Child's Nervous System (2019) 35:301–308
https://doi.org/10.1007/s00381-018-4008-2

ORIGINAL PAPER

Radiosurgical treatment of arteriovenous malformations in a retrospective study group of 33 children: the importance of radiobiological scores

Jody Filippo Capitanio[1] · Pietro Panni[1] · Alberto Luigi Gallotti[1] · Carmen Rosaria Gigliotti[2] · Francesco Scomazzoni[3] · Stefania Acerno[1] · Antonella del Vecchio[2] · Pietro Mortini[1]

Received: 22 October 2017 / Accepted: 19 November 2018 / Published online: 24 November 2018

Abstract

Purpose Arteriovenous malformations' (AVMs) obliteration depends on several factors; among the many factors that must be considered to obtain a high rate of obliteration and a low rate of complications, Flickinger-Pollock Score (FPS) seems to have an important role but still have to be validated in the pediatric population while Paddick-Conformity Index (PCI) still has no demonstration of its utility on the outcome and is considered only as a treatment quality marker.

Methods We retrospectively analyzed 33 consecutive children (2–18 years) with an AVM, treated with stereotactic radiosurgery Gamma Knife (SRS-GK) from 2001 to 2014 in our institution. We assess angiographic (DSA) Obliteration Rate (OR) as well FPS and PCI to draw conclusions.

Results DSA-OR was 60.6% with a rate of hemorrhage of 0%. median target volume (TV) was 3.60 cc (mean 4.32 ± 3.63; range 0.15–14.2), median PD was 22 Gy (mean 21.4 ± 2.6; range 16.5–25). Median percentage of coverage was 98% (mean 97 ± 3; range 84–100). The median modified FPS was 0.78 (mean 0.89 ± 0.52; range 0.21–2.1) and highly correlate with OR ($p = 0.01$). The median PCI was 0.65 (mean 0.65 ± 0.14; range 0.34–0.95) A PCI lower than 0.57 highly correlates with final OR ($p = 0.02$).

Conclusion SRS-GK was safe and gradually effective in children. A prescription dose-like that used in adult population (i.e. > 18 and between 20 and 25 Gy) is essential to achieve obliteration. A PD of 23 Gy and 22 Gy did impact OR, respectively ($p = 0.02$) and ($p = 0.05$). FPS and PCI are valuable scores that seem to correlate with the OR also in the pediatric population although further prospective studies are needed to confirm these observations.

Keywords Children · Gamma knife · Pediatric radiosurgery · Pediatric brain malformations

✉ Jody Filippo Capitanio
jody.capitanio@gmail.com

Pietro Panni
panni.pietro@hsr.it

Alberto Luigi Gallotti
gallotti.albertoluigi@hsr.it

Carmen Rosaria Gigliotti
carmen.gigliotti@hsr.it

Francesco Scomazzoni
Scomazzoni.francesco@hsr.it

Stefania Acerno
acerno.stefania@hsr.it

Antonella del Vecchio
delvecchio.antonella@hsr.it

Pietro Mortini
mortini.pietro@hsr.it

[1] Department of Neurosurgery and Gamma Knife Unit, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

[2] Department of Medical Physics, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

[3] Department of Neuroradiology, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

Abbreviations

AVM	Arterovenous malformations
GK	Gamma Knife
SRS	Stereotactic radiosurgery
DSA	Digital subtraction angiography
PD	Prescription dose
OR	Obliteration rate
PCI	Paddick Conformity Index
FPS	Flickinger Pollock Score
MRI	Magnetic resonance imaging

Introduction

Arteriovenous malformations (AVMs) are congenital lesions thought to arise because of failure of embryogenesis during the differentiation of vascular channels into mature arteries, capillaries, and veins, which results in direct, arteriovenous shunts without intervening capillary beds [1]. Current treatment choices involve microsurgical resection, endovascular embolization, stereotactic radiosurgery (SRS), and different combinations of the abovementioned techniques. Given the remarkable risk of hemorrhage, epilepsy, and neurologic deficits, observation is not usually considered as an acceptable option in the pediatric population [2–5]. Pediatric AVMs show different characteristics when compared to adults [6–12].

As clearly pointed out by Dinca and colleagues presenting the largest published experience so far on GK radiosurgery for pediatric cerebral AVMs, active management of childhood AVM is essential because the annual bleeding risk of 2–4% accrues over time, resulting in an unacceptable lifetime risk of hemorrhage, which could lead to severe neurological deficits or death [2].

Besides, Kano et al. mentioned previous experience reporting that children also have a higher risk of additional hemorrhages than adults, as well as higher morbidity and mortality rates after the initial intracranial hemorrhage [5].

