

# The risk of hemorrhage after radiosurgery for arteriovenous malformations

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Two hundred and one patients with arteriovenous malformations (AVM's) were treated radiosurgically between May 1988 and February 1995 and are analyzed in this study. Twelve patients sustained a posttreatment hemorrhage during this period. Pretreatment factors associated with increased hemorrhage risk were identified in 11 of these patients and included arterial aneurysms, venous aneurysms, venous outflow obstruction, peritumoral location, prior embolization, and prior surgical treatment. A detailed statistical analysis, using both Poisson regression and parametric survival regression techniques, was undertaken to determine whether radiosurgery had any effect on the risk of hemorrhage, when compared to the natural history of the disease, in those patients in whom a complete angiographic cure was not achieved. No evidence was found to support a statistically significant departure from the natural hemorrhage rate at any time period after radiosurgical treatment. Significant risk factors for hemorrhage appeared to correlate with increasing AVM volume.

KEY WORDS • arteriovenous malformation • radiosurgery • intracerebral hemorrhage

The most neurologically devastating presentation associated with arteriovenous malformations (AVMs) of the brain is intracerebral hemorrhage. Numerous studies have estimated the natural risk of intracerebral hemorrhage associated with AVMs at 3% to 4% per year.<sup>5 8 '4 '5 25</sup> When an AVM is identified in a young, otherwise healthy individual, one of several therapies (microsurgery, radiosurgery, or endovascular therapy) is often considered in an attempt to extirpate the lesion before a hemorrhage can occur.

Conflicting information has appeared regarding the effects of radiosurgery for AVMs on the risk of hemorrhage. Some have suggested that radiosurgery may increase the risk of hemorrhage in the 1st year after treatment.<sup>7 27</sup> Others have suggested that radiosurgery decreases the risk of hemorrhage, even in AVMs that are incompletely obliterated on follow-up angiography.<sup>'92' 22</sup> In addition, a variety of pretreatment factors have been identified as possibly increasing the natural risk of hemorrhage, including patient age,<sup>19</sup> AVM size,<sup>26 29 35</sup> history of hemorrhage,<sup>8'020</sup> and assorted "angiographic risk factors."<sup>24 34 36</sup>

All patients with AVMs treated with radiosurgery at the University of Florida from May 1988 to February 1995 were analyzed to elucidate the following questions: 1) does radiosurgery increase the risk of hemorrhage in the 1st year after treatment or decrease this risk at any time thereafter, prior to complete AVM occlusion; and 2) can any pretreatment factors be identified that are associated with an increased risk of hemorrhage after radiosurgical treatment?

## Clinical Material and Methods

### Study Methodology

Between May 1988 and February 1995, 214 AVMs were treated in 204 patients at the University of Florida. The treatment methodology has been detailed in other reports.<sup>3</sup> Three patients were completely lost to follow-up study (no subsequent radiographic or clinical information). The remaining 201 patients are analyzed in this study. Five of these patients were lost to follow-up review at various time intervals after imaging data were obtained; they are included in the analysis up to the time of their last follow-up image. Likewise, three patients died of intercurrent disease during the follow-up period, and they are included in the analysis up to the time of their last follow-up image. Data were grouped according to the last known time that AVM flow was detected (on angiography, magnetic resonance (MR) imaging, or MR angiography); the first known time that cessation of AVM flow was detected (on angiography, MR imaging, or MR angiography); and the time of occurrence of hemorrhage (12 patients). Age, history of AVM hemorrhage, dose, isodose line treated, Spetzler-Martin grade,<sup>30</sup> and AVM volume were also known for each patient. The AVM volumes were determined by three-dimensional dose-volume histogram analysis and categorized in the following classes: A (< 1 cc), B (1-4 cc), C (> 4-10 cc), and D (> 10 cc).

The 12 patients who sustained a hemorrhage during the follow-up period were further studied. The angiographic characteristics of their AVMs, including the presence of arterial or venous aneurysms, venous outflow obstruction, periventricular location, or unusual flow characteristics, were explored. Prior treatments, including embolization and surgery, were tabulated. These 12 patients form the "numerator" in the statistical analysis of hemorrhage risk.

