Outcomes of Volume-Staged Radiosurgery for Cerebral Arteriovenous Malformations Larger Than 20 cm^3 with More Than 3 Years of Follow-Up

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■ OBJECTIVE: **Treatment of extremely large cerebral arteriovenous malformations (AVMs) is challenging. Although volume-staged stereotactic radiosurgery (SRS) is a possible multimodal treatment option for such lesions, reports of these procedures are scarce. We evaluated the efficacy and safety of volume-staged SRS in patients with AVMs >20 cm^3 with >3 years of follow-up.**

■ METHODS: **Between 2005 and 2012, 18 patients with AVMs >20 cm^3 were treated by volume-staged SRS. The median target volume was 38 cm^3 (interquartile range, 31–53 cm^3). Treatment was conducted in 2–3 stages with a median interval of 6 months.**

■ RESULTS: **The median follow-up period from the last SRS treatment was 53 months (interquartile range, 41–75 months). Complete nidus obliteration was achieved in 6 patients (33%), and the obliteration rate at 5 years after initial SRS was 35% by the Kaplan-Meier method. The annual hemorrhage rate after last SRS treatment was 3.9% (95% confidence interval, 0.8%–11.5%). Radiation-induced adverse effects occurred in 2 patients.**

■ CONCLUSIONS: **In our series, volume-staged SRS for AVMs >20 cm^3 achieved a nidus obliteration rate of 35% at 5 years. There was still a high risk for hemorrhage (~4% per year) after treatment, which seemed to be higher than the rate commonly observed in the posttreatment course of single-session SRS for average-size AVMs. Further cases will help determine whether volume-staged SRS could be routinely considered, based on its efficacy and risks, including comparison with the natural history of large AVMs.**

INTRODUCTION

Despite advances in microsurgery techniques, endovascular treatment, and radiosurgery that have enabled safer treatment of even deeply located cerebral arteriovenous malformations (AVMs), large AVMs have often been regarded as inoperable.[1] Some of these lesions are aggressive, causing repetitive hemorrhages that necessitate treatment.[2,3] In stereotactic radiosurgery (SRS), the volume of the nidus is 1 of the most important factors in predicting the outcomes. Therefore, commonly used single-stage SRS is considered ineffective for treatment of large AVMs.[1,4] From the perspective of radiosurgery, lesions >20 cm^3 are considered untreatable; the volume of nidus receiving >12 Gy should be kept <20–25 cm^3, which is a possible safety limit, as reported previously.[5] In addition, previous series of SRS reported that lesions >30 cm^3 were a challenge to treat with single-stage SRS because of the high frequency of complications.[6-8] Based on these considerations, we reported the results of single-dose radiosurgery for AVMs measuring 10–20 cm^3,[9] which was comparable to the result for AVMs <10 cm^3. In addition, based on our limited experience, for AVMs >20 cm^3, the largest AVM nidus in which nidus obliteration was achieved with single-dose SRS was 21.5 cm^3. Adverse events were experienced after treatment in 2 of 6 patients with lesions >20 cm^3. Thus, we considered that the volume limit of single-dose SRS would be ~20 cm^3. In some institutions, several approaches, such as dose-staged or volume-staged SRS, have been devised to overcome this volume limitation.[10,11] However, the results of this challenging method, including obliteration rate, risk of adverse events, and hemorrhage events after treatment, have been inconsistent.[12,13] Furthermore, reports that include >10 cases with a sufficient follow-up period, especially for volume-staged SRS, are scarce.[11-13] As described in a preliminary report in the early 2000s,[11] volume-staged SRS for lesions >20 cm^3 was introduced in February 2005 at our institution. Although a few series of volume-staged SRS exclusively analyzed extremely large AVMs (>20 cm^3),[14,15] these studies had a

Key words
- Gamma Knife radiosurgery
- Large arteriovenous malformation
- Staged stereotactic radiosurgery

Abbreviations and Acronyms
AVM: Arteriovenous malformation
CI: Confidence interval
CT: Computed tomography
MRI: Magnetic resonance imaging
SRS: Stereotactic radiosurgery

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Citation: World Neurosurg. (2016) 87:242-249.
http://dx.doi.org/10.1016/j.wneu.2015.12.020

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

very small patient number (5–6 patients), and the analyses of the results in the series remain unclear. In the present study, we reviewed early results of volume-staged SRS for AVMs >20 cm^3 at our institution to evaluate the efficacy and limitations of this challenging strategy and to explore possible improvements in the future.

