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CLINICAL ARTICLE

Prognostic Factors of Gamma Knife Radiosurgery for Cerebral Arteriovenous Malformation : The Results from 218 Consecutive Patients

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Objective: We retrospectively evaluated our experience of the management and long-term outcomes of gamma knife radiosurgery (GKRS) on arteriovenous malformation (AVM) as a primary treatment as well as adjunct therapy. GKRS is widely used in many centers worldwide for the management of AVM. However, the long-term results of GKRS are not well known. In the present study, we retrospectively evaluated our experience of focusing on prognostic factors in the management and long-term outcomes of GKRS on AVM.

Materials and Methods: We performed a retrospective review of 218 patients. They were treated with GKRS in our institute from 2007 to 2013. The group included first-time GKRS for cerebral AVM, previous surgical resection, and embolization, excluding previously GKRS-treated patients. We analyzed the association between several factors (gender, age, marginal dose, hemorrhage, marginal dose, nidus volume) and the obliteration rate, which was the cumulative obliteration rate regardless of additional treatment, including repeat GKRS.

Results: The univariate analysis of our study identified that a high radiation dose [margin dose >16.0Gy (50%), p=0.017] rather than a low radiation dose [margin dose ≤16.0Gy (50%)] and small AVM volume (≤15.0mL, p=0.003) rather than large AVM volume (>15.0mL) were positive predictors of AVM nidus obliteration. Our study showed that young age (≤18 years) had a better obliteration rate compared with others (>18 years) in AVM after GKRS (p=0.053). Our findings did not show that gender (p= 0.427) or hemorrhage (p=0.191) had significant effects on nidus obliteration. Comparison of our results with prior studies showed that AVM volume and margin radiation dose had a significant role in the obliteration rate in common.

Conclusion: We suggest that AVM with a small volume can be considered good indications for GKRS, and a higher marginal dose [margin dose >16.0Gy (50%)] can be an effective factor for higher obliteration with the carefulness of post-radiosurgical complications. Finally, we can expect favorable GKRS results for appropriately selected AVMs in the young population.

KEY WORDS: Arteriovenous malformation (AVM) · Gamma knife radiosurgery (GKRS) · Obliteration rate · Prognostic factors.

INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are pathologic vascular lesions found in children and adults with a prevalence in adults of approximately 18 per 100,000.[1)] AVM is defined by an abnormal connection between the venous and arterial circulation, resulting in an arteriovenous shunt and the gross appearance of a tangle of blood vessels.[1)] The angioarchitecture of these lesions puts them at risk of hemorrhage as well as subjecting the adjacent parenchyma to the potential for ischemia and seizure.[1)5)] AVM has an annual hemorrhage rate of 2−3% that persists as long as the lesion exists.[1)3)5)] Management of these lesions can be observational, although lesion obliteration is typically considered to mitigate these risks.[1)]

Over the last decades, the management options for arteriovenous malformations (AVM) have expanded.[2)] Although microsurgical resection has been used as the primary treatment option, stereotactic radiosurgery and embolization have been established as effective treatment options for AVM.[2)5)10)] Moreover, recent advances in imaging technology and computerized radiation dose planning have improved the outcomes of radiosurgery.[2)] Gamma knife radiosurgery (GKRS) has emerged as a popular treatment tool for AVMs without the immediate risk of hemorrhage.[23)] GKRS is widely used

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in many centers worldwide for the management of AVM.[2)]

GKRS is usually applied as a single treatment for small AVMs (<3 cm) as well as a part of multimodal therapy in combination with microsurgical resection and embolization for large AVMs.[2)] Evidence from the literature reveals that GKRS had a significant impact on the obliteration of the AVM nidus in 65−94% patients over a 5-year observation interval.[2)] GKRS has been associated with a low risk of radiation-related complications, even for lesions located in areas that are difficult to access via microsurgery.[2)] However, little information is available regarding the intermediate or long-term outcomes of GKRS on AVM.[2)] In the present study, we retrospectively evaluated our experience, focusing on prognostic factors in the management and long-term outcomes of GKRS on AVM.

