Gamma Knife surgery for arteriovenous malformations in children

Clinical article

CHUN PO YEN, M.D., STEPHEN J. MONTEITH, M.D., JAMES H. NGUYEN, B.A., JESSICA RAINLEY, B.A., DAVID J. SCHLESINGER, PH.D., AND JASON P. SHEEHAN, M.D., PH.D.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia

Object. The aim of this study was to evaluate the long-term imaging and clinical outcomes of intracranial arteriovenous malformations (AVMs) in children treated with Gamma Knife surgery (GKS).

Methods. Between 1989 and 2007, 200 patients with AVMs who were 18 years of age or younger were treated at the University of Virginia Health System. Excluding 14 patients who had not reached 2-year follow-up, 186 patients comprised this study. Hemorrhage was the most common presenting symptom leading to the diagnosis of AVMs (71.5%). The mean nidus volume was 3.2 cm³ at the time of GKS, and a mean prescription dose of 21.9 Gy was used.

Results. After initial GKS, 49.5% of patients achieved total angiographic obliteration. Forty-one patients whose AVM nidi remained patent underwent additional GKS. The obliteration rate increased to 58.6% after a second or multiple GKS. Subtotal obliteration was achieved in 9 patients (4.8%). Forty-nine patients (26.3%) still had a patent residual nidus. In 19 patients (10.2%), obliteration was confirmed on MR imaging only. Ten patients had 17 hemorrhages during the follow-up period. The hemorrhage rate was 5.4% within 2 years after GKS and 0.8% between 2 and 5 years. Six patients developed neurological deficits along with the radiation-induced changes. Two patients developed asymptomatic meningiomas 10 and 12 years after GKS. After a mean clinical follow-up of 98 months, less than 4% of patients had difficulty attending school or developing a career.

Conclusions. Gamma Knife surgery offers a reasonable chance of obliteration of an AVM in pediatric patients. The incidence of symptomatic radiation-induced changes is relatively low; however, long-term clinical and imaging follow-up is required to identify delayed cyst formation and secondary tumors. (DOI: 10.3171/2010.8.PEDS10138)

Key Words • arteriovenous malformation • children • Gamma Knife surgery • pediatric neurosurgery • radiosurgery • secondary tumor

Although AVMs only account for 1%–2% of intracerebral hemorrhage in the adult population, they represent 14%–57% of the underlying causes of cerebral hemorrhage in pediatric patients. Given the fact that children harboring an AVM have a profound lifetime risk of hemorrhage, the goals of all treatment modalities are to completely obliterate or extirpate the nidi while at the same time preserve patients’ neurological function. In the past, some neurosurgeons have been hesitant to use radiosurgery to treat pediatric patients with AVMs. On one hand, radiosurgery has proven its effectiveness based on the experience in adult patients. In addition, compared with open surgery, the radiosurgical procedure is less invasive and more tolerable for children. On the other hand, one needs to be cautious in using radiosurgery for children (as young as 4 years old in this study), given that the neuronal tissues are still developing and taking into account that the possible long-term side effects of ionizing radiation. In the present study, we analyze the long-term imaging and clinical outcomes as well as complications of a series of children with AVMs treated using GKS at our institution.

Methods

Patient Demographics

Between May 1989 and December 2007, 200 patients with AVMs who were 18 years of age or younger were treated with GKS at the University of Virginia Health System. Patients were referred for evaluation for radiosurgical intervention when the risks of microsurgery were...
Gamma Knife surgery for arteriovenous malformations in children

deemed high or if there was residual AVM after a previous microsurgical attempt. Referral patterns resulted in many patients being referred from beyond traditional primary and secondary catchment areas, in addition to international patients. Fourteen cases with follow-up less than 2 years after GKS were excluded, leaving 186 patients for analysis in this study. Patients in whom angiographic obliteration of their AVMs was attained within 2 years after GKS were included. There were 98 boys and 88 girls with a mean age of 12.7 years (range 4–18 years) (Table 1). The presenting symptoms leading to the diagnosis of an AVM were hemorrhage in 133 patients (71.5%), seizure in 29 (15.6%), headache in 11 (5.9%), and neurological deficits in 8 (4.3%) (cranial nerve palsies in 3, long tract signs in 3, aphasia in 1, and drowsiness from hydrocephalus in 1). Five patients (2.7%) were asymptomatic, and the AVMs were an incidental finding.

