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Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations

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The benefits of radiosurgery for cavernous malformations are difficult to assess because of the unclear natural history of this vascular lesion, the inability to image malformation vessels, and the lack of an imaging technique that defines "cure." The authors selected for radiosurgery 47 patients who harbored a hemorrhagic malformation in a critical intraparenchymal location remote from a pial or ependymal surface. Of these, 44 patients had experienced at least two hemorrhages before radiosurgery. The mean patient age was 39 years; six patients had previously undergone attempted surgical removal. The malformation was located in the pons/midbrain in 24 cases, the medulla in three, the thalamus in nine, the basal ganglia in three, deep in a parietal lobe in four, and deep in a temporal lobe in four. Patients had sustained initial hemorrhages from 0.5 to 12 years prior to radiosurgery (mean 4.12 years). In these patients, who were not typical of the majority of patients with cavernous malformations, there were 109 bleeds before radiosurgery in 193 prior observation-years, for a 56.5% annual hemorrhage rate (including the first hemorrhage), or an annual rate of 32% subsequent to the first hemorrhage.

The mean follow-up period after radiosurgery was 3.6 years (range 0.33–6.4 years). The proportion of patients with hemorrhage after radiosurgery was significantly reduced ($p < 0.0001$), as was the mean number of hemorrhages per patient ($p = 0.00004$). In the first 2 years after radiosurgery, there were seven bleeds in 80 observation-years (8.8% annual hemorrhage rate). In the 2- to 6-year interval after radiosurgery, the annual rate decreased to 1.1% (one bleed). After radiosurgery, 12 patients (26%) sustained neurological worsening that correlated with imaging changes. In eight patients these deficits were temporary; two underwent surgical resection and died. Two patients had new permanent deficits (4%). A significant reduction was observed in the hemorrhage rate after radiosurgery in patients who had deep hemorrhagic cavernous malformations, especially after a 2-year latency interval. This evidence provides further support to the belief that radiosurgery is an effective strategy for cavernous malformations, especially when located within the parenchyma of the brainstem or diencephalon.

KEY WORDS • **cavernous malformation** • **hemorrhage** • **radiosurgery** • **gamma knife**

FEW concepts evoke as much controversy in the use of radiosurgical techniques as the management of brain cavernous (angiographically occult) malformations. In 1990, we reported our preliminary experience with radiosurgery in 24 patients to introduce our patient selection criteria, technique of treatment planning and dose selection, and initial short-term results.[10] At that time, few reports of successful microsurgical resection in patient series were available. Thus, for patients who had sustained multiple brain hemorrhages and harbored a malformation in a critical brain location, the options were limited, and such cases were generally managed with further conservative observation. We hypothesized that the vessels of angiographically occult vascular malformations (we believe most are cavernous malformations) would respond in a similar fashion to true arteriovenous malformations (AVMs) which had been proven to benefit from radiosurgery.[14] We anticipated that by using accurate stereotactic high-resolution imaging, we would be able to reduce the hemorrhage risk in individual patients, after a latency interval.[2]

Because there was no imaging test to confirm obliteration in such angiographically occult lesions, we knew that clinical benefit would be confirmed by observing a reduction in hemorrhage rate over time and a low risk of complications. In this report we compare the observed hemorrhage rate before irradiation to the rate observed after radiosurgery.

TABLE 1

Characteristics of 47 cavernous malformations selected for radiosurgery

Factor	No. of Cases
location of lesion	
pons/midbrain	24
medulla	3
thalamus	9
basal ganglia	3
temporal lobe	4
parietal lobe	4
no. of prior hemorrhages	
one	3
two	31
three	9
four	4

TABLE 2

Cavernous malformation radiosurgery dose planning

Parameter	Mean	Range
malformation volume (ml)	2.1	0.2–8.1
no. of isocenters	2.1	1–8
margin dose (Gy)	16	10–20
maximum dose (Gy)	32	20–40

Clinical Material and Methods

Between 1987 and 1994, we performed stereotactic radiosurgery on 47 patients with cavernous malformations at the University of Pittsburgh. The mean patient age was 39 years. There were 24 males and 23 females. The mean number of hemorrhages before radiosurgery was 2.3 per patient. Forty-four patients had suffered at least two hemorrhages (range two–five); three patients with malformations in critical brain locations had sustained only one documented hemorrhage. Six patients had undergone attempts at surgical resection of their malformation; two had received a biopsy. All patients had magnetic resonance (MR) imaging and angiography before radiosurgery. The MR appearance was typical of a cavernous malformation in each patient,[15] but no abnormality was identified on angiography. The brain locations of cavernous malformations in this series are shown in Table 1. No patient had a seizure disorder.

