Postradiosurgery Hemorrhage Rates of Arteriovenous Malformations of the Brain
Influencing Factors and Evolution With Time

Vera Parkhutik, MD; Aida Lago, MD, PhD; José Ignacio Tembl, MD; Juan Francisco Vázquez, MD; Fernando Aparici, MD; Esperanza Mainar, MD; Víctor Vázquez, MD

Background and Purpose—The long-term benefit of radiosurgery of brain arteriovenous malformations (AVM), especially nonhemorrhagic cases, is controversial. We calculated hemorrhage rates pre- and posttreatment and analyzed the risk factors for bleeding based on cases followed at our site.

Methods—One hundred eight patients, age 36±17 years, 56 men. The mean follow-up was 65±44 months (median, 54; interquartile range, 33–94). Most AVMs were small (74.1% <3 cm in diameter); 48.1% were located in an eloquent area, 27.8% had deep drainage, and 39.8% presented with hemorrhage.

Results—The annual hemorrhage rate for any undiagnosed AVM was 1.2%, and 3.3% for AVMs with hemorrhagic presentation. Older patients, cortical or subcortical AVMs, and cases with multiple draining veins were less likely to present with bleeding. During the first 36 months postradiosurgery, hemorrhagic AVMs had a rebleeding rate of 2.1%, and a rate of 1.1% from 3 years onwards. Nonhemorrhagic AVMs had a hemorrhage rate of 1.4% during the first 3 years and 0.5% afterward. Arterial hypertension and nidus volume were independent predictors of bleeding after treatment. Mean nidus obliteration time was 37±18 months (median, 32; interquartile range, 25–40), with hemorrhage rate of 1.3% before and 0.6% after obliteration, and 1.9% for AVMs that were not closed at the end of follow-up.

Conclusions—Both hemorrhagic and nonhemorrhagic AVMs benefit from radiosurgical therapy, with gradual decrease in their bleeding rates over the years. Albeit small, the risk of hemorrhage persists during the entirety of follow-up, being higher for cases with hemorrhagic presentation and nonobliterated AVM. (Stroke. 2012;43:00-00.)

Key Words: brain arteriovenous malformation ■ radiosurgery ■ bleeding rate ■ occlusion

Radiosurgery (RS) is a noninvasive method for treating surgically inaccessible brain arteriovenous malformations (AVM), based on proliferation of irradiated endothelial cells and progressive occlusion of the nidus. Its delayed efficacy and potential long-term side effects make the unbiased evaluation of its validity in preventing cerebral hemorrhages difficult. This is especially true in regards to radiosurgical treatment of nonruptured AVM, where controversy exists concerning different management alternatives. Although many centers use the same approach with unruptured AVMs as with hemorrhagic cases (surgery, RS, or embolization) to diminish their lifelong risk of first bleeding, others advocate for less aggressive behavior, to the point of no treatment.1,2

Our study analyzes bleeding rates and risk factors for hemorrhage in patients treated with RS, the aim being to evaluate the usefulness of this technique in preventing cerebral bleeds in both ruptured and nonruptured brain AVM.

Patients and Methods

Patients

This study comprises a series of consecutive patients with brain AVM followed at our site since 1994. Though the referral criteria for RS varied on an individual basis, general indications were small AVMs located in deep or eloquent areas of the brain (sensorimotor, language, visual, thalamus, hypothalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei) that made them unsuitable for surgery. In many cases, embolizations were performed before the RS to decrease nidus diameter. Briefly, catheterization was performed under general anesthesia with transfemoral approach by using standard coaxial techniques. Guiding catheter was located in carotid or vertebral artery, and a microcatheter was navigated to the nidus of the AVM. Once the tip was in the desired position, injection of embolization material was carried out. Until 2007, NBCA and lipiodol with Magic catheter (Balt) was used. After 2007, Onix with Marathon (ev3), UltraFlow (ev3), or Sonic (Balt) catheter was used according to standard embolization technique.3 Typically, several sessions were completed before the patient was referred to RS. Very occasionally, patients underwent RS after a surgical procedure.

