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Leksell Gamma Knife for pediatric and adolescent cerebral arteriovenous malformations: results of 100 cases followed up for at least 36 months

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OBJECT The goal of this study was to evaluate advantages, risks, and failures of Gamma Knife radiosurgery (GKRS) in a large series of pediatric and adolescent patients with cerebral arteriovenous malformations (cAVMs) who were followed up for at least 36 months.

METHODS Since February 1993, 100 pediatric and adolescent patients (≤ 18 years of age) with cAVMs have undergone GKRS at the authors' institution and were followed up for at least 36 months. Forty-six patients were boys and 54 were girls; the mean age was 12.8 years (range 3–18 years). Hemorrhage, either alone or combined with seizure, was the clinical onset in 70% of cases. The mean pre-GK cAVM volume was 2.8 ml; 92% of cAVMs were Spetzler-Martin (S-M) Grades I–III. Most lesions (94%) were in eloquent or deep-seated brain regions, according to S-M classification. The parameters for mean and range in treatment planning were prescription isodose 53.8% (40%–90%); prescription dose (PD) 20.2 Gy (9.0–26.4 Gy); maximal dose (MD) 37.8 Gy (18–50 Gy); and number of shots 4.7 (1–17). On the day of GKRS, stereotactic CT or stereotactic MRI and digital subtraction angiography were used.

RESULTS Obliteration rate (OR) was angiographically documented in 75 of 84 cases (89.3%) after single-session GKRS, with actuarial ORs at 3 and 5 years of 68.0% and 88.1%, respectively. A repeat treatment was performed in 7 patients (6 with obliteration), and 16 patients with cAVMs underwent staged treatment (9 of them were angiographically cured). Thus, the overall OR was 90%, with actuarial ORs at 3, 5, and 8 years of 59.0%, 76.0%, and 85.0%, respectively. Permanent symptomatic GK-related complications were observed in 11% of cases, with surgical removal of enlarged mass seen on post-RS imaging needed in 5 cases. Hemorrhage during the latency period occurred in 9% of patients, but surgical evacuation of the hematoma was required in only 1 patient. One patient died due to rebleeding of a brainstem cAVM. Radiosurgery outcomes varied according to cAVM sizes and doses: volumes ≤ 10 ml and PDs > 16 Gy were significantly associated with higher ORs and lower rates of permanent complication and bleeding during the latency period.

CONCLUSIONS The data from this study reinforce the conclusion that GKRS is a safe and effective treatment for pediatric and adolescent cAVMs, yielding a high OR with minimal permanent severe morbidity and no mortality. The very low frequency of severe hemorrhages during the latency period further encourages a widespread application of RS in such patients. Univariate analysis found that modified RS-based cAVM score, nidus volume, PD, integral dose, S-M grade, and preplanned treatment (the last 2 parameters were also confirmed on multivariate analysis) significantly influenced OR. Lower S-M grades and single-session planned treatments correlated with shorter treatment obliteration interval on univariate analysis. This statistical analysis suggests that a staged radiosurgical treatment should be planned when nidus volume > 10 ml and/or when the recommended PD is ≤ 16 Gy.

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KEY WORDS stereotactic radiosurgery; cerebral arteriovenous malformation; pediatric patients; Gamma Knife

ABBREVIATIONS ARE = adverse radiation effects; cAVM = cerebral arteriovenous malformation; EE = endovascular embolization; GK = Gamma Knife; LINAC = linear accelerator; MD = maximal dose; OR = obliteration rate; PD = prescription dose; RS = radiosurgery; S-M = Spetzler-Martin; TOI = treatment obliteration interval.

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Cerebral arteriovenous malformations (cAVMs) are the most frequent cause of intracranial hemorrhage in children after infancy[10,18] accounting for as many as half of all hemorrhagic strokes in the pediatric and adolescent population.[25] These cAVMs more frequently present after hemorrhage than those in adults,[6,10] and clinical presentation as spontaneous hemorrhage is reported in more than 80% of pediatric cases.[2,5,17,27] Furthermore, children have a higher risk of rebleeding (25% incidence of rebleeding within 5 years from initial hemorrhage) than adults (in whom cumulative rates of mortality and morbidity are presumably greater because of the prolonged risk period), with both higher mortality (24%) and morbidity rates than adults after initial hemorrhage.[1,11,18,25] These young patients are exposed to a 50% combined risk of permanent morbidity and mortality.[8,25,41] Therefore, the "gold standard" treatment should be represented by complete surgical removal, with the aim of removing the risk of further, devastating hemorrhagic strokes. However, cAVMs are more frequently located in deep regions or in eloquent brain areas in children and adolescents (up to 70%–90% of the time) than in adults,[14,24,25,27,42,44] exposing these younger patients to high morbidity and mortality risks in the event of surgery.

Endovascular embolization (EE) still carries the risks of an invasive technique, and it is uncommon that complete obliteration is achieved when it is used as a single modality of treatment.[5,7,42] There is also the concern that revascularization of obliterated vessels, despite its rarity, may occur more frequently in children than in adults.[13,43] Thus, embolization alone is often unsatisfactory as a single therapeutic strategy for the majority of inoperable vascular malformations. Therefore, taking into account this complicated and challenging management that the neurovascular team is tasked with, the use of a noninvasive treatment tool such as radiosurgery (RS) has become more and more prevalent worldwide.

