Radiosurgical Considerations in the Treatment of Large Cerebral Arteriovenous Malformations

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Objective: In order to establish the role of Gamma Knife radiosurgery (GKS) in large intracranial arteriovenous malformations (AVMs), we analyzed clinical characteristics, radiological features, and radiosurgical outcomes.

Methods: Between March 1992 and March 2005, 28 of 33 patients with large AVMs (> 10 cm³ in nidus-volume) who were treated with GKS underwent single session radiosurgery (RS), and the other 5 patients underwent staged volumetric RS. Retrospectively collected data were available in 23 cases. We analyzed treatment outcomes in each subdivided groups and according to the AVM sizes. We compared the estimated volume, defined as primarily estimated nidus volume using MR images, with real target volume after excluding draining veins and feeding arteries embedded into the nidus.

Results: Regarding those patients who underwent single session RS, 44.4% (8/18) had complete obliteration; regarding staged volumetric RS, the obliteration rate was 40% (2/5). The complete obliteration rate was 60% (6/10) in the smaller nidus group (10-15 cm³ size), and 25% (2/8) in the larger nidus group (over 15 cm³ size). One case of cerebral edema and two cases (8.7%) of hemorrhage were seen during the latent period. The mean real target volume for 18 single sessions of RS was 17.1 cm³ (10.1-38.4 cm³), in contrast with the mean estimated volume of 20.9 cm³ (12.0-45.0 cm³).

Conclusion: The radiosurgical treatment outcomes of large AVMs are generally poor. However, we presume that the recent development in planning software and imaging devices aid more accurate measurement of the nidus volume, therefore improving the treatment outcome.

KEY WORDS: Gamma Knife radiosurgery • Arteriovenous Malformation • Intracerebral Hemorrhage • Obliteration • Complication • Outcome.

INTRODUCTION

For the treatment of intracranial arteriovenous malformations (AVMs), one of three established methods or combinations of them-microsurgery, embolization, and stereotactic radiosurgery- have been applied. For the large AVMs, however, none of them gave rise to clinically acceptable outcomes to date. The important prognostic factors that affect the outcomes in treating AVMs are the volume of the nidus and its location along with hemodynamic characteristics of the AVM itself in relation to the surrounding vasculature. In the radiosurgical field of AVM treatment, the volume is the single most important factor among the aforementioned prognostic factors, because in cases of large volume AVMs, sufficient radiation dose cannot be delivered for a number of reasons. Therefore, planning for the minimization of target volume without surplus is the one of the most important procedures for the effective treatment. Aiming the goal of radiosurgery at delivering a sufficient dose to the AVM nidus itself while minimally affecting the normal brain tissue in vicinity, we would like to introduce the dosimetry, obliteration rate and complications from our experiences of treating large AVMs.

METHODS AND MATERIALS

Patients and AVM characteristics

Patients were enrolled in this study according to the following criteria: 1) a large AVM defined as 10 cm³ or more in volume; 2) a clinical and radiological follow-up
period of at least 36 months; 3) those patients who showed early complete obliteration or those who died from hemorrhage. Between March 1992 and March 2005, 355 patients with intracranial AVMs were treated with GKS at our institution. Thirty-three patients (9.3%) had large AVMs, and 23 of these patients (16 male; 7 female) were included in this study. The mean age at the time of GKS was 34.3 years (range, 10-58 years). Their clinical and radiological data were retrospectively analyzed.

Eighteen patients (78.3%) had a history of hemorrhage, and four patients had undergone microsurgeries, such as partial nidus resection or hematoma evacuation, beforehand. Four patients had undergone intravascular embolization before radiosurgery. The radiological characteristics of the AVMs, including the Spetzler-Martin Scale and location, are summarized in Table 1.

**Radiosurgical technique**

Single session radiosurgery (RS) was performed in 18 patients and two-stage volumetric RS was performed in the other 5 patients. Cerebral angiography and magnetic resonance (MR) imaging were performed with fixation of a Leksell stereotactic instrument to the skull. As a radiosurgical planning tool, the KULA system was used until 2001, and the Leksell Gamma Plan system (Elekta AB, Stockholm, Sweden) has been used since then. During the planning, feeding arteries and draining veins were maximally excluded to minimize the target volume. As seen in Fig. 1, estimated target volume was defined as primarily estimated nidus volume using Gamma Plan based on gadolinium enhanced Tetralogy of Fallot (TOF) MR images and real target volume as substantial volume after excluding draining veins embedded into the nidus and feeding arteries, which enables compaction of the target to be irradiated. In cases prior to 2001, KULA system was used with gadolinium enhanced T1 axial and coronal images as source. The gap between estimated target volume and real target volume was analyzed.

