Long-term follow-up results of intentional 2-stage Gamma Knife surgery with an interval of at least 3 years for arteriovenous malformations larger than 10 cm³

Clinical article

MASAAKI YAMAMOTO, M.D.,^{1,2} ATSUYA AKABANE, M.D.,³ YUJI MATSUMARU, M.D.,⁴ Yoshinori Higuchi, M.D.,⁵ Hidetoshi Kasuya, M.D.,² and Yoichi Urakawa, M.D.¹

¹Department of Neurosurgery, Katsuta Hospital Mito GammaHouse, Hitachinaka, Ibaraki; ²Department of Neurosurgery, Tokyo Women's Medical University Medical Center East; ³Department of Neurosurgery, Kanto Medical Center NTT EC; ⁴Department of Neurosurgery, Toranomon Hospital, Tokyo, Japan; and ⁵Department of Neurosurgery, Chiba University Graduate School of Medicine, Chiba, Japan

Object. Little information is available on staged Gamma Knife surgery (GKS) with an interval of 3 years or more when used to treat arteriovenous malformations (AVMs) with volumes larger than 10 cm³. The goal of this study was to increase knowledge in this area by reporting the authors' experience.

Methods. The authors describe an institutional review board–approved retrospective study in which they examined databases including information on 250 patients who consecutively underwent GKS for cerebral AVMs during a 16-year period (1988–2004). Among the 250 patients the authors identified 31 patients (12.4%, 15 female and 16 male patients with a mean age of 29 years [range 10–63 years]) in whom 2-stage GKS was intentionally planned at the time of initial treatment because the volume of the AVM nidus was larger than 10 cm³. The most common presentation was bleeding (14 patients), followed by seizures (9 patients), incidental findings (7 patients), and headache with scintillation (1 patient). One patient underwent GKS for the treatment of 2 AVMs simultaneously, and thus 32 AVMs are included in this study. The mean nidus volume was 16.2 cm³ (maximum 55.8 cm³). In all 31 patients, relatively low radiation doses (12–16 Gy directed at the periphery of the lesion) were intentionally used for the first GKS. The second GKS was scheduled for at least 36 months after the first.

Results. Complete nidus obliteration was obtained after the first GKS in 1 patient. To date, 26 patients have undergone a second procedure with a post-GKS mean interval of 41 months (range 24–83 months); 2 other patients refused to undergo the second GKS, and no further treatment was given because of severe morbidity in 1 case and death due to bleeding in the other case. Among the 26 patients who did undergo a second procedure, 3 patients refused follow-up digital subtraction (DS) angiography, another is scheduled for follow-up DS angiography, and 2 patients died, one of bleeding and the other of an unknown cause. The remaining 20 patients underwent follow-up DS angiography. Complete nidus obliteration was confirmed in 13 patients (65.0%) and remarkable nidus shrinkage in the other 7 patients (35.0%). In 2 of these 7 patients, a third GKS achieved complete nidus obliteration. Therefore, the cumulative complete obliteration rate in this series was 76.2% (16 of 21 eligible patients). Seven patients (22.6%) experienced bleeding. The bleeding rates were 9.7%, 16.1%, 16.1%, and 26.1%, respectively, at 1, 2, 5, and 10 years post-GKS. There were 2 deaths and 3 cases of morbidity (persistent coma, mild hemimotor weakness, and hemianopsia in 1 patient each). Hemorrhage did not produce neurological deficits in the other 2 patients. During the mean post-GKS follow-up period of 105 months (range 42-229 months) to date, mild symptomatic GKS-related complications occurred in 2 patients (6.5%); these were classified as Radiation Oncology Group Neurotoxicity Grade 1 in 1 patient and Grade 2 in the other. Among various pre-GKS clinical factors, univariate analysis showed only patient age to impact complications (hazard ratio 0.675, 95% CI 0.306–0.942, p = 0.0085). The rate of complications in the pediatric cases was 33.3%, whereas that in the adolescent and adult cases was 0% (p = 0.0323).

