

ORIGINAL ARTICLE

The Risk of Hemorrhage after Radiosurgery for Cerebral Arteriovenous Malformations

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ABSTRACT

BACKGROUND

Angiography shows that stereotactic radiosurgery obliterates most cerebral arteriovenous malformations after a latency period of a few years. However, the effect of this procedure on the risk of hemorrhage is poorly understood.

METHODS

We performed a retrospective observational study of 500 patients with malformations who were treated with radiosurgery with use of a gamma knife. The rates of hemorrhage were assessed during three periods: before radiosurgery, between radiosurgery and the angiographic documentation of obliteration of the malformation (latency period), and after angiographic obliteration.

RESULTS

Forty-two hemorrhages were documented before radiosurgery (median follow-up, 0.4 year), 23 during the latency period (median follow-up, 2.0 years), and 6 after obliteration (median follow-up, 5.4 years). As compared with the period between diagnosis and radiosurgery, the risk of hemorrhage decreased by 54 percent during the latency period (hazard ratio, 0.46; 95 percent confidence interval, 0.26 to 0.80; $P=0.006$) and by 88 percent after obliteration (hazard ratio, 0.12; 95 percent confidence interval, 0.05 to 0.29; $P<0.001$). The risk was significantly reduced during the period after obliteration, as compared with the latency period (hazard ratio, 0.26; 95 percent confidence interval, 0.10 to 0.68; $P=0.006$). The reduction was greater among patients who presented with hemorrhage than among those without hemorrhage at presentation and similar in analyses that took into account the delay in confirming obliteration by means of angiography and analyses that excluded data obtained during the first year after diagnosis.

CONCLUSIONS

Radiosurgery significantly decreases the risk of hemorrhage in patients with cerebral arteriovenous malformations, even before there is angiographic evidence of obliteration. The risk of hemorrhage is further reduced, although not eliminated, after obliteration.

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DURING THE PAST TWO DECADES, STEREOTACTIC radiosurgery has been widely used to treat cerebral arteriovenous malformations,¹⁻⁷ providing angiographic evidence of cure (obliteration of the malformation) in 80 to 95 percent of patients after a latency period of three to five years.^{2,8-11} Hemorrhage has been reported to occur in 2 to 5 percent of patients per year between the time of radiosurgery and angiographic obliteration of the malformation; however, it has been unclear whether — and to what extent — the risk is reduced during this period as compared with the risk before radiosurgery.^{4,12-19} The extent to which the risk of hemorrhage is further reduced after angiographic obliteration is also unclear. To address these questions, we performed a retrospective study involving 500 patients who were treated with stereotactic radiosurgery at our institute.

METHODS

PATIENTS

Between July 1990 and June 2003, 531 consecutive patients with angiographically visible cerebral arteriovenous malformations underwent stereotactic radiosurgery at our institute. Our institutional review board did not require informed consent for study participation because the study relied on information obtained as part of routine clinical care.

The selection criterion for radiosurgery was, in principle, the finding of small malformations (less than 3 cm) in critical, or eloquent, areas of the brain (including the sensorimotor, language, or visual cortex; the hypothalamus or thalamus; the internal capsule; the brain stem; the cerebellar peduncles; and the deep cerebellar nuclei) that, if injured, result in disabling neurologic deficits.²⁰ Surgical resection, rather than radiosurgery, was generally recommended for other types of malformation considered to be amenable to a surgical approach, although some patients chose radiosurgery because of its noninvasive nature. Radiosurgery was recommended for patients with coexisting conditions, such as chronic renal failure necessitating hemodialysis or respiratory dysfunction, who were considered at high risk for complications if they underwent direct surgery under general anesthesia. If a patient was considered a suitable candidate for radiosurgery, the procedure was performed within three months after evaluation at our center. In 10 patients with an aneurysm associated with the malformation, management involved clipping in 2 patients,

1 of whom later underwent embolization of the malformation; wrapping in 1 patient, who later underwent embolization of the malformation; embolization alone in 1 patient; and observation in 6 patients. The treatments in these 10 patients did not change the angiographic appearance of the malformations.