Our technique for cavernous malformation radiosurgery has been reported previously,[10] but will be described briefly here. After application of the Leksell model G stereotactic frame (Elekta Instruments, Atlanta, GA) under local scalp infiltration anesthesia and mild oral or intravenous sedation, a stereotactic scan is performed. Computerized tomography (CT) was used for planning in all patients prior to 1990. Patients treated from 1988 through 1990 had both CT and MR imaging. Since 1990, only stereotactic MR has been performed. After a sagittal short-repetition time (TR) scout image acquisition, axial short- and long-TR images are obtained at 3-mm image intervals. In patients with small malformations (less than 15 mm in diameter), a volume acquisition is performed with images at 1-mm intervals. After the administration of a contrast agent, repeat axial and coronal short-TR images are obtained. The dimensions of the malformation are measured in three planes. Although we acknowledge that definition of the cavernous malformation nidus is difficult, we define the malformation as the region characterized by mixed signal change within an outer hemosiderin

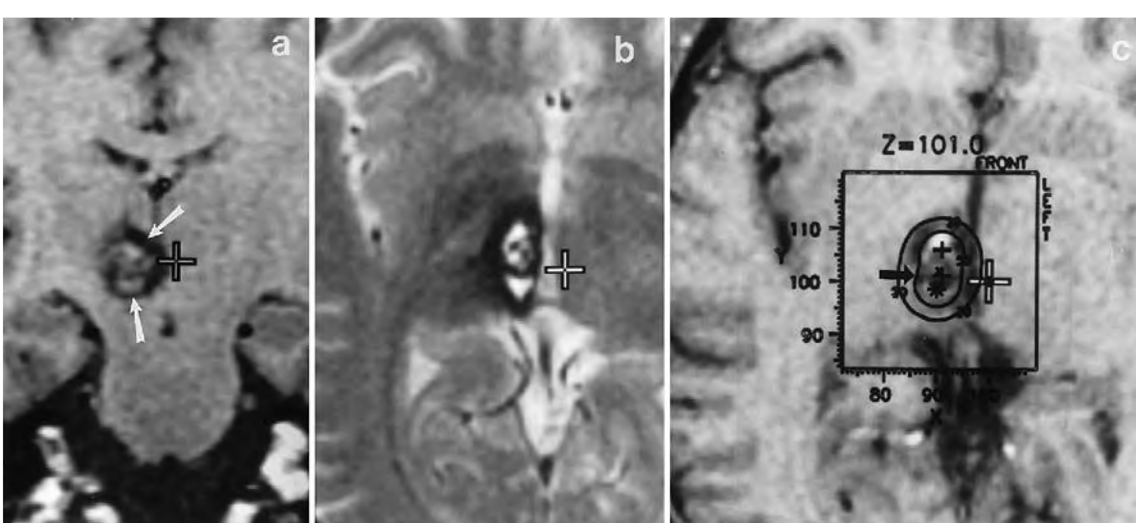

FIG. 1. Magnetic resonance images at the time of radiosurgery in a 33-year-old man with a right thalamic cavernous malformation. He had sustained two prior hemorrhages, each over 2.5 cm in diameter. The lesion is well identified on both short- and long-TR images. a and b: Coronal and axial views used for isodose planning. c: The margin isodose (50%, *black arrow*) for radiosurgery was kept within the peripheral hemosiderin ring (*white arrows*, a). Radiosurgery was performed with three 8-mm isocenters, and a maximum dose of 32 Gy was used. The 20% and 50% isodose lines are shown.

ring, typified by low signal intensity. Hematoma eccentric from the malformation is excluded from dose planning. Dose planning is performed at a computer workstation. Single- or multiple-isocenter plans are then used to construct a conformal irradiation volume for the cavernous malformation margin (Fig. 1). In all patients in this series, the 50% isodose or greater was used for the margin. Dose planning and target selection was performed by a neurosurgeon, radiation oncologist, and medical physicist. Selection of the dose for radiosurgery was dependent on malformation volume;[10] we reduced the dose below that advocated for an AVM of similar volume. Radiosurgery was performed with a 201-source cobalt-60 gamma unit (Elekta Instruments). The volume of the malformation was determined on the computer workstation as the sum of the voxels within the isodose used to envelop the malformation margin. Malformation volumes and dose-selection parameters are detailed in Table 2. After radiosurgery, all patients received 40 mg methylprednisolone intravenously. Patients were discharged from the hospital either the same afternoon or the next morning (range of hospital stay 6–24 hours).

