Outcome after hemorrhage following Gamma Knife surgery for cerebral arteriovenous malformations

Clinical article

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Object. Although the effects of Gamma Knife surgery (GKS) on the risk of hemorrhage are poorly understood, a certain subset of patients does suffer bleeding after GKS. This study was undertaken to analyze the outcome of patients sustaining hemorrhage after GKS; it is the most feared complication of radiosurgical management of cerebral arteriovenous malformations (AVMs).

Methods. Between May 1997 and June 2006, 494 cerebral AVMs in 489 patients were treated using a Leksell Gamma Knife Model B, and follow-up evaluations were conducted until June 2007 at the All India Institute of Medical Sciences in New Delhi. Fourteen patients who sustained a hemorrhage after GKS formed the study group. In most of these patients conservative management was chosen.

Results. The mortality rate was 0% and there was a 7% risk of sustaining a severe deficit following rebleeding after GKS. None of the patients sustained rebleeding after complete obliteration. Patients with Spetzler-Martin Grade III or less had increased chances of hemorrhage after GKS (p < 0.002). The presence of deep venous drainage, aneurysm, venous hypertension, or periventricular location on angiography was common in patients with hemorrhage after GKS.

Conclusions. The risk of hemorrhage that remains following GKS for cerebral AVMs is highest in the 1st year after treatment. The present study showed a relatively good outcome even in cases with hemorrhage following GKS, with no deaths and minimal morbidity, further substantiating the safety and efficacy of the procedure.

Key Words • arteriovenous malformation • hemorrhage • outcome • stereotactic radiosurgery

Intracranial AVMs form one of the most common causes of intracerebral hemorrhage in young adults and are responsible for significant incidences of morbidity and death. The management philosophy revolves around averting this risk of hemorrhage. Microsurgery, radiosurgery, and embolization are the various modalities available to treat these lesions. Although rehemorrhage remains the most feared complication during the latency period of obliteration following GKS, compared with microsurgery and embolization, which obviates the risk of hemorrhage immediately following treatment, very few studies have actually reported outcome and management following rebleeding after GKS. We have analyzed the outcome in our series of radiosurgically treated AVMs in patients who sustained an intracranial hemorrhage following GKS; an important factor that can affect management decisions in intracranial AVMs.

Methods

Between May 1997 and June 2006, 494 cerebral AVMs in 489 patients were treated using a Leksell Gamma Knife Model B (Elekta Instruments AB), and follow-up evaluations were conducted until June 2007 at the All India Institute of Medical Sciences in New Delhi. Gamma Knife treatment was offered to patients with the following types of lesions: an AVM in an eloquent area; a deep-seated AVM; residual AVM after surgery, embolization, or conventional radiotherapy; a large AVM.

Abbreviations used in this paper: AVM = arteriovenous malformation; GKS = Gamma Knife surgery.
not suitable for any other modality of treatment; patient’s preference; and residual AVM after failed radiosurgery. Treatment was performed using a 201-source $^{60}$Co Gamma Knife unit.

Treatment was performed using standard radiosurgical techniques. The stereotactic frame was fixed to the patient’s head after local anesthesia was induced (general anesthesia was used in children < 8 years of age or in uncooperative patients) and the position of the frame was adjusted on the head to bring the AVM nidus as close to the center of the frame as possible. All the patients underwent angiography along with MR imaging of the brain for stereotactic localization of the AVM. The software used for dose planning was Leksell Gamma Plan (Elekta Instruments, Inc.). The dose applied to the margin in the majority of cases was 25 Gy (using 50% isodose lines). Lower doses were given for lesions located in critical areas like the basal ganglia/thalamus and for large-volume AVMs.

