Stereotactic Radiosurgery for Pediatric Arteriovenous Malformations

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- Radiosurgery • Arteriovenous malformation
- Pediatric neurosurgery

Children with intracranial arteriovenous malformations (AVMs) have a high lifetime risk of hemorrhage, and appropriate treatment of these lesions in children is critical. It is estimated that 12% to 18% of all open resections for intracranial AVMs are performed on children.[1–4] Children are more likely than adults to present with hemorrhage, which often leads to significant morbidity, and mortality rates as high as 25% have been reported.[5] The annual hemorrhage rate from intracranial AVMs has been estimated to be between 2% and 4%, and some have suggested that the yearly risk of hemorrhage from AVMs may be higher in the pediatric population.[6–8] The options for treatment of intracranial AVMs in the pediatric population include open microsurgical resection of the nidus, embolization of feeding vessels, stereotactic radiosurgery (SRS), or a combination of these treatments. The role of SRS in the treatment of children with AVMs is the topic of this review.

INDICATIONS AND PATIENT CHARACTERISTICS

While firmly established as a treatment of AVMs in adults, concerns regarding the potential toxicity of radiation to the developing nervous system delayed the widespread use of SRS for children with intracranial AVMs.[9] Modern series of children treated with radiosurgery for AVMs, though, have shown this treatment modality to be effective and safe. While microsurgical resection is generally considered the treatment of choice for AVMs that can be resected safely, SRS is more often recommended for AVMs in critical cortical areas and deep brain locations such as the thalamus, basal ganglia, and brainstem.[10] An additional consideration for pediatric patients is that SRS may be better tolerated than surgical resection when significant intraoperative blood loss is anticipated. An important difference when comparing outcomes of microsurgical resection and SRS for AVMs is that patients remain at risk for hemorrhage following SRS until the AVM has gone on to complete obliteration. Also, while the early morbidity following SRS in children has been documented in several studies to be relatively low, the life expectancy of pediatric patients with AVMs is many decades and the long-term risk of SRS is not yet fully defined.

Over the last decade, several modern retrospective reviews have been published on the use of SRS in pediatric patients harboring AVMs.

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These reports suggest that pediatric patients are more likely than adults to present with hemorrhage. Not surprisingly, the number of patients undergoing SRS who have had a prior hemorrhage ranges from 53% to 79% of patients.[11–19] The average age of children undergoing SRS is remarkably similar over several series from different institutions, ranging from 11 to 15 years old.[11–19] The available series have not shown a significant difference in the male to female ratio of children treated with SRS.

RADIOSURGICAL TECHNIQUE

The technique for SRS varies from center to center depending on the method of radiation delivery and local practice. At the Mayo Clinic, the procedure is performed under general anesthesia for all patients younger than 13 years, with older children undergoing either general anesthesia or monitored anesthesia care based on the child's maturity level and the preference of the patient's parents. A stereotactic headframe is placed on the patient and a stereotactic magnetic resonance imaging (MRI) scan with gadolinium administration is performed for dose planning. In the majority of patients, biplanar stereotactic angiography is also used, and both imaging modalities are imported into the computer workstation. At the authors' institution, radiosurgery is performed using the Leksell Gamma Knife (Elekta Instruments, Inc, Norcross, GA, USA). The authors recently reported on 38 children undergoing Gamma Knife AVM radiosurgery. Of these, 32 were treated in a single session and 6 were treated with staged-volume radiosurgery.[11,20] The median margin dose in this series was 20 Gy (range, 16–25 Gy). The mean marginal dose in the available large studies of SRS for childhood AVMs ranges from 16.7 to 23.8 Gy.[11–19] In a study by Smyth and colleagues,[19] a multivariate analysis of factors associated with AVM obliteration following SRS for childhood AVMs showed a tenfold increase in obliteration rates in patients who had a treatment margin dose of 18 Gy or more. Although some centers have used pre-radiosurgical embolization as a method to reduce the AVM size in preparation for SRS, recent studies have questioned the usefulness of embolization as a meaningful adjunct to SRS.[21] Because the utility of this technique is not established, the authors do not recommend embolization before radiosurgery for their patients.

OUTCOMES AND PREDICTORS OF SUCCESS

The goal of AVM radiosurgery is nidus obliteration and reduction in annual hemorrhage rate. Recent studies have documented a total AVM obliteration rate between 61% and 86% with average follow-up between 26 and 71 months.[11–18] Smyth and colleagues[19] reported a lower obliteration rate than comparable studies. This group reported an obliteration rate of 35% with a mean follow-up of 62 months. Of note is that this center used a lower mean marginal dose (16.7 Gy) than most other reports (18.5–23 Gy), and on multivariate analysis showed a much higher rate of obliteration when the mean marginal dose prescribed was 18 Gy or higher. The lower obliteration rate likely reflects the lower mean marginal dose prescribed. While most pediatric patients with AVMs present with hemorrhage and the ultimate goal of treatment is to reduce the risk of intracranial hemorrhage, radiosurgery also seems to have a positive effect on seizure outcome for children presenting with AVM-associated seizure disorders. Although there are fewer studies regarding the seizure outcome following SRS for childhood AVMs, most series suggest a 50% to 90% improvement in seizure burden after SRS.[12,13,22]

