Management and outcome of hemorrhage after Gamma Knife surgery for arteriovenous malformations of the brain

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Object. Appropriate management of hemorrhage after Gamma Knife surgery (GKS) for arteriovenous malformations (AVMs) of the brain is poorly understood, although a certain proportion of patients suffer from hemorrhage.

Methods. Among 500 patients observed for 1 to 183 months (median 70 months) after GKS, 32 patients (6.4%) suffered a hemorrhage. Hemorrhage developed even after angiographically documented obliteration of the AVM in five (2%) of 250 patients followed for 1 to 133 months (median 75 months) post-GKS. These patients had been treated according to their pathological condition. Treatment of these patients and their outcomes were retrospectively reviewed. As a management strategy in patients with preobliteration hemorrhage, the intracerebral hematoma and the AVM nidus were removed in four patients, and chronic encapsulated hematoma was removed in three. Among 11 patients who were conservatively treated, AVMs were ultimately obliterated in five, including three patients who underwent repeated GKS. Intracerebral hematoma from angiographically documented obliterated AVMs was radically resected in two patients, including one who also underwent aspiration of an accompanying symptomatic cyst. Intraoperative bleeding was easily controlled in these patients. Outcomes after hemorrhage, measured with the modified Rankin Scale, were significantly better in patients with postobliteration hemorrhage than in those with preobliteration hemorrhage (p < 0.05).

Conclusions. Various types of hemorrhagic complications after GKS for AVMs can be properly managed based on an understanding of each pathological condition. Although a small risk of bleeding remains after angiographically demonstrated obliteration, surgery for such AVMs is safe, and the patient outcomes are more favorable. Radical resection to prevent further hemorrhage is recommended for ruptured AVMs after obliteration because such AVMs can cause repeated hemorrhages.

KEY WORDS • arteriovenous malformation • Gamma Knife surgery • hemorrhage • obliteration • outcome

ARTERIOVENOUS malformations of the brain are one of the cerebrovascular diseases predominantly observed in young people and hemorrhage from them can cause death or severe disabilities. The annual hemorrhage rate of AVMs is reported to be 2 to 4%. Microsurgical resection, stereotactic radiosurgery, and endovascular embolization, alone or in combination, are the treatment options currently available for these lesions. Among them, stereotactic radiosurgery, including GKS, has been widely performed during the last two decades as a minimally invasive treatment, and its safety and efficacy have been well documented. If an AVM can be totally resected, the risk of hemorrhage will be eliminated. Patients treated with radiosurgery must wait a few years from the time of treatment until obliteration can be confirmed with angiography. The risk of bleeding remains in 1.8 to 5% of patients per year during this period, which is one of the major drawbacks of radiosurgery compared with successful microsurgery. Although a certain number of patients suffer from hemorrhagic complications after radiosurgery, a strategy to treat them has not been discussed. Therefore, there is an immediate need to establish a legitimate approach to systematically manage these lesions. To address this issue, we retrospectively analyzed data in patients with hemorrhage after GKS for AVMs treated in our institute, both before and after angiographically documented obliteration, and we discuss our management recommendations for them.

Clinical Material and Methods

During the 14-year period between July, 1990, and June, 2003, 531 consecutive patients with AVMs of the brain were treated with a 201-source Co Gamma Knife
Managing hemorrhage after GKS for arteriovenous malformations

