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Original Investigation

Gamma Knife Radiosurgery for Arteriovenous Malformations: Clinical Series of 199 Patients

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ABSTRACT

AIM: Cerebral arteriovenous malformations (AVM) are pathological connections between arteries and veins without capillaries. Stereotactic radiosurgery (RS) is a proven and accepted treatment method for cerebral AVMs. Our objective was to analyze the factors influencing the clinical outcome in patients suffering from AVMs.

MATERIAL and METHODS: We retrospectively reviewed 199 patients who were treated with Gamma-Knife RS for intracranial AVMs between 13 October 2005 and 31 October 2010. There were 89 male, 110 female patients with a median age of 32 years (range, 3-74 years). Obliteration was assessed with MRI angiography and DSA imaging.

RESULTS: Complete obliteration rate after RS was 71 % (141 out of 199), including second RS treatments. In terms of obliteration rates, there was no significant difference between patients younger and older than 21 years old ($p=0.669$). After RS, 3 patients died due to intracranial hemorrhage and 1 died of heart disease. Death from AVM was determined as 1.5 %. Intracranial hemorrhage was observed in 7 (3.5 %) patients post-RS.

CONCLUSION: Obliteration was found to be associated with Spetzler-Martin Grade, Pollock-Flickinger Grade, AVM volume, RS dose, bleeding history before RS and no previous embolization before RS. Gamma knife RS is an effective treatment method for the treatment of AVMs both for pediatric and adult patients. It provides high obliteration and low mortality rates.

KEYWORDS: Arteriovenous malformations, Radiosurgery, Gamma Knife

INTRODUCTION

Cerebral arteriovenous malformations (AVM) are congenital and benign lesions detected in generally young and healthy individuals. AVMs are pathological connections between arteries and veins without capillaries (2,8,12,17,21,26,31). The prevalence of AVMs in general population is 1.4-4.3% (1,11,16,18,29), with a spontaneous hemorrhage risk of 2-5% in untreated AVMs, and 0.7-1% annual mortality rate (7,23,42). Permanent morbidity risk is 2-3% and annual mortality risk is 1% (8,30). Additionally, AVMs may cause headache, seizures and progressive neurological deficits due to ischemia of surrounding brain tissue, with

considerable effects on the patient's work activity and quality of life (8,17,22,30).

AVMs can be treated with microsurgery, stereotactic radiosurgery (RS) and endovascular embolization (8). Surgical removal is the initial treatment of choice in appropriate patients as it removes immediate relief from hematoma in ruptured AVMs and decreases the bleeding risk (3,8,38). However, rates of permanent morbidity and mortality related to microsurgery range between 3.9-25% and 0.7-4.2%, respectively (3,4,8,12,15,19,20,24,25).



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Stereotactic RS is a proven and accepted treatment method for cerebral AVMs (7,9). Indeed, SRS constitutes an important alternative for the treatment of AVMs in surgically inoperable areas with low side effects. Various studies have shown AVM obliteration appears generally in 1-5 years after RS with 5 year obliteration rates of 70-80% (6,7,33,41-43).

In this study, effectiveness of RS for the treatment of AVMs and factors affecting the obliteration rate were investigated.

■ MATERIAL and METHODS

Patient Characteristics

We retrospectively reviewed 199 patients who were treated with Gamma-Knife RS for intracranial AVMs in Acibadem University between 13 October 2005 and 31 October 2010. Only patients with a minimum follow-up time of 3 years were enrolled. There were 89 male, 110 female patients with a median age of 32 years (range, 3-74 years).

Gamma Knife RS was applied for patients with unresectable and/or deep brain AVMs in high-risk functional areas, patients who failed to have complete obliteration with endovascular embolization or opted for stereotactic RS instead of surgical resection, patients with residual AVM after surgical resection; patients whose general health status were unsuitable for surgery. The clinical features of these patients are summarized in Table I.

Pre-RS, presenting symptoms were hemorrhage in 86 (43%), seizure in 42 (21%), headache in 61 (31%), and other complaints in 9 (5%) patients. Arteriovenous malformation was an incidental finding in 1 (0.5%) patient. Total of 146 of 199 patients (73%) were treated primarily by RS (Figure 1A-E). Fifty-three patients (27%) were initially treated before RS as follows; endovascular embolization for 22 patients (11%) (Figure 2A-C), surgery for 20 patients (10%), shunt for 4 patients (2%), external ventricular drainage (EVD) for 3 patients (2%), ventriculostomy for 1 patient (0.5%), surgery and endovascular embolization for 1 patient (0.5%), surgery and RS for 1 patient (0.5%), endovascular embolization and RS for 1 patient (0.5%). 7 patients (3.51%) had accompanying aneurysm. Twenty-eight patients (14%) had neurological deficit prior to RS.

