The theoretical goal of radiosurgery for cavernous hemangiomas is to obliterate the lesion and thereby prevent its rebleeding; however, direct proof of the postradiosurgical obliteration of these lesions is not available and the process of evaluating the results of radiosurgery is not simple. There are difficulties in actually defining what constitutes cavernous hemangioma bleeding, as well as in establishing its correct diagnosis. Usually any sudden onset of new symptoms or exacerbation of the old ones is considered a hemorrhage, despite the lack of any neuroimaging evidence of overt bleeding. Overt bleeding of cavernous hemangioma (a blood clot inside or outside the hemosiderin ring of the lesion or evidence of hemorrhage on a lumbar puncture) is rarely diagnosed. The nature of cavernous hemangiomas crosses the borderline between hamartoma and tumor more frequently than that of arteriovenous malformations. Intracerebral cavernous hemangiomas have been documented to appear and grow after birth. In view of cavernous hemangiomas’ known growth potential, lesion regression and a decrease in volume can be regarded as positive treatment outcomes. Detailed information about the natural course and predictive factors for cavernous hemangioma growth, however, has not been recorded. Thus, radiosurgery of brain cavernous hemangiomas remains controversial and, when we consider that the incidence of cavernous hemangioma in the population is of the order of 0.4 to 0.5%, the number of patients referred for neurosurgical treatment, including GKS, is quite small.

### Clinical Material and Methods

Between 1992 and 2000, 112 patients with brain cavernous hemangioma underwent GKS. This was a heterogeneous group of patients. Initially there were no strict indication criteria. This evolved until criteria were applied for the final third of patients, in whom radiosurgery was considered in cases of a history of repeated bleeding and those in which resection was contraindicated or refused. The median age of the patients was 42 years (range 13–81 years). The male/female ratio was 54:58. The location of the lesions is detailed in Table 1. Half of the lesions were in deep inoperable...
ble locations. The lesion was solitary in 99 patients and multilocular in 13. Seven patients had undergone previous partial microsurgical resection of the cavernous hemangioma, and GKS was the primary treatment in 94% of cases. The presenting symptom was an epileptic seizure in 40 patients, headache in 30, hemiparesis in 22 patients, vertigo in nine, visual loss in five, oculomotor deficit in four, unconsciousness in two, and a facial nerve paresis in one patient. An established neurological deficit was present before radiosurgery in 51 patients (46%).

In the case histories there were 89 events reported as bleeding in 59 patients before radiosurgery. In 23 patients reported bleeding episodes were recorded (maximum four bleedings). Overt bleeding was observed in 29 patients. There was a 2% annual risk of bleeding before radiosurgery in this group of patients, and a 0.6% risk of overt bleeding. Epilepsy before radiosurgery was observed in 44 patients.

Computerized tomography was used for stereotactic localization in the first 26 patients and MR imaging was performed for the remaining 86 patients. A turbo spin echo, double-echo (PD and T2-weighted) MR imaging sequence was used for the stereotactic targeting. The slice thickness was 3 mm. High-field MR imagers, operating at 1- or 1.5-tesla were used (Siemens). The older planning system, KULA (Elekta Instruments AB, Stockholm, Sweden), was utilized for the first 24 patients, and the GammaPlan (Elekta Instruments AB) was used for the next 88 patients. The median maximum diameter was 1.3 cm (range 0.4–3.8 cm); the median was 0.9 cm³ (range 0.06–12.5 cm³); the median maximum dose was 30 Gy (range 16–50 Gy); the median margin dose was 16 Gy (range 9–36 Gy); the median prescription isodose was 50% (range 40–90%); and the median number of isocenters was one (range one–10). The Leksell gamma knife model B (Elekta Instruments AB) was used.

Results

Clinical follow-up information was available for 107, and the median time was 48 months (range 6–114 months).

Risk of Rebleeding

After GKS an ictal induction or deterioration of a neurological deficit was reported as rebleeding in seven patients. This event was observed at a median latency of 9 months after GKS (range 5–51 months), and it represented an annual rebleeding risk of 1.6%. In two patients signs of overt hemorrhage were detected 5 and 24 months, respectively, after radiosurgery, which brought the risk of overt rebleeding to 0.5% annually. Although there was only one rebleeding event and no overt rebleeding more then 2 years after radiosurgery, the medians follow-up duration of 4 years is insufficient to cite a statistically significant decrease in the risk of rebleeding.

