Hemorrhage Risk of Cerebral Arteriovenous Malformations Before and During the Latency Period After Gamma Knife Radiosurgery

Chun-Po Yen, MD; Jason P. Sheehan, MD, PhD; Lucia Schwyzer, MD; David Schlesinger, PhD

Background and Purpose—To evaluate the hemorrhage rates of cerebral arteriovenous malformations (AVM) and the risk factors of hemorrhage before and after Gamma Knife radiosurgery (GKS).

Methods—The annual hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. Characteristics of patients and AVM related to hemorrhagic or nonhemorrhagic presentation were evaluated by logistic regression. Risk factors predicting AVM hemorrhage during the period from the diagnosis to GKS of AVM and during the latency period after radiosurgery were evaluated using Cox regression hazards model.

Results—The annual hemorrhage rate before GKS was 2.0% assuming patients were at risk for hemorrhage since their birth. The hemorrhage rate calculated between the diagnosis and GKS of AVM was 6.6% and reduced to 2.5% after GKS until obliteration of the AVM. Although small and deep nidi and those with deep and single draining veins tended to present themselves with hemorrhage, only nidi with single draining veins and those ruptured before were more likely to bleed once the AVM had been diagnosed. These factors no longer predisposed the nidus to a rupture after radiosurgery and the only predicting factor for hemorrhage was a low radiosurgical prescription dose to the margin of nidus.

Conclusions—The AVM hemorrhage rate seems to reduce after GKS. After radiosurgery, none of the patients or nidus-related risk factors remained relevant to the occurrence of hemorrhage. The nidus treated with a high radiosurgical dose is less likely to bleed. (Stroke. 2011;42:1691-1696.)

Key Words: arteriovenous malformation ■ hemorrhage ■ radiosurgery

Influenced by the high morbidity and mortality associated with arterial aneurysms, neurosurgeons since the 1950s have been concerned that cerebral arteriovenous malformations (AVM) bear a high risk of hemorrhage.1 Therefore, AVM were often treated after their diagnosis and this has limited the amount of research on the natural hemorrhage rate in untreated patients with AVM. The currently accepted 2% to 4% annual hemorrhage rates are based on limited numbers of long-term follow-up studies of untreated AVM2-5 and some retrospective research evaluating the risk of hemorrhage between the diagnosis of the AVM and the time of intervention.6-9

Since the first AVM treated with the Gamma Knife in 1970,10 hundreds of thousands of AVM had been treated with radiosurgery. Unlike microsurgery, the obliteration process occurs over time after radiosurgery and patients remain at risk for hemorrhage during the latency period of 2 to 3 years before the total obliteration of the nidus.11 Compared with the natural hemorrhage rate, decreased,12,13 unchanged,14,15 or increased16 rates of hemorrhage after radiosurgery have been reported.

The aims of the present study are to calculate the hemorrhage rate in a large cohort of patients with AVM referred for Gamma Knife radiosurgery (GKS). We compare the hemorrhage rate after GKS with that of the natural history and the preradiosurgical hemorrhage rate in the same group of patients. Additionally, the risk factors of pre- and postradiosurgical AVM bleeding are analyzed.

Patients and Methods

Patient Population
A total number of 1204 patients with cerebral AVM were treated with Gamma Knife between 1989 and 2009 at the University of Virginia. Patients’ demographics are depicted in Table 1. There were 637 males and 567 females with a mean age of 35.3 years. The most common presenting symptom leading to the diagnosis of AVM was hemorrhage. Fifty patients (8 Spetzler-Martin Grade I, 19 Grade II, 17 Grade III, and 8 Grade IV) who initially presented with symptoms other than hemorrhage experienced at least 1 episode of bleeding before the total obliteration of their AVM and GKS.

AVM Characteristics
The location and Spetzler-Martin Grading17 of the AVM are detailed in Table 1. The nidus volume ranged from 0.1 to 33 mL (mean, 3.4
Table 1. Patient Demographics, AVM Characteristics, and GKS Parameters