**Follow-up evaluations**

All patients were evaluated during follow-up visits at 1 week, 1 month, and 6 months, and then annually after GKS. Radiologic follow-up was done using MR angiography annually after GKS. Conventional angiography was performed for confirmation of complete obliteration when there was no visualization of the nidus on follow-up MRI, or for planning of retreatment of the remnant nidus, even 2-3 years after primary GKS. Additional visits or telephone counseling were recommended when new symptoms developed. Radiologic imaging, including computed tomography (CT), was performed whenever needed.

**Estimation of radiosurgical outcomes**

Complete obliteration was defined as no remaining nidus

| Table 1. Clinical and angiographic characteristics |
|-----------------------------------------------|
| Patient characteristic | No. of patients (%) |
| Presenting symptom  |                  |
| Headache            | 18 (78.3)        |
| Hemorrhage          | 18 (78.3)        |
| Seizures            | 8 (34.8)         |
| Sensory-motor deficit | 11 (47.8)       |
| Visual defect       | 2 (8.7)          |
| Decreased mental status | 2 (8.7)        |
| Prior therapy       |                  |
| Embolization        | 3 (13.0)         |
| Surgical resection  | 4 (17.4)         |
| Spetzler-martin grade |              |
| II                 | 7 (30.4)         |
| III                | 10 (43.5)        |
| IV                 | 5 (21.7)         |
| V                  | 1 (4.3)          |
| Deep venous drainage | 10 (43.5)       |
| Location            |                  |
| Lobar              | 14 (60.9)        |
| Thalamus/Basal ganglia | 6 (26.1)    |
| Cerebellum         | 1 (4.3)          |
| Corpus callosum    | 2 (8.7)          |
| Biocautery         | 1 (47.8)         |

**Fig. 1.** An example of serial methods to minimize target volume is shown using Gamma Plan. A: Projective volume of nidus on conventional angiography. B: Primary target volume on TOF MR images. C: Minimized real target volume excluding draining vein and supplying arteries.
on angiography, and partial obliteration was defined as some obliteration on either MRA or angiography more than 3 years after GKS. Repeat GKS was considered in cases of partial obliteration.

To estimate outcomes in large AVM patients based on nidus volume, the authors classified the patients who received single session radiosurgery into two groups: a 10-15 cm$^3$ group and a larger than 15 cm$^3$ group. We also compared the treatment results between single session radiosurgery and staged volumetric radiosurgery patients. Complications following the treatments are also revised.

**RESULTS**

**Follow-up and characteristics**

The mean clinical follow-up period was 41.2 months (5.9-84.2 months) in all cases and 43.5 months (24.3-84.2 months) in non-bleeding cases. The mean nidus volume in the 23 AVM cases was 16.8 cm$^3$ (range, 10.1-38.4 cm$^3$). The prescription isodose lines ranged from 40% to 65% (mean 53%, median 50%). In single session RS cases, the mean marginal dose was 16.9 Gy (range, 7.2-25 Gy), and the mean nidus volume was 17.1 cm$^3$ (range, 10.1-38.4 cm$^3$). In two-stage volumetric RS cases, the mean nidus volume of 5 AVMs was 15.7 cm$^3$ (range, 11.6-20.2 cm$^3$), but the radiosurgical targets in 10 instances of GKS for these 5 AVMs ranged from 3.0 to 11.3 cm$^3$ in size. The mean marginal dose was 20.8 Gy (range, 17.0-24.0 Gy) for 10 separate radiosurgical targets. The interval between two staged GKS treatments varied from 1 to 7 months.

The mean real target volume for 18 single sessions of RS was 17.1 cm$^3$ (10.1-38.4 cm$^3$), in contrast with the mean estimated target volume of 20.9 cm$^3$ (12.0-45.0 cm$^3$). The real and estimated target volume was compared in Fig. 2.

**Nidus obliteration**

The mean clinical follow-up period was 41.2 months (5.9-84.2 months) in all cases and 43.5 months (24.3-84.2 months) in non-bleeding cases. Complete obliteration was achieved in 8 of 23 (34.8%) single session RS cases and in 2 of 5 (40%) staged volumetric RS cases (Table 2). The largest volume of total obliteration was 25.3 cm$^3$ (mean 13.4 cm$^3$). The minimal marginal dose that resulted in total obliteration was 18 Gy. In two fatal bleeding cases,

