43:**549–558, 1999
21. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, et al: A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. **Int J Radiat Oncol Biol Phys 53:**519–526, 2002
22. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al: Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. **Int J Radiat Oncol Biol Phys 77:**655–661, 2010
23. Yamamoto M: Radiosurgery for metastatic brain tumors. **Prog Neurol Surg 20:**106–128, 2007
24. Yamamoto M, Ide M, Nishio S, Urakawa Y: Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment? **Int J Radiat Oncol Biol Phys 53:**1279–1283, 2002

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Gamma Knife radiosurgery for hemangiomas of the cavernous sinus: a seven-institute study in Japan

Clinical article

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Object. Gamma Knife radiosurgery (GKS) is currently used for primary or postoperative management of cavernous sinus (CS) hemangiomas. The authors describe their experience with 30 cases of CS hemangioma successfully managed with GKS.

Methods. Thirty patients with CS hemangiomas, including 19 female and 11 male patients with a mean age of 53 years (range 19–78 years) underwent GKS at 7 facilities in Japan. Pathological entity was confirmed using surgical specimens in 17 patients, and neuroimaging diagnosis only in 13. Eight patients were asymptomatic before GKS, while 22 had ocular movement disturbances and/or optic nerve impairments. The mean tumor volume was 11.5 cm^3 (range 1.5–51.4 cm^3). The mean dose to the tumor periphery was 13.8 Gy (range 10.0–17.0 Gy).

Results. The mean follow-up period was 53 months (range 12–138 months). Among the 22 patients with symptoms prior to GKS, complete remission was achieved in 2, improvement in 13, and no change in 7. Hemifacial sensory disturbance developed following GKS in 1 patient. The most recent MR images showed remarkable shrinkage in 18, shrinkage in 11, and no change in 1 patient.

Conclusions. Gamma Knife radiosurgery proved to be an effective treatment strategy for managing CS hemangiomas. Given the diagnostic accuracy of recently developed neuroimaging techniques and the potentially serious bleeding associated with biopsy sampling or attempted surgical removal, the authors recommend that GKS be the primary treatment in most patients who have a clear neuroimaging diagnosis of this condition.
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Key Words • **cavernous sinus** • **hemangioma** • **radiosurgery** • **Gamma Knife**

Despite past confusion regarding the clinical entity of CS hemangiomas,[1] Gonzalez et al.[3] recently reported that this condition is now recognized as a histologically benign vascular tumor with characteristics completely different from those of intracerebral carvernous angiomas, which are vascular malformations. Recent advancements in neuroimaging techniques have allowed precise diagnosis of hemangiomas involving the CS prior to treatment.[7,16,20] The ideal treatment for CS hemangiomas, whether symptomatic or incidental, has long been total microsurgical resection.[8] However, because they involve extremely complex anatomical structures and tend to bleed excessively when removed, or even with attempted biopsy sampling, reported surgical results are still unfavorable,[9,14,21] i.e., relatively low rates of total removal, though with negligible morbidity rates, even when recently recommended surgical techniques are applied; the extradural approach[2,17] and induced systemic hypotension.[11] For cases in which total removal cannot be achieved, fractionated radiotherapy for the residual tumors has been recommended.[15] At present, GKS is being used for primary or postoperative management of patients with CS hemangiomas and favorable treatment results have been reported.[5,6,10,12,13,18] However, the incidence of this condition is extremely low. Thus, the small number of reported cases prompted this multiinstitutional analysis of the authors' experiences. Fortunately, GKS is relatively uniform such that treatment techniques using basically the same equipment vary little among institutes. Thus, GKS is considered to be suitable for a multiinstitutional study.

The authors describe 30 patients with CS hemangiomas who were successfully managed with GKS in our 7 institutes in Japan. All 7 facilities started performing

Abbreviations used in this paper: CS = cavernous sinus; GKS = Gamma Knife radiosurgery.