Follow-up imaging studies were requested at 6-month intervals for the first 2 years after radiosurgery, yearly thereafter for two years, and then biennially. Clinical follow-up data were obtained from the patients and their referring physicians when they lived at a distance from Pittsburgh. Results were analyzed by an independent bio-epidemiologist (J.R.K.).

Hemorrhage rates were calculated as: rate = total number of bleeds in all patients/total number of patient-years in the observation period. The proportion of patients who sustained a hemorrhage in observation periods before and after radiosurgery was compared using a McNemar chi-square test (for paired data). The number of hemorrhages per patient before and after radiosurgery was compared using a paired t-test. Patients were censored at the time of death or surgical resection; if a bleed was the cause of the death or resection, it was recorded as such.

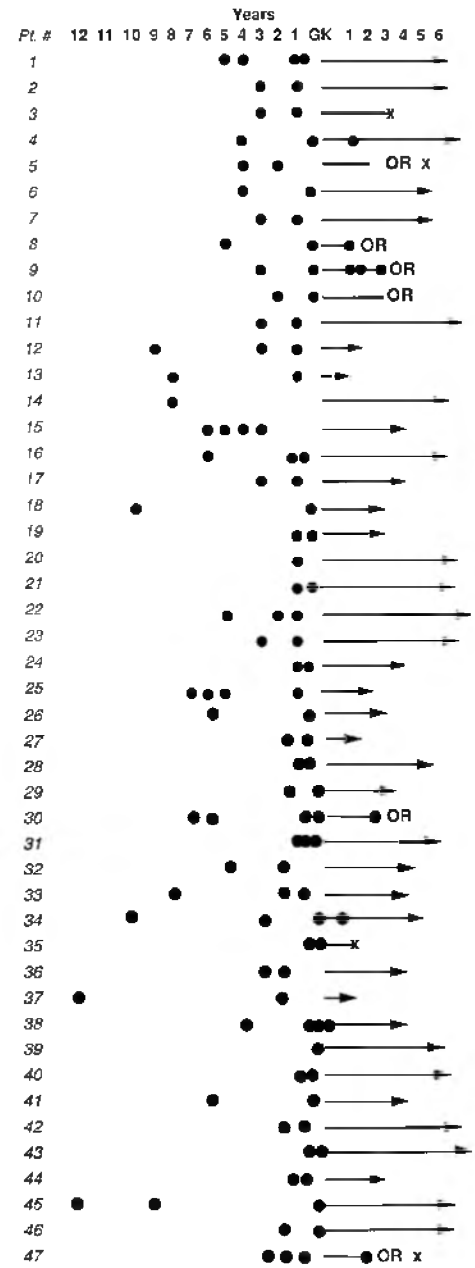

FIG. 2. Timeline (years) before and after gamma knife radiosurgery (GK) for all 47 patients with cavernous malformations. Each *black dot* represents the occurrence of a hemorrhage and during which year, either before or after treatment. *OR* signifies resection of the malformation. An *x* denotes death of the patient, either from unrelated causes or after surgery. An *arrow* indicates that the patient has remained hemorrhage-free.

Results

Risk of Hemorrhage

The occurrence of symptomatic hemorrhages before and after stereotactic radiosurgery is depicted in Fig. 2. In all, 47 patients were followed through the pre- and postradiosurgery observation periods.

Preradiosurgery Hemorrhage Rates

Prior to radiosurgery, there were 193 patient-years of observation in the 47 patients (calculated from date of first hemorrhage in each patient); 109 hemorrhages occurred in these patients (mean 2.34 bleeds per patient). Forty-four patients sustained at least two hemorrhages, and three patients had one hemorrhage. The mean observation interval before radiosurgery was 4.12 years (range 0.5–12 years). The occurrence of 109 bleeds in the 193 years of observation led to an annual hemorrhage rate of 56.5%.