In the last 2 decades, several studies on the radiosurgical treatment of pediatric and adolescent cAVMs have reported high obliteration rates (ORs) (74%–86%) and very low frequencies of permanent complications (1.1%–5.0%).[5,14,17,19,25,28,29,39,40,42] But considering the young age of such patients, large numbers of observations and very long follow-up times are needed to evaluate some issues related to the radiosurgical treatment of cAVMs, such as the risk of revascularization, the long-term adverse reaction effect, and permanent complication rates. To the best of our knowledge, only a few series of radiosurgically treated cAVMs in pediatric and adolescent patients, with at least 80 observations and at least 36 months of follow-up, have been published.[5,14,33,34,36,42] In this retrospective study, the authors describe the advantages, risks, and failures of Gamma Knife RS (GKRS) on 100 pediatric and adolescent patients with cAVMs who were followed up for at least 36 months. To our knowledge, this is one of the largest series of radiosurgically treated cAVMs in patients ≤ 18 years of age with an observation period of this length.

Methods

Patient Population

Between February 1993 and April 2014, 8347 patients were treated with GKRS at our institution. Of these patients, 957 had cAVMs and 151 were pediatric and adolescent patients (≤ 18 years of age). In 100 such cases, a follow-up period of at least 36 months was available. Patients' clinical characteristics are summarized in Table 1. Briefly, the mean age was 12.8 years (range 3–18 years). Most patients were girls (54%). Bleeding, either alone or combined with seizure, represented the clinical onset in 70% of patients. Before RS, EE procedures were undertaken with the aim of reducing the blood-flow rate within the cAVM and the size of the nidus to a volume more suitable for GKRS in 35 patients, whereas microsurgical incomplete cAVM resection was performed in 7 patients (1 combined treatment of EE and surgery). The median cAVM volume before GKRS was 2.8 ml (range 0.06–39.6 ml). According to the modified RS-based cAVM grading system score,[30,31] the cAVMs were grouped as follows: ≤ 1.0 in 76 cases; 1.01–1.5 in 12; 1.51–2.0 in 7; and ≥ 2.01 in 5.

Eloquent brain sites, according to the Spetzler-Martin (S-M) definition,[38] were involved in most cases (94%), and 82% of the cAVMs were located in deep-seated areas (i.e., corpus callosum, pineal region, basal ganglia, thalamus, or brainstem). Spetzler-Martin Grades I–III accounted for 92% of the whole series. Of the 100 cAVMs, the number assigned to low-, intermediate-, and high-flow subgroups was very similar. In 67% of cAVMs, the venous drainage was deep. Based on the volume and location, the cAVMs were preplanned for a single (81%) or staged (19%) treatment, either dose staged (15 of 19) or volume staged (4 of 19).

During the follow-up period, patients usually underwent postoperative MRI, MR angiography, and neurological evaluations. The first was at 6 months and at 12-month intervals thereafter to assess vascular response, identify delayed or late radiation injury and/or edema of the brain, and guide appropriate management. Follow-up angiography was performed when MRI suggested cAVM occlusion, and at 5 years from GK treatment in all other cases. After obliteration was documented by angiogram, patients were advised to have follow-up MRI every 10 years because of the reported risks of recurrence,[13,18,43] delayed postradiosurgical adverse effects,[16] and radiation-induced neoplasia.[41] Neurological morbidity was defined as transient or permanent, and the modified Rankin Outcomes Scale[4,31] was used to grade its severity. Any episode of bleeding during the latency period was registered. Follow-up data were obtained from hospital notes, imaging studies, and relatives and family physicians. Medical records, MR images, and angiography images for all patients were carefully reviewed. This study was reviewed and approved by the local ethics committee.

Radiosurgical Techniques

Our radiosurgical technique has been described in detail in previous reports.[20,21,24–27] Briefly, the MRI-compatible Leksell Model G stereotactic frame (Elekta Instruments) was applied to the patient's head. Then, neuroradiological localization was routinely performed using stereotactic 2D cerebral angiography or high-resolution magnification subtraction stereotactic angiograms. More recently, 3D rotational stereotactic angiography (with evaluation of the

TABLE 1. Summary of clinical characteristics of 100 pediatric and adolescent patients with cAVMs treated with GKRS

Clinical Characteristics	No. of Pts
Age, mean (range)	12.8 yrs (3–18 yrs)
Sex	
Female	54 (54.0%)
Male	46 (46.0%)
Pre-GK Tx	
None	57
EE only	32
Surgical removal	6
GK	2
Combined	3
Clinical onset	
Bleeding	66
Bleeding & seizure	4
Seizure	14
Other	16
Vol (ml)	
<4	63
4–7	21
8–10	8
>10	8
Modified RS-based AVM score	
≤1.0	76
1.01–1.5	12
1.51–2.0	7
≥2.01	5
Modified RS-based AVM score	
Hemispheric–callosal–cerebellar	69
Basal ganglia–thalamus–brainstem	31
Anatomical location	
Superficial	19
Deep	56
Median	25
Functional location	
Eloquent	94
Noneloquent	6
S-M grade	
I	4
II	30
III	58
IV	8
Blood flow	
Low	31
Intermediate	41
High	28
Drainage	
Superficial	33
Deep	67
Preplanned Tx	
Single session (re-Tx)	84 (7)*
Dose staged	12
Vol staged	4

Pts = patients; Tx = treatment.
* Three AVMs with dose-staged preplanned Tx were obliterated after the first GKRS.

early arterial to late venous phases) has also been used to define the cAVM nidus (target volume) and to determine target coordinates. Angiographic examination was supplemented with stereotactic CT/MRI, with specific algorithms and sequences, to obtain additional information about the 3D shape of the cAVM and the surrounding normal brain structure. Postcontrast 2-mm-thick coronal and axial images and, more recently, 1-mm-isovoxel volumetric images with gadolinium enhancement, 2-mm-thick T2-weighted MR images, and MR angiography sequences were acquired.

