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Radiosurgery for Unruptured Intervention – Naïve Pediatric Brain Arteriovenous Malformations

BACKGROUND: Long-term data regarding stereotactic radiosurgery (SRS) as a standalone therapy for unruptured pediatric brain arteriovenous malformations (AVMs) are incompletely defined.

OBJECTIVE: To evaluate, in a multicenter, retrospective cohort study, the outcomes after SRS for unruptured, intervention-naïve pediatric AVMs.

METHODS: To retrospectively analyze the International Radiosurgery Research Foundation pediatric AVM database from 1987 to 2018. Pediatric patients with unruptured, previously untreated AVMs who underwent SRS were included. The primary endpoint was a composite of hemorrhagic stroke, death, or permanently symptomatic radiation-induced changes.

RESULTS: The study cohort comprised 101 patients (mean follow-up 80.8 mo). The primary endpoint occurred in 14%, comprising hemorrhagic stroke, death, and permanent radiation-induced changes in 6%, 3%, and 8%, respectively. Estimated probabilities of the primary endpoint were 5.2%, 10.8%, and 23.0% at 2, 5, and 10 yr, respectively. Estimated probabilities of AVM obliteration at 5 and 10 yr were 64% and 82%, respectively. Single SRS treatment ($P = .007$) and higher margin dose ($P = .005$) were predictors of obliteration. Subgroup analysis of Spetzler-Martin grade I-III AVMs estimated primary endpoint probabilities of 3.7%, 8.4%, and 18.7% at 2, 5, and 10 yr, respectively.

CONCLUSION: Treatment of unruptured, intervention-naïve AVMs in the pediatric population with SRS carries an approximately 2% annual risk of morbidity and mortality, which appears to plateau after 10 yr. The poorly described natural history of pediatric AVMs renders any comparison of SRS vs conservative management imperfect.

KEY WORDS: Pediatric, Stroke, Arteriovenous malformation, Radiosurgery, Unruptured, Radiation

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The premise for recommending treatment of unruptured pediatric brain arteriovenous malformations (AVMs) rests upon the safety profile of intervention(s) exceeding that of the AVM's natural history. The natural history of unruptured pediatric AVMs is poorly described, and although younger patients may be less likely to suffer AVM rupture, the cumulative hemorrhage risk of an untreated AVM for the lifetime of a child is likely greater than 50% in most cases.[1-3] Among the available treatment options for AVMs, stereotactic radiosurgery (SRS) has been cemented as a definitive intervention that affords desirable results for patients.[4,5] However, long-term data regarding SRS as a standalone therapy for unruptured pediatric AVMs are not fully defined from the literature.[6] Therefore, the aim of this

multicenter, retrospective cohort study is to assess the outcomes after SRS for unruptured, intervention-naïve AVMs in pediatric patients.

METHODS

Patient Identification, Ethical Approval of Study, and Informed Consent

This study was approved and patient consent was waived by the institutional review board (IRB) of each contributing institution. We retrospectively reviewed a multicenter database of pediatric (age <18 yr) AVM patients who underwent SRS at 8 institutions participating in the International Radiosurgery Research Foundation (IRRF). Pediatric AVMs from the previous comprehensive IRRF database (1987-2014) were updated by each respective institution to include additional follow-up data occurring up to and including 2018.[4] Data from additional participating institutions and pediatric AVMs treated with SRS between 2014 and 2018 were also included.[7] To isolate the effects of SRS alone on pediatric AVMs, only patients with unruptured and previously untreated AVMs were included in the study cohort. Pediatric AVMs with a history of hemorrhage and those that underwent any prior intervention, including fractionated radiation therapy, embolization, or surgical resection, were excluded.

Primary and Secondary Endpoints

The primary endpoint was a composite of hemorrhagic stroke, death, or permanently symptomatic radiation-induced changes (RIC). Secondary endpoints included hemorrhagic stroke, death, AVM obliteration, and RIC (including any radiologically evident, transiently symptomatic, and permanently symptomatic RIC). Hemorrhagic stroke was defined as any AVM-related intracranial hemorrhage after SRS, regardless of the presence of neurological symptoms or lack thereof. Death was defined as all-cause mortality. AVM obliteration was defined on magnetic resonance imaging (MRI) as a lack of abnormal flow voids, on computed tomography angiography (CTA) as a lack of abnormal vasculature, or on digital subtraction angiography (DSA) as an absence of anomalous arteriovenous shunting. RIC was defined as fluid-attenuated inversion recovery (FLAIR) or perinidal hyperintensities on T2-weighted brain MRI. Transiently and permanently symptomatic RICs were considered as RIC when associated with decline of neurological condition with and without neurological recovery, respectively. Follow-up duration was defined as the time period between initial SRS and last follow-up.

