Analysis of treatment failure after radiosurgery for arteriovenous malformations

THOMAS L. ELLIS, M.D., WILLIAM A. FRIEDMAN, M.D., FRANK J. BOVA, PH.D., PAUL S. KUBILIS, M.S., AND JOHN M. BUATI, M.D.

Departments of Neurosurgery, Radiation Oncology, and Biostatistics, University of Florida, Gainesville, Florida

Object. The aim of this study was to evaluate the causes of treatment failure in patients with arteriovenous malformations (AVMs) who underwent radiosurgery, which is increasingly used as a treatment method for selected, surgically high-risk AVMs. Unfortunately, radiosurgical treatment fails in a small but significant percentage of patients. In the time period covered in this study, 72 patients attained angiographically confirmed cures after radiosurgery, and 36 were retreated after the initial radiosurgical treatment failed.

Methods. Using a computerized image fusion technique, the initial radiosurgical dosimetry plan was superimposed on the remaining AVM nidus at the time of retreatment. Twenty-six percent of the retreated cases were found to have AVM niduses outside the original treatment isodose line, which means that targeting error was a factor. The retreated group was also statistically compared with the cured group.

Conclusions. Multivariate analysis revealed that the following factors were statistically significant predictors of treatment failure: increasing AVM size, decreasing treatment dose, and increasing Spetzler–Martin grade.

KEY WORDS • radiosurgery • linear accelerator • arteriovenous malformation

SELECTED patients with arteriovenous malformations (AVMs) are candidates for treatment with radiosurgery, and in the majority of cases a cure is achieved. Unfortunately, in some cases radiosurgery fails to obliterate the nidus completely. The purpose of this paper is not to add to the abundant literature regarding the methodology of radiosurgery or to confirm the generally high efficacy of the technique in the treatment of AVMs. Rather, our intent is to evaluate the causes of failure in those patients in whom treatment fails. To accomplish this we analyzed a series of patients with AVMs who were treated with linear accelerator radiosurgery (LINAC) at the University of Florida to determine significant predictors of failure.

Clinical Material and Methods

Targeting Error Determination

Between May 19, 1988, and May 19, 1997, a total of 299 patients with AVMs were treated using radiosurgery at the University of Florida. The treatment method used and the results have been described in previous reports. A detailed system for categorizing all possible results after radiosurgery was elaborated in one of these studies. These categories include angiographic cure, angiographically confirmed failure, retreatment, cure or failure documented on magnetic resonance (MR) imaging, death, loss to follow up, and refusal of follow-up care. Angiographically confirmed cure, retreatment, and death due to hemorrhage were proposed as “definitive” outcomes. In this paper, in an attempt to analyze causes of failure after radiosurgery, we deal with only two of these potential outcome categories: angiographically confirmed cure (success) and retreatment (failure). As described, all patients are encouraged to undergo angiographic evaluation 3 years after radiosurgical treatment and, if a cure is not identified on angiographic studies, to undergo retreatment on the same day. During this study period, 36 patients underwent radiosurgical retreatment, which was categorized as treatment failure. The location, volume, and Spetzler–Martin grades of these AVMs at the time of the original treatment are listed in Table 1.

This population of retreated patients presents a unique opportunity to examine targeting error as a cause of failure. Radiosurgery for AVMs, because three-dimensional computerized treatment plans exist from the time of both the initial and secondary treatment. The initial treatment plan was recalled from the computer archive, and using image fusion software, the initial treatment isodose line was fused onto the bolus-enhanced volumetric computerized tomography (CT) scan (1-mm slice thickness) obtained at the time of the second treatment. The residual nidus, as identified on the CT scan, was then examined to determine whether it fell inside or outside the initial treat-
Treatment failure after radiosurgery for AVMs

Table 1
Location and Initial Volume of AVMs and Spetzler–Martin Grades in 36 Patients Retreated with Radiosurgery