Thirty-eight patients underwent embolization prior to GKS. Incomplete resection was carried out in 24 patients and the AVMs were an incidental finding.

Forty-one patients underwent a second GKS for still-patent AVM residuals, which was performed at a mean of 2.5 years after the initial GKS procedures. The maximum diameters of the nidi at the time of additional GKS ranged from 4 to 47 mm (mean 20 mm), and the volumes ranged from 0.2 to 15.9 cm³ (mean 2.3 cm³).

The GKS Technique

The GKS was performed under general anesthesia in patients younger than 16 years of age. For those older than 16 years, the patients remained conscious during the procedure except for frame placement when we attached the Leksell G frame after administration of intravenous sedation supplemented with a local anesthetic. The Leksell Gamma Unit Model U was used until July 2001 when the C model (Elekta Instruments, Inc.) replaced it. Gamma Knife Perfexion was installed and used after September 2007. Initially, stereotactic biplane angiography was the only imaging modality available for nidus definition and dose planning. Since 1991, stereotactic MR imaging had been routinely used in addition to cerebral angiography for treatment planning. The Kula software was used for dose planning from 1989 to June 1994, and was then replaced with GammaPlan software.

Treatment Parameters

The treatment parameters at the initial GKS were as follows: mean prescription dose 21.9 Gy (range 7.5–35 Gy); mean maximum dose 40.1 Gy (range 20–50 Gy); mean isodose line 56% (range 30%–90%); and mean number of isocenters 2.9 (range 1–14). The treatment parameters of the second GKS were as follows: mean prescription dose 20.7 Gy (range 4–27.5 Gy); mean maximum dose 39.6 Gy (range 8–50 Gy); mean isodose line 53% (range 50%–71%); and mean number of isocenters 4 (range 1–22).

Clinical and Imaging Follow-Up After GKS

Follow-up data were obtained from patients or parents and referring physicians. The patients treated earlier were subjected to a rigorous protocol of yearly angiograms.

---

**TABLE 1: Patient demographics, AVM characteristics, and initial and additional GKS parameters**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM Characteristic</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>predominant location</td>
<td></td>
</tr>
<tr>
<td>hemispheric</td>
<td>101 (54.3)</td>
</tr>
<tr>
<td>thalamus</td>
<td>24 (12.9)</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>23 (12.4)</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>brainstem</td>
<td>18 (9.7)</td>
</tr>
<tr>
<td>cerebellum</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>insula</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>location</td>
<td></td>
</tr>
<tr>
<td>noneloquent area</td>
<td>53 (28.5)</td>
</tr>
<tr>
<td>eloquent area</td>
<td>133 (71.5)</td>
</tr>
<tr>
<td>venous drainage</td>
<td></td>
</tr>
<tr>
<td>superficial only</td>
<td>62 (33.3)</td>
</tr>
<tr>
<td>deep venous system</td>
<td>124 (66.7)</td>
</tr>
<tr>
<td>Initial Treatment Parameters</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>vol of nidi (cm³)</td>
<td>3.2 (1–24.0)</td>
</tr>
<tr>
<td>prescription dose (Gy)</td>
<td>21.9 (7.5–35)</td>
</tr>
<tr>
<td>max dose (Gy)</td>
<td>40.1 (20–50)</td>
</tr>
<tr>
<td>isodose line (%)</td>
<td>56.0 (30–90)</td>
</tr>
<tr>
<td>no. of isocenters</td>
<td>2.9 (1–14)</td>
</tr>
<tr>
<td>Retreatment Parameters</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>vol of nidi (cm³)</td>
<td>2.3 (0.2–15.9)</td>
</tr>
<tr>
<td>prescription dose (Gy)</td>
<td>20.7 (4–27.5)</td>
</tr>
<tr>
<td>max dose (Gy)</td>
<td>39.6 (8–50)</td>
</tr>
<tr>
<td>mean isodose line (%)</td>
<td>53.0 (50–71)</td>
</tr>
<tr>
<td>mean no. of isocenters</td>
<td>4.0 (1–22)</td>
</tr>
</tbody>
</table>

* There were 98 boys and 88 girls with a mean age of 12.7 years (range 4–18 years).
Later, with the introduction of MR imaging, angiography was not performed until the nidus was no longer visible on MR imaging performed at 6-month intervals. Patients were always requested to undergo angiography to confirm the obliteration of the nidus when flow void signals could no longer be detected on MR imaging. Continuous MR imaging every 5 years was advised to rule out delayed adverse effects. The clinical outcome was obtained from review of medical records and by telephone interview.