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Statistical Analysis

All statistical analyses were performed using Stata (version 15.1; StataCorp; College Station, Texas). Descriptive statistics for categorical and continuous variables were reported using proportions and mean or median, respectively. Cumulative event probabilities and associated 95% CI for the primary endpoint, hemorrhagic stroke, death, permanent RIC, and obliteration up to 15 yr were estimated using the Kaplan–Meier method and Greenwood's formula, respectively. Time to the primary endpoint was defined by the earliest times to hemorrhagic stroke, death, and permanent RIC. Time to last follow-up was used to estimate the time to permanent RIC. The annual event probabilities for the primary endpoint, hemorrhagic stroke, death, permanent RIC, and obliteration were also computed. The at-risk period was measured in person-years from the time of initial SRS to the time of event or last follow-up, whichever occurred earlier. Subgroup analyses for SM grade I-III AVMs, with respect to the primary and secondary endpoints, were performed.

Univariable predictors of obliteration in the overall study cohort were assessed using univariable Cox proportional hazard regression models. Multicollinearity of variables was assessed using variance inflation factors and tolerance values. All baseline variables, with the exception of composite scores (SM grade, VRAS–Virginia radiosurgery arteriovenous malformation scale, and modified radiosurgery-based arteriovenous malformation score–RBAS), were entered into a multivariable forward selection Cox proportional hazard regression model using P value < .05 as entry criterion to identify independent predictors of obliteration. Proportional hazard assumption of the model was assessed using Schoenfeld residuals, and a time-varying covariate was included for predictors that violated the assumption. Hazard ratio (HR), hazard rate, and hazard rate difference plots as a function of time were generated for the time-varying covariates. The goodness of fit of the final model was assessed graphically using Cox-Snell residuals and the Nelson–Aalen cumulative hazard function. Statistical significance was defined as $P < .05$, and all tests were two-tailed.

RESULTS

Study Cohort

The IRRF pediatric AVM database comprised 539 patients, and all SRS procedures utilized the Gamma Knife (Elekta, Stockholm, Sweden). After excluding 438 patients for prior hemorrhage or intervention, the study cohort comprised 101 patients with unruptured, previously untreated AVMs; Table 1 details the baseline characteristics of the study cohort. The mean AVM volume was 9 cm³. Single-session SRS (ie, no repeat SRS) was performed in 87%, and the mean margin dose was 19.2 Gy. The mean follow-up duration was 81 mo.

Primary Endpoint

The primary endpoint was observed in 14% (Table 2). Over 652 at-risk person-years of cumulative follow-up, the primary endpoint occurred at an annual rate of 2.1% (1.3%-3.6%). The estimated probabilities of primary endpoint occurrence at 1, 2, 3, 5, 10, and 15 yr were 3.0% (1.0%-9.0%), 5.2% (2.2%-12.0%), 7.6% (3.7%-15.4%), 10.8% (5.7%-20.0%), 23.0% (13.0%-38.8%), and 23.0% (13.0%-38.8%), respectively (Figure 1A).

TABLE 1. Baseline Characteristics of the Study Cohort

Characteristic	Value
Age, mean yr (SD)	13.5 (3.7)
Female, n (%)	39/101 (38.6)
Presentation, n (%)	
Seizure	50/99 (50.5)
Neurological deficit	11/99 (11.1)
Headaches	23/98 (23.5)
Incidental	13/99 (13.1)
AVM maximum diameter, mean cm (SD)	3 (1.5)
AVM volume, mean cm^3 (SD)	9 (11.9)
Single SRS treatment, n (%)	85/98 (86.7)
Margin dose, mean Gy (SD)*	19.2 (3.3)
Isocenters, median (IQR)*	5 (3-12)
Eloquent AVM location, n (%)†	75/101 (74.3)
Deep AVM location, n (%)‡	23/101 (22.8)
Associated arterial aneurysm, n (%)	9/101 (8.9)
Deep venous drainage, n (%)	23/101 (22.8)
SM grade, n (%)	
I	9/101 (8.9)
II	39/101 (38.6)
III	36/101 (35.6)
IV	14/101 (13.9)
V	3/101 (3)
VRAS, n (%)	
0	6/101 (5.9)
1	20/101 (19.8)
2	37/101 (36.6)
3	38/101 (37.6)
RBAS, mean (SD)	1.3 (1.2)
Follow-up, mean months (SD)	80.8 (59.4)

n = number; SD = standard deviation; IQR = interquartile range; SM = Spetzler-Martin; VRAS = Virginia radiosurgery arteriovenous malformation scale; RBAS = modified radiosurgery-based arteriovenous malformation score.
*Initial SRS parameter.
†Sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.
‡Thalamus, basal ganglia, and brainstem.

