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Scientific Article

Pediatric Intracranial Arteriovenous Malformation: Long-Term Outcomes with Linear Accelerator (LINAC)-Based Radiosurgery

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Abstract

Purpose: To analyze and report the long-term outcomes of intracranial arteriovenous malformations (AVM) treated with linear accelerator (LINAC)-based radiosurgery (LBRS) in the pediatric population.

Methods and Materials: A series of 34 pediatric patients (≤18 years old) who were treated between 2002 and 2016 were analyzed. All patients were treated with LBRS in a single fraction, with a median dose of 16.8 Gy to the 80% isodose line. Median age at treatment was 14.4 years (range 5.5-18.9). Median AVM volume was 2.91 mL (range 0.228-27.313). Median modified radiosurgery-based AVM score was 0.83 (range 0.18-2.96). The most common presenting symptom was intracranial hemorrhage (ICH) (n = 22, 64.7%). Nine patients underwent intervention before LBRS, which included prior embolization or resection. Seven lesions were in eloquent locations, defined as basal ganglia, thalamus, or brainstem. Cerebral angiography was done to confirm obliteration.

Results: Median follow-up time was 98 months (range 36-200 months). Twenty-two of the 34 lesions were obliterated (64.7%) with median time to obliteration of 37 months (range 14-79). No deaths occurred during the follow up period; however, two patients experienced ICH after treatment. Three other patients were treated for symptomatic radiation necrosis.

Conclusions: Treatment of intracranial AVM with LBRS in the pediatric population is demonstrated to be safe and effective with long-term follow up.

Introduction

Intracranial arteriovenous malformations (AVM) are congenital abnormalities of blood vessels in which the arterial and venous systems communicate directly through shunts, bypassing the normal capillary bed.[1] Prospective population-based data found an average annual AVM detection rate of 1.34 per 100,000 person-years, first-ever AVM hemorrhage rates of 0.51 per 100,000 person-years, and an average presenting age of 31 years old.[2] Although

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neurologic deficits and seizures are clinical indicators that often lead to the discovery of an underlying AVM, hemorrhage represents the true mortality risk. The annual hemorrhage rate has been estimated to be about 3.0%, with a slightly lower rate of 2.2% for unruptured AVMs, and a higher rate of 4.5% for previously ruptured AVMs.[3] Multiple risk factors affect the likelihood of hemorrhage, including previous rupture, large size, deep AVM location, deep venous drainage, and associated aneurysms.[4] The mortality rate is approximately 1.0% per year, with a combined major morbidity and mortality rate of 2.7% per year.[5]

Pediatric AVM poses a unique challenge because this seemingly small yearly risk can become significant over time. Two hemorrhage risk formulations have been proposed:

$$\text{Risk of hemorrhage} = 1 - (\text{risk of no hemorrhage})^{\text{expected years of remaining life}}$$

Or the simpler:

$$\text{Risk of hemorrhage} = 105 - \text{patient age in years}$$

Thus, with the 3% hemorrhage rate, a 13-year-old boy with an intracranial AVM would be at an approximately 88% to 92% risk of hemorrhage during his lifetime, depending on which calculation is used.[6,7]

Multiple studies have shown that linear accelerator (LINAC)-based radiosurgery (LBRS) is safe and efficacious in the adult population.[8-10] Data from the International Gamma Knife Research Foundation showed that outcomes after stereotactic radiosurgery (SRS) for comparable AVMs in pediatric versus adult patients did not significantly differ, thus establishing SRS as a reasonable treatment option for appropriately selected pediatric patients.[11]

Although data concerning the utilization of LBRS in the pediatric population are sparse, even rarer are data involving long-term follow-up of such patients beyond the initial 3 years posttreatment. The extended life expectancy of pediatric patients renders them vulnerable not just to the risk of the lesion itself, but also to the early/late effects of the interventions.

This study represents the experience at 1 institution treating pediatric AVMs with LBRS and the ensuing outcomes with long-term follow-up.

Methods and Materials

Patient characteristics

Between 2002 and 2016, we used LBRS to treat 197 consecutive patients with intracranial AVMs. This series included 34 patients (17%) aged 18 or younger at the time of treatment (Table 1). Most AVM presentations are first assessed by neurosurgical specialists; thus, the prominent microsurgery-based predictive scores must be considered.

Table 1 Patient characteristics

Total patients	34
Median age in years (range)	14.4 (5.5-18.9)
Sex:	n (%)
Male	19 (55.9%)
Female	15 (44.1%)
Presenting symptoms:	n (%)
ICH	22 (64.7%)
Seizures	4 (11.8%)
Neurologic deficit	3 (8.8%)
Headache	1 (3%)
Incidental	4 (11.8%)
Prior treatments:	n (%)
Embolization	5 (14.7%)
Surgical resection	4 (11.8%)

Abbreviation: ICH = intracranial hemorrhage.