MATERIALS AND METHODS

A total of 218 patients were treated with GKRS in our institute from 2007 to 2013. The group included first-time GKRS for cerebral AVM, previous surgical resection, and embolization excluding previously GKRS-treated patients. We analyzed the correlation between several factors (gender, age, marginal dose, hemorrhage, marginal dose, nidus volume) and the obliteration rate, which was the cumulative obliteration rate regardless of additional treatment, including repeat GKRS.

Statistical analysis

Various factors that may affect the outcome were analyzed. Descriptive statistics is demonstrated as mean, median, standard deviation (SD), percentages, and range. Kaplan-Meier method and log-rank analysis were used for actuarial rates of outcome and related factors. Multivariate analyses were performed by using a Cox regression analysis. All analyses were performed using commercially available statistical software SPSS Statistics (version 21.0 ; IBM Co., Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Patients' demographics

The characteristics of the patients are listed in Table 1. Out of the 218 patients, 127 (58.3%) were men and 91 (41.7%) were women. Forty-five patients were younger than 18 years old at the time of GKRS. One hundred and thirteen (51.8%) patients had a history of prior ruptured hemorrhage. The AVM volume of 181 patients was ≤15.0mL, and that of the others was >16mL. The marginal dose for the AVM of 114 (52.3%) patients was ≤16.0Gy(50%), and that of 104 (47.7%) patients was >16.0Gy.

Table 1. Characteristics in 218 patients with intracranial AVM treated with GKRS

	Number	Percent (%)
Age		
≤18 yrs	45	20.6
>18 yrs	173	79.4
Gender		
Male	127	58.3
Female	91	41.7
Hemorrhage		
Ruptured	113	51.8
Unruptured	105	48.2
Margin dose		
≤16.0Gy (50%)	114	52.3
>16.0Gy (50%)	104	47.7
AVM voulme		
≤15.0mL	181	83.0
>15.0mL	37	17.0

AVM : arteriovenous malformation, GKRS : gamma knife radiosurgery

GKRS technique and treatment planning

The Leksell Gamma Knife model C was used until October 2008, when the Leksell Gamma Knife Perfexion (Elekta Instruments, Inc.) replaced it. Treatment planning was based on biplane digital subtraction angiography and magnetic resonance imaging (MRI). The MRI protocol includes T1 gadolinium-enhancing and T2 thin section, as well as time of flight (TOF) angiographic images if needed. The radiosurgical target was defined compactly to minimize complications using both imaging modalities. We performed dose control at the major artery, avoiding high-dose radiation, which was able to reduce the chance of cerebral infarction.

Follow-up evaluation

In our studies, the AVM obliteration was confirmed by MRI (6 months, 2 years, 3 years), computed tomography angiography (CTA) (1 year), and cerebral angiography (waiting up to 3 years after GKRS). If needed, repeated GKRS 2−3 years after previous GKRS was performed. The actuarial obliteration rate of the AVM was calculated using the Kaplan-Meier curve. The median duration of follow-up was 24.0 months (range : 6−77).

RESULTS

We analyzed the association between several factors, including gender, age, hemorrhage, margin dose, and AVM volume, with the obliteration rate of the nidus. The results of AVM obliteration after GKRS are below Fig. 1.

Following a single GKRS procedure, 152 (69.7%) of 218 patients still had a residual nidus shown on MRI or angiography. Additionally, 17 patients harboring residual AVMs underwent repeat GKRS, and a total AVM obliteration was identified in 5 of these patients. After all, in 71 (32.6%) patients, obliteration of the nidus was identified on follow-up angiography (60 patients) and MRI (11 patients). Clinical follow-up greater than 3 years was in 75 patients (34.4%), and 42 of these patients were confirmed as a total obliteration on both angiography and MRI. The actuarial angiographic or MRI obliteration rate was 10.64% at 24 months, 26.1% at 36 months, and 66.6% at 60 months, respectively (Fig. 1). Our overall obliteration rate was 32.6% through the follow-up duration (mean 33.8±2.7 months).