Radiosurgical procedures were performed with a model C 201-source Co60 Leksell Gamma Unit and, since June 2008, with GK Perfexion (both from Elekta Instruments). Three-dimensional treatment planning was developed using commercially available software; i.e., Kula (Elekta Instruments) from February 1993 to February 1998 and Leksell Gamma Plan (versions 4.12, 5.34, and 8.3; Elekta Instruments) after February 1998. The neurological surgeon, radiation oncologist, and medical physicist created highly conformal dose planning using multiple collimators and performed the dose selection.

The parameters for mean and range in treatment planning were prescription isodose 53.8% (40%–90%); prescription dose (PD) 20.2 Gy (9.0–26.4 Gy); maximal dose (MD) 37.8 Gy (18–50 Gy); number of shots 4.7 (1–17); integral dose (available in 46 patients) 117.1 mJ (2.0–553.3 mJ); and brain volume in 12-Gy isodose volume (available in 31 patients) 3.97 ml (0.24–21.7 ml).

General endotracheal anesthesia was induced in 52% of patients under 14 years of age and in selected cases in older patients. Patients were discharged from the hospital on the day after treatment.

Statistical Analysis

Obliteration rate curves were calculated using the Kaplan-Meier method.[15] The interval from treatment to permanent complication due to adverse radiation effects (ARE) was evaluated on an actuarial basis from the day of GKRS treatment to the time MRI showed postradiosurgical changes. The significance was calculated using Fisher's exact test.

Univariate statistical analyses were performed on 18 preidentified independent variables to evaluate whether they correlated significantly with the radiosurgical outcomes, defined as OR, treatment obliteration interval (TOI), permanent complications, and bleeding during latency period (dependent variables). Univariate analysis was performed using the independent samples t-test and nonparametric K-sample test on the equality of medians for continuous variables (i.e., age, cAVM volume, PD, integral dose, and brain volume in 12-Gy isodose volume) and Pearson chi-square and Fisher's exact tests for categorical variables (i.e., sex, cAVM clinical onset, pre-GK treatment, anatomical location, hemispheric–corpus callosum–cerebellar vs basal ganglia–thalamus–brainstem, venous drainage, nidus blood flow, critical vs noncritical location, S-M grade, single vs staged treatment, and stereotactic CT vs stereotactic MRI). Subsequently, to test the significance more accurately, regression analyses were performed using a logistic model.

On the basis of internationally accepted criteria, p values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using Stata software, version 13.1 (Stata Corp.). Because this was a retrospective, single-center study, the possibility of bias in patient selection cannot be ruled out.

Results

Clinical Results

The mean and median follow-up period was 92.0 and 82.2 months, respectively (range 36.4–234.9 months). At the end of the study, 99 patients were still alive. The only death in our series was due to rebleeding of a brainstem cAVM 42.8 months after radiosurgical treatment. The patient was 18 years old at the time of GKRS and died at the age of 22 years.

Among the other 99 patients, 38 with no deficit prior to radiosurgical treatment remained free from symptoms at last follow-up. In 27 patients neurological complaints were stable, and in 22 patients neurological improvements of their clinical conditions were achieved. Symptomatic worsening occurred in 12 cases: 9 due to GK-related ARE, 1 associated with bleeding, and 2 following symptomatic ARE combined with bleeding of incompletely obliterated cAVMs. Of the 11 patients with permanent symptomatic ARE, 8 were a Grade I–II and 3 were a Grade III, according to the Rankin Handicap Scale.[4]

Obliteration Rate

A single radiosurgical treatment was planned in 81% of cAVMs, with complete obliteration angiographically documented in 72 patients (88.9%). However, 3 of 19 cAVMs with preplanned dose-staged treatment showed disappearance following the first GK procedure. Thus, the overall number of patients in whom the cAVM cure was achieved after a single GK session was 75 of 84 (89.3%) (Fig. 1), with an actuarial OR of 68.0% at 3 years and 88.1% at 5 years (Table 2). The median TOI for these 75 patients was 26.9 months.

In the 9 patients with an incompletely obliterated cAVM, a repeat treatment with GK was performed in 7 cases. A cAVM cure was achieved in 6 of these patients (85.7%), with a median TOI (from first radiosurgical treatment to an angiogram demonstrating complete cAVM obliteration) of 78.2 months.

In 16 patients with particularly critically located cAVMs (deep brainstem and basal ganglia) and/or with nidus volume > 10 ml, a radiosurgically staged treatment was scheduled: this was volume staged in 4 cases and dose staged in 12. Complete obliteration occurred in 9 patients (56.3%) (Table 2), and the median TOI was 90.3 months.

Finally, the overall OR for the whole series of 100 patients (followed for at least 36 months) was 90%, with a median TOI of 27.4 months (Table 2). The actuarial ORs at 3, 5, and 8 years were 59.0%, 76.0%, and 85.0%, respectively (Fig. 1).

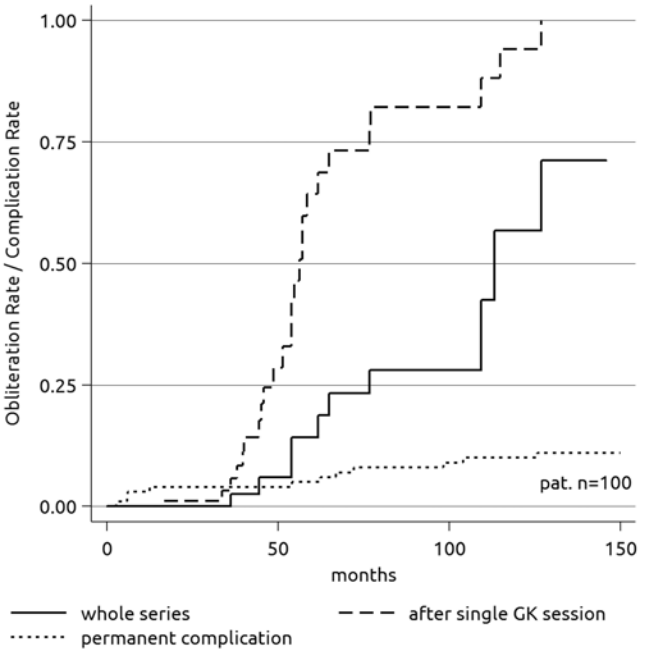

FIG. 1. Kaplan-Meier curves showing the OR after a single GK session in 84 pediatric and adolescent patients with cAVMs *(dashed line)*, the OR of the whole series of 100 patients *(solid line)*, and the interval rates of GK treatment-related permanent complications due to ARE in 11 cases *(dotted line)*.

