Gamma knife surgery for cavernous hemangiomas: an analysis of 125 patients

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Object. The authors sought to determine the value of gamma knife surgery (GKS) in the treatment of cavernous hemangiomas (CHs).

Methods. Between 1993 and 2002, a total of 125 patients with symptomatic CHs were treated with GKS. Ninety-seven patients presented with bleeding and 45 of these had at least two bleeding episodes. Thirteen patients presented with seizures combined with hemorrhage, and 15 patients presented with seizures alone. The mean margin dose of radiation was 12.1 Gy and the mean follow-up time was 5.4 years.

In the 112 patients who had bled the number of rebleeds after GKS was 32. These rebleeds were defined both clinically and based on magnetic resonance imaging for an annual rebleeding rate of 32 episodes/492 patient-years or 6.5%. Twenty-three of the 32 rebleeding episodes occurred within 2 years after GKS. Nine episodes occurred after 2 years; thus, the annual rebleeding rate after GKS was 10.3% for the first 2 years and 3.3% thereafter (p = 0.0038). In the 45 patients with at least two bleeding episodes before GKS, the rebleeding rate dropped from 29.2% (55 episodes/188 patient-years) before treatment to 5% (10 episodes/197 patient-years) after treatment (p < 0.0001). Among the 28 patients who presented with seizures, 15 (53%) had good outcomes (Engel Grades I and II). In this study of 125 patients, symptomatic radiation-induced complications developed in only three patients.

Conclusions. Gamma knife surgery can effectively reduce the rebleeding rate after the first symptomatic hemorrhage in patients with CH. In addition, GKS may be useful in reducing the severity of seizures in patients with CH.

KEY WORDS • gamma knife surgery • cavernous hemangioma • hemorrhage • seizure • complication

Authors reporting on the natural history of CHs describe a range of annual bleeding rates from less than 1% to higher than 20%. Intracranial CHs may behave aggressively with repetitive hemorrhage or may remain quiescent for many years. Changes that may occur with these lesions include enlargement, regression, and de novo formation. The main clinical manifestations in intracranial CHs include recurrent hemorrhages, seizures, and progressive neurological deficits. It is difficult to evaluate the outcomes of treatment by any neuroradiological method or by changes of lesion volume. Authors of most reports used more than three major parameters to evaluate the efficacy of treatment. Although microsurgical resection of symptomatic CHs is well established, there is still some controversy regarding the surgical treatment of CHs in eloquent locations. Since its introduction, stereotactic radiosurgery has been shown to obliterate cerebral AVMs with a high success rate and a low morbidity rate. Following this experience with AVMs, some authors have used radiosurgery to treat CHs but its efficacy remains in doubt.

Clinical Material and Methods

Between 1993 and 2002, 128 patients with symptomatic CHs underwent GKS. After treatment, three patients were excluded from the study. Two patients underwent microsurgical resection for their CH at other hospitals due to worsening of neurological signs, and one patient was lost to follow up. The remaining 125 patients were followed up regularly at the outpatient department. Based on clinical presentation, the 125 patients were divided into three groups. The first group consisted of 97 patients presenting with symptomatic hemorrhage (45 of these had at least two bleeding episodes before treatment). The second group con-
sisted of 13 patients presenting with seizures only, and the third group consisted of 15 patients presenting with combined hemorrhage and seizures. An example of symptomatic CH is shown in Fig. 1. The location of CHs varied: 49 patients had solitary lesions located in the brainstem, 39 were cortical/subcortical, 14 were in deep nuclei (thalamus and basal ganglion), 10 were in the cerebellum and/or the fourth ventricle, and 13 patients had multiple lesions (four of 13 had a family history of same). All 125 patients were treated within 6 months of the initial onset of symptoms. The mean lesion volume was 3.12 cm$^3$ (range 0.032–25.9 cm$^3$). The mean margin dose was 12.1 Gy (range 9–20 Gy). Every attempt was made to achieve a highly conformal dose distribution by using multiple small shots so that we could maximize the mean dose and minimize the radiation volume outside the target. After treatment, 438 MR images were obtained in the 125 patients (range one–10 images per patient). The mean clinical follow-up time was 5.4 years (range 9 months–10.2 years). Statistical comparisons were performed using the t-test and chi-square test for analysis of the seizure outcomes. A probability value of less than 0.05 was considered statistically significant.