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>No. or Mean</th>
<th>Range or Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>637/567</td>
<td>53/47</td>
</tr>
<tr>
<td>Age at GKS, y</td>
<td>35.3</td>
<td>3–82</td>
</tr>
<tr>
<td>Prior partial resection/embolization</td>
<td>138/298</td>
<td>11.5/24.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Hemorrhages</th>
<th>Seizures</th>
<th>Headaches</th>
<th>Neurological deficits</th>
<th>Others</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>605</td>
<td>271</td>
<td>163</td>
<td>89</td>
<td>33</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location Characteristics</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>772</td>
<td>64.1</td>
</tr>
<tr>
<td>Thalamus</td>
<td>104</td>
<td>8.6</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>92</td>
<td>7.6</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>47</td>
<td>3.9</td>
</tr>
<tr>
<td>Brainstem</td>
<td>99</td>
<td>8.2</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>90</td>
<td>7.5</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noneloquent/eloquent area</td>
<td>422</td>
<td>35/65</td>
</tr>
<tr>
<td>Venous drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial only/venous system</td>
<td>600</td>
<td>50/50</td>
</tr>
<tr>
<td>Spetzler-Martin grading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I/II/III/IV/V</td>
<td>204</td>
<td>16.9/37.8/37.5/7.6/0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GKS Treatment Parameters</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of the nidus, mL</td>
<td>3.4</td>
<td>0.1–33</td>
</tr>
<tr>
<td>Prescription dose, Gy</td>
<td>21.2</td>
<td>5–36</td>
</tr>
<tr>
<td>Maximum dose, Gy</td>
<td>39.4</td>
<td>10–60</td>
</tr>
<tr>
<td>Isocenters</td>
<td>2.8</td>
<td>1–22</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformations; GKS, Gamma Knife radiosurgery.

mL). The nidus volume was <3 mL in 627 patients, between 3 and 5 mL in 298, between 5 and 10 mL in 249, and >10 mL in 30. The venous drainage was superficial only in 600 AVM nidi, deep only in 475, and both in 129.

Gamma Knife Technique

The details of the Gamma Knife procedure have been presented in a previous publication.14 In brief, a Leksell G-Frame was affixed to the patient’s head. Stereotactic biplane angiography was then performed to delineate the nidus. Later with introduction of MRI, stereotactic MRI was also obtained for dose planning. The dose selection was based on the size and location of the nidus. The mean prescription dose to the margin of the nidus was 21.2 Gy (range, 5 to 36 Gy), and the mean maximum dose was 39.4 Gy (range, 10 to 60 Gy). The mean number of isocenters was 2.8 (range, 1 to 22).

Follow-Up

Patients underwent MRI every 6 months for 2 years and then yearly. Angiography was not performed until MRI showed an absence of flow voids. A CT or MRI was performed if patients developed new or worsened symptoms such as headaches, seizures, or neurological deficits. Hemorrhagic events in this study were defined as clinically symptomatic events along with signs of bleeding on CT or MRI as well as asymptomatic hemorrhage identified only on follow-up images as a recent bleed.

Statistic Analysis

The preradiosurgical annual hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. Because AVM are generally considered as congenital anomalies, we assumed that patients were at risk for hemorrhage from their dates of birth. As an alternative metric, we also calculated the hemorrhage rate starting from the dates that AVM were diagnosed to the dates that AVM were treated. To calculate the annual rebleeding rate, the number of recurrent hemorrhages was divided by the total number of risk years from the dates of initial hemorrhage to the dates of GKS.

None of our patients had hemorrhage after the nidus was declared obliterated based on angiography; therefore, the postradiosurgical annual hemorrhage rate was calculated dividing the hemorrhagic events by the patient risk years from the dates of GKS to the dates that the AVM were judged to be obliterated on MRI or the dates of last follow-up if the nidi remained patent. We chose the dates that the AVM were concluded obliterated on MRI because angiography was usually performed after the MRI suggested that the nidi had obliterated. Furthermore, because the nidi should have obliterated before the final imaging studies, we assumed that the AVM obliterated at the midpoint between the dates of the last images showing the AVM were still patent and the dates of the first images showing that the AVM obliterated. For hemorrhage-free survival, Kaplan-Meier analysis was used and log-rank test was applied to compare pre- and postradiosurgical hemorrhage risk.

Univariate and multivariate logistic regressions were applied to test the association of patient demographics (age, gender) and nidus characteristics (size, lobar versus deep locations, superficial only versus deep venous drainage, single versus multiple draining veins) with hemorrhagic or nonhemorrhagic presentation of the AVM. Univariate and multivariate Cox regression hazards model were used to test the risk factors of hemorrhage during the period from the diagnosis to the treatment of AVM and the follow-up period after GKS. Patients were censored from the postradiosurgery bleeding risk group when the AVM obliterated. In addition, patients were censored if they underwent further treatment, were lost to follow-up, or died. Additional factors evaluated from diagnosis to GKS of AVM included hemorrhagic or nonhemorrhagic presentation. Radiosurgical treatment parameters were added to evaluate the postradiosurgical risk of hemorrhage.