Factors related to AVM obliteration

The results of factors related to AVM obliteration after GKRS are below Fig. 2. Statistical analysis demonstrated that a margin dose of more than 16.0Gy (50%) showed statistical significance for better AVM obliteration (Log Rank p=0.017).

Small nidus volume (Log Rank p=0.003) was also associated with increased AVM obliteration. Gender (Log Rank p=0.427) and hemorrhage (Log Rank p=0.191) were not related to nidus obliteration. In our study, a younger age (Log Rank p=0.053) showed some association with AVM obliteration.

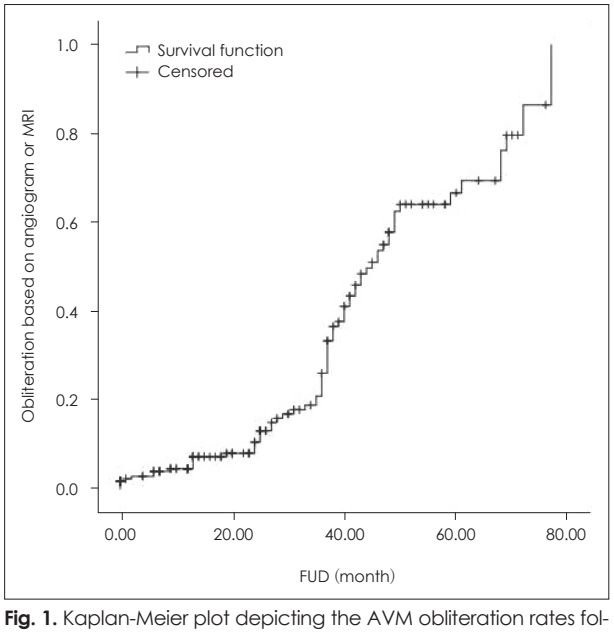

Fig. 1. Kaplan-Meier plot depicting the AVM obliteration rates following GKRS in the present series.

Statistical analysis demonstrated that gender (Log Rank p=0.427) was not related to AVM obliteration. Age (Log Rank p=0.053) was relatively associated with AVM obliteration. The mean time for obliteration was 41.1±3.6 months at ≤18 years and 49.7±2.3 months at >18 years. The younger group showed a shorter obliteration time. The mean time for the obliteration of ruptured AVM was 44.7±3.1 months, and that of unruptured AVM was 50.4±2.6 months. Hemorrhage (Log Rank p=0.191) was not related to nidus obliteration. Our study showed that a high median marginal dose [>16.0Gy (50%)] rather than a low median marginal dose [≤16.0Gy (50%)] was significantly associated with an increased rate of AVM obliteration (Log Rank p=0.017). The group with the >16.0Gy (50%) marginal dose had a shorter obliteration time (41.5±2.8 months) than the one with ≤16.0Gy (50%) (51.7±2.6 months). Small volume (≤15.0mL) rather than large volume (>15.0mL) revealed a significant statistical difference of AVM obliteration (Log Rank p=0.003). The mean time for the obliteration of small volume (≤15.0mL) was 44.4±2.2 months, and that of large volume (>15.0mL) was 59.1±3.3 months. In multivariate analysis, only small nidus volume (p=0.045) was significantly associated with increased rate of AVM obliteration (Table 2).

Complication associated with treatment

Overall, a post-GKRS complication was recorded for 40 patients (18.3%). Posttreatment hemorrhage occurred in 12 patients (5.5%), 1 of whom was brain death after emergency hematoma removal. Eight (3.7%) patients developed brain edema and seven (3.2%) patients developed GKRS related cyst formation. One of 7 patients having brain cyst underwent Ommaya reservoir insertion. Four (1.8%) patient had newly developed post-GKRS seizures and two (0.9%) had preexisting seizures. Hydrocephalus, paresthesia on limbs, memory impairment, radiation necrosis, character change, and cerebral infarction were developed in each one (0.5%) patient. The patient with hydrocephalus recovered his heath after a ventriculoperitoneal shunt. In addition to being mentioned, there were not in life-threatening conditions. Most of them had responded to conservative treatment.

