Stereotactic radiosurgery for brainstem arteriovenous malformations: factors affecting outcome

Keisuke Maruyama, M.D., Douglas Kondziolka, M.D., F.R.C.S.(C), Ajay Niranjani, M.Ch., John C. Flickinger, M.D., and L. Dade Lunsford, M.D.

Departments of Neurological Surgery and Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Object. Management options for arteriovenous malformations (AVMs) of the brainstem are limited. The long-term results of stereotactic radiosurgery for these disease entities are poorly understood. In this report the authors reviewed both neurological and radiological outcomes following stereotactic radiosurgery for brainstem AVMs over 15 years of experience.

Methods. Fifty patients with brainstem AVMs underwent gamma knife surgery between 1987 and 2002. There were 29 male and 21 female patients with an age range of 7 to 79 years (median 35 years). Anatomical locations of these AVMs included the midbrain (39 lesions), pons (20 lesions), and medulla oblongata (three lesions). The radiation dose applied to the margin of the AVM varied from 12 to 26 Gy (median 20 Gy). Forty-five patients were followed up from 5 to 176 months (mean 72 months). The angiographically confirmed actuarial obliteration rate was 66% at the final follow-up examination. Two patients experienced a hemorrhage before obliteration. The annual hemorrhage rate was 1.7% for the first 3 years after radiosurgery and 0% thereafter. Patients who had received irradiation at two or fewer isocenters had higher obliteration rates (80% compared with 44% for > two isocenters, p = 0.006), and this was related to a more spherical nidus shape. The rate of persistent neurological complications in patients treated using magnetic resonance imaging–based dose planning after 1993 was 7%, compared with 20% in patients treated before 1993. An older patient age, a lesion located in the tectum, and a higher radiosurgery-based score were significantly associated with greater neurological complications.

Conclusions. Stereotactic radiosurgery provided complete obliteration of AVMs in two thirds of the patients with a low risk of latency-interval hemorrhage. Better three-dimensional imaging studies and conformal dose planning reduced the risk of adverse radiation effects. Younger patients harboring more spherical AVMs that did not involve the tectal plate had the best outcomes.

Key Words • arteriovenous malformation • stereotactic radiosurgery • gamma knife surgery • brainstem

Clinical Material and Methods

Patient Population

Between October 1987 and April 2002, 50 patients with angiographically visible brainstem AVMs underwent stereotactic radiosurgery at the Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center. All patients had undergone preoperative MR or CT imaging of the brain, which confirmed the AVM location within the brainstem. Our series consisted of 29 male and 21 female patients, whose ages ranged from 7 to 79 years (median age 35 years). Thirty-six patients (72%) presented with one or more episodes of hemorrhage 1 month to 9 years before radiosurgery. Four patients had received prior embolization, and five had undergone a microsurgical partial resection of the AVM. Because of previous hemorrhage or surgery, 36 patients (72%) had neurological deficits at the time of radiosurgery. Locations of the AVMs included the midbrain in 39 patients (the tectum in 21 and the cerebral peduncle or tegmentum in 18), the pons in 20, and the medulla oblongata in three. Twelve AVMs extended across two locations. The Spetzler–Martin grade was II in one patient (2%), III in six (12%), and VI in 43 (86%). No patient had an AVM of Grade IV or V. A radiosurgery-based grading system score was calculated according to the following equation:

Abbreviations used in this paper: AVM = arteriovenous malformation; CT = computerized tomography; MR = magnetic resonance.
A VM score = (0.1)(A VM volume in cm$^3$) / H11001 (0.02)(patient age in years) / H11001 (0.3)(location of lesion: frontal or temporal, 0; parietal, occipital, intraventricular, corpus callosum, or cerebellar, 1; or basal ganglia, thalamus, or brainstem, 2). This score pursuant to the Pollock–Flickinger Scale score ranged from 0.84 to 2.89. Clinical characteristics of the treated patients are summarized in Table 1.

Radiosurgical Technique

Radiosurgery was performed using the 201-source 60 Co gamma knife (Elekta Instruments, Norcross, GA). Between 1987 and 1992, dose planning was based on biplanar stereotactic cerebral angiography. After 1993, angiography was combined with MR imaging studies. Because of implanted metal material in one patient, a CT scanning study was substituted for the MR imaging study. The method of dose selection evolved according to the accumulated experience over time, although we always used the integrated logistic formula to help predict the risk of permanent adverse radiation effects to surrounding brain. The prescribed maximal dose varied from 22.2 to 50 Gy (median 34.5 Gy), and the dose to the tumor margin varied from 12 to 26 Gy (median 20 Gy). One patient harboring a large AVM—not a dural arterovenous fistula—fed by multiple vessels and draining into the vein of Galen, was treated in two stages separated by a 6-month interval. The patient was treated again 9 years later because of a persistent AVM residue.