The "denominator" in any analysis of hemorrhage risk consists of the number of patient-years for which the studied population remains at risk for hemorrhage. Virtually all investigators agree that once an AVM has been angiographically obliterated after radiosurgery, there is no remaining hemorrhage risk (at least no such case has ever been reported). In practice, radiosurgically treated patients are followed with MR imaging, MR angiography, and/or angiography until occlusion is identified. These studies are generally performed at 6- to 12-month intervals. It is therefore not possible to know the exact day when an AVM becomes occluded and the patient becomes free of risk for hemorrhage.

Because the time of cessation of AVM flow cannot be determined exactly, three different methods were used to determine the postsurgical interval during which a patient would be at risk for AVM-related hemorrhage. The "midpoint" method estimated the time of cessation of AVM flow as the midpoint between the time of the last patient visit at which flow was radiographically observed and the time of the first patient visit at which no flow was observed. It is known that MR imaging and MR angiography may spuriously indicate no flow when, in fact, a small nidus can be demonstrated on angiography. Nonetheless, we elected to use MR imaging and MR angiography data for the following reasons: 1) there were many more MR imaging/MR angiography data points than angiographic data points. 2) The error introduced by "false negative" MR imaging/MR angiography data would presumably reduce the time during which a patient was believed to be at risk, thereby increasing the calculated risk of hemorrhage in this

analysis. As will be shown later, because no statistically significant increase in hemorrhage risk was in fact observed, this assumption does not seem to have altered the principal conclusions of the analysis. 3) Most spurious MR imaging/MR angiography data were corrected with follow-up angiograms. This definitive test was unavailable only if the patient refused angiography.

The "last flow" method estimated the time of cessation of AVM flow as occurring immediately after the time of the last patient visit at which flow was observed. In other words, it was assumed that the AVM became occluded the day after the last flow study. This assumption would minimize the period of time during which this patient population would theoretically be at risk for hemorrhage.

The "no flow" method estimated the time of cessation of AVM flow as occurring immediately before the time of the first patient visit at which no flow was observed. This assumption would maximize the period of time during which this patient population would theoretically be at risk for hemorrhage.

## Statistical Methods

Poisson regression<sup>4</sup> was used to estimate postsurgery AVM-related hemorrhage rates per 100 person-years of follow up and to determine rate ratios for the aforementioned covariates (such as AVM size and patient age). A rate ratio can be thought of as the factor by which the baseline hemorrhage rate changes as a result of membership in a risk group (prior hemorrhage) or as a result of change in a continuous variable (AVM volume). A commercially available epidemiological statistics software package (EGRET; Statistical and Epidemiological Research Corp., Seattle, WA) was used to compute hemorrhage rates and rate ratios with 95% confidence intervals (CIs). For each of the three sets of follow-up times, hemorrhage rates were computed for each yearly interval postsurgery and also for the entire postsurgery follow-up interval (up to 5 years). In yearly intervals containing no hemorrhage events, an upper 95% CI for the hemorrhage rate was estimated using the method of Haenszel, et al.<sup>6</sup> Covariate rate ratios were computed for the entire postsurgery follow-up interval. Variables such as AVM volume and dose were treated as continuous and were also stratified using the median as a cutpoint.

In a parallel analytical approach to the data, parametric survival regression assuming exponential hemorrhage times (that is, a constant time-specific hemorrhage rate) was used to estimate yearly percentage failure rates piecewise in the 1st- and 2nd-year intervals postsurgery and for the entire postsurgery follow-up interval. Kaplan-Meier product-limit estimation was used to generate survival curves for the entire cohort of patients and for patient strata defined by the various covariates. The log-rank test was used to compare survival curves between strata. Cox proportional hazards regression was used to estimate hazard ratios for the aforementioned covariates. A hazard ratio can be thought of as the factor by which the baseline hazard rate (such as time-specific hemorrhage rate) changes as a result of membership in a risk group or change in a continuous risk factor. The EGRET package was again used to compute hemorrhage rates, hazard ratios, and 95% CIs. Covariate hazard ratios were computed for the entire postsurgery follow-up interval, and continuous variables were handled

as they were for Poisson regression. Each of the three sets of follow-up times was analyzed in this manner.

