Stereotactic radiosurgery for arteriovenous malformations of the cerebellum

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 AND L. DADE LUNSFORD, M.D.1,3

Departments of 1Neurological Surgery and 2Radiation Oncology and the 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. Arteriovenous malformations (AVMs) of the posterior fossa have an aggressive natural history and propensity for hemorrhage. Although the cerebellum accounts for the majority of the posterior fossa volume, there is a paucity of stereotactic radiosurgery (SRS) outcome data for AVMs of this region. The authors sought to evaluate the long-term outcomes and risks of cerebellar AVM radiosurgery.

Methods. This single-institution retrospective analysis reviewed the authors’ experience with Gamma Knife surgery during the period 1987–2007. During this time 64 patients (median age 47 years, range 8–75 years) underwent SRS for a cerebellar AVM. Forty-seven patients (73%) presented with an intracranial hemorrhage. The median target volume was 3.85 cm³ (range 0.2–12.5 cm³), and the median marginal dose was 21 Gy (range 15–25 Gy).

Results. Arteriovenous malformation obliteration was confirmed by MRI or angiography in 40 patients at a median follow-up of 73 months (range 4–255 months). The actuarial rates of total obliteration were 53% at 3 years, 69% at 4 years, and 76% at 5 and 10 years. Elevated obliteration rates were statistically higher in patients who underwent AVM SRS without prior embolization (p = 0.005). A smaller AVM volume was also associated with a higher rate of obliteration (p = 0.03). Four patients (6%) sustained a hemorrhage during the latency period and 3 died. The cumulative rates of AVM hemorrhage after SRS were 6% at 1, 5, and 10 years. This correlated with an overall annual hemorrhage rate of 2.0% during the latency interval. One patient experienced a hemorrhage 9 years after confirmed MRI and angiographic obliteration. A permanent neurological deficit due to adverse radiation effects developed in 1 patient (1.6%) and temporary complications were seen in 2 additional patients (3.1%).

Conclusions. Stereotactic radiosurgery proved to be most effective for patients with smaller and previously nonembolized cerebellar malformations. Hemorrhage during the latency period occurred at a rate of 2.0% per year until obliteration occurred.

(keywords: arteriovenous malformation • cerebellum • stereotactic radiosurgery • Gamma Knife • posterior fossa • vascular disorders)

Abbreviations used in this paper: ARE = adverse radiation event; AVM = arteriovenous malformation; GKS = Gamma Knife surgery; SRS = stereotactic radiosurgery.
hemorrhage rates seen in supratentorial AVMs.\textsuperscript{20,47} Posterior fossa AVMs have a striking mortality rate of 60% for patients who present with an AVM hemorrhage.\textsuperscript{8} Furthermore, natural history studies have demonstrated an increased rate of rebleeding, often several times the rate seen in patients without a previous hemorrhage.\textsuperscript{3,10,37,54} This information highlights the aggressive nature of these AVMs.

Cerebellar AVMs are usually grouped together with posterior fossa AVMs in the AVM literature. Although accurate, the cerebellum is a distinct cellular and architectural location that accounts for two-thirds of the posterior fossa AVMs.\textsuperscript{3,6,33,49} Our review found a paucity of information on outcome data related to SRS for cerebellar AVMs. This prompted us to review the outcomes and risks of cerebellar AVM SRS at our center.

**Methods**

**Patient Population**

A single-institution retrospective analysis approved by the University of Pittsburgh institutional review board was conducted. This study evaluated outcomes in cerebellar AVMs treated between 1987 and 2007. During this time 1052 patients underwent GKS (Leksell, Elekta AB) for AVMs. We identified 64 patients who underwent a single cerebellar SRS procedure. The outcome data were collected through medical record review and were analyzed by neurosurgeons who did not participate in the initial patient management. At the time of SRS, the median patient age was 47 years (range 7.6–74.7 years). Forty patients were male. The initial presentation of these patients included intracranial hemorrhage in 47 patients (73%), headache in 11 patients (17%), and progressive neurological deficits in 2 patients (3%). Four patients (7%) had their AVM diagnosed incidentally (Table 1). Neurological deficits prior to SRS were present in 24 patients (38%). Hemorrhage was the cause of the deficit in 21 patients. Two patients suffered brain infarcts after initial embolization. Ataxia was the most common finding (19 patients), followed by hemiparesis (4 patients), dysarthria (3 patients), and diplopia (2 patients). Four patients experienced more than 1 deficit.