Patients were evaluated clinically every 6 months after the treatment. The MR imaging and/or CT scanning in the follow-up period was done only in symptomatic patients (those with new neurological deficits after GKS, worsening of previous deficits, headache, suspected re-bleeding, and so on) and for evaluation of response to treatment in patients with radiation edema. Hemorrhage was defined as a clinically symptomatic event such as sudden headache, seizure, focal deficits, death, or a combination of these, along with signs of fresh bleeding from the previously diagnosed AVM detected using MR imaging or CT studies. Follow-up angiography was performed at 2 years after GKS (some patients were advised to have an angiography study done earlier than 2 years in the initial phase of the treatment or if MR imaging findings suggested complete obliteration), and yearly thereafter in the presence of residual AVM, until 4 years posttreatment. The presence of a residual AVM on an angiogram even after 4 years post-GKS was considered to be radiosurgical failure, and a second treatment (either radiosurgical or embolic) was performed depending on residual AVM characteristics. Total angiographic obliteration was defined as the absence of abnormal vessels in the former nidus, or the disappearance or normalization of draining veins from the area. For all patients who did not show up for follow-up evaluation, we tried to contact them by mail or phone if possible and to update the data in the database. Data for patients with incomplete angiographic follow-up were censored back to their last follow-up evaluation.

**Statistical Analysis**

Statistical analysis was performed using STATA 9.0 (StataCorp LP). Data are presented as the number (with the percentage in parentheses) and median (with the range in parentheses) as appropriate. The differences in proportions were compared using the chi-square test. The Kaplan-Meier method was used to calculate the probability of hemorrhage-free survival. A probability value < 0.05 was considered statistically significant.

**Results**

The clinical characteristics of the 14 patients who sustained hemorrhage as well as the overall group are depicted in Table 1. The details of the patients sustaining a postradiosurgical hemorrhage are shown in Table 2. Follow-up angiography was performed at regular intervals to document complete obliteration. Total follow-up ranged from 6 to 121 months. Fourteen AVMs (2.8%) bled following GKS during the latency time in the analyzed period. None of the patients suffered a hemorrhage after angiography demonstrated complete AVM obliteration. The 14 patients who sustained postradiosurgical hemorrhage formed the study group, and the angioarchitecture, treatment parameters, disease management, and outcome in these individuals were evaluated in detail. Except for 2 patients who presented with an intraventricular hemorrhage the rest all had suffered an intracerebral hemorrhage. Due to their relatively well-preserved neurological status, in most of these patients the AVMs were managed conservatively to treat symptoms of raised intracranial pressure.

**TABLE 1: Clinical and treatment parameters in patients who sustained hemorrhage after GKS compared with the overall group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Group Treated w/ GKS</th>
<th>Patients w/ Hemorrhage Post-GKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>494*</td>
<td>14 of 494 (2.8%)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>3–72 (mean 27)</td>
<td>8–57 (mean 26)</td>
</tr>
<tr>
<td>M/F</td>
<td>342:152*</td>
<td>12:2</td>
</tr>
<tr>
<td>no. w/ hemorrhagic present (%)</td>
<td>332 of 494 (67)</td>
<td>9 of 14 (64)</td>
</tr>
<tr>
<td>no. w/ AVM location (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lobar</td>
<td>315 (64)</td>
<td>8 of 14 (57)</td>
</tr>
<tr>
<td>deep</td>
<td>179 (36)</td>
<td>6 of 14 (43)</td>
</tr>
<tr>
<td>nidus vol (cm$^3$)</td>
<td>0.0021–37.5 (mean 4.117)</td>
<td>0.66–36.6 (mean 9.8)</td>
</tr>
<tr>
<td>marginal dose (Gy)</td>
<td>5–27 (mean 24.46)</td>
<td>18–26 (mean 24)</td>
</tr>
<tr>
<td>interval btwn GKS &amp; hemorrhage (mos)</td>
<td>not applicable</td>
<td>1–80 (median 16)</td>
</tr>
</tbody>
</table>

* Five patients (4 males and 1 female) had 2 nidi each. Total nidi (494) were considered for statistical purposes.
Outcome after hemorrhage following Gamma Knife surgery