RADIOSURGERY TECHNIQUE

Stereotactic radiosurgery was performed with the patient under local anesthesia, which was supplemented with intravenous sedation when necessary, in a single session with the use of a gamma knife (Elekta Instruments), which irradiated the malformation defined by imaging. Radiosurgery was guided by angiography alone until February 1992; thereafter, computed tomography (CT) or magnetic resonance imaging (MRI) was included. Image-integrated treatment planning was performed jointly by neurosurgeons and radiation oncologists with the aid of commercially available software (KULA or Leksell GammaPlan, Elekta Instruments). During radiosurgery, the patients lay on a gamma-knife couch and were attached to a gamma-knife collimator helmet with a stereotactic frame. In principle, the dose applied to the margin of each malformation was designed to be at least 20 Gy with the use of 50 percent isodose lines; however, doses were occasionally reduced, depending on the volume and location of malformations or the patient's status.

FOLLOW-UP EVALUATIONS

Patients were evaluated clinically every six months after radiosurgery. Whenever patients had any acute deterioration in their neurologic condition, they were asked to come to our institute or to see their referring physicians, who, in turn, provided us with the appropriate information. Hemorrhage was defined as a clinically symptomatic event (sudden onset of headache, seizure, focal deficits, death, or a combination of these) along with signs of fresh bleeding from the previously diagnosed arteriovenous malformations, detected by means of CT or MRI.²¹ Every year after radiosurgery until the end of 1992, patients underwent serial cerebral angiography; less invasive imaging techniques, such as MRI or CT, were used every six months thereafter. Angiography was generally delayed until obliteration was suggested by these studies.²² Angiographic obliteration was defined as the absence of abnormal vessels in the former nidus of the malformation, the disappearance or normalization of draining

veins from the area, and a normal circulation time on angiography.²³ The determination that obliteration of the malformation had occurred was made independently by both neurosurgeons and neuroradiologists who were aware of the patients' histories.

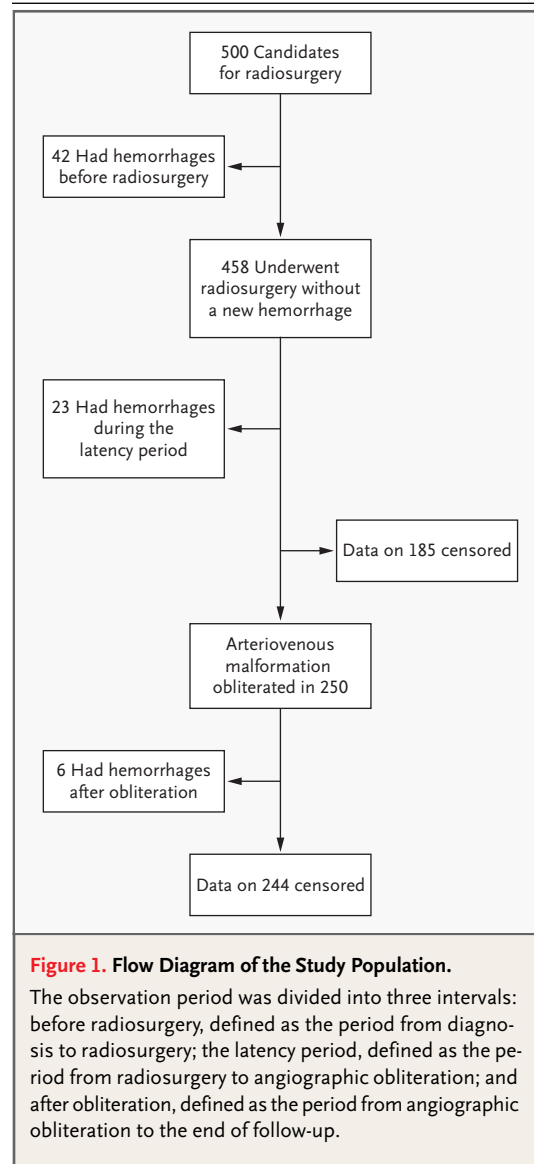
Clinical follow-up was continued even after obliteration in the majority of patients, and if malformations were not occluded, patients were asked to undergo angiography again 6 to 12 months later. A second radiosurgical treatment was generally recommended if obliteration was not observed by three years after the initial treatment.

Information on all patients was prospectively entered into a computer database at the time of their treatment and at each clinical follow-up visit. The dates of diagnosis, radiosurgical treatment, previous or additional hemorrhage, angiographic obliteration, and the last follow-up visit were included in the analyses, along with data on the initial clinical presentation and treatment history. The observation period was divided into the following three intervals: before radiosurgery, the interval from diagnosis to radiosurgery; the latency period, the interval from radiosurgery to angiographic obliteration; and after obliteration, the interval from angiographic obliteration to the end of the follow-up period (Fig. 1).

