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Clinical Article

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Retrospective Analysis on 76 Cases of Cerebral Arteriovenous Malformations Treated by Gamma Knife Radiosurgery

Objective : Outcome of gamma knife radiosurgery (GKS) in the consecutive 100 cases with cerebral arteriovenous malformations (AVMs) was analyzed.

Methods : Data from initial 100 patients treated with GKS in the authors' institute were reviewed retrospectively. Spetzler-Martin grade at diagnosis were I in 18 patients, II in 27, III in 36, IV in 11, and V in 8. Thirty-five patients had experienced previous bleeding, 27 patients presented with seizure, and 31 patients presented with headache. The mean volume of the lesion was 4.3 cm^3 (0.1-29.3 cm^3). The median radiation dose delivered to the margin was 20.0 Gy (13-32 Gy). Mean follow-up period was 37.5 months (5-63 months).

Results : Angiographic follow-up was performed in 48 patients at least 2 years after GKS. Sixteen patients were lost in follow up following 2 years from GKS. Twenty-eight of 48 patients (58%) showed complete obliteration and 20 patients (42%) showed partial obliteration. Seven patients presented with post-GKS hemorrhage. Adverse radiation effect (ARE) was observed at follow-up MRI in 25 of 76 patients, and it was symptomatic in 5 patients. Complete obliteration was confirmed in 24 of 31 (77%) patients with volume less than 4 cm^3, meanwhile only 4 of 17 (24%) patients with volume of 4 cm^3 or more showed complete obliteration. Complete obliteration rate was 67% with 20 Gy or higher marginal dose, 63% with 15-20 Gy, and 17% with less than 15 Gy.

Conclusion : GKS can provide high rates of obliteration with acceptable risk of morbidity in a subgroup of small AVMs. However, overall outcome in whole spectrum of AVMs, in which large proportion of cases have unfavorable characteristics for radiosurgery, is much worse. More effective therapeutic strategy needs to be developed for large AVMs that are difficult to be managed with current available treatment modalities.

KEY WORDS : Gamma knife radiosurgery · Arteriovenous malformation · Outcome.

INTRODUCTION

Gamma knife radiosurgery (GKS) is accepted as an effective treatment modality for patients with a cerebral AVM[1,7,14,19,23]. The obliteration rate for cerebral AVMs at 3 years after GKS varies from 61.2 to 86.6%, mostly dependent upon the size of AVM and marginal dose[17,20,23]. However, most of the data have been derived from selected patients and overall outcome after GKS is usually extrapolated from a portion of monitored patients. With increasing tendency of more use of radiosurgery than microsurgery, AVMs of large size are being treated frequently by radiosurgery[16,23,24]. Therefore, excellent outcome from the strictly selected patients who have favorable characteristics for radiosurgery should not be generalized. We have reviewed the outcome of 100 consecutive cases of AVMs treated with GKS in our institute, which comprised majority of the patients with AVMs treated in the same period and included AVMs with wide spectrum of clinical characteristics.

MATERIALS AND METHODS

Patient populations

A total of 107 patients with AVM were treated in our institute between January 2002 and August 2004 (Fig. 1). Microsurgery was performed in 22 patients, GKS in 100 patients and embolization in 28 patients.

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Table 1. Distribution of the patients according to Spetzler-Martin classification and clinical outcome

Spetzler-Martin Grade	Patients No.	Total obliteration	Partial obliteration	Result not known	Obliteration rate (%)
I	18	6	2	10	75
II	27	6	3	18	66.7
III	36	13	8	15	61.9
IV	11	2	5	4	28.6
V	8	1	2	5	33.3

