Radiosurgery for cavernous malformations

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Object. The authors examined 22 patients with cavernous malformations (CMs) who had undergone gamma knife radiosurgery (GKRS) to assess the value of this procedure in treating these lesions.

Methods. At the Karolinska Hospital, GKRS was used to treat 23 patients with CMs during the period of 1985 through 1996. One of the patients was lost to follow up and the treatment results of the 22 remaining patients were analyzed. In the first half of the series, the CMs were treated with high doses of radiation (> 15-Gy dose to the periphery); in the second half of the series, lower doses were used.

Nine of the 22 patients suffered a post-GKRS hemorrhage and six developed a radiation-induced complication (two of these patients experienced both). Some time after GKRS was performed, surgical removal of the CM had to be undertaken in four patients because of hemorrhage and in two patients because of radiation-induced complications. Four of the nine patients who experienced no post-GKRS hemorrhage or radiation-induced complication were treated before 1990; recent magnetic resonance imaging revealed a decrease in the size of the CM in three of these individuals and no size change in the other.

The annual post-GKRS hemorrhage rate was 8% in this group. There was a trend in the hemorrhage rate to decrease 4 years postsurgery. There was also a trend for higher radiation doses administered to the periphery of the lesion to result in a lower risk of posttreatment hemorrhage. However, it could not be concluded whether GKRS affects the natural course of a CM. The incidence of radiation-induced complications was approximately seven times higher than that expected if the same number of patients had been treated by GKRS with the same radiation dose distributions for arteriovenous malformations instead of CMs.

Conclusions. The high incidence of radiation-induced complications does not seem to justify the limited protection the treatment may afford in only exceptional cases. A prospective randomized study is needed before the role of radiosurgery in the management of these lesions can be defined. Until such a study has proved differently, a caveat must be raised for the treatment of CM with GKRS.

KEY WORDS • cavernous malformation • hemorrhage • radiosurgery • postoperative complication

GAMMA knife radiosurgery (GKRS) has been used for the treatment of arteriovenous malformations (AVMs) since 1970; the favorable results of this procedure prompted pilot series in which GKRS was used to treat venous angiomas and cavernous malformations (CMs). We first used GKRS to treat a patient with a CM in 1985. In the first half of the present series, we used radiation doses comparable to those used in the treatment of AVMs. This resulted in a high incidence of complications, and we changed the protocol to lower radiation doses for the second half of the series.

The problem with evaluating treatment results in cases of CMs is that, unlike in AVMs, an obvious end point does not exist. The protection from hemorrhage that the treatment may provide cannot be detected by any neuroradiological method, including magnetic resonance (MR) imaging. To evaluate the potential protection against hemorrhage, the incidence of posttreatment hemorrhage must be compared with the natural course of the disease. This poses a significant problem, however, because a greater than 100-fold difference in the annual bleeding risk exists among different published analyses of the natural course of CMs. In some publications, the annual risk of hemorrhage is reported to be less than 1% (range 0.1–0.7%) and the annual risk of hemorrhage in patients with familial CMs seems to be of similar magnitude (1.1%). In other publications, the risk of hemorrhage is reported to be significantly higher and dependent on the presenting symptoms. Aiba, et al., reports an annual risk of 0.4% for patients whose CMs exhibited no previous hemorrhage and a 23% risk for those whose lesions showed a previous hemorrhage. In the same categories of patients, Kondziolka, et al., found annual risks of 0.6% and 4.5%, respectively. One possible reason for the dis-
crepancy in findings may be subclinical microhemorrhages that occur in almost all patients, as evidenced by findings on MR images.\textsuperscript{5,17,18} Moreover, occasionally sudden neurological symptoms may occur with no corresponding finding of acute hemorrhage on imaging studies. Consequently, there will be a significant difference in the estimated risk of hemorrhage, depending on whether subclinical hemorrhages or symptomatic hemorrhages that cannot be verified on imaging are included.