Conclusions. Although a final conclusion awaits further studies and patient follow-up, these results suggest 2-stage GKS to be beneficial even for relatively large AVMs. (*http://thejns.org/doi/abs/10.3171/2012.6.GKS12757*)

Key WORDS • arteriovenous malformation • stereotactic radiosurgery • Gamma Knife surgery • 2-stage procedure

B ASED on the 40-plus-year history of GKS for patients with AVMs, it is now widely accepted that angiographic evidence of nidus obliteration, considered to reduce the risk of hemorrhage nearly as effec-

Abbreviations used in this paper: AVM = arteriovenous malformation; DS = digital subtraction; GKS = Gamma Knife surgery; TAE = transarterial embolization.

tively as resection, can be achieved after a 2- to 3-year latency period for 80%-90% of small AVMs irradiated at the nidus margin with an optimal radiation dose.^{1,4,15-} ^{17,29,37} In such cases, the risk of radiation-related complications is acceptably low.33,35 However, optimal radiation doses, considered necessary to obliterate the nidus completely with a single GKS session, cannot be delivered in some cases in which there are relatively large nidi. In such cases, nidus obliteration rates after a single GKS session are reportedly low.^{6,7,12,18,21,23,37} In 1992, we began to treat some patients harboring AVMs with a volume greater than 10.0 cm³ by using intentional 2-stage GKS with an interval of 3 years or more (dose-staging technique); preliminary results of this 2-stage procedure have been described in our previous publications.³² To the best of our knowledge, although 2-stage (or occasionally, 3or even 4-stage) GKS performed using a volume-staging technique was reported by Sirin et al.²⁷ and, most recently, by Kano et al.⁸ from the same institution, this is the first report to describe a dose-staging technique. In this article, we describe our long-term follow-up treatment results and associated risks.

Methods

Patient Population

This retrospective study was approved by the institutional review board of Tokyo Women's Medical University. We reviewed databases including 250 patients who consecutively underwent GKS for cerebral AVMs during the 16-year period from 1988 through 2004. In 31 (12.4%) of the 250 patients, 2-stage GKS was intentionally planned at the time of the initial treatment (Table 1). This treatment strategy was explained in detail by one of the authors (M.Y.) to each patient and also to at least one adult relative. Written informed consent was obtained from all 31 patients before the initial treatment. Some patients at our institution were originally scheduled for only 1 procedure, but the treatment failed despite delivery of optimal doses to the nidus. These patients also underwent a second GKS but were excluded from this study because a 2-stage GKS was not originally planned.

There were 15 female and 16 male patients in the study population. Their mean age at the time of the first GKS was 29 years (range 10–63 years). The most common presentation was hemorrhage (14 patients [45.2%]), followed by seizure (9 patients [29.0%]) and headache with scintillation (1 patient [3.2%]). In 7 patients (22.6%), the AVM was found incidentally. Although TAE had been attempted in 8 patients (25.8%) and surgical removal in 1 patient (3.2%) before GKS, the nidus volume at the time of radiosurgery was \geq 10 cm³ in all 9 patients.

One patient (Case 15) harbored 2 AVMs: one in the right frontal lobe and the other in the left occipital lobe; thus, 32 AVMs were included in this study. The mean and median nidus volumes were 16.2 cm³ and 14.0 cm³, respectively, and the volumes ranged from 10.0 to 55.8 cm³; only 3 lesions had nidus volumes exceeding 20.0 cm³. Among the 32 lesions, 4 were located in the basal ganglia and/or the thalamus, 27 in the lobes of the cerebrum, and

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1 in the cerebellum. The initial surgical grading based on the Spetzler-Martin Scale²⁸ was Grade II in 6 AVMs (18.8%), Grade III in 15 AVMs (46.9%), and Grade IV in 11 AVMs (34.4%). The initial radiosurgical grades, as proposed by Pollock and Flickinger,¹⁹ ranged from 1.47 to 6.52, with a mean grade of 2.37 and a median grade of 2.11. Among the 31 patients, 25 had no neurological symptoms before GKS; hemorrhage was found in 14 patients but only 6 of these patients suffered from neurological deficits. Among the latter 6 patients, the modified Rankin Scale scores³⁰ were 1 in 3 patients and 2 in the other 3 patients.

All DS angiography studies were performed by 1 author (Y.M.) or by the late Dr. Naotoshi Kobayashi, acknowledged later in this paper. Another author (A.A.), who did not participate in other aspects of this study, evaluated all follow-up DS angiography studies.