Follow-Up Evaluation and Statistical Analysis

Postradiosurgical clinical examinations and MR imaging studies were requested by personnel at our center or by referring physicians at 6-month intervals for the first 3 years. If MR imaging results obtained before 3 years postradiosurgery demonstrated nidus obliteration, angiography studies were generally delayed until 3 years had actually elapsed. If angiography results obtained 3 years postradiosurgery demonstrated that the AVM nidus was not obliterated, repeated stereotactic radiosurgery was recommended.

The actuarial obliteration rate was calculated using the Kaplan–Meier method. The log-rank test and forward-conditional univariate and multivariate logistic regression analyses were used to analyze factors potentially affecting AVM obliteration, latency-interval hemorrhage, and neurological complications following radiosurgery.

Results

Forty-five patients were evaluated 5 to 176 months (mean 72 months, median 56 months) after stereotactic radiosurgery; no follow-up information was available in five patients. Complete nidus obliteration after single-session radiosurgery was confirmed on angiography studies in 18 patients 4 to 65 months (median 35 months) after radiosurgery (Figs. 1 and 2) and by MR imaging studies alone in three patients. Among these 21 patients, AVM obliteration

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**TABLE 1**

**Patient demographics**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>50</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>29:21</td>
</tr>
<tr>
<td>median patient age in yrs (range)</td>
<td>35 (7–79)</td>
</tr>
<tr>
<td>no. w/ history of hemorrhage (%)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>no. w/ prior resection/embolization</td>
<td>5/4</td>
</tr>
<tr>
<td>no. w/ neurological deficits at treatment (%)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>median KPS score (range)</td>
<td>90 (40–100)</td>
</tr>
<tr>
<td>nidus location (no. of patients [%])†</td>
<td>midbrain 39 (78)</td>
</tr>
<tr>
<td></td>
<td>tectum 21 (42)</td>
</tr>
<tr>
<td></td>
<td>cerebral peduncle or tegmentum 18 (36)</td>
</tr>
<tr>
<td></td>
<td>pons 20 (40)</td>
</tr>
<tr>
<td></td>
<td>medulla oblongata 3 (6)</td>
</tr>
<tr>
<td>median nidus volume in cm$^3$ (range)</td>
<td>1.5 (0.14–11.3)</td>
</tr>
<tr>
<td>mean nidus diameter in cm (range)</td>
<td>1.4 (0.7–4.8)</td>
</tr>
<tr>
<td>Spetzler–Martin Grade (no. of patients [%])</td>
<td>II 1 (2)</td>
</tr>
<tr>
<td></td>
<td>III 6 (12)</td>
</tr>
<tr>
<td></td>
<td>IV &amp; V 0 (0)</td>
</tr>
<tr>
<td></td>
<td>VI 43 (86)</td>
</tr>
<tr>
<td>median Pollock–Flickinger score (range)</td>
<td>1.63 (0.84–2.89)</td>
</tr>
<tr>
<td>median maximal radiation dose in Gy (range)</td>
<td>34.5 (22.2–50)</td>
</tr>
<tr>
<td>median dose to tumor margin in Gy (range)</td>
<td>20 (12–26)</td>
</tr>
<tr>
<td>median no. of isocenters (range)</td>
<td>2 (1–7)</td>
</tr>
<tr>
<td>median follow-up period in mos (range)</td>
<td>56 (5–176)</td>
</tr>
</tbody>
</table>

* KPS = Karnofsky Performance Scale.
† Twelve nidi extended across two locations.

AVM score = (0.1)(AVM volume in cm$^3$) + (0.02)(patient age in years) + (0.3)(location of lesion: frontal or temporal, 0; parietal, occipital, intraventricular, corpus callosum, or cerebellar, 1; or basal ganglia, thalamus, or brainstem, 2). This score pursuant to the Pollock–Flickinger Scale score ranged from 0.84 to 2.89. Clinical characteristics of the treated patients are summarized in Table 1.