TABLE 1: Summary of characteristics in 30 patients*

Case No.	Age at GKS (yrs), Sex	Initial Presentation	Surgery Pre-GKS	CN Symptoms Pre-GKS	Tumor Vol (cm^3)	Min Dose (Gy)	Length of FU (mos)	Symptom Changes Post-GKS	Most Recent MR Findings
1	33, M	diplopia	no	III	5.2	15.00	30	resolved	remarkable shrinkage
2	54, F	incidental	no	none	3.5	16.00	30	none	remarkable shrinkage
3	44, M	incidental	yes	III	12.3	13.00	50	resolved	shrinkage
4	54, F	incidental	no	none	4.1	13.00	30	none	shrinkage
5	48, M	diplopia	yes	III, IV, V	8.5	13.00	27	improved	no change
6	50, F	ocular pain	no	III, V	1.5	16.20	138	improved	remarkable shrinkage
7	38, F	diplopia	yes	II, VI	3.4	17.00	116	stable	remarkable shrinkage
8	66, F	incidental	yes	II, III, IV, VI	11.1	14.00	83	stable	shrinkage
9	73, F	diplopia	no	II, III	7.7	16.00	78	improved	shrinkage
10	69, F	decreased visual acuity	yes	II, III, IV, V, VI	39.7	10.00	56	stable	shrinkage
11	77, M	ocular pain	yes	III	11.9	13.00	43	stable	shrinkage
12	67, F	diplopia	no	none	19.7	12.50	41	none	shrinkage
13	59, M	decreased visual acuity	yes	II, III	33.4	11.0 × 2†	26	improved	shrinkage
14	46, M	diplopia	yes+RT	none	51.4	15.00‡	84	none	remarkable shrinkage
15	68, F	diplopia	yes	III	6.0	12.00	74	stable	shrinkage
16	54, F	headache	no	none	10.5	15.00	64	none	shrinkage
17	54, F	incidental	yes	none	10.2	15.00	24	none	remarkable shrinkage
18	78, F	diplopia	yes	III	8.5	15.00	52	improved	remarkable shrinkage
19	51, F	diplopia	no	VI	7.9	14.00	26	improved	remarkable shrinkage
20	61, M	diplopia	yes	VI	2.9	16.00	81	improved	remarkable shrinkage
21	45, F	diplopia	no	VI	3.9	15.00	25	improved	remarkable shrinkage
22	46, M	diplopia	no	III	4.9	15.00	13	improved	remarkable shrinkage
23	50, F	diplopia	no	III, IV, VI	19.0	10.00	38	improved	remarkable shrinkage
24	54, F	diplopia	no	III	6.4	16.00	57	improved	remarkable shrinkage
25	35, F	decreased visual acuity	no	II	4.5	12.00	12	improved	remarkable shrinkage
26	19, M	diplopia	yes	none	1.9	14.00	36	none	remarkable shrinkage
27	40, M	diplopia, facial numbness	yes	III, V, VI	5.3	12.00	96	stable	remarkable shrinkage
28	58, F	headache	yes	II	13.6	10.00	52	improved	remarkable shrinkage
29	51, F	diplopia	yes	III	20.8	8.0 × 2†	66	stable	shrinkage
30	56, M	diplopia	yes	none	4.9	12.00	48	none	remarkable shrinkage

* CN = cranial nerve; FU = follow-up; RT = radiation therapy.
† Indicates 2-stage GKS.
‡ Indicates partial coverage.

GKS between 1991 and 1998. Each of the study authors, all of whom are chief neurosurgeons at their facilities, has more than 10 years of GKS experience and each has treated more than 3000 patients with a GK.

Methods

Thirty patients who underwent GKS at 7 GK facilities in Japan and who were followed using MR imaging for 12 months or more after treatment were studied (Table 1). All patients signed consent forms allowing their data to be used, after the study had been fully explained. Five (Cases 6, 7, 8, 18, and 27) of these 30 patients have been described elsewhere[5,6,10,13] but are included in this study with further long-term follow-up results. As summarized in Table 1, there were 19 female and 11 male patients with a mean age at the time of GKS of 53 years (range 19–78 years). The most common initial presentation was ocular

TABLE 2: Summary of postsurgical changes in symptoms (17 patients)

Preop Symptoms	Ocular Movement Disturbance	Decreased Visual Acuity	Ocular Pain/ Headaches	No Deficits	Total (%)
no. of patients	10	2	2	3	17
improved	3	0	0	0	3 (17.6)
no changes	3	0	0	1	4 (23.5)
additional disturbance	4	2	2	2	10 (58.8)

movement disturbances, seen in 18 patients (60.0%). One of the 18 patients had hemifacial sensory disturbance, 4 (13.3%) ocular pain and/or headache, and 3 (10.0%) visual disturbances. The remaining 5 patients were asymptomatic.

Prior to GKS, surgical removal was performed in 17 patients, one of whom underwent postoperative fractionated radiotherapy (Case 14). The nature of the pathological entity was confirmed using surgical specimens in these 17 patients and neuroimaging diagnosis only in 13. Postoperative symptom changes are shown in Table 2. Among 10 patients with ocular movement disturbances, symptom palliation was achieved in 3, there were no changes in 3, and additional neurological deficits developed in the remaining 4. Additional ocular movement disturbances occurred postoperatively in 2 patients with preoperative visual disturbances. Among the remaining 5 patients with no neurological deficits, additional ocular movement disturbances developed postoperatively in 3, and visual disturbance in 1. These postoperative results can be summarized as follows: no neurological deficits before or after surgery in 1 patient (5.9%), improvement in 3 (17.6%), no change in 3 (17.6%), and worsening in 10 patients (58.8%).

Eight patients were asymptomatic before GKS, while 15 had ocular movement disturbances, 2 had optic nerve impairments, and 5 patients had both. The mean tumor volume was 11.5 cm^3 (range 1.5–51.4 cm^3). Due to the relatively large tumor volumes, staged GKS with intervals of a few weeks was applied in 2 patients (the selected dose at the tumor periphery was 11.0 Gy each time for the patient in Case 13, and 8.0 Gy for the patient in Case 29), and only the tumor base was irradiated in 1 patient (Case 14). In all other patients, the entire tumor volume was fully covered with a 50–60% isodose gradient, and the mean and median doses at the tumor periphery were 13.8 Gy and 14.0 Gy, respectively (range 10.0–17.0 Gy).