Statistical Analysis

All statistical analyses were performed using the commercially available statistical software package SPSS version 17.0. Time to obliteration was calculated using the Kaplan-Meier method. Cox proportional hazards modeling was performed to identify factors predicting AVM obliteration. Factors examined include sex, age, history of preradiosurgical embolization, history of prior AVM rupture, nidus volumes, prescription doses, maximum doses, number of isocenters, radiosurgery-based grading, and presence of radiation-induced changes after GKS. Univariate and multivariate logistic regression were used to analyze factors potentially affecting the radiation induced changes and neurological deficits following GKS. A p value < 0.05 was used as the limit for statistical significance.

Results

Imaging Outcome After GKS

Following a single GKS procedure, 69 patients (37.1%) had a residual nidus. In 15 patients (8.1%), the last MR imaging study revealed an absence of flow voids; however, patients or parents refused angiography to confirm the obliteration of nidus. In 92 patients (49.5%), total obliteration was confirmed on follow-up angiography (Figs. 1 and 2). Ten patients (5.4%) had a subtotal obliteration (no visible nidus; however, an early filling draining vein was still present).45

Forty-one patients underwent additional GKS for AVMs that remained patent despite initial treatment. Seventeen of these patients achieved a total obliteration based on angiography. Three patients obtained nidus obliteration based on MR images only. In 16 patients, the nidus remained patent. Five patients had subtotal AVM obliteration.

In total, after 1 or more GKS sessions, a complete obliteration was confirmed in 109 (58.6%) and subtotal obliteration in 9 (4.8%) patients. Forty-nine patients (26.3%) still had a patent residual nidus. In 19 patients (10.2%), obliteration was confirmed on MR imaging only. Of 112 patients with AVM nidi smaller than 3 cm³, 72.3% obtained an angiographic total obliteration and 9.8% had no flow voids visible on MR imaging. Of 48 patients with AVM nidi between 3 and 5 cm³, 37.5% obtained an angiographic total obliteration and 12.5% had no flow voids visible on MR imaging. Of 26 patients with AVM nidi larger than 5 cm³, 38.5% obtained an angiographic total obliteration and 7.7% had no flow voids visible on MR imaging. The actuarial angiographic obliteration rate was...
34% at 2 years, 46% at 3 years, and 51% at 5 years. The obliteration rates based on Spetzler-Martin grading are detailed in Table 2.

**Factors Related to Nidus Obliteration**

The analysis of possible factors related to nidus obliteration was based on the outcome of initial GKS. Fifteen patients with no evidence of residual AVM on MR imaging but not confirmed by angiography were excluded from the analysis. Nidi obliterated after the initial GKS on angiography were compared with those that were still patent (including patients with patent nidi and patients with subtotally obliterated AVMs). Univariate analysis demonstrated that negative history of pre-GKS embolization ($p = 0.001$), small nidus volume ($p < 0.001$), high prescription dose ($p < 0.001$), high maximum dose ($p = 0.009$), small number of isocenters ($p = 0.023$), and low radiosurgery-based grade ($p < 0.001$) were significantly associated with an increased rate of AVM obliteration. Sex ($p = 0.844$), age ($p = 0.208$), history of hemorrhage before GKS ($p = 0.160$), and presence of radiation-induced imaging changes following GKS ($p = 0.625$) were not related to the nidus obliteration. In multivariate analysis, a negative history of pre-GKS embolization ($p = 0.042$), small nidus volume ($p = 0.001$), and a high prescription dose ($p = 0.025$) were significantly associated with an increased rate of obliteration.

