Stereotactic radiosurgery for sylvian fissure arteriovenous malformations with emphasis on hemorrhage risks and seizure outcomes

Clinical article

GREG BOWDEN, M.D., M.Sc.,1,3,5 HIDEYUKI KANO, M.D., PH.D.,1,3 DANIEL TONETTI, M.S.,4 AJAY NIRANJAN, M.C.H., M.B.A.,1,3 JOHN FLICKINGER, M.D.,2,3 YOSHIO ARAI, M.D.,2,3 AND L. DADE LUNSFORD, M.D.1,3

Departments of 1Neurological Surgery and 2Radiation Oncology, and 3Center for Image-Guided Neurosurgery, 4University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and 5Department of Neurological Surgery, University of Western Ontario, London, Ontario, Canada

Object. Sylvian fissure arteriovenous malformations (AVMs) present substantial management challenges because of the critical adjacent blood vessels and functional brain. The authors investigated the outcomes, especially hemorrhage and seizure activity, after stereotactic radiosurgery (SRS) of AVMs within or adjacent to the sylvian fissure.

Methods. This retrospective single-institution analysis examined the authors’ experiences with Gamma Knife surgery for AVMs of the sylvian fissure in cases treated from 1987 through 2009. During this time, 87 patients underwent SRS for AVMs in the region of the sylvian fissure. Before undergoing SRS, 40 (46%) of these patients had experienced hemorrhage and 36 (41%) had had seizures. The median target volume of the AVM was 3.85 cm³ (range 0.1–17.7 cm³), and the median marginal dose of radiation was 20 Gy (range 13–25 Gy).

Results. Over a median follow-up period of 64 months (range 3–275 months), AVM obliteration was confirmed by MRI or angiography for 43 patients. The actuarial rates of confirmation of total obliteration were 35% at 3 years, 60% at 4 and 5 years, and 76% at 10 years. Of the 36 patients who had experienced seizures before SRS, 19 (53%) achieved outcomes of Engel class I after treatment. The rate of seizure improvement was 29% at 3 years, 36% at 5 years, 50% at 10 years, and 60% at 15 years. No seizures developed after SRS in patients who had been seizure free before treatment. The actuarial rate of AVM hemorrhage after SRS was 5% at 1, 5, and 10 years. This rate equated to an annual hemorrhage rate during the latency interval of 1%; no hemorrhages occurred after confirmed obliteration. No permanent neurological deficits developed as an adverse effect of radiation; however, delayed cyst formation occurred in 3 patients.

Conclusions. Stereotactic radiosurgery was an effective treatment for AVMs within the region of the sylvian fissure, particularly for smaller-volume AVMs. After SRS, a low rate of hemorrhage and improved seizure control were also evident.

(http://thejns.org/doi/abs/10.3171/2014.5.JNS132244)

Key words • arteriovenous malformation • sylvian fissure • seizure • stereotactic radiosurgery • Gamma Knife • epilepsy • vascular disorders

The prevalence of an intracranial arteriovenous malformation (AVM) is approximately 18 cases per 100,000 persons.41 The frontal and temporal regions that surround the sylvian fissure account for 9%–11% of such AVMs and present substantial management challenges because of the critical adjacent blood vessels and functional brain.25,26 Hemorrhage from a sylvian fissure AVM can result in major neurological morbidity and warrants therapeutic intervention once recognized.15,43 Cortical regions near the sylvian fissure are often associated with seizure activity. Seizures account for the initial presentation for 24%–40% of patients with intracranial AVMs.2,16,39 For patients with AVMs and seizures, reduced life expectancy and quality of life have been documented.4,5,44

Over the past 25 years, management options for AVMs have evolved. However, the goals of intervention remain complete obliteration of the AVM (to prevent hemorrhage) and preservation of neurological function.45 Over 5 years of observation, rates of AVM occlusion after stereotactic radiosurgery (SRS) range from 70% to 80%.8,20,27,29 Gamma
Knife SRS is associated with relatively low risk for adverse radiation effects. Our overall experience with more than 1200 patients with intracranial AVMs suggests that patients with AVMs in the region of the sylvian fissure are at higher risk for hemorrhage before and after SRS. Such patients are also at higher risk for seizure development than are patients with deep-seated AVMs. The study reported here was designed to evaluate hemorrhage risks and seizure outcomes in this subgroup of patients with AVMs in the region of the sylvian fissure.