Results

Preradiosurgical Hemorrhage Rate and Rebleeding Rate

A total of 657 patients had 803 hemorrhagic events over 42,495 risk-years before GKS assuming that patients were at risk for hemorrhage since their birth. The annual hemorrhage rate was 2.0%. If we calculate the hemorrhage rate after the diagnosis of the AVM, there were 68 hemorrhagic events in 52 patients who initially presented with symptoms other than hemorrhage and 130 rebleeds in 90 patients who experienced hemorrhage before the diagnosis of AVM, yielding a hemorrhage rate of 6.6% (198 bleeds in 2984 risk-years).

The hemorrhage rate in the subgroup of 605 patients who initially presented with hemorrhage was 735 events divided by 19,712 risk years yielding a 3.7% annual hemorrhage rate assuming patients were at risk for hemorrhage since their birth. The hemorrhage rate would be 10.4% per year if we only calculated the 130 hemorrhagic events in 1243 risk-years from the diagnosis to GKS of AVM. In the subgroup of
599 patients who initially presented with symptoms other than hemorrhage, 50 patients experienced 68 episodes of hemorrhage within 1741 risk-years between the diagnosis and GKS of AVM. The hemorrhage rate was 3.9% (Table 2).

The annual rebleeding rate was 8.6% during the period from the diagnosis to GKS of AVM (146 rebleeds in 1581 risk-years). The rebleeding rate was 10.0% in the first year after the initial hemorrhage; 10.8% between 1 and 2 years; 6.5% between 2 and 5 years; 6.7% between 5 and ten 10; and 8.8% after 10 years. Of note, the mean time between the diagnosis and GKS of AVM was 2.5 years. Limited patients were available for calculating long-term rebleeding rate because they were referred for radiosurgery.

Patient Demographics and Nidus Characteristics in Hemorrhagic or Nonhemorrhagic Presentation

Patients tended to present with hemorrhage were those with young age, small nidi, deep AVM, nidi with deep venous drainage, or single draining veins (Table 3). The same risk factors were checked for the period between diagnosis of the AVM and GKS. Deep AVM and those with deep or single draining veins had a high risk of bleeding in univariate analysis. In multivariate analysis, a single draining vein was the only predicting factor for AVM rupture. After the diag-

| Table 2. Summary of Hemorrhage Rates Before and After GKS in the Present Series and in Subgroups of Patients With Hemorrhagic or Nonhemorrhagic Presentation |
|---------------------------------|-----------------|-----------------|-----------------|
|                              | Pre-GKS Hemorrhage Rate (Birth to GKS) | Pre-GKS Hemorrhage Rate (Diagnosis to GKS) | Post-GKS Hemorrhage Rate (GKS to Last Follow-Up) |
| All patients                  | 2.0%            | 6.6%            | 2.5%            |
| Patients with hemorrhagic presentation | 3.7%            | 10.4%           | 2.8%            |
| Patients with nonhemorrhagic presentation | ...              | 3.9%            | 2.2%            |

GKS indicates Gamma Knife radiosurgery.

Table 3. Univariate and Multivariate Analysis of Risk Factors for Hemorrhagic Presentation of AVM and Predicting Factors for Hemorrhage After Diagnosis of AVM and After Gamma Knife Surgery