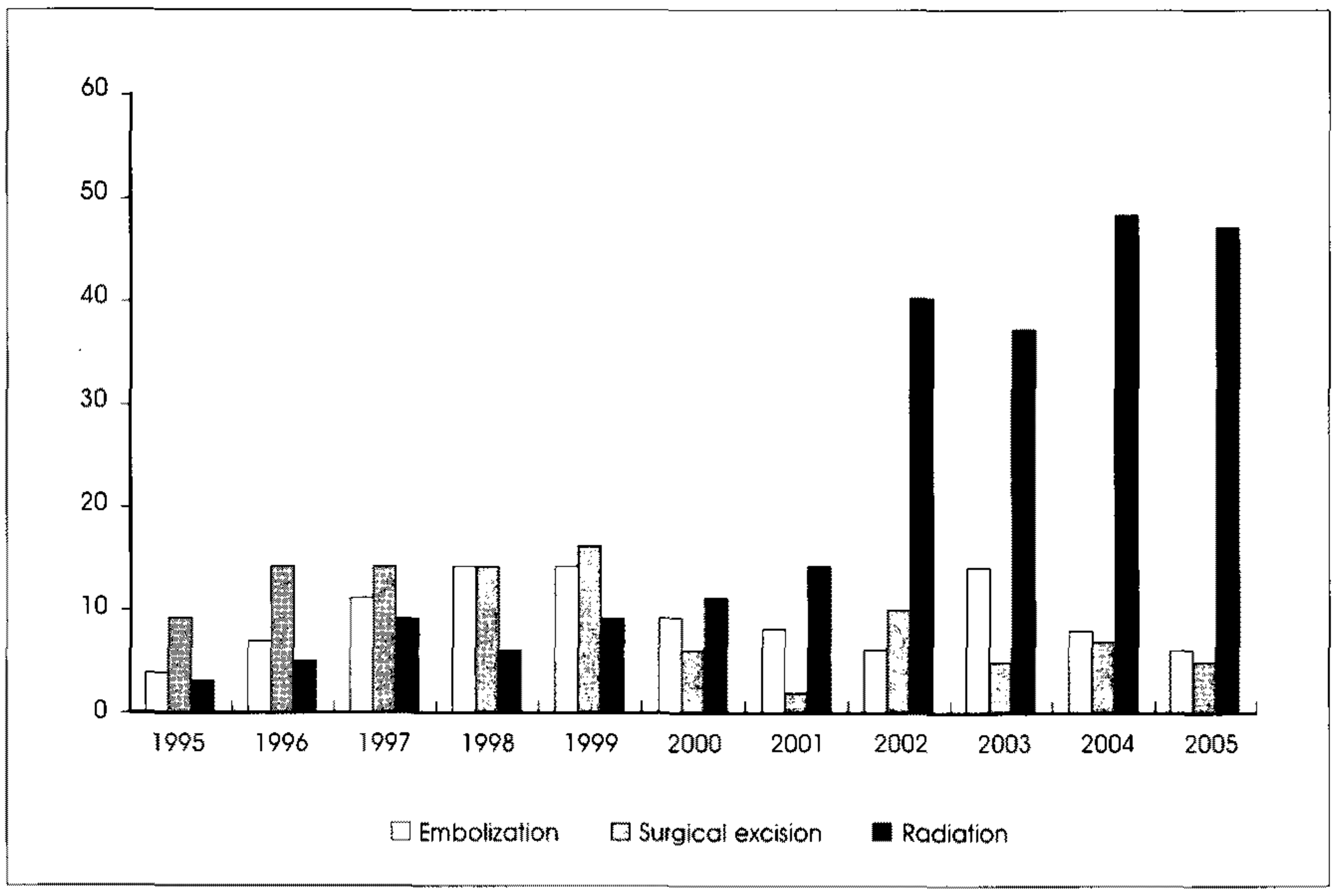

Fig. 1. Distribution of treament modality for arteriovenous malformations in the author's institute. Since the introduction of gamma knife in 2002, majority of the patients has been treated with radiosurgery.

Among hundred patients treated with GKS, 10 patients had been managed with additional modalities other than GKS. Pre-GKS embolization had been performed in 5 cases, microsurgery in 2, and radiosurgery with linear accelerator in 3. Gamma knife radiosurgery was performed as an initial treatment in 89 patients and one patient among them underwent microsurgery subsequently due to hemorrhagic episode. Therefore, 88 patients were treated with GKS alone.