Results

All 30 patients underwent periodic MR imaging follow-up. The mean and median follow-up periods after GKS were 53 and 49 months, respectively (range 12–138 months). The most recent MR images demonstrated remarkable tumor shrinkage (> 50% tumor volume reduction) in 18 patients (60.0%), slight shrinkage in 11 (36.7%) and no change in 1 (3.3%). No tumors showed transient enlargement after GKS. In the 18 tumors in which remarkable shrinkage was attained, a marked tumor volume decrease had occurred by 12 months after GKS. To date, no patients have experienced tumor recurrence.

TABLE 3: Summary of postradiosurgical changes in symptoms (30 patients)

Symptoms Pre-GKS	Ocular Movement Disturbance	Decreased Visual Acuity	Both*	No Deficits	Total (%)
no. of patients	15	2	5	8	30
recovery	2*	0	0	0	2† (6.7)
improved	9	2	2	0	13 (43.3)
no changes	4	0	3	8	15 (50.0)
additional disturbance	1†	0	0	0	1† (3.3)

* Indicates both ocular movement disturbance and decreased visual acuity.

† Ocular movement recovered completely but additional trigeminal nerve disturbance occurred in 1 patient.

Post-GKS changes in neurological symptoms are listed in Table 1 and summarized in Table 3. Among the 20 patients with ocular movement disturbances, including 5 who also had visual disturbances, complete remission of symptoms was obtained in 2, improvement in 12, and no change in 6. Additional trigeminal nerve disturbance occurred in 1 patient (Case 3). Among the 7 patients with visual disturbances (including the 5 with ocular movement disturbances), improvement was noted in 4 and no change in 3. Thus, among the 22 patients with cranial neuropathy before GKS, complete remission was achieved in 2 (9.1%), improvement in 13 (59.1%), and no change in 7 (31.8%). No additional disturbances occurred in the remaining 8 patients who did not have neurological deficits before GKS.

Illustrative Cases

Case 14

Presentation and First Operation. In 1982, an ophthalmologist recommended further examination after this 29-year-old man presented with diplopia. At another institution, neurological examination revealed left oculomotor nerve paresis and a left CS tumor was demonstrated on CT. The patient received a preoperative diagnosis of meningioma and underwent craniotomy, despite failed biopsy sampling due to massive bleeding. The patient's symptoms subsided after steroid treatment.

Second Operation. In 1995, left oculomotor nerve paresis recurred and MR images obtained on January 17, 1996, demonstrated the presence of a left CS tumor extending into the middle fossa (Fig. 1A). The patient underwent a left frontotemporal craniotomy followed by biopsy sampling. Because of massive hemorrhaging, however,

TABLE 4: Summary of the 16 cases reported in the literature*

Authors & Yr	Age at GKS (yrs), Sex	CN Symptoms Pre-GKS	Tumor Vol (cm^3)	Min Dose (Gy)	Length of FU (mos)	Symptom Changes Post-GKS	Tumor Vol at Latest FU (cm^3)	Vol Reduction Rate (%)
Iwai et al., 1999	40, M	III, V, VI	5.3	12.0	20	no change	shrinkage	NA
Thompson et al., 2000	24, F	III	5.6	14.0	24	improved	0.8	14
	14, F	V, VI, VII	5.2	19.0	18	improved	0.9	17
	44, M	III, IV	10.8	15.0	12	improved	10.9	101
Seo et al., 2000	79, F	III, IV	8.5	15.0	24	recovery	shrinkage	NA
Kida et al., 2001	50, F	III, V	1.5	16.2	33	no change	0.7	47
	38, F	II, VI	3.4	17.0	36	improved	1.4	41
	66, F	II, III, IV, VI	11.1	14.0	12	no change	5.1	46
Nakamura et al., 2002	75, F	II, III	9.5	12.0–14.0†	60	improved	4.3	45
	68, F	II	3.3	12.0–14.0†	48	no change	3.0	91
	55, F	none	6.6	12.0–14.0†	24	none	4.6	70
Peker et al., 2004	39, F	none	3.8	15.0	52	none	1.5	39
	60, M	III	5.8	16.0	32	no change	2.1	36
	37, M	V, VI	6.2	15.0	45	improved	1.3	21
	39, F	III, V	4.6	15.0	29	improved	1.1	24
	44, M	II, III	4.4	14.0	6	no change	1.7	39

* NA = not applicable.

† The selected dose for the individual patient was not described.

an attempt at tumor removal had to be discontinued. The pathological report was consistent with a hemangioma. Postoperatively, the patient received fractionated radiotherapy with a total dose of 51 Gy, and significant tumor shrinkage was noted on follow-up MR imaging (Fig. 1B). His oculomotor function gradually improved after radiotherapy, eventually normalizing.

Gamma Knife Radiosurgery. Although there was no neurological deterioration, MR images obtained 60 months posttreatment demonstrated apparent regrowth of the tumor (Fig. 1C). The patient underwent GKS at the Katsuta Hospital Mito GammaHouse on January 19, 2000. Because of prior radiotherapy and a relatively large tumor volume (51.4 cm^3) the lower half of the tumor was covered with a 50% isodose gradient and irradiation was administered with the maximum dose of 30.0 Gy; that is, 56% of the entire tumor received a radiation dose of ≥ 15.0 Gy. The patient's neurological status has been stable since radiosurgery. Follow-up MR images obtained 6 months after GKS revealed remarkable shrinkage through the 12th postradiosurgical month and confirmed the absence of growth thereafter up to the most recent follow-up MR imaging studies obtained 84 months after radiosurgery (Figs. 1D and E and 2).