|                               | Univariate |          |          |          |
|                               | Odds Ratio/ Hazard Ratio | 95% CI     | P       |          |
| Before diagnosis of AVM       |            |          |          |          |
| Female                        | 0.988      | 0.788–1.239 | 0.988   | ...      | ...      | ...      | ...      | ...      | ...      | ...      | ...      | ...      | ...
| Age                           | 0.983      | 0.976–0.990 | <0.001*  | 0.986    | 0.978–0.993 | <0.001*  | ...      | ...      | ...
| Volume                        | 0.857      | 0.817–0.899 | <0.001*  | 0.877    | 0.835–0.921 | <0.001*  | ...      | ...      | ...
| Deep location                 | 2.950      | 2.279–3.818 | <0.001*  | 1.715    | 1.277–2.303 | <0.001*  | ...      | ...      | ...
| Deep draining vein            | 2.868      | 2.270–3.623 | <0.001*  | 2.194    | 1.682–2.861 | <0.001*  | ...      | ...      | ...
| Single draining vein          | 2.110      | 1.675–2.660 | <0.001*  | 1.753    | 1.366–2.250 | <0.001*  | ...      | ...      | ...
| Between diagnosis and GKS     |            |          |          |          |
| Female                        | 0.936      | 0.672–1.302 | 0.693    | ...      | ...      | ...      | ...      | ...
| Age                           | 1.001      | 0.990–1.012 | 0.858    | ...      | ...      | ...      | ...
| Volume                        | 0.943      | 0.888–1.003 | 0.061    | ...      | ...      | ...
| Deep location                 | 1.837      | 1.319–2.559 | <0.001*  | 1.397    | 0.948–2.060 | 0.091   | ...      | ...      | ...
| Deep draining vein            | 1.614      | 1.150–2.267 | 0.06*    | 1.103    | 0.740–1.643 | 0.631   | ...      | ...      | ...
| Single draining vein          | 1.869      | 1.324–2.640 | <0.001*  | 1.530    | 1.073–2.281 | 0.019*  | ...      | ...      | ...
| Prior hemorrhage              | 2.364      | 1.676–3.335 | <0.001*  | 1.969    | 1.373–2.285 | <0.001*  | ...      | ...      | ...
| After GKS                     |            |          |          |          |
| Female                        | 1.017      | 0.702–1.474 | 0.928    | ...      | ...      | ...      | ...
| Age                           | 0.999      | 0.987–1.011 | 0.826    | ...      | ...      | ...
| Volume                        | 1.044      | 1.003–1.086 | 0.035*   | 1.030    | 0.983–1.080 | 0.214   | ...
| Deep location                 | 1.594      | 1.093–2.324 | 0.015*   | 0.757    | 0.461–1.242 | 0.271   | ...
| Deep draining vein            | 1.004      | 0.693–1.456 | 0.982    | ...      | ...      | ...
| Single draining vein          | 0.950      | 0.655–1.378 | 0.787    | ...      | ...      | ...
| Prior hemorrhage              | 1.314      | 0.901–1.918 | 0.156    | ...      | ...      | ...
| Prescription dose             | 0.931      | 0.884–0.980 | 0.006*   | 0.944    | 0.892–0.999 | 0.046*  | ...
| Maximum dose                  | 0.984      | 0.959–1.010 | 0.231    | ...      | ...      | ...
| Isocenters                    | 1.031      | 0.948–1.121 | 0.480    | ...      | ...      | ...

AVM indicates arteriovenous malformations; GKS, Gamma Knife radiosurgery.

*P<0.05.
nosis of AVM, small and deep AVMs were no longer the predicting factors for hemorrhage. Additionally, patients with prior hemorrhage were more likely to have recurrent hemorrhage.

**Postradiosurgical Hemorrhage Rate**

After GKS, 94 patients had 1 hemorrhage and 18 patients had 2 (Figure 1). The postradiosurgical hemorrhage rate was 2.5% (130 hemorrhagic events in 5239 risk-years), which was lower than the 6.6% hemorrhage rate if we calculate the rate since the diagnosis of AVM (Figure 2). The median hemorrhage-free survival was 14.2 years from diagnosis to GKS of AVM and 16.8 years during the latency period after GKS ($P<0.001$).

In the subgroup of patients with preradiosurgical hemorrhage, 55 patients had 1 hemorrhage and 12 patients had 2 after GKS. The postradiosurgical hemorrhage rate in this subgroup was 2.8% (79 hemorrhagic events in 2868 risk-years), which was lower than the preradiosurgical hemorrhage rate of 10.4% calculated after diagnosis of the AVM.

**Figure 1.** A 57-year-old woman presented with seizures leading to the diagnosis of a left temporal AVM (A). The patient was treated with GKS. Sixteen months after GKS, the patient had an AVM rupture with intracerebral hemorrhage (B). Follow-up angiography showed a small residual nidus (C). The nidus obliterated completely 3 months after the hemorrhage (D). AVM indicates arteriovenous malformations; GKS, Gamma Knife radiosurgery.

