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Long-term Outcomes of Gamma Knife Surgery for Posterior Fossa Arteriovenous Malformations

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Abstract

The long-term outcomes of gamma knife surgery (GKS) in patients with posterior fossa arteriovenous malformations (AVMs) were retrospectively analyzed in 82 patients followed up for more than 5 years to evaluate the efficacy and safety. The median AVM volume at GKS was 0.95 cm^3. The prescribed dose to the AVM margin was median 18 Gy with 1–18 isocenters. The actual complete AVM obliteration rate was 58.5% at 3 years and 78.0% at 5 years. The significant factors for higher complete obliteration rate were younger patient age and smaller maximum/minimum nidus diameter ratio. Two patients experienced hemorrhage caused by residual AVM rupture at 4 and 49 months. Twenty patients developed peri-nidal edema as an adverse radiation-induced reaction at median 13 months. One patient developed radiation-induced necrosis at 6.8 years. Neurological complication was observed in 12 patients and 6 patients remained with neurological dysfunction permanently. Larger nidus volume and location adjacent to an eloquent area significantly increased the risk of neurological complication. Pittsburgh radiosurgery-based AVM grading scale was significantly correlated with the outcome of neurological symptoms after GKS. GKS achieved acceptable and complete obliteration rate for posterior fossa AVM with relatively low risk of morbidity on neuroimaging and neurological symptoms for the long-term period after treatment. We recommend conformable and selective treatment planning to achieve both obliteration of the AVM nidus and preservation of neurological function.

Key words: arteriovenous malformations, posterior fossa, radiosurgery, gamma knife

Introduction

Intracranial arteriovenous malformations (AVMs) located in the posterior fossa are less common than supratentorial AVMs, accounting for 7–15% of all intracranial AVMs, but carry high risk of annual hemorrhage of 10–15%, and re-hemorrhage of 6–15%, almost 5-fold those of supratentorial AVMs.[1–4] Therefore, posterior fossa AVMs are generally treated with active therapy, such as microsurgical resection, endovascular embolization, stereotactic radiosurgery, or combinations of these procedures, if possible with acceptable risk.[1–4] However, these treatment procedures should be carefully selected, based on the characteristic neural structures in proximity to vital regions of the brain and the presence of complex hemodynamic anatomy within the infratentorial region which increase the pressure gradient in the AVM nidus and the rupture risk. The treatments are intended to reduce the risk of hemorrhage resulting from rupture of the AVM nidus and to preserve neurological functions, and less morbidity and mortality than that occurs in the natural course. Therefore, the optimal treatment for posterior fossa AVMs will depend on the characteristics of the individual patient. Surgical resection is believed to be hazardous, because of the high rates of surgical morbidity and low rates of complete resection, especially for AVMs located in the parenchyma of the brainstem.[4,5] The role of endovascular therapy is mainly an adjunctive therapy that reduces the blood flow and/or the volume of the malformation prior to resection or radiosurgery because endovascular treatment alone rarely leads to complete cure.[3,4] On the other hand, stereotactic radiosurgery has become an accepted treatment option with high obliteration rate and low risk for cerebral AVMs, but the long-term outcomes for patients with posterior fossa AVMs after radiosurgical procedures remain unclear.[2–4]

The present study retrospectively reviewed the outcomes of gamma knife surgery (GKS) in patients with posterior fossa AVMs to assess the efficacy and

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identify the potential factors affecting nidus obliteration and prevention of neurological deterioration in the long term after GKS.

Patients and Methods

This retrospective study included 82 patients, 54 men and 28 women aged from 13 years to 73 years (mean 43.3 ± 17.5 years), with intracranial AVM located in the posterior fossa including the brainstem and cerebellum followed up for more than 5 years at least with clinical and radiographical examinations, among 86 patients with posterior fossa AVMs who underwent GKS at Yokohama Rosai Hospital from February 1992 to December 2006. All patients were confirmed to have AVM nidus in the infratentorial region detected by cerebral angiography before the radiosurgical procedure.