This study used the Spetzler-Martin system, which considers the AVM largest diameter, location, and venous drainage.[12-14]

Recent comparative analysis has shown the continuous scoring modified radiosurgery-based AVM score (mRBAS) as outperforming other grading systems, and thus it was used for this analysis.[15-20] The score is calculated as follows:

$$\text{AVM Score} = (0.1)(\text{volume, cc}) + (0.02)(\text{age, year}) + (0.5)(\text{location, basal ganglia / thalamus /brain stem} = 1;\ \text{other sites} = 0)$$

Treatment and follow-up

Patients underwent regular follow-up with magnetic resonance imaging (MRI) and then subsequent cerebral angiography for confirmation of nidus obliteration. Most patients underwent confirmatory angiogram approximately 3 years posttreatment. Only 4 of the patients did not undergo follow-up angiogram.

All patients underwent stereotactic radiosurgery using a linear accelerator (Novalis, Brainlab, Helmstetten, Germany) with minimultileaf collimation, 6-MV x-rays, and single isocenter technique. From 2002 to 2010, a stereotactic frame was used for immobilization during LBRS treatment. From 2010 to present, a frameless, image-guided technique was employed. This technique has been described in detail elsewhere.[21,22] A high-resolution computed tomography scan of the brain was obtained in the thermoplastic mask with a head and neck fiducial localizer. MRI, angiography, and computed tomography images were imported to the planning software and fused. Plans were done using various iterations of BrainLab iPlan planning software. Final prescription dose and isodose line selection did not follow a strict protocol and was left to the discretion of the treating physicians.

The maximum allowable hot spot for each treatment was 102% of prescription.

Outcome and statistical analysis

The primary outcome was the proportion of patients who achieve AVM obliteration. Patients were followed with serial MRIs annually unless a significant intercurrent event prompted a sooner scan. Cerebral angiograms were done after 3 years to confirm obliteration if suspected by MRI. Obliteration was defined as the absence of any angiographically visible arteriovenous shunt. If obliteration had not been achieved within 3 years, further treatment was considered, including surgery, embolization, or repeat radiosurgery.

Complications studied included post-LBRS hemorrhage or increasing neurologic deficits. MRI imaging was evaluated for radiation-induced change (RIC), which initially manifests as perinidal T2 signal change. Although most RICs are asymptomatic, a subset of patients with radiologically evident RIC develop neurologic symptoms, such as headache, seizure, or focal neurologic deficit. Most of these are transient and can be managed medically; however, a minority of LBRS-treated AVM patients suffer permanent neurologic deficits or require more invasive intervention such as surgical resection of radiation necrosis.[23]

Univariate analysis was performed using R version 3.5.3 to evaluate factors affecting obliteration. X^2 test and Fisher exact test were used for categorical variables. The following variables were studied: age, sex, presenting symptom, prior interventions, prior intracranial hemorrhage (ICH), Spetzler-Martin (SM) grade, nidus diameter, location, nidus volume, mRBAS, and prescription dose. Similar analysis was done for posttreatment side effects. The results were considered statistically significant if $P < .05$ after 2-sided test.

This work was approved by the Kaiser Permanente Southern California Medical Group Institutional Review Board.

Results

Follow-up and obliteration outcomes

Table 1 summarizes the patients' clinical characteristics. The median age at time of treatment was 14.4 years (range, 5.5-18.9). The most common presenting symptom was ICH (n = 22, 64.7%). Seizures, neurologic deficits, and headaches led to diagnosis in 4 (11.8%), 3 (8.8%), and 1 (3%) patient, respectively. Four patients (11.8%) had their AVM found incidentally on imaging while being evaluated for other reasons. Nine (26.5%) patients underwent intervention before LBRS, with 5 (14.7%) undergoing embolization and 4 (11.8%) undergoing partial surgical resection. In this cohort the median AVM diameter was 26 mm (range, 11-50) and the Spetzler-Martin system distribution was as follows: grade 1, n = 2 (5.9%); grade 2, n = 11 (32.4%); grade 3, n = 15 (44.1%); grade 4, n = 6 (17.6%); grade 5 to 6, n = 0.

Table 2 AVM characteristics

Spetzler-Martin grade	n (%)
Grade I	2 (5.9)
Grade II	11 (32.4)
Grade III	15 (44.1)
Grade IV	6 (17.6)
Grade V-VI	0
AVM characteristic	
Median target volume (cc) (range)	2.91 (0.228-27.313)
Median mRBAS (range)	0.83 (0.18-2.96)
AVM location	n (%)
Eloquent	7 (20.6)
-Basal ganglia	3 (8.8)
-Thalamus	4 (11.8)
Noneloquent	27 (79.4)
-Choroid plexus	2 (5.9)
-Frontal	5 (14.7)
-Parietal	5 (14.7)
-Temporal	4 (11.8)
-Occipital	6 (17.6)
-Multisupratentorial lobar	5 (14.7)

Abbreviations: AVM = arteriovenous malformations; mRBAS = modified radiosurgery-based AVM score.