The AVM was located predominantly within the cerebellar hemispheres in 43 patients and the vermis in the remaining patients. A coexisting aneurysm was identified in 16 patients (25%) and a venous outflow varix in 5 patients (8%). Endovascular embolization was performed in 12 patients (19%) prior to SRS, and 2 patients (3%) underwent endovascular coil treatment for their aneurysms. Twelve patients (19%) underwent surgical intervention prior to SRS. Four patients (6%) had partial AVM resection, 5 patients (8%) had clipping of a coexisting aneurysm, and 3 patients (5%) required hematoma evacuation. The Spetzler-Martin grade was determined before SRS by 2 experienced neurosurgeons.\textsuperscript{45} A Grade I AVM was diagnosed in 4 patients (6%), Grade II in 20 patients (31%), Grade III in 31 patients (48%), and Grade IV in 9 patients (14%). The Pollock-Flickinger score was calculated as < 1 for 12 patients (19%), 1.01–1.50 for 30 patients (47), 1.51–2 for 19 patients (30), and > 2 for 3 patients (5%).\textsuperscript{36,52}

**Radiosurgery Technique**

Patients presented on the day of treatment and intravenous sedation was administered; in the case of children, general anesthesia with endotracheal intubation was used. The Leksell stereotactic frame was applied with local anesthetic applied to the pin sites. High-resolution axial imaging (MRI after 1991) was then performed, followed by biplanar stereotactic angiography. Radiosurgery planning was calculated with a margin dose covering the entire nidus volume. This study spans the use of several Leksell Gamma Knife units (models U, B, C, and 4C). At the conclusion of treatment all patients received 20–40 mg of intravenous methylprednisolone. Patient discharge from the hospital occurred within 2–24 hours postprocedure. The cerebellar location required no variation of our standard treatment protocol. Expanded technical elements of this technique have been detailed in our previous publications.\textsuperscript{26,27,39}
Radiosurgery for cerebellar AVM

The median target volume was 3.85 cm$^3$ (range 0.2–12.5 cm$^3$), and the median maximum AVM nidus diameter was 2.0 cm (range 0.5–4.3 cm). The median marginal dose was 21 Gy (range 15–25 Gy) and the maximum dose was 40 Gy (range 27–50 Gy). The median number of isocenters used was 3 (range 1–12) (Table 2).

Patient Follow-Up

Clinical and imaging follow-up (MRI when possible) was requested at 6, 12, 24, and 36 months after SRS. If any changes in neurological symptoms occurred after treatment, the patient was investigated promptly with imaging to assess for potential AREs. After 3 years, if MRI demonstrated total obliteration (no flow voids identified), then angiography was requested. Complete AVM obliteration via angiography was defined as an elimination of the AVM nidus and the absence of early draining veins. However, if a residual nidus was evident on imaging, then additional SRS was considered to obtain complete obliteration. Any patient receiving a second SRS treatment was once again followed with a similar protocol.

Statistical Analysis

Kaplan-Meier survival analysis was used to demonstrate correlations between obliteration rates and various potentially significant factors. The obliteration was calculated based on the time that MRI or angiography demonstrated complete occlusion of the AVM. The accuracy of MRI confirmation of obliteration is 96% as demonstrated by Pollock et al. We have previously shown that both MRI and angiography provide satisfactory evidence of AVM obliteration. Cox regression was used for univariate analysis to calculate significant interactions between obliteration rates and related factors; $p$ values < 0.05 were defined as statistically significant.

Hemorrhage results were calculated based on the time of a postradiosurgical bleeding event or when a patient was lost to follow-up. The hemorrhage statistics were obtained through Kaplan-Meier survival analysis. The annual hemorrhage rate during the latency period was calculated based on the years of at risk follow-up and the number of hemorrhages that occurred. Comparisons between variable groups were performed where appropriate using the Fisher exact test.

Results

The median imaging follow-up after SRS was 73 months (range 4–255 months). At the time of this review 11 patients had died. Three deaths were directly attributable to AVM hemorrhage, 5 were unrelated, and 3 were undetermined. There were 24 patients with neurological deficits prior to SRS; at the end of follow-up 9 patients had improved, and the remaining patients were unchanged.

Total Obliteration

Arteriovenous malformation obliteration was confirmed by MRI and angiography in 40 patients. The actuarial rates of total obliteration were 53% at 3 years, 69% at 4 years, and 76% at 5 and 10 years (Fig. 1). The median time until obliteration was documented was 35 months (95% CI 29–41 months). If angiography was used alone to confirm obliteration (9 patients with MRI evidence of obliteration did not have a confirmatory angiogram), then 31 patients had total obliteration. Angiography-confirmed obliteration rates were 44% at 3 years, 54% at 4 years, and 59% at 5 and 10 years. The median time until angiography-confirmed obliteration was 38 months (95% CI 22.41–53.19 months) (Figs. 2 and 3). As documented in previous studies angiography results are falsely lowered...
by patients who do not undergo angiography after obliteration is determined on MRI. Patients without a prior hemorrhage had an obliteration rate of 45% at 3 years and 65% at 5 years.