**Figure 2.** Hemorrhage rates before and after GKS in the present study. A total of 198 hemorrhagic events occurred in 2984 risk-years between the diagnosis and GKS of the AVM, yielding a 6.6% hemorrhage rate. One hundred thirty hemorrhagic events occurred in 5239 risk-years after GKS until the end of follow-up or date of nidus obliteration, yielding a 2.5% hemorrhage rate. There were 47 hemorrhage in 2029 risk-years within the first 2 years after GKS; 34 hemorrhage in 1547 risk-years from the third to the fifth years; 31 hemorrhage in 1220 risk-years from the fifth to the tenth years; and 18 hemorrhage in 443 risk-years after the tenth years. GKS indicates Gamma Knife radiosurgery; AVM, arteriovenous malformations; Dx, diagnosis.
The median hemorrhage-free survival was 10.1 years from diagnosis to GKS of AVM and 17.9 years during the latency period after GKS ($P<0.001$). In the subgroup of patients who never had hemorrhage before GKS, 51 hemorrhage occurred in 2371 risk-years yielding an annual hemorrhage rate of 2.2%, which is slightly lower than the 3.9% hemorrhage rate calculated after the diagnosis of the AVM. The median hemorrhage-free survival was 18.6 years from diagnosis to GKS of AVM and 20.0 years during the latency period after GKS ($P=0.001$).

Risk Factors Predicting Hemorrhage After GKS

Risk factors of postradiosurgical hemorrhage were deep AVM, large nidus size, and low prescription dose in univariate analysis. In multivariate analysis, only a low prescription dose remained to be associated with a high risk of hemorrhage (Table 3).

Discussion

Natural Hemorrhage Rate of AVM

AVM had traditionally been considered a potentially fatal disease and most patients were treated with microsurgery, embolization, or radiosurgery. Ondra et al published their landmark study that prospectively followed untreated patients with AVM for 24 years and reported an annual bleeding rate of 4%. Additional studies from Crawford et al ($2\%$ annual hemorrhage rate), Itoyama et al ($2.1\%$), and Yamane et al ($4.2\%$) led to the generally accepted $2\%$ to $4\%$ natural hemorrhage rate of cerebral AVM. Although the conclusion from these studies demonstrated that the risks of AVM hemorrhage are not as high as arterial aneurysms, the cumulative risk of hemorrhage remains significant because the disease usually manifests itself in adolescents.

Retrospective studies to calculate the hemorrhage risk of the AVM usually face the problem of determining since when the patients start to be at risk for hemorrhage. Although AVM are considered congenital anomalies and theoretically patients are at risk for hemorrhage since their birth, hemorrhage usually occurs in adolescence or young adulthood. It is believed that AVM are dynamic lesions with ongoing morphological and hemodynamic changes and some unknown factors might play a significant role causing rupture of nidi later in the progression of the vascular malformations.

Because it is not known when the patients with AVM start to be at risk for hemorrhage and most of the patients received treatment after the diagnosis, the alternative to determine the bleeding risk of AVM would be to calculate the hemorrhage rate after the diagnosis of the AVM until the dates of intervention. This calculation can be severely biased. As most studies have shown, AVM tend to rebleed for some period of time after prior hemorrhage and additionally treatment was usually prompted by hemorrhage. The high numbers of hemorrhagic events after the initial bleeding and a prematurely terminated follow-up between the diagnosis of AVM and intervention will erroneously overestimate the hemorrhage rate.

The hemorrhage rate before treatment in the present series is 2.0% if we assumed that patients were at risk for hemorrhage since their birth. If the hemorrhage rate were to be calculated after the diagnosis of the AVM, the hemorrhage rate would be 6.6%. The hemorrhage rate even increased to 10.5% in the subgroup of patients who had a hemorrhagic presentation. The last two numbers definitely need to be interpreted with caution.

Hemorrhage Rates of Patients With AVM With or Without Prior Bleeding

It has been reported that patients would be at a higher risk of hemorrhage after a prior one. Forester reported that patients who had bled once had a $25\%$ chance of rebleeding in 4 years and those who had bled twice had a $25\%$ chance of rebleeding within 1 year. In the present series, the hemorrhage rate after initial bleeding was 8.6%. The rebleeding rate was approximately $10\%$ in the first and second years and reduced slightly thereafter. Ondra et al, however, observed no difference in hemorrhage rate in patients who initially presented with hemorrhage or other symptoms.

In contrast to patients with AVM with a history of hemorrhage, the natural history of unruptured AVM is largely unknown. Brown et al followed a group of 168 patients with unruptured AVM after a mean of 8.2 years and reported a $2.2\%$ annual hemorrhage rate. None of their patients had a recurrent hemorrhage. Recent natural history data suggest that the annual hemorrhage rate of unruptured AVM may be as low as 1%. In our series, the hemorrhage rate of AVM diagnosed due to symptoms other than hemorrhage was $3.9\%$ until the time of GKS. The rebleeding rates were similar in patients with or without hemorrhage as the initial presentation.