Another approach to the calculation of the rate of hemorrhage is to use the first bleed as an indicator that the patient has a malformation and count that as time zero for that patient's pretreatment observation. If this is done and the first hemorrhage excluded, there are then 62 bleeds in 193 observation years for an annual rate of 32%. Thus, in the period of hemorrhagic activity before treatment, these patients had a calculated risk of over 30% for sustaining a symptomatic hemorrhage each year. It can be argued that, because the malformation was present since birth, the pretreatment observation period should be the patient's lifetime. This would result in an annual hemorrhage rate of 5.9% (109 bleeds in 1833 years of observation).

Postradiosurgery Hemorrhage Rates

The posttreatment observation period was from the time of radiosurgery until last follow-up examination, surgery, or death. The follow-up period after radiosurgery varied from 0.33 to 6.4 years (mean 3.6 years). The shortest follow-up time (0.33 years) was in a single patient who sustained a hemorrhage shortly after radiosurgery and underwent malformation resection (the hemorrhage provided a resection corridor through the floor of the fourth ventricle). After irradiation, a total of eight hemorrhages were observed in 169 patient-years of observation. Because of an estimated 2-year latency interval for maximum vascular effects, we stratified results from 0 to 2 years and from 2 to 6 years after treatment. From 0 to 2 years after radiosurgery, seven bleeds in 80 observation years were found (annual hemorrhage rate of 8.8%). From 2 to 6 years, only one bleed in 89 observation years was found, for an annual hemorrhage rate of 1.1%.

If the first bleed in each patient is ignored and serves simply to identify the beginning of the observation period for that patient, then 44 of the 47 patients had at least one hemorrhage before radiosurgery. Only six of these 47 patients bled after radiosurgery (McNemar chi-square = 36, $p < 0.0001$). The mean number of hemorrhages per patient was also compared before and after radiosurgery, and a significant reduction was identified ($t = 4.51$, $p = 0.00004$).

Morbidity of Radiosurgery

Within 3 to 18 months after irradiation, 12 patients (26%) developed new neurological deficits associated with parenchymal imaging changes (regions of increased signal on long-TR images surrounding the lesion) on MR imaging. Associated symptoms were location-dependent. Two patients with thalamic cavernous malformations developed hemiparesis requiring prolonged oral corticosteroid use before recovery. In eight patients, these deficits were temporary with full recovery. In two patients, the malformation was resected. Thus, two patients (4%) were left with permanent neurological deficits from radiosurgery; both patients remain functional with Karnofsky performance scores of 80 and 90, respectively.

Two patients died of causes unrelated to their cavernous malformation. In an additional two patients, an attempt at resection of the malformation was made at a time of increased neurological symptoms (one from related edema and one from hydrocephalus). One patient had a cavernous malformation within the midbrain and the other at the pontomedullary junction. Both patients died after attempted resection. In summary, a total of six patients had surgical resection subsequent to radiosurgery. In this group, four patients are doing well (three with brainstem malformations and one with a thalamic lesion) and two died.

Imaging Changes

Serial MR studies were performed initially at 6-month intervals for the first 2 years, then yearly. Twelve patients had increased long-TR signal changes associated with neurological symptoms, as mentioned above. Ten patients had a reduction in the size of their malformation, which represented either a treatment-related effect on the malformation's vessels or continued resorption of hematoma/microhemorrhage. In all other patients, the imaging appearance of the malformation remained unchanged.

Discussion

Reduction in Hemorrhage Risk

At a maximum follow-up time now past 6 years, 41 patients (87%) with high-risk cavernous malformations remained hemorrhage-free after radiosurgery. All six patients who sustained a hemorrhage after irradiation did so within 2 years of the procedure. One sustained three hemorrhages within 3 years and underwent resection. Although the mean follow-up period in this study after radiosurgery was only 3.6 years, 22 patients were followed for more than 4 years and none had a rehemorrhage. We submit that a latency interval for protection from repeat hemorrhage within the first 2 years appears reasonable.

Within the first 2 years after radiosurgery (total of 80 observation years), seven hemorrhages occurred. This equaled an 8.8% annual hemorrhage rate. After the initial 2 years following radiosurgery, only one bleed occurred in the next 89 years of total observation, a reduction in the annual hemorrhage rate to 1.1%. This reduced rate now approximated that identified in natural history studies of cavernous malformation.[3,17] Such a latency interval for radiation effect would be similar to that expected in AVM radiosurgery.[14] The total length of the latency interval (the time required for maximum therapeutic effect) is not known, although if it were to parallel the AVM response, we would estimate this time to be within 3.5 years of irradiation.