Radiosurgical Technique

At the first treatment, the entire nidus was targeted, and a radiation dose of 12–16 Gy was delivered to the lesion periphery. Selection of a dose between 12 and 16 Gy was based primarily on the nidus volume, while also taking into consideration surrounding critical anatomical structures. For the second GKS, performed 3 years or more after the first, all of the residual nidus was again targeted and a higher dose, if possible, was delivered to the lesion periphery. The final DS angiography study was performed at least 3 years after the second irradiation.

As of January 2012, 26 patients (83.9%) had undergone a second GKS and 2 patients (6.5%) a third. For all 59 GKS procedures, stereotactic DS angiography was performed using femoral artery catheterization. Both stereotactic CT scans and MR images were used for dose planning in all 59 procedures. An earlier computer system, the Kula system (1988–1995, Elekta AB), was used for initial dose planning in 3 patients (Cases 1–3) and also for the second treatment in 1 of these patients (Case 1). For the remaining 55 GKS procedures, we used a newer system, the GammaPlan (1995-present, Elekta AB). Before 2000, conventional film angiograms were employed for dose planning (7 of 59 procedures); with the development of a distortion correction program, DS angiography was used thereafter (52 procedures). Gamma Knife surgery was performed using a Leksell Gamma Knife model B unit (1988–2003, Elekta AB) in 26 of the 31 initial procedures and in 7 of the 20 second procedures. The Leksell Gamma Knife model C unit (2003–present, Elekta AB) was used for the other 26 procedures.

Statistical Analysis

All data were analyzed according to the intention-totreat principle. For time-to-event outcomes, times elapsed until a first event were compared using the log-rank test, whereas the Kaplan-Meier method⁹ was used to estimate the absolute risk of each event for each group, and hazard ratios and 95% confidence intervals were estimated using the Cox proportional hazards model.² To identify baseline and clinical variables associated with post-GKS bleeding

TABLE 1: Characteristic of 31 patients with 32 AVMs*

Case	Age	Δ\/Μ				Previous		mRSS		Bleeding/Complications
No.	Sex	Location	SMG	PFS	Presentation	Procedures	FU (mos)	Pre-GKS	Last FU	(onset in mos post-GKS)
1	20, M	FL		1.92	seizure	no	229	0	0	
2	54, M	TL	IV	2.58	bleeding	no	226	0	0	
3	20, M	TL	II	1.65	seizure	no	203	0	0	
4	53, M	Th	111	2.66	bleeding	no	65 (died)	1	6	bleeding/death (65)
5	23, M	Th	IV	2.08	bleeding	TAE	2 (died)	2	6	bleeding/death (2)
6	29, M	TL		3.48	seizure	no	156	0	0	
7	23, F	FL	111	1.47	incidental	no	120	0	0	
8	28, F	PL	111	4.19	seizure	TAE	144	0	1	bleeding/hemiparesis (22)
9	15, M	FL	III	1.98	seizure	no	117	0	5	bleeding/persistent coma (14)
10	22, F	FL	III	1.74	seizure	no	121	0	0	
11	53, M	FL	11	2.11	incidental	no	109	0	0	
12	34, F	TL	III	1.69	bleeding	no	81	2	2	
13	27, F	OL	111	2.09	bleeding	no	105	0	0	bleeding/no deficits (25)
14	25, M	PL	III	2.66	incidental	no	42	0	0	
15	24, M	FL	IV	1.96	seizure	no	100	0	0	
		OL	IV	2.26		no				
16	13, F	С	IV	2.06	bleeding	TAE	120	2	2	
17	46, F	FL	II	2.32	bleeding	surgery	108	0	0	
18	36, M	PL	111	2.36	incidental	no	109	0	0	
19	42, M	TL	IV	6.52	bleeding	TAE	96	0	0	
20	63, F	OL	IV	2.95	incidental	no	97	0	0	
21	10, F	OL	IV	2.37	bleeding	TAE	99	0	1	bleeding/hemianopsia (99)
22	24, M	BG	IV	2.38	bleeding	no	62	1	1	
23	24, F	FL		2.46	seizure	no	108	0	0	
24	15, M	FL	111	1.82	seizure	no	55 (died)	0	6	death (55)
25	22, M	OL	IV	2.30	HA & scintillation	no	47	0	0	
26	11, F	Th	IV	2.11	bleeding	no	97	0	1	right-handed paresis (38)
27	13, F	TL	III	1.55	bleeding	no	86	0	1	bleeding/no deficits (38)
28	54 F	01	Ш	2 41	incidental	TAF	94	0	0	
20	20 F	TI		1 79	incidental	no	77	0	0	
30	20,1 19 F	FI		1.86	hleeding	TAF	84	1	1	
31	36, M	TL		1.96	bleeding	TAE	83	0	0	

