Treatment of arteriovenous malformations using Gamma Knife surgery: the experience at the University of Washington from 2000 to 2005

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Object. The purpose of this study was to examine the efficacy and toxicity of treating arteriovenous malformations (AVMs) with the model 3C Gamma Knife at the University of Washington Medical Center.

Methods. Ninety-five evaluable patients with 99 treatable AVMs were treated at the University of Washington Medical Center from April 2000 through June 2005. The median patient age at the time of treatment was 40 years (range 6–68 years). The male to female patient ratio was 0.98:1. The median AVM volume treated was 3.8 cm³ (range 0.12–32 cm³). Forty-four percent of the patients had hemorrhaged prior to treatment. The median peripheral Gamma Knife surgery dose was 20 Gy with a median of 12 isocenters treated. The median follow-up duration was 38 months (range 3–91 months). Eighty-one percent of the patients had no previous stereotactic radiosurgery (SRS), whereas the remaining 19% had previously been treated with linear accelerator–based SRS.

Results. The Kaplan–Meier estimated 6-year AVM obliteration rate for the entire cohort was 71.4%. The Kaplan–Meier estimated 6-year obliteration rate was 72% for patients having no prior SRS and 54.5% for those undergoing repeat SRS. The median time to AVM obliteration was 47 months, with 90% of the obliterations occurring between 24 and 58 months. Eight patients (7.4%) experienced late toxicities. There were 2 fatal bleeds and 13 (13.8%) non-fatal bleeds after Gamma Knife surgery.

Conclusions. Gamma Knife surgery is an effective treatment for AVMs, resulting in an excellent obliteration rate with acceptable toxicity. (DOI: 10.3171/JNS/2008/109/12/S9)

KEY WORDS • arteriovenous malformation • Gamma Knife surgery • stereotactic radiosurgery

STEREOTACTIC radiosurgery using either GKS technology (Elekta Instruments AB) or a LINAC–based system has been shown to be an effective treatment for AVMs that are not amenable to resection.1–11,14,16,19,20,22,23,25 Arteriovenous malformation obliteration rates reported in the literature generally range between 60 and 80%, are dependent on several factors that have been variously described, and most commonly include peripheral dose, volume of the AVM, and embolization status.2,3,6,9,10,15,20,22,25,27,29 We report our institutional experience treating AVMs with the Leksell Gamma Knife model C from April 2000 through June 2005.

Methods

One hundred nine patients with AVMs were treated with the Gamma Knife model 3C at the University of Washington Medical Center from April 2000 through June 2005 (inclusive). Seven of the 109 patients had no follow-up and were excluded from this evaluation. An additional 7 patients were treated with staged procedures for large AVMs and were also excluded, leaving 95 patients for this analysis. Seventy-seven patients (81%) had no previous SRS, whereas 22 (19%) had previously undergone LINAC-based SRS (16 patients) at the University of Washington Medical Center or GKS (2 patients) at an outside institution. One patient was treated for 3 separate AVMs and 2 patients were treated for 2 separate AVMs for a total of 99 evaluable AVMs. Additionally, 9 patients in the GKS group who did not attain AVM obliteration were retreated with GKS for a total of 108 GKS procedures reported.

The median patient age at the time of treatment was 40 years (range 6–68 years). Forty-four percent of the patients had previously hemorrhaged prior to undergoing their first SRS. The male to female patient ratio was 0.98:1. The median follow-up duration was 38 months (range 3–91 months). The median AVM volume treated was 3.8 cm³ (range 0.12–32 cm³); the median treatment volume was 5.25 cm³ (range 0.25–33 cm³); and 21 patients (21.2% of the 99 AVMs) had 1 or more embolizations prior to SRS.

Abbreviations used in this paper: AVM = arteriovenous malformation; GKS = Gamma Knife surgery; LINAC = linear accelerator.
Treatment parameters consisted of the following: the median peripheral dose was 20 Gy (range 13–24 Gy); the median AVM coverage by the prescription isodose was 92% (range 83–100%); the median prescription isodose used was 50%; and the median number of treated isocenters was 12 (range 2–30 isocenters). The assignment of a particular dose was determined by our previous experience with LINAC-based SRS, as well as by the dose-response data and complication data reported by The University of Pittsburgh investigative group. The relationship between AVM volume and Gamma Knife dose is portrayed in Fig. 1 and demonstrates a near inverse linear relationship between AVM volume and Gamma Knife dose.