With the introduction of MR imaging, a technique became available to allow accurate preoperative diagnosis of CM.\textsuperscript{6,18,19} This has increased the number of diagnosed cases, resulting in an increasing demand for knowledge about the natural course of the disease as well as the results of different treatments including GKRS.

**Clinical Material and Methods**

**Patient Population**

At the Karolinska Hospital, 23 patients with CMs were treated with GKRS between 1985 and 1996. One patient was lost to follow-up review and thus was excluded from the study. In one case, the CM had been partially removed before the patient underwent GKRS; in the other cases, no previous treatment had been given. Six patients had epilepsy as the presenting symptom, whereas the other 16 had suffered at least one hemorrhage. In 12 cases an angiogram was obtained before treatment to rule out the presence of an AVM. In one of those cases, angiography revealed a venous angioma, but it was not included within the treatment volume. All patients had a Karnofsky Performance Scale\textsuperscript{11} score of at least 80 at the time of treatment. Eight CMs were located in the cerebral hemispheres, seven in the thalamus or basal ganglia, six in the mesencephalon, and one in the cerebellum.

**Radiation Dose**

In the total patient population, maximum radiation doses varied between 11 and 60 Gy with a median and mean value of 33 Gy; minimum doses varied between 9 and 35 Gy with a median and mean value of 18 Gy. Eleven patients were treated with a high and 11 with a low prescribed dose of radiation. A low dose was defined as 15 Gy or less. In 11 patients the procedure was based on a stereotactic computerized tomography (CT) scan, in nine patients it was based on an MR image, and in two patients both examinations were used. The CMs were clearly visible on both examinations. In all cases in which treatment was based on MR imaging, the CMs appeared to be surrounded by a low-signal hemosiderin rim. It is important to stress that the low-signal zone does not represent a lack of tissue. It is due to a magnetic susceptibility effect that is caused by the hemosiderin.\textsuperscript{16} This results in observer uncertainty in defining the exact periphery of the CM. The dose reduction prescribed in the second half of the series coincided with, but was not due to, the switch to using stereotactic MR instead of CT imaging.

**Posttreatment Hemorrhage and Radiation-Induced Complication**

A posttreatment hemorrhage was considered to have occurred if a patient displayed signs of clinical deterioration with CT or MR imaging evidence of a hemorrhage and no demonstration of a radiation-induced complication. A radiation-induced complication was defined as a clinical deterioration associated with radiation-induced edema or radionecrosis shown on posttreatment CT or MR images.

The incidence of posttreatment hemorrhage was compared with what could be expected from the natural course of the CM. To minimize the risk of selection bias, we used the 0.6% and 4.5% annual risks reported by Kondziolka, et al,\textsuperscript{13} because the patient population on which their report was based, like our own, was referred to a gamma knife center. Only the first posttreatment hemorrhage was
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included in this study. The risk time for the patients who bled was defined as the time between treatment and hemorrhage. For the other patients, the time at risk was defined as the time between radiosurgery and microsurgery for those who were surgically treated for radiation-induced complications. The clinical condition of each patient was determined at their latest follow-up visit, independent of whether the patient had suffered a posttreatment hemorrhage or undergone microsurgical removal of the CM.

Duration of Follow-Up Review

Follow-up review in the 11 patients who had no subsequent hemorrhage or surgery lasted from 1.3 to 11.3 years (mean 6.9 years, median 8.8 years). Follow-up review for the other patients lasted from 0.5 to 13.8 years (mean 6.1 years, median 6.6 years).

Statistical Analysis

The Mann–Whitney U-test was used for statistical analysis when a continuous parameter and a two-group parameter were compared; Fisher’s exact test was used when two-group parameters were compared. A difference was considered to be statistically significant when the probability value was less than 0.05. The 95% confidence interval (CI) is expressed parenthetically.