* BG = basal ganglia; C = cerebellum; dist = disturbance; FL = frontal lobe; FU = follow-up; HA = headache; mRSS = modified Rankin Scale Score; OL = occipital lobe; PFS = Pollock-Flickinger score; PL = parietal lobe; SMG = Spetzler-Martin grade; Th = thalamus; TL = temporal lobe.

or complications, univariate analyses were performed using the Cox proportional hazard model with a step-wise selection procedure.² We compared patient characteristics using the Fisher exact test for categorical data, as appropriate.

All comparisons were planned and the tests were 2-sided. A p value < 0.05 was deemed indicative of a statistically significant difference. All statistical analyses were conducted by one author (Y.H.), who was not involved in either GKS treatment or patient follow-up. That author used JMP (Japanese version 9.0) for the Windows system (SAS Institute Inc.).

Results

Obliteration Rates

Characteristics of all 31 patients are listed in Tables 1 and 2, and their courses are summarized in Fig. 1. Stereotactic angiography for a planned second GKS, performed 84 months after the first, demonstrated complete nidus obliteration in 1 patient (3.2%, Case 11), and thus repeat GKS was not required. This patient had long been reluctant, despite our repeated recommendations, to undergo the second treatment. Due to this reluctance, stereotactic angiography for the second GKS was not per-

Two-stage Gamma Knife surgery for AVMs >10 cm³

TABLE 2: Treatment results of the first and second GKSs*

		1st GKS		Interval	2nd GKS				
	Nidus	Max	Min	btwn 1st &	Nidus	Max	Min	Vol	
Case	Vol	Dose	Dose	2nd GKS	Vol	Dose	Dose	Reduction	
No.	(cm ³)	(Gy)	(Gy)	(mos)	(cm ³)	(Gy)	(Gy)	Rate (%)	Angiographic FU Results*
1	15.2	40.00	14.00	36	2.7	33.33	20.00	18	comp oblit
2	15.0	36.00	12.00	81	1.6	30.30	20.00	11	comp oblit
3	12.5	30.00	15.00	83	0.6	36.67	22.00	5	part oblit†
4	10.0	32.00	16.00	39	4.2	32.00	16.00	42	
5	10.2	28.00	14.00						
6	29.0	28.00	14.00	36	9.9	25.00	15.00	34	part oblit†
7	10.1	30.00	15.00	36	0.7	33.33	20.00	7	comp oblit
8	33.3	28.00	14.00	24	1.8	33.33	20.00	5	comp oblit
9	16.8	28.00	14.00						
10	13.0	30.00	12.00	36	8.6	32.00	16.00	66	
11	10.5	32.00	16.00						comp oblit‡
12	10.1	30.00	15.00	50	0.6	30.00	21.00	6	
13	12.5	28.00	14.00	37	9.7	25.00	15.00	78	part oblit
14	18.6	30.00	15.00						
15	14.8	23.33	14.00	38	3.1	25.00	15.00	21	comp oblit
	16.6	23.33	14.00	38	13.3	25.00	15.00	80	part oblit
16	15.0	28.00	14.00	38	9.4	25.00	15.00	63	part oblit
17	14.0	28.00	14.00	36	0.9	24.00	18.00	6	comp oblit
18	13.4	25.00	15.00	38	6.0	30.00	18.00	45	comp oblit
19	55.8	30.00	15.00	36	17.2	30.00	15.00	31	
20	13.9	25.00	15.00	38	13.9	25.00	15.00	100	part oblit
21	18.7	28.00	14.00	37	13.4	25.00	15.00	72	part oblit
22	13.0	30.00	15.00	50	10.2	30.00	15.00	78	
23	19.8	23.33	14.00	35	3.8	25.00	15.00	19	comp oblit
24	15.2	23.33	14.00	41	3.6	30.00	18.00	24	
25	15.6	28.00	14.00						
26	12.9	28.00	14.00	36	7.7	26.27	16.00	60	comp oblit
27	12.9	23.33	14.00	38	1.3	30.00	18.00	10	comp oblit
28	10.3	25.00	15.00	37	2.6	30.00	18.00	25	comp oblit
29	13.9	25.00	15.00	37	1.8	35.00	21.00	13	comp oblit
30	14.8	25.00	15.00	36	1.6	30.00	20.00	11	comp oblit
31	12.4	25.00	15.00	36	0.8	25.71	18.00	6	comp oblit

* Comp oblit = complete obliteration; part oblit = partial obliteration.

