Long-Term Outcomes of Single-Session Stereotactic Radiosurgery for Cerebellar Arteriovenous Malformation, with a Median Follow-Up of 10 Years

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■ OBJECTIVE: **Cerebellar arteriovenous malformation (C-AVM) is poorly tolerated because of its aggressive natural history. The aim of this study was to delineate long-term outcomes of Gamma Knife stereotactic radiosurgery (GKRS) for C-AVM.**

■ METHODS: **The outcomes of 45 patients who underwent GKRS for C-AVMs at our institution were retrospectively analyzed. Event-free survival was defined as free from any neurologic deficits caused by AVMs or adverse phenomena from the treatment.**

■ RESULTS: **The median age and follow-up were 41 years (range, 6—77 years) and 120 months (range, 5—291 months), respectively. The median volume and Pollock-Flickinger radiosurgical AVM score were 1.3 cm^3 (range, 0.1—8.3 cm^3) and 1.26 (range, 0.5—2.06), respectively. Actuarial obliteration rates were 46%, 75%, and 90% at 3, 5, and 6 years, respectively. Multivariate analysis showed that the maximal diameter ≤15 mm ($P = 0.021$) and margin dose >20 Gy ($P = 0.0008$) were significantly associated with better obliteration. Four patients experienced posttreatment hemorrhages, and annual hemorrhage rates were 1.9% and 0.30% before and after obliteration, respectively. One patient died because of hemorrhage, whereas the other 3 patients spontaneously recovered. Perifocal edema was confirmed in 8 (16%); however, no symptomatic edema was observed. Overall, neurologic deteriorations were noted in 4 patients; 3 were because of posttreatment hemorrhage, and 1 was because of pretreatment angiography. The event-free survival rates were 96%, 93%, and 93% at 4, 10, and 15 years, respectively.**

■ CONCLUSIONS: **GKRS is a reasonable intervention for C-AVMs. Symptomatic complications are rare, and the long-term outcomes are favorable.**

INTRODUCTION

Cerebral arteriovenous malformation (C-AVM) is a rare cerebrovascular disease, with its prevalence presumed to be 1—18 per 100,000.[1-4] Approximately half of patients with AVM present with intracranial hemorrhage, and its annual bleeding rate ranges from 1% to 4%.[1-4] Death may result from hemorrhage in 10%—18% of cases, whereas neurologic deficits are caused more frequently, occurring in 53%—81% of cases.[2] Regarding functional outcomes, approximately 16% of the patients were moderately or severely disabled after hemorrhage.[2]

The outcomes of AVMs are different individually, and the nidus location is one of the most important factors to predict the probability of hemorrhage as well as adverse events after interventions. Compared with other AVMs, C-AVM, a rare disease accounting for less than 15% of all AVMs,[4-8] has a higher annual bleeding rate, ranging from 4.4% to 11.6%.[6,9] Severe outcomes can be observed even with smaller hematoma volume.[6,9,10] Regardless of an aggressive surgical treatment, up to 25% mortality has been reported.[6-9,11] Thus, C-AVM is poorly tolerated, and

Key words
- Arteriovenous malformation
- Cerebellum
- Gamma Knife
- Intracranial hemorrhage
- Posterior fossa
- Stereotactic radiosurgery

Abbreviations and Acronyms
AVM: Arteriovenous malformation
C-AVM: Cerebellar arteriovenous malformation
DSA: Digital subtraction angiography
EFS: Event-free survival
GKRS: Gamma Knife radiosurgery
MRI: Magnetic resonance imaging
mRS: modified Rankin Scale
SRS: Stereotactic radiosurgery

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treatment should be considered; however, 2 controversies as to the treatment of C-AVM remain.

First, the choice of optimal treatment modality is open to debate, especially when treating ruptured C-AVM. Similar to AVMs in the other locations, therapeutic interventions for C-AVM include monomodal or multimodal use of microsurgery, endovascular embolization, and radiosurgery. Because of a high rate of rebleeding of up to 34%[1,9] and the following poor neurologic sequelae, microsurgery tends to be favored because it can immediately exclude AVMs from blood circulation and prevent additional hemorrhage when treating ruptured AVMs.[7,8,12,13] In the meantime, surgeons should recognize that the surgical procedures are sometimes complicated and highly invasive because of the tight eloquent anatomic structures within the small space of the posterior fossa.[9,14,15]

The second controversy is the validity of treatment for unruptured AVMs. In 2014, a prospective randomized study that compared intervention with medical management (ARUBA [A Randomized Trial of Unruptured Brain Arteriovenous Malformations]) denied the superiority of intervention against unruptured AVMs.[16] Although debate needs to be continued regarding the validity of this study, surgeons should recognize that one of the main reasons for this failure was considered to be significant invasiveness related to the intervention itself. Acceptable therapeutic strategy should have an adequate safety profile; otherwise, any intervention types for C-AVMs are a debatable issue.