Fig. 1. Stereotactic vertebral artery arteriogram (left) and MR image (center) obtained in a 25-year-old patient, revealing a small, spherical, pontine AVM with superimposed 50 and 20% isodose lines. A follow-up angiogram (right) obtained 50 months after radiosurgery, demonstrating complete obliteration of the AVM.
was confirmed within 3 years posttreatment in 13 patients and 3 to 6 years posttreatment in eight patients. The actuarial AVM obliteration rate following single-session radiosurgery and confirmed on angiography among the evaluated patients was 28 and 66% at 3 or 6 years, respectively, and 35 and 69%, respectively, when obliteration was confirmed on MR imaging as well (Fig. 3 upper). Six patients underwent repeated radiosurgery for a persistent AVM nidus after the initial 3-year observation interval. Of these six patients, complete AVM obliteration was confirmed on angiography or MR imaging studies alone in two patients 51 and 53 months, respectively, after the second procedure. When the results of repeated radiosurgery were included, the actuarial obliteration rate confirmed on angiography was 61 and 78% at 6 and 10 years, respectively. Of 45 evaluated patients, 32 were followed up for at least 36 months, and the AVM obliteration in three patients was confirmed on angiography before 36 months had elapsed (an angiography study was rarely ordered before 36 months postradiosurgery). The actuarial obliteration rate after single-session radiosurgery in these 35 patients was 30 and 66% at 3 or 6 years, respectively—a rate similar to that found in the entire patient series.

Patient age, sex, history of hemorrhage, nidus volume, Spetzler–Martin grade, Pollock–Flickinger score, radiosurgical dose to the AVM margin, and number of isocenters were included in the analysis of successful nidus obliteration judged according to angiography or MR imaging studies. The number of isocenters was significantly related to successful AVM obliteration in both univariate and multivariate analyses (Table 2). When two or fewer isocenters were used, we found a significant, higher obliteration rate (80% at 6 years; \( p = 0.006 \), log-rank test), compared with AVMs treated using more than two isocenters (44% at 6 years; Fig. 3 lower).

The difference between AVMs treated with two or fewer isocenters and those treated with more than two isocenters was analyzed. To approximate the AVM’s similarity to a sphere, the ratio of maximal to minimal nidus diameter was calculated. This ratio ranged from 1 to 2.55 (median 1.35) and was significantly lower in the group of AVMs treated using two or fewer isocenters, based on the Fisher exact probability test \( (p = 0.001) \). This ratio was also a statistically significant factor related to successful nidus obliteration

![Stereotactic vertebral artery arteriogram (left) and MR image (center), obtained in a 12-year-old patient, exhibiting a moderate-sized pontine AVM (nonspherical with an ill-defined nidus) with 70, 55, and 30% isodose lines. A follow-up angiogram (right), obtained 24 months after radiosurgery, revealing complete nidus obliteration.](image)

**Fig. 2.** Stereotactic vertebral artery arteriogram (left) and MR image (center), obtained in a 12-year-old patient, exhibiting a moderate-sized pontine AVM (nonspherical with an ill-defined nidus) with 70, 55, and 30% isodose lines. A follow-up angiogram (right), obtained 24 months after radiosurgery, revealing complete nidus obliteration.

![Graph of Kaplan–Meier curve of the angiographic obliteration rate following single-session radiosurgery for brainstem AVMs (66% at 6 yrs). Lower: Graph of Kaplan–Meier curve of the angiographic obliteration rate for brainstem AVMs. The obliteration rate in the group of patients treated using two or fewer isocenters was significantly higher than that in patients treated using more than two isocenters (\( p = 0.006 \)).](image)

**Fig. 3.** Upper: Graph of Kaplan–Meier curve of the angiographic obliteration rate following single-session radiosurgery for brainstem AVMs (66% at 6 yrs). Lower: Graph of Kaplan–Meier curve of the angiographic obliteration rate for brainstem AVMs. The obliteration rate in the group of patients treated using two or fewer isocenters was significantly higher than that in patients treated using more than two isocenters (\( p = 0.006 \)).
in a univariate analysis (p = 0.03; Table 2). The difference in the mean nidus volume in the two groups, calculated with the Mann–Whitney U-test, was not significant (2.29 and 2.87, respectively; p = 0.37). More spherical AVMs presented less of a challenge for conformal dose planning.

Latency-interval hemorrhage occurred in two patients. One patient with a right midbrain AVM suffered a left hemiparesis 3 months after radiosurgery, and the hematoma within the brainstem parenchyma was then surgically removed. This patient's neurological deficits from the post-radiosurgical hemorrhage were deemed to be permanent at the last follow up. Another patient with a right midbrain AVM suffered the sudden onset of headache 15 months after radiosurgery, and a subarachnoid hemorrhage was demonstrated on CT scanning. His headache resolved spontaneously, and no new neurological deficit occurred. No patient with confirmed AVM obliteration suffered a later hemorrhage. The annual hemorrhage rate following radiosurgery was calculated to be 1.7% for the first 3 years and 0% thereafter. Patient age, sex, history of hemorrhage, nidus volume and location, Spetzler–Martin grade, Pollock–Flickinger score, and prescribed tumor margin dose were included in a univariate analysis (p = 0.03; Table 2). The difference in the mean nidus volume in the two groups, calculated with the Mann–Whitney U-test, was not significant (2.29 and 2.87, respectively; p = 0.37). More spherical AVMs presented less of a challenge for conformal dose planning.