Gamma Knife Radiosurgery Procedure

All patients underwent stereotactic RS with Leksell Gamma Knife Unit model 4C with 201-Co60 source (A.B. Elekta, Stockholm, Sweden). The treatment procedure began with the positioning of Leksell stereotactic coordinate frame using local anesthesia. Preoperative magnetic resonance imaging (MRI) with contrast and 1 mm slice thickness was performed. In addition, digital subtraction angiography (DSA) was performed in all patients. Obtained images were transferred to Gamma-Plan treatment planning system. Target volumes were delineated by neurosurgeon and radiation oncologist on MRI and DSA images. Treatment was planned with 4, 8, 14 and 18 mm collimators using single or multiple shots to ensure target coverage. Plans were then transferred to the treatment machine through network system and treatment

was performed with automatic or manual positioning systems. Radiation dose rate changed from 3.42 Gy/m to 1.5 Gy/m between 2005 and 2010. The median peripheral prescription dose was 22 Gy (range 10-26 Gy) to 50% isodose in all but 3 patients. The median volume of AVMs was 2.50 cc (range 0.05-39 cc). Intravenous prednisone (10 mg) was administered 1 hour before and 4 hours after the treatment to avoid brain edema and patients were generally discharged after 4 hours post RS. Previous treatments were considered when deciding the RS dose.

Table I: Patient Characteristics

Patient Number	199	
Age		
Mean (median)	33 years	(32 years)
Range	3-74 years	
Follow-up		
Mean (median)	64 months	(60 months)
Range	7-100 months	
	No. of patients	(%)
Sex		
Female	89	45
Male	110	55
Presentation		
Hemorrhage	86	43
Seizure	42	21
Headaches	61	31
Other	9	5
Incidental	1	1
Neurological deficit		
Yes	28	14
No	171	86
Primary RS	146	73
Previous procedures		
Embolisation	22	11
Surgery	20	10
Shunt	4	2
EVD	3	2
Ventriculostomy	1	0.5
Embolisation + RS	1	0.5
Surgery + RS	1	0.5
Surgery + Embolisation	1	0.5

Follow-up Protocol

Follow-up protocol consisted of clinical examination and MRI at 3, 12, 24 and 36 months and DSA at 3 years after RS. Observation of no flow in MRI or DSA was considered as complete obliteration (CO). In order to confirm obliteration, patients with a CO at the MRI-angiography were ordered a DSA 3 years after GKRS. However, 23% of patients refused DSA and underwent cranial MRI follow-up only for the assessment of AVM obliteration. Patients with confirmed CO were then followed-up every 2 years with cranial MRI. Patients with residual lesions after 3 years of initial RS treatment were offered a second RS.

Statistical Methods

Several parameters including age, gender, AVM grade, AVM volume, treatment dose, previous treatments and performance scores were assessed. Spetzler-Martin and Pollock-Flickinger 2002 and 2008 classification systems were used for classification (32,34,39) and relationship of these factors with obliteration was investigated.

A Roc analysis was performed in order to analyze the AVM closure at follow-up and to find a cut-off value for AVM volume correlated with AVM obliteration. The date of the DSA or MRI demonstrating no residual nidus was considered as the date of AVM closure. Predictive factors for AVM nidus obliteration were identified using T test or Mann-Whitney U test. Kolmogorov-Smirnov test was used to assess normality and Chi-square test was used for categorical variables.

For the evaluation of the data obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 18.0 program was used for statistical analysis. Results were evaluated in 95% confidence interval and $p < 0.05$ was considered to be statistically significant.

■ RESULTS

A total of 228 RS treatments were applied to 199 patients. The median follow-up period was 60.2 months (range 7–100.1 months). Total obliteration rate after RS was 71% (141 out of 199), including second RS treatments. Forty-one patients (20%) were ≤ 21 years old and were also evaluated separately as pediatric and young adults group. In terms of obliteration rates, there was no significant difference between patients younger and older than 21 years old ($p=0.67$). A second RS treatment was applied to a total of 29 patients. In patients where there was a necessity for a second RS because of a residual lesion, median volume of AVM was 4.5 cc (mean 5.6 cc) and median dose was 20 Gy during their first RS. The AVM features are summarized in Table II.