At the time of treatment, the median AVM nidus volume was 2.91 mL (range, 0.228-27.313 mL). Of the AVMs treated, 7 (20.6%) were in eloquent locations, defined as within the basal ganglia, brain stem, or thalamus (Table 2). Median mRBAS score was 0.83 (range, 0.18-2.96) for this cohort.

The dose varied depending on lesion size and location (Table 3). The median prescription dose was 16.8 Gy (range, 14-20) delivered to the 80% isodose line in 4 to 5 dynamic noncoplanar conformal arcs. Six patients were treated to the 90% isodose line.

As seen in Table 4, the 34 patients had a median follow-up of 98 months (range, 36-200). Twenty-two of the 34 lesions were obliterated (64.7%) with median time to obliteration of 37 months (range, 14-79). All of these were confirmed with angiography. The earliest documented obliteration at 14 months was an SM grade 1 lesion with an mRBAS of 0.31. The next earliest confirmation was at 24 months. The latest documented obliteration at 79 months was for a patient who had initially been lost to follow-up and so confirmatory angiography was delayed. Two other patients had similar delays, with confirmatory angiography at 53 and 73 months. All other patients underwent confirmatory angiography between 24 and 42 months.

Three patients underwent surgical resection after their AVMs failed to obliterate within the first 3 years of

Table 3 Comparison of AVM characteristics and dose

AVM size (cc)	n (%)
<1.0	7 (20.6)
1.0–4.0	12 (35.3)
4.1–10.0	10 (29.4)
>10.0	5 (14.7)
AVM size (cc)	Median dose (cGy)
<1.0	1800
1.0–4.0	1800
4.1–10.0	1600
>10.0	1500
AVM location (n)	Median dose (cGy)
Eloquent (7)	1600
Noneloquent (27)	1760

Abbreviation: AVM = arteriovenous malformations.

Table 4 Follow-up and confirmed obliteration

Median follow-up (m) (range)	98 (36-200)
Confirmed obliteration	22 (64.7%)
Median time to obliteration (m) (range)	37 (14-79)
Post-RT treatment	n (%)
Additional SRS	5 (14.7%)
Embolization	1 (2.9%)
Surgical resection	5 (14.7%)
Morbidity	n (%)
Post-RT hemorrhage	2 (5.9%)
Radiation necrosis	3 (8.8%)

Abbreviations: RT = radiation therapy; SRS = stereotactic radiosurgery.

treatment, and surgical cure was achieved in all cases. These were not counted in the obliteration percentage; they did contribute to a cure of 73.5%. Overall, 8 of the patients underwent some form of post-LBRS treatment, 5 underwent additional LBRS, 1 underwent embolization and resection, and 2 others underwent resection alone. Four of these 8 patients achieved complete obliteration with ensuing treatment.

After univariate analysis for obliteration, only male sex was found to be significant ($P = .03$).

Morbidity

Two patients (5.9%) experienced hemorrhage after treatment at 29 and 31 months. Both patients developed hemorrhagic cysts requiring surgical intervention to control. Neither patient died and both have been followed for multiple years after the complication. The first patient was a 17-year-old male who presented with ICH undergoing embolization of intranidal aneurysm before LBRS treatment. His initial MRI showed cystic encephalomalacia with the presence of 2 parenchymal cysts as well as a large hemorrhagic collection likely related to the presence of the AVM, the initial ICH, and treatment. He underwent emergent craniectomy for evacuation of the hemorrhagic collection and decompression of the 2 cysts almost 3 years after treatment. He then underwent cerebral angiogram 1 month later, which confirmed obliteration of the AVM nidus. He fully recovered without new deficits.

The second patient was an 8-year-old female who also presented with ICH and underwent evacuation of the hemorrhage and subtotal resection of the AVM nidus at that time. Two years after the initial presentation she underwent LBRS at the age of 10. She underwent cerebral angiogram 2 years after treatment, which showed obliteration of the AVM; however, MRI showed increased development of encephalomalacia and presence of a large cystic lesion. Approximately 1 year after confirmatory angiogram, the patient suffered a hemorrhage from the large cyst, which prompted an emergent craniotomy and evacuation of the hemorrhage and resection of the cyst. The second patient suffered permanent neurologic deficits from this hemorrhage.