Several variables were significant for AVM obliteration based on univariate analysis (Table 3). A smaller AVM nidus volume showed an increased obliteration rate using both MRI (p = 0.03) and angiographic (p = 0.011) confirmation. Obliteration rates were higher in patients whose AVM was smaller than 4 cm³ (Fig. 4). Prior embolization reduced the probability of obliteration (p = 0.005) (Fig. 5). The presence of an aneurysm was significantly more common in patients with cerebellar hemisphere AVMs than in patients with AVMs of the vermis (p = 0.031).

Complication Risks

Four patients (6%) had a single hemorrhage during the latency period. Three of these patients died as a result of the hemorrhage (at 4.3, 4.9, and 5.6 months) after SRS. The cumulative rate of AVM hemorrhage after SRS was 6% at 1, 5, and 10 years (Fig. 6). In the 197 patient-years of estimated hemorrhage risk during the latency interval (time from treatment until obliteration or last follow-up with a patent AVM), the overall annual rate was 2.0%. The likelihood of having a hemorrhage during the latency period was significantly greater in patients who also had an aneurysm (p = 0.018). A prior hemorrhage was not associated with statistically higher rates of post-SRS hemorrhage. One patient unexpectedly had a hemorrhage 9 years after obliteration was confirmed by MRI and angiography. The cause of the hemorrhage was unknown since the patient had no evidence of a residual AVM or a treatment-related cyst. The annual risk of hemorrhage during the postobliteration period was 0.3% based on 306 patient-years of follow-up.

Symptomatic AREs (confirmed by T2 MRI signal changes and new neurological deficits in the absence of
hemorrhage) were seen in 3 patients. These patients had all sustained an AVM hemorrhage prior to SRS. The median time to onset of ARE symptoms was 13 months (range 2.3–36.5 months) after SRS. A new and permanent neurological deficit developed in 1 patient, who developed a reduction in unilateral hearing of approximately 60%. Temporary deficits occurred in 2 patients (3%). The T2 signal changes surrounding the AVM target resolved in these patients at 7 and 26 months. Women had a higher chance of developing symptomatic edema (p = 0.02). Delayed cyst formation was identified after SRS in 1 patient. This patient had also experienced temporary ARE, although no neurosurgical intervention was required.

Additional SRS

Five patients with patent AVMs underwent a second SRS procedure at a median of 39 months (range 30–107 months) after the initial procedure. The median margin dose was 18 Gy (range 14–20 Gy). Four of the 5 patients had MRI-confirmed obliteration at a median interval of 27 months (range 21–53 months) (Fig. 7). The remaining patient had a residual AVM at 26 months of follow-up. No complications were noted in the repeat radiosurgery treatment group.

Discussion

Factors Related to Obliteration

A perfect algorithm for AVM management has long eluded surgeons. Angioarchitecture,58 volume, and Spetzler-Martin grade18 are among the factors that influence both patient selection and surgical results. In this radiosurgical study we confirmed that the obliteration rate based on MRI or angiography was 76% at 5 years.

Fig. 4. Magnetic resonance imaging and angiographic AVM obliteration data compared for margin dose volume of larger than or smaller than 4 cm³.

Fig. 5. Magnetic resonance imaging and angiographic obliteration data comparing prior embolization and nonembolized AVMs.

Fig. 6. Bleed rate during the latency period prior to complete obliteration.
Two factors were prominent in predicting success based on statistical analysis. The first factor was AVM volume, and we noted that obliteration rates were reduced in patients with larger AVM volumes. This was especially evident when volumes greater than and less than 4 cm$^3$ were compared. This 4-cm$^3$ volume effect has been noted by others. Although volume does influence dose, we could not define a statistically significant relationship in this series between obliteration rates and dose delivered to the margin. Higher doses in general were given to smaller-volume AVMs. Arteriovenous malformations smaller than 4 cm$^3$ received a median of 22.5 Gy, compared with 18 Gy in AVMs larger than 4 cm$^3$. Dose optimization is related to location, volume, and the risk of AREs. The Pollock-Flickinger score trended toward, but did not reach, significance. Kano et al. also noted failure of the Pollock-Flickinger score to predict outcomes accurately in patients with brainstem AVMs.