Permanent Complications

Permanent neurological GK-related complications were registered in 11% of cases. The permanent ARE documented by imaging examinations during the follow-up period were radiation necrosis in 8 cases, edema in 2, and delayed cyst formation in 1. The median interval between RS treatment and symptomatic ARE onset was 63.33 months (range 2.8–125.77 months) (Fig. 1). Permanent ARE appeared after nidus obliteration in 7 of 11 cases: 6 consisted of radia-

TABLE 2. Outcomes of 100 cAVMs in pediatric and adolescent patients followed up for at least 36 months

Type of RS Tx	No. of Pts	OR (%)	Median TOI (mos)	Actuarial OR		
				At 3 Yrs	At 5 Yrs	At 8 Yrs
Single Tx	84*	75/84 (89.3)	26.9	68.0	88.1	—
Re-Tx	7	6/7 (85.7)	78.2	—	—	—
Overall OR for nonstaged Tx	84	81/84 (96.4)	—	—	—	—
Staged RS	16	9/16 (56.3)	90.3	—	—	—
Overall OR	100	90/100 (90.0)	27.4	59.0	76.0	85.0

— = not evaluated or not estimable.

* Three AVMs with dose-staged preplanned Tx were obliterated after the first GKRS.

TABLE 3. Relationship between cAVM treated volume and complete obliteration after single GK treatment, permanent symptomatic adverse reaction, and bleeding during latency period

	Single Treatment			Permanent Symptomatic ARE			Bleeding During LP		
Vol (no. of patients)	No Obl	Obl	p Value	No	Yes	p Value	No	Yes	p Value
≤10 ml (92)	18	74	<0.001	84	8	0.012	87	5	<0.001
>10 ml (8)	7	1		5	3		4	4	
Total	25	75		89	11		91	9	

LP = latency period; obl = obliteration.

tion necrosis and 1 consisted of cyst formation. Surgical intervention was needed to remove the mass effect on the surrounding normal brain parenchyma in 5 of 11 patients, resulting in rapid improvement in neurological deficits.

At the end of the study, the final outcomes for the whole series according to the Pollock-Rankin classification[31] were excellent in 80 patients, good in 7, fair in 3, unchanged in 8, and poor in 1. One patient died.

Bleeding During the Latency Period

Bleeding during the latency period occurred in 9% of patients, with a median interval from GK to hemorrhagic stroke of 42.8 months (range 2.6–71.43 months). Three of 9 patients had new hemorrhages and the other 6 patients had repeat hemorrhages. As reported above, cAVM rebleeding in 1 case led to the death of the patient. Among the other 8 patients, hemorrhage resulted in a permanent neurological worsening in 1 case. In another case, surgical removal of the intracerebral clot was needed to completely resolve the intracranial hypertension syndrome. In the remaining 6 patients, hemorrhagic stroke did not lead to permanent worsening of neurological conditions.

Of the 9 patients with bleeding during the latency period, 2 bled within 3 years after GKRS and 7 bled more than 3 years after GKRS. It is worth noting that 6 of 7 of these later hemorrhagic strokes occurred in patients who underwent a planned staged RS, and in 1 patient the bleeding followed a repeat treatment for incompletely obliterated cAVM.

Statistical Analysis/Prognostic Factors

Tables 3 and 4 show a highly significant correlation between the independent variables (nidus volume and PD) and the end points (OR, GK-related permanent complications, and bleeding during the latency period across the whole series). It seems that a clear cutoff appears for both volume and PD. The probability of complete obliteration highly increases, and the risks of symptomatic permanent complications due to ARE and bleeding during the latency period highly decrease, when the nidus volume is ≤ 10 ml and a PD > 16 Gy can be delivered. In cAVMs with nidus volume exceeding 10 ml and when it is not recommended to deliver a PD > 16 Gy (due to a critical location or large nidus volume), the probability that a single-session planned treatment will be unsuccessful appears to be very high. In such pediatric cAVMs, we propose an algorithm (Fig. 2) in which a staged treatment is scheduled.

When ORs after a single radiosurgical session were taken into consideration, univariate analysis showed a significant correlation with modified RS-based cAVM score, nidus volume, PD, integral dose (Table 5), S-M grade, and scheduled treatment (Table 6). However, multivariate regression analysis confirmed a highly significant correlation for S-M grading (Cox model) and for type of scheduled treatment (probit model) alone (Table 7). That is, patients with higher S-M grades and preplanned staged treatment have an extremely low probability of cAVM cure after the first radiosurgical procedure. Of 19 pediatric patients with cAVMs in our series for whom a staged treatment was scheduled, 3 patients (15.8%) achieved complete obliteration of nidus after the first GK session only.