The volume of the AVMs treated with radiosurgery has been variable across institutions reporting significant experience treating childhood AVMs. Studies have reported an average treated volume between 1.7 cm^3 and 5.37 cm^3.[11–19] Many studies have documented a statistically significant decrease in obliteration rate for larger volume AVMs. Levy and colleagues[12] reported a series of 53 children treated with SRS for AVMs with at least 36 months of follow-up. On multivariate analysis the only factor associated with obliteration rate in their series was AVM volume. Shin and colleagues,[18] in a series of 100 patients, found that age younger than 12 years, smaller AVM volume and diameter, and Spetzler-Martin grade of III or less were associated with improved obliteration rate. Nicolato and colleagues[15] observed that younger age and lower Spetzler-Martin grade correlated with improved obliteration rate, and that Spetzler-Martin grade and noneloquent location correlated with improved time to obliteration after treatment with SRS. In one recent series, Pan and colleagues[16] reported a significantly higher average volume treated (11.7 cm^3) than for previous studies, but this group was still able to achieve a relatively high obliteration rate for large AVMs (64%).

In the series from their own center, the authors observed a 68% obliteration rate with a median follow-up of 42 months.[11] None of the patients suffered a new neurologic deficit after treatment despite the majority of patients having Spetzler-Martin grade III or higher AVMs. The authors also showed that the radiosurgery-based AVM

score[23,24] was useful in predicting outcomes in children treated with SRS. Age is one of the key measures in the radiosurgery-based AVM score (along with AVM volume and location). The authors found that children with a radiosurgery-based AVM score less than 1 had an 88% chance of excellent outcome compared with a 52% chance in children who had a score greater than 1. Other centers tested the radiosurgery-based AVM system and found that it effectively predicted outcomes after radiosurgery for pediatric AVMs.[25]

HEMORRHAGE RISK AND MORBIDITY

Whereas direct surgical resection of an AVM nidus immediately removes the hemorrhage risk in children harboring AVMs, radiosurgery has a much longer interval between treatment and obliteration of the AVM nidus. This factor is of particular concern, as hemorrhage is the most common presenting symptom in children and the vast majority of children treated with SRS in the literature presented with intracranial hemorrhage. The post-radiosurgery hemorrhage rate in large modern series is between 1.3% and 8.2%.[11–19] The annual bleeding rate following radiosurgery is between 0.56% and 4.3%. In the study by Smyth and colleagues[19] an overall 8% bleeding rate was found, with a rate of 4.3% per year over the first 3 years following treatment. Shin and colleagues[18] found that posterior fossa AVMs were at a significantly greater risk of posttreatment hemorrhage. Rare deaths have been reported following SRS due to hemorrhage.[17,18] Permanent neurologic morbidity following SRS is low in reported series. In the authors' own series, one patient presented with an intraventricular hemorrhage following treatment but had no permanent neurologic morbidity. No patient had new permanent neurologic morbidity after treatment. Other series have put the risk of neurologic morbidity between 0% and 6%.[12,13,16,17,19] One method to reduce the incidence of post-radiosurgical hemorrhage is to delay SRS for at least 6 months after a patient's most recent bleeding event. By waiting this interval, the period of highest risk of AVM rebleeding has passed and the annual risk of hemorrhage is again approximately 2% to 4%.

It should also be mentioned that children who undergo successful SRS or microsurgery for intracranial AVM should be followed closely, as recurrence of these lesions has been documented in the pediatric population.[3–5,26–29] Many have hypothesized that AVM vessels in childhood have a more immature phenotype than adult AVM vessels. It is possible that immature, angiographically undetectable AVM vessels may persist after treatment and lead to delayed regrowth of an AVM nidus.[28] Furthermore, recanalization of previously obliterated AVM vessels may account for regrowth in the pediatric population.[27] It is advised that children with documented AVM obliteration continue to be followed into adulthood to rule out regrowth of these lesions. Lastly, one must consider the risk of radiation-induced tumors in this population with an extended life expectancy. Whereas the risk of second tumor formation is between 2% and 3% following fractionated radiation therapy, the risk of radiation-induced tumors after radiosurgery has been estimated to be approximately 1 in 1000 or less. Rowe and colleagues[28] from the National Center for Stereotactic Radiosurgery in Sheffield compared the incidence of new central nervous system malignancies in their patient population with the national incidence in the United Kingdom. Based on more than 30,000 patient-years of follow-up, they did not find an increased incidence in their radiosurgical patients compared with the age- and sex-adjusted national cohort. The primary weakness of this study is the relative short mean follow-up interval (6.1 years) after radiosurgery relative to the life expectancy of patients having radiosurgery for benign conditions. Neurocognitive deficits after small-volume, single-session radiosurgery have not been reported.