Stereotactic radiosurgery was performed with the Leksell gamma unit (model B; Elekta Instrument AB, Stockholm, Sweden) and Gamma Plan treatment software or KULA dose-planning system (Elekta Instrument AB) using magnetic resonance (MR) imaging, computed tomography (CT), and cerebral angiography after fixation of the Leksell stereotactic G-frame. All treatments were performed in a single session.

The maximum nidus diameter and minimum nidus diameter which was the shortest distance perpendicular to maximum diameter were measured on axial, coronal, or sagittal MR imaging at the time of GKS treatment, and the maximum/minimum nidus diameter ratio was evaluated.

After the initial radiosurgical procedure, follow-up examinations with MR imaging were scheduled every 3 to 6 months and obtained directly or from referring physicians. We recommended cerebral angiography for the confirmation of complete AVM obliteration. If patients refused angiographic examination, AVM obliteration was defined based on only the findings of MR imaging. After the confirmation of AVM obliteration, follow-up MR imaging or CT was performed at every 6 months to 1 year to assess the development of radiation-induced complications. The end point of the follow-up period in this study was the date of the last follow-up examination, secondary radiosurgery for remnant AVM nidus demonstrated by angiography more than 3 years after initial GKS, or occurrence of latency-interval hemorrhage.

The prognostic factors for complete AVM obliteration, development of radiation-induced edema, and neurological dysfunction after GKS included age (continuous variable), sex (male or female), previous modified Rankin scale (mRS) score (continuous variable), history of hemorrhage (yes or no), prior microsurgery (yes or no), prior embolization (yes or no), nidus volume (continuous variable), maximum nidus diameter (continuous variable), maximum/minimum nidus diameter ratio (continuous variable), nidus location (eloquent or non-eloquent), venous drainage (deep or superficial), and prescribed marginal dose (continuous variable). The Pittsburgh radiosurgery-based AVM grading scale proposed by Pollock and Flickinger was determined using the published equation: AVM score = (0.1)* (AVM volume in cm^3) + (0.02)* (patient's age in years) + (0.3)* (AVM location: frontal or temporal, 0; parietal, occipital, interventricular, corpus callosum, or cerebellar, 1; or basal ganglia, thalamus, or brainstem, 2).[6]

Patient and AVM nidus characteristics at GKS are summarized in Table 1. Clinical presentation of the AVM included intracranial hemorrhage in 69, trigeminal neuralgia in 1, hemifacial spasm in 1, and incidental in 11. Prior partial resection of the AVM nidus and/or evacuation of intracranial hematoma were performed in 5 patients, and prior intravascular embolization in 11 patients, all with the AVM nidus

Table 1 Patient and AVM nidus characteristics

Characteristic	Value
Total no. of patients	82
Male/Female	54/28
Age (years), median (range)	45 (13–73)
Prior mRS	
0	11
1–5	71
History of hemorrhage	69
Procedures prior to gamma knife surgery	
Surgical resection	5
Embolization	11
Nidus location	
Medulla oblongata	3
Pons	11
Midbrain	13
Cerebellar vermis	20
Cerebellar hemisphere	35
Nidus volume (cm^3), median (range)	0.95 (0.03–22.9)
Maximum nidus diameter (cm), median (range)	1.7 (0.4–5.5)
Maximum/minimum nidus diameter ratio, median (range)	1.68 (1.13–5.00)
Aneurysm related to AVM	12

AVM: arteriovenous malformation, mRs: modified Rankin scale.

located in the cerebellum. The AVM was located in eloquent regions in the deep cerebellar nuclei in 20 patients, cerebellar peduncle in 13, and brainstem in 27. Spetzler-Martin AVM grading system classified the AVM as grade 1 in 14 patients, grade 2 in 37, grade 3 in 30, and grade 4 in 1. Median score of the Pittsburgh radiosurgery-based AVM grading scale was 1.42 (range 0.58–3.22). The target of radiosurgery was defined as the complete nidus, and the dose prescription depended on the nidus volume and location. The dose at the AVM margin was 12–25 Gy (median 18 Gy) delivered to the median 50% (range 40–90%) isodose curve surrounding the nidus, and the maximum dose was 15–50 Gy (median 36 Gy) with 1–18 (median 3) isocenters. The follow-up period after GKS ranged from 5 years to 18.3 years (mean 7.7 years, median 6.1 years).