For TOI, univariate analysis showed a statistically significant correlation for type of scheduled treatment and for S-M grade (Table 8). S-M Grades I, II, and III, and single-

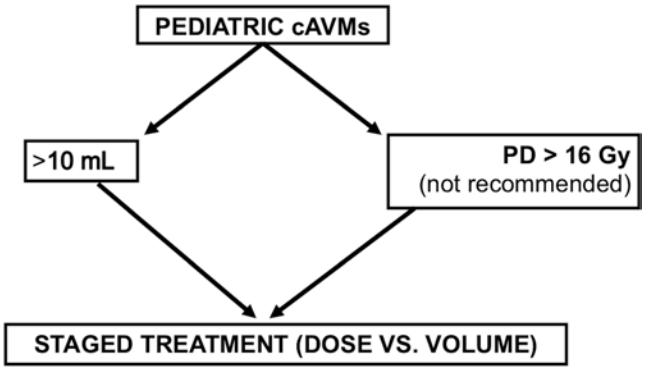

FIG. 2. Proposed algorithm for the management of large and/or eloquent or deep-seated cAVMs in pediatric and adolescent patients.

TABLE 4. Relationship between PD and complete obliteration after single GK treatment, permanent symptomatic ARE, and bleeding during latency period

	Single Treatment			Permanent ARE			Bleeding During LP		
Radiation Dose (no. of patients)	No Obl	Obl	p Value	No	Yes	p Value	No	Yes	p Value
≤16 Gy (12)	10	2	<0.001	8	4	0.026	6	6	<0.001
>16 Gy (88)	15	73		81	7		85	3	
Total	25	75		89	11		91	9	

TABLE 5. Univariate analysis of 6 continuous variables related to OR after first GK treatment in 100 children and adolescents with cAVMs followed up for at least 36 months

Continuous Variables	Mean		Median		p Value	
	No Obl	Obl	No Obl	Obl	t-Test	Median t-Test
Age, yrs	12.920	12.880	13.000	13.000	0.988	0.817
Modified RS-based AVM score	1.432	0.657	0.930	0.700	<0.001	0.011
Vol (ml)	9.534	2.695	6.700	2.300	<0.001	0.002
PD (Gy)	17.458	21.126	16.000	21.000	<0.001	0.027
Integral dose (mJ)*	213.600	70.419	151.100	66.500	<0.001	0.005
Brain vol in 12-Gy isodose vol†	3.893	3.973	2.250	2.800	0.965	0.916

* Forty-six observations only.
† Thirty-one observations only.

TABLE 6. Univariate analysis of 12 categorical variables related to OR after first GK treatment in 100 children and adolescents with cAVMs followed up for at least 36 months

Categorical Variables	No Obl (%)	Obl (%)	Statistical Test	
			Pearson Chi-Square	Fisher's Exact
Sex			0.105	0.164
Male	8 (32.00)	38 (50.67)		
Female	17 (68.00)	37 (49.33)		
Clinical onset			0.450	0.460
No bleeding	9 (36.00)	21 (28.00)		
Bleeding	16 (64.00)	54 (72.00)		
Pre-GK Tx			0.276	0.335
No EE	14 (56.00)	51 (68.00)		
EE	11 (44.00)	24 (32.00)		
Anatomical location			0.890	0.860
Superficial	5 (20.00)	14 (18.67)		
Median	7 (28.00)	18 (24.00)		
Deep	13 (52.00)	43 (57.33)		
Modified RS-based AVM score			0.105	0.135
Hemispheric–callosal–cerebellar	14 (56.00)	55 (73.33)		
Basal ganglia–thalamus–brainstem	11 (44.00)	20 (26.67)		
Venous drainage			0.902	1.000
Superficial	8 (32.00)	25 (33.33)		
Deep	17 (68.00)	50 (66.67)		
Blood flow through the cAVM			0.065	0.067
Slow	4 (16.00)	27 (36.00)		
Intermediate	10 (40.00)	31 (41.33)		
High	11 (44.00)	17 (22.67)		
Functional location			0.627	0.638
Noneloquent	2 (8.00)	4 (5.33)		
Eloquent	23 (92.00)	71 (94.67)		
S-M grade			<0.001	0.001
I	1 (4.00)	3 (4.00)		
II	6 (24.00)	24 (32.00)		
III	11 (44.00)	47 (62.67)		
IV	7 (28.00)	1 (1.33)		
Planned Tx			<0.001	<0.001
Single session	9 (36.00)	71 (94.67)		
Staged	16 (64.00)	4 (5.33)		
Imaging localization			0.851	0.853
Angio	4 (16.00)	14 (18.67)		
Angio + CT	5 (20.00)	17 (22.67)		
Angio + MRI	16 (64.00)	44 (58.67)		

angio = angiography.

TABLE 7. Probit and Cox model regression analysis of significant continuous and categorical variables with appropriate number of observations on univariate analysis for OR after first GK treatment

Selected Factors	Probit Model	Cox Model Coefficient, HR
Blood flow through the cAVM		
Low	Reference	Reference
Intermediate	−0.437	1.635, 5.130
High	−0.894	1.516, 4.553
S−M grade		
I	Reference	Reference
II	−0.439	2.930, 18.739*
III	−0.198	3.568, 35.454*
IV	−1.263	4.179, 65.327*
Planned Tx	−2.683†	1.015, 2.760
Modified RS−based AVM score	−0.229	−1.399, 0.247
PD (Gy)	−0.159	−0.003, 0.997
Vol (ml)	−0.099	0.095, 1.100
Constant	6.005	—

* Significance values: $p < 0.05$.
† Significance values: $p < 0.001$.

session planned treatment of cAVMs, seemed to show a shorter TOI. However, these data were not confirmed on regression analysis.

Due to the small number of observations, statistical analysis was not applicable to the other end points of the study: ARE-related permanent complications and bleeding during the latency period.