† Complete obliteration was obtained after the third GKS.

‡ Complete obliteration was obtained after the first GKS.

formed until 84 months after the first GKS. Two patients experienced severe hemorrhage after the first procedure. One eventually died (Case 5), while the other remains so severely disabled (Case 9) that a second GKS could not be performed. Two patients have thus far refused repeat GKS (Cases 14 and 25). Therefore, to date, a second GKS has been performed in 26 (27 lesions) of the 31 patients (32 lesions), with a mean interval between procedures of 41 months and a median interval of 37 months (range 24–83 months). The second treatment was postponed for 81 months after the first GKS in Case 2 because stenosis of the middle cerebral artery trunk occurred, as reported previously.³⁴ Also, in Case 3 the second treatment was performed 83 months after the first GKS because the patient had long been reluctant, despite our repeated recommendations, to undergo the second treatment. The nidus volumes of the 27 lesions at the second procedure ranged from 0.6 cm³ to 17.2 cm³ (mean 5.6 cm³, median 3.7 cm³) (Fig. 2 left). The volume reduction rates in all 27 lesions ranged from 5% to 100% (mean 36%, median 25%) (Fig. 2 right). A volume reduction exceeding 50% was achieved in 20 (74%) of the 27 lesions. The selected



Fig. 1. Flowchart showing outcomes after staged GKS. The number of patients is shown in parentheses. CKRS = CyberKnife radiosurgery; F/u = follow-up; GKRS = Gamma Knife radiosurgery; SD = severely disabled.

doses at the lesion periphery ranged from 15.0 Gy to 22.0 Gy (mean 17.4 Gy, median 17.0 Gy) for the second GKS.

Among the 26 patients who underwent a second GKS, 2 died (1 patient due to severe hemorrhage and the other of an unknown cause), 1 patient is awaiting followup DS angiography, and 3 others have refused further DS angiography. Thus, to date, 20 patients have undergone follow-up DS angiography 36 months or more after the second GKS. Complete nidus obliteration was confirmed in 13 (65.0%) and remarkable shrinkage, albeit with a small remnant, in the other 7 patients (35.0%). In 1 of these (Case 15), 2 AVM nidi were irradiated; 1 nidus was confirmed to be completely obliterated and the other partially obliterated. Of the 7 patients in whom there was nidus shrinkage, 2 patients have already undergone a third GKS, and complete nidus obliteration was confirmed by DS angiography at 29 months in 1 patient and 36 months in the other after the third GKS. Therefore, including the 1 aforementioned patient in whom the second treatment was not required, the complete obliteration rate in this series was 76.2% (16 of 21 eligible patients).

Post-GKS Bleeding and GKS-Related Complications

After the initial GKS, 7 patients (22.6%) experienced bleeding, 6 patients before and 1 patient after the second GKS. There were 2 deaths (Cases 4 and 5) and 3 cases of morbidity, including persistent coma (Case 9), mild hemimotor weakness (Case 8), and hemianopsia (Case 21). Hemorrhage produced no neurological deficits in the other 2 patients. According to a Kaplan-Meier analysis, the bleeding rates were 9.7%, 16.1%, 16.1%, and 26.1%,

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respectively, at 1, 2, 5, and 10 years post-GKS. Among various pre-GKS clinical factors, the univariate analysis showed none that impacted bleeding.

Excluding 3 deceased patients, the follow-up period after the first treatment ranged from 42 to 229 months (mean 105 months, median 99 months). Symptomatic complications occurred in 2 patients (6.5%, Cases 26 and 27); in 1 patient the Radiation Oncology Group Neurotoxicity grade was 1 and in the other the grade was 2.²⁴ According to a Kaplan-Meier analysis, the symptomatic complication rates were 5.6% at both 5 and 10 years post-



Fig. 2. Graph depicting changes in AVM nidus volumes between the first and second GKS sessions. Left: Absolute volumes. Right: Volume reduction rates.