**Clinical Outcome**

Clinical follow-up ranged from 24 to 240 months (mean 98.4 months). After GKS, 10 patients had a single hemorrhage while 7 patients had 2 hemorrhages. In total, 17 patients experienced 24 episodes of hemorrhage in 1013 risk-years (assuming patients with completely obliterated AVMs were no longer at risk for hemorrhage), yielding an annual hemorrhage rate of 2.4%. We did not observe any hemorrhage after angiography confirmed total obliteration of the nidus or any recurrence of an angiographically obliterated AVM. If the 14 patients with follow-up shorter than 2 years were included (2 episodes of hemorrhages in these patients), there were 26 hemorrhages in 1016 risk-years, yielding a hemorrhage rate of 2.6%. The hemorrhage rate was 5.4% per year for the first 2 years and reduced to 0.8% per year from 2 to 5 years after GKS. There were no deaths in our series. Five patients still had neurological deficits due to hemorrhage at the end of follow-up.

**Complications**

Serial follow-up with MR imaging was performed

**TABLE 2: Imaging and clinical outcomes based on Spetzler-Martin grading**

<table>
<thead>
<tr>
<th>Spetzler-Martin Grade</th>
<th>Total</th>
<th>w/ Angiographic Obliteration</th>
<th>w/ New Nonhemorrhage-Related Neurological Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>23</td>
<td>12 (52.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>II</td>
<td>55</td>
<td>36 (65.5)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>III</td>
<td>87</td>
<td>56 (64.4)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
<td>5 (25)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Fig. 2. Angiograms obtained in a 4-year-old girl who presented with an intracerebral hemorrhage leading to the diagnosis of a right thalamic AVM measuring $20 \times 20 \times 12$ mm. **A-D:** Right internal carotid artery and vertebral injection angiograms. **E and F:** The nidus was obliterated 2 years after GKS without adverse effects.
for patients even after the obliteration of the AVM was confirmed angiographically to evaluate for long-term complications. The follow-up duration for MR imaging ranged from 6 to 222 months with a mean of 80 months. Imaging changes visualized as increased T2 signal intensity surrounding the nidi in the absence of a new hemorrhage were observed in 68 (37.8%) of 180 patients who underwent serial MR imaging follow-up (Fig. 3). It is not clear whether these imaging changes seen after radiosurgery are due to radiation, ischemia, gliosis, or hemodynamic changes, or a combination of these. These imaging changes were identified after a mean of 12.2 months after GKS (range 3–95 months). The changes resolved after a mean of 20.3 months (range 5–62 months). A negative history of prior hemorrhage before GKS and an increased prescription dose were statistically significant in association with changes on post-GKS MR images.

Fifty-five patients (30.6%) were asymptomatic upon the finding of imaging changes after radiosurgery, 7 (3.9%) presented with headache, and 6 (3.3%) developed new or aggravated neurological deficits. Among the patients with neurological deficits, 4 (2.2%) had a full recovery but 2 patients (1.1%) had residual neurological deficits at the last follow-up.

Five patients developed a cyst after GKS. A 7-year-old boy and a 12-year-old girl each developed a small asymptomatic meningioma 12 and 10 years after GKS. These meningiomas (1 tentorial and 1 convexity) have remained small, stable in size, and have not required further intervention.36

Performance Status

In addition to the 5 patients with residual neurological deficits from post-GKS hemorrhages and 2 with radiation-induced changes associated with permanent neurological deficits, 2 patients were incapacitated by large AVMs with persistent shunting, 2 by medically refractory seizures, and 2 with ongoing personality disorders. In total, 13 patients deteriorated following GKS. Eight patients had difficulty attending a regular school or developing a career: 1 because of the new neurological deficits following the development of radiation-induced changes, 2 because of neurological deficits from the prior hemorrhage before GKS, 2 because of persistent seizures, and 3 because of personality problems or neurological deficits of persistent AVMs.