Case 15

This 68-year-old woman presented with a 3-month history of diplopia, and further examination was recommended by the ophthalmologist. At another institution (not one of the 7 GKS institutions), neurological examination revealed right oculomotor nerve paresis and a right CS tumor was demonstrated on MR imaging. Biopsy sampling through a frontotemporal craniotomy was performed, and the lesion was confirmed to be consistent with a hemangioma.

The patient underwent GKS at the Katsuta Hospital Mito GammaHouse on August 7, 2001. The tumor, with a volume of 6.0 cm^3, was covered with a 60% isodose gradient and irradiated with a peripheral dose of 12.0 Gy (Fig. 3A). Postradiosurgically, to date, her oculomotor nerve function has remained unchanged. Follow-up MR images obtained 6 months after GKS showed a slight shrinkage of the lesion that continued through the 12th postradiosurgical month, and absence of growth was confirmed thereafter up to the most recent follow-up MR imaging, conducted 74 months after GKS (Fig. 3B and C).

Case 16

This 54-year-old woman presented to an outside institution with a 2-month history of headaches. Neuroimaging examinations showed typical findings of a hemangioma involving the left CS. Her headaches were nonspecific and not considered to be caused by the tumor. Therefore, a watch and wait approach was recommended. However, the patient was extremely concerned about not being treated, and GKS was therefore undertaken at Katsuta Hospital Mito GammaHouse on February 9, 2002. The tumor, with a volume of 10.5 cm^3, was covered with a 60% isodose gradient and irradiated with a maximum dose of 25.0 Gy (the entire tumor received an irradiation dose of 15.0 Gy or more; Fig. 4 *left*). Periodic follow-up MR images showed slight shrinkage. No growth has been seen to date, with the most recent follow-up MR images having been obtained 64 months after radiosurgery (Fig. 4 *right*).

