Role of Gamma Knife surgery in the treatment of intracranial dural arteriovenous fistulas

Clinical article

SHUNYA HANAKITA, M.D.,¹ TOMOYUKI KOGA, M.D., PH.D.,¹ MASAHIRO SHIN, M.D., PH.D.,¹
MASAAKI SHOJIMA, M.D., PH.D.,¹ HIROSHI IGAKI, M.D., PH.D.,²
AND NOBUHITO SAITO, M.D., PH.D.¹

Departments of ¹Neurosurgery and ²Radiology, University of Tokyo Hospital, Tokyo, Japan

Object. The goal of this study was to assess the efficacy of Gamma Knife surgery (GKS) in the management of dural arteriovenous fistulas (dAVFs).

Methods. The authors performed a retrospective analysis of a group of 22 patients who underwent GKS for dAVFs at the University of Tokyo Hospital between 1991 and 2009. The patients underwent CT or MR imaging with contrast enhancement every 6 months after GKS; when obliteration of a dAVF was indicated by these images, patients also underwent angiography. Follow-up in these patients ranged from 12 months to 100 months (median 33 months) after GKS.

Results. Obliteration of the dAVF was confirmed by neuroimaging in 12 patients (55%). According to a Kaplan-Meier analysis, obliteration rates for the dAVFs were 51% at 3 years and 80% at 5 years. The obliteration rate for lesions without cortical venous drainage (CVD) was 86%, which was significantly higher than the rate for dAVFs with CVD (47%) ($p = 0.007$). Hemorrhage at presentation ($p = 0.03$), a target volume less than 1.5 cm³ ($p = 0.009$), and Cognard Type III or IV dAVF ($p = 0.005$) were factors associated with a higher obliteration rate. Among 10 patients whose dAVFs were not obliterated by the initial GKS, 5 patients underwent additional treatment and complete obliteration was achieved in all. Relief of tinnitus was obtained in 5 (83%) of 6 patients with transverse-sigmoid sinus dAVFs, and ophthalmic symptoms improved in 2 (67%) of 3 patients with cavernous sinus dAVFs. No patient experienced interval hemorrhage or radiation-induced complications after treatment.

Conclusions. Gamma Knife surgery is a safe and effective treatment for dAVF. It can be a first line of therapy in the multidisciplinary treatment strategy for dAVFs, especially when significant morbidity is anticipated with other therapeutic options. One should be very careful about recommending GKS for patients harboring dAVFs with CVD because of the expected natural history of such a lesion and the possibility of other therapeutic options. (<http://thejns.org/doi/abs/10.3171/2012.7.GKS12967>)

KEY WORDS • Gamma Knife surgery • dural arteriovenous fistula • stereotactic radiosurgery

GAMMA Knife surgery is widely accepted as an effective treatment option for a variety of brain disorders including brain neoplasms, vascular lesions, and functional disorders.¹⁴ Arteriovenous malformation is the most common vascular disorder treated by GKS, and there have been numerous reports regarding outcomes of GKS for large numbers of patients with AVMs.^{9,14,15,22,23} Intracranial dAVF is another cerebrovascular disorder that can cause devastating symptoms due to cerebral venous congestion or intracranial hemorrhage.^{1,4,27–29} Surgery and endovascular intervention are usually applied as primary treatment modalities for this disease.¹¹ Gamma Knife surgery has been performed on dAVFs that are difficult to treat using other treatment modalities.^{5,12,13,19,22,24,26,31}

Compared with AVMs, the angioarchitecture of dAVFs is more complex and is often difficult to fully understand.^{16,18,24,28} In addition, these lesions frequently require earlier radical treatment because of impending associated symptoms.^{4,8,29} It takes at least several months for complete obliteration of a fistula following GKS.^{17,18,26} Therefore, the role of GKS in the treatment of dAVF remains controversial, with an ongoing debate over whether it should be a first choice of treatment or only a last resort, as an alternative to endovascular treatment or resection.^{5,12,13,19,22,24,26,31}

In the present study we analyzed outcomes of GKS for dAVFs, and in this report we discuss the role of GKS in the treatment of this disease.