Demographic data and presence of cardiovascular risk factors were documented. Arterial hypertension was defined as repeatedly
elevated blood pressure exceeding 140/90 mm Hg, or as use of antihypertensive drugs. Current smoking habits were also noted. Nidus characteristics (size, location, drainage, presence of aneurysms) as seen on diagnostic digital angiography and brain magnetic resonance (MR) were all recorded according to published standards.4

For the purpose of this study, AVMs were classified as hemorrhagic or nonhemorrhagic based on their presentation. Hemorrhagic AVM were defined as having radiological signs of acute bleeding on computed tomography (CT) scan or MR together with compatible clinical symptoms. Nonhemorrhagic AVMs had no such signs, and were subsequently subclassified as having presented with epileptic seizures, headaches, focal symptoms, or none of the above.

This study was approved by the hospital ethics committee.

Radiosurgery Technique
Stereotactic RS was performed in a single session with the use of Gamma knife. A Leksell stereotaxic frame was affixed to the patient’s head (Elekta AB). Virtual simulation and planification were performed based on MR and digital arteriography. Per protocol, a dose of 18 Gy was applied to the 80% isodose line encompassing the margin of the nidus.

Follow-Up
Patients were followed biannually from the moment of diagnosis up until 1 year post radiosurgery, and annually afterward. Serialized contrast enhanced MR studies were performed annually, and also if the patient complained of new or worsening symptoms. Digital arteriography was scheduled 3 years after RS, unless a previous MR clearly showed the persistence of anomalous vessels or a patient refused the procedure. Nidus obliteration was defined based on angiographic criteria: absence of abnormal vessels in the area of the nidus, normalization of the draining veins and normal circulation time.5 If the malformation was still patent on MR or angiography after 4 years, the possibility of a second RS was explored. At any time during the follow-up, newly acquired symptoms warranted an urgent CT and a scheduled MR. Hemorrhage was defined as any clinically relevant event with fresh blood in the vicinity of the malformation confirmed through CT or MR.

Statistical Analysis
Hemorrhage rates were calculated as the number of events during a predefined period divided by the sum of the duration of individual observation periods. We performed the calculations for birth-to-diagnosis, diagnosis-to-RS, and postradiosurgery time periods. To calculate birth-to-diagnosis bleeding rates, we assumed that patients were at risk for hemorrhage from the moment of their birth.6 For the diagnosis-to-RS and postradiosurgery bleeding rates, we performed separate analysis for hemorrhagic and nonhemorrhagic subgroups. Last, for the postradiosurgery analysis, we calculated the hemorrhagic rates during and after a predefined period of 3 years to correct for the delayed effect of treatment. Three years is a widely accepted postradiosurgical observation period and, therefore, lower hemorrhagic rates during the latency period.

Univariate tests ($\chi^2$, t test) and multivariate logistic regression analysis were used to describe the association of demographic and clinical variables and nidus characteristics with the initial hemorrhagic presentation of the AVM. Kaplan-Meier survival curves, together with log-rank tests, were used to represent the evolution of hemorrhagic and nonhemorrhagic cohorts in time. Univariate and multivariate Cox regression hazard models were used to test for risk factors for hemorrhage during follow-up. Patients were censored at first postradiosurgical hemorrhage, if they underwent another treatment (microsurgery or second radiosurgery), were lost to follow-up, or died. Data are reported as mean±SD, median, and interquartile range. Hazard ratios with 95% CIs are presented. $P<0.05$ is considered to be statistically significant.