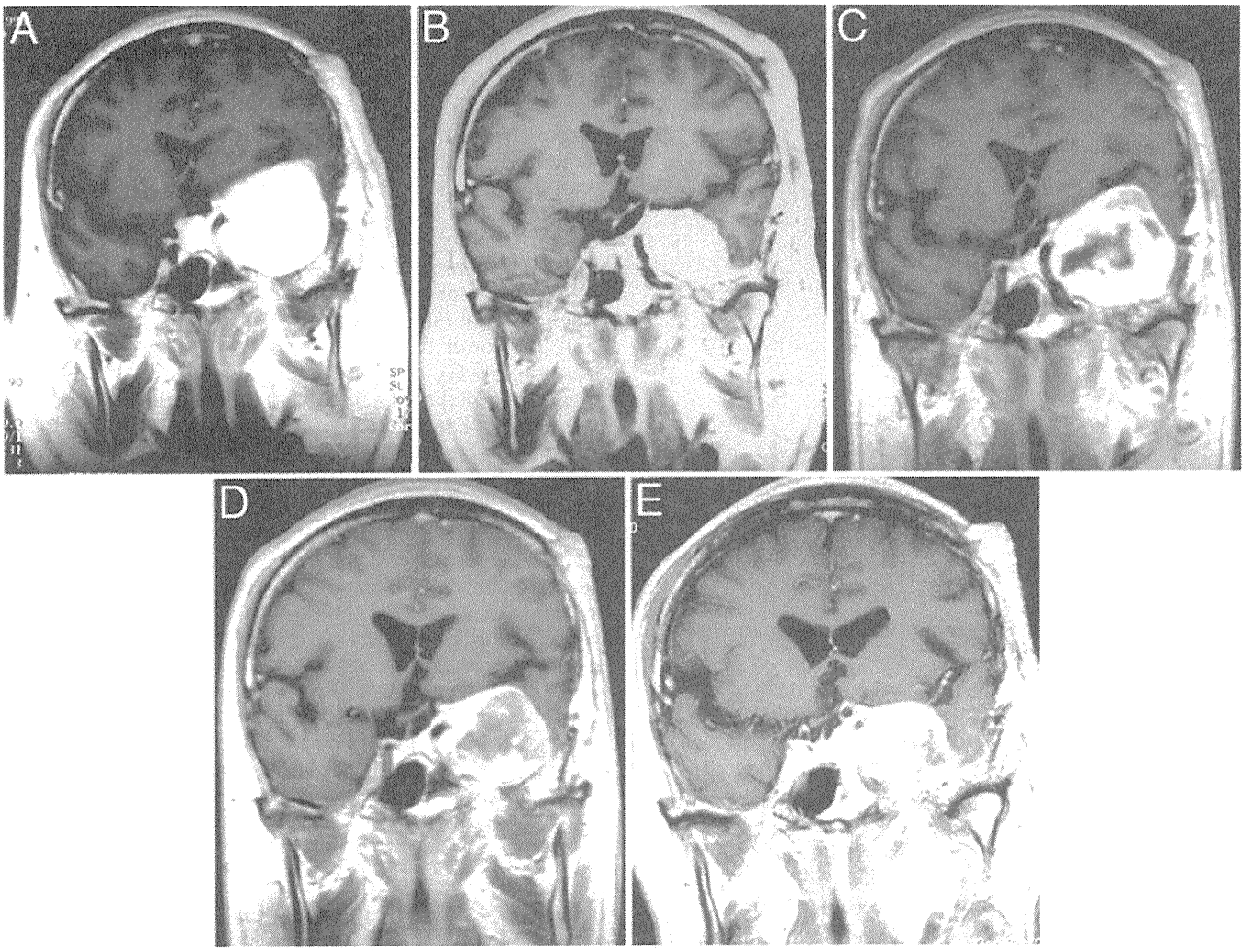

FIG. 1. Case 14. Sequential contrast-enhanced coronal T1-weighted MR images obtained before the second surgery and radiation therapy (A), 31 months after treatment (B), 60 months after these treatments but before GKS (C), and 12 (D) and 84 months after GKS (E).

Discussion

Since the first patient with a CS hemangioma who underwent successful treatment with GKS was described (Case 27 in this article),[5] 16 cases have been reported in the literature (Table 4).[5,6,10,12,13,18] These 16 cases have included 11 female and 5 male patients with a mean age of 48 years (range 14–79 years) at the time of GKS, and a mean tumor volume of 6.0 cm^3 (range 1.5–11.1 cm^3). Selected doses at the tumor periphery have ranged from 12.0 to 19.0 Gy, with a mean and median of 14.8 and 15.0 Gy, respectively. Magnetic resonance images obtained 6–60 months (mean 30, median 27 months) after GKS demonstrated tumor shrinkage in 14 patients and no change in 2. Excluding 2 patients in whom the tumor volume on the most recent MR imaging studies was not available, postradiosurgical volume reduction rates ranged from 14 to 101% (mean and median of 45 and 40%, respectively). Among the 14 of these 16 patients with cranial nerve impairments prior to GKS, complete resolution was achieved in 1 patient, improvement in 7, and in 6 these impairments remained essentially unchanged. No additional symptoms occurred in any of these 16 patients reported in the literature.

In these previously reported cases, however, postradiosurgical follow-up periods were not sufficiently long: the follow-up period was ≤ 36 months in 12 (75.0%) of the 16 patients, and the maximum was 60 months. In the present study of 30 patients, 19 (63.3%) underwent post-GKS follow-up for 3 years or longer, and 10 (33.3%) for 5 years or longer, with a maximum of 138 months. Even in the group of patients with a longer follow-up period, good control of tumor growth was obtained.

We analyzed dose-treatment responses based on 38 cases: 27 of the 30 cases we reported here (the 2 with staged GKS and 1 with partial coverage were excluded) plus 11 previously reported cases. Duplicate citations were avoided.[5,6,10,13] As shown in Fig. 5, there was a tendency for remarkable tumor shrinkage (volume reduction rates of ≥ 50% relative to those before GKS) in the tumors receiving higher doses. Remarkable shrinkage was demon-

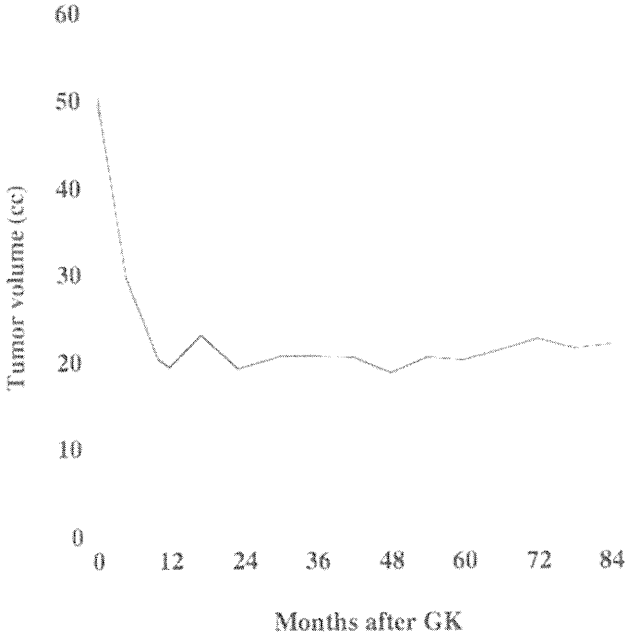

FIG. 2. Case 14. Graph showing postradiosurgical volume changes in this patient.

strated in 15 (83.3%) of 18 tumors that received radiation doses of ≥ 15 Gy, and in 10 of the 20 lesions that received < 15 Gy (not statistically significant; $p = 0.0377$). On the other hand, remarkable tumor shrinkage was demonstrated even in tumors irradiated with relatively low doses: 2 (66.7%) of 3 tumors that received 10.0 Gy, and 3 (60.0%) of 5 that received 12.0 Gy showed shrinkage. We divided these 38 cases into 3 groups based on treatment response shown on the most recent MR images available. Remarkable shrinkage was seen in 25 cases, some shrinkage in 10, and no change in 3. The doses delivered to the tumor periphery differed little among the 3 groups (no statistically significant difference). It can be concluded that a peripheral dose of 14–15 Gy is sufficient to control the growth of CS hemangiomas and that a dose of 10.0–12.0 Gy is the threshold level for tumor growth control.