Neuroimaging Follow-Up Examinations

At least one posttreatment MR imaging session was performed in the 110 patients, at a median interval after GKS of 36 months (range 6–114 months). In 49 patients (45%) shrinkage was observed at a median interval of 24 months after GKS (range 8–73 months) (Figs. 1–3). In two patients (1.8%) the lesion increased in volume at 24 and 34 months, respectively, after radiosurgery, which brought the risk of overt rebleeding to 0.5% annually. Although there was only one rebleeding event and no overt rebleeding more then 2 years after radiosurgery, the medians follow-up duration of 4 years is insufficient to cite a statistically significant decrease in the risk of rebleeding.

Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Cases</th>
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<tr>
<td>brainstem</td>
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<tr>
<td>temporal</td>
<td>24</td>
</tr>
<tr>
<td>frontal</td>
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</tr>
<tr>
<td>parietal</td>
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<td>thalamus</td>
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<td>basal ganglia</td>
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</tr>
<tr>
<td>cerebellar</td>
<td>8</td>
</tr>
<tr>
<td>occipital</td>
<td>7</td>
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Fig. 1. Neuroimages obtained in a 26-year-old man with a history of overt bleeding and epilepsy. Left: The cavernous hemangioma had an 8.1 cm³ volume and was treated with a marginal dose of 15 Gy in the 50% isodose line. Right: Image obtained 2 years after radiosurgery revealing regression of the cavernous lesion.

Fig. 2. Neuroimages acquired in a 28-year-old woman, without a history of bleeding, exhibiting visual impairment. Left: The volume of the cavernous hemangioma was 4.5 cm³, and 15 Gy was delivered to the 50% isodose. Right: Regression of the cavernous hemangioma was observed 4 years after radiosurgery.
Neurological Deficits

There were 51 patients with a stable neurological deficit before radiosurgery and 17 (33%) improved at a median post-GKS interval of 9 months (range 5–48 months). A temporary deterioration of neurological dysfunction was observed in 22 patients (20.5%) at a median interval of 7 months after GKS (range 3–24 months). The cause of this impairment was rebleeding in six patients and perilesional edema in 16. This impairment of neurological dysfunction resolved after a median follow-up duration of 24 months (range 12–51 months). Persistent morbidity remained in five patients (4.5%).

Before radiosurgery epileptic seizures were observed in 44 patients. Improvement after radiosurgery occurred in 20 (45%) after a median post-GKS interval of 6 months (range 1–30 months). Epilepsy deterioration caused by perilesional edema was observed in two patients 6 and 8 months, respectively, after radiosurgery and resolved 12 months after radiosurgery. There was no persistent treatment-related morbidity from epilepsy.

Four patients died. Two patients died 6 and 51 months, respectively, after radiosurgery, and the cause of death was rebleeding in both patients, but neither MR imaging nor computerized tomography scanning was performed and the autopsy results were not available to prove it. The other two patients died from trauma and suicide.

Statistical Analysis

Nine different factors were analyzed: sex, age, prior surgery, prior hemorrhage, treatment volume, location, margin radiation dose, maximum radiation dose, and number of isocenters.

A total of six different events were studied as potentially dependent on these proposed factors: rebleeding, edema, worsening of neurological status, lesion shrinkage, improvement of epilepsy, and improvement of the neurological deficit.

To distinguish those factors having an influence on the time dependence of the above listed events, univariate and multivariate statistical analysis methods were employed. Univariate analysis was performed using the Kaplan–Meier survival curve statistics with a log-rank test. Multivariate analysis was performed using the Cox proportional hazards model with the backward stepwise (conditional likelihood ratio) method. The analyses were performed using the SPSS version 10.0 statistical software. Variables with significant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rebleeding</th>
<th>Edema</th>
<th>Clinical Deterioration</th>
<th>Decrease in Volume</th>
<th>Epilepsy Improved</th>
<th>Clinical Improvement</th>
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<td>sex</td>
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<td>0.017 (log rank)</td>
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<td>prior op</td>
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<td>0.002 (log rank)</td>
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<td>0.038 (log rank)*</td>
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<td>0.008 (Cox), 0.036 (log rank)*</td>
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<td>max dose</td>
<td>0.032 (Cox)</td>
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</table>

* Significant using both Cox proportional hazards and log-rank test.

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p values (p < 0.05) at least in one of two actuarial analyses were considered possible risk factors for the event. Factors having a significant influence on the events under study are indicated and the significant p values for both univariate and multivariate analyses are listed in Table 2.

On the basis of this study, cavernous hemangioma rebleeding after GKS can be expected more frequently in female patients, in middle-aged patients (between 30–50 years), in patients with a history of hemorrhage, and in those in whom the dose to the cavernous hemangioma margin was less than 13 Gy and in whom the maximal dose to the cavernous hemangioma was delivered.

Edema after GKS can be expected more frequently in patients who have undergone prior surgery, in patients with a larger cavernous hemangioma volume, and in those in whom the dose to the cavernous hemangioma margin was higher than 13 Gy (Fig. 4 upper).