STATISTICAL ANALYSIS

We used a time-dependent Cox proportional-hazards model to analyze the effect of radiosurgery on the incidence of intracranial hemorrhage, with use of SPSS software, version 11.^{24,25} We defined two sets of trinary time-dependent covariates — for example, as -1 for the period before radiosurgery, as 0 for the latency period, and as 1 for the period after obliteration. The primary end point was the first hemorrhage after the date of diagnosis. For patients who had received other treatments before radiosurgery, the last date of the previous treatment was substituted for the time of diagnosis in an attempt to eliminate any effects of this therapy. Data on patients who underwent a second radiosurgical treatment were censored at that time. Data on patients who declined to undergo angiography to confirm obliteration were censored on the date of the first less invasive imaging study that suggested obliteration. In the overall analysis, the patients were also divided into two groups: those initially presenting with hemorrhage and those without hemorrhage at presentation.

Next, we included hemorrhage as an initial clin-



ical presentation in the analysis as a fixed covariate. Finally, we added six conditions (three intervals each among patients presenting with hemorrhage and those presenting without hemorrhage) in defining time-dependent covariates. To compare the results of these two models, we used the likelihood-ratio test to detect interaction terms between presentation with or without hemorrhage and trinary time-dependent covariates.

To adjust for potential biases, we performed four additional analyses as follows. First, for patients who had received previous treatment, we reanalyzed the data including the period between diagnosis and previous treatment in the period before radio-

surgery. Second, because the exact date of obliteration was unclear (since obliteration was identified only after the fact, at the time of angiography), we performed a secondary analysis assuming that obliteration occurred six months before it was confirmed by angiography, as previously described.¹⁵ Third, because the rate of repeated hemorrhages from ruptured arteriovenous malformations is reported to be highest in the first year and to decline rapidly thereafter,²⁶⁻²⁸ we reanalyzed the data excluding the data from the first year after diagnosis. Fourth, because we could not eliminate the possibility that hemorrhage occurred in patients for whom no information was available after radiosurgery, we performed an analysis including all 531 patients and assuming that all patients without any information had hemorrhages three months after radiosurgery (within the recommended six-month follow-up interval) and that in patients whose neurologic state was stable, malformations were obliterated at three years (when most malformations are expected to have been obliterated).

The reduction in the incidence of hemorrhage in the periods after radiosurgery was calculated as $100 \times (1 - \text{hazard ratio})$. A two-sided P value of less than 0.05 was considered to indicate statistical significance. The annual hemorrhage rate was calculated as the number of hemorrhages divided by the sum of the observation periods. The cumulative rate of obliteration was calculated according to the Kaplan–Meier method.²⁹

RESULTS

Of the 531 patients, 31 were unable to return for serial follow-up after radiosurgery for personal reasons and were excluded from the analyses: 2 of these patients had a hemorrhage before radiosurgery, 17 were confirmed not to have had a clinically significant hemorrhage through subsequent communication by telephone or mail, and no information was available for the remaining 12 patients, 3 of whom lived overseas. Therefore, the final study group contained 500 patients. Their baseline characteristics are summarized in Table 1.

The diagnosis was based on the initial clinical presentation in 441 patients and was incidental in 59 patients, who underwent imaging for other reasons. Partial resection, several sessions of endovascular embolization, or both, had been performed before radiosurgery in 62, 65, and 10 patients, respectively. Radiation doses were less than 20 Gy in

35 patients. The median observation period was 7.8 years (Table 1). For most patients who had a long delay between diagnosis and radiosurgery, the interval reflected the time between diagnosis and referral to our institute. The cumulative rates of obliteration were 81 percent at four years and 91 percent at six years. Transient radiation-induced neurologic deterioration was noted in 26 patients (5.2 percent) between 1 and 34 months (median, 7) after radiosurgery (dysesthesia in 11 patients, hemiparesis in 9, aphasia in 1, and cranial-nerve deficits in 5). Seven patients (1.4 percent) had persistent neurologic deterioration (three had dysesthesia, two had hemiparesis, one had aphasia, and one had cranial-nerve deficits).

