Application of Single-Stage Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations >10 cm³

Shunya Hanakita, MD; Tomoyuki Koga, MD, PhD; Masahiro Shin, MD, PhD; Hiroshi Igaki, MD, PhD; Nobuhito Saito, MD, PhD

Background and Purpose—Stereotactic radiosurgery (SRS) is a safe and effective treatment for small arteriovenous malformations (AVMs), the use of this modality for the treatment of large AVMs is still controversial, although it has been used in difficult cases. The aim of this study was to evaluate the treatment outcomes of patients who underwent single-stage SRS for large AVMs and to discuss the role of SRS in the treatment of these challenging lesions.

Methods—Between 1998 and 2010, 65 patients with AVMs >10 cm³ underwent single-stage SRS using the Leksell Gamma Knife. Patients who had prospective volume-staged SRS were excluded from this series. Outcomes including the rates of obliteration, hemorrhage after treatment, and adverse events were retrospectively evaluated.

Results—The mean nidus volume was 14.9 cm³ (±3.8 cm³), and a mean margin dose of 20 Gy (±1.5 Gy) was applied. The mean observation period was 60 months (range, 7–178 months). The nidus obliteration rates after SRS were 44%, 76%, and 81% at 3, 5, and 6 years, respectively. The annual hemorrhage rate after SRS was 1.94% and permanent adverse events were observed in 2 patients (3%).

Conclusions—For large AVMs <20 cm³, single-stage radiosurgery by applying >16 Gy marginal dose presented favorable obliteration rates with relatively low rate of morbidity. Further accumulation of cases is awaited to fully evaluate the results of single-stage radiosurgery for large AVMs. (Stroke. 2014;45:00-00.)

Key Words: arteriovenous malformations ■ Gamma Knife radiosurgery ■ radiosurgery

Despite recent progress in microsurgical techniques, endovascular treatments and radiosurgery that allow for the safer treatment of even the deep cerebral arteriovenous malformations (AVMs), large AVMs still remain difficult to treat. In addition, some of these lesions are associated with repetitive hemorrhage, which necessitates proper treatment. As for stereotactic radiosurgery (SRS), previous studies have shown that nidus volume was one of the most important factors for predicting outcomes. When single, high-dose irradiation is applied, as in Gamma Knife radiosurgery, the irradiated margin dose must be lowered when the target lesions are larger to avoid unacceptable morbidity; thus, the efficacy of treatment is reduced according to the dose–response curve. SRS has often been recommended for small, deep-seated lesions, where direct surgery is difficult. Although the size limitation in radiosurgery for AVM is often a maximum diameter of 3 cm, diameter cannot be a strict criterion for treatment decision because volume is not always correlated with maximum diameter. Even lesions with a diameter >3 cm can sometimes be safely treated because of their thin and long, shape, as often observed in the corpus callosum lesions. Therefore, when considering the indications for SRS, not only the maximum diameter but also the nidus volume should be taken into account. Lesions with volume less than ≈10 cm³ can be good candidates for radiosurgery. However, there are still many cases with larger lesions that are also difficult to be treated with other options. For those cases, staged radiosurgery has been applied in some centers. This approach seems to have treatment effects to certain extent, but the results are not favorable, showing <50% obliteration rates at 5 years with adverse events observed in 11% to 13% of the cases.

Here, we review the results of a single-session SRS for a nidus volume ranging from 10 to ≈20 cm³ and speculate the efficacy and volume limit for a single-session SRS treatment strategy for patients with AVMs.

Methods

Patients and Characteristics of Lesions
Between September 1998 and October 2010, 67 patients with cerebral AVM with a nidus volume >10 cm³ underwent single-stage SRS using the Leksell Gamma Knife at our institute. Of these, 2 patients died of unrelated events within 3 months of their SRS procedures. As a result, we retrospectively reviewed the medical records of 65 patients. If the lesions were too large to apply ≥16 Gy for keeping the volume receiving 12 Gy smaller than ≈20 to 25 cm³, which was considered as the safety limit, we decided to treat them with staged radiosurgery. Patients who underwent prospective volume-staged
SRS for large AVMs were excluded from this study. The institutional review board of our institute approved the study protocol, and written informed consent was obtained from all patients.