Hemorrhagic Stroke, Death, and Permanent RIC

Hemorrhagic stroke occurred in 5.9% (Table 2). Over 652 at-risk person-years of cumulative follow-up, the annual postSRS hemorrhagic stroke rate was 0.9% (0.4%-2.0%). The estimated probabilities of hemorrhagic stroke at 1, 2, 3, 5, 10, and 15 yr were 2.0% (0.5%-8.8%), 4.2% (1.6%-10.8%), 4.2% (1.6%-10.8%), 5.8% (2.4%-13.6%), 9.4% (3.8%-22.5%), and 9.4% (3.8%-22.5%), respectively (Figure 1B).
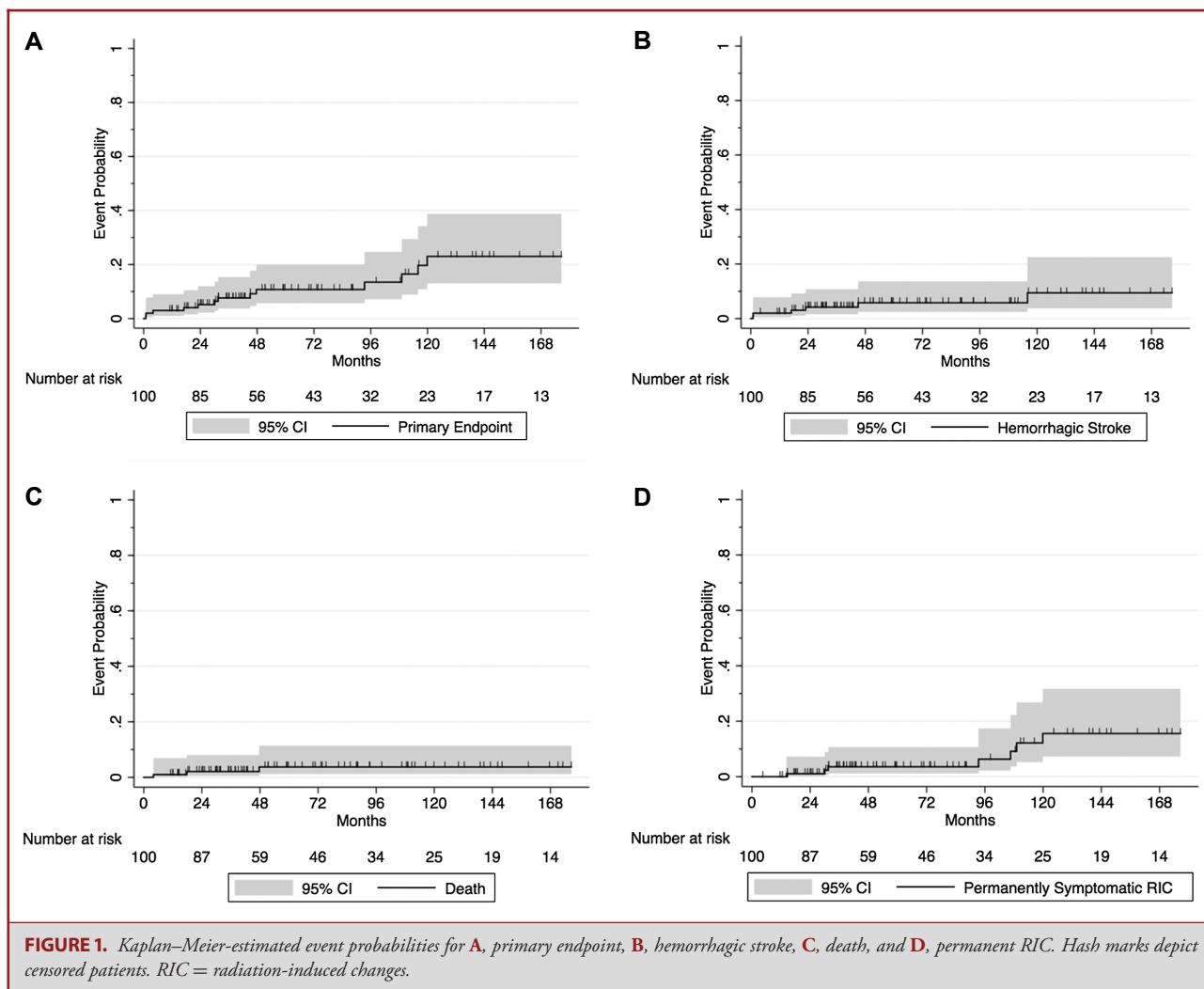
The crude mortality rate was 3% (Table 2). Over 680 at-risk person-years of cumulative follow-up, the annual mortality rate was 0.4% (0.1%-1.4%). The estimated probabilities of death at 1, 2, 3, 5, 10, and 15 yr were 1.0% (0.1%-6.9%), 2.1% (0.5%-8.1%), 2.1% (0.5%-8.1%), 3.7% (1.2%-11.4%), 3.7% (1.2%-11.4%), and 3.7% (1.2%-11.4%), respectively (Figure 1C).