Discussion

Stereotactic RS is a well-established treatment for cAVMs in pediatric and adolescent patients. The decision whether to use RS rather than resection is influenced by a number of factors, which include clinical presentation, patient age, natural history risk for AVM, location of AVM in eloquent or deep areas, nidus volume, and patient preference.[12]

In the last 3 decades, the use of RS in such patients (either alone or included in combined planned management strategies) has progressively increased and spread worldwide. There are numerous publications on the radiosurgical treatment of pediatric cAVMs, with reported ORs usually varying between 62.5% and 82.7% (Table 9). However, studies with long follow-up observation periods (at least 36 months) and large population sizes (at least 80 observations) are uncommon.[5,14,33,34,36,42]

In a recent series of 80 pediatric cAVMs with follow-up data after GKRS, Potts et al.[33] reported an OR of 59.0% following the first radiosurgical treatment. This low cure rate was explained by the fact that the authors favored a lower prescription marginal dose (median 17.5 Gy) and tended to treat larger, more complex AVMs with RS and smaller, less complex AVMs with resection. In other large series of pediatric and adolescent patients with long periods of observation, the ORs after a single-session radiosurgical procedure varied between 62.9% and 75%. Additional RS for cAVMs that remained patent despite initial treatment achieved overall ORs of between 62.5% and 82.7%. In our experience also, the overall OR of the whole series was similar to those reported by other studies (90%), but the rate of cured patients following the first radiosurgical treatment was higher (89.3%) than those of others. This difference is due to the fact that this percentage was calculated only on the number of patients who underwent a preplanned single treatment; i.e., patients usually affected with smaller nidus volume and/or less "critical" cAVMs. The actuarial ORs at 4 and 5 years varied between 65% and 86%[17,44] and 64% and 94%,[2,14,36] respectively. We reported an 88.1% actuarial OR at 5 years in the 84 patients who underwent single treatments and 59.0%, 76.0%, and 85.0% actuarial ORs at 3, 5, and 8 years, respectively, for the whole series.

The mean or median TOI reported in several series was about 2 years, in either GK or linear accelerator (LINAC) series. In our experience, the interval from treatment to cure was very similar after the first treatment (median 26.9 months) and across the whole series (median 27.35 months). This time interval is briefer than in older patients. This result is noteworthy because it is well known that cAVMs in pediatric and adolescent patients present a higher radiosensitivity with shorter obliteration interval than in adults.[9,21,28,40] In cases with repeat RS—so-called salvage retreatment—for cAVMs that remained patent despite initial treatment, the TOIs (considered from the first radiosurgical procedure) in our series (median 78.2 months) and in other radiosurgical series (range 61.0–79.0 months) were similar.[5,14]

For permanent ARE-related complications, we registered an 11% worsening of neurological condition, usually of mild severity (8 of 11 cases with Rankin Handicap Scale Grades I–II).[4] In other series, symptomatic permanent complication rates were between 1.9% and 7.7% (Table 9). In 2 LINAC studies, permanent side effects occurred more frequently, affecting between 13.3% and 17.6% of patients.[22,45]

The risk of bleeding during the latency period generally ranged from 1.3% to 9.1% in most series, including ours (Table 9). When higher rates of hemorrhagic stroke following radiosurgical treatment were reported (16.0%–22.7%),[33,37,44] it was always in series of patients treated with a low prescription marginal dose, with large nidus volumes, or both. These radiosurgical strategies are associated with longer TOI and lower ORs, thus leaving these patients exposed to a higher risk of bleeding during the latency period and explaining the high rates of intracerebral hemorrhage.

Indeed, several authors reported a strong correlation among treated volume, PDs, and radiosurgical outcomes (defined as OR, TOI, ARE-related permanent complications, and bleeding during the latency period). Potts et al.[33] reported on a series of children with cAVM treated with a relatively low prescription marginal dose. They described angiographic outcomes, rates of posttreatment hemorrhage, other treatment-related adverse events, and functional outcomes. They found that PD is a critical factor associated with OR, posttreatment hemorrhage, and ARE-related complications. In particular, a PD ≥ 18 Gy was associated with an improved OR and provided protection from posttreatment hemorrhage, even if only a partial response was obtained. On the contrary, these authors observed that a low marginal dose minimized overt neuro-

TABLE 8. Univariate analysis of 12 categorical variables related to TOI after first GK treatment in 100 children and adolescents with cAVMs followed up for at least 36 months

Categorical Variables	No. of Pts	Mean, Median	Median t-Test p Value
Sex			
Male	46	33.76, 28.91	0.254
Female	54	38.47, 32.93	0.688
Clinical onset			
No bleeding	30	41.56, 34.23	0.094
Bleeding	70	34.05, 27.77	0.081
Pre-GK Tx			
No EE	65	34.65, 28.20	0.276
EE	35	39.37, 33.27	0.529
Modified RS-based AVM score			
Hemispheric–callosal–cerebellar	69	34.97, 28.30	0.334
Basal ganglia–thalamus–brainstem	31	39.28, 38.73	0.280
Venous drainage			
Superficial	33	39.83, 28.20	0.230
Deep	67	34.57, 32.83	0.523
Functional location			
Noneloquent	6	44.34, 30.92	0.326
Eloquent	94	35.79, 30.63	1.000
Planned Tx			
Single session	84	32.71, 27.33	<0.001
Staged	16	50.71, 49.10	<0.001
Anatomical location*			0.967
Superficial	19	35.52	
Median	25	37.11	
Deep	56	36.21	
S-M grade*			0.008
I	4	56.06	
II	30	35.77	
III	58	32.80	
IV	8	53.87	
Blood flow through the cAVM*			0.428
Slow	31	34.68	
Intermediate	41	34.59	
High	28	40.62	
Imaging localization*			0.4588
Angio	18	41.33	
Angio + CT	22	33.12	
Angio + MRI	58	36.53	

* ANOVA test.

logical deficits directly associated with RS, but also resulted in lower ORs and higher rates of posttreatment hemorrhage. Therefore, the authors recommended a prescription marginal dose of ≥ 18 Gy to maximize AVM obliteration and minimize posttreatment hemorrhage.