Method

Patient Population

This single-institution retrospective analysis was approved by the University of Pittsburgh institutional review board. The study evaluated the outcomes of patients with sylvian fissure AVMs who underwent Gamma Knife SRS at the University of Pittsburgh from 1987 through 2009. All 87 patients underwent initial single-stage SRS for an AVM nidus that was located within or immediately adjacent to the sylvian fissure. The outcome data were collected through an independent medical records review and were analyzed by neurosurgeons who did not initially participate in management of these patients.

The median patient age at the time of SRS was 38 years (range 9–77 years); 40 patients were male and 47 were female. At the initial visit, the signs and symptoms that led to a diagnosis for these patients included intracranial hemorrhage for 40 patients (46%), seizures for 30 (34%), headache for 15 (17%), and an incidental finding for 2 (2%). Neurological deficits before SRS were present in 24 patients (28%); intracranial hemorrhage was the cause of the deficit for 21 patients, and a stroke caused by therapeutic embolization was the cause for 3 patients. The primary deficit was hemiparesis for 16 patients, followed by speech abnormalities (4 patients), paresthesias (2 patients), dysphagia (1 patient), and hemianopia (1 patient). A total of 36 patients (22 male and 14 female) had a history of seizures before SRS; 23 had had partial seizures and 13 had had generalized seizures, and all were receiving treatment with anticonvulsants.

Additional AVM characteristics included a coexisting aneurysm in 7 patients (8%) and a venous outflow varix in 12 (14%). Endovascular embolization was performed before referral for SRS for 19 patients (22%). Also before SRS, 15 patients (17%) underwent a craniotomy; 6 patients underwent partial AVM resection, 5 patients underwent hematomatoma evacuation, and 4 underwent hematomatoma evacuation and AVM resection. Before patients underwent SRS, the Spetzler-Martin grade was determined by 2 experienced neurosurgeons. A grade II AVM was diagnosed for 26 patients (30%), grade III for 43 (49%), grade IV for 16 (18%), and grade VI for 2. The Pollock-Flickinger score was calculated as grade I (< 1) for 22 patients (25%), grade II (1.0–1.50) for 37 (43%), grade III (1.51–2.0) for 15 (17%), and grade IV (> 2) for 13 (15%).

Radiosurgery Technique

On the day of the procedure, patients were adminis-
Calculations of hemorrhage were based on the time of a post-SRS bleeding event or loss of patient to follow-up. The hemorrhage statistics were obtained through Kaplan-Meier survival analysis. Calculation of the annual rate of hemorrhage during the latency period was based on the years of at-risk follow-up evaluations and the number of hemorrhages that occurred. Where appropriate, we compared various groups by using the Fisher exact and Mann-Whitney U-tests.

Results

Patient Follow-Up

The median time of follow-up imaging after SRS was 64 months (range 3–275 months). At the time of this review, 6 patients had died; 1 death was directly attributable to AVM hemorrhage, 2 deaths were from cancer (lung and pancreatic), and 3 were from undetermined (nonhemorrhagic) causes.

A total of 24 patients had neurological deficits before SRS. Of these, deficits improved for 10 patients and remained unchanged for 14 patients.

AVM Obliteration

Obliteration of the AVM was confirmed by MRI or angiography for 43 patients. The actuarial rates of confirmed obliteration were 45% at 3 years, 60% at 4 years, 60% at 5 years, and 76% at 10 years (Fig. 1). The median time to obliteration was 40 months (95% CI 38–42 months). Obliteration was confirmed by angiography for 31 patients and indicated only by MRI for 12 patients. When only patients with follow-up angiography were included in the analysis, the obliteration rates dropped artificially to 25% at 3 years and 45% at 4, 5, and 10 years. As documented by previous studies, angiography results are falsely lowered when patients decline repeat angiography after obliteration is determined by MRI.