TABLE 2. Primary and Secondary Endpoints of the Study Cohort, Stratified by SM Grade

Endpoint	Unruptured AVMs (n = 101)
Primary	
Hemorrhagic stroke, death, or permanent RIC, n (%)	14/100 (14)
SM grade I	4/9 (44.4)
SM grade II	3/39 (7.7)
SM grade III	3/36 (8.3)
SM grade IV	4/13 (30.8)
SM grade V	0/3 (0)
Secondary	
Hemorrhagic stroke, n (%)	6/101 (5.9)
SM grade I	1/9 (11.1)
SM grade II	0/39 (0)
SM grade III	1/36 (2.8)
SM grade IV	4/14 (28.6)
SM grade V	0/3 (0)
Death, n (%)	3/100 (3)
SM grade I	1/9 (11.1)
SM grade II	0/39 (0)
SM grade III	1/36 (2.8)
SM grade IV	1/13 (7.7)
SM grade V	0/3 (0)
AVM obliteration, n (%)	58/101 (57.4)
SM grade I	6/9 (66.7)
SM grade II	26/39 (66.7)
SM grade III	16/36 (44.4)
SM grade IV	8/14 (57.1)
SM grade V	2/3 (66.7)
Radiological RIC, n (%)	52/100 (52)
SM grade I	4/9 (44.4)
SM grade II	19/39 (48.7)
SM grade III	15/35 (42.9)
SM grade IV	12/14 (85.7)
SM grade V	2/3 (66.7)
Symptomatic RIC, n (%)	15/101 (14.9)
SM grade I	2/9 (22.2)
SM grade II	5/39 (12.8)
SM grade III	3/36 (8.3)
SM grade IV	5/14 (35.7)
SM grade V	0/3 (0)
Permanent RIC, n (%)	8/101 (7.9)
SM grade I	2/9 (22.2)
SM grade II	3/39 (7.7)
SM grade III	1/36 (2.8)
SM grade IV	2/12 (14.3)
SM grade V	0/3 (0)

AVM = arteriovenous malformation; n = number; SRS = stereotactic radiosurgery; SM = Spetzler-Martin; RIC = radiation-induced changes.

The permanent RIC rate was 7.9% (Table 2). Over 680 at-risk person-years of cumulative follow-up, the annual permanent RIC rate was 1.2% (0.6%-2.4%). The estimated probabilities of permanent RIC at 2, 3, 5, 10, and 15 yr were 1.1% (0.2%-7.2%), 3.6% (1.2%-10.7%), 3.6% (1.2%-10.7%),

FIGURE 1. *Kaplan–Meier-estimated event probabilities for* **A**, *primary endpoint,* **B**, *hemorrhagic stroke,* **C**, *death, and* **D**, *permanent RIC. Hash marks depict censored patients. RIC = radiation-induced changes.*

15.6% (7.2%-31.7%), and 15.6% (7.2%-31.7%), respectively (Figure 1D).
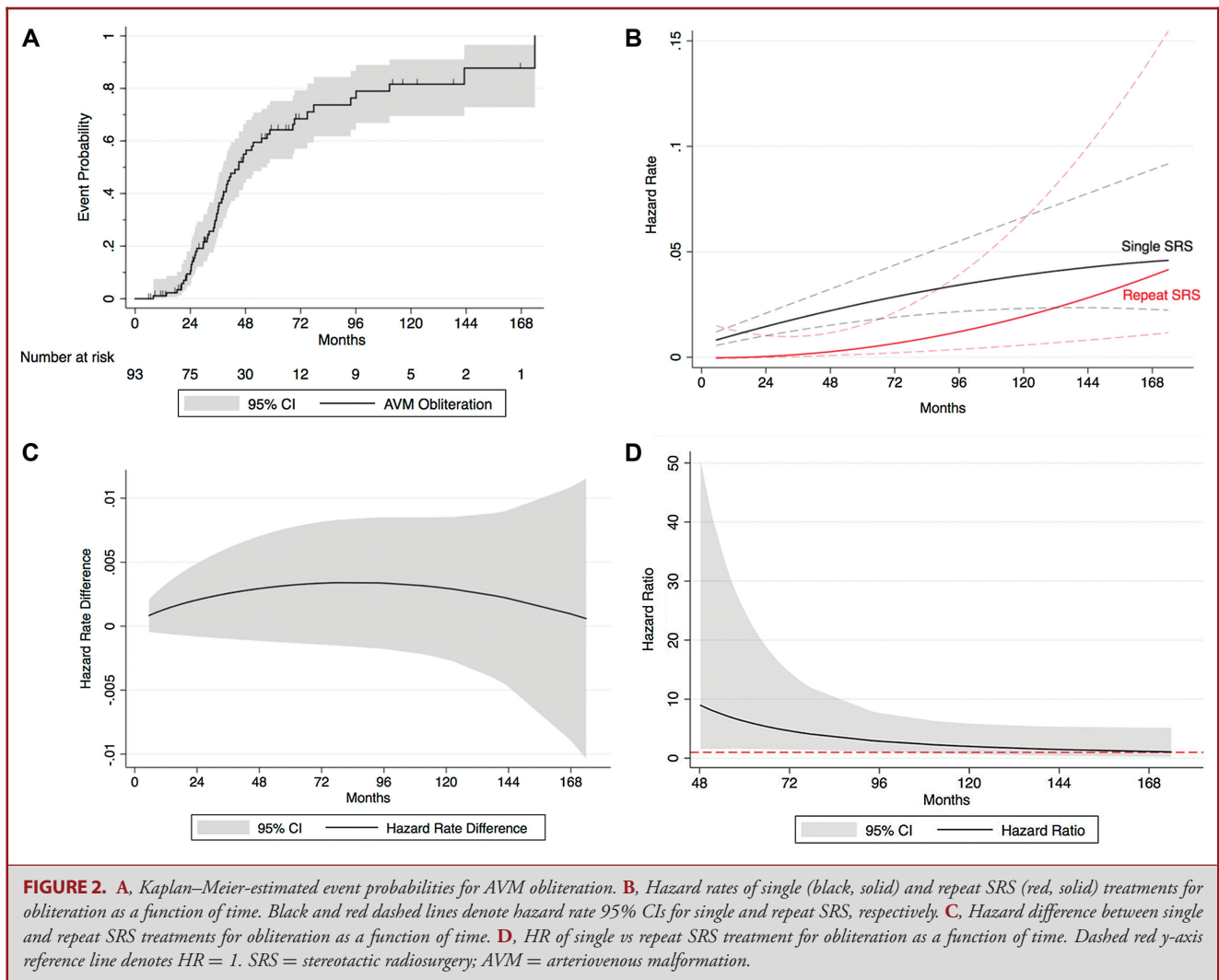
AVM Obliteration