Gamma Knife radiosurgery (GKRS) is one of the methods of stereotactic radiosurgery (SRS), and it can treat even deep-seated niduses without direct manipulation of the brain, providing approximately 75%—85% of complete obliteration after 2—5 years from treatment and dramatically decreasing the risk of hemorrhage.[17-24] However, few previous studies have reported outcomes of GKRS for C-AVM.[25,26] The long-term outcomes are still unknown and of primary concern, considering that rare but significant delayed radiation-induced complications have recently been reported along with the accumulation of cases.[27] Therefore, to examine the validity of GKRS as the main therapeutic intervention for C-AVM and determine the long-term safety and effectiveness, we conducted a retrospective analysis of GKRS for C-AVMs based on the data of our institution.

METHODS

Patient Selection

After receiving institutional review board approval, we retrospectively reviewed clinical and radiographic data of patients with brain AVMs treated with GKRS (Elekta Instruments AB, Stockholm, Sweden) at our institution. All patients provided written, informed consent. To evaluate long-term outcomes, we selected patients who were treated between April 1990 and March 2010 to enroll those who were followed up for >5 years.

To examine detailed outcomes of GKRS for unruptured C-AVM, we performed secondary analysis for ARUBA-eligible patients, selecting patients who fulfilled the criteria used in the ARUBA study.[16] This study period was set between April 1990 and March 2013 to obtain ≥3 years follow-up because the length of follow-up in the ARUBA study was <3 years. Patients who had an unruptured C-AVM and were ≥18 years old were included. Exclusion criteria were as follows: 1) evidence of previous hemorrhage, 2) previous AVM treatment, 3) AVM that is deemed untreatable, 4) modified Rankin Scale (mRS) score ≥2, 5) life expectancy <10 years, 6) pregnancy, 7) thrombocytopenia or uncorrectable coagulopathy, 8) multiple AVMs, 9) previous diagnosis of other intracranial vascular malformations, and 10) any neurocutaneous syndromes.

The course of treatment was meticulously determined via a neurosurgical conference with radiation oncologists and an endovascular treatment surgeon. We fully explained to all patients that microsurgery was also a rational treatment, particularly for hemorrhagic cases, wherein Spetzler-Martin grade was I or II. GKRS was primarily performed in cases with the following findings: small nidus (generally, diameter <30 mm); nidus location deep in the cerebellar parenchyma, cerebellar nuclei, or cerebellar peduncles, where disabling neurologic morbidities would be caused if injured. Those who declined microsurgery and those who had coexisting diseases that were considered risk factors for aggressive surgery under general anesthesia were also considered as candidates for GKRS.

The nidus locations were recorded and classified into the following 4 groups: hemisphere, exclusively located at the noneloquent cerebellar hemisphere; vermis, exclusively located at the vermis with or without slight extension to the adjacent parenchyma; peduncle/nucleus, located mainly in eloquent cerebellar lesions, including the cerebellar nucleus and peduncle; cerebellopontine angle, located mainly in the cerebellopontine angle, frequently involving a small anterior surface of the cerebellar peduncle and trigeminal nerve. From the definition used in Spetzler-Martin grading, the peduncle/nucleus were considered eloquent locations. Locations of a postoperative or postembolized residual nidus were determined as the location of the residual nidus and not as the location of the original nidus. Similarly, the Spetzler-Martin grade of a postoperative or postembolized residual nidus was determined with the findings of a residual nidus. Drainage veins were considered superficial when the drainage route was solely cerebellar hemispheric veins that drained directly into the straight sinus or transverse sinus.[28]

Radiosurgical Techniques

Details of the radiosurgical techniques in our hospital have been previously reported in other articles.[20,29,30] After head fixation by using a Leksell frame (Elekta Instruments Inc., Stockholm, Sweden), stereotactic imaging was performed to obtain precise data on the shape, volume, and three-dimensional coordinates of AVMs. Digital subtraction angiography (DSA) was solely used before February 1991; thereafter, computed tomography (March 1991—July 1996) or magnetic resonance imaging (MRI) (August 1996—present) was combined to increase treatment planning accuracy. Dedicated neurosurgeons and radiation oncologists used commercially available software to plan treatments (KULA planning system until 1998; Leksell Gamma Plan thereafter [Elekta Instruments Inc.]).

Follow-Up Protocols

Patients were evaluated after GKRS at regular intervals. We performed less-invasive imaging modalities (mainly MRI) at 6-month intervals for the first 3 years. When nidus obliteration was strongly