A stepwise procedure (forward stepping) was used to construct multivariate Poisson regression and multivariate Cox proportional hazards regression models from among the covariates volume, size class, Spetzler-Martin grade, dose, isodose, prior hemorrhage, and age, using the last flow, midpoint, and no flow definitions for follow-up and event times. Power to detect a difference in Poisson rates was computed using the EGRET package.

## Results

The mean patient age was 39 years, the mean AVM volume was 10 cc, and the mean dose to the periphery of the lesion was 1505 cGy. Further descriptive statistics (size classification, incidence of prior hemorrhage, Spetzler-Martin grade, size versus posttreatment hemorrhage, and pretreatment versus posttreatment hemorrhage) are displayed in Tables 1 to 3. Piecewise and overall yearly hemorrhage rates per 100 person-years were estimated using Poisson regression, piecewise and overall yearly percentage hemorrhage rates were estimated via parametric survival regression ("midpoint" data assumption), and both are summarized in Table 4. These rates and associated CIs changed insignificantly as a function of which set of follow-up time assumptions ("midpoint," "last flow," or "no flow") was used. The computed hemorrhage rates and the 95% CIs for the true hemorrhage rate of patients represented by the cohort do not provide evidence to suggest that the rate of hemorrhage differs at any time from the expected natural history rate of 3% to 4% per year.

**TABLE 1**

Descriptive statistics in 199 patients with radiosurgically treated arteriovenous malformations\*

Parameter	No. of Patients	Percent
size		
A(<1 cc)	6	3.0
B (1-4 cc)	51	25.6
C (>4-10 cc)	56	28.1
D (>10 cc)	86	43.2
prior hemorrhage		
yes	121	60.8
no	78	39.2
Spetzler-Martin grade		
I	7	3.5
II	77	38.7
III	81	40.7
IV	34	17.1

\* In two patients it was unclear whether a pretreatment hemorrhage had occurred, and these patients were excluded from the analyses in Tables 1 to 3.

**TABLE 2**

Posttreatment hemorrhage versus size category in 199 patients with radiosurgically treated arteriovenous malformations

Posttreatment Hemorrhage	Size Category (%)*				Total
	A	B	C	D	
no	6 (100)	51 (100)	54 (96)	76 (88)	187
yes	0 (0)	0 (0)	2 (4)	10 (12)	12
total	6	51	56	86	199

\*A=<1 cc;B= 1-4cc;C=>4 IOcc;D=>IOcc.

**TABLE 3**

Hemorrhage risk versus prior hemorrhage in 199 patients with radiosurgically treated arteriovenous malformations

Posttreatment Hemorrhage	Pretreatment Hemorrhage (%)		
	No	Yes	Total
no	113 (93)	74 (95)	187
yes	8 (7)	4 (5)	12
total	121	78	199

**TABLE 4**

Poisson and exponential hemorrhage rate analysis in 201 patients with radiosurgically treated AVMs\*

Interval Post-surgery	No. of Cases	No. of Hemorrhages	Person Yrs Follow Up	No. of Hemorrhages/100 Person-Yrs	95% CI	
					Lower	Upper
Poisson estimated hemorrhage rates						
years 1-5	201	12	270.38	4.44	2.52	7.82
year 1	201	8	166.13	4.82	2.41	9.63
year 2	102	4	71.25	5.62	2.11	14.96
year 3	36	0	25.30	0	>0	11.86
year 4	14	0	6.50	0	>0	46.15
year 5	2	0	1.20	0	>0	248.30
Exponential failure estimated hemorrhage rates						
years 1-5	201	12	262.17	4.58	2.6	8.06
year 1	201	8	162.57	4.92	2.46	9.84
year 2	99	4	68.81	5.81	2.18	15.48

\* Abbreviations: AVMs = arteriovenous malformations; CI = confidence interval

Kaplan-Meier survival plots for the strata defined by the covariates of AVM volume, Spetzler-Martin grade, treatment dose, and isodose line treated are displayed in Fig. 1. Log-rank test probability values are displayed in Table 5. Rate and hazard ratios for the covariates yielded nearly identical results and are not tabulated here.