Obliteration was achieved in 57% (Table 2). The estimated probabilities of AVM obliteration at 1, 2, 3, 5, and 10 yr were 1.1% (0.2%-7.5%), 10.6% (5.7%-19.4%), 33.8% (24.5%-45.4%), 64.3% (53.2%-75.2%), and 81.6% (69.6%-91.0%), respectively (Figure 2A). Table 3 details the univariable and multivariable Cox proportional hazards regression models for predictors of obliteration. In the multivariable Cox proportional hazards regression model, single SRS treatment (HR = 65.25 [3.10-1372.85], *P* = .007) and higher margin dose (HR = 1.11 [1.03-1.19], *P* = .005) were independent predictors of obliteration. However, the hazard rate of single SRS treatment was not proportional to that of repeat SRS. Specifically, the HR of single SRS treatment as predictor of obliteration declined over time

(HR = 0.96 [0.92-0.99], *P* = .024; Figure 2B-2D). The obliteration rates were 46.4%, 61.1%, and 77.8% for margin doses of ≤19 Gy, 19 to 21, and >21 Gy, respectively (**Figure, Supplemental Digital Content**).

Outcomes of Spetzler-Martin Grade I-III AVMs

A subgroup analysis of SM grade I-III AVMs found that the estimated probabilities of primary endpoint occurrence at 1, 2, 3, 5, 10, and 15 yr were 2.4% (0.6%-9.3%), 3.7% (1.2%-11.1%), 6.6% (2.8%-15.2%), 8.4% (3.8%-17.9%), 18.7% (9.4%-35.3%), and 18.7% (9.4%-35.3%), respectively (Figure 3A). The estimated probabilities of hemorrhagic stroke at 1, 2, 3, 5, 10, and 15 yr were 1.2% (0.2%-8.3%), 2.5% (0.6%-9.8%), 2.5% (0.6%-9.8%), 2.5% (0.6%-9.8%), 2.5% (0.6%-9.8%), and 2.5% (0.6%-9.8%), respectively (Figure 3B).

The estimated probabilities of death at 1, 2, 3, 5, 10, and 15 yr were 1.2% (0.2%-8.3%), 1.2% (0.2%-8.3%), 1.2%

FIGURE 2. A, *Kaplan–Meier-estimated event probabilities for AVM obliteration.* **B**, *Hazard rates of single (black, solid) and repeat SRS (red, solid) treatments for obliteration as a function of time. Black and red dashed lines denote hazard rate 95% CIs for single and repeat SRS, respectively.* **C**, *Hazard difference between single and repeat SRS treatments for obliteration as a function of time.* **D**, *HR of single vs repeat SRS treatment for obliteration as a function of time. Dashed red y-axis reference line denotes HR = 1. SRS = stereotactic radiosurgery; AVM = arteriovenous malformation.*

(0.2%-8.3%), 3.0% (0.7%-11.9%), 3.0% (0.7%-11.9%), and 3.0% (0.7%-11.9%), respectively (Figure 3C). The estimated probabilities of permanent RIC at 3, 5, 10, and 15 yr were 2.9% (0.7%-11.1%), 2.9% (0.7%-11.1%), 13.5% (5.4%-31.2%), and 13.5% (5.4%-31.2%), respectively (Figure 3D). The estimated probabilities of AVM obliteration at 1, 2, 3, 5, and 10 yr were 1.4% (0.2%-9.2%), 12.7% (6.8%-23.0%), 36.9% (26.6%-49.6%), 64.3% (52.3%-76.2%), and 81.1% (67.1%-91.8%), respectively.