Although fractionated radiosurgery, also known as stereotactic radiotherapy, is commonly performed for benign intracranial lesions at facilities using a linear accelerator–based radiosurgery system,[4] it is performed only rarely at GKS facilities. Debate continues as to whether stereotactic radiotherapy and staged radiosurgery are effective and safe for benign lesions. In the 2 patients we have described in the present study who underwent staged radiosurgery, good control of tumor growth was observed at 26 and 66 months using a 2-stage GKS technique with doses at the tumor periphery of 11.0 and 8.0 Gy, respectively. On the other hand, as we have described in detail, only the lower half of the tumor was irradiated with a dose of 15.0 Gy in 1 patient, and tumor growth has been well-controlled for 84 months to date. This technique has been applied to relatively large meningiomas,[19] and the treatment concept assumes that the blood supply from the tumor base can be reduced, allowing tumor growth to be controlled (radiosurgical thrombolization). According to a hypothesis proposed by Linskey et al.,[8] most small CS hemangiomas are supplied with blood by the meningeal tributaries of the intracavernous carotid artery, and in cases in which the tumors extend toward the middle fossa, there is an additional blood supply from the middle meningeal and accessory middle meningeal arteries. Though we have only 1 such case, the achievement of tumor growth control using radiosurgical thrombolization can be considered to support this hypothesis. Although a final conclusion awaits further experiences, either staged radiosurgery or radiosurgical thrombolization can be applied to relatively large CS hemangiomas.

Conclusions

The GKS treatment results for CS hemangiomas we report in the present study are more favorable than those previously reported after surgical removal.[9,14,21] Therefore, if a tumor shows clear neuroimaging characteristics of CS hemangioma, and the lesion is small, without evidence either of meningioma or schwannoma, GKS can be performed as the primary treatment procedure.

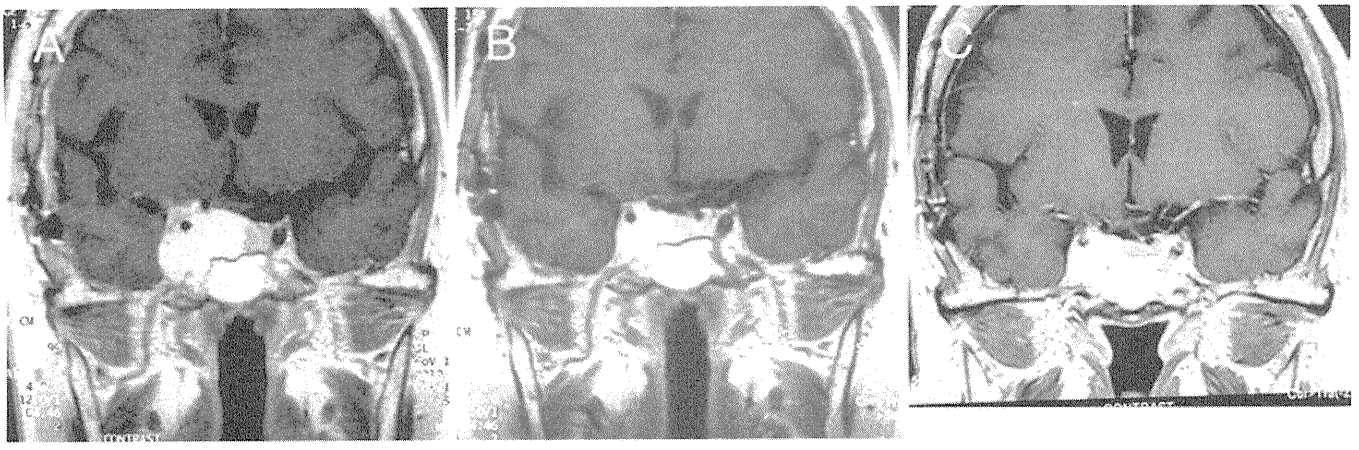

FIG. 3. Case 15. Sequential contrast-enhanced T1-weighted coronal MR images obtained before (A), and 12 (B) and 74 months after GKS (C).