In fact, although AVMs only account for 1–2% of intracerebral hemorrhage in the adult population, they represent 14–57% of the underlying causes of cerebral hemorrhage in pediatric patients [13–15]. The longer life expectancy peculiar of the pediatric population as compared to the adult one and the supposed higher annual bleeding risk (2–4 vs 1–3%) poses the need for a well-designed treatment strategy effective in both reducing the cumulative bleeding risk and the expected side effects of any proposed treatment [16]. Stereotactic radiosurgery gamma knife (SRS GK) has been proposed as a valid method in order to achieve the aforementioned goals even though prognostic factors related to AVM obliteration are less well defined than for the adult counterpart. In this paper, we present the results of our last 14 years' experience with pediatric AVMs treated with SRS GK at our institution, focusing on radiosurgical factors and radio-clinical evolutions that seem to have a correlation with the outcome.

Materials and methods

Study population and treatment algorithm

Thirty-three consecutive pediatric patients treated with GK SRS between 2001 and 2014 have been prospectively included in our AVM database. Clinical, radiological, and radiobiological characteristics and treatment outcomes as well results have been retrospectively evaluated. All patients performed stereotactic digital subtraction angiography (DSA) and magnetic resonance imaging (MRI) examination the day of the programmed SRS treatment.

Digital subtraction angiography protocol

All patients underwent biplanar DSA (Philips ® Allura FD 20/20) as part of the treatment plan with an image frame rate of 3 frames per second and injector-controlled contrast injection rates (4 cm^3/s for a total of 8 cm^3). Angioarchitectural features examined were on the arterial side: feeding artery enlargement (no or mild: feeding artery is of the same size or only slightly more prominent than the contralateral vessel; dilated feeder is at least 1.5 times larger than the contralateral vessel, associated aneurysms, and perinidal angiogenesis as previously described [17]. The nidus was evaluated for the volumetric size (determined from the original radiation plan based on cross-sectional imaging), location (eloquent vs non-eloquent), nidus type (compact vs diffuse), and flow pattern (arteriovenous transit time), which was estimated by determining the number of DSA frames between the first depiction of the nidus and the first visualization of a vein (high flow: venous drainage appearing in the same frame of AVM nidus or arterial feeders; moderate flow: 1-frame difference from visualization of the nidus and venous drainage and low flow for venous drainage seen in > 2 frames after nidal visualization [18]. Considering the venous compartment of the brain arteriovenous malformation, we recorded the number of venous drainage/s (single VS multiple), their location (deep vs superficial) and the presence or absence of venous varices/stenoses. Each DSA was examined by an interventional neuroradiologist with at least 10 years of experience (FS). We never performed superselective microcatetherization of AVM feeders for SRS treatment planning.

Radiosurgery treatment plan

The Elekta Leksell Gamma Knife Model C ® was used until 2007, later replaced by an Elekta Leksell Gamma Knife Perfexion Model®. Treatment plans have been generated by

using the GammaPlan® system version 10.1.1. Patients underwent stereotactic volumetric MRI, T2-weighted MRI, and cerebral DSA prior to GK session, then transferred to the planning station for treatment optimization. Subsequently, the AVM total volume is estimated from the dose-planning software and this step allows for number of stages definition as well as staging strategy. In case of large AVM (volume > 10 cc volume), volume-fractionated radiosurgery was used. Treatment strategy for fractionated GKRS was routinely performed as already reported [19].

Statistical analyses

Descriptive statistics is demonstrated as mean, median, range, and percentages. Various factors that may affect the outcome were analyzed, comparing continuous variables with Mann–Whitney *U* test and categorical ones with the Fisher's exact test.

Clinico-radiological follow-up

Neurological examination and MRI imaging were performed for each patient every 6 months for the first 2 years and then annually. Digital subtraction angiography was proposed to all patients after 3 years of follow-up or as soon as MRI suggested complete or near-complete AVM obliteration. Nidus obliteration has been defined as complete when no residual nidus was visible on DSA or MRI for patients who refused the angiographical exam. Near-complete when a reduction of more than 90% of the original nidal volume was evident at DSA or MRI follow-up; sub-total obliteration when a reduction of more than 75–80% of the original nidal volume was not evident at DSA or MRI follow-up; and partial obliteration when the reduction was confined to 50% of the original nidal volume. Complication rate was updated at each follow-up. Seizure status or eventual modification of prior antiepileptic drugs (AEDs) regimens was evaluated at each outpatient visit and recorded according to the Engel [20] classification. All DSAs have been performed by an interventional neuroradiologist with at least 10 years of experience (F.S.) and compared to the original one to verify eventual changes of the treated AVMs.