Hemorrhage occurred before radiosurgery in 42 of 500 patients (median follow-up, 0.4 year), during the latency period in 23 of 458 patients (median follow-up, 2.0 years), and after obliteration in 6 of 250 patients (median follow-up, 5.4 years) (Fig. 1). Repeated angiography in the six patients who had a hemorrhage after obliteration revealed no recanalization of the original malformations; we previously reported on the clinical course and imaging studies of one of these patients.⁸ Of 29 hemorrhages observed during the latency period or after obliteration, 19 were directly confirmed at our institute (12 immediately after clinical presentation and 7 after diagnosis by referring physicians). Seven patients died suddenly from hemorrhages, and we reviewed the radiologic studies provided by the referring physicians. In the case of three patients, the diagnosis of hemorrhage was made by the referring physicians, but radiologic test results were not provided.

Of the 429 patients without additional hemorrhages, 319 reached the latest cutoff of our data set. Reasons for censoring data on patients without complete follow-up included loss to follow-up (63 patients), refusal to undergo angiography to confirm obliteration (25 patients), a second radiosurgical treatment (16 patients), and death from unrelated causes (lung cancer in 2 and gastric cancer, pneumonia, suicide, and ileus in 1 patient each).

As compared with the overall risk of hemorrhage before radiosurgery, the risk was reduced by 54 percent during the latency period after radiosurgery (hazard ratio, 0.46; 95 percent confidence interval, 0.26 to 0.80; $P=0.006$) and by 88 percent after obliteration (hazard ratio, 0.12; 95 percent confidence interval, 0.05 to 0.29; $P<0.001$) (Table 2). As compared with the risk of hemorrhage during the la-

Table 1. Characteristics of 500 Patients Treated with Radiosurgery.*

Characteristic	Value
Age at treatment — yr	31.5±15.5
Female sex — no. (%)	213 (42.6)
Initial clinical presentation — no.†	
Hemorrhage	310
Seizure	91
Headache	24
Transient focal ischemic deficits	8
Hydrocephalus	4
Bruit	2
Embolism	1
Trigeminal neuralgia	1
Details of arteriovenous malformations	
Diameter — cm	2.1±0.9
Small size (<3 cm) — no. (%)	417 (83.4)
Eloquent brain location — no. (%)‡	316 (63.2)
Deep venous drainage — no. (%)§	282 (56.4)
Median Spetzler–Martin grade¶	III
Interquartile range	I
Details of radiosurgery	
Maximal dose — Gy	40.9±5.0
Dose to margins — Gy	21.0±2.4
Median observation period — yr	
From diagnosis to radiosurgery	0.4
Interquartile range	0.7
From radiosurgery to obliteration	2.0
Interquartile range	1.8
After obliteration	5.4
Interquartile range	7.0
Whole period	7.8
Interquartile range	9.6

* Plus–minus values are means ±SD.

† The diagnosis was incidental in 59 patients.

‡ An eloquent brain location included the sensorimotor, language, or visual cortex; the hypothalamus or thalamus; the internal capsule; the brain stem; the cerebellar peduncles; and the deep cerebellar nuclei, according to the criteria of Spetzler and Martin.²⁰

§ Deep venous drainage included the internal cerebral veins, basal veins, or pre-central cerebellar vein, according to Spetzler and Martin.²⁰

¶ The Spetzler–Martin grade is based on a scoring system reflecting the size of lesion, the neurologic eloquence of adjacent brain, and the pattern of venous drainage. Grades can range from I (small, superficial malformations in noneloquent areas) to VI (inoperable arteriovenous malformations). A grade of IV or V (large, deep malformations in neurologically critical areas) is associated with the highest risk of persistent neurologic deficits after surgery.²⁰

tency period, the risk was reduced by 74 percent after obliteration (hazard ratio, 0.26; 95 percent confidence interval, 0.10 to 0.68; $P=0.006$). For each comparison, the decrease in risk was greater among the 310 patients who presented with hemorrhage than among the 190 without hemorrhage at presentation. Although the risk of hemorrhage among the 190 patients without hemorrhage at presentation also tended to decrease during the latency period and after obliteration, the difference from the value before radiosurgery was not significant. The reduction in risk was similar in analyses that included presentation with or without hemorrhage as a fixed covariate (Table 2). There was a significant interaction between the period relative to radiosurgery and whether or not a patient presented with hemorrhage ($P=0.045$).