Results
General Patient Characteristics
A total of 108 cases were included in the study. Mean age at diagnosis was 36 years (range, 4–73 years), and 55% were men. There were 12 children younger than age 18 years. Patient demographics and medical history, radiological characteristics of AVM (location, size, Spetzler-Martin scale, aneurysms, and drainage), as well as details of other treatments undergone before RS are presented in Table 1. The same table also lists the presentation symptoms of nonhemorrhagic AVMs. Forty-three patients presented with hemorrhage, and 3 of them had a second bleeding event before the diagnosis was made. The Kaplan-Meier curve representing hemorrhages of undiagnosed AVMs is shown in Figure 1.

Hemorrhage Rates Before Diagnosis
Assuming that patients were at risk for hemorrhage since their birth, their collective time at risk amounted to 3909 years. The annual hemorrhage rate for any undiagnosed AVM was 1.2%. The hemorrhage rate for AVMs that had presented with a hemorrhage was 3.3% (46 events in 1397 risk-years).

Age, location of the nidus, single draining vein, and exclusively deep drainage were associated with hemorrhagic presentation on univariate analysis. Older patients and cortically or subcortically located AVM were less likely to have presented with bleeding. On multivariate analysis, the first 3 factors retained their influence on the likelihood of initial hemorrhagic presentation (Table 2).

Hemorrhage Rates Between Diagnosis and Radiosurgery
Mean time between diagnosis and radiosurgery was 25±49 months (median, 11; interquartile range, 2–27). In 69 cases (64%), embolizations were performed before the RS (median of 3 sessions). Four patients underwent surgery. Three interventions happened more than 10 years before RS (2 were presumably successful, but persistence of nidus was discovered during follow-up, and 1 failed to remove the AVM). One patient underwent evacuation of a brain hematoma.

Seven additional bleedings were registered. Four of them were rebleedings. Annual rebleeding rate in hemorrhagic AVMs was 3.8% (4 cases in 1276 risk-months). Nonhemorrhagic AVMs had an annual bleeding rate of 2.6% (3 events in 1401 risk-months). Figure 2A presents survival curves for this period (log-rank, 0.22).
Hemorrhage Rates After Radiosurgery

There were 6 new bleeds during a mean observation period of 65±/44 months (median, 54; interquartile range, 33–94). Twenty patients underwent second radiosurgery after the initial 1 failed to obliterate the nidus. Two underwent a microsurgery. Four patients died, 2 of them from cerebral hemorrhage.

The cohort of patients with hemorrhagic AVM had an annual rebleeding rate of 2.1% during the first 3 years after radiosurgery (2 cases in 1113 risk-months). After the initial 3 years, the rate was reduced to 1.1% per year (1 case in 1060 risk-months). Patients with nonhemorrhagic presentation had an annual hemorrhage rate of 1.4% during the first 3 years (2 cases in 1683 risk-months), and 0.3% afterward (1 in 3582 risk-months). Kaplan-Meier curves are presented in Figure 2B (log-rank, 0.53). The overall evolution of the bleeding rates is summarized in Table 3.

Influence of AVM Closure on the Hemorrhage Rate

There were 3 hemorrhagic events among the 52 patients with angiographic evidence of nidus obliteration. Mean time between radiosurgery and confirmation of closure was 37±18 months (median, 32; interquartile range, 25–40). Before the obliteration was confirmed, the annual hemorrhage rate was 1.3%. After the obliteration of the nidus, the rate decreased to 0.6% (1 case in 2034 risk-months). Kaplan-Meier curves are presented in Figure 2B (log-rank, 0.53). The overall evolution of the bleeding rates is summarized in Table 3.

Factors Influencing Postradiosurgical Hemorrhage

Smoking and arterial hypertension were independent risk factors in univariate analysis, increasing the postradiosurgical bleeding risk more than 2-fold and 4-fold, respectively. Diameter of less than 3 cm, smaller AVM volume, Spetzler-Martin scale of 1 or 2, and absence of aneurisms were protective factors. When entered in a multivariate model, only hypertension, diameter, and aneurisms retained their significance (Table 4).