The mean age of patients treated with GKS was 34.0 years (range 5-66 years). The ratio of male/female patients was 62 to 48. The mean follow-up time was 37.5 months (range 5-63 months).

Presenting symptoms

Presenting symptom at diagnosis was hemorrhage in 34 patients, seizure in 25, headache in 25 and neurologic deficit due to steal phenomenon in 4. Therefore, 92 patients presented with symptomatic AVMs, which include 25 patients with ruptured AVMs and 75 with unrutured AVMs. Eight patients presented with asymptomatic incidental lesions.

Anatomical location, volume and Spetzler-Martin grade

Locations of AVMs were cerebral hemisphere in 67 patients, corpus callosum in 4, deep nuclei such as thalamus and basal ganglia in 17, cerebellum in 11, and brainstem in 1. Volume of the AVM nidus treated with GKS ranged from 0.1 to 29.3 cm^3 (mean 4.3 cm^3). Spetzler-Martin grade was I in 18 patients, II in 27, III in 36, IV in 11, and V in 8 of 100 patients (Table 1).

Radiosurgical technique

Radiosurgery was performed using Leksell Gamma Knife Type B and 3C (Elekta Co., Stockholm, Sweden). Leksell stereotactic frame was applied under local anesthesia. Magnetic resonance imaging (MRI) and stereotactic angiography were performed. T2-weighted axial images and 3D-SPGR images with double dose contrast enhancement were obtained with 1-1.5 mm slice thickness and 512×512 matrixes. MRI and angiography images were transferred to planning workstation and radiosurgical planning was done with Gammaplan version 5.31-5.34. The median marginal dose was 20.8 Gy (range 13-32 Gy) and the median prescription isodose was the 50% (range 35-65%).

Post-GKS evaluation

Follow up MRI was performed with 6 months - 1 year interval after GKS. Angiographic follow up was performed at least 2 years after GKS. Earlier angiographic follow up was performed at the time of hemorrhagic episode or complete occlusion suggested by MRI finding.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences software, version 11.5 (SPSS, Chertsey, 2004). The cumulative occlusion rate was calculated using the Kaplan-Meier method. Univariate and multivariate analyses were computed using log-rank and Cox proportional hazards models.

Table 2. Distribution of the patients according to AVM nidus volume and clinical outcome

Volume	Patients No.	Total obliteration	Partial obliteration	Result not known	Obliteration rate (%)
< 1 cm^3	31	12	6	13	66.7
1 - 4 cm^3	37	12	1	24	92.3
4 - 10 cm^3	20	3	8	9	27.3
> 10 cm^3	12	1	7	4	12.5

Table 3. Factors influencing AVM nidus obliteration rate

	Univariate (Log rank)	Multivariate (Cox)
Sex	$p = 0.061$	-
Previous hemorrhage	$p = 0.071$	-
Spetzler-Martin grade (Grade I-III vs. IV-V)	$p = 0.010$	$p = 0.089$
AVM volume (<4 cm^3 vs. >4 cm^3)	$p < 0.001$	$p = 0.004$
Dose to margin (<20 Gy vs. >20 Gy)	$p = 0.035$	$p = 0.092$