Similar results were obtained in analyses that included the period between diagnosis and prior therapy in the interval before radiosurgery and in analyses that considered the time of obliteration to be six months before angiographic confirmation. The results were also materially unchanged by the exclusion of data obtained during the first year after diagnosis and the inclusion of all 531 patients in the analysis (Table 2).

Among the patients presenting with hemorrhage, the annual rates of subsequent hemorrhage in the period before radiosurgery appeared similar over a period of three or more years. However, the numbers of events were small (Table 3).

DISCUSSION

We found that the risk of hemorrhage from cerebral arteriovenous malformations was significantly decreased after radiosurgery, both during the latency period (between radiosurgery and angiographic obliteration) and after angiographic obliteration. Previous studies have reported that the risk of hemorrhage during the latency period decreases,^{13,14} remains unchanged,^{15,16} or even increases,^{4,17} as compared with the natural course of the disease. These studies tended to compare the risk of hemorrhage among selected patients who underwent radiosurgery with patients who did not undergo radiosurgery, whereas we analyzed changes in the rate of hemorrhage relative to the timing of radiosurgery in a large cohort of consecutive patients.

Most previous studies assumed that angiographic obliteration was the ultimate goal of radiosurgery,^{3,5,6,23} because hemorrhage was rare once

Table 2. Risk of Hemorrhage from Arteriovenous Malformations According to the Observation Period.*

Type of Analysis	No. of Patients	No. of Hemorrhages			Latency Period vs. before Radiosurgery		After Obliteration vs. Latency Period		After Obliteration vs. before Radiosurgery		Hemorrhage at Presentation vs. No Hemorrhage at Presentation	
		Before Radio-surgery	Latency Period	After Obliteration	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Overall												
All patients with follow-up	500	42	23	6	0.46 (0.26–0.80)	0.006	0.26 (0.10–0.68)	0.006	0.12 (0.05–0.29)	<0.001	—	—
Patients presenting with hemorrhage	310	34	12	4	0.35 (0.17–0.71)	0.004	0.21 (0.06–0.71)	0.01	0.07 (0.03–0.22)	<0.001	—	—
Patients presenting without hemorrhage	190	8	11	2	0.83 (0.31–2.23)	0.71	0.47 (0.08–2.66)	0.39	0.39 (0.07–2.11)	0.27	—	—
Including hemorrhagic presentation as a fixed covariate												
All patients with follow-up data	500	42	23	6	0.46 (0.27–0.81)	0.007	0.24 (0.09–0.64)	0.004	0.11 (0.05–0.28)	<0.001	1.50 (0.90–2.51)	0.12
Including clinical presentation in defining the time-dependent covariates†												
All patients with follow-up data	500											
Hemorrhage		34	12	4	0.30 (0.15–0.61)	0.001	0.26 (0.08–0.86)	0.03	0.08 (0.03–0.23)	<0.001	—	—
No hemorrhage		8	11	2	1.14 (0.44–2.93)	0.79	0.28 (0.06–1.31)	0.11	0.32 (0.06–1.54)	0.15	—	—
Secondary												
Including the period before previous treatment	500	42	23	6	0.42 (0.25–0.71)	0.001	0.19 (0.08–0.49)	0.001	0.09 (0.04–0.23)	<0.001	1.39 (0.86–2.24)	0.18
Assuming the occurrence of earlier obliteration‡	500	42	23	6	0.53 (0.31–0.93)	0.03	0.19 (0.07–0.48)	0.001	0.10 (0.04–0.24)	<0.001	1.54 (0.92–2.57)	0.10
Excluding the 1st year after diagnosis§	459	29	18	6	0.48 (0.25–0.89)	0.02	0.24 (0.09–0.65)	0.005	0.11 (0.05–0.29)	<0.001	1.36 (0.76–2.42)	0.30
Including all patients¶	531	44	35	6	0.59 (0.36–0.96)	0.03	0.22 (0.09–0.54)	0.001	0.13 (0.05–0.32)	<0.001	1.47 (0.92–2.34)	0.11

* CI denotes confidence interval.

† Six conditions (three intervals each among patients presenting with hemorrhage and those presenting without hemorrhage) were prescribed in defining time-dependent covariates.

‡ The time of obliteration was assumed to be six months before angiographic obliteration.