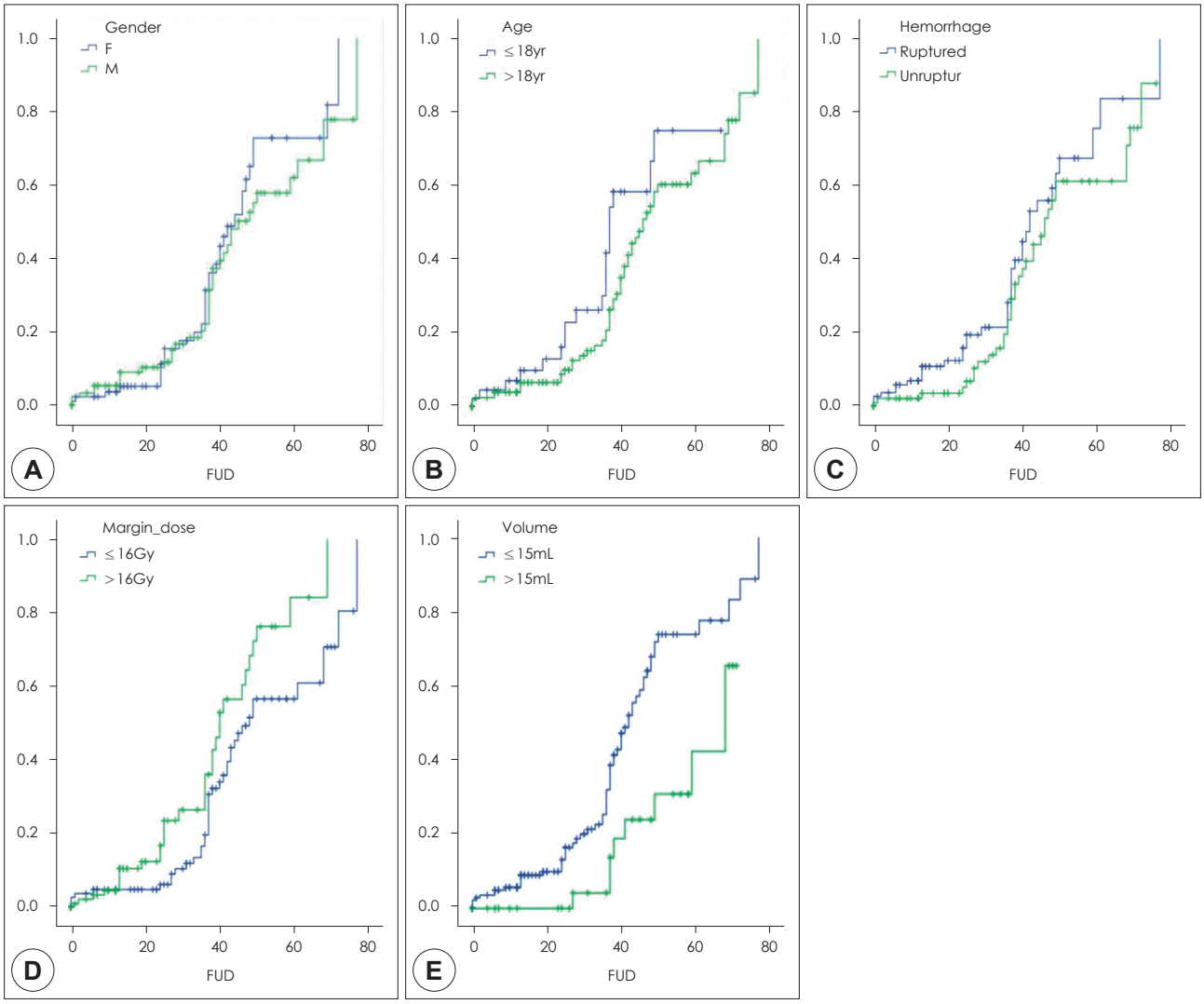

Fig. 2. Kaplan-Meier plot demonstrating the obliteration rates of the patient population throughout the follow-up period (months). (A) Gender (the mean time for obliteration was 49.2±2.9 months at male and 45.8±2.8 months at female) (B) age (the mean time for obliteration was 41.1±3.6 months at ≤18 years and 49.7±2.3 months at >18 years) (C) hemorrhage (the mean time for obliteration was 44.7±3.1 at ruptured cases and 50.4±2.6 at unruptured cases) (D) margin dose [the mean time for obliteration was 51.7±2.6 at ≤16.0Gy (50%) and 41.5±2.8 at >16.0Gy (50%)] (E) volume [the mean time for the obliteration was 44.4±2.2 months at small volume (≤15.0mL) and 59.1±3.3 months at large volume (>15.0mL)].

DISCUSSION

AVM radiosurgery is a well-established strategy for AVMs. Despite the risk of post-radiolosurgical complications, including the risk of a latency-interval hemorrhage, delayed cyst formation, and radiation-induced normal brain tissue damage.[22] GKRS is considered an effective, safe, and minimally invasive treatment option for AVM obliteration. However, the risk-benefit profile of GKRS on AVM is not well understood. Here, we retrospectively evaluated our experience of the long-term outcomes of GKRS on AVM, including obliteration of the nidus after GKRS and prognostic factors affecting the outcomes in patients with AVM. GKRS on AVM has a protective effect against the risk of future hemorrhage and helps the majority of AVM patients continue their normal daily activities. The obliteration of the AVM nidus and absence of any signs or symptoms are the treatment goals of GKRS for AVM. Many studies on GKRS for AVM suggest that the obliteration rate is 65−94%.16,17,20 This obliteration can be accomplished within 2−3 years with some exceptions, where it may require 3−5 years to obliterate the nidus.[7]

