Pediatric arteriovenous malformations (AVMs) are rare, complex lesions. In the pediatric population, AVMs have a tendency to cause intracerebral hemorrhage, and they are responsible for 14% to 57% of cerebral hemorrhages in this age group. The rate of intracerebral hemorrhage caused by AVMs in adults is significantly lower, accounting for 1% to 2% of hemorrhages. The natural history of AVMs in the pediatric population can be hazardous; therefore, observation is less favorable for lesions that have bled. Many pediatric AVMs can be treated through surgery, embolization, stereotactic radiosurgery, or a combination of these.

It was Cushing and Bailey in 1927 who recorded obliteration of an irradiated AVM after it was surgically explored. After this, refinements in the radiation delivery method through the use of the stereotactic technique and image guidance have made treatment of AVMs with elegant systems such as the Gamma Knife safe and effective. Nowhere is the need for an accurate radiosurgery device more necessary than in children. The pediatric brain is in constant development; the vasculature is immature; and the consequences of nonconformal dosing to normal brain may be permanent and impede neurological development. There are further concerns regarding the long-term complications of radiation treatment in the pediatric patient such as secondary malignancies (including brain tumors), cyst formation, and radiation necrosis. The following is a review of the treatment of pediatric AVMs with Gamma Knife radiosurgery based on the literature and experience from our institution with Gamma Knife surgery (GKS) for 1300 AVM patients, 200 of whom were children.

**Natural History of Pediatric AVMs**

Population-based studies of AVMs demonstrate an incidence of approximately 1.34 per 100 000 patient-years, with an estimated prevalence of AVM hemorrhage among detected cases to be 0.68 per 100 000 person-years. Several natural history studies have been performed in an attempt to determine the natural history of intracranial AVMs. Hernesniemi et al identified 238 patients with a mean follow-up of 13.5 years. They found that the risk of hemorrhage was highest during the first 5 years after diagnosis and decreased thereafter. Risk factors for further hemorrhage included young age, previous rupture, deep and infratentorial locations, exclusively deep venous drainage, and large AVM size. Patients without previous hemorrhage may have a risk of bleeding as low as 0.9%/y; however, the rate may increase to 34.4% for those with hemorrhagic presentation, deep AVM location, and deep venous drainage. Overall, the annual risk of hemorrhage is within the range of 1% to 4%, and the annual risk of death is 1%. A useful formula for calculating a patient’s risk of lifetime hemorrhage in percentage is the following: 105 — patient’s age in years.

In addition to a high cumulative risk of hemorrhage, pediatric AVMs are believed to behave differently than adult AVMs. They are more frequently found in the basal ganglia, thalamus, and posterior fossa. They have a higher rate of hemorrhage and more extensive hemorrhage when they do bleed. Because of the inherent risks of leaving these lesions patent in the pediatric patient, identification of an AVM mandates definitive treatment whenever reasonably possible.

**Surgical Excision**

The most appropriate treatment modality for pediatric AVMs remains a topic of debate. When possible, surgical excision should remain the first choice. Surgical resection is the quickest and most complete method of nidus obliteration and allows removal of concurrent intracerebral hemorrhage. Surgery allows a total extirpation of AVMs in 50% to 98% of pediatric patients. In addition, some authors have demonstrated superior surgical outcomes in children compared with adults and cite neural plasticity as the reason for increased tolerance of the surgical procedure. Major operative complications occur in about 10% of patients, with mortality between 0% and 8%. Further refinements in operative technique, including the use of microscope-integrated intraoperative indocyanine green videoangiography
and intraoperative digital subtraction angiography,\textsuperscript{35} will continue to improve on current surgical results.

In general, the recurrence rate after complete surgical excision is low, on the order of 1.5\% to 5.5\%.\textsuperscript{36} Although surgery provides immediate eradication of the nidus, there is still a need for long-term follow-up because AVMs in the pediatric population have been reported to recur despite a negative postoperative angiogram. It is not clear whether these recurrences are due to residual AVM or if there is de novo formation of a new AVM component. It is clear, however, that follow-up must continue for a prolonged period. Akimoto et al\textsuperscript{37} reported a case of a de novo AVM appearing 17 years after total resection of 2 other AVMs in the same patient. Several theories have attempted to address the reasons for AVM growth and recurrence, including recruitment of collateral vessels, hemodynamic stress on dysplastic vessels, and the presence of a “reserve nidus,” which may initially have low or no flow on preoperative imaging and appear only after initial surgery.\textsuperscript{38}