MATERIALS AND METHODS

Patient Characteristics

The internal review board of the University of Tokyo Hospital approved the study protocol, and written informed consent was obtained from all included patients. Between February 2005 and January 2012, 170 consecutive patients underwent SRS using the Leksell Gamma Knife (Elekta Instruments, Norcross, GA) for intracranial AVMs. Among them, 18 patients (10%) with large cerebral AVMs (nidus volume >20 cm^3) were treated by volume-staged SRS. All patients received follow-up care during this study. In all patients, the diagnosis was confirmed with cerebral angiography in combination with computed tomography (CT) or magnetic resonance imaging (MRI). One patient had undergone surgical extirpation of an intracerebral hematoma 30 years ago. None of the other patients had a history of resection. Before this study, 5 patients had received endovascular treatment, 3 for AVM-related aneurysms and 2 for nidus embolization. Both patients who received embolization of nidi before SRS at other hospitals were referred to our hospital to receive SRS for the residual nidi. Although the embolization before SRS was reported as a failure factor for obliteration,[16] these 2 patients had AVMs at the peripheral lobe regions, which were fed by the extracranial arteries and other vessels, and these extracranial arteries were mainly treated with a liquid agent (Onyx; ev3 Neurovascular, Irvine, California) at the referring hospitals. For 13 patients, SRS was the primary treatment. The treatment decisions for patients with AVMs were made at neurosurgical conferences. Radiation oncologists, endovascular surgeons, and neurosurgeons jointly discussed treatment strategies, which included endovascular treatment, surgical resection, and radiosurgery. The radiosurgery-based grading system scores (AVM scores) proposed by Pollock and Flickinger[17] were also used to evaluate patient outcomes, based on the following equation: 0.1 × (AVM volume in cm^3) + 0.02 × (patient age in years) + 0.5 × (location, hemispheric/corpus callosum/cerebellar = 0; basal ganglia/thalamus/brainstem = 1).

The characteristics of all 18 patients are summarized in Table 1. The median observation period was 53 months (interquartile range, 41–75 months) after the last SRS. One patient (case 16) died of epilepsy 11 months after the last procedure, and the other patients were followed until this time. Findings at initial presentation leading to the diagnosis were hemorrhage (n = 7 patients), seizure (n = 4 patients), headache (n = 2 patients), and incidental finding (n = 5 patients). Of the 11 patients who did not present with hemorrhage, 5 experienced subsequent hemorrhages between initial diagnosis and SRS treatment. Before treatment, 19 hemorrhages were observed in 12 patients. When excluding the first hemorrhages in the 7 patients who initially presented with hemorrhages, 12 hemorrhages were observed in 140 person-years between diagnosis and treatment. Thus, the annual bleeding risk was calculated as 8.6% before SRS. When the risk of hemorrhage was calculated during the life span of the patients, the risk of hemorrhage was 2.9% per year. The range of target volume was 21–71 cm^3 (median 38 cm^3; interquartile range, 31–53 cm^3), and the AVM score range was 2.81–8.49 (median 4.94; interquartile range, 3.80–6.29). When graded according to Spetzler-Martin grading,[18] 4 patients had grade III AVMs, 7 had grade IV AVMs, and 7 had grade V AVMs (Table 1). Grade III AVMs have diverse characteristics and consist of 4 subtypes ranging in size from small to large; among the 4 patients with grade III AVMs in this cohort, the AVMs were further classified as medium/deep (size 3–6 cm, presence of deep venous drainage, noneloquent region) in 2 patients, medium/eloquent (size 3–6 cm, absence of deep venous drainage, eloquent region) in 1 patient, and large (size >6 cm, absence of deep venous drainage, noneloquent region) in 1 patient. The volume of all these lesions was >20 cm^3, which was a challenging volume for the typical single-dose radiosurgery method; therefore, we considered staged therapy for these patients.

Radiosurgical Treatment

After the Leksell stereotactic frame was fixed on the head, each patient underwent stereotactic imaging to obtain precise information about the shape, volume, and three-dimensional coordinates of the AVM nidi. CT scans of 1.0-mm slice thickness or gadolinium-enhanced time-of-flight MRI was used in combination with angiography. Treatment planning was performed using commercially available software (Leksell Gamma Plan; Elekta Instruments). According to the preliminary reports of volume-staged SRS,[11,19] the whole nidus was covered in the first procedure to measure the entire volume. We generally divided the whole nidus into equal volumes using anatomic landmarks, such as major vessels, ventricles, and other structures. When the nidus was fed by many feeders, the volume was divided according to the perfused area (e.g., 1 area was fed by the anterior circulation and another area was fed by the posterior circulation). When the volume of each divided part was >20 cm^3, the whole nidus was further divided into 2 parts. If the same perfused area was divided, we initially applied radiation at the deep side and to the superficial part. Ultimately, 10 patients underwent 2-staged SRS, and 8 patients underwent 3-staged SRS. There was a median 6-month interval between treatments except in 1 case in which the patient was found to be pregnant after the first stage; this patient received the second treatment after giving birth (14 months after the initial treatment). We principally applied 40% of the treatment isodose line of 16 Gy.

Follow-Up Evaluation

After SRS, follow-up clinical examinations were performed at our hospital or by referring physicians. The patients underwent MRI or CT every 6 months, 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 (Figure 1).

Statistical Analysis

Statistical analyses were performed using JMP 11 (SAS Institute Inc., Cary, North Carolina, USA). The actuarial obliteration rate