In a separate study of 122 patients managed conservatively and prospectively followed for a mean of 34 months, we found an overall annual symptomatic hemorrhage risk of 2.6%. However, patients with at least one prior hemorrhage had an annual risk of 4.5%, and patients without prior clinical hemorrhage, a 0.6% risk.[12] These hemorrhage risks are lower than in the patients we selected for radiosurgery, who had a mean of 2.3 hemorrhages prior to irradiation. Thus, the late, reduced hemorrhage risk of our radiosurgery patients (1.1%) approaches the low risk we identified in that study for nonhemorrhagic cavernous malformations. We stress that the patients selected in this study for radiosurgery were not typical of the majority of patients with cerebral cavernous malformations in that they were considered to be poor candidates for microsurgery and because they had sustained multiple hemorrhages. Prior reports indicate that for patients without prior hemorrhage, the annual hemorrhage rate is below 1%.[3,17]

We cannot guarantee complete obliteration of a cavernous malformation just because the patient survived several years after treatment without sustaining a new hemorrhage. There is currently no neurodiagnostic test that can confirm such a curative result. Although patients may be encouraged by a reduction in hemorrhage risk, they cannot be told that this risk is eliminated. Perhaps in the future imaging tools that detect blood volume within the malformation, rather than blood flow, will prove valuable. For example, metabolic imaging studies such as positron emission tomography or single-photon emission CT may identify the blood volume of the lesion before radiosurgery. A subsequent reduction after radiosurgery would support the concept of obliteration. Unfortunately, the small volume of many of these malformations make them poorly resolved by currently available techniques. For the present, the clinical course before and after radiosurgery remains the most important tool we have to evaluate these patients.

The Rationale for Radiosurgery

Current neurosurgical strategies for cavernous malformations are significantly different from those reported prior to 1988. At that time, the successful resection of deeply located cavernous malformations associated with low morbidity was reported in anecdotal form only.[6,20,25,26] The hazards of operating within the brainstem or diencephalon for these lesions were stressed by several authors.[19,25] Lacking appreciable surgical experience with safe, successful removal of these lesions, we managed most patients conservatively even after hemorrhage. Thus, in 1988 we began our use of stereotactic radiosurgery as an alternative management approach to hemorrhagic cavernous malformations. We recommended radiosurgery only for intraparenchymal malformations in deep brain locations where the risks of surgical resection were thought to be excessive. Referred patients who were clinically stable and who had sustained only one hemorrhage were not accepted as candidates for radiosurgery. Rather, we recommended either microsurgical resection (depending upon location) or further conservative observation. The latter patients were entered into a separate prospective natural history study.

The Importance of Neuroimaging

Clearly, the introduction of MR imaging led to a significant increase in the diagnosis of intracerebral cavernous malformations. We recognized that high-resolution MR imaging provided graphic anatomical and vascular detail that enhanced microsurgical results; it could also identify malformations that presented on a pial or ependymal surface, thereby making them suitable for resection.

It is likely that the majority of angiographically occult vascular malformations are cavernous-type malformations.[18] We performed high-resolution subtraction angiography to determine whether each vascular malformation was truly angiographically occult. Venous angiomas identified on either MR images or angiograms were not accepted for radiosurgery.[9] We and others[16] believe that some patients have cavernous malformations in association with venous malformations. In the clinical context of observed hemorrhage, it is most likely that the bleed was from the cavernous malformation.[16] We performed radiosurgery on one patient who had a thalamic cavernous malformation (and adjacent venous malformation) with two hemorrhages.

The Role of Microsurgery

During the 7-year interval of our radiosurgery study, several publications reported the successful and relatively safe removal of deep-seated cavernous malformations. Kashiwagi and colleagues[8] reported four patients treated with surgical resection of their brainstem cavernous malformations; only one had additional morbidity (from hydrocephalus). Zimmerman, *et al.*,[27] described 24 patients with brainstem cavernous malformations, 16 of whom underwent resection. Although four patients had new deficits after surgery, all were transient. Twelve patients were the same or improved in the immediate postoperative period, but one died 6 months after resection from shunt infection and sepsis. Seven of the eight patients who were managed conservatively remained stable, although one died from rehemorrhage.