Obliteration rate was 56% (10 patients) for 18 of the 29 patients who underwent second RS with more than 3 years follow-up. No follow-up data is available for 11 patients because their RS treatments were performed more recently.

After RS, 3 of our patients died due to intracranial hemorrhage and 1 died of heart disease. Death from AVM was determined as 1.5%.

Table II: AVM Characteristics

	No. of patients	%
Location		
Frontal	61	(31)
Parietal	25	(13)
Temporal	48	(24)
Occipital	16	(8)
Cerebellar	9	(5)
Corpus callosum	5	(3)
Basal ganglia	10	(5)
Thalamus	10	(5)
Brainstem	15	(8)
Concurrent aneurysm		
Yes	7	(4)
No	192	(96)
Target volume		
Range cc	0.05 – 39	
< 4 cc	122	(61)
≥ 4 cc	77	(39)
Spetzler-Martin grade		
I	16	(8)
II	45	(22)
III	119	(60)
IV	14	(7)
V	5	(3)
Pollock-Flickinger classification 2002		
Mean	1.34	
Median	1.18	
Range	0.29 - 4.90	
<1	74	(37)
1 - 1.5	64	(32)
1.51 – 2	36	(18)
> 2	25	(13)
Pollock-Flickinger classification 2008		
Mean	1.24	
Median	1.07	
Range	0.18 – 4.80	
< 1	89	(45)
1 - 1.5	54	(27)
1.51 – 2	35	(18)
> 2	21	(11)

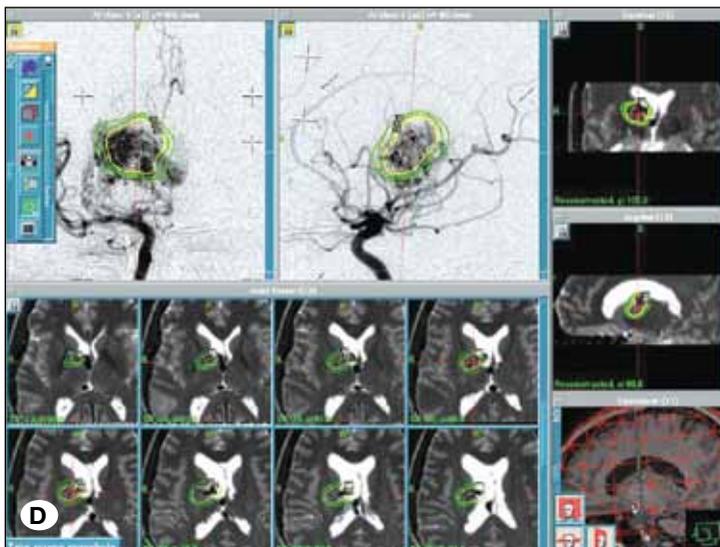
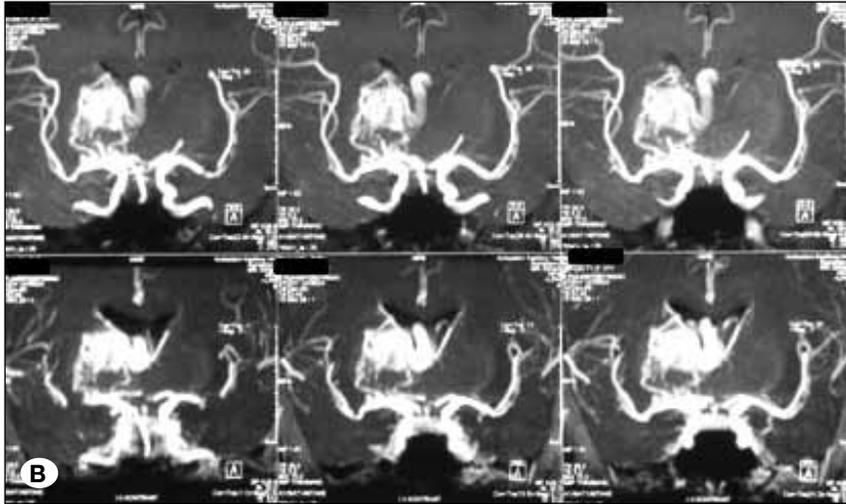
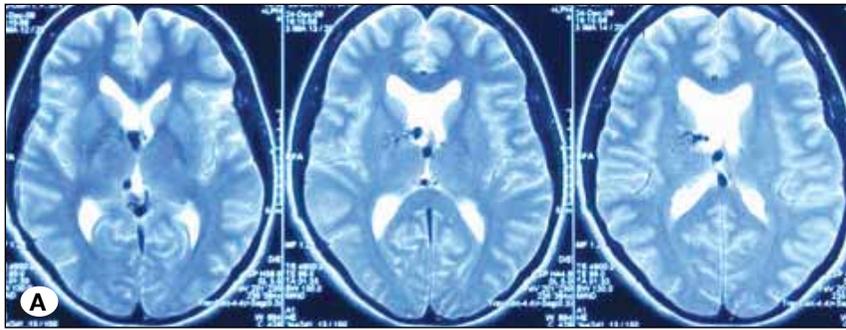
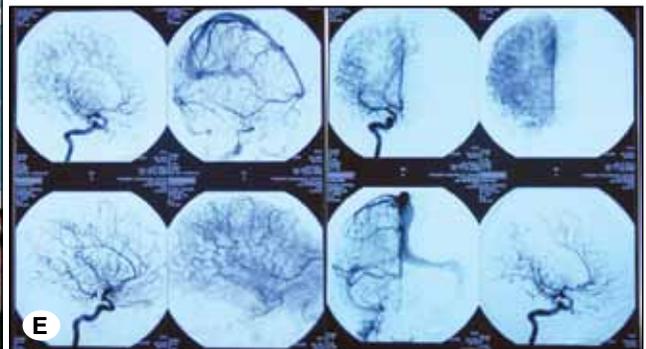