### TABLE 1
Clinical characteristics of 27 patients with hemorrhage after GKS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hemorrhage Preobliteration</th>
<th>Hemorrhage Postobliteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>patient age at hemorrhage (yrs)</td>
<td>11–65 (median 37 yrs)</td>
<td>25–44 (median 37 yrs)</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>19:8</td>
<td>1:4</td>
</tr>
<tr>
<td>prior hemorrhages (%)</td>
<td>16 (59%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>AVM location (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebral hemisphere</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>basal ganglia and thalamus</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>cerebellum</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>brainstem</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>AVM vol at GKS (cm³)</td>
<td>0.1–12.7 (median 2.6)</td>
<td>0.6–8.8 (median 2.0)</td>
</tr>
<tr>
<td>Spetzler–Martin grade (no. of patients)</td>
<td>I/II/III</td>
<td>I/VII/XIII</td>
</tr>
<tr>
<td></td>
<td>IV/V/VI</td>
<td>I/III/0</td>
</tr>
<tr>
<td>margin dose (Gy)</td>
<td>10–25 (median 20)</td>
<td>19–25 (median 20)</td>
</tr>
<tr>
<td>interval between GKS &amp; hemorrhage (mos)</td>
<td>1–111 (median 13)</td>
<td>50–153 (median 65)</td>
</tr>
</tbody>
</table>

(Elekta Instruments, Norcross, GA) at the University of Tokyo Hospital. Of these, 500 patients were observed for 1 to 183 months (median 70 months) after treatment. Patients were evaluated clinically every 6 months after GKS, during the periods both before and after the subsequent hemorrhage. Hemorrhages from treated AVMs before angiographically documented obliteration were observed in 27 patients (5.4%). Obliteration was defined as angiographically demonstrated complete disappearance of pathological vessels including the nidus of the AVM, the draining veins, and the early venous filling phase.\(^{11}\) Two hundred fifty patients were followed for 1 to 133 months (median 75 months) after AVM obliteration. Hemorrhage was observed in five (2%) of 250 patients.\(^{14,21}\) Repeated angiography was performed after hemorrhage in all five patients, and did not reveal de novo nidi or recanalization of obliterated AVMs. No patient suffered hemorrhage both before and after obliteration of the AVM.

These 27 patients with preoblation hemorrhage and five patients with postobliteration hemorrhage were included in this study. The median interval between GKS and hemorrhage in all 32 patients was 16 months. The interval between AVM obliteration and hemorrhage was 16 to 84 months (median 39 months) in those with postobliteration hemorrhage.

We reviewed the types of management used in our patients, and their outcomes were measured using the mRS\(^\text{24}\) before and after hemorrhage. A score of 6 was given for a death. Outcome was defined as severely deteriorated when the decline of the mRS score after hemorrhage, which was assessed more than 6 months after the last bleeding, was two or more points when compared with that before hemorrhage.

### Results

The actuarial hemorrhage rate from the time of GKS to obliteration was 8.4 and 15% at 5 and 10 years, respectively (Fig. 1). The hemorrhage rate after obliteration was 2.5 and 3.5% at 5 and 10 years, respectively.

### Management of Preobliteration Hemorrhage

Clinical presentations of 27 patients with preobliteration hemorrhage were acute ICH in 20 patients, chronic encapsulated ICH in three, subarachnoid hemorrhage in two, and intraventricular hemorrhage in two. Eight of these patients underwent surgical treatment (Table 2). Four patients underwent evacuation of acute ICH and resection of the ruptured AVM nidus. Despite prompt surgical intervention, one patient died of severe damage in the brainstem caused by initial massive hemorrhage in the cerebellum. All three patients with chronic encapsulated ICH underwent surgical removal of the ICH and a degenerated AVM nidus, as previously described (Fig. 2).\(^{10}\) One patient with acute hydrocephalus caused by intraventricular hemorrhage was treated with ventricular drainage. None of those eight patients had any surgery-related complications.