Discussion

Postradiosurgical Bleeding Risk of Hemorrhagic and Nonhemorrhagic AVM: Does 1 Therapy Benefit All?

It is known that radiosurgery obliterates 70% to 90% of brain AVM after a latency period of about 3 years.10 The expecta-
tion behind this treatment is that obliterating the malformation will decrease its risk of cerebral hemorrhage; but, in reality, the effect of radiotherapy on the bleeding rate has not been proven to be universally positive.11 Latest series attest to the fact that radiosurgery does lower the overall hemorrhage risk of unselected AVM, but the conclusions are less clear-cut when it comes to exclusively nonhemorrhagic cases. A retrospective observational study of 500 patients by Maruyama et al revealed an overall decrease in the hazard ratio for bleeding by 54% during the latency period and by 88% after the latency period (when compared with the diagnosis-to-radiosurgery period). The decrease was greater for hemorrhagic AVM. For nonhemorrhagic AVM, there was a decreasing trend that did not reach statistical significance.12

A recent study of Yen et al, who reviewed 1204 patients treated with gamma knife, provides even more comprehensive data.13 In the hemorrhagic AVM subgroup, the rebleeding rate was 10.4% during the diagnosis-to-treatment period and 2.8% during the latency period. In the nonhemorrhagic subgroup, the bleeding rates were 3.9% and 2.2%, respectively.

Our own data also show a progressive decrease in bleeding rates: from 3.8% before treatment, to 2.1% during latency period, to 1.1% after latency period for the hemorrhagic AVM subgroup, and from 2.6% to 1.4% to 0.3% for the nonhemorrhagic subgroup, respectively.

One must remember, though, that preradiosurgery bleeding rates do not equal natural, untreated bleeding rates. In our series, as well as in most other studies, AVMs were fre-

### Table 2. Univariate and Multivariate Logistic Regression Analysis of the Pretreatment Bleeding Risk Factors

<table>
<thead>
<tr>
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<th>Univariate Analysis</th>
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<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>P</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (decades)</td>
<td>0.784</td>
<td>0.784–0.994</td>
<td>0.044*</td>
<td>776</td>
<td>0.609–0.991</td>
<td>0.043*</td>
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<tr>
<td>Men</td>
<td>1.115</td>
<td>0.515–2.415</td>
<td>0.782</td>
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<td>Previous medical history</td>
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<tr>
<td>Smoking</td>
<td>0.971</td>
<td>0.402–2.342</td>
<td>0.947</td>
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<td>Hypertension</td>
<td>0.850</td>
<td>0.233–3.096</td>
<td>0.805</td>
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<tr>
<td>Spetzler-Martin scale (items)</td>
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<tr>
<td>Size &lt;3 cm</td>
<td>0.890</td>
<td>0.365–2.174</td>
<td>0.799</td>
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<tr>
<td>Eloquent area</td>
<td>1.047</td>
<td>0.484–2.262</td>
<td>0.907</td>
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<tr>
<td>Deep drainage</td>
<td>1.312</td>
<td>0.548–3.135</td>
<td>0.541</td>
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<tr>
<td>Cortico-subcortical AVM</td>
<td>0.380</td>
<td>0.158–0.921</td>
<td>0.032*</td>
<td>0.371</td>
<td>0.152–0.917</td>
<td>0.036*</td>
<td></td>
</tr>
<tr>
<td>Nidus volume (cm³)</td>
<td>1.037</td>
<td>0.991–1.085</td>
<td>0.131</td>
<td></td>
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<tr>
<td>Aneurysms</td>
<td>1.033</td>
<td>0.357–2.989</td>
<td>0.952</td>
<td></td>
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<tr>
<td>Exclusively deep drainage</td>
<td>3.086</td>
<td>1.152–8.264</td>
<td>0.025*</td>
<td>2.242</td>
<td>0.705–7.143</td>
<td>0.171</td>
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<tr>
<td>Single draining vein</td>
<td>5.988</td>
<td>2.439–14.706</td>
<td>0.001*</td>
<td>5.650</td>
<td>2.033–15.625</td>
<td>0.001*</td>
<td></td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformations. *P<0.05.