Results

Risk of Hemorrhage

In nine patients, posttreatment hemorrhage occurred in a total of 155 risk years, yielding an 8% annual posttreatment incidence of hemorrhage. The time distribution of the hemorrhages was compared with the time distribution of the years at risk, as illustrated in Fig. 1. After the procedure, the annual risk of hemorrhage was 10% during the first 2 years, 12% for Years 3 or 4, 5% for Years 5 or 6, and 7% for the Years 7 or 8. Within the 16 years at risk applicable to the whole patient population after the first 8 years of treatment, no hemorrhage occurred. A trend toward a lower incidence of hemorrhages could be seen after the first 4 years after GKRS. However, this trend was not significant. This is also illustrated in Fig. 2, in which the cumulative number of hemorrhages in the patients who underwent GKRS is compared with the cumulative number of hemorrhages that would be expected if the patients had not undergone any treatment.

The location of the CM was not related to the incidence of posttreatment hemorrhage. Six of the 13 CMs found in a central location (thalamus, basal ganglia, or mesencephalon) hemorrhaged after treatment compared with three of the nine CMs that were located elsewhere (p = 0.55). There was a trend in the correlation between radiation dose administered to the periphery of the lesion and the incidence of posttreatment hemorrhage, although it did not reach statistical significance (p = 0.17).

Clinical Outcome

Radiation-induced complications occurred in six patients, two of whom also suffered a hemorrhage. Permanent sequelae were seen in five of the six patients; in the sixth the symptoms resolved. The radiation-induced complications occurred between 6 and 41 months after GKRS (mean 16 months, median 12 months). The radiation dose to the periphery of the lesion was related to the incidence of these complications (p = 0.005). Five of the 13 patients in whom the CM occupied a central location developed a radiation-induced complication, whereas one of the nine patients in whom the CM was located elsewhere suffered from one (p = 0.15). The number of complications was significantly higher than would have been expected if the same patients had had AVMs treated with the same radiation dose distribution. Six complications occurred in our CM series, whereas in an AVM patient population, according to our risk estimation model, a total of 0.8 complications were predicted.

Microsurgical removal of the CM after GKRS was performed in four cases because of recurrent hemorrhage and in two cases because of radiation-induced mass effect. Thirteen of the patients in this series are presently in the same clinical condition as they were before they underwent GKRS. Posttreatment deterioration occurred in nine patients, three due to radiation-induced complications and four due to hemorrhage. Two of these patients suffered from both hemorrhage and radionecrosis.

Outcome on Follow-Up Imaging

Follow-up MR imaging examinations were performed between 0.2 and 13.4 years after treatment. In the four patients treated before January 1, 1990, in whom no posttreatment hemorrhage or radiation-induced complication occurred, the latest MR images were obtained 8.7 to 9.6 years after treatment. The MR images revealed size decreases in three CMs and no change in the fourth (Figs. 3 and 4). Epilepsy was the presenting symptom in two of the three patients in whom a CM decreased in size, whereas in the third a pretreatment hemorrhage was the presenting symptom. Hemorrhage occurred prior to GKRS in the patient in whom the CM remained unchanged on MR imaging.

Discussion

Microsurgery, when feasible with reasonable risks, is the treatment of choice for CMs. Despite the fact that CMs...
are often small and well circumscribed without any intervening brain tissue, they are not good targets for GKRS. Considering the risk/benefit ratio as it can be determined from our findings, GKRS appears to be an inappropriate treatment for CM.

**Outcome on Follow-Up Imaging**

Changes in the size of the CM after GKRS, as revealed on neuroimaging, usually are unimpressive. In the present series only four patients who did not suffer rebleeding and/or radiation-induced complications were available for long-term follow-up imaging reviews. The MR images revealed a decrease in the size of the CM in three patients and no size change in the other. The efficacy of using the GKRS for treatment of CM can be better illustrated by a case observed by Steiner and colleagues.\(^2,23\) In that case the imaging demonstrated no shrinkage of the CM over a 5-year period following GKRS; however, extensive obliteration of the CM was apparent in a specimen extirpated by microsurgery (Fig. 5). Findings in this case suggest that MR imaging may fail to display changes in the CM that occur as a result of GKRS and that some degree of obliteration may occur more frequently than is indicated by imaging. If so, the possibility that GKRS has some impact on the natural course of the disease cannot be totally excluded.