Three patients experienced symptomatic radiation necrosis requiring treatment. Two of the patients were put onto dexamethasone regimens and recovered without permanent deficits. One patient was a 14-year-old male with a 0.387 cm^3 occipital lesion that received 2000 cGy to the 80% isodose line, and another was a 12-year-old male with a 5.808 cm^3 basal ganglia lesion that received 1600 cGy to the 80% isodose line. The third patient required surgical intervention to remove the necrotic tissue, after which they suffered permanent deficits. This patient was a 16-year-old female with a 5.88 cm^3 occipital lesion that received 1800 cGy to the 80% isodose line. She had initially presented at the age of 6 with an ICH requiring surgical intervention at that time. All 3 patients had presented with ICH.

Reviewing follow-up brain MRIs, 20 of the 34 patients (59%) displayed some form of RIC. Of those 20 cases, the majority were asymptomatic (14 of the 20). Five of the 6 patients have been previously described: 3 cases of radiation necrosis and 2 cases of hemorrhagic cysts. The final patient suffered a single seizure 11 months posttreatment, requiring 6 years of therapy with daily levetiracetam.

Discussion

Intracranial AVMs pose a unique challenge to pediatric patients as their young age increases the number of years for which they are at risk for future hemorrhage. There is a relative paucity of published data, with no randomized clinical trials, evaluating the long-term outcomes of pediatric patients with intracranial AVMs treated with LBRS.

The International Gamma Knife Research Foundation published data showing outcomes after treatment of comparable AVMs in pediatric versus adult patients with

Table 5 Comparison of LINAC-based pediatric AVM studies

Author Location	Year	No. of patients	Median age (y)	Median AVM volume (cc) (range)	Median follow-up (range)	Median prescription dose (Gy)	Obliteration rates	Hemorrhage
Nataf/France[28]	2003	49	12	3.5 (0.6-16)	34 (7-172)	25	61.2%	8.2%
Maity/USA[29]	2004	17	12	6.9 (0.7-25)	21 (9.4-63.1)	18	47%	0%
Zabel-Du Bois/ Germany[30]	2006	22	11.8	4.2 (0.4-26.5)	37.2 (20.4-87.6)	18	64%	23%
Reyns/France[31]	2006	100	12	1.7 (0.9-21.3)	26 (11-126)	23*	70%	1.7%
Buis/ Netherlands[32]	2008	22	13.8	1.8	24	19	68%	4.5%
Blamek/Poland[25]	2012	10	15.4	13.4 (0.56-36.81)	38.5 (13-120)	19	80%	0%
Galvan De la Cruz/Mexico[33]	2014	45	12.9*	3.67* (0.36-15.01)	37.7 (10-112)	17	66.7%	0%
Rajshekhar/ India[34]	2016	69	14	8.4* (0.6-41.8)	27.5*	15	63.8%	2.2%
Present study/USA	2019	34	14.4	2.9 (.23-27.31)	98 (36-200)	17	64.7%	5.9%

Abbreviation: AVM = arteriovenous malformations.
* Mean

Gamma Knife RS. These data showed no appreciable difference between the 2 cohorts, thus supporting the hypothesis that SRS is safe and efficacious in the pediatric population.[11]

A meta-analysis published in 2019 by Borcek et al.[24] collates and evaluates all the AVM studies that focus on the pediatric population. This study further supported the results from the International Gamma Knife Research Foundation that SRS is a safe treatment alternative that achieves a high percentage of obliteration (65.9%) and acceptable occurrence of complications (8%) for AVMs in pediatric patients.

Table 5 consolidates the known publications involving pediatric AVM patients treated with LBRS. These 8 studies represent the only resources for practitioners looking for assistance in guiding LINAC-based treatment decisions. This study fits into this cohort, with similar patient and AVM characteristics, obliteration achieved, and post-LBRS hemorrhage rates.

Of the previous studies, the longest median follow-up was 38.5 months (Blamek et al[25]). This present study monitored patients for a significantly longer period. Long-term follow-up of patients with AVMs is also an area without much published data. In 2019, both Gupta et al[26] and Hasegawa et al[27] published long-term follow-up data for AVMs treated with Cyberknife and Gamma Knife, respectively.

Limitations

Because this is a retrospective study, there are several limitations that affected the analysis. Because there was no predetermined treatment protocol, the dose and other individualized treatment decisions were left to the discretion of the treating physician. Thus, the isodose line used varied between patients and was not always 80%. In addition, both size and location affected total dose, though this was not done according to any systematic standard.

One other limitation was the result of the univariate analysis. Only sex was determined to be statistically significant for obliteration, but this is likely a product of the small sample size. The small cohort size limits the ability to determine predictive features of response. Future clinical trials or meta-analysis involving larger sample sizes would be more beneficial in properly answering questions pertaining to predictive features of obliteration.

Conclusions

Here we present our data involving a pediatric population with intracranial AVMs treated with LBRS and followed for a median span of 8 years. Our results demonstrate with long-term follow-up the safety and efficacy of LBRS for pediatric intracranial AVM.

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