MAYO CLINIC EXPERIENCE

In 2006 the authors published their experience on pediatric AVM radiosurgery for 38 patients managed between 1990 and 2001.[11] To date, the authors have now performed AVM radiosurgery for a total of 60 AVM patients 18 years or younger. Excluded from further analysis are 3 patients managed early in the series with had partial AVM treatment and 9 patients without any (n = 2) or less than 12 months of clinical and radiologic follow-up (n = 7). The median age of the remaining 48 patients (20 boys, 28 girls) was 15 years (range, 3–18 years). Twenty-seven patients (57%) had a previous hemorrhage, whereas 10 patients (21%) had headaches, 7 patients (15%) had seizures, and 4 patients (8%) had their AVM discovered incidentally. The AVM locations included the cerebral hemispheres (n = 32), thalamus (n = 11), brainstem (n = 2), basal ganglia (n = 2), and cerebellum (n = 1).

Single-session radiosurgery was performed for 43 patients and 5 patients underwent staged-volume procedures. A median of 6 isocenters of radiation (range, 1–25) were used to cover a median AVM volume of 3.5 cm^3 (range, 0.2–32.5 cm^3). The median AVM margin dose was 18 Gy (range, 15–25 Gy) and the median maximum

radiation dose was 36 Gy (range, 22–50 Gy). The median modified radiosurgery-based AVM score was 0.93 (range, 0.26–3.47).[30] Twelve patients (25%) underwent repeat radiosurgery at a median of 52 months (range, 41–73 months) after their initial radiosurgical procedure. The median follow-up after radiosurgery was 73.5 months (range, 12–151 months).

Nidus obliteration was confirmed in 25 patients (52%) after their initial radiosurgery by angiography (n = 16) or MRI (n = 9). Five additional patients had AVM obliteration after repeat radiosurgery, for a total obliteration rate of 63%. Three patients (6%) had radiation-related deficits after initial (n = 1) or repeat radiosurgery (n = 2). One patient had diplopia from a third nerve paresis after initial radiosurgery of a midbrain AVM, one patient developed hand numbness after repeat radiosurgery of a thalamic AVM, and one patient developed an intentional tremor after repeat radiosurgery of a thalamic AVM. No patient had AVM bleeding following radiosurgery. No patient has had a documented neurocognitive decline or radiation-induced tumor after radiosurgery. Patients with a modified AVM score of less than 1 more frequently had nidus obliteration without new deficits (23/30, 77%) compared with patients with a modified AVM score greater than 1 (6/18, 33%) (P = .005, Fisher Exact test).

COMPARISON WITH ADULT OUTCOMES FOLLOWING SRS

The number of studies on AVM radiosurgery in children is far fewer than the published experience of adult AVM radiosurgery. However, it is unclear whether these data can be directly applied to the pediatric population. Many believe that AVM vessels in children have less mature morphology, and that children with AVMs may have a more nebulous natural history. The fact that AVMs treated in childhood have the capacity in rare instances to reoccur has been touted as evidence of the dynamic character of these lesions in childhood.[26,31] Obliteration rates in pediatric patients may be better when compared with adult patients. A study by Tanaka and colleagues[32] reported outcomes for 26 pediatric and 76 adult patients following SRS for intracranial AVMs. Both groups of patients had similar characteristics with regard to AVM grade, treated volume, and radiation dose. Complete obliteration was noted in 45% of adults and 72% of children 1 year after treatment; this rose to 85% for adults and 95% for children 2 years after treatment. Complications were only seen in the adult population (radiation necrosis and bleeding); however, the population of pediatric patients was smaller.

More recently, Nicolato and colleagues[15] reported similar findings in a cohort of 62 children and 193 adult patients. Overall obliteration rates were found to be similar in adults and children (87.6% and 85.5%, respectively); however, the pediatric cohort had a statistically significant decrease in the time to obliteration following treatment and a higher actuarial obliteration rate 36 months after treatment. Although the radiobiological basis of this difference is not clear, it is hypothesized that the endothelium of childhood AVMs has a more robust reaction to radiation. Nicolato and colleagues[14] also showed in a similar study that children had a similar hemorrhage risk during the latency period between treatment and nidus obliteration and that children had a slightly smaller rate of permanent neurologic morbidity following SRS for AVMs, although this difference was not statistically significant. It should be noted, however, that there were statistically significant differences between the cohort of adults and the cohort of children. The pediatric cohort had a significantly greater number of deep-seated AVMs treated with SRS, and children presented with hemorrhage at a much higher rate.[14] Pan and colleagues[16] also recently reviewed their experience with 105 pediatric patients and 458 adult patients treated with SRS for intracranial AVMs. Their results stand in some contrast to the previous reports. Pan and colleagues found that obliteration rates were lower in children for medium-sized (3–10 cm^3) AVMs compared with those of the adult cohort (57.5% compared with 77.9%).

SUMMARY

Stereotactic radiosurgery is a safe and effective option for properly selected pediatric AVM patients. SRS is of particular benefit for children with critically located or deep lesions for which surgical resection would pose a tremendous risk to the patient. The time to AVM obliteration appears to be shorter in children when compared with adult AVM patients.

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