In all patients, the diagnosis of AVM was confirmed with cerebral angiography in combination with computed tomography or MRI. Twelve patients (18%) were initially treated with other modalities (surgical resection in 2, endovascular treatment in 10) and were referred to our hospital to receive SRS for the residual nidus. In the other 53 patients, SRS was the primary treatment. The treatment decisions for patients with AVM were made based on neurosurgical conferences. Radiation oncologists jointly discussed treatment strategies that included radiosurgery. The radiosurgery-based grading score (AVM score) proposed by Pollock and Flickinger\textsuperscript{11} was used to evaluate patient outcomes. The score was calculated according to the following equation: AVM score=0.1×(AVM volume in cm\textsuperscript{3})+0.02×(patient age in years)+0.5×(location: hemispheric/corpus callosum/cerebellar=0; basal ganglia/thalamus/brain stem=1). The clinical characteristics of all patients are summarized in Table 1. In total, 65 patients were followed up for 7 to 178 months (mean, 60 months; median, 55 months) after SRS. Among these, 49 patients (75%) were followed up for >3 years. The patient age at the time of SRS ranged from 9 to 66 years (mean, 35 years; median, 34 years). When graded using the Spetzler–Martin classification,\textsuperscript{12} 16 (25%) were grade II, 38 (58%) were grade III, and 11 (17%) were grade IV. There were no patients in grade V or grade VI. The maximum nidus diameter ranged from 25 to 68 mm (mean±SD, 39±7.7 mm; median, 36 mm; interquartile range, 35–43 mm). Sixty-one patients (94%) had nidi of maximum diameter >3 cm. Of these, 2 had nidi of maximum diameter >6 cm. The nidus volume ranged from 10 to 23.5 cm\textsuperscript{3} (mean±SD, 14.9±3.8 cm\textsuperscript{3}; median, 14.2 cm\textsuperscript{3}; interquartile range, 11.3–18.1 cm\textsuperscript{3}; Figure 1). The mean radiosurgery-based AVM score was 2.25±0.49 (range, 1.2–3.4). For SRS using the Gamma Knife, the marginal dose ranging from 15 to 20 Gy (mean, 18.9±1.5 Gy; median, 20 Gy; interquartile range, 18–20 Gy) was applied. Twenty patients (31%) experienced 37 hemorrhagic events before SRS. Between the time of diagnosis and SRS, excluding the first hemorrhagic event in 17 patients who presented with hemorrhage, 20 hemorrhagic events were observed >180 patient-years. Using the person-years method, the annual hemorrhage rate after initial presentation until SRS was 11.1%.

**Radiosurgical Treatment**

After the Leksell stereotactic frame was fixed on the patient’s head, the patient underwent stereotactic imaging to obtain precise information on the shape, volume, and 3-dimensional coordinates of the AVM nidus using computed tomography or MRI in combination with angiography. Treatment planning was performed jointly by neurosurgeons and radiation oncologists using commercially available software. The planning software (Leksell GammaPlan, Elekta Instruments AB) allowed for the display of multiple radiographic images on a computer screen with simultaneous superimposition of isodose lines. The nidus volume was calculated using the Leksell Gamma Plan by depicting the nidus based on the judgment of neurosurgeons and radiation oncologists. In principle, the ideal dose applied to the margin of each AVM nidus was 20 Gy. To avoid complications when the nidus volume was larger, the marginal dose was reduced (but not to <16 Gy), which resulted in an obliteration rate of >70% in previous reports.\textsuperscript{4,13} Only 1 patient was treated with a marginal dose of <16 Gy (15 Gy) to reduce irradiation of the optic nerve.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients in analysis</th>
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<tr>
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<td>17 (26%)</td>
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<tr>
<td>Seizure</td>
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<td>17 (26%)</td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Incidental</td>
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<td>2 (3%)</td>
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<tr>
<td>Headache</td>
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<td>Follow-up period, mo</td>
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<tr>
<td>Spetzler–Martin grade, n</td>
<td>II 16 (23%)</td>
<td>III 38 (58%)</td>
<td>IV 11 (17%)</td>
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</tbody>
</table>