To define the relationship between the lesion and spike sources, several patients underwent an MEG study before treatment.

**Results**

**Rebleeding Rate**

The rebleeding rate was analyzed in 112 hemorrhagic patients (97 patients in Group 1 and 15 patients in Group 3). The locations of CHs are provided in Table 1. Before GKS, the most common clinical findings were hemiparesis in 34% of patients and cranial nerve deficits in 33% (Table 2). After GKS, 32 rebleeding episodes occurred during the follow-up period. Patients were defined as experiencing a rebleeding episode if they presented with clinical symptoms of hemorrhage rate and risk factors, and the Student t-test and chi-square test for analysis of the seizure outcomes. A probability value of less than 0.05 was considered statistically significant.

To define the relationship between the lesion and spike sources, several patients underwent an MEG study before treatment.

**TABLE 1**

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Patients</th>
<th>No. of Rebleeding Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>brainstem</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>basal ganglion/thalamus</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>cortical/subcortical</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>cerebellum/4th ventricle</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>multiple lesions</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>total</td>
<td>112</td>
<td>32</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache &amp; dizziness</td>
<td>34</td>
</tr>
<tr>
<td>cranial nerve deficits</td>
<td>35</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>43</td>
</tr>
<tr>
<td>hemisensory deficit</td>
<td>24</td>
</tr>
<tr>
<td>consciousness change</td>
<td>4</td>
</tr>
<tr>
<td>cerebellar signs</td>
<td>13</td>
</tr>
<tr>
<td>seizure attack</td>
<td>13</td>
</tr>
</tbody>
</table>

**Fig. 1.** A series of MR images obtained in a 30-year-old woman who experienced seizures and hemorrhage from a mesial temporal CH. The patient was treated with GKS (margin dose 13 Gy, 50% isodose at the lesion margin). Before GKS, T$_1$- and T$_2$-weighted MR images revealing subacute hemorrhage (left). Magnetic resonance images at 12 months (center) and 32 months (right) after GKS, revealing marked shrinkage of the lesion. The patient became seizure free.
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TABLE 3
Location of CH in 28 patients who presented with seizures

<table>
<thead>
<tr>
<th>Location</th>
<th>No. w/ Combined Hemorrhage</th>
<th>No. w/ Sporadic Seizure (≤6 mos) Pre-GKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>temporal</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>parietal</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>frontal</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>corona radiata</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>insula</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

and only one in cerebellum (Table 1). The total follow-up time was 492 patient-years, and the annual rebleeding rate was 6.5% (32 episodes/492 patient-years). The 2-year cut-off point was also used for further analysis. A total of 23 rebleeding episodes were reported within the 2 years after GKS, with a rebleeding rate of 10.3% (23 episodes/224 patient-years). After 2 years, only nine rebleeding episodes were reported, producing a rebleeding rate of 3.3% (nine episodes/268 patient-years). This drop in the rebleeding rate from 10.3% within 2 years to 3.3% beyond 2 years is significant (p = 0.0038). Among the 45 patients who sustained at least two bleeding episodes prior to GKS, there were 55 rebleeding episodes reported before treatment, and the follow-up time was 188 patient-years from the time of first symptomatic bleeding to the time of GKS. The rebleeding rate was 55 episodes per 188 patient-years before treatment or 29.2%. After GKS, the rebleeding rate significantly dropped from 10.3% within 2 years to 3.3% beyond 2 years (nine episodes/268 patient-years). This drop in the rebleeding rate from 10.3% within 2 years to 3.3% beyond 2 years is significant (p = 0.0038). Among the 45 patients who sustained at least two bleeding episodes prior to GKS, there were 55 rebleeding episodes reported before treatment, and the follow-up time was 188 patient-years from the time of first symptomatic bleeding to the time of GKS. The rebleeding rate was 55 episodes per 188 patient-years before treatment or 29.2%. After GKS, the rebleeding rate significantly dropped from 10 episodes per 197 patient-years (5%) (p < 0.0001).