All statistical analyses were calculated using the statistical package for predictive analytics software (PASW Statistics version 17.0, SPSS Inc., Chicago, Illinois, USA). The significant factors affecting complete AVM obliteration, and development of radiation-induced edema and neurological deterioration associated with the radiosurgical procedure were calculated using the Mann-Whitney U test for univariate analysis and logistic regression model for multivariate analysis. Cumulative survivals for AVM obliteration and preservation of neurological function after GKS were estimated using the Kaplan-Meier method and compared using the log-rank test. A probability value of less than 0.05 was considered to be statistically significant.

Results

Complete obliteration of the AVM nidus was confirmed in 65 patients at an estimated median time of 2.2 years (range 0.5–5.3 years) after GKS, using angiography in 41 patients and only MR imaging in 24 patients. Among 46 patients who underwent both angiography and MR imaging, 5 patients had residual nidus on angiogram despite complete disappearance on MRI. The actuarial complete obliteration rate was 58.5% and 78.0% at 3 and 5 years, respectively (Fig. 1). The obliteration rate at 3 years and 5 years was 58.3% and 83.3% for brainstem AVMs, and 58.5% and 78.0% for cerebellar AVMs, respectively. The difference was not statistically significant ($p = 0.602$). Partial reduction was also found on neuroimaging, and 5 patients underwent second GKS for the remaining AVM nidus at 3–4.3 years after initial radiosurgery. Of these 5 patients, 2 patients had complete AVM obliteration at 3 years and 3.2 years after repeat GKS.

Univariate analysis indicated that younger age, smaller maximum/minimum nidus diameter ratio, smaller nidus volume, and larger marginal dose were significantly correlated with complete obliteration. Furthermore, multivariate analysis showed that younger age and smaller maximum/minimum

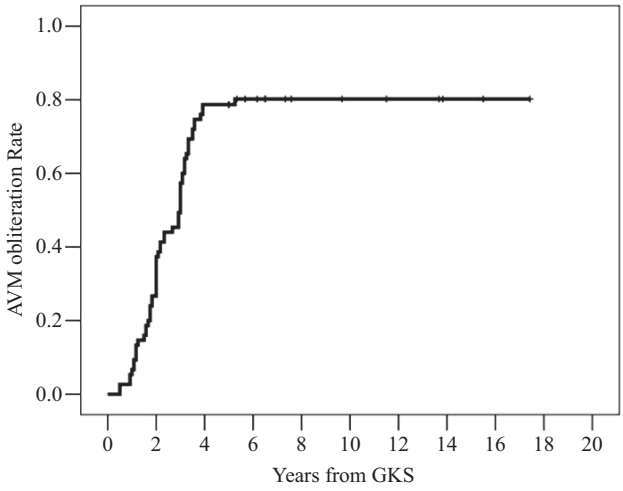

Fig. 1 Graph showing the Kaplan-Meier survival curve for the cumulative complete arteriovenous malformation (AVM) obliteration rate following gamma knife surgery (GKS) for posterior fossa AVMs. The actuarial rate of complete AVM obliteration was 58.5% and 78.0% at 3 and 5 years, respectively.