DISCUSSION

The ideal management of unruptured AVMs for the pediatric population is unclear. Although the Scottish Audit of Intracranial Vascular Malformations (SAIVM) and A Randomized Trial of Unruptured Brain AVMs (ARUBA) studies found poorer interim outcomes in the intervention arms when compared to conser-vative care for unruptured AVMs, the lower age limits for inclusion were 18 and 16 yr, respectively.[8,9] When one also considers both the inherent limitations of the 2 aforementioned studies, which have been critiqued extensively, and their exclusion of pediatric patients, the conclusions of these studies cannot be generalized to unruptured pediatric AVMs Although untreated AVMs have been reported to harbor an annual hemorrhage risk of 2% to 4%, this same risk in pediatric unruptured AVMs is poorly defined.[1,2,10,11] In a patient-level meta-analysis derived from 4 cohorts comprising the Multicenter AVM Research Study, a 34% increase in hemorrhage risk per decade of age was observed.[1] However, patients ≤20 yr old comprised only 21% of the cohort. In an earlier population-based study, observed cumulative hemor-rhage risks were 4.6% and 11.8% in the first and second decades of life for untreated AVMs, respectively.[2] Because of the under-representation of pediatric patients, inclusion of both ruptured and unruptured AVMs, and selection bias for lower risk lesions

TABLE 3. Univariable and Multivariable Cox Proportional Hazards Regression Models for Predictors of AVM Obliteration After SRS

Characteristic	Univariable model		Multivariable model[§]	
	HR [95% CI]	*p* value	HR [95% CI]	*P* value
Age	1.016 [0.947-1.090]	.662	NS	NS
Sex	0.780 [0.450-1.353]	.377	NS	NS
AVM diameter	0.758 [0.616-0.933]	**.009**	NS	NS
AVM volume	0.973 [0.946-1.000]	.051	NS	NS
Single SRS treatment	3.921 [1.408-10.915]	**.009**	65.247 [3.101-1372.848]	**.007**
Margin dose*	1.104 [1.029-1.186]	**.006**	1.110 [1.032-1.194]	**.005**
Isocenters*	0.969 [0.934-1.005]	.093	NS	NS
Eloquent location[†]	0.905 [0.485-1.688]	.753	NS	NS
Deep location[‡]	0.589 [0.304-1.141]	.117	NS	NS
Aneurysm	2.186 [0.654-7.310]	.204	NS	NS
Deep venous drainage	0.788 [0.462-1.345]	.383	NS	NS
Single SRS treatment × Time	–	–	0.957 [0.922-0.994]	**.024**

n = number; AVM = arteriovenous malformation; SRS = stereotactic radiosurgery; NS = not significant.

*Initial SRS parameter.

[†]Sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.

[‡]Thalamus, basal ganglia, and brainstem.

[§]Forward selection Cox proportional hazard regression model using entry criterion *P* value of <.05.

Bold = statistically significant (*P* < .05).

in natural history studies, a reliable estimate of the hemorrhage risk of an untreated, unruptured pediatric AVM remains elusive. Because the cumulative hemorrhage risk of an unruptured AVM over the relatively long lifetime of a child remains quite high, an intervention with a favorable risk-benefit profile continues to represent an attractive management option for unruptured AVMs in the pediatric population.

Key Findings

In this multicenter, retrospective cohort study, we critically assessed the outcomes after SRS for unruptured, intervention-naïve pediatric AVMs in order to isolate the effects of SRS on unruptured AVMs in pediatric patients and to derive a more homogeneous cohort than prior pediatric AVM SRS reports. To date, the present analysis is the first ever to evaluate the efficacy and safety profile of SRS for this subset of AVMs. Because of the heterogeneity of AVM patients comprising natural history studies and incongruities in the primary event of interest (eg, hemorrhage, seizure, death, or composite endpoint of death or symptomatic stroke), it is difficult to directly compare the outcomes of our study cohort to the generally undefined natural history of unruptured pediatric AVMs[1,2,9-12] In our cohort, the primary endpoint was encountered in 14% of patients over a mean follow-up of 6.7 yr. This translated into an annual primary endpoint occurrence rate of 2.1%, which compares favorably to the often quoted 2% to 4% annual hemorrhage risk of AVMs in the general population.[1,2,9-11] When examining the probability of primary endpoint occurrence as a function of time, this probability plateaued at approximately 10 yr after SRS at 23%.

Therefore, the majority of the risk associated and benefits in terms of obliteration with SRS for unruptured pediatric AVMs is accrued in the first decade after SRS. When compared to the hemorrhage risk of untreated AVMs that has not been reported to plateau, but instead appears to increase, over time, the cumulative risk of hemorrhage, death, or permanent neurological complications following SRS is likely outweighed by the natural history of a conservatively managed, unruptured pediatric AVM over the course of a child's lifetime.[13]