Yen, et al. showed various factors related to nidus obliteration, such as female gender, age, pre-GKRS embolization,

AVM volume, location, deep-draining vein, single-draining vein, margin dose, maximum dose, isodense line, isocenters, radiation-induced changes, and radiosurgery-based AVM score.[23] Their univariate analysis demonstrated that high margin dose (p=0.042), high maximum dose (p=0.035), deep-drain vein (p=0.042), and small nidus volume (p=0.015) were associated with increased AVM obliteration rate. Sex, age, prior embolization, locations of nidi, radiosurgery-based AVM scores, single-draining vein, isodose line, number of isocenters, and presence of radiation-induced imaging changes were not related to nidus obliteration.[23] Bir, et al. identified female sex (p=0.04) and Spetzler-Martin Grade I-III (p=0.002) as positive predictors of AVM nidus obliteration, but history of hemorrhage and history of embolization did not affect nidus obliteration. Some studies said that nidus volume is a critical factor that impedes the complete obliteration of AVMs.[13][15] The lowest dose delivered to the AVM is an important factor related to the obliteration rate.[13] It is relatively easy to deliver an insufficient radiation dose to the nidus of a large AVM, and the operator wants to avoid adverse radiation effects (ARE).[14][15] The above studies showed that AVM nidus volume and radiation dose had the effect on nidus obliteration in common.

Table 2. Prognostic factors for obliteration of nidus

Factor	Mean time for obliteration (month)	Univariate analysis (p value)	Multivarite Analysis (p value)
Gender			
Male	49.2±2.9	p=0.427	p=0.672
Female	45.8±2.8		
Age			
≤18yr	41.1±3.6	p=0.053	p=0.292
>18yr	49.7±2.3		
Hemorrhage			
Ruptured	44.7±3.1	p=0.191	p=0.670
Unruptured	50.4±2.6		
Margin dose			
≤16.0Gy (50%)	51.7±2.6	p=0.017	p=0.128
>16.0Gy (50%)	41.5±2.8		
Volume			
≤15.0mL	44.4±2.2	p=0.003	p=0.045
>15.0mL	59.1±3.3		