**EMBOLIZATION**

The role of endovascular embolization of AVMs remains controversial. Early studies demonstrated a cure rate from embolization of between 0\% and 20\%.\textsuperscript{39} Wisoff and Berenstein\textsuperscript{40} similarly found that cure is not likely to be achieved by embolization alone. However, cure rates as high as 94\% with embolization alone have been reported.\textsuperscript{41} Morbidity with permanent neurological deficit is reported to be between 0.4\% and 12.5\%, with mortality in 0.4\% to 7.5\% of patients.\textsuperscript{42} One of issues arising from studies of embolization is that it is often unclear whether the operator began the procedure with an intention to cure or an intention to decrease the volume of the AVM to allow treatment of the residual with other techniques. Embolization often is used to decrease the size of the lesion for subsequent microsurgery or stereotactic radiosurgery. In general, embolization currently plays a role in advance of resection or radiosurgery. Before radiosurgery, embolization should be used to decrease the total volume of the nidus but maintain as compact a 3-dimensional volume as possible. Moreover, embolization should be used to obliterate flow to aneurysms associated with the AVM.

In addition, newer cohesive liquid embolics such as Onyx (EV3) have increased in popularity as a result of their increased control during injection compared with traditional embolics such as N-butyl cyanoacrylate (N-BCA). A recent multicenter randomized trial of presurgical embolization with Onyx and N-BCA demonstrated equivalence of Onyx to N-BCA in terms of reducing AVM volume by at least 50\%. Safety parameters, including resection time and blood loss, and adverse events from the embolization procedure were similar between the groups.\textsuperscript{33} It appears that with these newer embolic agents, even higher rates of cure will be achieved with embolization alone. However, results with long-term angiographic follow-up from large series are still pending.

**RADIOSURGERY**

Radiosurgery was successful in treating AVMs in adults. Accordingly, radiosurgery has been used to treat AVMs in children with satisfactory results (Table).\textsuperscript{44-49} Obliteration rates of 45\% to 86\% have been achieved. One of the factors that must be taken into consideration in comparisons of outcomes between series is the method of follow-up. Many families and patients prefer to have a non-invasive study such as magnetic resonance imaging (MRI) rather than a catheter angiogram. If MRI is used alone, the obliteration rates may appear to be slightly increased. It should also be noted that the size of the nidus varies between series. Although most series cover volumes of approximately 1.7 to 3.5 cm\(^3\) with similar results, Pan et al\textsuperscript{46} achieved excellent results with obliteration in 81\% of patients, with an average treated volume of 11.7 cm\(^3\) and a follow-up of 35 months.

Currently, the largest pediatric series with the longest duration of follow-up is from the University of Virginia.\textsuperscript{49} Yen et al\textsuperscript{49} found that of the 200 patients \(\leq 18\) years of age (mean age, 12.7 years) treated, 186 had follow-up of \(> 2\) years (mean, 80 months; range, 6-222 months). The most common presenting symptom was hemorrhage (71.5\%). As a case example, the patient in Figures 1 through 3 was a 12-year-old boy presenting with intraventricular hemorrhage from a 3.2-cm\(^3\) parietal AVM successfully treated with a prescription dose of 25 Gy to the 50\% isodose line. In the University of Virginia series, the mean nidus volume treated was 3.2 cm\(^3\) at the time of GKS, and a mean prescription dose of 21.9 Gy was used. After the initial treatment, 49.5\% of patients achieved total obliteration of the nidus. After repeat GKS in 41 patients, the overall obliteration rate increased to 58.6\%. With the inclusion of those patients who had only MRI to confirm nidus obliteration, the rate of cure increased to 69\%.\textsuperscript{49}

Statistical analysis demonstrated that a negative history of pre-GKS embolization (\(P = .001\)), small nidus volume (\(P < .001\)), high prescription dose (\(P < .001\)), high maximum dose (\(P = .009\)), small number of isocenters (\(P = .02\)), and low radiosurgery-based grade (as described by Pollock et al\textsuperscript{50} (\(P < .001\)) were significantly associated with an increased rate of AVM obliteration. Of the 112 patients with nidi < 3 cm\(^3\), 72.3\% obtained an angiographic obliteration, and a further 9.8\% had no flow voids visible on MRI. Sex (\(P = .84\)), age (\(P = .21\)), history of hemorrhage before GKS (\(P = .16\)), presence of radiation-induced imaging changes after GKS (\(P = .63\)), and Spetzler-Martin grade were not related to nidus obliteration.