Table 2 Factors affecting AVM nidus obliteration after gamma knife surgery

Factor (tested for favorable outcome)	Univariate p value*	Multivariate p value**
Age (low)	0.015†	0.019†
Sex (male)	0.212	0.624
Previous mRS score (low)	0.419	0.368
Prior hemorrhage (no)	0.820	0.600
Prior microsurgery (no)	0.999	0.999
Prior embolization (no)	0.823	0.890
Nidus volume (small)	0.025†	0.704
Maximum nidus diameter (small)	0.274	0.532
Maximum/minimum nidus diameter ratio (small)	0.023†	0.029†
Nidus location (non-eloquent)	0.056	0.065
Venous drainage (superficial)	0.930	0.157
Marginal dose (large)	0.039†	0.888

*Mann-Whitney U test, **logistic regression analysis. †Significant difference at $p < 0.05$. AVM: arteriovenous malformation, mRS: modified Rankin scale.

nidus diameter ratio were significantly correlated with complete obliteration (Table 2). On the other hand, Spetzler-Martin grade had no significant correlation with complete obliteration.

Hemorrhage caused by rupture of the treated AVM nidus after GKS was seen in two patients. One patient with the AVM nidus located in a cerebellar hemisphere suffered sudden onset of loss of consciousness with intracranial hemorrhage 4 months after GKS, and underwent microsurgical resection of the AVM nidus and hematoma. Cerebellar ataxia became permanent after surgical treatment. The other patient had a small quantity of subarachnoid hemorrhage found incidentally on follow-up neuroimaging at 49 months after GKS. Repeat GKS was performed 2 months after disappearance of the hemorrhage on MR imaging and AVM nidus obliteration was confirmed with angiography at 36 months after second GKS. Annual bleeding risk after GKS was 1.2% at 1 year and 0.49% at 5 years.

Twenty patients (24.4%) developed peri-nidal edema, which appeared as increased white matter intensity on T2-weighted MR imaging, representing an adverse radiation-induced reaction at median 13 months (range 4–41 months) after GKS. All these findings had reversed within 5–140 (median 12) months, excluding 6 patients at the last follow-up examination. One patient with AVM located in a cerebellar hemisphere experienced radiation-induced necrotic change appearing as an abnormal enhancing mass with hematoma on CT in the irradiated region at 6.8 years after GKS and 4 years after angiographic confirmation of AVM nidus obliteration. No radiation-induced cyst formation or neoplasm was detected during the follow-up period. The significant factors affecting development of radiation-induced edema after GKS was larger nidus volume by uni- and multivariate analyses (Table 3). Among 20 patients who showed radiation-induced edema after GKS, 12 patients developed new neurological deficits at 3–43 months (median 12 months) after GKS. Cumulative survival rate for preservation of neurological function after GKS was 86.6% at 3 years (Fig. 2A). Of these 12 patients, 6 patients experienced transient neurological dysfunction including trigeminal dysesthesia in two, cerebellar ataxia in three, and hemiplegia in one. Six patients suffered permanent deficits including trigeminal dysesthesia in two, hemiplegia in one, and cerebellar ataxia with deterioration of mRS in three. The significant factors affecting prevention of neurological dysfunction after GKS were smaller nidus volume and non-eloquent location at treatment by uni- and multivariate analyses (Table 4). On the other hand, AVM nidus with Pittsburgh radiosurgery-based AVM grading scale score of less than 1.42, the median value in this study, was associated with significantly better neurological outcome ($p = 0.007$) (Fig. 2B).

Table 3 Factors affecting development of radiation-induced edema after gamma knife surgery

Factor (tested for favorable outcome)	Univariate p value*	Multivariate p value**
Age (high)	0.659	0.423
Sex (female)	0.328	0.070
Previous mRS score (high)	0.337	0.092
Prior hemorrhage (yes)	0.207	0.124
Prior microsurgery (yes)	0.999	0.999
Prior embolization (yes)	0.657	0.275
Nidus volume (large)	0.046†	0.021†
Maximum nidus diameter (large)	0.411	0.844
Maximum/minimum nidus diameter ratio (large)	0.910	0.490
Nidus location (eloquent)	0.260	0.216
Venous drainage (deep)	0.433	0.126
Marginal dose (small)	0.914	0.287

*Mann-Whitney U test, **logistic regression analysis. †Significant difference at $p < 0.05$. mRS: modified Rankin scale.