Methods

Patient Population

Between July 1991 and December 2009, 22 patients

Abbreviations used in this paper: AVM = arteriovenous malformation; CVD = cortical venous drainage; dAVF = dural arteriovenous fistula; GKS = Gamma Knife surgery; MR-DS = magnetic resonance–digital subtraction.

harboring dAVFs were treated with GKS at the University of Tokyo Hospital. We retrospectively reviewed the medical records of these 22 patients. The internal review board of the University of Tokyo Hospital approved the study protocol, and written informed consent was obtained from all subjects prior to participation in this study. Diagnoses of the dAVFs were confirmed by performing cerebral angiography in combination with CT or MR imaging. The pattern of venous drainage was determined based on the Cognard and Borden systems.^{3,6}

In general, at our institution endovascular treatment is the first line of treatment because it is less invasive than open surgical procedures and, with endovascular treatment, it is possible to obtain immediate obliteration of a dAVF. However, if a dAVF is located at the venous sinus and involves critical cerebral venous drainage, surgery is deemed more appropriate. Radiosurgery can be selected as a first line of treatment when both surgery and endovascular treatment are not advisable, for instance, when the lesion is in a deep location or there are associated risks of damaging critical venous sinuses. Gamma Knife surgery is also recommended when other treatments have resulted in partial obliteration. Among the 22 patients enrolled in this study, 8 patients (36%) were referred to our department for residual lesion following endovascular treatment and 2 patients (9%) were referred after surgery combined with endovascular treatment. In the other 12 patients (55%), GKS was the initial treatment.

Radiosurgical Treatment

After the Leksell stereotactic frame had been affixed to the patient's head, the patient underwent stereotactic imaging so that we could obtain precise information on the shape, volume, and 3-dimensional coordinates of the dAVF. Computed tomography or MR imaging was used in combination with biplanar angiography. Treatment planning was jointly performed by neurosurgeons and radiation oncologists using commercially available software. First-generation treatment-planning software (KULA, Elekta AB), with which prescribed dose planning was manually superimposed on imaging films, was used until September 1998. Advanced planning software (Leksell GammaPlan, Elekta AB), which enables the operator to display multiple images on the computer screen and simultaneously superimpose isodose lines on them, was used thereafter. Targeted areas were limited to sites of arteriovenous communication. On angiographic images obtained during early to late arterial phases, the sites at which dural arteries drain directly into the dural sinus were located and treated with more than 20 Gy. Follow-up clinical examinations were performed at our hospital or by referring physicians. Patients underwent CT or MR imaging with contrast enhancement every 6 months. Recently, MR-DS angiographic images were obtained to evaluate outcomes. Angiography was performed when these images strongly suggested obliteration of the dAVF. Despite recent progress in the development of less invasive imaging modalities such as MR imaging or MR angiography,²⁰ it is still difficult to confirm obliteration of dAVFs reliably based solely on those imaging studies. Angiography remains the gold standard for revealing

the precise angioarchitecture and flow pattern of dAVFs.⁵ Thus, after a certain period of time, we recommend that each lesion be evaluated with angiography not only to confirm obliteration of the fistula but also to consider additional therapeutic options for residual lesions.

Estimated obliteration rates were calculated using the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analyses to evaluate factors that potentially affected fistula obliteration among the pool of patients: age, sex, existence of CVD, hemorrhage at presentation, target volume, location of the fistula, treatment with stereotactic radiosurgery alone, and draining venous pattern. All statistical analyses were performed using JMP 9 software (SAS Institute Inc.).

Results

Characteristics of Patients

The clinical characteristics of all patients are summarized in Table 1. Follow-up in these patients ranged from 12 to 100 months (mean 35 months, median 33 months) after GKS. Patient age at the time of GKS ranged from 31 to 73 years (mean 57 years, median 60 years). The median target volume was 1.5 cm³ (range 0.1–9.5 cm³). Locations of treated dAVFs included the following: transverse-sigmoid sinus junction in 9 patients, falcotentorial region in 6 patients, cavernous sinus in 3 patients, middle fossa in 2 patients, and anterior fossa and superior sagittal sinus in 1 patient each. The initial symptoms included hemorrhage in 6 patients, tinnitus in 6 patients, and orbital congestion in 3 patients. At the time of GKS, 9 patients exhibited neurological deficits caused by past hemorrhage or prior treatment. Motor weakness was seen in 3 patients, diplopia in 3 patients, and disturbance of consciousness in 3 patients.