The crude hemorrhagic stroke rate was 5.9%, yielding an annual postSRS hemorrhage rate of 0.9%. The probabilities of hemorrhagic stroke at 2, 5, and 10 yr were 4.2%, 5.8%, and 9.4%, respectively. Although we cannot adjust for baseline differences in patient and AVM characteristics, the crude and annual hemorrhagic stroke rates after SRS appeared to be slightly higher in this study compared to those of unruptured pediatric AVMs in the previous IRRF study.[5] However, the cumulative probability of hemorrhagic stroke plateaued with AVM obliteration over time. The rates of symptomatic and permanent RIC were 15% and 8%, respectively. The rate of permanent RIC in this study is higher than that of unruptured and ruptured pediatric AVMs in the previous IRRF study.[5] However, previously reported RIC rates could be confounded by potential protective effects of prior AVM hemorrhage, embolization, and resection.[14]

A crude obliteration rate of 57% was achieved, with cumulative probabilities of 64% and 82% at 5 and 10 yr, respectively. These obliteration rates are relatively lower compared to those reported in previous pediatric AVM SRS series that included both ruptured and unruptured AVMs[5,15-18] After the exclusion of previously treated unruptured pediatric AVMs, the
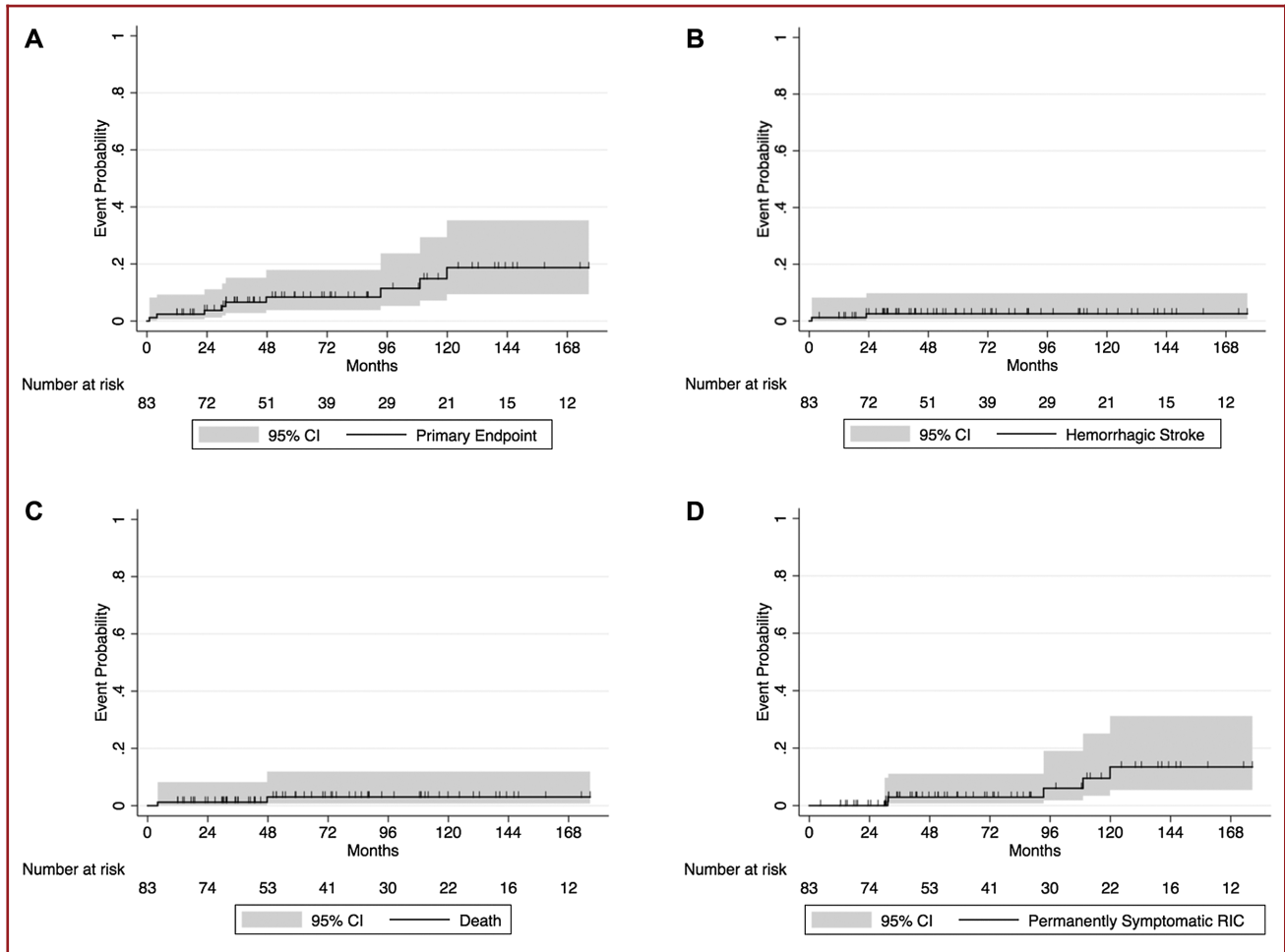
FIGURE 3. *Kaplan–Meier-estimated event probabilities for **A**, primary endpoint, **B**, hemorrhagic stroke, **C**, death, and **D**, permanent RIC in a subgroup analysis of Spetzler-Martin grade I-III AVMs Hash marks depict censored patients. AVM = arteriovenous malformation; RIC = radiation-induced changes.*