A worsening of the neurological deficit after GKS can be expected more frequently in younger patients up to age 30 years, in patients who have undergone a prior operation, and in those in whom the dose to the cavernous hemangioma margin was higher than 13 Gy.

A decrease in cavernous hemangioma volume after GKS is shown in Fig 4 lower and can be expected more frequently in younger patients up to age 30 years, in patients who had undergone previous operations, and in those with a history of hemorrhage.

Improvement of epilepsy after GKS can be expected more frequently in patients with a larger cavernous hemangioma volume.

Improvement of the neurological deficit after GKS was not significantly dependent on any of the factors monitored.

Discussion

Neuroimaging of cavernous hemangiomas involving MR imaging is standard and diagnosis can be established without histological investigation. Cavernous hemangiomas do not display uniform behavior and their status can vary from indolent, through bleeding, epileptogenic to growing lesions. The incidental diagnosis of asymptomatic cavernous hemangiomas is increasing and these cases should be treated conservatively. In cases in which brain cavernous hemangiomas have bled and caused a neurological deficit, it is probable that future rebleeding would cause further neurological deterioration. Problems can arise in cases in which the lesion is in a critical location. The risk of open resection of cavernous hemangiomas varies according to the location. Amin-Hanjani, et al., reported an incidence of transient neurological morbidity in 20.6%, persistent disabling complications in 4.1%, and nondisabling complications in 2.1%. Microsurgical resection of cavernous hemangiomas in the brainstem was associated with a 12 to 14% risk of serious permanent morbidity and an 8% risk of death. On the other hand, 35.7% of patients exhibited an improvement in their neurological condition after microsurgery. Mathiesen, et al., reported a 69% transient morbidity rate and significant permanent morbidity in 8% of deep and brainstem cavernous hemangiomas. Good functional results can only be expected in selected cases in which the cavernous hemangioma is in a more favorable location and in the hands of a specialized and well-trained neurosurgeon with sophisticated microsurgical and electrophysiological equipment.

In contrast to microsurgical resection, GKS does not remove the intracranial pathological process. The theoretical goal of radiosurgery in these cases is total obliteration of the malformation, thereby preventing any risk of rebleeding and deterioration of the clinical condition. Direct proof of the obliteration of cavernous hemangiomas after radiosurgery, however, is not available. The only way to evaluate the risk of rebleeding is clinical observation during a longer follow-up period, and here we meet some controversy. Should rebleeding be considered to cover any impairment of the neurological status without proof of overt bleeding—that is, a blood clot or subarachnoid hemorrhage on the
Radiosurgery of cavernous hemangiomas

- Neurodeficit after radiosurgery - 20.5%
  - Complication of radiosurgery
    - edema 15%
    - radiosurgery with no adverse effect
  - Rebleeding - 5.5%
    - Temporary 14%
    - Persistent 1%
    - Temporary 2%
    - Persistent 3.5%

Mortality after radiosurgery

- Radiosurgery curative
  - Mortality of radiosurgery 0%
- Radiosurgery not curative
  - Mortality of natural course of the disease 2%

Fig. 5. Upper: Occurrence of the neurological deficit during follow up after radiosurgery. Lower: Mortality caused by the cavernous hemangioma during the follow-up period after GKS.

imaging studies? Because the most decisive factor for the patient is his clinical condition, it is suggested that a less rigorous definition of bleeding without signs of overt bleeding should be accepted. Although the median follow-up period was 4 years and we only observed one rebleed and no overt rebleeding later than 2 years after radiosurgery, this is not a statistically significantly difference compared with the risk before treatment. Thus, a longer follow-up period will be needed to verify the protective effect of the radiosurgery on cavernous hemangiomas, which should probably exceed 4 years. In summary, in this material the risk of rebleeding after GKS was the same as before treatment for the first 2 years. Between 2 to 4 years after GKS this risk was lower, but the difference was not statistically significant.

Lesion shrinkage or failure to enlarge is an important parameter in relation to the effect of GKS on a cavernous hemangioma. Shrinkage was seen in 45% of cases 2 years after radiosurgery and only 1.8% of the lesions increased in volume after GKS. In contrast, Clatterbuck, et al.,7 reported a shrinkage or regression of untreated cavernous hemangiomas in 35 to 55% of followed cases, depending on the follow-up time; however, they also observed that 35 to 43% of cavernous hemangiomas enlarged. Kupesmith, et al.,23 observed that the natural course of cavernous hemangiomas showed regression in 18% and growth in 15%; however, what is recorded as spontaneous regression of a cavernous hemangioma could be expected as a hematoma resorbs. In our series because GKS was delayed for 3 but more often 6 months after the hemorrhage, in the majority of cases, shrinkage is not due to hematoma resorption and therefore is unlikely to be a reflection of the natural course of the disease. We suggest that the recorded shrinkage represents a positive result of the treatment. Some authors have also observed a regression of the cavernous hemangioma after radiosurgery,6,15,21 although others found little change.4