Fig. 3. Case 26. A–C: Sequential left internal carotid artery angiograms obtained before the first GKS (A) as well as 36 months (B, at the time of the second treatment) and 74 months (C, 38 months after the second GKS) after the procedure. D–G: Sequential MR images obtained before the first GKS (D) as well as 36 months (E), 42 months (F), and 97 months after the procedure. Appearance of a cyst associated with hydrocephalus is evident in panels E and F. After placement of an Ommaya reservoir, the patient's cyst and ventricle decreased in size (G).

GKS. The patient in Case 26 experienced slight difficulty in writing 2 months after the second GKS (38 months after the first GKS), which gradually worsened for a few months. Magnetic resonance images showed cyst enlargement as well as the development of hydrocephalus, necessitating Ommaya reservoir placement (Fig. 3). Postoperatively, this patient experienced symptom amelioration but her difficulty in writing has persisted to date. In the patient in Case 27, a left hemisensory disturbance developed 54 months after the first GKS (26 months after the second GKS). Magnetic resonance imaging showed an area of slightly increased hyperintensity on T-weighted images (Fig. 4), compared with that seen at the time of the first GKS. Despite incomplete symptom resolution, the patient has remained fully active and is pursuing her college education. Among various pre-GKS clinical factors, univariate analysis showed only patient age to impact complications (hazard ratio 0.675, 95% CI 0.306-0.942, p = 0.0085). The incidence of complications in the pediatric cases was 33.3%, whereas that in adolescent and adult cases was 0% (p = 0.0323).

Discussion

The most important factor predicting incomplete nidus obliteration after a single GKS session is the lower dose treatment necessitated by relatively large nidus volumes.^{5,6,12,15,16,21,23,26,37} Pan et al.¹⁸ reported an obliteration rate of only 25% in 48 patients who underwent GKS once for AVMs larger than 15 cm³; the average margin doses were 17.7 Gy for AVMs with volumes of 10–20 cm³ and 16.5 Gy for AVMs with volumes larger than 20 cm³. The authors also observed moderate adverse effects in 37% of patients and severe adverse effects in 12% of patients in whom AVM volumes were 10 cm³ or larger. Very recently, Karlsson et al.¹⁰ obtained an angiographically confirmed obliteration rate of 28.1% after single-session GKS in 133 patients in whom the AVM nidus volumes were 9.0 cm³ or larger. Although historically conventional fraction-ated radiotherapy has been used for a small number of patients, success rates have been low.^{13,25}

Since the mid-1990s, fractionated stereotactic radiation treatment, performed using a linear accelerator system, has been applied to treating large AVMs. Veznedaroglu et al.³¹ reported on 5 patients with AVMs whose volumes were 14 cm³ or larger and who underwent this procedure with a total dose of 42 Gy (7-Gy fractions delivered over 2 weeks); complete obliteration was angiographically confirmed 5 years after treatment in 4 (80%)of the patients. Since the morbidity rate in their patients was very high, the authors switched to a total dose of 30 Gy (5-Gy fractions delivered over 2 weeks). However, complete obliteration was achieved in only 1 (10.0%) of 10 patients in this subgroup. Lindval et al.¹⁴ reported treating 10 patients harboring 10.0-cm³ or larger AVMs using hypofractionated conformal stereotactic radiotherapy; nidus obliteration was angiographically confirmed in 7 (70%) of these patients 5 years after irradiation. Those authors also described a 50% obliteration rate (3 of 6 patients) in a subgroup of patients in whom AVM volumes were 15.0 cm³ or larger.

Two-stage (or occasionally, 3-stage or even 4-stage) GKS has also been applied to relatively large AVMs. Pollock et al.²² first reported this technique, which was used for 10 patients in whom the median AVM volume was 17.4 cm³ (range 7.4–53.3 cm³). Among these 10 patients, in whom follow-up was brief, complete nidus oblit-



Fig. 4. Case 27. A–F: Sequential right carotid artery and left vertebral artery angiograms obtained before the first GKS (A and B) as well as 38 months (C and D, at the time of the second treatment) and 86 months (E and F) after the procedure. **G and H:** Sequential T2-weighted MR images obtained before (G) and 54 months (H) after the first GKS. A hyperintense area seen on T2-weighted images increased in size (*arrows* in H).