**Table 1. Clinical Characteristics and Radiosurgical Dosimetry for Patients With AVMs >10 cm\textsuperscript{3}**

AVM indicates arteriovenous malformation; and SRS, stereotactic radiosurgery.

**Figure 1.** Distribution of maximum nidus diameter and nidus volume. **A**, Maximum nidus diameter ranged from 25 to 68 mm (mean±SD, 39±7.7 mm; median, 36 mm; interquartile range [IQR, 35–43 mm]). **B**, The nidus volume ranged from 10 to 23.5 cm\textsuperscript{3} (mean±SD, 14.9±3.8 cm\textsuperscript{3}; median, 14.2 cm\textsuperscript{3}; IQR [11.3–18.1 cm\textsuperscript{3}]).
Follow-Up Evaluation and Statistical Analysis

After SRS, follow-up clinical examinations were performed either at our hospital or by the referring physicians. The patients underwent radiological imaging (mainly MRI) every 6 months on a regular basis, and additional imaging was performed when the patients presented with new or worsened symptoms. Images were evaluated independently by neurosurgeons and radiologists. Angiography was performed when the results of these imaging modalities strongly suggested nidus obliteration.

Statistical analyses were performed using JMP 10 (SAS Institute, Inc. Cary, NC). The actuarial obliteration rate was calculated using the Kaplan–Meier method. A Cox proportional hazards model was used for univariate and multivariate analyses to evaluate factors that could potentially affect nidus obliteration. Factors associated with adverse events were also evaluated by univariate and multivariate logistic regression models.

Results

Obliteration Rate

In this series, 18 patients achieved nidus obliteration within 3 years and 23 patients had nidus obliteration after >3 years of follow-up as assessed by angiography (n=32) or MRI (n=9) at a mean time of 40 months after SRS (range, 15–73 months). Thus, among 53 patients who were followed up for >3 years or had confirmed nidus obliteration within 3 years, 41 patients (77%) had nidus obliteration. When calculated by the Kaplan–Meier method, the actuarial obliteration rates were 44%, 76%, and 81% at 3, 5, and 6 years, respectively. When the group of patients with AVMs ≥14 cm³ (approximately volume of a 3 cm diameter sphere) was assessed, 14 of 23 patients (61%) who were followed up for >3 years showed obliteration. Using the Kaplan–Meier method, the accumulated obliteration rates for AVMs ≥14 cm³ at 3, 5, and 6 years were 36%, 74%, and 74%, respectively, and there was no significant difference between lesions with a volume of 10 to 14 cm³ and larger lesions (P=0.31; Figure 2). When we analyzed the factors for successful obliteration, higher margin dose was the only significant associated factor in the univariate analysis (hazard ratio, 1.30; 95% confidence interval, 1.04–1.67; P=0.02). In multivariate analyses, there was no significant factor for higher obliteration rate. Factors, including target volume, AVM score, history of hemorrhage, previous endovascular treatment, deep location (basal ganglia or thalamus), and deep drainage, did not significantly influence the obliteration rate (Table 2). The largest volume of angiographically obliterated case was 21.5 cm³.

Among 41 patients whose lesions were obliterated, the lesions in 18 patients showed complete obliteration until 3 years after treatment. Univariate analysis for age, volume, maximum diameter, previous treatment, location (eloquent area or deep seated), deep drainage vein, and presentation (hemorrhagic versus nonhemorrhagic presentation) did not reveal any significant factors associated with the earlier response.