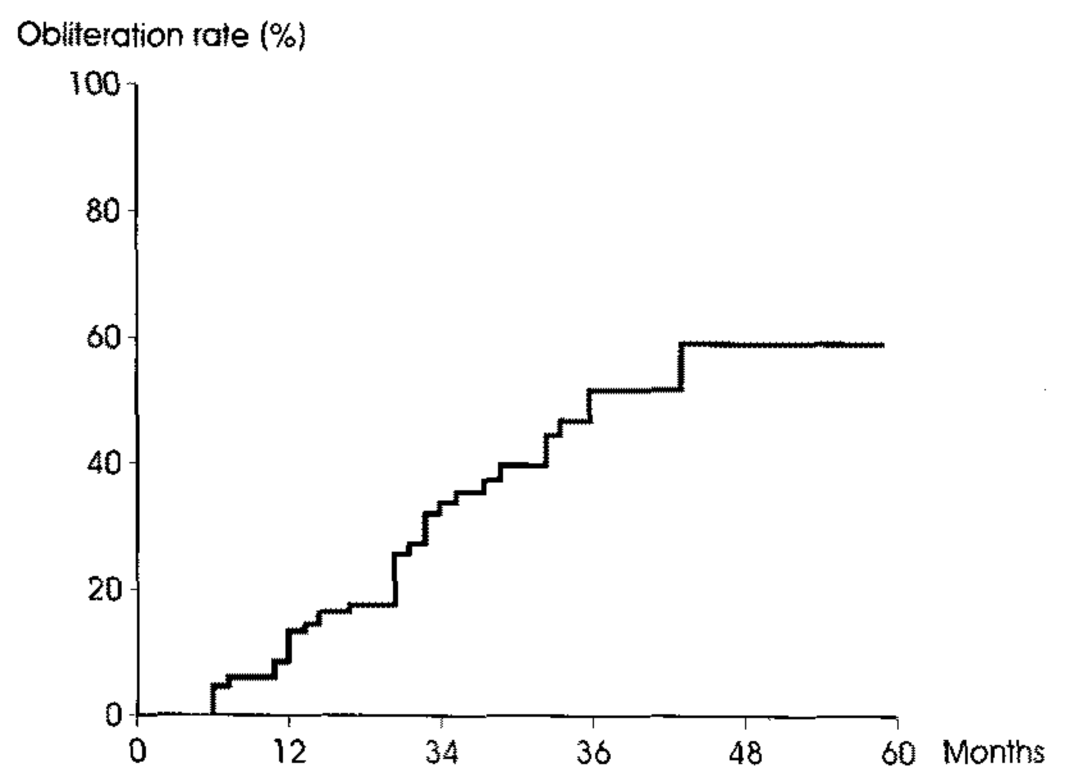

Fig. 2. Angiographically confirmed cumulative obliteration rate of arteriovenous malformations treated by gamma knife radiosurgery. Among 100 pateints, follow up angiography was performed in 48 patients and finally complete obliteration was confirmed in 28 patients (58%).