obliteration rate in this study was slightly higher than that of all unruptured pediatric AVMs in the prior IRRF study.[5] Similar to other AVM SRS studies in children and adults, margin dose was an important predictor of obliteration in the present analysis.[5,6,19] In our multivariable Cox proportional hazards regression model, we also identified single SRS treatment and its interaction with time as independent predictors of obliteration. Specifically, unruptured pediatric AVM patients who underwent 1 SRS treatment were more likely to have obliteration compared to those who underwent repeat SRS treatment. However, this association waned over time, as demonstrated by the convergence of the hazard functions and a HR that approaches 1. A previous single-center-matched cohort study comparing initial vs repeat SRS for AVMs found worse outcomes, including lower obliteration and higher postSRS hemorrhage rates, after repeat SRS.[20] Therefore, although repeat SRS continues to be a treatment option for residual AVMs after initial SRS, its relatively lower

efficacy should be taken into account when considering alternative therapies, such as resection.

Subgroup Analysis Findings

A subgroup analysis of low and intermediate (ie, SM I-III) grade AVMs found a lower probability of the primary endpoint over time. The lower primary endpoint rate was primarily driven by the considerably lower postSRS hemorrhage rate of SM grade I-III AVMs, with minor contributions from slightly lower mortality and permanent RIC rates. If one approximates the annual hemorrhage risk of an unruptured, untreated AVM to be 2.2% (derived from the medical management arm of ARUBA), the cumulative hemorrhage risk exceeds the 10-yr probability of the primary endpoint for unruptured, intervention-naïve pediatric AVMs (23%) at 12 yr follow-up, and it exceeds the 10-yr probability of the primary endpoint for the subgroup of SM grade I-III AVMs (19%) at 10 yr follow-up.[9] Therefore,

preferential employment of SRS for unruptured SM grade I-III AVMs in children may afford an even greater advantage over conservative management at long-term follow-up.

Limitations

It is important to recognize the limitations of our study. Our results are dependent upon the accuracy and reliability of data provided by each participating center, and therefore, they may be subject to reporting bias. Our attempt to generate a relatively homogeneous study cohort may also contribute to selection bias, as decisions to offer SRS could depend on patient factors and feasibility of this treatment. However, decisions by treating clinicians or patients in selecting SRS over other treatment modalities were not captured. Because conservative management is an option for unruptured pediatric AVMs, patients who were selected for SRS may have been deemed to have a higher risk of hemorrhage. The use of final follow-up as a surrogate for time to permanent RIC and the reduced number of at-risk patients after 10 yr of follow-up may falsely elevate the probability of primary endpoint occurrence at these later time points. The 12-Gy volume was not captured in the database, so it could not be factored into the analyses of complications. The time interval between initial and repeat SRS was also not captured in the database, and thus, no inference could be made regarding the optimal timing for repeat SRS in patients incompletely obliterated AVMs. Because of the nature of each contributing institution as a tertiary referral center for AVM SRS, we did not have sufficiently detailed data to determine the neurological impact of postSRS hemorrhage or permanent RIC, functional outcome, educational status, or cause of death for some patients. Although no radiation-induced tumors were encountered in this group of patients, this may represent a rare complication that is difficult to detect in a modest sample size.

Generalizability

As the IRRF database comprised only pediatric AVM patients who were treated with SRS, no control cohort of untreated, unruptured AVMs was available. Therefore, direct comparisons of outcomes between SRS and conservative management could not be made, and the timepoint at which an AVM's natural history overtakes the risk of SRS could only be extrapolated from the sparse available literature. As outcomes data for unruptured AVMs treated with nonSRS modalities (eg, resection or embolization) were also unavailable, we do not believe that our results were sufficient to formulate a management algorithm for unruptured pediatric AVMs. Our findings may not be generalizable to all unruptured pediatric AVMs, as SM grades II and III AVMs comprised the majority of the study cohort.

CONCLUSION

The annual risk of morbidity and mortality after treatment of unruptured, intervention-naïve AVMs in pediatric patients with SRS is approximately 2%, although this risk appears to plateau after the first decade. Because of the lack of reliable natural history data for unruptured pediatric AVMs, the comparative safety and efficacy of SRS vs conservative management has been difficult to extrapolate. However, SRS affords the advantage of nidal obliteration in up to 80% of unruptured, previously untreated pediatric AVMs at 10 yr. When one considers the combination of early diagnosis at a young age and an excessive cumulative lifetime risk of hemorrhage associated with AVMs in children, SRS emerges as a reasonable treatment option for unruptured pediatric AVMs with an overall-favorable risk-benefit profile.

Disclosures

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Supplemental Digital Content. Figure. Bar plot of AVM obliteration rate stratified by margin dose. The obliteration rates were 46.4%, 61.1%, and 77.8% for margin doses of ≤19, 19 to 21, and >21 Gy, respectively. AVM = arteriovenous malformation; Gy = Gray.