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>location</td>
<td></td>
</tr>
<tr>
<td>frontal lobe</td>
<td>5</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>3</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>17</td>
</tr>
<tr>
<td>occipital lobe</td>
<td>4</td>
</tr>
<tr>
<td>thalamus</td>
<td>3</td>
</tr>
<tr>
<td>internal capsule</td>
<td>1</td>
</tr>
<tr>
<td>cerebellum</td>
<td>2</td>
</tr>
<tr>
<td>brainstem</td>
<td>1</td>
</tr>
<tr>
<td>volume (ml)</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>2</td>
</tr>
<tr>
<td>1.0–3.9</td>
<td>3</td>
</tr>
<tr>
<td>4.0–9.9</td>
<td>6</td>
</tr>
<tr>
<td>≥10</td>
<td>25</td>
</tr>
<tr>
<td>Spetzler–Martin grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>13</td>
</tr>
</tbody>
</table>

An analysis similar to that performed for treatment failure was conducted for the outcome of target error assessed in patients in whom treatment failed. Because the sample size was much smaller for this group of patients, at most only three predictors (or two predictors and pairwise interaction) were assessed simultaneously by using multiple logistic regression.

### Results

#### Targeting Error

Thirty-six retreated patients were analyzed for targeting error. Two patients were excluded from the analysis because the AVM nidus at the time of retreatment was too small to be visualized on the CT scan alone. Of the remaining 34 patients, nine (26%) had a residual nidus partially outside the first treatment isodose line. In the other 25 patients (74%), the residual nidus fell entirely within the first treatment isodose line, indicating that targeting error did not contribute to failure in this group. An example from each group of patients is illustrated in Figs. 1 and 2.

Computerized volume determination revealed the mean AVM volume at the time of the first treatment to be 15 ml. The mean volume at the time of retreatment was 4.4 ml, yielding a mean percentage reduction in AVM volume of 70% after the first radiosurgical treatment.

#### Statistical Analysis

Univariate logistic regression indicated that the number of isocenters, size, Spetzler–Martin grade, and dose each had odds ratios that differed significantly from 1 (p = 0.036–0.001; see univariate odds ratios Table 2). The odds ratio for prior hemorrhage status was only marginally significant (p = 0.053). Areas under the ROC curve were highest for dose (c = 0.78), Spetzler–Martin grade (c = 0.78), and size (c = 0.76). For dose, a classification cutpoint less than or equal to 1500 for treatment failure yielded 83% sensitivity and 53% specificity. A sensitivity of 75% and a specificity of 67% were achieved if a Spetzler–Martin grade of III or higher was used to define treatment failure. Treatment failure defined as an AVM size of 10 ml or larger achieved 69% sensitivity and 72% specificity (Table 3).

These specificity and sensitivity figures can be understood as follows: of all lesions in which treatment failed, 69% were 10 ml or larger in volume (sensitivity). For all lesions in which therapy did not fail, 72% were less than 10 ml in volume (Table 4). Of all lesions in which therapy failed, 83% received a dose of 1500 cGy or less. Of all lesions in which therapy did not fail, 53% received a dose greater than 1500 cGy (Table 3). For all lesions in which treatment failed, 75% had a Spetzler–Martin grade of III or higher. For all lesions in which treatment did not fail, 67% had a Spetzler–Martin grade of II or lower (Table 3).

Multiple logistic regression analysis yielded two best predictive models for treatment failure, models that contained either dose and Spetzler–Martin grade or size and Spetzler–Martin grade (see multivariate odds ratios, Table 4). Both models had similar areas under the ROC curve (c = 0.82), and standardized regression coefficients indicated Spetzler–Martin grade had a slightly greater relative
importance than either dose or size. The addition of size to the dose and Spetzler–Martin grade model and the addition of dose to the size and Spetzler–Martin grade model did not improve diagnostic performance, which was not surprising given the high correlation already noted between size and dose ($r = -0.77$).

Univariate logistic regression analysis for predictors of targeting errors indicated that only prior hemorrhage status had an odds ratio that differed significantly from 1 ($p = 0.030$). The area under the ROC curve for prior hemorrhage status was $c = 0.70$. Standardized regression coefficients also indicated prior hemorrhage status to be of greatest relative importance. This predictor achieved 56% sensitivity and 84% specificity for targeting error. No multivariate models assessed using multiple logistic regression analysis were found to be significantly better at predicting targeting error than prior hemorrhage status, a univariate predictor.

**Discussion**

Whereas numerous authors have proven the angiographically documented obliteration rates and complications associated with AVM radiosurgery, relatively few have analyzed the causes of treatment failure. The purpose of this study was to analyze two distinct questions. First, to what extent does targeting error contribute to radiosurgical failure? Second, what factors other than targeting error are statistically significant in predicting radiosurgical failure?