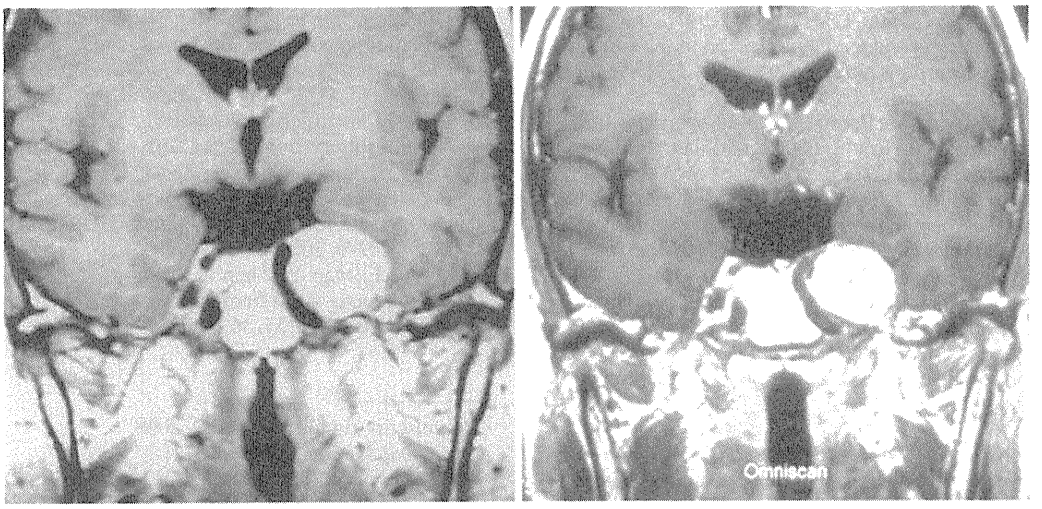

FIG. 4. Case 16. Sequential contrast-enhanced T1-weighted coronal MR images obtained before *(left)* and 64 months after GKS *(right)*.

Disclaimer

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

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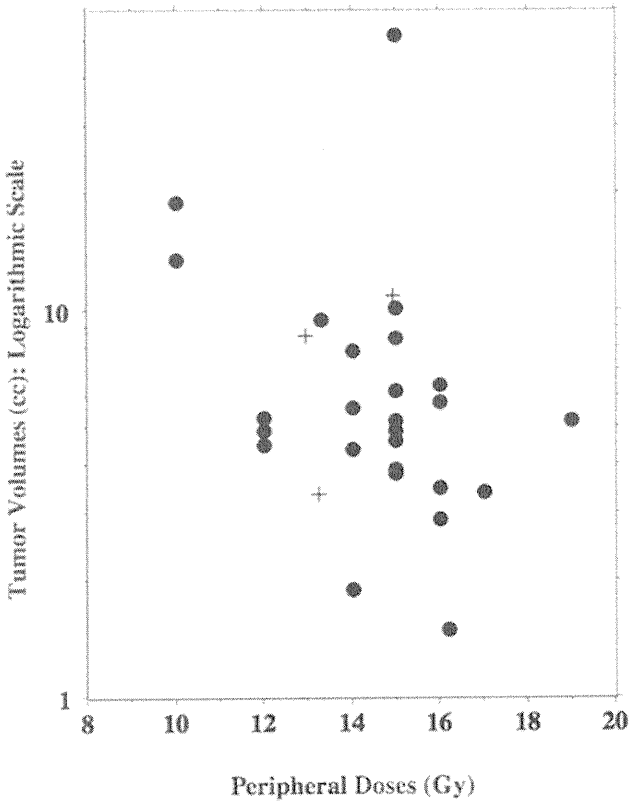

FIG. 5. Scatter plot showing dose, tumor volume, and treatment response. *Circles* indicate remarkable shrinkage, *triangles* indicate some shrinkage, and *plus signs* indicate no change.

References

1. Biondi A, Clemenceau S, Dormont D, Deladoeuille M, Ricciardi GK, Mokhtari K, et al: Intracranial extra-axial cavernous (HEM) angiomas: tumors or vascular malformations? **J Neuroradiol 29:**91–104, 2002
2. Goel A, Muzumdar D, Sharma P: Extradural approach for cavernous hemangioma of the cavernous sinus: experience with 13 cases. **Neurol Med Chir (Tokyo) 43:**112–118, 2003
3. Gonzalez LF, Lekovic GP, Eschbacher J, Coons S, Porter RW, Spetzler RF: Are cavernous sinus hemangiomas and cavernous malformations different entities? **Neurosurg Focus 21 (1):**E6, 2006
4. Grosu AL, Nieder C: Stereotactic fractionated radiotherapy for recurrent capillary hemangioma of the cavernous sinus. **Strahlenther Onkol 182:**179–182, 2006
5. Iwai Y, Yamanaka K, Nakajima H, Yasui T: Stereotactic radiosurgery for cavernous sinus cavernous hemangioma: case report. **Neurol Med Chir (Tokyo) 39:**288–290, 1999
6. Kida Y, Kobayashi T, Mori Y: Radiosurgery of cavernous hemangiomas in the cavernous sinus. **Surg Neurol 56:**117–122, 2001
7. Latchaw RE, Rothfus WE, Mitchell SL: Imaging of the orbit and its contents, in Wilkins RH, Rengachary SS (eds): **Neurosurgery, ed 2.** New York: McGraw-Hill, 1996 pp 1465–1480
8. Linskey ME, Sekhar LN: Cavernous sinus hemangioma: a series, a review, and a hypothesis. **Neurosurgery 30:**101–107, 1992
9. Meyer FB, Lombardi D, Scheithauer B, Nichols DA: Extra-axial cavernous hemangiomas involving the dural sinuses. **J Neurosurg 73:**187–192, 1990
10. Nakamura N, Shin M, Tago M, Terahara A, Kurita H, Nakagawa K, et al: Gamma knife radiosurgery for cavernous hemangiomas in the cavernous sinus. Report of three cases. **J Neurosurg 97 (5 Suppl):**477–480, 2002