Discussion

Natural History of Pediatric AVMs

Natural history studies of intracranial AVMs have demonstrated that in general, the annual risk of hemorrhage is within the range of 2%–4%, and the annual risk of death is 1%.30,43 The lifetime risk of hemorrhage can be calculated using the following formula: lifetime risk in percentage = 105 – patient’s age in years.3,20 In ad-

![Fig. 3.](image-url)
tion to a high cumulative risk of hemorrhage because of a long life expectancy, studies have indicated that the AVMs in children seem to behave differently from those in adults.\textsuperscript{5,19,26} The AVM nidi in children seem to bleed more frequently and with more extensive hemorrhage.\textsuperscript{5,11,19,25,26} Furthermore, a higher incidence of nidi located in the basal ganglia, thalamus, and posterior fossa has been reported.\textsuperscript{9,26} Therefore, the life-long risk of hemorrhage and associated high morbidity and mortality justify a definitive treatment for pediatric patients with AVMs to obliterate or extirpate the nidi, thus eliminating the risk of hemorrhage.

### Surgery and Embolization for Pediatric AVMs

The most appropriate management option for pediatric AVMs remains a matter of debate. It is widely accepted that conservative treatment for AVMs is associated with poor prognosis.\textsuperscript{11,39} Humphreys et al.\textsuperscript{16} reviewed 105 cases of AVMs in children and reported a hemorrhage rate of 32% in 10 years with a mortality rate of 24%. In their experience, the operative mortality rate was 8%, which was significantly lower than that of conservative management. Luessenhop and Rosa\textsuperscript{24} reported that the surgical risk is less than the natural one for patients with Spetzler-Martin Grades I and II and more than half of those in Grade III. Currently, surgery allows a total extirpation of AVMs in 50%–90% of pediatric patients.\textsuperscript{7,19} Severe complications after surgery occur in about 10%, with the mortality rate ranging between 0% and 8%.\textsuperscript{5,10,16} Therefore, in general, surgery should be considered as a first-line treatment in patients with a superficially located nidal, outside of eloquent cortex. It eliminates the risk of hemorrhage immediately, although recurrence of AVMs following a complete extirpation has been reported in pediatric patients.\textsuperscript{7,16,18}

The reported cure rates of AVMs by embolization range between 0% and 20%.\textsuperscript{9} Wisoff and Berenstein\textsuperscript{44} reviewed their experience with AVMs in children and stated that a complete obliteration of the AVMs is seldom achieved by embolization alone. Although endovascular treatment allowed size reduction in AVMs, studies have shown that partial embolization provided little to no protection against hemorrhage, and therefore endovascular treatment has mainly played an adjunct role in reducing the size of AVMs, making subsequent treatment more feasible. The use of new embolization materials, such as Onyx, seems to afford a higher chance of total obliteration, but large series and the long-term results are pending.

The role of each treatment modality will depend on the expertise and resources available at each institution. When feasible, surgery should be considered the first-line therapy. If endovascular therapy is considered, a specific goal must be kept in mind—whether to completely embolize the AVM or to leave an angiographically inaccessible residual nidus for microsurgical or radiosurgical management. Radiosurgery should be considered the first-line treatment for inaccessible lesions or those in eloquent locations.

### Radiosurgery for Pediatric AVMs

Following the success for AVMs in adults, radiosurgery has also been used in children. The angiographic obliteration rates after radiosurgery have been satisfactory, ranging from 45% to 86% (Table 3).\textsuperscript{21,27,28,31,33,37} The only exception is the report by Smyth et al.\textsuperscript{38} who reported an obliteration rate of only 27%. If MR imaging findings demonstrating obliteration and patients in whom obliteration was attained after additional radiosurgery were included, the obliteration rates increased to a range of 58%–86%.\textsuperscript{21,27,28,31,33,37} One has to note that most of the radiosurgical series treated small nidi with a mean nidus volume between 1.7 and 3.2 cm\textsuperscript{3}. Smyth et al.\textsuperscript{38} explained that their meager result might be due to larger nidi and more conservative prescription doses. The only radiosurgical series with relatively large AVMs was reported by Pan et al.,\textsuperscript{41} in which an obliteration rate of 65% after 1 GKS session and 81% after additional GKS were recorded in a group of patients with a mean nidus volume of 11.7 cm\textsuperscript{3}. Although it is reasonable to assume that there is no architectural difference between small and large AVMs and they should respond the same way to radiosurgery, the long-term results of volume-staged radiosurgery for large AVMs is not generally thought to be as favorable as for those with small to moderately sized AVMs.