p<0.05 is considered as signigicant

In this study, we had an interest in the young age effect on the AVM obliteration rate as a prognostic factor. The optimal management of unruptured AVMs in pediatric patients is now incompletely understood.[9] A Randomized Trial of Unruptured Brain AVMs (ARUBA) was a prospective, randomized controlled trial that showed superior outcomes with medical management compared with intervention for patients with unruptured AVMs.[18] However, pediatric patients (aged less than 18 years) were specifically excluded from ARUBA. Therefore, the efficacy of radiosurgery for unruptured pediatric AVMs is poorly understood.[9] From our review of the major series, the reported obliteration rates derived from retrospective studies of pediatric patients vary widely, ranging from 45% to 84% in studies reporting 3-year radiographic outcomes.[4][6][8][11][12][19][21][24][25]

We evaluated several factors, gender, age, hemorrhage, margin dose, and AVM volume, with the obliteration rate of the nidus. The univariate analysis of our study identified that a high radiation dose (margin dose >16.0Gy (50%), p=0.017) rather than a low radiation dose [margin dose ≤16.0Gy (50%)] and small AVM volume (≤15.0mL, p=0.003) rather than large AVM volume (>15.0mL) were positive predictors of AVM nidus obliteration. Our study showed that young age (≤18 years) had a better obliteration rate compared with others (>18 years) in AVM after GKRS (p=0.053). Our findings did not show that gender (p=0.427) or hemorrhage (p=0.191) had significant effects on nidus obliteration.

Comparison of our results with prior studies showed that AVM volume and margin radiation dose had a significant role in the obliteration rate in common. However, the age effect as a prognostic factor is not well defined. Yen, et al.[23] and Bir, et al.[2] showed that age was not related to nidus obliteration (Table 3). Previous studies reported a lower obliteration rate for GKRS in young-age AVM because the young

Table 3. Summary of published prognostic factors associated with obliteration of AVM Gamma Knife radiosurgery

	Patients, N	Volume (p value)	Age (p value)	Gender (p value)	Hematoma presentation (p value)	Margin dose (p value)
Yen et al.,[23] 2014	31	**0.015**	0.619	0.778	NR	**0.042**
Borcek et al.,[3] 2014	58	**0.018**	0.584	**0.049**	**0.049**	NR
Bir et al.,[2] 2015	85	NR	NR	**0.04**	0.24	NR
Ding et al.,[9] 2015	51	**0.001**	NR	NR	NR	**<0.0001**
Present study, 2015	218	**0.003**	0.053	0.427	0.191	**0.017**

NR : not reported, Values that appear in boldface are statistically significant at p<0.05

ages had a more aggressive flow-dynamic tendency and more diffuse nidus anatomy than old ages. On the other hand, our study showed that young age (≤18 years) tended to have a better obliteration rate (p=0.053).

To explain this, we consider the possibility that our study could have selection bias. Nonetheless, this result suggests that GKRS can provide an effective management option for appropriately selected AVMs in the young population.

The limitations of this study include its retrospective nature and the lack of a control group, which confines us in assessing the full benefits and complications of GKRS.

CONCLUSION

Although surgical resection is known to be the gold standard for the treatment of AVM, GKRS for AVM is also a well-established treatment option with an obliteration rate of approximately 70−80% if surgical resection is not feasible. In our study, the overall obliteration rate increased in AVMs with small volumes (≤15.0mL), higher marginal dose (margin dose >16.0Gy (50%)), and young age (≤18 years). The obliteration rates were 10.6% at 24 months, 26.1% at 36 months, and 66.6% at 60 months, respectively.

We suggest that AVM with a small volume can be considered good indications for GKRS, and a higher marginal dose (margin dose >16.0Gy (50%)) can be an effective factor for relative higher obliteration with the carefulness of post-radiosurgical complications.

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