On angiographic images at the time of radiosurgical dose planning, CVD was evident in 15 patients. Among those cases with CVD, 8 patients underwent GKS as the initial treatment and 7 patients after failure of other treatment modalities. The maximum radiation dose ranged from 33 to 50 Gy (mean 40 Gy, median 40 Gy) and the margin dose ranged from 18 to 25 Gy (mean 21 Gy, median 20 Gy).

Obliteration Rate of dAVFs After GKS

Of the 22 patients, complete obliteration of the fistula (Fig. 1) was confirmed by angiography in 9 patients between 12 and 50 months (median 27 months) after GKS. In 3 patients, obliteration of the fistula with remarkable improvement in patients' symptoms was confirmed only by MR imaging and MR-DS angiography 19 to 43 months after GKS. Further angiographic evaluation was scheduled for 2 of these 3 patients. In 1 patient, angiographic confirmation was not obtained because the patient has a history of anaphylaxis in response to the contrast enhancement used during the initial angiography. The overall Kaplan-Meier projected obliteration rates of dAVFs after a single GKS session were 51% at 3 years and 80% at 5 years. The rates of fistula obliteration were not significantly different between the GKS-only group

TABLE 1: Summary of 22 patients with dAVFs treated by GKS

Variable	Value
no. of patients	22
no. of dAVFs	22
median age of patients in yrs (range)	60 (31–74)
male/female ratio	14:8
median observation period in mos (range)	33 (12–100)
median prescribed dose in Gy (range)	20 (18–25)
median target volume in cm ³ (range)	1.5 (0.1–9.5)
initial symptom (no. of patients)	
hemorrhage	6
tinnitus	6
orbital congestion	3
disturbance of consciousness	3
location of dAVFs (no. of patients)	
transverse-sigmoid sinus junction region	9
falcotentorial region	6
cavernous sinus	3
middle fossa	2
anterior fossa	1
superior sagittal sinus	1
treatment modality (no. of patients)	
GKS alone	12
endovascular treatment + GKS	8
endovascular treatment + surgery + GKS	2
classification of draining venous (no. of patients)	
Borden grade 1	4
2	11
3	7
Cognard type I	3
IIa	3
IIb	4
IIa + IIb	4
III	3
IV	5
CVD present (no. of patients)	15

and the multimodal treatment group (67% vs 40%, $p = 0.30$, log-rank test).

In 15 patients who harbored dAVFs with CVD, complete obliteration of the fistula was apparent in 7 cases (47%; 43% at 3 years and 43% at 5 years in the Kaplan-Meier projected obliteration rate). In contrast, in 7 patients with dAVFs without CVD, obliteration of the fistula was confirmed in 6 cases (total 86%; 64% at 3 years and 83% at 5 years in the Kaplan-Meier projected obliteration rate)—a significantly higher rate compared with those with CVD in a multivariate analysis ($p = 0.007$, Table 2). Other factors associated with a higher obliteration rate of dAVFs in the multivariate analysis were hemorrhage at presentation ($p = 0.03$), target volume smaller than 1.5 cm³ ($p = 0.009$) and Cognard Type III or IV dAVF ($p = 0.005$). No statistical differences were found for patient

FIG. 1. **A and B:** Left external carotid artery (ECA) (A, lateral view) and left vertebral artery (VA) (B, lateral view) angiograms obtained before GKS, demonstrating a dAVF at the transverse-sigmoid sinus junction with an arterial supply from the left occipital artery (OA) (long arrows in A) and branches of the left VA (short arrows in B). **C and D:** Intraoperative contrast-enhanced axial MR images showing the dAVF in the region of the left transverse-sigmoid sinus junction. **E and F:** Left ECA and left VA angiograms demonstrating complete obliteration of the dAVF without neurological complication 40 months after GKS.

age, sex, location of the lesion, and whether or not there was another previous treatment (Table 2).