![Fig. 2. Gadolinium enhanced Tetralogy of Fallot (TOF) MR images are incorporated into the Gamma Plan to assess estimated target volume (Black line) as a primarily estimated nidus volume. The gray line depicts substantial volume, which is the real target volume, where the embedded draining veins and feeding arteries have been removed. A: 18 cases of single sessional gamma knife radiosurgery (GKS). B: 10 cases of staged volumetric GKS.](image)

| Outcome                  | Single session RS (%) | Staged volumetric RS (%) |
|--------------------------|-----------------------|--------------------------|
| Complete obliteration    | 8 (44)                | 2 (40)                   |
| Partial obliteration     | 6 (33)                | 3 (60)                   |
| Unchanged                | 2 (11.1)              | 0 (0)                    |
| Bleeding during follow-up| 2 (11.1)              | 0 (0)                    |

**Table 2. Radiosurgical outcomes**

RS : radiosurgery

![Fig. 3. A and B: Large arteriovenous malformation in the right frontoparietal lobe, fed by the ipsilateral anterior cerebral artery and the middle cerebral artery draining into the superior sagittal sinus in a 52-year-old man who presented with seizures. C and D: Complete obliteration is seen on follow-up conventional angiography 4 years after gamma knife radiosurgery. Target volume = 20.1 cm$^3$, maximal volume = 50 Gy, marginal dose = 25 Gy.](image)
AVM evaluation could not be obtained. A case of complete obliteration is shown in Fig. 3. In the single session RS group, the complete obliteration rate was 60% (6 of 10 cases) when the nidus volume was less than 15 cm$^3$ and 25% (2 of 8 cases) when it was 15 cm$^3$ or more. The obliteration rates for each volumetric group are shown in Table 3. Partial obliteration was seen in the other three patients who underwent staged RS, and all of them were re-treated with GKS thereafter.

**Complications**

ARE were found in 1 of 23 cases. A patient who received a marginal dose of 25.0 Gy and a maximal dose of 50.0 Gy suffered edema around the irradiated area. The patient had no distinguishable difference in either volume or dose compared to those patients who had no complications.

Bleeding occurred after GKS in 2 of 23 patients (8.7%); both died from hemorrhage. One of these patients had a history of hemorrhage prior to radiosurgery. Hemorrhage occurred at 5.9 months after radiosurgery in the first patient and at 36.5 months after radiosurgery in the other patient.

**DISCUSSION**

Although GKS is generally thought to be an effective treatment modality with great safety, the treatment results remain unsatisfactory for large AVMs$^{14,19}$. Several factors affect the results of radiosurgical treatment for large AVMs. Flickinger et al.$^{4-7}$ reported that location, size, and hemodynamic characteristics should be considered in radiosurgical planning. Additionally, volume is one of the most important factors influencing prognosis$^{5,8,9}$. Friedman et al.$^{9}$, reported a complete obliteration rate of 69% after radiosurgery for AVM nidi of 10 cm$^3$. Pan et al.$^{20}$, reported a 77% complete obliteration rate in nidi 10 to 15 cm$^3$ in size and a 25% complete obliteration rate in nidi over 15 cm$^3$ during a follow-up period of 40 months. Moreover, when volumes over 15 cm$^3$, the complete obliteration rate increased to 58% after a 50-month follow-up period. The investigators suggested that the latency period for large AVMs may be longer than that for small AVMs. In this study, the overall complete obliteration rate for single session RS was 44% (8 of 18 cases) : 60% when the nidus volume was less than 15 cm$^3$ and 25% when it was 15 cm$^3$ or more (Table 3).

The relatively low radiation dose could be one of the most potent factors contributing to the poor obliteration rate of large AVMs compared to small lesions$^{20}$. There is a tendency for the radiation dose to decrease as the volume of the AVM increases, because normal intracranial structures surrounding the lesion might be irradiated in the case of larger AVM target volumes. Miyawaki et al.$^{18}$ suggested that the dose-volume range for the optimal balance between successful obliteration and the risk of complications narrows as AVM size increases. In the present study of single session RS, the minimal marginal dose that resulted in total obliteration was 18 Gy. However, when the marginal dose was less than 20 Gy, the complete obliteration rate was only 25% (3 of 12 cases). The likelihood of cure has been shown to be dependent on the marginal dose$^{8,15,16}$ whereas the risk of complications has been shown to be related primarily to the dose and volume irradiated$^{9}$.

On the other hand, only two of five staged volumetric radiosurgery cases achieved complete obliteration. Through a decrease in the nidus volume to be irradiated, a higher marginal dose can be applied to the nidus$^{24}$. However, there are always limitations in the application of abundant radiation doses for fear of complications, resulting in partial obliteration during the latency period. If an effective dose can be given to the nidus, the outcome can be expected to improve.