TABLE 2: Characteristics of 14 patients who suffered post-GKS hemorrhages*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Nidus Vol (cm³)</th>
<th>Dose (Gy)</th>
<th>Iso-dose Line†</th>
<th>Prior Hemorrhage</th>
<th>Periventricular Location</th>
<th>Associated Aneurysm (arterial/venous)</th>
<th>Venous Hypertension</th>
<th>Venous Drainage</th>
<th>SM Grade</th>
<th>Time of Hemorrhage Post-GKS (mos)</th>
<th>New Deficit</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35, M</td>
<td>5.9</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep III</td>
<td>16</td>
<td>rt hemiplegia</td>
<td>evacuation</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8, M</td>
<td>2.2</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep III</td>
<td>80</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22, M</td>
<td>5.1</td>
<td>25</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>super I</td>
<td>6</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>29, M</td>
<td>3.6</td>
<td>25</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>deep II</td>
<td>1</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>20, F</td>
<td>11.1</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>deep IV</td>
<td>22</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>25, M</td>
<td>9.1</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep III</td>
<td>12</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20, M</td>
<td>36.6</td>
<td>18</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep IV</td>
<td>36</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>18, M</td>
<td>13.3</td>
<td>24</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep IV</td>
<td>2</td>
<td>rt hemiparesis (power 4/5)</td>
<td>conservative</td>
<td>mild deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>46, F</td>
<td>0.66</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>deep III</td>
<td>6</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>15, M</td>
<td>0.93</td>
<td>25</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>deep III</td>
<td>24</td>
<td>severe pain on rt side of body, which resolved</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>20, M</td>
<td>6.2</td>
<td>25</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>deep IV</td>
<td>30</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>57, M</td>
<td>5.8</td>
<td>25</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>deep III</td>
<td>12</td>
<td>It hemiparesis post-bleed, which resolved to normal in 1 mo</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>28, M</td>
<td>6.3</td>
<td>20</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>deep III</td>
<td>1</td>
<td>none</td>
<td>conservative</td>
<td>status quo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>23, M</td>
<td>31.6</td>
<td>26</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>super II</td>
<td>7</td>
<td>It hemiplegia (power 0/5)</td>
<td>removal of bone flap</td>
<td>severe deficit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Vac = evacuation; SM = Spetzler-Martin; super = superficial.
† Values represent the percentage of the AVM receiving the 50% isodose line.

Two patients required surgery; evacuation of the hematoma was done in one and a decompressive craniectomy was performed in the other; the bone flap was eventually replaced after the resolution of raised pressure symptoms in the patient who underwent bone flap removal. There were no deaths in patients who suffered a hemorrhage after GKS. None of the patients bled more than once after GKS. The distribution of hemorrhage-free survival after GKS is shown in the Kaplan-Meier plot (Fig. 1); the probability of sustaining a hemorrhage was maximum in the 1st year after GKS.

Eight patients had their AVM obliterated after various intervals after the first GKS despite the rebleeding, and were symptom free at their last follow-up (Fig. 2). Two patients who suffered hemorrhages post-GKS underwent repeat radiosurgery due to persistent nidus even > 4
years after the first GKS treatment (Fig. 3); one of them had total obliteration of the nidus by 2 years after the second radiosurgical treatment, whereas the second patient was lost to follow-up after the repeat radiosurgical procedure. The rest of the 4 patients were neurologically stable and were awaiting angiography for assessment of the status of AVM.

Following rebleeding, the neurological status remained unchanged in majority of the patients (12 of 14), whereas it deteriorated, with persistence of mild deficit and severe deficit in 2 of 14 patients. Statistical analysis was performed to analyze the association between age, sex, history of hemorrhage before GKS, Spetzler-Martin grade, marginal dose, prior embolization before GKS, and AVM nidus volume, with potential relationship to increased chances of rebleeding after GKS, especially during the latency period. Only a Spetzler-Martin grade of III or less was significantly related to increased chances of hemorrhage after GKS (p < 0.002, Table 3). The presence of deep venous drainage (85%) or 1 of the following 3 risk factors (aneurysm [arterial/venous], venous hypertension, or periventricular location [92%]) was seen more commonly, being present more frequently in patients with hemorrhage.