§ Forty-one patients who were followed up for less than one year were excluded.

¶ This analysis includes all 531 patients treated according to the assumption that all 12 patients for whom no information after radiosurgery was available had hemorrhages three months after radiosurgery and that malformations in 17 patients with a stable neurologic state were obliterated at three years.

obliteration was confirmed.³⁰ Although recanalization of malformations can lead to hemorrhages after obliteration,^{31,32} this phenomenon was not observed in the six patients who had hemorrhage after obliteration in our study. We found that a small risk of hemorrhage remained after obliteration, although it was markedly lower than that before radiosurgery.

We did not address the mechanisms by which

the risk of hemorrhage may be reduced. However, histopathological studies of arteriovenous malformations after radiosurgery suggest potential mechanisms. Progressive thickening of the intimal layer,³³ which begins as early as three months after radiosurgery,³⁴ appears to decrease the stress to the vessel walls.¹³ In addition, partial or complete thrombosis of the irradiated vessels may decrease the number of patent vessels in the malformation.³⁵

Table 3. Annual Rate of Repeated Hemorrhage before Radiosurgery among 310 Patients Presenting with Hemorrhage.*

Period	Annual Rate of Hemorrhage (95% Confidence Interval)	No. of Patients Analyzed	No. of Hemorrhages
Year 1	6.3 (3.0–11.7)	310	10
Year 2	6.8 (1.8–17.3)	78	4
Year 3	6.4 (1.3–18.7)	52	3
After year 3	6.3 (3.7–10.1)	44	17

* The annual rate was calculated as the number of hemorrhages divided by the sum for the observation periods.

In vessels with a decreased diameter, thickening of the endothelium may cause occlusion at a relatively early stage. When blood flow declines below the threshold of detection by angiography, malformations, in effect, become invisible (angiographic obliteration), although they may still be evident histologically.³⁰

Our study has some limitations. Because we did not include a control group of patients who did not undergo radiosurgery, one concern is whether the decrease in the risk of hemorrhage after radiosurgery reflects, at least in part, the natural history of malformations, rather than effects of the procedure itself. A natural decline in the rate of recurrent bleeding has been reported within one year after the rupture of arteriovenous malformations.^{21,26-28} Because the criteria for conservative management were not well described in previous reports of the natural history of ruptured malformations,²⁶⁻²⁸ it has remained unclear whether small malformations that can be effectively treated with radiosurgery have a similar natural decline in the rate of repeated hemorrhage. However, the Cox models we used accounted for the time since diagnosis. In addition, hemorrhage rates before radiosurgery in our cohort appeared stable over a period of more than three years after diagnosis, although the number of patients observed for longer periods before radiosurgery was limited. In addition, our results did not

materially change in an analysis that excluded data obtained during the first year after diagnosis.

Another potential problem is the delay in confirming angiographic obliteration.^{15,16} The exact time of obliteration was not known but, instead, was inferred on the basis of findings on consecutive imaging studies. Angiography was initially carried out at six-month intervals; after 1993, less invasive imaging was performed every six months.²² However, our results were materially unchanged after adjustment for a potential delay of six months in identifying obliteration. Although some patients had prior treatments, these treatments are not expected to have a delayed effect, and the results were more conservative when the period before these treatments was excluded. Because our clinical practice incorporates close follow-up of our patients according to standard schedules, the retrospective nature of our analysis should not pose a problem. The lack of blinding among those reviewing studies and judging outcomes is also acceptable, since obliteration and hemorrhage were diagnosed separately. There was some loss to follow-up, but the assignment of extreme outcomes to these patients also did not substantively affect the results of the analyses.

The gold standard for evaluating the effect of radiosurgery on the risk of hemorrhage would be a randomized trial comparing a group undergoing radiosurgery with a group receiving no treatment. However, this approach is not possible, because the beneficial effects of radiosurgery in terms of angiographic cure are well recognized and hemorrhage is rare after complete obliteration.^{3,7-9} The large size and close follow-up of our cohort made it well suited to an assessment of the outcomes of radiosurgery.

In conclusion, we found that the risk of hemorrhage from cerebral arteriovenous malformations was significantly reduced after stereotactic radiosurgery during the latency period (after radiosurgery and before angiographic obliteration) and that it was reduced even further after obliteration. However, a risk of hemorrhage remained even after malformations were no longer visible on imaging studies.

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