Ten GKS treatments were delivered to 5 AVMs in this series of staged volumetric RS. Only three of 10 cases had marginal doses less than 20 Gy. Despite a sufficient marginal dose, complete obliteration was seen in only two of five AVMs, with partial obliteration seen in the rest. We concluded that several factors, including insufficient experience with multi-session RS, influenced the poor results (Fig. 4). Technical problems, especially planning errors, can also contribute to the higher rate of incomplete obliteration of large AVMs.

AVM nidus can be indentified from conventional cerebral angiography and from gadolinium enhanced TOF MR images. From the angiographic images, projective volume of the nidus enables inclusion of the draining vein as illustrated in Fig. 5. On the other hand, from the TOF

| Parameter | Nidus Volume |
|-----------|--------------|
|           | 10-15 mm$^3$ | ≥ 15 mm$^3$ |
| Marginal dose | | |
| Mean (range) | 20.3 Gy (18-25) | 15.0 Gy (7.2-25) |
| Less than 20 Gy | 4 (40%) | 6 (75%) |
| 20 Gy or more | 6 (60%) | 2 (25%) |
| Treatment outcome | | |
| Total obliteration | 6 (60%) | 2 (25%) |
| Partial obliteration | 2 (20%) | 4 (50%) |
| No change | 1 (10%) | 1 (12.5%) |
| Bleeding during follow-up | 1 (10%) | 1 (12.5%) |
MR images, tomographic volume of the malformed vessels excluding the draining veins comprises the supplying arteries. Therefore, as seen in Fig. 1, in combination of the two imaging techniques, the supplying arteries and draining veins could be discarded and true AVM nidus can be condensed. Recent developments in neurodiagnostic techniques allow accurate radiosurgical targeting which facilitates minimization of nidus volume to be irradiated. The present study also demonstrated that true large AVMs may be fewer in number in these reasons.

Irradiation to surrounding normal tissues contributes to several AREs, such as cerebral edema, necrosis, vascular stenosis, cyst formation, and hemorrhage, and many previous studies have suggested that lower radiation dose decreases the incidence of ARE5,7,28). Flickinger et al.5) offered several hypotheses about complications related to AVM radiosurgery. They suggested that radiation-induced complications were due not only to irradiation of perilesional normal brain tissue, but also to irradiation of the AVM nidus inside the treatment volume. It is generally agreed that lower radiation dose decreases the incidence of ARE. Inoue et al.13) reported a low incidence of ARE during a 10- to 15-year follow-up in 76 patients treated with doses lower than 20 Gy. In this study, cerebral edema occurred in one case in which the marginal dose was 25.0 Gy. The factor, which contributed to the development of edema after GKS, remains obscure, but relatively high dose irradiation or planning error could be one of most reliable reasons. Evolution of imaging tools like MR and angiogram serves more accurate images, which helps more effective planning.

Potent risk factors for AVM hemorrhage are most likely to correlate with AVM volume10). The hemorrhage risk correlated statistically with increasing AVM volume, decreasing dose, and treatment isodose lines less than or equal to 70. The investigators also reported that neither patient age nor incidence of prior hemorrhage correlated with the risk of post-treatment bleeding. In a retrospective study, Friedman
et al.\(^8\) found that 10 of 12 AVM cases with hemorrhage had angiographic risk factors, including arterial aneurysm, venous aneurysm, venous outflow stenosis, and periventricular location. They also found that GKS did not influence the hemorrhage rate of AVMs during the latency interval before obliteration. No protective benefit was conferred on patients who had incomplete nidus obliteration on early (< 60 mo) follow-up after radiosurgery\(^20\). Miyawaki et al.\(^8\) reported that the rate of post-radiosurgical hemorrhage was 2.7% per person-year for AVMs with treatment volumes < 14 cm\(^3\) and 7.5% per person-year for AVMs > 14 cm\(^3\). There were two cases of fatal hemorrhage. One case of hemorrhage occurred at 5.9 months, which is latent period after GKS. The target volume was 12.1 cm\(^3\) and the marginal dose was 19.6 Gy. In the other case of hemorrhage, occurred at 36.5 months after radiosurgery, partial obliteration was shown at follow up angiogram.

**CONCLUSION**

Large AVMs are more fastidious, in terms of favorable treatment outcomes, compared to that of the smaller ones. The reason is that the larger AVMs cannot be irradiated with desired radiation dose with minimal effects on surrounding structures. Recent development of imaging devices and planning software, however, enable exclusion of feeding arteries and draining veins, thereby minimizing the target volume and delivery of sufficient treatment dose. We look forward to more investigations on various radiosurgical strategies in order for better outcomes with large AVMs.

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