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New or worsened neurological symptoms caused by presumed adverse radiation effects were observed in 12 patients (27%). Neurological deterioration was transient in five patients (11%), but was persistent at the last follow up in seven (16%). Consequently, 15 patients achieved complete obliteration (confirmed on angiography) without new permanent neurological deficits. The rate of persistent adverse radiation effects in patients treated before 1993 was 20%, but declined to 7% in those treated after 1993. Neurological deterioration occurred 2 to 26 months following radiosurgery. One patient harboring a tectal AVM with imaging evidence of adverse radiation effects died of unrecognized hydrocephalus 35 months after radiosurgery. Two other patients died of unrelated causes. Neurological complications were classified into three categories of dysfunction: ocular, motor, and sensory (Table 3). Ocular dysfunction occurred in seven patients, including oculomotor, trochlear, and abducens nerve dysfunction in one patient each; internuclear ophthalmoplegia in two patients; and diplopia of unknown nerve origin in three. Seven patients experienced motor dysfunction, which included the development or worsening of existing hemiparesis in two patients and ataxia in six. Sensory dysfunction was observed in two patients. Patient age, sex, nidus volume and location, Spetzler–Martin grade, Pollock–Flickinger score, prescribed tumor margin dose, and number of isocenters were included in the analysis of neurological complications. Patient age, nidus location in the tectum, and Pollock–Flickinger score were statistically significant in a univariate analysis (Table 4). The Pollock–Flickinger score was the only factor affecting neurological complications in a multivariate analysis.

Imaging changes (that is, perilesional long TR signal changes) were demonstrated in 14 patients (32%) 3 to 28 months after radiosurgery (Fig. 4). Eight patients (18%) were symptomatic and six had no accompanying symptom. Statistical analysis of the factors noted earlier revealed no predictive relationship for the development of such postradiosurgery imaging changes.

Discussion

Obliteration of AVMs

The obliteration rate for a brainstem AVM following ste-
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resected radiosurgery has been reported to be 52.2 to 73% at 3 years. The obliteration rate in the present study is comparable to these results. Nonetheless, the rate is lower than those associated with cerebral AVMs in other locations, which have been reported to be 70 to 87%. We believe that the rate of obliteration was also slower than that for other brain locations, although this hypothesis cannot be proven in the absence of annual angiographic studies. These less satisfactory obliteration results likely resulted from the dose reduction used in the brainstem compared with non-brainstem locations. As such, although we adhered to an initial principle of recommending repeated radiosurgery if angiography studies obtained at 3 years demonstrated a still patent AVM nidus, close observation without additional treatment and repeated diagnostic angiography for further obliteration would be occasionally justified, especially when a low dose was selected to reduce the chance for adverse radiation effects.

It is appropriate to include all 45 evaluated patients in a calculation of the actuarial obliteration rate. If we limited our study to patients with at least 3 years of follow up, the actuarial obliteration rate could be overestimated because insufficient data with shorter follow-up periods are eliminated more frequently and more favorable data with longer follow-up periods are enhanced. In this study, the obliteration rate from among all 45 patients and in the group of patients with more than 3 years of follow up was similar.

Factors associated with successful AVM obliteration following radiosurgery have been reported to be tumor margin dose, nidus volume, patient age, sex, hemispheric nidus location, and the number of draining veins. A figure of at least two isocenters was also a statistically significant factor in this study, a finding not reported previously. Arteriovenous malformations treated using fewer isocenters were more spherical, a factor proven by the ratio of the maximal nidus diameter to its minimal diameter. In general, more spherical lesions provided a simpler target for dose planning and facilitated more conformal radiosurgery. Furthermore, in these more spherical lesions a greater percentage of the nidus volume received a higher radiation dose, perhaps facilitating successful obliteration. Another explanation might be that the possibility for undertreating part of the AVM margin occurred less frequently with spherical AVMs as opposed to irregularly shaped ones.