Another important effect of GKS for cavernous heman-
gioma is the effect on lesion-induced epilepsy. Improvement of epilepsy was observed in 45% of affected patients. Régis and colleagues\(^1\) reported even better results: 53% of 49 patients were free of seizures after radiosurgery and there was a decrease in the number of seizures in another 20% of those patients. Our results need to be placed in the context of the ongoing debate around the use of GKS to treat cavernous hemangiomas. Karlsson, et al.\(^2\) do not support the treatment of these lesions with GKS because they do not consider the treatment results to be significant enough. They observed a tendency toward a decrease in the risk of rebleeding after a period of 4 years following radiosurgery. The risk of complications was relatively high compared with other indications. Nonetheless, this group did note some decrease in lesion volume. Kondziolka and colleagues\(^3\) considered the treatment of cavernous hemangiomas by GKS to be useful in selected cases. They observed a decrease in the risk of rebleeding after 2 years and shrinkage in 21% of cases. Radiosurgery was associated with temporary morbidity in 26% of cases, and 4% of patients showed permanent deterioration of neurological deficit. Along with the 2-year latency period, the decrease in the risk of rebleeding was observed in the group of patients treated by another group.\(^3\) Using a cyclotron, radiosurgery achieved in 16% of cases. Chang, et al.\(^4\) observed a decrease in the risk of rebleeding after the treatment of angiographically occult vascular malformations 3 years after radiosurgery, which was associated with a morbidity rate of 11% of cases. Protection from rebleeding after GKS of cavernous hemangiomas was also observed by Mitchell, et al.\(^5\) Others were limited in their experience by having only a relatively short follow up and therefore the efficacy of radiosurgery of cavernous hemangiomas cannot be unambiguously established.\(^6,7,8\)

The complication rate of cavernous hemangioma radiosurgery with the same volume and radiation dose seems to be higher than in the other commonly treated vascular lesion the AVM.\(^9,10\) Nevertheless, the treatment-induced complication rate could be overestimated considering the impairment of the neurological deficit. Neurological deficit after radiosurgery deteriorated in 20.5% of our patients, but radiosurgery itself caused temporary morbidity in 14% and permanent morbidity in only 1% of cases as illustrated in Fig. 5 upper. This morbidity was not disabling for any of the patients. Compared with AVMs, cavernous hemangiomas are reported to grow and appear de novo more frequently. Growth of AVMs is uncommon and their de novo appearance is extremely rare. For tumors, the endothelial vascular growth factor is thought to be responsible for both the neovascularization and edema.\(^11,12,13,15,16,18\) This factor has also been detected in cerebral vascular malformations.\(^14\)

The relationship of dose to the development of perilesional edema is in keeping with the findings of others and is comparable with the relationship of dose to edema with other diagnoses such as meningiomas. In our center we found that with meningiomas temporary postirradiation edema occurred more often when the margin dose exceeded 15 Gy.\(^14\) In the current series material cavernous hemangiomas developed significantly higher incidence of posttreatment perilesional edema when the margin dose exceeded 13 Gy. We observed postirradiation edema in 27% of cases, and the median marginal dose in this group of patients was 16 Gy. Pollock and colleagues\(^15\) had a similar experience observing complications in 59% of cases with a median margin dose of 18 Gy. Currently, the margin dose for cavernous hemangiomas in our practice does not exceed 15 Gy, even for small lesions.

There were two deaths after GKS both of which occurred in patients with brainstem lesions; however, the deaths did not seem to be related to a complication of radiosurgery. It would appear that the effect of the radiosurgery was not sufficient or fast enough and the outcome simply corresponded to the risk of the natural history of the disease. The end point when evaluating complications after radiosurgery is different compared with the 30-day morbidity after open surgery. There is a need to separate the adverse effects caused by irradiation after radiosurgery from the sequelae of the disease itself, when radiosurgery failed to ameliorate the patient’s disease, but caused no adverse effect itself. These relationships for this series are illustrated in Fig. 5 lower.

Conclusions

Gamma knife treatment of cavernous hemangiomas appears to have an acceptable morbidity rate if the prescription dose is not too high. A prescription dose of 15 Gy is proposed. After radiosurgery 45% of cavernous hemangiomas shrank and less then 2% enlarged. It is appropriate to offer GKS as a treatment option for cavernous hemangiomas.

References

Radiosurgery of cavernous hemangiomas