A cutoff of 18 Gy for PD was also reported by Smyth et al.[37] and Zabel-du Bois et al.[44] In these studies, doses delivered to the margin of nidus volume ≥ 18 Gy improved the ORs but also increased the frequency of permanent neurological worsening.[22] Kano et al.[14] and Yeon et al.[43] identified their PD cutoffs as 20 Gy. These studies found that patients treated with marginal doses ≥ 20 Gy showed a statistically significant increase in angiographically documented cure, but there was no correlation with permanent complications and occurrences of bleeding during the latency period. It is interesting to note that for PD levels higher than 20 Gy, no significant improvements of OR rates were reported. Indeed, Dinca et al.[5] described that 3 different cohorts of patients treated with PDs of 25 Gy, 22.5 Gy, and 20 Gy achieved similar OR percentages: 86.31%, 77.75%, and 82.6%, respectively. In their study, TOI did not differ significantly among the 3 PDs, possibly because this range was relatively narrow. They affirmed that there was a somewhat surprising lack of correlation between outcome and radiosurgical dose when the peripheral (therapeutic) dose was between 20 and 25 Gy, at least as far as OR and TOI are concerned.

Relationships between nidus volume and radiosurgical outcomes have also been well documented. Studies by Pan et al.[29] and Reyns et al.[34] identified a cutoff of 10 ml for

TABLE 9. Summary of literature results for radiosurgical treatments of pediatric and adolescent cAVMs

Authors & Year	Period	FU (mos)	No. of Pts w/ FU	Device	OR at 1st RS (%)	TOI After 1st GK (mos)	Overall OR (%)	Repeat RS TOI From 1st Tx (mos)	Perm Compl (%)	RS/Symptomatic ARE Interv (mos)	Bleeding During LP (%)	RS/Bleed During LP Interv (mos)
Present study	1993–2011	92.0 M, 82.2 Med	100	GK	89.3	26.9 Med	90.0	78.2 Med	11.0	63.33 Med	9.0	42.8
Potts et al., 2014	1991–2010	>36.0	80	GK	59.0	—	62.5	—	0.0	—	20.0	15.0 Med
Sheth et al., 2014	2000–2012	>36.0	42	GK	30.0	—	—	—	3.6	—	2.2	—
Dinca et al., 2012	1985–2010	—	220	GK	71.3	32.4 M	82.7	79.0 M	3.6	—	2.2	—
Kano et al., 2012	1987–2006	71.3 Med	135	GK	70.4	37.0 Med	81.5	61.0 Med	1.5	—	6.0	41.0 Med
Yeon et al., 2011	2002–2008	45.0 Med	34	GK	44.0	23.2 M	51.0	—	7.7	—	7.7	—
Yen et al., 2010	1989–2007	98.4 M	186	GK	62.9	—	73.7	—	1.1	—	9.1	—
Pan et al., 2008	1993–2006	35.0 M, 25.0 Med	100	GK	65.0	—	81.0	—	5.0	—	4.0	—
Kiran et al., 2007	1997–2006	26.4 M	103	GK	87.0	—	—	—	3.8	8.7 M	2.9	24.0 Med
Cohen-Gadol & Pollock, 2006	1990–2001	42.0 Med	38	GK	66.0	—	68.0	—	0.0	—	2.6	—
Nicolato et al., 2006[28]	1993–2004	>36.0	62	GK	85.5	25.7 Med	—	—	1.3	—	1.3	—
Shin et al., 2002	1990–2000	71.0 Med	100	GK	75.0	21.5 Med	—	—	2.0	13.5 Med	4.0	40.5 Med
Smyth et al., 2002	1991–1997	61.9 M, 60.0 Med	31	GK	35.0	—	51.6	—	6.5	—	16.0	—
Levy et al., 2000	1987–1996	36.0 Med	53	GK	71.7	—	79.2	—	1.9	—	7.5	62.5 M, 62.0 Med
Buis et al., 2008	1992–2005	41.0 M, 29.0 Med	22	LINAC	68.0	37.5 M, 25.0 Med	—	—	4.5	—	4.5	—
Reyns et al., 2007	1988–2002	>36.0	100	LINAC	65.0	25.5 M	72.0	—	6.0	—	2.0	—
Zadeh et al., 2007	1989–2004	>36.0	30	LINAC	66.7	—	—	—	13.3	—	3.3	—
Zabel-du Bois et al., 2006	1996–2002	3.1 yrs Med	22	LINAC	64.0	27.1 Med	64.0	—	0.0	—	22.7	13.9 Med
Maity et al., 2004	1994–2002	29.6 Med	17	LINAC	53.0	—	—	—	17.6	52.0 M, 47.0 Med	0.0	—
Nataf et al., 2003	1984–2000	40.0 M, 34.0 Med	49	LINAC	61.2	34.0 M, 30.0 Med	—	—	0.0	—	8.2	48.5 M, 32.0 Med

FU = follow-up; interv = interval; M = mean; Med = median; perm compl = permanent complications.