Bertalanffy, *et al.*,[1] reported results on 26 patients treated with microsurgery for deep-seated cavernous malformations. Eighteen patients underwent surgery because of progressive neurological deficits; 15 of whom had sustained a hemorrhage. Successful total resection without morbidity was achieved in 11 patients and seven patients had new deficits after surgery. An additional eight patients suffered major deficits, five of these with lesions of the basal ganglia, thalamus, or insula. Based on their unsatisfactory results, these authors questioned whether the indications for deep cavernous malformation surgery should be limited.[1] Other groups, however, presenting small patient series, emphasized the importance of intraoperative localization followed by meticulous microsurgical technique to attain a good surgical outcome in deep brain locations.[4,5,7,13,21–24] These reports provided evidence that, at experienced centers, many cavernous malformations can be totally resected with low risk of permanent morbidity, provided that the malformation or hematoma presents on a pial or ependymal surface (brainstem or thalamus) or is located in a noncritical region.

Potential Vascular Effects of Radiosurgery

Although the vascular obliterative response of a true AVM after radiosurgery is well documented, we speculate that the vessels of a cavernous malformation may respond similarly to high, single-session doses of irradiation. This response might consist of endothelial cell proliferation, vessel wall hyalinization and thickening, and eventual luminal closure. A latency interval of 2 to 3 years might be necessary to achieve this result. All of our patients are warned of the potential risk of hemorrhage during the initial years after radiosurgery before the maximum obliterative response may have occurred. However, because there is no imaging test to confirm such obliteration, patients and their referring physicians must be aware that the absence of further hemorrhage is an indication, and not a confirmation, that a positive response has occurred. Clearly, the absence of hemorrhage after radiosurgery may only be part of the natural history of that individual patient's cavernous malformation. In our comparison of the proportion of patients with a hemorrhage before radiosurgery with that following irradiation, we found a significant reduction ($p < 0.001$) up to 6 years. This statistical analysis assumes that the natural history of the lesions (if left untreated) in this study would have been to continue to have a high risk of bleeding in the absence of any other intervening factors. However, we must admit that the natural history in individual patients is unknown and may be composed of a brief interval of accelerated risk of hemorrhage followed by a more prolonged period with a reduced risk of hemorrhage.

Morbidity of Radiosurgery

In our 1990 report, we provided dose-selection guidelines for cavernous malformation radiosurgery.[10] These guidelines represented a reduction in the dose that would be administered to an AVM of similar volume. The risk of radiosurgery for cavernous malformations may be greater than the risks for other pathological entities. The critical location of these malformations may be an explanation for the observed increased morbidity as compared to our general experience with AVMs or tumors. In comparison to our brainstem AVM series (for which we found a temporary morbidity rate of 16%),[11] the 26% temporary morbidity rate in this cavernous malformation series was higher. Whether the increased risk is a function of the lesion itself or the altered tolerance of the surrounding brain tissue remains to be shown.

The reduction in the prescribed radiation dose for cavernous malformations, as suggested in our earlier report, was evaluated in the 23 patients managed subsequently. Despite the dose reduction, we were not able to reduce the incidence of complications; however, the severity of complications was reduced. In the later group, most new symptoms consisted of temporary cranial neuropathy or mild ataxia whereas, in the initial group, larger regions of altered long-TR signal change on MR images were associated with hemiparesis, hemisensory deficits, and cranial neuropathies. We do not believe that a further reduction in dose is necessary, as this could reduce the obliterative response.

Conclusions

In this group of patients with hemorrhagic cavernous malformations located in critical brain regions that were thought to pose an excessive risk for microsurgical resection, radiosurgery using the gamma unit appears to reduce the rate of hemorrhage, especially after a 2-year latency interval. Only a prospective randomized trial of microsurgery versus radiosurgery will answer questions as to the efficacy and necessity of these different approaches. The morbidity associated with this treatment strategy for cavernous malformations, the majority of which were located in the brainstem or diencephalon, was not negligible; however, in most patients these delayed effects were temporary. Although we have shown for the first time the benefits of radiosurgery for cavernous malformations, we do not advocate its use for minimally symptomatic lesions or for patients who would be better managed with open surgical resection.

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