Computerized tomography angiography, MR imaging using a spoiled gradient–recalled acquisition postcontrast sequence, and angiography were used to identify the AVM target for treatment planning. A radiation oncologist, neurosurgeon, and neuroradiologist participated in target identification and treatment planning. Patients were treated using the model 3C Leksell Gamma Knife, with progressively updated Leksell GammaPlan software used for treatment planning.

Follow-up studies were performed at 6 and 12 months and yearly thereafter from the time of the initial GKS. Patients underwent either CT angiography or MR imaging angiography at those time points. Once there was no longer an AVM nidus visualized by CT angiography or MR imaging angiography and 3 years had elapsed, patients then underwent angiography to substantiate AVM obliteration.

**Statistical Analysis**

The AVM obliteration and bleed rates were calculated using the Kaplan–Meier product limit method. A 2-tailed log-rank test was used to evaluate statistically significant differences between groups. Univariate and multivariate analysis were performed using SPSS statistical package Version 13 (SPSS Inc.). A probability value < 0.05 was considered statistically significant. Factors achieving a probability value of $\leq 0.35$ after univariate analysis were entered into the multivariate analysis.

**Results**

**Arteriovenous Malformation Obliteration Rates**

The Kaplan–Meier estimated 6-year obliteration rate for the entire group was 71.4% (Fig. 2). Ninety percent of the AVM obliterations occurred between 24 and 58 months and the median time to obliteration was 47 months. The latest documented obliteration occurred 80 months after GKS.

The Kaplan–Meier estimated 6-year obliteration rate for patients who were retreated with SRS was 72.5% (28 retreated AVMs). The Kaplan–Meier estimated 6-year obliteration rate for the 16 patients who were retreated after previous LINAC–based SRS was 100%, and the estimated 6-year obliteration rate for patients undergoing GKS for a second time (9 of whom underwent both treatments at our institution) was 54.5%, but with a late obliteration (80 months) as noted previously (Fig. 3). These differences were not statistically significant ($p = 0.73$, log-rank test).

The following factors were analyzed by univariate analysis to determine any association with AVM obliti-
Gamma Knife surgery for arteriovenous malformations

Fig. 2. Kaplan–Meier plot of AVM obliteration for the entire patient cohort.

Fig. 3. Kaplan–Meier (KM) plot of AVM obliteration rates according to treatment status.

eration: sex, age, AVM volume, peripheral dose, prior hemorrhage, prior embolization, and treatment status (Table 1). The peripheral dose delivered to the AVM was statistically significantly associated with an improved AVM obliteration rate by univariate analysis, and the factor AVM volume nearly achieved statistical significance. After multivariate analysis, no factors were identified as being statistically significant (Table 1). The relationship
between AVM volume and Gamma Knife dose is shown in Fig. 1. When volume was removed from the multivariate analysis, peripheral dose did achieve statistical significance (p = 0.047). A comparison between AVM volumes < 10 versus > 10 cm$^3$ revealed a trend toward improved AVM obliteration in the smaller lesions (Fig. 4; p = 0.12).

Posttreatment Hemorrhage

There were 15 hemorrhages after SRS for a crude rate of 13.9% (occurring in 15 of 108 AVMs treated), with 2 of the bleeds resulting in fatalities. Eleven (73.3%) of the 15 patients had hemorrhaged prior to the GKS and this factor was statistically significant when comparing the 2 groups (p = 0.043).

Chronic Toxicity

Chronic toxicity was defined as any new deficit or worsening neurological deficit, or a new or worsening seizure disorder, which were either not reversible with the introduction of dexamethasone or required > 3 months of treatment with dexamethasone. Eight patients experienced chronic toxicity (Table 2) for a crude rate of 7.4% (of 108 AVMs treated) and a 6-year Kaplan–Meier estimated rate of 11.2% (Fig. 5). The following factors were examined by univariate and multivariate analysis for possible associations with the development of toxicity: sex, age, AVM volume, peripheral dose, treatment status, prior hemorrhage, and previous embolization(s). No factors were statistically associated with an increase in toxicity, although previous SRS treatment nearly achieved statistical significance upon univariate analysis (p = 0.06; Table 3) but not by multivariate analysis.