According to univariate analysis, several variables that affect AVM obliteration were significant. The obliteration rate for smaller AVMs (< 4 cm³) was increased (p = 0.041) (Fig. 2). As the maximum AVM diameter increased, the rate of obliteration decreased (p = 0.027). The rate of total AVM obliteration was higher among patients who received a marginal dose greater than 20 Gy (p = 0.002) (Fig. 3). Obliteration rates were also higher among patients whose Pollock-Flickinger score was less than 1.20 (p = 0.035).

Seizure Activity

A total of 36 patients experienced seizures before SRS. The risk for seizures tended to be lower for younger patients (< 18 years) (p = 0.013), and male patients were more likely than female patients to have experienced seizures (p = 0.018). Seizures were less likely among patients with a history of previous intracranial hemorrhage (p = 0.0004) (Table 1).

Seizure activity follow-up examinations by a neurosurgeon and imaging were conducted concomitantly. At the last follow-up visit, the Engel seizure outcome scores for the 36 patients were as follows: Class I (free of disabling seizures) for 19 patients (53%), Class II (rare disabling seizures) for 4 (11%), Class III (significant improvement) for 2 (6%), and Class IV (no improvement) for 11 (31%). After SRS, clinically significant seizure reduc-

![Fig. 1. Kaplan-Meier curve for probability of total AVM obliteration after SRS, based on MRI and angiography combined. The numbers of patients remaining in the study at 3, 5, and 10 years were 68, 46, and 24, respectively.](image-url)
Fig. 2. Kaplan-Meier curve for probability of total AVM obliteration after SRS (determined by MRI or angiography) based on AVM volume (< 4 cm³ or > 4 cm³).

Fig. 3. Kaplan-Meier curve for probability of total AVM obliteration after SRS (determined by MRI or angiography) based on marginal dose ≤ 20 Gy.
Radiosurgery for sylvian fissure AVMs

Within the improved seizure group, the median nidus volume was 7.15 cm³ among those for whom obliteration was not achieved and 3.75 cm³ among those for whom obliteration was achieved. Among patients for whom complete obliteration was achieved, seizures improved at a median of 19 months after SRS; among patients for whom obliteration was not achieved, seizures improved at a median of 29 months after SRS. Seizure reduction was less among patients with a history of prior hemorrhage (p = 0.028). A smaller nidus diameter was associated with seizure improvement (p = 0.031) and was most notable among patients for whom average AVM diameter was less than 20 mm (p = 0.028). No seizure activity developed after SRS among patients who had been seizure free before SRS.

Hemorrhage During Latency Interval and Risk for Complications

A single hemorrhage occurred during the latency period at a median of 6 months (range 4–13 months) for 4 (5%) patients. One patient died as a result of a hemorrhage that occurred 8 months after SRS. The cumulative rate of AVM hemorrhage after SRS was 5% at 1, 5, and 10 years. This rate correlated with 387 patient-years of estimated hemorrhage risk for an overall annual rate of 1.0% during the latency interval (the time from SRS treatment until obliteration or last follow-up of a patent with a known residual AVM). The likelihood of hemorrhage occurring during the latency period was significantly greater for patients who had a coexisting proximal aneurysm (p = 0.018). No patient sustained a hemorrhage after AVM obliteration had been confirmed by MRI or angiography.