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. Kaplan-Meier survival curves for hemorrhages during the diagnosis-to-radiosurgery period (2A) and postradiosurgery period (2B).
quently treated with embolization before undergoing radiosurgery. This treatment may carry its own risk of periprocedural hemorrhage, and also of delayed hemorrhage because of continued blood inflow into a nidus with impaired outflow. In our series, 2.6% of nonhemorrhagic AVMs bled in the time between diagnosis and RS. Embolization had a hazard ratio of 2.793 for postradiosurgical bleeding rates; however, this number was not significant.

Another potential bias is a selection bias, particularly for voluminous, deep, untreatable AVMs, where obliteration is hardly the expected outcome no matter the initial combination of treatments used. In these cases, the use of radiosurgery might be spurred on by rebleeding and result in falsely higher pretreatment bleeding rates. Figure 1A illustrates this fact, highlighting that most of the radiosurgeries performed late in follow-up happened after the patient had rebleeding. Therefore, numbers pertaining to preradiosurgical bleeding risk must be interpreted with caution, both in our study and in the others.

Examining the natural history of nonhemorrhagic AVM is an alternate way to gauge the usefulness of radiosurgery. Historical and recent studies all provide very similar results, with bleeding rates of 2% to 4.2% and more recently of 1.3%. Those rates are very similar to the ones obtained during the latency period both by Yen et al (2.2%) and in our study (2.6%). Extending the follow-up beyond the latency period reveals an important additional reduction to 0% to 0.3%. Therefore, if we use natural history for comparison, we can again conclude that radiosurgery does indeed lower the bleeding risk of both ruptured and unruptured AVM.

### Table 3. Evolution of Annual Hemorrhage Rates

<table>
<thead>
<tr>
<th></th>
<th>Hemorrhagic AVM</th>
<th>Non-Hemorrhagic AVM</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-to-diagnosis</td>
<td>3.30%</td>
<td>N/A</td>
<td>1.20%</td>
</tr>
<tr>
<td>Diagnosis-to-radiosurgery</td>
<td>3.80%</td>
<td>2.60%</td>
<td>3.10%</td>
</tr>
<tr>
<td>Post-radiosurgery (first 3 y)</td>
<td>2.10%</td>
<td>1.40%</td>
<td>1.70%</td>
</tr>
<tr>
<td>Post-radiosurgery (3 y onward)</td>
<td>1.10%</td>
<td>0.30%</td>
<td>0.50%</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformations.

### Obliterated AVM: No Risk or Still at Risk?

In their recent article, Yen et al reported no bleeds whatsoever after nidus obliteration, but the length of postobliteration follow-up is not clear. Other studies usually report some residual risk of hemorrhage. For example, Shin et al have found a 0.3% annual hemorrhage risk for obliterated AVMs, and 2.2% cumulative risk over 10 years (4 patients from a series of 236 angiographically confirmed cases). In our series, the annual hemorrhage rate after obliteration was 0.6%. Interestingly, nidus closure was not a statistically significant protective factor in multivariate analysis. This may be because only angiographically confirmed cases were considered positive for this analysis, leaving the patients who did not want to undergo invasive procedures as false-negatives.

There can be several causes for persistence of the bleeding risk in nidi that have been exhaustively studied and confirmed closed. First, compared with the finality offered by complete microsurgical resection, the closure of a nidus via slow endothelial proliferation may prove not to be as definitive, as there are instances of repermeabilization years after complete occlusion.