Among the patients in this study with symptomatic hemorrhages, 45 had CHs located in the brainstem, 10 had CHs located in the deep nucleus, and 13 had multiple lesions. The relationship between location and rebleeding rate almost reached statistical significance (p = 0.051). In this study, six patients had CHs associated with a venous anomaly (demonstrated by MR imaging). Although only the lesion part was treated and the venous part was spared rebleeding episodes still occurred in five patients.

Seizure Outcomes

A total of 28 patients presented with seizures. Of these 28 patients, 13 presented with seizures alone and the remaining 15 presented with seizures and hemorrhage. The locations of CHs in these patients are provided in Table 3. The patients were classified into two groups, sporadic seizure and chronic epilepsy. Patients in the sporadic seizure group reported a seizure history of no more than 6 months before GKS (11 patients). The remaining 17 patients reported a seizure history of more than 6 months and they were defined as having chronic epilepsy. The Engel classification for evaluating the seizure outcome was used. Engel Grades I and II were defined as good outcomes. After GKS, 11 (39%) were seizure free (Engel I) and four (14%) reported only rare seizures (Engel II). Overall, 53% of patients reported having good control of their seizures (Table 4). The achievement of a good result with sporadic seizures was 10 (91%) of 11 patients compared with four (24%) of 17 in the chronic group (p = 0.001) (Table 5). Other prognostic factors such as age, lesion site, presence of combined hemorrhage, mean margin dose, and maximum dose were not associated with the seizure outcomes.

An epileptogenic focus on MEG was successfully detected in only one patient (Fig. 2). In this patient with epileptogenic foci detected on MEG, we treated not only the lesion but also the spike sources detected; this patient became seizure free. The existence of distinct spike sources makes the delineation more difficult in treating CHs in patients with seizures.

Complications

After GKS, AREs developed in 17 (13.1%) patients; however, these were symptomatic in only three (2.5%) patients. The true complication rate of clinically significant complications was 2.5%. The only parameter to have a statistically significant relationship to the development of AREs was the maximum dose (p = 0.005). Other complications included cyst formation (one patient) and hydrocephalus (five patients). In addition to these complications, 12 patients had permanent neurological deficits, all of which were induced by rebleeding episodes.

Discussion

Rebleeding Rate

The rebleeding rate of untreated CHs has been reported by Aiba, et al.,2 to be a 23% annual risk for patients who had experienced a previous hemorrhage. In another prospective study, however, Kondziolka, et al.,14 reported the annual risk was only 4.5%. The large variation in the reports of rebleeding rates is probably caused by differences in patient selection, definition of bleeding episodes, follow-up time, mode of lesion diagnosis, and variation in the frequency of image follow up. In this study, a rebleeding episode was defined as any new or worsening neurological deficit accompanied by MR imaging–verified new hemorrhage. Based on that definition, the post-GKS annual rebleeding rate in this study was 6.5% (32 episodes/492 patient-years). There are sever-

TABLE 5
Analysis of outcomes in patients with sporadic or chronic seizures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>sporadic seizures (≤6 mos pre-GKS)</td>
<td>11</td>
</tr>
<tr>
<td>good (Engel I &amp; II)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>poor (Engel III &amp; IV)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>chronic epilepsy (&gt; 6 mos pre-GKS)</td>
<td>17</td>
</tr>
<tr>
<td>good (Engel I &amp; II)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>poor (Engel III &amp; IV)</td>
<td>13 (76)</td>
</tr>
</tbody>
</table>