**Targeting Error**

Pollock, et al.,$^{10}$ reviewed a group of 45 patients who underwent a second radiosurgical procedure after an initial failure to obliterate their AVMs. In identifying the potential causes of initial treatment failure in this group of patients, they described five factors: in five patients
(11%), the entire AVM was not visualized secondary to incomplete angiography (two vessel instead of four vessel) or inadequate angiographic technique (failure to perform superselective angiography). In three patients (7%), the AVM recanalized after embolization. In four patients (9%), the AVM nidus reexpanded after resorption of a hematoma that had compressed the vessels within the nidus. In 21 patients (46%), the true three-dimensional shape of the AVM nidus was not appreciated because of reliance on biplanar angiography alone. In the remaining 12 patients (27%), a definite cause for failure could not be determined. The authors believed that the AVMs in these patients were demonstrating some form of “radiobiological resistance,” that is, failure to be obliterated despite proper planning and adequate dose delivery. In summary, in 73% of these patients, a targeting error factor (whether resulting from inadequate angiography, recanalization, compression by hematoma, or lack of three-dimensional imaging) was identified as a contributing factor in radiosurgical failure.

Yamamoto, et al., 27 reviewed the long-term follow-up results in a group of 40 Japanese patients who underwent gamma knife radiosurgery for AVMs in three different countries (Argentina, Sweden, and the United States). In their retrospective analysis they discovered that the nidus had been only partially covered at the time of the first treatment in six (46%) of the 13 patients in whom treatment subsequently failed.

In this study, a sophisticated computed technique was used to analyze the presence of targeting error. Using image fusion software, we fused the original treatment plan, based on 1-mm-thick CT slices, pixel for pixel onto the enhanced CT scan obtained on the day of the second treatment. The residual nidus was found to be partially outside

Fig. 2. Angiograms obtained in a patient who presented with headache. Evaluation with MR imaging and, eventually, angiographic studies, revealed a 5.4-ml right occipital AVM (upper left, anteroposterior vertebral angiography; upper right, lateral vertebral angiography). The AVM was treated radiosurgically with a dose of 1500 cGy prescribed to the 80% isodose line of a 22-mm collimator. A coronal dosimetry view through the isocenter shows the prescription isodose line and the enhanced AVM (lower left). Angiographic studies 4 years later revealed a 1.2-ml residual nidus, and retreatment was administered. The original treatment isodose line is shown superimposed on the second treatment CT scan (lower right). All of the residual nidus is located entirely within the initial treatment isodose line, indicating that targeting error was not the cause of treatment failure in this patient.
the original treatment isodose line in only 26% of cases. In the remainder, the residual nidus had been targeted correctly at the time of original treatment. Statistical analysis showed that only previous hemorrhage was a significant factor in predicting targeting error. It is possible that, as in the series of Pollock, et al., the presence of a previous hemorrhage distorted or compressed the AVM nidus such that its full extent was not appreciated and targeted.

Why is the percentage of targeting error lower in this report than in other series? Radiosurgical treatment planning for cerebral AVMs requires accurate definition of the true three-dimensional size and shape of the nidus. Over- or underestimation of these parameters may result in unnecessary irradiation of normal brain tissue or suboptimal irradiation coverage of the malformation, leading to treatment failure. As addressed in several previous publications, angiographic studies are not an ideal database for radiosurgery of AVMs. Their shortcomings include planar representation of a three-dimensional volume and simultaneous visualization of feeding arteries and draining veins that overlap with the nidus and obscure its outline. In selected cases, stereotactically guided contrast-enhanced CT scanning or stereotactically guided MR imaging may provide better spatial definition of the nidus and superior anatomical detail for the final design of the radiosurgical isodose distribution. In another paper, we compared the representation of the AVM nidus on angiographic and CT studies obtained in 81 consecutive cases. In 44 cases, the nidus isocenter differed by an average of 3.6 mm. Fourteen niduses were larger on CT studies but 30 were smaller (average 4 mm). Overall, the niduses confirmed on angiographic and CT studies differed in 75% of cases. We believe that the routine use of a three-dimensional imaging modality (1-mm slice thickness bolus-enhanced CT scans) as a part of computerized dosimetry planning may account, in part, for our relatively low incidence of targeting error.