Based on our early experience in which nidus obliteration in most cases was obtained by 5 years after treatment, we considered additional treatment if the nidi were still present 5 years after initial treatments. The outcome was analyzed based on the results of the initial treatments and those patients who received additional treatments were censored at the time of those procedures for the Kaplan–Meier analysis. In this series, 3 patients received additional SRS for their residual nidi after a 5-year follow-up. Two achieved nidus obliteration on angiography at 27 and 28 months after their second SRS, respectively. None of these patients presented with neurological deterioration after additional treatment. One patient received resection of his residual nidi 64 months after SRS. This patient was discharged without neurological events and showed no adverse events during the follow-up period.

Complications and Hemorrhagic Events

Thirty-one patients (48%) developed T2 hyperintense regions around the irradiated field that were confirmed by MRI at 3 to 24 months (mean, 10 months; median, 11 months) after SRS. Adverse events were observed in 11 patients (17%) at 3 to 17 months (mean, 10 months; median, 11 months) after SRS.
Of these 11 patients, 9 patients (14%) had newly developed symptoms (3 had seizures, 2 hemiparesis, 3 dysesthesia, 1 visual field defect, and 1 aphasia). When the patients developed neurological symptoms related to T2 signal changes surrounding the lesions, we principally administrated oral corticosteroids. Fortunately, these symptoms resolved during the follow-up period, and no patient had a permanent deficit. For 2 other patients who had existing symptoms that worsened (1 had hemiparesis, 1 dysarthria, and 1 increasing frequency of seizures), both patients (3%) showed permanent symptoms (one showed mild hemiparesis and the other showed mild dysarthria). Therefore, in a single-stage SRS, transient neurological events were observed in 9 patients (14%) and permanent neurological consequences were observed in 2 patients (3%). The presence of lesions at the eloquent area was the only significant factor associated with the adverse events after SRS in the univariate analysis (hazard ratio, 8.62; 95% confidence interval, 1.49–163; P=0.01); however, there was no significant factor associated with adverse events in multivariate analyses (Table 3).

Five patients experienced 6 hemorrhagic events 6 to 24 months (median, 17 months) after the treatment during 309 patient-years. The annual hemorrhage risk after SRS was 1.94%. The status of these 5 patients scored with modified Rankin scale (mRS) was mRS 4 for 3 patients and mRS 5 for 2 patients. Pretreatment mRS of these patients was mRS 0 for 4 patients and mRS 1 for 1 patient. All the post-treatment hemorrhagic events occurred before radiological confirmation of nidus obliteration. There was no bleeding after nidus obliteration in this cohort during 90 patient-years. About correlation between the nidus volume and treatment outcomes, the annual bleeding rate after SRS was 1.93% for AVM with volume of 10 to 14 cm³ and ≥14 cm³ were 1.93% and 1.96%, respectively (P=0.62), and the rate of adverse events was 19% and 15%, respectively (Table 4).

### Discussion

In this study, we showed that the single-stage SRS for the treatment of AVMs >10 cm³ achieved a 78% obliteration rate at 5 years with a 2% rate of adverse events. Because AVMs have a complex shape in many cases, there are diverse treatment strategies for this disease. SRS is particularly recommended for deep-seated lesions, where surgical resection can be difficult and a functional field probably exists. The use of SRS for the treatment of small- or medium-sized AVMs has been accepted widely in the past. However, because larger AVMs require higher radiation doses that increase the risk of
radiosurgery-induced complications, there has been skepticism over their use for larger lesions. Therefore, there is still controversy over which treatment strategy, including conservative management, is optimal for larger AVMs. In our series, patients with nidi volumes ranging from 10 to 23 cm³ were treated. The limit for SRS is usually considered as 3 cm, which means ≈14 cm³ when lesions are sphere shaped. However, not all AVMs are spheres. They often show complex shapes from which it is difficult to predict nidus volume. Considering radiosurgery, volume >10 cm³ is still challenging because related complications have been well reported. We mainly applied ≥16 Gy to the margin of the lesions aiming for favorable obliteration. However, it was impossible to apply >16 Gy for lesions >20 cm³ while keeping the volume receiving >12 Gy smaller than ≈20 to 25 cm³, which is one of the possible safety limits suggested by a dose–response analysis, although it should be noted that they are variable depending on the location of AVMs. Indeed, the largest lesion for which complete obliteration was obtained in our series was 21.5 cm³, and 2 among 6 patients with lesions >20 cm³ experienced post-treatment adverse events. Therefore, we speculate that the size limit of AVM for which single-session radiosurgery can safely and effectively be applied is ≈20 cm³.