eration was obtained in only 1 patient. That patient, however, experienced a severe complication. Initially, Sirin et al.²⁷ and, most recently, Kano et al.⁸ reported favorable treatment results for a relatively large patient series. Their treatment strategy was to divide the AVMs into 2 (or occasionally, 3 or even 4) separate anatomical portions and treat 1 portion in a single GKS session followed by irradiation of the other portion(s) 3-8 months (mean 5 months) later. The median margin dose was 16.0 Gy (range 13.0–18.0 Gy) at each stage. Using this technique, the authors treated 47 patients with AVMs 10.2-56.9 cm³ (median 22.0 cm³) in volume. In 17 of their 47 patients, AVM obliteration was confirmed after 2-4 GKS procedures at a median follow-up of 87 months (range 0.4–209 months). The major problem with their method was that, despite meticulous dose-planning aimed at avoiding irreversible radiation-induced injury, it was apparently not possible to avoid irradiation overlap in normal brain structures between the 2 (or among 3 or 4) procedures. This problem contributed to a relatively high incidence of symptomatic GKS-related complications-13% of patients, as compared with our incidence of 6.5%.

As reported previously,³² we used a different strategy with an interval between procedures of at least 3 years, thereby avoiding complicated dose-planning procedures. It is widely known that postirradiation radiobiological repair may occur quite quickly, such that radiosurgical treatment can be repeated in just 3–6 months.^{8,27} Even using a low radiation dose, however, complete obliteration can be expected 3 or more years after irradiation in some patients. In fact, a second treatment was not required in 1 (3.2%) of our 31 patients because complete obliteration was achieved by a single GKS session. Furthermore, the longer we wait, the smaller the nidus is expected to become, allowing us to deliver a higher dose during the second treatment. We therefore decided that the interval between the 2 procedures should be at least 3 years. Furthermore, our technique has the advantage of being less complicated than the one used by Sirin et al.²⁷

The major problem with our technique is that at least 6 years are necessary for nidus obliteration to be achieved. Therefore, the incidence of hemorrhage-22.6% in this study (7 of 31 patients)—is apparently higher than those in all previous reports.^{1,3,4,11,15–17,20,32,34,35} However, in 5 of these 7 patients, hemorrhage occurred within 38 months after the first GKS. Thus, even if a single GKS session or a volume-staging technique, as Sirin et al.²⁷ reported, had initially been planned, instead of our dose-staging technique, hemorrhage during the latency period might not have been avoidable. In addition, Kano et al.⁸ reported that 10 (21.3%) of 47 patients experienced bleeding and 5 (10.6%) of those patients died. There is controversy as to whether larger AVMs carry a higher risk of bleeding after radiosurgery.^{3,7,11,17,20} Jokura et al.⁷ reported that larger AVMs were associated with a higher bleeding risk. In the aforementioned series published by Karlsson et al.,¹¹ 23.3% of patients suffered a hemorrhage after treatment.

In our present series, despite the fact that the mean and median follow-up periods were relatively long—105 and 99 months, respectively, after the first GKS—symptomatic complications occurred in only 2 patients (6.5%), and the complication rate was 5.6% at 10 years post-GKS. As we reported elsewhere,³⁶ in 181 patients with relatively small AVMs, who were followed up for more than 5 years after GKS, symptomatic complications occurred in 15 (8.3%) and the complication rate was 8.2% at 10 years post-GKS. Despite the fact that relatively large AVMs were treated in the present study, both the calculated complication rate and the estimated cumulative complication rate at 10 years post-GKS, determined using a Kaplan-Meier analysis, were similar in our 2 groups.

Conclusions

Although further studies are needed, these results allow us to conclude that GKS may be beneficial, even for patients with relatively large AVMs. The major problem with our technique is that at least 6 years are necessary to achieve nidus obliteration. Therefore, the incidence of hemorrhage during the latency period is apparently higher than in all other previously published series.

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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. Analysis and interpretation of data: Yamamoto, Akabane. Drafting the article: Yamamoto. Approved the final version of the manuscript on behalf of all authors: Yamamoto. Statistical analysis: Yamamoto, Higuchi. Administrative/technical/ material support: Urakawa. Study supervision: Yamamoto, Kasuya. Performed stereotactic DS angiography for Gamma Knife surgery: Matsumaru.

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Address correspondence to: Masaaki Yamamoto, M.D., Katsuta Hospital Mito GammaHouse, 5125-2 Nakane, Hitachi-naka, Ibaraki 312-0011, Japan. email: BCD06275@nifty.com.

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