In 10 patients, the residual fistula was evident on imaging studies 29 to 50 months (median 42 months) after GKS. Five of these patients underwent additional treatment, and obliteration of dAVF was achieved in all of them. One patient underwent a second GKS 38 months after the first treatment; and complete obliteration was confirmed 14 months after the second GKS (52 months after the initial one). In 2 patients, endovascular treatment was performed. In these 2 cases, the lesions were located at the transverse sinus and were accompanied by a diffuse arterial supply. Although these lesions did not disappear during the available follow-up period (44 months in 1 patient and 50 months in the other), the initial presenting symptom (tinnitus) resolved, and the fistula flow was reduced without any complication (Figs. 2 and 3). In both cases, the angioarchitecture of the dAVF became simpler

TABLE 2: Factors associated with obliteration of the dAVF after GKS

Factor	Hazard Ratio (95% CI) (multivariate analysis)	p Value
patient age > 60 yrs	1.06 (0.23–5.75)	0.94
patient sex	3.70 (0.10–133.5)	0.44
lack of CVD	29.7 (2.29–951.4)	0.007*
hemorrhage at presentation	28.7 (0.0002–0.70)	0.03*
target volume < 1.5 cm ³	40.5 (2.13–7670)	0.009*
location at transverse-sigmoid sinus junction region	0.05 (0.0008–1.45)	0.08
Cognard Type III or IV dAVF	31.3 (2.49–965)	0.005*
treated w/ GKS alone	1.06 (0.11–9.27)	0.95

* Significant at the level of $p < 0.05$.

after the initial GKS, but no further response of radiosurgery was expected. In 1 patient, the residual fistula consisted of a very small fistula with relatively slow flow, which could be safely treated with a simple transarterial embolization 55 months after the initial GKS. In another case, the residual fistula became rather small 46 months after GKS, but it was still accompanied by CVD. That

FIG. 3. Right ECA angiograms (lateral view). **A:** Angiogram revealing the transverse sinus dAVF with an arterial supply from the right OA and right MMA. This patient underwent radiosurgery alone. **B:** Angiogram depicting a residual lesion fed by the MMA (arrowheads) 44 months after treatment. **C:** Magnified angiogram. Following GKS, a reduction in flow from the arterial supply was achieved in this case, and the border between the transverse sinus and draining vein (arrows) was clearly defined. However, there was still cortical venous drainage. **D:** Angiogram demonstrating complete obliteration of the lesion 6 months after endovascular treatment was added to the therapeutic strategy (46 months after GKS).

FIG. 2. **A and B:** Right ECA angiogram (A) and axial MR image (B) selected from the dose plan, revealing a dAVF in the region of the transverse sinus. A margin dose of 20 Gy was prescribed for a 1.7 cm³ region. **C:** Right ECA angiogram (lateral view) depicting a residual fistula fed by the middle meningeal artery (MMA) (arrowheads) and draining into the vein of Galen via the pial vein (arrows) 52 months after the initial stereotactic radiosurgery. This patient underwent endovascular treatment using transarterial embolization 55 months after the initial GKS. **D:** Right common carotid artery angiogram (lateral view) demonstrating complete disappearance of the lesion 7 months after the additional therapy.

patient was treated with transvenous embolization with the expectation of an earlier response. Complete obliteration was achieved in both patients. Another 2 patients underwent open resection, and complete obliteration of the dAVF was confirmed immediately after treatment in both of them.

No patient exhibited a latency interval hemorrhage after GKS.

We reviewed previous reports of radiosurgery using GKS for dAVFs and summarized the results in Table 3.

Clinical Symptoms After GKS

In 9 patients who initially presented with clinical symptoms associated with dAVF (tinnitus in 6 patients and chemosis in 3 patients), the symptoms resolved in 7 patients following GKS (5 patients with tinnitus and 2 patients with chemosis). In 2 patients, the clinical symptoms remarkably improved but remained persistent because of a residual dAVF. No patient exhibited radiation-induced neurological deterioration after GKS during the follow-up period.