Five-year obliteration rate in our series was 76%, which was higher than or similar to that of single-session radiosurgery for large AVMs in other series (22%–77%; Table 4), whereas the rate of morbidity was comparable (3% versus 3.9%–27%; Table 4). A possible cause for this difference may be because of the higher doses applied in our series compared with others (15–20 Gy [mean, 18.9 Gy] in our series versus 10–20 Gy [mean, 14.1 Gy] in others). We tried not to reduce the marginal doses to <16 Gy, which was a suggested dose that can obliterate >70% of AVM in a dose–response analysis. Thus, the upper limit of the volume in our study cohort was ≈20 cm³, whereas other studies contained large number of patients with AVMs >30 cm³ and this may have resulted in different outcomes.

For excessively large AVMs (>20 cm³), single-session SRS may be limited because of the high frequency of treatment-related complications despite of low efficacy. For treating excessively large AVM, there are few reports mainly using radiotherapy procedure. Historically, conventional fractionated radiotherapy for large AVM was known to be less effective; therefore, hypofractionated radiotherapy was applied. Although the results were not conclusive, the author mentioned the possibility of volume reduction by hypofractionated radiotherapy and a combined therapy with other modalities was recommended. Some institutes have reported the preliminary results of staged SRS, particularly using Gamma Knife. There are scarce reports on staged SRS that showed 28% to 29% rate of angiographic obliteration with 11% to 13% of adverse events and 4% to 5% risk of hemorrhage in the latency period. Although these results may not seem promising, it must be noted that the majority of patients included in these series had excessively large volumes (>20 cm³) relatively low marginal doses <18 Gy were applied to avoid adverse radiation effects in the earlier cases and additional SRS increased the obliteration rates to 56% at 10 years. Evidently, the reduction of hemorrhage risk in the present series from 11.1% before treatment to 1.9% after treatment seemed preferable. However, because the goal of AVM treatment is to eliminate bleeding, and having considered the severity of morbidity experienced by 5 patients in our series after hemorrhage, the residual nidus should be treated with multimodal approaches, such as additional SRS, endovascular treatment, and surgical resection after a sufficient follow-up to further eliminate the risk of bleeding.

The limitations of this study include a selection bias. As for the analysis of hemorrhagic risk before and after treatment, the relatively short observation period before treatment (mean, 29 months; median, 5 months) may have elevated the apparent pretreatment risk and thus the risk of hemorrhage after treatment may seem to have reduced. Another limitation of this study is the limited number of patients in this series. Although we could not see any significant factors related to higher obliteration rate or morbidities in multivariate analyses, absence of certain, well-known factors associated with the outcomes such as volume and history of hemorrhage may suggest the lack of statistical power in these analyses. For example, the fact that the lesions in the eloquent regions did not result in a significantly higher morbidity (P=0.07) does not allow us to treat those lesions in the same way as the lesions in noneloquent areas.

Conclusions

Single-stage radiosurgery was safely and effectively applied to limited cases of AVMs with nidus volume between and 20 cm³. Delivering ≥16 Gy to the margin of the lesions in one session resulted in favorable obliteration rates with relatively low morbidity for this size range of AVM. About the severe morbidity associated with post-treatment hemorrhage, additional treatment for the residual nidus after a sufficient follow-up should be considered. Further accumulation of cases is awaited to fully evaluate the results of single-stage radiosurgery for large AVMs.

Disclosures

None.

References


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