### Discussion

Radiosurgery offers a minimally invasive treatment for cerebral AVMs, the efficacy of which is well established in various reported studies.\(^6,9,19,22,30\) The natural history of cerebral AVMs represents a risk of rebleeding varying from 2 to 4%, with a 1% risk of death and a 2.7% combined risk of major morbidity and death annually.\(^2,5,13,15,26\) Patients remain at risk for rebleeding during the delay between treatment and complete obliteration, which is reported to be between 1 and 3 years after the treatment, with a hemorrhage rate varying from 3.4 to 10%;\(^6,10,14,16,19,27\) the rate was 2.7% in our study.

Hemorrhage during the latency period is more common compared with rebleeding after complete angiographic obliteration, which nevertheless is being reported recently as data from longer follow-up periods after GKS are available.\(^22,23,29\) Mortality rates following hemorrhage after radiosurgery have been reported to vary from 20 to 40% in various studies.\(^4,7,20,23,28\) We, however, encountered relatively good outcome, with no deaths and only a 7% chance of sustaining a severe deficit; a figure quite less than in other studies.\(^4,7,20,23,28\) Risk factors have been identified that predispose a patient to rebleeding after GKS, namely, angiographic factors like venous ectasia/stenosis/hypertension, the presence of intranidal aneurysm or periventricular location, lower marginal dose, large volume of the nidus, dose given to the nidus, and prior hemorrhage.\(^7,10,14,17,27\) Individual analysis in our study did reveal an association between the presence of one of the
angiographic factors mentioned above and rebleeding in almost all patients (12 of 14). Male sex, the presence of deep venous drainage, prior hemorrhage, and volume < 10 cm³ were also more common in patients with rebleeding after GKS. These are the same factors that are associated with increased chances of hemorrhagic presentation as reported in various studies, and the persistence of increased chances of rebleeding in these groups of patients may just reflect the progression of the natural history of the disease even after radiosurgery, especially in the initial period following GKS.\(^1,5,8,12,13,21,25,26,31\) Increased risk of hemorrhage in patients with lower nidus volume (< 10 cm³) is contradictory to other reported studies, which found increased chances of rebleeding with larger AVMs.

We observed that the hemorrhage risk remained until the complete obliteration of the nidus, with the maximum number of hemorrhages (58%) occurring in the 1st year after GKS.

Analysis of factors reported in various studies as well as in our series can provide insight about risk factors for bleeding after GKS and can lead to changes in treatment strategies such as use of adjunctive therapy in the form of targeted embolization, appropriate dose selection, and consideration of microsurgery in patients at high risk of postradiosurgical hemorrhage to decrease chances of hemorrhage during the latency period. Once it has occurred, the management of hemorrhage from an AVM after GKS should follow the same principles as with un-
treated ruptured AVMs, based on the lesion’s location and the clinical status of the patient. In a significant number of patients, the AVM will tend to get obliterated if the hemorrhage is too early after GKS, in which case angiographic follow-up after either hematoma evacuation or conservative management should be the best treatment option, as reported in the present study and by Maruyama et al.23 If the AVM persists for 4 or 5 years after the first GKS, hematoma evacuation if required and resection of the AVM if possible or repeat GKS is a feasible treatment. We had no experience with management of hemorrhage after complete obliteration because none of the AVMs in our cases bled after complete obliteration. However, we have started doing angiograms in patients with total obliteration, especially in children, to detect rare cases of recanalization of the AVM as reported in recent studies.

Conclusions

Hemorrhage, with its attendant risks of morbidity and death, forms the major reason for treating AVMs. With a period of latency until complete obliteration following GKS, the patient remains at risk for rebleeding, which can be fatal or can result in significant morbidity. Our study, however, shows that not only do very few patients experience rebleeding in the latency period, but the outcome in this subgroup of patients is good, with no deaths and minimal morbidity, an important parameter that does have therapeutic implications.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

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