Discussion

Gamma Knife surgery has been shown in numerous studies to be a viable treatment option for surgically inaccessible AVMs.\(^7\)\(^–\)\(^11\),\(^14\)\(^–\)\(^16\),\(^19\),\(^20\),\(^22\),\(^23\),\(^25\) The AVM obliteration rate of the entire cohort in this study was 71.4% and is similar to the rate noted in other series mentioned above. Patients treated for the first time or who were retreated after failed LINAC-based SRS or GKS had nearly identical obliteration rates (72.8 vs 72.5%). The major factor associated with AVM obliteration in this series was the peripheral dose delivered to the AVM. This finding is consistent with those in other reported series.\(^2\),\(^3\),\(^6\),\(^24\) Although the factor of AVM volume did not reach statistical significance, there was a clear trend toward improved obliteration with AVMs < 10 cm$^3$ in size. We did not find an association between obliteration and prior embolization as has been reported in some studies, although that procedure has generally been used for larger AVMs.\(^11\)

The rehemorrhage rate in this series is somewhat higher than that reported by other centers.\(^5\),\(^6\),\(^17\) The majority of hemorrhages after GKS occurred in patients

### TABLE 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td>0.31</td>
<td>0.63</td>
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<td>age</td>
<td>0.36</td>
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<tr>
<td>AVM volume</td>
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<td>0.32</td>
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<tr>
<td>peripheral dose*</td>
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<tr>
<td>prior hemorrhage</td>
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<td>0.34</td>
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<tr>
<td>prior embolization</td>
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<td>treatment status*</td>
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</table>

* First treatment versus retreatment.

### TABLE 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Toxicity</th>
<th>Time* (mos)</th>
<th>Intervention</th>
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<tr>
<td>1</td>
<td>cyst formation, increased seizures</td>
<td>43</td>
<td>resection†</td>
</tr>
<tr>
<td>2</td>
<td>edema and radiation necrosis</td>
<td>12</td>
<td>prolonged steroid use</td>
</tr>
<tr>
<td>3</td>
<td>increasing seizures, increasing hemiparesis</td>
<td>14</td>
<td>medical management</td>
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<tr>
<td>4</td>
<td>radiation necrosis</td>
<td>38</td>
<td>rebleed, resection of residual AVM and necrosis</td>
</tr>
<tr>
<td>5</td>
<td>right spastic hemiparesis, radiation necrosis, increased seizures</td>
<td>33</td>
<td>medical management, dexamethasone, antiepileptics</td>
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<tr>
<td>6</td>
<td>right-sided sensory changes</td>
<td>27</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>edema and radiation necrosis</td>
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<td>prolonged steroid use</td>
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<tr>
<td>8</td>
<td>mild cranial nerve deficit</td>
<td>33</td>
<td>occupational therapy</td>
</tr>
</tbody>
</table>

* Interval until onset of the complication.
† Patient refused follow-up for the first 3.5 years after GKS.

### TABLE 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment status*</td>
<td>0.06</td>
<td>0.18</td>
</tr>
<tr>
<td>prior hemorrhage</td>
<td>0.11</td>
<td>0.12</td>
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<tr>
<td>prior embolization</td>
<td>0.28</td>
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<tr>
<td>sex</td>
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<tr>
<td>age</td>
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<tr>
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<tr>
<td>peripheral dose</td>
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<td>not tested</td>
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</table>

* First treatment versus retreatment.
who had previously hemorrhaged (73.3%). In this series almost half of the patients treated (44%) had previously hemorrhaged and that most likely is the explanation for our higher rehemorrhage rate and is consistent with the data of Pollock et al. Although somewhat controversial, there are data to suggest that the risk of hemorrhaging is greater in patients who have had a previous hemorrhage without any intervention, which also supports our findings. We could find no other factors that were associated with a higher risk of rebleeding.

The long-term or chronic (crude) toxicity rate of 7.4% is similar to the rate reported in other studies. The paucity of events makes the analysis of associated factors difficult to evaluate and, although no factor reached statistical significance, there was a trend (p = 0.06) for prior SRS treatment to correlate with an increased risk of chronic toxicity. This also is consistent with previous reports in the literature. In addition, 6 of the 8 patients who developed chronic toxicity had experienced previous hemorrhages and had some residual symptoms related to that event. It is possible that antecedent central nervous system damage either from previous SRS or hemorrhage may increase the likelihood of further injury from GKS in an already compromised tissue.

**Conclusions**

Gamma Knife surgery for surgically inaccessible AVMs is an effective treatment modality, achieving high obliteration rates and acceptable chronic toxicity.

**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**


Manuscript submitted June 12, 2008.
Accepted July 23, 2008.
Presented in part at the 14th Leksell Society Meeting, Quebec, Canada, May 2008.
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