J. Neurosurg. / Volume 102 / January, 2005
Factors that increase the risk of experiencing a rebleeding episode. The first is the location of the CH. Some authors reported that patients with CHs located in infratentorial area or brainstem had a higher rebleeding rate.\(^8,25,27,28\) The location of lesions that rebled in this series supports this notion. Other than location, it is conceivable that CHs associated with a venous anomaly present a higher risk of hemorrhage than do CHs alone.\(^1,18,28\) The findings of this current series are also in agreement with this notion. Additionally, patients with a family history or with multiple lesions also had a higher rebleeding rate.\(^19,28,35\) A major contribution to the total rebleeding rate in this series was made by three patients who experienced nine rebleeding episodes between them. One of these patients had a CH in the midbrain that was associated with a venous anomaly (Fig. 3). The second patient had a CH in the thalamus. The third patient had multiple lesions, and the lesion with repetitive bleeding was located in pons. Nonetheless, the study demonstrated a significant reduction in the rebleeding rate after GKS, with a mean follow up of 5.4 years. Our results are similar to reports in the literature in which a useful effect of GKS in CH is found. Kondziolka, et al.,\(^15\) observed a rebleeding rate of 32% in 47 patients before GKS. After GKS, the rebleeding rate dropped to 8.8% within the first 2 years and 1.1% from 2 to 6 years. Amin-Hanjani, et al.,\(^3\) reported a decrease in the rebleeding rate in 73 lesions from 17.3% per lesion per year before proton beam treatment to 10.4% after treatment. These results suggest that GKS can reduce the rebleeding rate and thus the danger of CH.

Seizure Outcome

The correlation between epilepsy and CHs has been widely reported in the literature.\(^4,8,13,14\) The epileptogenicity of these lesions resulted from the ongoing deposition of iron and blood products at the margin of the lesion.\(^11,21\) Several
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articles on the management of CHs associated with seizures have been published, and the general consensus is that microsurgical resection of the lesion is the best treatment. More recently, several authors have used GKS to treat epilepsy patients with CHs safely and effectively. Gamma knife surgery has been established as an alternative treatment option for patients with CHs in eloquent and inaccessible areas. Régis, et al. reported the results of GKS in 40 patients with epilepsy associated with CHs and demonstrated that 53% (26 of 49) of patients were seizure free and 20% (10 of 49) of patients were significantly improved. A good result (Engel Grades I and II) was obtained in 73% of patients reported by Régis, et al. In the current study, good results (Engel Grades I and II) were achieved in 53% of patients. The duration of seizure history before treatment was the only parameter to show an association with the effect of treatment on the seizures. The results of this study are similar to the results of several epilepsy surgery studies, in which it was reported that patients with shorter seizure histories and fewer preoperative seizures could be more effectively treated by lesionectomy alone. In this study, most patients in the sporadic seizure group reported epilepsy combined with bleeding episodes before treatment. We hypothesize that preventing the risk of rebleeding and decreasing the deposition of blood products may play a role in the improved seizure control. Under the secondary epileptogenicity theory, in patients with a longer seizure history, the primary active epileptogenic foci may lead to cortical loci of seizure onset that are anatomically distinct from the primary lesion. Based on this theory, some authors suggest that a wider extent of resection might be necessary in such cases.

Complication and Radiation Dose

To reduce the incidence of radiation-induced complications, most authors use a lower margin dose for treating CHs than for treating AVMs. Nonetheless, the optimal radiosurgery dose for treating CHs is still unknown. In this study, most CHs were deep seated or located in eloquent regions; therefore, our mean margin dose was lower than that reported by other groups. Our mean dose to the margin was 12.1 Gy. In addition the treatments were very conformal. It is suggested that only ARE-induced neurological deficits can truly reflect the complications of GKS. The low margin dose and maximal conformity was aimed at reducing these effects. On analysis the only factor associated with a risk of AREs was the maximum dose. All other complications observed in this series—permanent neurological deficits in 12 patients and hydrocephalus in five patients—were secondary to the natural course of the lesions or to the hemorrhagic episodes.

Conclusions

In this study, GKS was used to treat patients with symptomatic CHs, with a mean follow up of 5.4 years. The rebleeding rate appeared to be reduced after GKS. The seizure frequency also improved after GKS in patients with a short duration of CH-induced epilepsy. Gamma knife surgery seems to have a useful role to play in the management of selected patients with CHs.

References:

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