Other Factors Contributing to Radiosurgical Failure

Many groups have reported on the efficacy and safety of radiosurgery for AVMs, and many have noted significantly higher failure rates in larger AVMs and in lesions treated with lower doses of radiation. Steiner and colleagues have published many reports on gamma knife radiosurgery for AVMs. They have reported 1-year occlusion rates ranging from 33.7 to 39.5% and 2-year occlusion rates ranging from 79 to 86.5%. However, these results were “optimized” by retrospectively selecting patients who received a minimum treatment dose of 20 Gy. For example, in one report it was stated, “... a large majority of patients received at least 20–25 Gy of radiation. ... Of the 248 patients treated before 1984, the treatment specification placed 188 in this group.” Steiner, et al., recognized that AVMs treated with peripheral doses lower than 20 Gy had a lower success rate.

More recently, Karlsson and colleagues have reported, in more detail, on a series of 1319 AVMs treated with gamma knife radiosurgery at the Karolinska Institute. Of this group, data for 945 patients were available for analysis. The mean minimum dose in cases in which AVMs were obliterated was 23 Gy and the minimum dose in cases of treatment failure was 13 Gy. The incidence of obliteration increased with the minimum dose, as a logarithmic function. At a minimum dose of 15 Gy, an obliteration rate of approximately 50% was achieved, whereas at a minimum dose of 20 Gy, the obliteration rate was approximately 70%. The mean volume of obliterated AVMs was 2.1 ml and the mean volume of AVMs in which treatment failed was 5.3 ml.

Kemeny, et al., reported on 52 patients with AVMs who were treated with gamma knife radiosurgery. They each received 2500 cGy to the 50% isodose line. At 1 year, 16 patients (31%) had complete thrombosis and 10 patients (19%) had “almost complete” thrombosis. These authors found that the results were better in younger patients and in patients with relatively lateral location of AVMs. There was no difference in outcome between small (< 2 ml), medium (2–3 ml), and large (> 3 ml) AVMs.

Lunsford, et al., reported on 227 patients with AVMs who were treated with gamma knife radiosurgery. The mean dose delivered to the AVM margin was 21.2 Gy. Among 75 patients who were followed for at least 2 years,
2-year follow-up angiographic studies were performed in 46 (61%), and complete obliteration was confirmed in 37 (80%) of the 46. This thrombosis rate strongly correlated with AVM volume as follows: less than 1 ml, 100%; 1 to 4 ml, 85%; 4 to 10 ml, 58%.

Steinberg, et al., in an analysis of 86 AVMs treated with a particle-beam radiosurgical system, reported 29% 1-year, 70% 2-year, and 92% 3-year thrombosis rates. At 3 years posttreatment, the following success rates were attained for AVMs according to size: less than 4 ml, 100%; 4 to 25 ml, 95%; greater than 25 ml, 70%. Initially a treatment dose of 34.6 Gy was used, but a higher than expected neurological complication rate (20% for the entire series) led to the currently used dose range of 7.7 to 19.2 Gy.

Colombo, et al., reported on 97 patients with AVMs who were treated by using a LINAC system. Doses ranging from 18.7 to 40 Gy were delivered in one or two sessions. Of 56 patients who were followed longer than 1 year, 50 underwent 12-month follow-up angiographic evaluation. In 26 (52%) of these patients complete thrombosis was demonstrated. Fifteen (75%) of 20 patients who underwent 2-year angiographic studies showed complete thrombosis. Colombo and colleagues reported a definite relationship between AVM size and thrombosis rate, as follows: lesions less than 15 mm in diameter had a 1-year obliteration rate of 76% and a 2-year rate of 90%. Lesions 15 to 25 mm in diameter had a 1-year thrombosis rate of 37.5% and a 2-year rate of 80%. Lesions greater than 25 mm in diameter had a 1-year thrombosis rate of 11% and a 2-year rate of 40%.

In a more recent publication, Colombo, et al., reported on 180 patients with AVMs. Again, the obliteration rate was significantly correlated with AVM diameter: lesions less than 15 mm in diameter had a 96.5% thrombosis rate; lesions 15 to 25 mm in diameter had a 73.9% obliteration rate; and those greater than 25 mm in diameter had a 33.3% obliteration rate.