Discussion

This study showed that the overall obliteration rates of posterior fossa AVMs at 3 years and 5 years after radiosurgery with marginal dose of 18 Gy were 58.5% and 78.0%, respectively. The lower obliteration rates compared to the published results for intracranial AVMs in the literature (65–94% at 2–5 years) are attributed to the relatively low marginal dose in the present series.[7,8] The obliteration rates for brainstem AVMs (58.3% at 3 years and 83.3% at 5 years) are comparable to those reported in the literature (50–76% at 3–6 years).[9–19] Those results included the cases demonstrated AVM obliteration with only MR imaging which provided false-negative rate of 17.2% in this study. Therefore, we should take a notice of the possibility of overestimation for these obliteration rates, as past reports.[20,21] Univariate analysis showed that smaller nidus volume and larger marginal dose were significantly related to complete AVM obliteration as in past reports of radiosurgical procedures for intracranial AVM,[7,8,22,23] but multivariate analysis indicated only smaller maximum/minimum diameter ratio and younger age

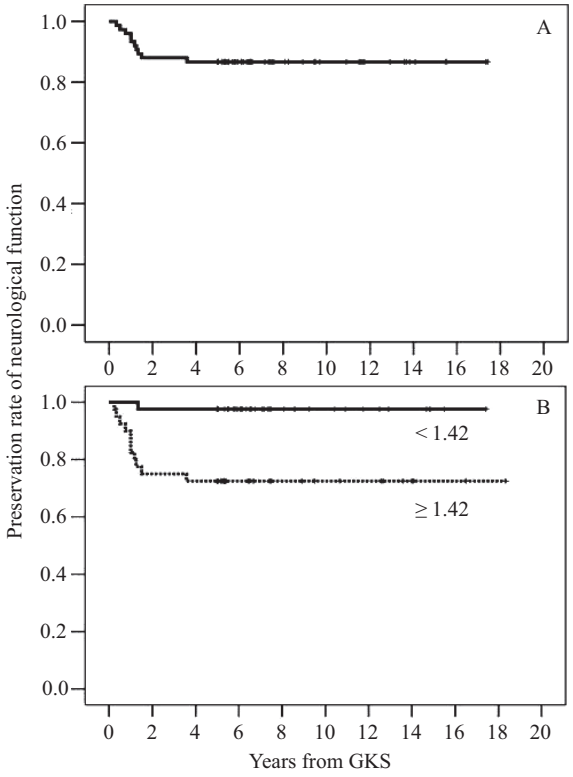

Fig. 2 Graphs showing the Kaplan-Meier survival curves for the cumulative preservation rate of neurological functions after gamma knife surgery (GKS) for posterior fossa arteriovenous malformations (AVMs). A: The actuarial rate of prevention of clinical deterioration was 86.6% at 3 years for all patients. B: Patients with AVM with Pittsburgh radiosurgery-based AVM grading scale score of less than 1.42, the median value in this study, is associated with significantly better neurological outcome (p = 0.007).

were favorable factors for complete AVM obliteration. AVM nidus with smaller ratio of maximum/minimum nidus diameter represented a more compact and spherical lesion, and identification of such AVM margin was relatively easy, resulting in higher obliteration rate. On the other hand, larger ratio of maximum/minimum nidus diameter tended to represent an irregular and extended lesion, and the confirmation of such AVM margin was relatively difficult and the treatment plan resulted in lower obliteration rate. Therefore, this study showed that the maximum/minimum nidus diameter ratio indicated the configuration of the AVM nidus and the difficulty of identification of the AVM margin, and this factor consequently might reflect the lower complete AVM obliteration rate in this study after GKS, compared to intracranial AVMs, regardless of the nidus volume at GKS or the prescribed radiological dose.