Table 1: Univariate analysis of variables associated with seizure activity before SRS and seizure improvement after SRS for sylvian fissure AVMs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Seizures Before SRS (36 patients)</th>
<th>Improvement After SRS (17 patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>0.019</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td>0.018</td>
<td>0.793</td>
<td></td>
</tr>
<tr>
<td>AVM diameter</td>
<td>0.321</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>volume</td>
<td>0.135</td>
<td>0.129</td>
<td></td>
</tr>
<tr>
<td>marginal dose</td>
<td>not applicable</td>
<td>0.876</td>
<td></td>
</tr>
<tr>
<td>prior hemorrhage</td>
<td>0.0004</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>neurological deficit</td>
<td>0.409</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>varix</td>
<td>0.983</td>
<td>0.543</td>
<td></td>
</tr>
<tr>
<td>aneurysm</td>
<td>0.934</td>
<td>0.620</td>
<td></td>
</tr>
<tr>
<td>diffuse nidus</td>
<td>0.816</td>
<td>0.487</td>
<td></td>
</tr>
<tr>
<td>deep venous drainage</td>
<td>0.752</td>
<td>0.132</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Kaplan-Meier curve for probability of improved seizure control after SRS. The numbers of patients with seizures remaining in the study at 3, 5, 10, and 15 years after SRS were 30, 24, 12, and 7, respectively.
Temporary symptomatic adverse radiation effects developed in 2 patients (2%). These effects are defined as new T2 signal change surrounding the AVM target on MRI and were associated with the development of new neurological signs in the absence of hemorrhage. One patient experienced transient deterioration of neurocognitive status 3 months after SRS, and another patient experienced increased seizure activity 9 months after SRS. For both of these patients, baseline status was achieved after the administration of a short course of oral corticosteroids. The associated MRI signal changes in these patients resolved at 5 and 27 months, respectively. No permanent new neurological deficit associated with adverse radiation effects developed in any patient. Delayed cyst formation in the target region was detected in 3 patients; the median time until detection of the cyst was 31 months (range 6–67 months). The cysts were asymptomatic for 2 patients but required surgical cyst fenestration for the other patient.

Repeat SRS

A total of 15 patients with residual AVMs underwent a second SRS procedure at a median of 40 months (range 36–73 months) after the initial procedure. Among these patients, obliteration was confirmed by MRI at a median interval of 37 months (range 33–50 months) for 5 patients. No complications were noted for patients who underwent repeat SRS.

Discussion

Factors Associated With Obliteration

Paradigms for management of AVMs have evolved over the past 25 years, and an individualized patient outcome–centered approach has been widely adopted. As we reviewed the SRS literature about AVM management, we found surprisingly little information specifically about AVMs of the sylvian fissure, an anatomical location we suspected of being of high risk. In fact, almost half of the diagnoses for patients reported in this series were made after an ictal bleeding event. In the study reported here, obliteration was confirmed by MRI or angiography for 60% of patients at 5 years and 76% at 10 years. This obliteration rate is consistent with rates reported by other authors after SRS for AVMs in other critical brain locations. We noted that seizure control improved for 17 (47%) of 36 patients, which compares favorably with previously reported rates of 41%–51%. Seizure control tends to improve over time; we noted that seizure control was improved for 60% of patients at 15 years. Among patients in our study for whom complete obliteration was not confirmed, seizure reduction occurred more often. This finding might be a reflection of the relatively small sample size and larger AVM volumes. Although others have noted that AVM obliteration is not required to improve seizure outcomes, prior reports have indicated that seizure reduction is more frequent among those for whom AVM obliteration is achieved. Our data also indicate that a history of prior hemorrhage is a negative prognostic factor for seizure improvement. Kida et al. noted a similar correlation of reduced seizure control in patients who had previously experienced hemorrhage. A smaller AVM diameter was associated with seizure improvement, which is similar to the finding reported by Schäuble et al. In our study, the median time to seizure reduction was 20 months. This finding is similar to the 20.5-month time until seizure reduction that was noted by Hyun et al. after radiosurgery and embolization. Previous studies have reported a risk for new-onset seizures of 5%–10% after SRS and up to 36% after microsurgery. However, in our study, among patients who were seizure free before SRS, no seizures developed after SRS. For 1 patient, transient exacerbation of seizure frequency was correlated with interval T2 MRI detection of the cyst was 31 months (range 6–67 months). The cysts were asymptomatic for 2 patients but required surgical cyst fenestration for the other patient.