Figure 1: Spetzler-Martin Grade III lesion successfully treated with Gamma Knife radiosurgery. **A)** T2 MRI images. **B)** MR Angiography. **C)** DSA. **D)** Treatment plan. **E)** Follow-up DSA.



Intracranial hemorrhage was observed in 7 (3.5%) of the patients post-RS. Median bleeding time after RS was 19.1 months (range 7-48 months). Three of the patients who died as a consequence of bleeding, had experienced intracranial hemorrhage at 7, 17 and 34 months post RS, respectively. The AVM volumes of these patients were 14 cc, 8.2 cc and 30.1 cc, respectively. Staged RS had been planned for the patient with 30.1 cc AVM volume but the patient did not present for the second treatment. Other 3 patients were operated on and

their AVM was totally excised. Bleeding after AVM occurred in these patients at 12, 19 and 36 months after RS and their AVM volumes were 3.6 cc, 1.4 cc and 4.3 cc, respectively. A patient who experienced bleeding total of 3 times after RS at 4th, 5th and 6th years, she underwent shunt surgery and was recommended to undergo second RS, however the patient did not present for retreatment.

Complications were observed after RS treatment in 3 (1.5%) pediatric patients. Existing seizures increased in 1 patient and

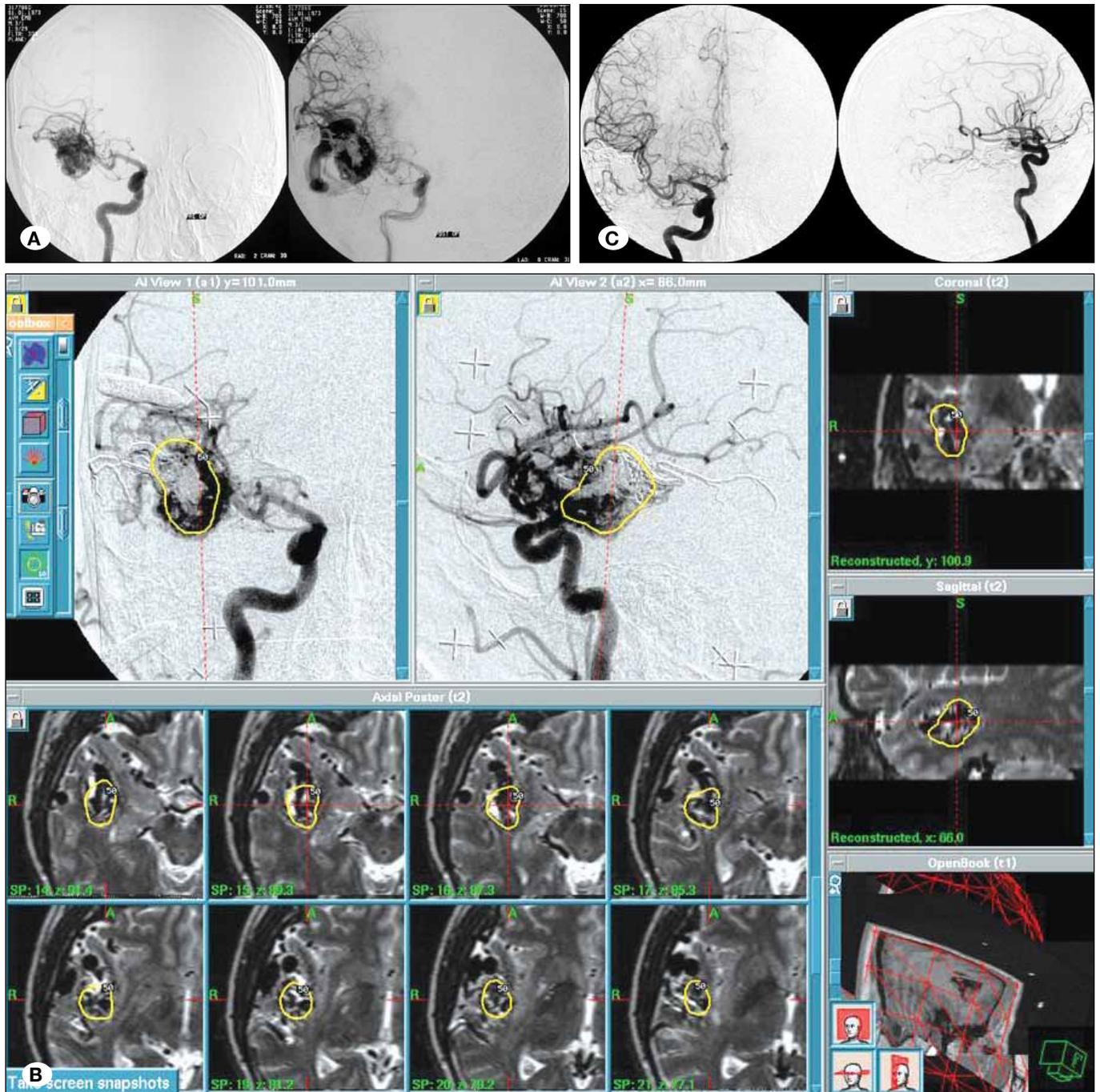


Figure 2: Partially embolized lesion treated with radiosurgery. A) Post-embolization DSA. B) Treatment plan. C) Follow-up DSA.