**TABLE 5**

Log-rank test comparison of survival curves defined by various strata in 199 patients with radiosurgically treated arteriovenous malformations

Covariate	Strata	Midpoint	p Value	
			Last Flow	No Flow
size	A+B+C:D	0.01	0.02	0.009
prior hemorrhage	yes:no	0.74	0.89	0.67
Spetzler-Martin	I:II:III:IV	0.008	0.02	0.005
age	continuous	0.91	0.94	0.88
volume	continuous	0.0009	0.002	0.0005
dose	continuous	0.01	0.02	0.007
isodose	<70>70	0.03	0.04	0.02

The covariate results indicate that patient age and prior history of AVM hemorrhage do not appear to influence the risk of hemorrhage postradiosurgery significantly. The results do indicate that AVM volume, Spetzler-Martin grade, dose, and isodose line treated influenced the risk of hemorrhage. Risk increases significantly as AVM volume increases and is significantly greater in larger class sizes (especially Class D). Twelve percent of the Size D AVMs rebled, versus 4% of Size C, and 0% of Sizes A and B lesions (see Table 2). Hemorrhage risk is also significantly greater in the largest Spetzler-Martin grade stratum. The Spetzler-Martin grade correlates with two putative risk factors for hemorrhage after radiosurgery: AVM size and deep venous drainage (which also relates to periventricular location). Risk increases significantly as radiation dose decreases. Because larger AVMs are generally treated with smaller doses, this is probably not an independent effect. Those AVMs treated to the 70% isodose line or lower had a significantly increased risk of hemorrhage when compared to those treated more homogeneously (the 80% isodose line was almost always used). Again, larger AVMs tend to be treated with multiple isocenters, which necessitates use of the 70% or lower isodose line, so this is probably not an independent effect. Multivariate analysis confirmed that once volume was entered, no other covariates entered into any of the models, indicating that no further significant level of AVM risk was explained by covariates beyond that explained by volume alone.

Pretreatment hemorrhage (Table 3) did not correlate with posttreatment bleeding frequency. Five percent of those with a history of hemorrhage rebled versus 7% of those with no history of hemorrhage. Patient age also did not correlate with frequency of bleeding.

Power analysis showed that, assuming a constant baseline AVM occurrence rate of three per 100 person-years of follow up (or 3%/year) in untreated patients, 726 person-years of follow up (see Clinical Material and Methods) would be required to have a 95% chance of detecting a reduction in the AVM rate to one per 100 person-years of follow up (or 1 %/year) in treated patients at a significance level of 0.05.

Detailed information on the 12 patients who experienced a hemorrhage is provided in Table 6. The data in this table confirm the significant factors identified in the statistical analysis: all but two of the AVMs were in the largest size category (D); four of the 12 patients were treated to the 70% isodose line; and six of the 12 patients were treated with doses of 1250 cGy or less.