### Table 4. Univariate and Multivariate Cox Regression Models for Postradiosurgical Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Univariate Cox Regression</th>
<th>Multivariate Cox Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>CI Interval</td>
</tr>
<tr>
<td>Age at diagnosis (decades)</td>
<td>1.006</td>
<td>0.737–1.372</td>
</tr>
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<td>Men/women</td>
<td>1.135</td>
<td>0.423–3.049</td>
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<td>Previous medical history</td>
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<tr>
<td>Smoking</td>
<td>2.849</td>
<td>1.058–7.692</td>
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<tr>
<td>Hypertension</td>
<td>4.651</td>
<td>1.473–14.706</td>
</tr>
<tr>
<td>Hemorrhagic presentation</td>
<td>1.424</td>
<td>0.529–3.831</td>
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<tr>
<td>Spetzler-Martin items</td>
<td></td>
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<tr>
<td>Size &lt;3 cm</td>
<td>0.221</td>
<td>0.077–0.633</td>
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<tr>
<td>Eloquent area</td>
<td>2.257</td>
<td>0.814–6.250</td>
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<td>Deep drainage</td>
<td>0.978</td>
<td>0.333–2.865</td>
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<td>Spetzler-Martin scale &gt;2</td>
<td>3.021</td>
<td>1.127–8.065</td>
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<td>Cortico-subcortical AVM</td>
<td>1.250</td>
<td>0.401–3.891</td>
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<td>Embolization</td>
<td>2.793</td>
<td>0.794–9.804</td>
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<tr>
<td>AVM volume (cm³)</td>
<td>1.050</td>
<td>1.014–1.087</td>
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<tr>
<td>Second radiosurgery</td>
<td>0.796</td>
<td>0.252–2.506</td>
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<tr>
<td>Nidus obliteration</td>
<td>0.496</td>
<td>0.185–1.328</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>4.032</td>
<td>1.055–15.385</td>
</tr>
<tr>
<td>Exclusively deep drainage</td>
<td>1.241</td>
<td>0.304–5.076</td>
</tr>
<tr>
<td>Single draining vein</td>
<td>0.864</td>
<td>0.278–2.684</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformations.

*P < 0.05.
Second, some AVM with negative arteriographies can still have evidence of nidus persistence on histological examination.\textsuperscript{24–26} Last, brain-blood barrier disruption, edema, and cyst formation have been described in post radiosurgical MR studies. They are presumably unrelated to the presence of anomalous flow inside the nidus, and represent radiation-induced changes of the adjoining brain tissue. These imaging changes have been positively associated with hemorrhage.\textsuperscript{22}

**Risk Factors for Post radiosurgical Hemorrhage: Medical History Also Counts**

As far as AVM characteristics go, several items such as age, deep location, smaller size, and deep drainage have been consistently identified as risk factors for hemorrhagic presentation.\textsuperscript{13,22} The first 2 were also true in our study. Interestingly, many of those factors tend to lose relevance during the postradiosurgical period. In our case, size <3 cm and presence of aneurysms were the only significant postradiosurgical AVM-related factors after multivariate analysis.

Patient-related items other than age and sex are often not entered in hazard models for AVM bleeding. We have identified only 1 study that sought to correlate cardiovascular risk factors with initial hemorrhage, finding a positive association with hypertension.\textsuperscript{27} We reviewed the medical history of all our patients, retrieving data on cardiovascular risk factors, and focused on smoking and arterial hypertension as potential risk factors based on data available for brain aneurysms. Both proved relevant in univariate analysis, though only hypertension was shown to be an independent factor for hemorrhage after therapy, with hazard ratio of 4.5. Beside the fact that this finding is both unconfirmed and unsurprising, it does prove that selected details of patients’ medical history should be stressed in future studies.

**Conclusions**

Our series provide additional evidence that RS offers protection against cerebral hemorrhage caused by AVM rupture, regardless of the manner of its initial presentation. Successful obliteration, small nidus size, and absence of arterial hypertension reduce the risk of postsurgical bleeding.

**Disclosures**

None.

**References**

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