TABLE 10. Prognostic factors in radiosurgical treatments of pediatric cAVMs: summary of literature results

Dependent Variable	Prognosticators (univariate analysis)	Authors & Year	Prognosticators (multivariate analysis)	Authors & Year
OR	Nidus diameter <2.5 cm	Sheth et al., 2014	Preplanned Tx	Present study
	Solitary draining vein	Sheth et al., 2014	Larger margin dose	Kano et al., 2012; Yen et al., 2010; Nataf et al., 2003
	Smaller AVM target vol	Kano et al., 2012; Yen et al., 2010; Kiran et al., 2007; Reyns et al., 2007; Nataf et al., 2003; Shin et al., 2002; Levy et al., 2000; present study	No previous EE	Yen et al., 2010
	Larger margin dose	Kano et al., 2012; Yeon et al., 2011; Yen et al., 2010; Nataf et al., 2003; Smyth et al., 2002; present study	Smaller AVM target vol	Yen et al., 2010
	Compact nidus structure	Yeon et al., 2011	—	—
	No previous EE	Yen et al., 2010; Kiran et al., 2007; Reyns et al., 2007	—	—
	Low RS-based AVM score (≤1)	Yen et al., 2010; Buis et al., 2008; Cohen-Gadol & Pollock, 2006; present study	—	—
	Lower S-M grade	Kiran et al., 2007; Reyns et al., 2007; Nicolato et al., 2006;[28] Shin et al., 2002; present study	—	—
	Age ≤12 yrs (younger age)	Reyns et al., 2007; Nicolato et al., 2006;[28] Shin et al., 2002	—	—
	Onset of focal edema after RS	Zabel-du Bois et al., 2006	—	—
	Integral dose	Present study	—	—
	Preplanned Tx	Present study	—	—
TOI	Increasing AVM size	Pan et al., 2008	Larger margin dose	Nataf et al., 2003
	Lower S-M grade	Nicolato et al., 2006;[28] present study	—	—
	Noneloquent cAVM locations	Nicolato et al., 2006[28]	—	—
	Preplanned Tx	Present study	—	—
Perm compl	AVM in brainstem, thalamus, or basal ganglia	Kano et al., 2012; Shin et al., 2002	—	—
	Higher RS-based AVM score	Kano et al., 2012; Yeon et al., 2011	—	—
	Larger AVM vol	Yeon et al., 2011; Kiran et al., 2007; Reyns et al., 2007	—	—
	S-M Grade IV–V AVMs	Kiran et al., 2007	—	—
	Male sex	Reyns et al., 2007	—	—
	MD >40 Gy	Shin et al., 2002	—	—
Bleeding during LP	Larger target vol	Kano et al., 2012	—	—
	Lower RS-based AVM score	Kano et al., 2012	—	—
	AVM vol ≥6 ml	Zabel-du Bois et al., 2006	—	—
	Feeding arteries in PCF	Shin et al., 2002	—	—
	Nidus location in the cerebellum	Shin et al., 2002	—	—

PCF = posterior cranial fossa.

treated volumes. These studies found that large cAVMs, i.e., > 10 ml according to the International RadioSurgery Association's algorithm,[12] are associated with lower ORs and higher risk of permanent complications. No correlation was found between the volume of cAVM and hemorrhage occurrence during the latency period.

Our data strongly confirm the correlation among nidus volume, PD, and radiosurgical outcomes or end points. We found that when the treated nidus volume is > 10 ml, the OR decreases and the risks of permanent side effects and hemorrhages dramatically increase. The relationship among these variables is highly significant (Table 3). The same is the case for PD. When the dose delivered to the margin of nidus volume was < 16 Gy, the probability of cure decreased and the frequencies of hemorrhage and permanent sequelae achieved worrisome rates (Table 4). The relationship between doses < 16 Gy and an increasing rate of permanent complications registered in our series is explained by the observations that in such cases, cAVMs were located in brainstem and basal ganglia, which are regions where PDs < 16 Gy are recommended. Furthermore, we propose an algorithm for the management of these "critical" patients (Fig. 2), suggesting that when the nidus volume > 10 ml and/or when the recommended PD is < 16 Gy, a staged radiosurgical treatment be planned.

Finally, several prognostic factors correlating with radiosurgical outcomes have been identified (Table 10). The most frequently reported are solitary draining vein, smaller AVM target volume (confirmed on multivariate analysis), larger margin dose (confirmed on multivariate analysis), no previous EE (confirmed on multivariate analysis), low RS-based AVM score (≤ 1), lower S-M grade, and age ≤ 12 years for OR; lower S-M grade and larger margin dose (confirmed on multivariate analysis) for TOI; and cAVM in brainstem–thalamus–basal ganglia, higher RS-based AVM score, and larger AVM volume for ARE-related permanent complications. The univariate statistical analysis performed in the present series showed a significant correlation between smaller AVM target volume, larger margin dose, lower S-M grade, integral dose, and type of preplanned treatment (single-session GKRS) for OR; and lower S-M grade and type of preplanned treatment for TOI. Nevertheless, multivariate analysis confirmed the prognostic role of S-M grade and type of preplanned treatment for OR only.

Conclusions

Our results reinforce the conclusion that GKRS is a safe and effective treatment for pediatric and adolescent patients with cAVMs, yielding a high OR with minimal permanent severe morbidity and no mortality. Furthermore, the very low frequency of severe hemorrhages during the latency period further encourages a widespread application of RS in treatment of pediatric and adolescent cAVMs. Univariate analysis found that modified RS-based cAVM score, nidus volume, PD, integral dose, S-M grade, and preplanned treatment (the last 2 also confirmed on multivariate analysis) significantly influenced ORs. S-M Grades I, II, and III, and single-session planned treatment, correlated with shorter TOI on univariate analysis. Finally, our statistical analysis suggests that a staged radiosurgical treatment should be planned when nidus volume > 10 ml and/or when the recommended PD is ≤ 16 Gy.

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Disclosure

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

Supplemental Information

Previous Presentation

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Conception and design: Nicolato, Longhi, Spinelli. Acquisition of data: Ricciardi, Spinelli, Zivelonghi, Zironi, Dall'Oglio. Analysis and interpretation of data: Nicolato, Longhi, Ricciardi, Spinelli, Foroni, Zivelonghi, Zironi, Dall'Oglio. Drafting the article: Nicolato, Ricciardi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nicolato. Statistical analysis: Tommasi. Study supervision: Nicolato.

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