Nineteen patients were treated without surgical intervention. Repeated GKS was performed in three of them because angiograms obtained more than 3 years after initial GKS disclosed residual nidi. Eight patients were followed up with observation only because of the

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**Fig. 1.** Graph showing Kaplan–Meier curves of hemorrhage rates following GKS for obliterated and nonobliterated AVMs.
TABLE 2
Types of treatment strategies used in 32 patients

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>No. of Patients</th>
<th>Hemorrhage</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>evacuation of acute ICH</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>removal of chronic encapsulated ICH</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventricular drainage</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>repeated GKS</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>conservative treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>continuous follow up</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>follow up ended w/ fatal hemorrhage</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

comparatively short interval between GKS and hemorrhage and because of the benign nature of their hemorrhages, and all treatment options were abandoned. In the 11 patients who were treated with repeated GKS or continuously followed up after hemorrhage, AVMs were finally obliterated in five patients (45%). The actuarial obliteration rate for these 11 patients, calculated by the Kaplan–Meier method, was 58% at 5 years.

Management of Hemorrhage From Obliterated AVMs

All five patients who experienced a postobliteration hemorrhage presented with acute intracerebral hemorrhage. The ICH in four of five patients was less than 3 cm in maximum diameter on neuroimaging studies.

One patient underwent radical resection of the obliterated AVM to eliminate any further risk of hemorrhage. The other three patients suffered intracerebral hemorrhage from deep-seated AVMs (Fig. 3). The possibility of radical surgery was discussed as one of the treatment options to prevent further hemorrhage; however, the risk of serious neurological deterioration after surgery was of paramount concern so conservative management was selected. During the follow-up period after the hemorrhage, one patient was found to have delayed cyst formation adjacent to the hematoma cavity; however, the cyst spontaneously regressed over time. The remaining patient was also found to have delayed cyst formation; this cyst progressively enlarged and aggravated her neurological symptoms. Thus, resection of the obliterated AVM nidus with evacuation of the enlarging cyst was performed. In the two patients who underwent surgery, bleeding from the nidus was easily controlled, compared with those in whom the AVM nidus had not been obliterated.

Outcomes After Hemorrhage

The mRS scores before hemorrhage ranged from 0 to 4 (median 1), and the scores after hemorrhage ranged from 0 to 6 (median 3). Compared with the scores before hemorrhage, the scores after hemorrhage were unchanged in six patients, declined by 1 point in nine, by 2 in four patients, and more than 2 points in 13 patients.

Patient age at the time of hemorrhage, history of hemorrhage, AVM volume, Spetzler–Martin grade,23 margin
dose at GKS, and the absence of AVM obliteration were included in the analysis of factors potentially related to outcome after hemorrhage. Among these factors, only the absence of AVM obliteration was significantly related to severely deteriorated outcome (p < 0.05; Table 3).

**Discussion**

**Management of Preobliteration Hemorrhage**

There are various management options for AVMs ruptured after GKS, such as removal of acute or chronic ICH with or without simultaneous excision of the nidus, repeated GKS, and conservative treatment. In AVMs ruptured before obliteration, the nature of the hemorrhage was almost equivalent to that of untreated AVMs; the characteristics of chronic encapsulated ICH were completely different. Based on our experience, the pathological findings revealed repetitive bleeding from a degenerated nidus with accumulation of exudate. Surgical removal is the most effective and reliable method to eliminate the risk of further hemorrhage, whether progression of the hematoma is rapid or slow. Generally, GKS is performed to treat AVMs in surgically inaccessible areas; direct surgical intervention for those lesions is often difficult.

To reduce any further risk of hemorrhage and minimize treatment-related complications, we recommend our strategy, in which the pathological condition of each hemorrhage is considered. Following this strategy helps us manage these hemorrhages. Our recommendations for hemorrhage from AVM after GKS are as follows.

1. For acute massive intracerebral hemorrhage, the treatment approach should be the same as that for an untreated ruptured AVM. If the ruptured AVM nidus is surgically accessible, the first choice is surgical removal of the hematoma and the AVM nidus. When the AVM is located in an eloquent area and the risk of surgery-related morbidity is unacceptably high, evacuation of the hematoma alone should be performed. A second GKS is another treatment option.