**TABLE 6**  
Data for 12 patients who sustained posttreatment hemorrhage of radiosurgically treated AVMs\*

Case No.	Age (yrs)	Vol (cc)	Radiation Dose (cGy)	Isodose	Prior Hemorrhage	Periventricular Location	Spetzler Martin Grade	Aneurysm	Venous Obstruction	Status
1	61	5.6	1500	80	yes	no	II	none	no	baseline
2	17	11.9	1250	94	no	yes	IV	venous	yes	moderate deficit
3	62	14	1500	80	no	yes	II	arterial	no	mild deficit
4	34	45.3	1000	70	yes	yes	IV	none	no	baseline
5	48	14	1500	80	no	yes	III	arterial	yes	dead
6	19	17.4	1250	70	no	no	III	venous	no	baseline
7	45	16	1250	70	yes	no	IV	none	no	severe deficit
8	39	13.5	1500	80	no	yes	III	none	no	severe deficit
9	39	9.2	1500	80	no	no	11	none	yes	baseline
10	40	14.3	1500	80	no	no	IV	venous	no	dead
11	52	37.8	1000	80	yes	yes	IV	venous	no	baseline
12	10	19.6	1000	70	no	yes	IV	venous	no	baseline

\* Abbreviation : AVMs = arteriovenous malformations.

Three angiographic features thought to be predictive of AVM hemorrhage risk were analyzed in these 12 patients: seven patients had either arterial or venous aneurysms. One of the patients with an unsecured arterial aneurysm died from his hemorrhage. Three had a venous outflow anomaly. Seven had AVM nidi that extended to a periventricular surface. Ten of these 12 patients had at least one of these angiographic risk factors present. In addition, the patient in Case 1 had undergone prior partial surgical resection of the AVM, and the patient in Case 2 had undergone prior embolization. Thus, 11 of the 12 patients had at least one clinical or radiographic factor possibly associated with an increased risk of hemorrhage.

The devastating effects of AVM hemorrhage are documented. Although six patients returned to their neurological baseline status, two patients died, and four were left with significant neurological deficits.

## Discussion

### *The Natural History of AVMs*

Many studies have addressed the issue of the natural history of AVMs. Unfortunately, most are tainted by selection bias, the use of a variety of therapeutic techniques, relatively short follow-up duration, and the inclusion of only certain subgroups of AVM patients, such as patients presenting with hemorrhage. The follow-up analysis of the series published by Troupp, *et al.*,<sup>33</sup> performed by Ondra and colleagues<sup>25</sup> provides a fairly pure look at a series of 160 patients with AVMs. Forty percent of the patients experienced a hemorrhage during the 24-year follow-up period, for a 4% per year risk of hemorrhage after entry in the study. There was a 7.7-year mean interval to hemorrhage, and these investigators found a 2.7% yearly incidence of significant morbidity and mortality (1%/year). Others have reported an annual hemorrhage rate for AVMs ranging from 2% to 4%.<sup>5 8 14 15</sup>

Some have suggested that a history of hemorrhage predisposes a patient to an increased incidence of subsequent hemorrhages.<sup>8</sup> For example, Forster, *et al.*,<sup>10</sup> noted that if a patient had one hemorrhage, there was a 25% risk of rebleeding over the next 4 years. If the patient had two hemorrhages, the risk of rebleeding was 25% over the next year. Others, including Ondra, *et al.*,<sup>25</sup> do not support this view and believe that after the first 6 months, the risk of hemorrhage reverts to baseline.

A number of investigators have identified a tendency for smaller AVMs to hemorrhage.<sup>14 18 26 29 35</sup> Others believe that this is an artifact due to the fact that smaller lesions are less likely than larger AVMs to present with seizures or vascular steal. Likewise, an increased risk of hemorrhage during pregnancy has been postulated but never proven.<sup>9 17</sup>

A variety of angiographic abnormalities have been purported to increase the likelihood of AVM hemorrhage. Vinuela, *et al.*,<sup>34</sup> evaluated the venous drainage of 53 deep-seated AVMs, 41 of which presented with hemorrhage. They found irregularity, stenosis, or absence of the vein of Galen in 11 cases. Willinsky, *et al.*,<sup>36</sup> studied 178 patients and found that arterial aneurysms or venous stenosis were present in 73% of those presenting with hemorrhage. Marks, *et al.*,<sup>24</sup> found a statistically significant association of periventricular location, intranidal aneurysm, and central venous drainage with the occurrence of AVM hemorrhage.