Discussion

In this study, we found GKS to be safe and effective, achieving sufficient neurological improvement and a Kaplan-Meier projected obliteration rate of 80% at 5

TABLE 3: Results of GKS for dAVF in previous reports*

Authors & Year	No. of Patients	Location of dAVF (no. of dAVFs)	Obliteration Rate (%)	No. of Patients w/ CVD	Median Margin Dose (Gy)	Median Target Vol (cm ³)	Median Clinical FU Period (mos)	Adverse Events
Guo et al., 1998	15	CS (15)	12 (80%)	6	NA	NA	12	none
Pollock et al., 1999	20	CS (20)	14 (70%)	4	20	2.8	36	1 recurrence of visual symptom
Koebbe et al., 2005	18	CS (10) T-S (4)	12 (67%)	4	20†	2.2†	43†	1 transient hemiparesis
Söderman et al., 2006	41	T-S (16) FT (12)	28 (68%)	36	22†	NA	24†	2 hemorrhage; 1 transient abducent nerve palsy; 1 transient focal anopia
Cifarelli et al., 2010	55	CS (4) T-S (16)	30 (54%)	39	21	NA	11.4 yrs	3 hemorrhage; 1 radiation-related event
Yang et al., 2010	40	CS (13) T-S (18)	28 (70%)	20	20	2.0	45	1 hemorrhage
present series	22	CS (3) T-S (9) FT (6)	12 (55%)	15	20	1.5	33	no hemorrhage; no radiation-related event

* CS = cavernous sinus; FT = falcotentorial region; FU = follow-up; NA = not available; T-S = transverse-sigmoid sinus junction.

† Mean value.

years. Higher obliteration rates could be expected without adverse events, especially in dAVFs with small volumes ($p = 0.009$) and hemorrhage at presentation ($p = 0.03$), which is in line with GKS for AVMs.²⁵ Even if total obliteration was not achieved, in 2 of our cases a marked reduction of arteriovenous shunt flow resolved the patients' presenting symptoms and the angioarchitecture of the lesions was simplified, which facilitated additional endovascular treatment. These results suggest that GKS can be a first line of treatment in the multidisciplinary treatment strategy used for dAVFs when significant morbidity is expected to be associated with other therapeutic options because of the location of the lesion and the draining pattern,^{5,19,24,26,30} regardless of the history of hemorrhage.

It is true that, in addition to the benefits of GKS for the treatment of dAVFs, there are some concerns we hold when we recommend this treatment to patients. During the last 2 decades, we have gradually learned a great deal about dAVFs, their natural history, and associated mechanisms that cause clinical symptoms. According to the literature, the risks of hemorrhage associated with dAVFs largely depend on the location and draining pattern of the fistula, the presence of CVD, and the galenic drainage.^{1,21,29} Among those factors, the presence of CVD on imaging studies is regarded to be an important sign, indicating very aggressive behavior on the part of the lesion, which requires early radical treatment. According to studies focused on hemorrhagic events, the annual risks of hemorrhage associated with dAVFs range from 3.7% to 8.9%,^{4,8,26,28,29} which are similar to those associated with intracranial AVMs. However, reported outcomes included patients who were treated only partially. When dAVFs with CVD presented with hemorrhage, the annual risk of hemorrhage was reported to range from 7.4% to 20%.^{4,27,28} Combined with the characteristics classified by Cognard

Type IV, the annual risk of a hemorrhagic event is raised to 27%.⁴ To immediately abolish these risks, which are not negligible, endovascular intervention^{2,10,11,21} or resection to occlude a single draining route is recommended.⁷ According to previous reports, a latency period of at least 6 months follows GKS before obliteration of the fistula.¹⁸ Therefore, GKS can be a good choice of therapeutic option for a dAVF with CVD when other treatments could significantly reduce the impending risk of hemorrhage but could not achieve total obliteration of the dAVF.

Conclusions

Gamma Knife surgery is a safe and effective treatment modality for dealing with dAVFs. It can be a first line of treatment in the multidisciplinary treatment strategy for dAVFs, especially when significant morbidity is anticipated with other therapeutic options. If the dAVF is accompanied by CVD, we have to be very careful in recommending GKS for the patient, given the expected natural history of such lesions and the possibility of other therapeutic options.

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: Hanakita, Shin. Acquisition of data: Hanakita, Koga. Analysis and interpretation of data: Hanakita, Igaki. Drafting the article: Hanakita. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hanakita. Administrative/technical/material support: Koga, Igaki. Study supervision: Koga, Shin, Shojima, Igaki, Saito.

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Address correspondence to: Shunya Hanakita, M.D., Department of Neurosurgery, University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. email: hanakita-s@umin.ac.jp.