A comparison of our experience at the University of Virginia and other series shows that the factors detailed above are generally consistent. In contrast to our study, Shin et al\textsuperscript{48} and Reyns et al\textsuperscript{47} reported a higher obliteration rate in younger
TABLE. Summary of Recent Reports on Pediatric Arteriovenous Malformations Treated With Radiosurgery\textsuperscript{a}

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Patients, n</th>
<th>AVM Volume, cm\textsuperscript{3}</th>
<th>Prescription Dose, Gy</th>
<th>Obliteration Rate After 1 GKS Based on Angiography/Angiography or MRI, %/%</th>
<th>Obliteration Rate After Repeat GKS Based on Angiography/Angiography or MRI, %/%</th>
<th>Annual Hemorrhage Rate, %</th>
<th>Non–Hemorrhage-Related Neurological Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin et al\textsuperscript{48} (2002)</td>
<td>100</td>
<td>1.8 (0.1-19.2)</td>
<td>20 (17-28)</td>
<td>71/75</td>
<td>1.5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nataf et al\textsuperscript{44} (Linac) (2003)</td>
<td>57</td>
<td>3.5 (0.6-16)</td>
<td>23.8 (18-28)</td>
<td>61/NA</td>
<td>4.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nicolato et al\textsuperscript{45} (2006)</td>
<td>92</td>
<td>2.9 (0.1-25)</td>
<td>22 (14-26)</td>
<td>86/NA</td>
<td>0.6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Reyns et al\textsuperscript{47} (Linac) (2007)</td>
<td>100</td>
<td>2.8 (0.9-21.3)</td>
<td>23 (15-25)</td>
<td>65/NA and 70/NA</td>
<td>1.7</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Pan et al\textsuperscript{46} (2008)</td>
<td>105</td>
<td>11.7 (0.4-63)</td>
<td>18.5 (14.5-25)</td>
<td>65/NA and 81/NA</td>
<td>1.9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Yen et al\textsuperscript{49} (2010)</td>
<td>186</td>
<td>3.2 (0.1-24)</td>
<td>21.9 (7.5-35)</td>
<td>50/58 and 59/69</td>
<td>2.6</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}AVM, arteriovenous malformation; GKS, Gamma Knife surgery. Values are mean or median (range) as appropriate.

FIGURE 1. A, a 12-year-old boy presenting with intraventricular hemorrhage. Right internal carotid artery injection (anteroposterior projection) demonstrating a 27.8 × 9.1 × 13.2-mm right parietal arteriovenous malformation (AVM) fed by middle cerebral artery branches with both superficial and deep venous drainage. B, right internal carotid artery injection (lateral projection) demonstrating the parietal AVM. C, post-Gamma Knife surgery (GKS) right internal carotid artery injection (anteroposterior projection) demonstrating obliteration of the AVM with no residual AVM filling 16 months after GKS. D, post-GKS right internal carotid artery injection (lateral projection) demonstrating obliteration of the AVM.
patients. In our experience of > 1300 AVM patients treated with GKS, we did not observe a difference in obliteration rates between pediatric and adult patients (unpublished data). Some authors have demonstrated a more rapid obliteration in children compared with adults. Tanaka et al\textsuperscript{51} reported a 1-year obliteration rate in adults of 45% compared with 74% in children, with the rates increasing to 81% and 94% at 2 years, respectively. Interestingly, Nicolato et al\textsuperscript{45} reported a similar rate of obliteration between adults and children but also noted that children achieved obliteration earlier. The reason behind higher failure rates for embolized patients remains to be completely elucidated. It is possible that improvements in targeting resulting from the advent of high-resolution MRI and MR angiography may lead to more accurate targeting. Laboratory investigations are emerging that support the notion that embolization materials, including newer varieties such as Onyx, may attenuate radiation dose to a certain degree and thus contribute to dosage errors and treatment failures.\textsuperscript{52} Regardless of preoperative embolization status, we prefer to use a combination of contrast MRI and traditional digital subtraction angiography to help clearly delineate the nidus for treatment planning (Figure 3).