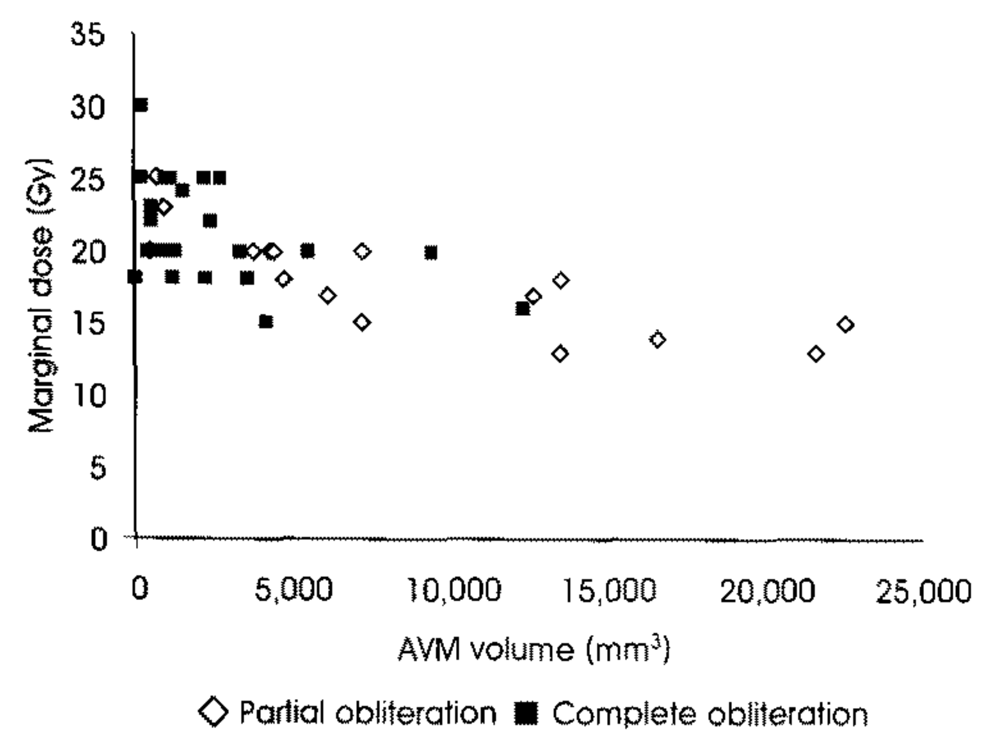

Fig. 3. Relation between arteriovenous malformation volume, marginal dose and complete obliteration in 48 patients with follow up angiography at least 2 years after radiosurgery.

RESULTS

Overall obliteration rate

Forty-eight patients underwent angiography after GKS, and MRI was done in 76 patients once or more. The mean interval of the first angiography from GKS was 25.3 months (range 6-43 months). The complete obliteration was confirmed in 28 (58%) of 48 patients with follow up angiography. Partial obliteration rate was 42% (20 of 48) and 16 patients underwent the second GKS. Thirty-five patients underwent follow-up angiography 3 years after GKS. Among them, 29 patients (83%) showed complete obliteration and 6 patients (17%) showed partial obliteration. Cumulative rate of complete obliteration calculated from follow up angiography was 40% at 2 years and 58% at 3 years after GKS (Fig. 2).

Factors affecting obliteration

Complete obliteration rate in low Spetzler-Martin grade (I-III) was 66% (25 of 38 patients). Meanwhile, it was only 30% (3 of 10 patients) in high grade (IV-V) AVMs (Table 1).

Complete obliteration rate was seen in 77% in AVMs with volume less than 4 cm^3 (24 of 31). Meanwhile, it was 24% (4 of 17) in AVMs with volume of 4 cm^3 or more (Table 2). Large AVMs (volume of 10 cm^3 or more) showed only 13% of complete obliteration rate (1 of 8).

Complete obliteration rate was 67% in AVMs with marginal dose more than 20 Gy, and it was 63% in AVMs with margianl dose 15-20 Gy. Meanwhile, it was 17% in AVMs with marginal dose less than 15 Gy (Fig. 3)

Statistical analyses of factors influencing studied events are indicated and significant p values are listed for both univariate and multivariate analyses in Table 3.

Post-GKS hemorrhage and complication

Hemorrhage occurred in 7 of 100 patients after raidosurgery, with a mean interval of 15.6 months (range 7-36 months) after GKS. Annual hemorrhagic risk was 3.2%. One patient died due to complication of hemorrhage. No hemorrhage occurred in patients after complete obliteartion.

Among 76 patients with follow-up MRI available, adverse radiation effects (AREs) were observed in 24 patients (32%), symptomatic AREs were observed in 5

Table 4. Rate of adverse radiation effects (AREs) among the patients with follow up magnetic resonance image scan according to volume

Volume	Patients No.	Radiologic AREs	Symptomatic AREs
< 1 cm^3	23	4	1
1 - 4 cm^3	27	9	2
4 - 10 cm^3	16	6	2
> 10 cm^3	10	5	1

patients (6.6%, Table 4) and permanent disability remianed in no patients.

Salvage treatment

Two patients underwent surgical excision and one patient underwent embolization after hemorrhage. Sixteen patients underwent additional GKS as salvage treatment (mean duration after first radiosurgery : 31.1 months, range 18-49 months), and final outcome was pending because of short follow-up duration.