11. Ohata K, El-Naggar A, Tamaki T, Morino M, El-Adawy Y, El-Sheik K, et al: Efficacy of induced hypotension in the surgical treatment of large cavernous sinus cavernomas. **J Neurosurg 90:**702–708, 1999
12. Peker S, Kilic T, Sengoz M, Pamir MN: Radiosurgical treatment of cavernous sinus cavernous haemangiomas. **Acta Neurochir (Wien) 146:**337–341, 2004
13. Seo Y, Fukuoka S, Sasaki T, Takanashi M, Hojo A, Nakamura H: Cavernous sinus hemangioma treated with gamma knife radiosurgery: usefulness of SPECT for diagnosis: Case report. **Neurol Med Chir (Tokyo) 40:**575–580, 2000
14. Shi J, Hang C, Pan Y, Liu C, Zhang Z: Cavernous hemangiomas in the cavernous sinus. **Neurosurgery 45:**1308–1314, 1999
15. Shibata S, Mori K: Effect of radiation therapy on extracerebral cavernous hemangioma in the middle fossa. **J Neurosurg 67:**919–922, 1987
16. Sohn CH, Kim SP, Kim IM, Lee JH, Lee HK: MR imaging findings of cavernous hemangiomas in the cavernous sinus. **AJNR Am J Neuroradiol 24:**1148–1151, 2003
17. Suri A, Ahmad FU, Mahapatra AK: Extradural transcavernous approach to cavernous sinus hemangiomas. **Neurosurgery 60:**483–488, 2007
18. Thompson TP, Lunsford LD, Flickinger JC: Radiosurgery for hemangiomas of the cavernous sinus and orbita: technical case report. **Neurosurgery 47:**778–783, 2000
19. Yamamoto M, Kamiyo T, Barfod BE, Urakawa Y: Gamma knife radiosurgery for relatively large meningiomas: an interim result. **Neurol Med Chir** (Abstract #03A0544609)
20. Yao Z, Feng X, Chen X, Zee C: Magnetic resonance imaging characteristics with pathological correlation of cavernous malformation in cavernous sinus. **J Comput Assist Tomogr 30:**975–979, 2006
21. Zhou LF, Mao Y, Chen L: Diagnosis and surgical treatment of cavernous sinus hemangiomas: an experience of 20 cases. **Surg Neurol 60:**31–36, 2003

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PHYSICS CONTRIBUTION

THE DEVELOPMENT AND CLINICAL USE OF A BEAM ON-LINE PET SYSTEM MOUNTED ON A ROTATING GANTRY PORT IN PROTON THERAPY

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Purpose: To verify the usefulness of our developed beam ON-LINE positron emission tomography (PET) system mounted on a rotating gantry port (BOLPs-RGp) for dose–volume delivery-guided proton therapy (DGPT).
Methods and Materials: In the proton treatment room at our facility, a BOLPs-RGp was constructed so that a planar PET apparatus could be mounted with its field of view covering the iso-center of the beam irradiation system. Activity measurements were performed in 48 patients with tumors of the head and neck, liver, lungs, prostate, and brain. The position and intensity of the activity were measured using the BOLPs-RGp during the 200 s immediately after the proton irradiation.
Results: The daily measured activity images acquired by the BOLPs-RGp showed the proton irradiation volume in each patient. Changes in the proton-irradiated volume were indicated by differences between a reference activity image (taken at the first treatment) and the daily activity-images. In the case of head-and-neck treatment, the activity distribution changed in the areas where partial tumor reduction was observed. In the case of liver treatment, it was observed that the washout effect in necrotic tumor cells was slower than in non-necrotic tumor cells.
Conclusions: The BOLPs-RGp was developed for the DGPT. The accuracy of proton treatment was evaluated by measuring changes of daily measured activity. Information about the positron-emitting nuclei generated during proton irradiation can be used as a basis for ensuring the high accuracy of irradiation in proton treatment. © 2010 Elsevier Inc.

Dose–volume delivery guided proton therapy (DGPT), Beam ON-LINE PET system on rotating gantry port (BOLPs-RGp), Target nuclear fragment reaction.

INTRODUCTION

Proton therapy is a form of radiotherapy that enables the concentration of a dose onto a tumor by the use of a scanned or modulated Bragg peak. Therefore, it is very important to evaluate the proton-irradiated volume accurately.

Recently, to ensure the high accuracy of proton therapy, imaging studies of positron-emitting nuclei that are generated by target nuclear fragment reactions involving incident protons and nuclei from a patient's body have been performed (1–14). The annihilation gamma rays from the positron-emitting nuclei were measured by a positron emission tomography (PET) system (specifically a beam OFF-LINE PET system using commercial PET apparatus or PET-computed tomography [CT] apparatus postirradiation or a beam ON-LINE PET system in a proton treatment room). The beam OFF-LINE PET system using the commercial PET-CT apparatus has the advantage of being able to easily acquire fusion images and the ability to reconstruct three-dimensional images. However, the time required for the movement of the patient to the PET room (10–30 min) and the resulting deterioration of the statistical accuracy of the acquired data are large disadvantages. With the beam ON-LINE PET system, capturing a large view and the acquisition of three-dimensional images are difficult because of geometrical problems caused by the beam direction and the PET apparatus (7, 15, 16).

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