seizures appeared in 1 patient after RS treatment, however seizures gradually disappeared in both patients. One patient developed contralateral hemiplegia, it regressed in time but mild motor weakness remained as a sequale. Increase seizures were observed in 7 (3.5%) adult patients. Total of 13 (6.5%) adult patients experienced transient hemihypoesthesia. Headache was observed in 4 (2%) patients and completely regressed with medical treatment. Radiation necrosis was observed in none of the patients. There were transient perinidal T2 changes on MRI in 27% (54) of the patients after RS.

Obliteration was found to be significantly associated with Spetzler-Martin Grade, Pollock-Flickinger Grade, AVM volume, dose, bleeding history before RS and no previous embolization before RS. Obliteration rate for patients that received <20 Gy was 51% while 77% for patients who received ≥ 20 Gy ($p=0.007$). When lesions were grouped according to their sizes as 0.1-3.5 cc, 3.51-10.0 cc and >10 cc, obliteration rates were 69%, 22% and 9%, respectively. When lesions with Spetzler Martin Grade 1-3 were compared to those with 4-5, obliteration rates were significantly lower for higher grade lesions; 96% and 4%, respectively ($p=0.002$). Obliteration rate was higher ($p=0.014$) for patients who presented with bleeding. Obliteration rate was lower ($p=0.007$) for patients with previous embolization. The correlation between Pollock-Flickinger 2002 classification and obliteration was not significant ($p=0.063$), however, Pollock-Flickinger 2008 classification was found to be statistically significant ($p=0.006$).