DISCUSSION

Although we report experience in single institute and practice pattern in our institute does not exactly reflect general trend, case series presented here show recent change in neurosurgical practice, shifting from microsurgery to radiosurgery. In our institute, gamma knife has been used for radiosurgery since 2002 and has become the most frequently used treatment modality for AVMs. It is thought that many factors influenced this change. In an insitute with gamma knife, more patients are referred for the purpose of radiosurgery than microsurgery. However, there are other factors besides referral bias. It seems that there is increasing preferrence to radiosugery by both patients and neurosurgeons due to many reasons (i.e. refusal of surgery, relatively low complications, short hospital day and so on). Consequently, more patients with AVMs are being treated by radiosurgery than before not necessarily guided by strict selection criteria. Advantages of GKS in cases selected with classical criteria (i.e. small lesion, eloquent location or location of difficult surgical access, and serious comorbidity and so on) are well known and relevant information can be acquired easily through numerous literatures[6,14,17,19,22,23]. However, there is relatively insufficeint data on radiosurgical outcome in the patients with more unfavorable chracteristics. It is thought that more concern needs to be concentrated on the role of radiosurgery for whole spectrum of AVMs, particularly large size AVMs.

Results in our series reveal findings compatible to those already reported in the other literautres[5,7,10,12,13]. We observed fair outcome in AVMs with samll volume or low SM grade and much worse outcome with large volume or high SM grade. Because volume is the more detrimental factor than SM grade, it seems that better results in low SM grade reflect more small AVMs in low SM grade group. Higher marginal dose resluted in higher obliteration rate than lower dose[1,5,7,11,12]. Rate of post-GKS hemorrhage was not sigfinificantly different from reported results in the lietrautres too[12,14,17-19,21].

One remarkable finding in our results is that overall complete obliteration rate is far from satisfaction and relatively lower even in comparison with that in the literature[13,14,17,19,22]. It can be explained by the fact that our data are from incomplete short term follow up and include relatively more cases of difficult AVMs with high SM grade. It needs to be mentioned that unfortunately large proportion of the patients with AVMs we meet in practice are difficult cases that can not be managed satisfactorily either radiosurgery nor microsurgery. It was suggested that some AVMs of high SM grade should be left without therapeutic intervention (microsurgery or embolization) because outcome after intervention might not be better than natural course of the disease[5,8]. The same question should be answered concerning radiosugery. It is technically easy to apply radiosurgery for difficult AVMs without immeidate adverse effect. However, successful outcome is not reliably guaranteed and it was achieved in only 30% of our cases with SM garde IV or V in 2 years. Although we believe that there are some benefits with radiosurgical treatment of this group of the patients, it is certain that benefis of radiosurgery in large AVMs are much less than that in small AVMs. More information from long term follow up is necessary and hopefully prospective trial for comparison of natural course and treatment outcome needs to be done to justify the radiosurgical treatment of large AVMs with high SM grade.

It should be noted that failure of complete obliteration after radiosurgery is not rare and consequently repeated treatment is needed frequently. Nineteen percent of the patients needed repeated GKS and the rate is compatible to a recent report in which one-quarter of the patients required repeated treatment[14,19,23]. It may be more reasonable that repeated treatmment is considered more usual than exceptional, particulalry in case of AVMs with large volume.

Unlike microsurgery or embolization, outcome after radiosurgery for AVMs should be waited for long time before final evaluation[9,10,25]. Therefore, it is difficult to obtain complete follow-up data after radiosurgery for AVMs and a signifcant proportion of lost patients before reaching final outcome decreases reliability of the analyzed data and its interpretation. This study is not free from the problem and it is commonly observed in other literatures. However, this limitation seems more prominent in the articles published in domestic journals and it may be partly due to medicosocial environment[2-4,11,15]. Multiinstitutional data collection and cooperative study is essential to acquire strong evidence for or against application of radiosurgery.

CONCLUSION

Gamma knife radiosurgery provides high obliteration rate with a low risk of morbidity in a group of AVMs with favorable characteristics for radiosurgery. However, overall treatment outcome for whole spectrum of AVMs is not yet satisfactory. More comprehensive and systematic data collection is needed and more effective tretament techniques need to be explored at the same time.

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