The second statistically significant factor was an observed decrease in the rate of total obliteration when embolization was performed prior to SRS. A similar negative effect on obliteration has been reported in prior publications that describe the results of SRS for AVMs in other brain regions. The potential causes of this negative effect of embolization include the difficulties noted in imaging the residual target after embolization. Artifacts created by embolization materials often obscure visualization of the remaining AVM nidus when using MRI, CT, or angiography. Revascularization of previously embolized but SRS-untreated regions leads to failure as well. Despite claims that even partial embolization reduces the hemorrhage risk in the latency period after SRS, we have noted no such reduction of hemorrhage risks. Because pre-radiosurgery embolization has demonstrated no value in either volume or risk reduction, we believe that post-radiosurgery embolization leading to flow reduction after SRS might improve or accelerate obliteration rates with an acceptable risk profile.

The posterior fossa is often described as a singular entity in clinical reports. The brainstem has received special attention because of the high morbidity associated with AVMs in this region. Obliteration rates ranging from 52% to 73% have been reported for brainstem AVMs. These results are similar to the 76% obliteration rate defined in the current study of cerebellar AVMs. The rate of hemorrhage in reported studies on brainstem AVMs was 3%–17% and appeared to be consistent with the current cerebellar AVM results. Permanent neurological deficits occurred in less than 2% of patients with cerebellar AVMs, compared with complication rates of 5% and 12% in patients with brainstem AVMs.

**Decision Making**

Cerebellar AVMs provide a challenge for clinical decision making. Although complete surgical removal provides the benefit of early hemorrhage protection, it is associated with a higher risk profile. Attempts at surgical removal have been associated with mortality rates of 6% and morbidity rates that average 16%. In contrast, in the present study 1 patient developed a permanent neurological deficit and 2 additional patients had temporary morbidity. However, 3 patients (5%) died of hemorrhage during the first 6 months after SRS.

Deep and infratentorial AVMs are associated with a higher risk of hemorrhage in comparison with supratentorial AVMs. Gross and Du performed a meta-analysis (3923 patients) and noted significantly increased bleeding risks in patients with prior hemorrhage, aneurysms, and deep venous drainage. We also noted an incidence of 25% in the current study 73% of patients presented with a hemorrhage, 25% had an associated aneurysm, and 66% demonstrated deep venous drainage. The incidence of aneurysm detection in this study correlates with previous data for posterior fossa AVMs. Prior reports also note an incidence of 25%. The presence of an aneurysm has also been demonstrated as a risk factor for hemorrhage after SRS. Our experience in the management of patients who harbor aneurysms proximal to the AVM also suggests that such aneurysms should undergo clipping or coil in addition to SRS for the AVM.

In comparison with supratentorial AVMs, cerebellar AVMs have a higher annual AVM rehemorrhage rate (6%–15%) in the 1st year after a hemorrhage. The annual hemorrhage rate then declines but remains elevated from baseline at 5%–6% for up to 5 years after the initial hemorrhage. We also noted a 6% rehemorrhage rate in the 1st year after SRS. The rehemorrhage rate averaged after 5 years decreased to 1.5% annually.

Additional SRS to reduce the hemorrhage risk has been undertaken when incomplete AVM obliteration was noted on MRI at 3 or more years after initial SRS. We confirmed that total obliteration was attained in 4 of 5 patients. This result is consistent with the 10-year data of 80% reported by Kano et al. There were no side effects in this re-treatment group, although previous studies have reported permanent neurological deficits ranging from 2.8% to 3.6%.

**Study Limitations**

Limitations of this study are largely related to the duration of follow-up and the retrospective review of outcomes.

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**Fig. 7.** Complete obliteration rate of AVM for patients requiring repeat SRS.
Radiosurgery for cerebellar AVM

In this subseries of our AVM database, we could not obtain adequate clinical outcome data in 17% of patients.

Conclusions

Patients with cerebellar AVMs smaller than 4 cm³ in volume who did not undergo previous embolization had the highest rates of obliteration. The hemorrhage rate during the latency period after SRS was not increased. However, 3 patients died during the latency period. After obliteration was confirmed 1 patient suffered a hemorrhage. Despite the unfavorable location of cerebellar AVMs, a permanent neurological deficit was seen in only 1 patient. This study indicates that SRS was a relatively safe and effective means of treating symptomatic AVMs in the cerebellum.

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Disclosure

Dr. Lunsford is a consultant for and stockholder with Elekta AB.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kano, Bowden, Lunsford. 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: Bowden. Study supervision: Kano, Lunsford.

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