Factors related to obliteration of AVMs have generally been consistent across all pediatric radiosurgical studies. In essence, a small nidus volume and a high prescription dose are the most important factors related to a high obliteration rate. Shin et al.\textsuperscript{33} and Reyns et al.\textsuperscript{31} reported that younger patients responded more favorably to radiosurgery in their pediatric population. The imaging outcomes of radiosurgery comparing AVMs in children and adults have been conflicting. Tanaka et al.\textsuperscript{42} compared the results of 70 adults with those of 23 children and reported a 1-year obliteration rate in 45% of the adults and 74% of the children after GKS. The rates at 2 years increased to 81% and 94%, respectively. Nicolato et al.\textsuperscript{29} reported a similar overall obliteration rate in children and adults, but AVMs in children had a higher 36-month actuarial obliteration rate and the obliteration occurred earlier. Pan et al.\textsuperscript{31} reported similarly good results in AVMs in children and adults with volumes smaller than 3 cm\textsuperscript{3} and similar poor results with volumes larger than 20 cm\textsuperscript{3}. However, they observed a less favorable outcome in pediatric patients with volumes between 3 and 20 cm\textsuperscript{3}. They proposed that there might be some inherent differences in sensitivity of pediatric or adult vessels to radiation-induced damage. In research from the same group, the authors demonstrated that radiosurgical efficacy is inversely related to the cellular repair capacity, which is supposed to be more active in immature AVM vessels in children.\textsuperscript{13} From our experience, we did not observe a difference in obliteration rates between pediatric and adult patients (unpublished data).

### Hemorrhage and Complications Following GKS

Based on the reported series of pediatric AVMs treated with radiosurgery, the hemorrhage rate during the latency period ranged from 0.6% to 3.2%,\textsuperscript{21,27,28,31,33,37} which is similar to the natural history of untreated AVMs. This again demonstrates that partial obliteration offered by radiosurgery provides no protection against rupture of residual AVMs (Table 3).
TABLE 3: Summary of reports on pediatric AVMs treated with radiosurgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Type of Radiosurgery</th>
<th>AVM Vol (cm³)</th>
<th>Prescription Dose (Gy)</th>
<th>Duration of Imaging Follow-Up (mos)</th>
<th>Obliteration Rate Based on Angio Only/Angio or MRI (%)</th>
<th>Nonhemorrhage-Related Neurological Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy et al., 2000</td>
<td>53</td>
<td>GKS</td>
<td>1.7 (0.1–10.2)†</td>
<td>20.0 (15–25)†</td>
<td>36 (6–103)†</td>
<td>45/74</td>
<td>1.9</td>
</tr>
<tr>
<td>Shin et al., 2002</td>
<td>100</td>
<td>GKS</td>
<td>1.8 (0.1–19.2)†</td>
<td>20.0 (17–28)†</td>
<td>71 (6–124)†</td>
<td>71/75</td>
<td>1.5</td>
</tr>
<tr>
<td>Smyth et al., 2002</td>
<td>40‡</td>
<td>GKS</td>
<td>5.4 (0.2–37.4)§</td>
<td>18.0 (12–19)§</td>
<td>62 (6–99)§</td>
<td>27/35</td>
<td>4.3</td>
</tr>
<tr>
<td>Nataf et al., 2003</td>
<td>57¶</td>
<td>LINAC</td>
<td>3.5 (0.6–16)†</td>
<td>23.8 (18–26)§</td>
<td>40 (7–172)§</td>
<td>61/NA</td>
<td>4.7</td>
</tr>
<tr>
<td>Nicolato et al., 2006</td>
<td>92**</td>
<td>GKS</td>
<td>2.9 (0.1–25)†</td>
<td>22.0 (14–26)†</td>
<td>29 (7–77)†</td>
<td>86/NA</td>
<td>0.6</td>
</tr>
<tr>
<td>Reynolds et al., 2007</td>
<td>100</td>
<td>LINAC</td>
<td>2.8 (0.9–21.3)§</td>
<td>23.0 (15–25)§</td>
<td>26 (11–126)§</td>
<td>65/NA</td>
<td>1.7</td>
</tr>
<tr>
<td>Pan et al., 2008</td>
<td>105††</td>
<td>GKS</td>
<td>11.7 (0.4–63)§</td>
<td>18.5 (14.5–25)§</td>
<td>35 (6–134)§</td>
<td>65/NA</td>
<td>1.9</td>
</tr>
<tr>
<td>present study</td>
<td>186</td>
<td>GKS</td>
<td>3.2 (0.1–24)§</td>
<td>21.9 (7.5–35)§</td>
<td>80 (6–22.2)§</td>
<td>50/58</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* Angio = angiography; NA = not available.
† Median value (range).
‡ Nine patients that were either lost to follow-up or their families refused confirmatory MR imaging or angiography were excluded from analysis.
§ Mean value (range).
¶ The 8 patients in whom follow-up angiography was not performed were excluded.
** The hemorrhage rate and complications were analyzed in 75 patients, and outcomes were analyzed in 62 patients who underwent follow-up longer than 36 months.
†† The obliteration rate was analyzed in 74 patients who underwent angiographic follow-up.
The neurological complications related to radiosurgical treatment were in the range of 0%–6.7%, \textsuperscript{21,29,31,33,37} which is comparable to the overall complication rates of 3%–6% in microsurgical series.\textsuperscript{15,35} However, in patients with Spetzler-Martin Grade III or higher AVMs, the incidence of nonhemorrhage-related neurological complications associated with GKS ranged between 0% and 8.6%, \textsuperscript{21,27,33,38} which is significantly lower than the reported complication rates of 12%–38% in microsurgical series.\textsuperscript{14,41} In general, deep venous drainage is less of a concern in radiosurgery, but size and location still play an important role in predicting the development of complications.