COMPLICATIONS OF GKS

Clinical follow-up in the series from our institution ranged from 24 to 240 months (mean, 98.4 months). After radiosurgery, 10 patients had a single hemorrhage, and 7 patients had 2 hemorrhages. Assuming that patients with completely obliterated AVMs were no longer at risk of hemorrhage, there was an annual hemorrhage rate of 2.4%. No patients with a completely obliterated AVM on follow-up angiography experienced a hemorrhage. The hemorrhage rate decreased from 5.4%/y for the first 2 years after treatment to 0.8%/y from years 2 to 5. At the end of the follow-up period, 5 patients still had neurological deficits caused by hemorrhage during the latency period.\textsuperscript{49} Our results were similar to other series in the literature that demonstrated a hemorrhage rate during the latency period of 0.6% to 3.2%.\textsuperscript{44-48,53,54} As is the case with incomplete embolization of the nidus, partial obliteration by radiosurgery does not appear to protect against AVM rupture from the residual. Some authors have found that there appears to be some decreased risk from partial obliteration.\textsuperscript{55} However, it is not clear whether this decrease in hemorrhage rate may represent a return to the natural history of AVM hemorrhage. It is therefore important to counsel patients and their families that hemorrhage is possible during the latency period and appears similar to that of the natural history of the disease during this time.

It is important to perform serial MRI to look for postprocedural complications. In the series from the University of Virginia, MRI follow-up ranged from 6 to 222 months (mean, 80 months). We observed increased T2 signal change in 37.8% of 180 patients who underwent serial MRI. The changes occurred at a mean of 12 months after GKS and resolved at a mean of 20 months after the first appearance of the imaging changes. Although these changes were associated with an increased prescription dose and a negative history of prior hemorrhage, the cause of these changes is not clear. Various combinations of radiation, gliosis, hemodynamic changes, and ischemia have been suggested as reasons for these changes. Of the 68 patients with these changes, 55 were asymptomatic, 7 presented with headache, and 6 had new or worse neurological deficits. A full neurological recovery over time occurred in 4 of the 6 patients with deficit. The complication rate in our series is comparable to other radiosurgical series, \textsuperscript{49,56} 0% to 6.7%.\textsuperscript{44-48,53}

In our series, cysts developed in 5 patients. No cyst was large enough to require operative intervention to drain it. Two children (a 7-year-old boy and a 12-year-old girl) developed meningiomas (1 tentorial and 1 convexity) after treatment. Both of these lesions have been followed up with serial MRI and have not required operative intervention because they have not increased in size.\textsuperscript{49,56}

NEUROCOGNITIVE FUNCTION AND PERFORMANCE STATUS

Full neuropsychiatric testing of pediatric patients undergoing GKS is generally not performed. Riva et al\textsuperscript{57} used age-matched siblings or first cousins as control subjects and reported no neurological, cognitive, memory, or attention deficits after a follow-up of 6 years after GKS. In our experience of 186 patients, there were 5 patients with residual neurological deficits from post-GKS hemorrhages and 2 with permanent neurological deficits from radiation-induced changes.
A further 2 patients had medically refractory seizures, 2 patients were incapacitated by persistent shunting from residual large AVMs, and 2 patients had personality disorders. Overall, 13 patients deteriorated after GKS. Of these 13, 8 patients were unable to attend a regular school, gain employment, or pursue higher education. We cannot say with certainty whether some of these issues were treatment related or persistent effects of the pretreatment condition.

CONCLUSIONS

The correct treatment for pediatric AVMs needs to be tailored for each patient. The characteristics of the AVM and the local expertise and experience with endovascular and microvascular surgery will determine the appropriate treatment paradigm for a patient. In general, microsurgery should be performed whenever reasonably possible because it provides immediate extirpation of the nidus. Radiosurgical patients treated with smaller nidus volumes, no prior embolization, and higher prescription doses are likely to achieve obliteration with a low likelihood of complication. The risk of hemorrhage during the latency period persists, and patients must be followed up with serial imaging to detect late complications.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.
REFERENCES


© 2011 The Congress of Neurological Surgeons