Latency-Interval Hemorrhage

The annual hemorrhage rate following radiosurgery in this study (1.7% for the first 3 years) was relatively low compared with that in previous reports. Although no patient in this series died of latency-interval hemorrhage, investigators have previously reported a high mortality rate in patients with such a hemorrhage after radiosurgery for a brainstem AVM. Given that most patients (72%) in this study presented with one or more episodes of hemorrhage, this rate was considered to be low. Furthermore, a history of prior hemorrhage was not a significant factor for latency-interval hemorrhage based on our statistical analysis. Although no convincing data substantiate the theory that radiosurgery protects AVMs prior to complete obliteration, data from the current study raises the intriguing possibility that AVM radiosurgery may provide some degree of protection, at least in the interval that we were able to assess. Some authors have asserted that the risk for hemorrhage was decreased during the latency period, based on the observation that almost one half of the postradiosurgical hemorrhages occurred within the first 6 months. Further analysis will be needed to address this issue after even longer follow-up periods.

Adverse Radiation Effects

We believe that the reduction in the persistent risk for complications in patients treated after 1993 was due to more conformal dose planning, which was facilitated by the addition of MR imaging and MR angiography studies. When a greater radiation dose was delivered to the tumor margin, a higher obliteration rate was expected, based on a mathematical dose–response curve. The complication rate was projected to rise as well, however. Higher rates of symptomatic adverse radiation effects in brainstem AVMs compared with lesions in other locations has also been reported previously. The compact nature of brainstem parenchyma, having critical neurological function, undoubtedly increases both radiosurgical and microsurgical complication rates. During radiosurgery conformal dose planning and appropriate dose selection are key to the reduction of adverse radiation effects.

According to the Spetzler–Martin grading system, the majority of intraparenchymal brainstem AVMs can be clas-
sified as Grade VI (inoperable). The Spetzler–Martin grading system was developed to indicate the risks associated with resection and probably was inadequate to classify AVMs in terms of the risks for brainstem AVM radiosurgery. Thus, because of the limitations of this grading scale with regard to AVM radiosurgery, the need for a radiosurgery-based AVM grading scale has arisen. In the current study, the radiosurgery-based grading scale by Pollock and Flickinger, which is calculated from AVM volume, patient age, and AVM location with constant ratios, was significantly related to adverse radiation effects. Although this grading system was, in fact, produced from data obtained at our center, these data were quite different in two ways. First, Pollock and Flickinger were limited to older data collected between 1987 and 1991. Second, they included data from AVMs in all locations as opposed to those in the brainstem alone. We believe that the radiosurgery-based grading system can be a valuable outcome predictor following radiosurgery for brainstem AVMs.

The tectal portion of the midbrain was also significantly related to neurological complications. The tectum contains multiple cranial nerve nuclei. Tracts affecting ocular movement are confined to a very small area. The medial longitudinal fasciculus connects the nuclei of oculomotor and abducens nerves; disruption of fibers can cause internuclear ophthalmoplegia. Although the entire brainstem consists of various neurons and fibers, a particularly high density of critical anatomical structures positioned within the tectum may make this region more vulnerable to adverse radiation effects.

Best Candidates for Radiosurgery

From the factors evaluated in this study, we attempted to determine the optimal candidate to undergo brainstem AVM radiosurgery. The ultimate goal in treating brainstem AVMs is, of course, successful obliteration with no complication. Although nidus volume was not significantly related to successful obliteration in our study, most AVMs were relatively small (median volume 1.5 cm³). Because a greater radiation dose can be delivered to smaller AVMs with a lower expected complication rate, better outcomes would be expected in patients with smaller brainstem AVMs.

Provided that patients with large brainstem AVMs have no other therapeutic options short of observation, staged radiosurgery might be effective, as asserted by other authors. We found that more spherical AVMs requiring fewer isocenters demonstrated higher obliteration rates. Also, an older patient age and a nidus location in the tectum were related to neurological complications. Based on our statistical analysis, better outcomes would be expected in younger patients harboring spherical AVMs located in nonectal regions (Fig. 2).

Conclusions

Gamma knife surgery was a generally safe and effective treatment in patients with brainstem AVMs. Complete obliteration was achieved in two thirds of patients with a low risk of latency-interval hemorrhage based on long-term analysis. Highly conformal dose planning as well as optimal dose selection can reduce the risk of adverse radiation effects. Younger patients harboring more spherical AVMs in nonectal regions are excellent candidates for radiosurgery and are associated with higher obliteration rates and lower complication rates. High-resolution multiplanar imaging is critical to successful conformal dose planning, dose selection, and ultimately obliteration with low rates of adverse radiation effects.

References

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Address reprint requests to: Douglas Kondziolka, M.D., Department of Neurological Surgery, University of Pittsburgh, Suite B-400, 200 Lothrop Street, Pittsburgh, Pennsylvania 15213. email: kondziolkads@msx.upmc.edu.