In our experience, the incidence of radiation-induced imaging changes (increased T2 signal on MR imaging) is similar between pediatric and adult populations, but fewer pediatric patients developed neurological deficits (unpublished data). The pediatric nervous system appears to be somewhat more tolerable to the adverse effects of radiosurgery.

Although radiation-induced neoplasia is rare, only a few children who underwent radiosurgery had follow-up for 10 years or longer. We found 2 patients in whom meningiomas developed 10 and 12 years following radiosurgery.\textsuperscript{36} The incidence seems to be low from a total population of more than 1300 patients with AVMs treated at our institution. It should be noted that if we only considered the 250 patients with follow-up longer than 10 years, the incidence was 0.7%, which is not negligible. As these secondary tumors may develop decades after radiosurgery, the importance of follow-up imaging even after obliteration of the nidus cannot be overemphasized.

**Neurocognitive Function of Children Undergoing GKS for AVMs**

Very few systematic studies had been conducted to evaluate the cognitive function of pediatric patients undergoing radiosurgery. Radiosurgical series in children have mentioned briefly that few or none of their patients developed neurocognitive or endocrine dysfunction.\textsuperscript{31,33} Riva et al.\textsuperscript{34} evaluated the cognitive and neuropsychological performance in 8 children with AVMs treated with GKS using age-matched siblings or first cousins as controls and reported no neurological, cognitive, memory, or attention deficits after a mean of 6 years after GKS.

**Conclusions**

In children with AVMs, GKS offers a reasonable rate of obliteration. Patients with smaller nidus volumes, those treated with higher prescription doses, and those who have not undergone prior embolization are more likely to achieve post-GKS obliteration. Patients remained at risk for hemorrhage during the latency period. Patients with imaging changes after GKS are generally asymptomatic. In the absence of another hemorrhage, the risk of permanent neurological injury after GKS for a child with a small to moderately sized AVM is very low. Nevertheless, long-term follow-up is needed to detect and treat late complications.

**Disclosure**

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

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Yen, Nguyen, Rainey, Schlesinger. Analysis and interpretation of data: all authors. Drafting the article: Monteth, Yen. Critically revising the article: Sheehan, Monteith. Yen. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Yen, Schlesinger. Administrative/technical/material support: Schlesinger. Study supervision: Sheehan.

**Acknowledgments**

The authors thank Drs. Neal Kassell and Ladislau Steiner who treated many of these patients at the University of Virginia Health System.

**References**


Address correspondence to: Jason Sheehan, M.D., Ph.D., Department of Neurological Surgery, University of Virginia Health System, Box 800212, Charlottesville, Virginia 22908. email: jsheehan@virginia.edu.