**Impact of GKRS on the Natural Course of the CM**

If the patients in the present study had been left untreated, then 0 to 37 hemorrhages would have been expected to occur, using the 0.1 to 32% annual rates for risk of hemorrhage that have been published.\(^1,3,4,12,13,19\) Consequently, it cannot be defined whether GKRS affects the natural course of CMs or not. At first glance, however, the post-treatment incidence of hemorrhage seems higher than what would be expected from the natural course of the lesion. This cannot be ascribed to the GKRS treatment. If radiation were to increase the risk of rupture, the incidence of a posttreatment hemorrhage would be expected to increase with an increased treatment dose. Findings in the present study suggest that this is not the case. In fact, the trend was for a higher dose of radiation to result in a lower risk of posttreatment hemorrhage, although this did not reach statistical significance (\(p = 0.17\)). Of the 11 patients treated with a prescribed high dose, three suffered from a posttreatment hemorrhage, whereas of the 11 patients treated with a low dose, six had a posttreatment hemorrhage. This is also what could be expected if the response to radiation is similar in CMs and AVMs. For the latter, the risk of posttreatment hemorrhage decreased and the probability of obliteration increased with an increased treatment dose.\(^7,9,10\) In the present series the risk of hemorrhage had a tendency to decrease with time after the treatment. The risk of hemorrhage was 11% (95% CI 3–19%) for the first 4 years, dropping to 6% (95% CI 0–14%) for the next 4 years.

Our findings do not support or contradict the assumption that partial protection from hemorrhage occurs 2 years after treatment.\(^12\) After a latency period of 2 years, Kondziolka, et al.,\(^12\) observed one hemorrhage in 89 risk years; in this study we observed five hemorrhages in 76 risk years after the same latency period. The difference between findings, however, is not significant (\(p = 0.1\)). The 32% incidence of hemorrhage before GKRS reported in another paper is more a reflection of the timing of the treatment than the natural course of the disease.\(^12\)

**Clinical Outcome**

Over 27% of the patients in this series later required microsurgical excision either because of hemorrhage or radiation-induced mass effect. Neurological conditions in
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41% of the patients deteriorated after they underwent treatment. In making any decisions regarding management of a CM, this high incidence of complications should be compared with any positive impact of GKRS on the natural course of the disease; this still has not been convincingly proved.

There are a number of possible flaws in this study. The most important shortcoming is the limited number of patients and the relatively short observation time. Another problem, which makes the comparison with the natural course of the lesion difficult, is the uncertainty of the risk of hemorrhage in an untreated CM. The fact that the patients in the present study may be at a significantly higher risk to hemorrhage than those in other studies cannot be excluded. If so, the comparison illustrated in Fig. 2 is of limited value. To minimize this risk, we compared our results with those from an analysis of a patient population that was referred to another gamma knife center.13

Conclusions

Gamma knife treatment in this small series of patients resulted in a high incidence of neurological sequelae caused by either radiation- and/or hemorrhage-induced damage.

The posttreatment incidence of hemorrhage was within the range of annual risk reported for untreated CMs: 0.1 to 32%.1,3,4,13,19 Hence, some trend for protection against hemorrhage cannot be verified by comparing the effects of GKRS with the natural course of the disease. A prospective randomized study would be needed to determine whether GKRS provides a limited protection, if any, against hemorrhage. Until the results of such a study can be made available, the limited protection against hemorrhage that GKRS may offer is not sufficient to accept the high risk for radiation-induced brain damage.

References