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**TABLE 3**

Factors related to severely deteriorated outcomes after hemorrhage

<table>
<thead>
<tr>
<th>Factor</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient age &gt;37 yrs</td>
<td>0.08</td>
</tr>
<tr>
<td>prior hemorrhage</td>
<td>0.43</td>
</tr>
<tr>
<td>AVM vol &gt;2.55 cm³</td>
<td>0.49</td>
</tr>
<tr>
<td>Spetzler–Martin Grade =IV</td>
<td>0.27</td>
</tr>
<tr>
<td>margin dose &gt;20 Gy</td>
<td>0.52</td>
</tr>
<tr>
<td>no angiographic obliteration</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

*Statistically significant.
2. When the hematoma is small and poses little risk for neurological deterioration or when surgical intervention will not prompt neurological improvement, the ruptured AVM can be treated conservatively. If the AVM nidus remains 3 to 5 years after the initial treatment, a second GKS is recommended.

3. For chronic encapsulated ICH, close clinical follow up with serial neuroimaging studies should be the initial management strategy, particularly if the patient is asymptomatic. If the ICH progressively enlarges and the patient presents with neurological deterioration, surgical removal is recommended. When the associated AVM nidus is located in a surgically accessible area, it should also be removed to prevent future formation of an ICH. If complete removal is not possible, palliative debulking of the ICH would be appropriate, and a second radiosurgery is another treatment option.

Hemorrhage From Obliterated AVMs

Angiographically documented obliteration of an AVM has generally been considered the visual criterion of cure after stereotactic radiosurgery, but we have recently encountered several patients in whom hemorrhage occurred from an obliterated AVM. In our study the neurological conditions of the patients after postobliteration hemorrhage were less severe than those after preobliteration hemorrhage. The histological findings in those obliterated nidi consisted of tiny residual AVM vessels and newly developed capillaries. It appears that hemorrhage after AVM obliteration may be caused by rupture of microscopic remnants of the nidus or fragile capillary vessels that cannot be detected with cerebral angiography—not from breakthrough of an active arteriovenous shunt. The risk of hemorrhage from obliterated AVMs after GKS is similar to that reported for angiographically occult vascular malformations. Given that the neuroimaging characteristics for both entities are also very much alike, they may also share similar clinical behavior. Considering these facts, management for postobliteration hemorrhage should be much the same as it is for angiographically occult vascular malformations.

At present, there is not sufficient information to definitely determine how to treat patients in whom this rare phenomenon occurs. Based on our intraoperative experience in patients with obliterated AVMs, hemostasis was much easier to achieve than in those harboring AVMs that had not yet been obliterated; the degenerated nidus could be safely removed with ease. Based on our experience, our recommendations for them are as follows.

1. When the AVM is surgically accessible, evacuation of the hematoma with resection of the degenerated nidus is recommended to eliminate further problems such as repeated hemorrhagic events or delayed cyst formation.

2. When resection of the nidus could produce an unacceptable risk of morbidity and the ICH is small, close clinical follow up with serial neuroimaging studies can be selected. If the hematoma progressively enlarges with or without an associated cyst, evacuation of the ICH or cyst is recommended.

3. If the AVM is surgically inaccessible and the ICH is small but the associated cyst progressively enlarges, placement of a cystoperitoneal shunt is recommended, followed by close clinical follow up of the obliterated nidus with serial neuroimaging studies.

Conclusions

Various types of hemorrhagic complications can be better managed based on an understanding of the pathological condition involved. Conservative management may culminate in obliteration in approximately half of patients in whom minor bleeding has occurred. The risk of hemorrhage exists even after AVM obliteration, but patient outcome after postoblation hemorrhage is more favorable, and surgery for patients with these AVMs is safer. Radical resection to prevent further hemorrhage is recommended for surgically accessible AVMs that bleed after obliteration because the clinical behavior of obliterated AVMs is similar to that of angiographically occult vascular malformations, which are known to rebleed.

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Managing hemorrhage after GKS for arteriovenous malformations


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