Solidary fissure AVMs present special management challenges. These challenges include the complex neurovascular relationship of the middle cerebral artery as well as the critical functional cortex and connecting pathways located outside the AVM nidus. Although the published results of microsurgical removal of AVMs in the sylvian fissure are relatively sparse, some authors have reported transient morbidity for as few as 0 to as many as 44% of patients. Permanent new neurological morbidity
or death occurred for up to 3% of patients. The data generated from our study indicate a transient morbidity in 3% of patients; no disabilities were permanent. However, 1 patient died of hemorrhage that occurred during the latency interval.

Complete surgical removal provides the benefit of early hemorrhage protection but can be associated with immediate postoperative morbidity. Forty-six percent of patients presented with an intracranial hemorrhage, which was consistent with the rate of 52% provided by meta-analysis data. In the study reported here, the annual overall rate of hemorrhage during the latency interval was 1%. This is a reflection of the finding that all 4 (5%) hemorrhages occurred during the first year after treatment, which is comparable to results for motor cortex AVMs. The risk for hemorrhage during the latency interval was increased among patients with a prenidal aneurysm, which has been demonstrated as a risk factor. Despite our initial concern that the risk for hemorrhage during the latency interval was higher for AVMs in the sylvian region, we found no evidence of such risk.

Cysts formed in 3 patients at a median of 31 months after SRS. Two patients were asymptomatic, and treatment was observation only. However, 1 patient required surgical fenestration of the cyst to relieve mass effect. Pollock and Brown also described late cyst development in 6 patients whose target volume cyst was identified at an average of 4 years after SRS. This finding further indicates the need for long-term follow-up evaluations to verify the reduction of the risk for hemorrhage, confirm AVM obliteration, and monitor the risk for long-term complications. Repeat SRS was undertaken when incomplete AVM obliteration was noted on MR images at 3 or more years after initial SRS. We confirmed that for 5 of 15 additional patients, obliteration was achieved within a further interval of 3–5 years. No patient who underwent repeat SRS experienced additional morbidity or rebleeding.

Study Limitations

The limitations of this study include the need for even longer follow-up periods and the retrospective nature of this review. The population of patients with seizures was relatively small, which affected the statistical power regarding seizure outcomes. Data on long-term anticonvulsant medication management were not incorporated into this analysis because of the limited availability and reliability of the required information. Because medication had not been providing adequate seizure control at the time of SRS, we believe that AVM volume reduction or obliteration is important for seizure control. We were also unable to gather information about patient compliance with regard to taking anticonvulsant medication.

Conclusions

Rates of total AVM obliteration were highest among patients with sylvian fissure AVMs of less than 4 cm in volume and who received more than 20 Gy of radiation to the nidus. Seizure control improved after SRS for 60% of patients with seizures, and 53% of patients were free of disabling seizures on or off anticonvulsants. Seizure disorders did not develop after SRS in patients who had not had seizures before SRS. The annual hemorrhage rate during the latency interval after SRS was 1%, regardless of whether hemorrhage had occurred previously. After confirmation of AVM obliteration, no patients experienced a hemorrhage. Despite the unfavorable location of sylvian fissure AVMs, no permanent neurological deficits occurred. This study indicates that SRS is a relatively safe and effective way to manage sylvian fissure AVMs.

Disclosure

Dr. Lunsford is a consultant for and stockholder in Elekta AB. Author contributions to the study and manuscript preparation include the following. Conception and design: Kano. Acquisition of data: Kano, Bowden, Tonetti. Analysis and interpretation of data: Kano, Bowden. Drafting the article: Kano, Bowden, Lunsford. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kano. Statistical analysis: Kano, Bowden. Study supervision: Kano.

References


30. Monaco EA III, Niranjan A, Kano H, Flickinger JC, Kon-


Please include this information when citing this paper: published online June 13, 2014; DOI: 10.3171/2014.5.JNS13224.

Address correspondence to: Hideyuki Kano, M.D., Ph.D., Department of Neurological Surgery, University of Pittsburgh, Ste. B-400, UPMC Presbyterian, 200 Lothrop St., Pittsburgh, PA 15213. email: kano@upmc.edu.