■ DISCUSSION

The main purpose of AVM RS is to ensure total nidus obliteration to avoid future brain hemorrhage and protect the patient from possible side effects. Radiosurgery has been a preferred treatment method with high obliteration and low mortality rates especially for AVMs that are small and in surgically risky areas. Permanent morbidity related to RS is extremely low (0.6-9%) when compared to surgery. However, AVM RS holds the continuation of hemorrhage risk until the formation of complete AVM obliteration. Annual risk of bleeding even after the obliteration is 0.3% and annual cumulative risk is 2.2% (35). So it is deemed necessary to follow the patients even after the angiographically confirmed obliteration, and follow-up protocols should be designed for long-term management.

Obliteration of the AVM was defined by Lindquist and Steiner in Cerebral Angiography in 1988 as "a normal circulation time, complete absence of pathological vessels in the former nidus malformation, normalization or disappearance of draining veins in the area" (40).

In 1996, Pollock et al. described DSA as the gold standard for determining obliteration, although he suggested the use of MRI, a non-invasive method with which we can also observe the radiation effects on neighboring brain tissue, in patients who refuse DSA (36). We used DSA (77%) and MRI (23%) for determining obliteration rates in our patients.

Obliteration rates found in our study (71%) was consistent with the previously reported rates of 30-95% in adult and pediatric cohorts. Although it is suggested that children might respond

earlier to RS, in the current study there was no significant difference between the obliteration rates of patients younger and older than 21 years old. Nicolato et al. investigated the difference between children/adolescents and adult patients treated with RS for AVMs (28). They found similar rates of RS-related complications and latency period bleeding in the two populations. In our study, there were similar complication rates after RS for adult and pediatric patients.

Some investigators refuse to treat AVM patients younger than 5 years old with RS to avoid radiation side effects (27,28,40) however we treat these patients and they were also included in this cohort for review. There were no findings of increased side effects or sequale for this age group.

In the current study, intracranial hemorrhage was observed in 7 (3.5%) of the patients post-RS, all but 1 patient bled during the latency period. Although, some studies found similar natural bleeding rates at any time period after RS, Karlsson et al. and Maruyama et al. found lower rates of hemorrhage after RS during the latency period (23,37).

The most important factor related to the formation of obliteration post AVM RS was marginal radiation dose to the nidus (5,13,36). Higher obliteration rates with higher RS doses in AVM treatment were reported in many studies. Flickinger et al. mentioned a dose-response curve and reported that doses ≥ 19 Gy were more effective, however there was no significance in doses >25 Gy (5). In our study, median RS dose was 22 Gy (range 10-26 Gy) and treating with doses ≥ 20 Gy was found to be significantly correlated with higher obliteration rates.

The current study shows that high rates of AVM obliteration could be achieved with lower doses than previously reported studies. As a result, the similar treatment success could be achieved with a lower incidence of radiation related adverse effects. This is especially important for the pediatric cohort included in our study.

In studies reporting on RS for AVM treatment, AVM volume was found to be related to obliteration. We investigated AVM volume in 3 groups as 0.1-3.5 cc, 3.51-10.0 cc and >10 cc. Obliteration rates in groups were 69%, 22% and 9%, respectively. In other studies, obliteration rates in patients with AVM volume <10 cc was determined as 74-100%. This rate was 91% in our study and therefore in line with these rates.

Although, Spetzler-Martin is a grading system developed for the surgical resection, and its suitability for RS is debated, it is frequently used. When lesions with Spetzler-Martin Grade 1-3 were compared to those with 4-5 in our study, obliteration rates were found as 96% and 4%, respectively. These results indicate that Spetzler-Martin grading system could be a predictor for post-RS obliteration results. Pollock-Flickinger classification system developed in 2002 was not associated with obliteration in our study, while its modified 2008 version was statistically related to obliteration.

Correlated with the literature, obliteration rate in our study was significantly lower for patients with pre-RS embolization (37). In our study, obliteration rate was significantly higher for patients presented with pre-RS intracranial hemorrhage.

While some studies found correlation between hemorrhage presentation and higher obliteration rates (10,36), Kasliwal et al. suggested no difference in the obliteration rates (14).

Staged RS was planned for 8 patients; however it could be carried out only for 2. Remaining 6 patients did not present for the planned treatment. One of these patients died of intracranial bleeding at 34 months after RS. Remaining 5 patients still have open AVMs. Compliance factor must be taken into account for the patients planned with staged RS. Large lesions can also be considered for fractionated stereotactic radiotherapy.

■ CONCLUSION

Gamma knife RS is an effective treatment method for the treatment of AVMs both for pediatric and adult patients. It provides high obliteration and low mortality rates. In our series, RS dose and AVM volume were found to be related to the success of this treatment method.

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