Table 4 Factors affecting prevention of neurological dysfunction after gamma knife surgery

Factor (tested for favorable outcome)	Univariate p value*	Multivariate p value**
Age (low)	0.991	0.312
Sex (male)	0.554	0.330
Previous mRS score (low)	0.111	0.405
Prior hemorrhage (no)	0.355	0.770
Prior microsurgery (no)	0.999	0.999
Prior embolization (no)	0.581	0.365
Nidus volume (small)	0.009†	0.046†
Maximum nidus diameter (small)	0.516	0.159
Maximum/minimum nidus diameter ratio (small)	0.320	0.911
Nidus location (non-eloquent)	0.002†	0.040†
Venous drainage (superficial)	0.913	0.342
Marginal dose (large)	0.749	0.799

*Mann-Whitney U test, **logistic regression analysis. †Significant difference at $p < 0.05$. mRS: modified Rankin scale.

In the present series, peri-nidal edema was detected on T_2-weighted MR imaging in 24.4% of cases, comparable to 30% in other series.[17] On the other hand, preservation of existing neurological function before GKS was satisfactory, with a total neurological complication rate of 14.6%, compared to 6.9–11% in recent reports of radiosurgery for intracranial AVMs.[7,8] AVM nidus with larger volume and location adjacent to eloquent areas were prognostic factors for worse clinical status after GKS. Therefore, the Pittsburgh radiosurgery-based AVM grading scale reflecting nidus volume and location were valuable for predicting the occurrence of neurological complications in our series, and we recommend use of this grading scale. We think that AVM nidus normally incorporates normal brain tissue and a relatively wide region of eloquent area adjacent to the AVM nidus might be irradiated with more than the tolerable radiological dose. In addition, the tolerable dose for this area may be reduced because of damage caused by the mass effect of the AVM nidus and/or prior hemorrhage, and the eloquent area contiguous to the AVM nidus might be easily injured by radiosurgery. We presumed that the relatively lower neurological complication rate in our series was due to the avoidance of eloquent areas by highly selective dosimetry and controlled lower-than-standard radiation dose. Therefore, there exists a trade-off between the risk of long-term complications including radionecrosis and cyst formation

which are functions of the irradiated dose and the risk of hemorrhage from incompletely obliterated nidus.[24,25] Nonetheless, we believe that patients with posterior fossa AVM benefit from radiosurgery using lower-than-standard radiation dose. Our results strongly support that the risk of hemorrhage from residual AVM is sufficiently offset by the decreased risk of radiation-induced adverse effects, and the overall prognosis for neurological status is far better compared to that of the natural history.

GKS in our series was performed almost 5–20 years ago using the conventional radiological method with two-dimensional imaging providing lower spatial analysis functions, whereas modern radiosurgery has improved with high-resolution neuroimaging and advanced planning software. We expect improvement of the obliteration rate and decrease of the neurological complication in the future. Furthermore, the incidental detection of asymptomatic posterior fossa AVM may increase with the wider availability of high-quality diagnostic imaging. GKS may become more beneficial as the initial or adjuvant treatment following microsurgical resection and/or endovascular embolization as a method of minimally invasive treatment.

GKS achieved good complete obliteration rate for posterior fossa AVMs on follow-up radiological imaging with low neurological complication rate in the long term. More compact and spherical AVM nidus with smaller maximum/minimum diameter ratio could be effectively irradiated and obliterated, but we should be careful of posterior fossa AVMs adjacent to eloquent areas, which is an unfavorable prognostic factor for the development of neurological deterioration after GKS. Therefore, we recommend conformable and selective radiosurgical planning for posterior fossa AVM nidus, considering preservation of neurological function after GKS in addition to complete obliteration.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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