### *Radiosurgery and Risk of AVM Hemorrhage*

Does radiosurgery increase the risk of hemorrhage in the 1st year after treatment or decrease the risk at any time thereafter prior to complete AVM occlusion? The issue of AVM hemorrhage after radiosurgical treatment was first raised by investigators using particle beam methodology. Kjellberg and colleagues<sup>22</sup> reported two deaths from hemorrhage in the 1st year after treatment of their first 75 patients. In a subsequent report of 389 patients followed for at

least 2 years, eight had succumbed from hemorrhage in the first 2 years after treatment.<sup>20 21</sup> Only one died thereafter, for a 0.27% mortality in those patients more than 2 years posttreatment. Initially, these investigators suggested that only patients presenting with hemorrhage were at risk for subsequent lethal rebleeding. The later reports, however, documented fatal hemorrhage in patients presenting with seizure only. It should be emphasized that these authors reported a total hemorrhage rate of 2.4% per year (lethal and nonlethal) for those patients more than 2 years posttreatment. Whether this differs from the natural history of the disease has been the subject of debate.

Other particle-beam proponents have also addressed the hemorrhage question. Steinberg, *et al.*,<sup>31</sup> reported 10 hemorrhages (12%), two fatal, occurring between 4 and 34 months after radiosurgical treatment in a series of 86 patients. Two of these patients had hemorrhages in the 3rd year after treatment, suggesting no protective effect unless complete obliteration was achieved. Seifert and colleagues<sup>28</sup> analyzed a series of 68 patients treated with proton beam therapy in the United States. Eighteen patients deteriorated neurologically. Five of them had hemorrhages, of which two were fatal.

Gamma-knife radiosurgeons have studied this question as well. Lunsford, *et al.*,<sup>23</sup> in an initial report on AVM treatment with the Pittsburgh gamma knife, noted that 10 (4%) in a series of 227 patients had experienced hemorrhage. Two of these patients died. Pollock, *et al.*,<sup>27</sup> in a study of 65 patients with "operable" AVMs, noted that five patients (7.7%) had a hemorrhage, all within 8 months of radiosurgery. Two of these patients died. Steiner and colleagues<sup>32</sup> statistically analyzed bleeding in 247 consecutive AVM cases. The Kaplan-Meier approach demonstrated a risk of nearly 3.7% per year until 5 years after radiosurgery, at which point a plateau was reached.

This plateau was believed to be due to the small number of data points for that time period and not indicative of any true protective effect. Karlsson, *et al.*,<sup>19</sup> reported an analysis of bleeding in 1565 patients treated with the Stockholm gamma knife. They believed the risk of hemorrhage was decreased, even with incomplete obliteration. They also reported that increasing age and increasing AVM volume correlated with an increased risk of hemorrhage.

Betti, *et al.*,<sup>2</sup> in a pioneering report on linear accelerator radiosurgery for AVMs, documented hemorrhage in five (8%) of 66 of their patients. These hemorrhages occurred at 12, 18, 22, 25, and 29 months posttreatment. All patients had prior hemorrhages; two of these died. Colombo, *et al.*,<sup>7</sup> recently reported a detailed analysis of 180 patients. Fifteen patients had hemorrhages and five of them died. In cases in which the AVM nidus was totally irradiated, the bleeding risk decreased from 4.8% during the first 6 months to 0% starting from the 12th month of follow-up review. In partially irradiated cases, the bleeding risk increased from 4% in the first 6 months to 10% from the 6th through 18th months and then decreased to 5.5% from the 18th to the 24th month. No bleeding was observed thereafter.