Risk Factors of Hemorrhage in AVM

Contradictory observations have been seen in different studies regarding whether age, size, or pregnancy is related to a high risk of AVM rupture. In general, most studies have agreed that AVM in deep locations and nidi with certain angioarchitectural features (deep draining veins, single draining veins, venous outlet stenosis) are associated with a high risk of hemorrhage. In the present study, the size of AVM was smaller in patients who initially presented with hemorrhage. However, after the AVM were diagnosed, there was actually no difference in terms of risk of rebleeding in small or large AVM. Crawford et al found that small AVM more often presented with hemorrhage, but the rehemorrhage rate was comparable with $21\%$ in small and $18\%$ in large AVM. It is likely that small AVM are less likely to cause neurological deficits by mass effects or steal phenomenon and would not be diagnosed until rupture. A similar observation was noted in deeply located AVM, which are less likely to present symptoms other than hemorrhage.

Does Radiosurgery Reduce the Hemorrhage Rate in Patients With AVM?

Histopathologic studies have shown that detectable radiation effects can occur as early as 3 months after radiosurgery and remain for years. Thickening of the intima as well as proliferation and accumulation of subendothelial matrix decrease the tension of vessel wall. Furthermore, thrombosis or occlusion of vascular channels in the nidi decreases the patent vessels; thus, less numbers of vessels are prone to
rupture. Whether radiosurgery reduces the risk of AVM hemorrhage remains debated. The incidence of postradiosurgical hemorrhage has been reported between 2.1% and 5%. Because there is no control group in all the studies, the best way to evaluate if radiosurgery has a protective effect for hemorrhage is to compare the postradiosurgical hemorrhage rates with the 2% to 4% hemorrhagic risks obtained from published natural history studies. Obviously, there does not seem to be a significant change of hemorrhage rates in patients with AVM treated with radiosurgery until total obliteration is achieved.

Based on our data, the postradiosurgery hemorrhage rate is 2.5%, which seems to be lower than the preradiosurgical rate of 6.6% calculated after the diagnosis of the AVM. We cannot exclude that the preradiosurgical hemorrhage rate is an overestimate and the decline of hemorrhage rate is not part of the natural course of the disease. However, none of the risk factors for AVM rupture remained relevant after GKS and nidi treated with a high radiosurgical dose were less likely to bleed implicates possible protective effects of GKS against AVM rupture.

Conclusions
The present study provides further evidence that patients with AVM remain at risk for hemorrhage as long as the nidus is patent after radiosurgery. However, radiosurgery seems to reduce the hemorrhage rate during the latency period. This phenomenon is more prominent in patients who present with hemorrhage before GKS.

Acknowledgments
We acknowledge the contributions of Dr Ladislau Steiner who conducted the patient follow-up.

Disclosures
None.

References
Hemorrhage Risk of Cerebral Arteriovenous Malformations Before and During the Latency Period After Gamma Knife Radiosurgery
Chun-Po Yen, Jason P. Sheehan, Lucia Schwyzer and David Schlesinger

Stroke. 2011;42:1691-1696; originally published online April 21, 2011;
doi: 10.1161/STROKEAHA.110.602706

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/6/1691

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/02/28/STROKEAHA.110.602706.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
背景および目的：ガンマナイフ放射線治療（GKS）前後の脳動静脈奇形（AVM）の出血率および出血の危険因子を評価する。方法：出血回数をリスクのある患者・年で割ることにより，年間出血率を算出した。出血性または非出血性の症状に関連する患者背景と AVM の特徴を，ロジステック回帰分析により評価した。AVM の診断から GKS までの期間および放射線治療後の潜伏期の AVM 出血を予測する危険因子を，Cox 回帰ハザードモデルを用いて評価した。結果：出生以来出血のリスクがあったと仮定すると，GKS 前の年間出血率は 2.0%であった。AVM の診断から GKS までの期間について算出された出血率は 6.6%であり，GKS 後，AVM の消失までの期間には 2.5%に低下した。小さく深い病巣および深い単一の流出静脈をもつ病巣は出血を呈する傾向がみられたが，AVM と診断された後で出血する可能性が高いのは，単一の流出静脈をもつ病巣および以前に破壊した病巣のみであった。放射線治療後の 2 年目までに，これらの因子はもはや病巣の破壊の要因となりず，唯一の出血予測因子は病巣の周辺部への放射線治療の処方線量が低くことであった。結論：AVM の出血率は GKS 後に低下すると考えられる。患者または病巣関連の危険因子はいずれも，放射線治療後に出血の発生に関与することなく，高い放射線治療線量で治療した病巣は出血する可能性が低い。