Souhami, et al., reported on 33 AVMs treated with a LINAC system in which the prescribed dose at isocenter varied from 50 to 55 Gy. A complete obliteration rate of 38% was seen on 1-year angiographic studies. For patients whose AVM nidus was covered by a minimum dose of 25 Gy, the total obliteration rate was 61.5%, whereas none of the patients who received less than 25 Gy at the edge of the nidus attained a total obliteration.

In a previous study, we reported on 158 patients treated with the University of Florida radiosurgery system. Using traditional reporting standards we achieved an angiographically confirmed cure rate by size category as follows: B, 81%; C, 89%; D, 69%. The overall angiographically confirmed cure rate was 80%. The thrombosis rates in size categories C and D were substantially better than those previously reported in gamma knife or LINAC series.

This study provides a much more detailed statistical analysis of 108 patients with AVMs who reached a definitive outcome of either angiographically confirmed cure or retreatment. Simple statistics revealed that treatment failure was more likely in patients treated with multiple isocenters, patients with higher Spetzler–Martin grades, those treated with lower peripheral doses, and those with a history of hemorrhage. Univariate logistic regression analysis confirmed that these factors had odds ratios that were significantly different from 1. The number of isocenters in this series correlated highly with AVM volume and was not as significant on multivariate analysis. As mentioned earlier, a history of hemorrhage was the only factor predictive of targeting error, and this may account for its marginal significance in predicting overall radiosurgical failure.

Notably, a classification cutpoint of 1500 cGy was significantly predictive for treatment results. In the AVMs treated with lower doses (1000 or 1250 cGy) we had a very low success rate (17%), in AVMs treated with 1500 cGy the success rate was 71%, and in AVMs treated with yet higher doses we saw incrementally higher success rates (87.5% at 20 Gy and 100% in the few patients treated with higher doses). Thus, we can confirm the generally held contention that higher peripheral doses produce incrementally higher success rates. However, we cannot confirm the oft-repeated suggestion that 20 Gy is the optimal treatment dose for AVM radiosurgery. Perhaps because many of the AVMs treated in this series were of larger volume, we have had the opportunity to observe comparably high success rates with the 1500 cGy dose. If we had to select a statistically validated optimal dose in our series, it would be 1500 cGy. Additionally, it is of interest that those AVMs that received a dose of less than 1500 cGy had a mean volume decrease of 68% (essentially the same as the 70% volume reduction seen for the entire retreatment group) as a result of the first, failed treatment. Thus, although the lesion were not cured by the first treatment, it is possible that they decreased in size enough to be salvaged with a retreatment.

An AVM volume of 10 ml or less was also a statistically significant cutpoint for failure in our series. A Spetzler–Martin grade of III or more, which is highly correlated with AVM volume, was a similarly significant cutpoint. Thus, we can also confirm the generally held contention that radiosurgical failures increase as AVM volume increases. As noted earlier, the success rates remain high up to an AVM volume of 10 ml, unlike the results previously reported in some gamma knife or LINAC series, in which success dropped off at much lower volumes.

Multivariate analysis yielded two highly predictive models for radiosurgical success. The first model uses dose and Spetzler–Martin grade score. The second uses AVM volume and Spetzler–Martin grade score.

Almost all groups performing radiosurgery use some
dose–volume guidelines during treatment. In other words, larger lesions are deliberately treated with lower doses, to reduce the risk of complications. This results in a very high inverse correlation between dose and volume and accounts for the fact that we cannot distinguish by using multivariate analysis which factor, if either, is more important in predicting radiosurgical failure.

Conclusions

In this analysis of 108 patients who reached the definitive endpoints of either angiographically confirmed cure or retreatment after radiosurgery for AVMs, three conclusions have been reached.

1) Targeting error was a factor in 26% of the cases of treatment failure. It occurred more frequently in patients with a history of hemorrhage.

2) Statistically significant factors that were predictive of radiosurgical failure included multiple isocenters, higher Spetzler–Martin grades, increasing AVM volume, lower peripheral doses, and a history of hemorrhage.

3) Statistically significant “cutpoints” for treatment failure included Spetzler–Martin grade of III or higher, radiation doses of 1500 cGy or lower, and AVM volumes of 10 ml or more.

References