In this study, exhaustive statistical analysis using two parallel approaches does not reveal any alteration from the expected natural history bleeding risk of 3% to 4% per year. It should be noted that there are significant pitfalls to be avoided in the analysis of hemorrhage

risk after radiosurgery. First, because radiosurgery is usually successful, a large number of patients are eliminated from the at-risk pool (the denominator) during the 1st and 2nd year after radiosurgery. Failure to adequately account for this fact leads to the false impression that the smaller number of hemorrhages occurring more than 1 year after treatment is due to some "protective" effect. In fact, the decreasing number of hemorrhages is statistically due simply to the decreasing number of patients at risk. Second, because there is a significant number of patients presenting with hemorrhage in any radiosurgery series and because these patients may have an increased risk of rebleeding for the first 6 months after hemorrhage,<sup>10i415</sup> the incidence of bleeding in the first 6 months after treatment may appear in some series to be artificially elevated. This is likely not a direct effect of radiosurgery but rather a reflection of the inclusion of this group of patients with a higher than normal risk of hemorrhage. Series that treat a larger percentage of patients presenting with hemorrhage (as opposed to seizures or headache) might be expected to have an elevated hemorrhage rate during the first 6 months after treatment for this reason.

Third, and most important, the natural incidence of hemorrhage in AVM patients is quite small. This means that the effect of a few more hemorrhages over a given period of time may significantly skew the conclusions in this type of study without the benefit of statistical analysis. Assuming a constant baseline AVM occurrence rate of three per 100 person-years of follow-up review (or 3%/year) in untreated patients, 726 person-years of follow-up review (see *Clinical Material and Methods*) would be required to have a 95% chance of detecting a reduction in the AVM rate to one per 100 person-years of followup review (or 1%/year) in treated patients at a 0.05 significance level. Given the relatively high cure rate of radiosurgery, a very large number (thousands) of patients would need to be treated to generate a sufficient number of patient follow-up years in years 2, 3, and 4 to yield statistically valid information. These factors must be kept in mind when interpreting some of the papers discussed above. Any attempt to elucidate the question of AVM bleeding after radiosurgery without benefit of detailed statistics must be viewed with some skepticism.

#### *Pretreatment Factors Associated With Increased Risk of Hemorrhage*

Can any pretreatment factors be identified that are associated with an increased risk of hemorrhage after radiosurgical treatment? As discussed above, Karlsson and colleagues<sup>9</sup> reported an increased risk of AVM hemorrhage with increasing AVM size. Colombo, *et al.*,<sup>7</sup> found a higher incidence in subtotally irradiated AVMs, most of which were presumably larger lesions. They also reported a statistically increased risk in patients treated more inhomogeneously (to a lower isodose line). In a subsequent paper<sup>6</sup> his group attributed this observation to the earlier thrombosis of the portion of the AVM receiving the highest dose of radiation, with shunting of blood into the remaining nidus, increasing the risk of hemorrhage.

In this series, we also found a strong correlation between AVM volume and the risk of hemorrhage. Ten of the 12 AVMs that bled had a volume greater than 10 cc (Table 2). In addition, the correlation of hemorrhage with lower dose and lower isodose line treated was likely due to the deliberate use of lower doses and multiple isocenter treatments (to lower isodose lines) in the larger AVMs. This observation is especially interesting in view of other published reports in which it is suggested that smaller AVMs are those that are most likely to

hemorrhage if left untreated. Of equal importance are those factors that were not found to correlate statistically with bleeding risk. These factors include age and a history of hemorrhage (see Table 3).

As documented above, 10 of these 12 patients also had angiographic risk factors for bleeding, including arterial aneurysms, venous aneurysms, venous outlet obstruction, and periventricular location. Although these angiographic factors were not subject to statistical analysis, one might certainly conclude that their absence could be associated with a decreased risk.

## **Conclusions**

In this series of 201 patients followed after radiosurgical treatment of AVMs, 12 experienced a posttreatment hemorrhage. Detailed statistical analysis did not reveal any departure from the expected natural history bleeding rate of 3% to 4% per year. The risk of hemorrhage correlated statistically with increasing AVM size, decreasing dose, and treatment isodose lines less than or equal to 70. Patient age and incidence of prior hemorrhage did not correlate with the risk of posttreatment bleeding. Retrospective analysis of the angiographic findings in the 12 patients with hemorrhage revealed that 10 had angiographic risk factors, including arterial aneurysm, venous aneurysm, venous outflow stenosis, and periventricular location.

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