Results

Patient population

Data have been collected from a group of 33 consecutive pediatric patients treated with GKRS between January 2001 and January 2014. There were 16 (48.5%) boys and 17 (51.5%) girls; median age 15 years-old (mean 13 ± 4; range 2–18). Diagnosis was established after intracranial hemorrhage in 17 patients (51.5%) and after seizures in 13 patients (39.4%). Eighteen patients (54.5%) presented with a neurologic deficit, while 5 (15.2%) cases, AVMs have been incidentally diagnosed. Twenty-one (57%) patients had no history of previous treatment whereas 3 (3.3%) underwent hematoma evacuation and/or hydrocephalus treatment, while 6 (18%) had a previous embolization history. Three patients received both surgery and embolization before treatment (9.1%). Median follow-up was 65 months (mean 78.5 ± 43.5; range, 30–174 months). Data are summarized in Table 1.

Table 1 Main characteristics of the population and of the AVMs

Gender	No. of patients	%
Male	16	48.5
Female	17	51.5
Age GKSR (years)		Years
Mean (median)	13	(15)
Standard deviation (range)	± 4	(2–18)
Presentation	No. of patients	%
Hemorrhage	17	51.5
Seizure	13	39.4
Neurological deficit	18	54.5
Incidental	5	15.2
Previous interventions	No. of patients	%
Embolization	6	18
Surgery	3	3.3
Surgery + embolization	3	9.1
None	21	64%
Spetzler-Martin grade	No. of patients	%
I	1	3.0
II	8	24.2
III	13	39.4
IV	9	27.3
V	2	6.1
Modified Pollock-Flickinger Score	No. of patients	%
< 1.00	19	57.6
1.00–1.50	9	27.3
1.51–2.00	4	12.1
> 2.00	1	3.0
AVM volume (cc)	No. of patients	%
< 3 cc	16	48.5
3–10 cc	11	33.3
> 10 cc	6	18.2
AVM location	No. of patients	%
Eloquent	29	87.9
Non-eloquent	4	12.1
Venous drainage	No. of patients	%
Superficial	13	39.4
Deep or both	20	60.6

AVM features

According to Spetzler Martin (SM) Grading system [21], there were 1 (3%) grade I, 8 grade II (24.2%), 13 grade III (39.4%), 9 grade IV (27.3%), and 2 grade 5 AVMs in this cohort (6.1%). Sixteen patients had a volume < 3 cc, 11 patients between 3 and 6 cc, and 6 patients had a volume > 6 cc. 29/33 (87.9%) AVMs were considered to affect eloquent portions of the cerebral cortex. Twenty-three AVMs were superficially located (69.7%) while 10 (30.3%) were deep seated. Superficial venous drainage was angiographically detected in 13 (39.4%) cases and deep or mixed in the remaining 20 cases (60.6%). Arterial feeders were evaluated only in 25 cases; in 23 out of 25 (92%) were multiple and in 2 cases (8%) were single. Data are summarized in Table 1.

SRS gamma knife planning parameters

The median target volume (TV) was 3.60 cc (mean 4.32 ± 3.63; range 0.15–14.20;) Median prescription dose (PD) in Gy for the cohort was 22 Gy (mean 21.4 ± 2.6; range 16.5–25). The median maximum dose in Gy was 44 (47.2 ± 5.3; range 33–51). Median number of isocenters was 14 (mean 13 ± 5; range 3–25). V12 has been calculated for all plans and resulted as follows: median 11.80 (mean 13.68 ± 9.66; range 1–39). Median V10 was 15.60 (mean 17.90 ± 12.57; range 1.–51.40). Median percentage of coverage of the plans was 98% (mean 97 ± 3; range 84–100%). Median Gradient Index 2.86 (mean 2.89 ± 0.23 range 2.52–3.36).

Median modified Pollock-Flickinger score [22] (mPFS) in our population was 0.78 (mean 0.89 ± 0.52; range 0.21–2.1); 19 patients (57.6%) scored < 1.00; 9 (27.3%) between 1.00 and 1.50; 4 (12.1%) scored between 1.51 and 2.00 and one patient achieved > 2.00. To determine the conformity index of the GK treatment plans, we used the formulation described by Ian Paddick [23]. Our cohort median Paddick Conformity Index (PCI) was 0.65 (mean 0.65 ± 0.14; range 0.34–0.95). Radiosurgical treatment parameters are resumed in Table 2.

Table 2 Gamma Knife planning parameters

Target volume [cc]		
Mean (median)	4.32	(3.60)
Standard deviation (range)	± 3.63	(0.15–14.20)
Prescription dose [Gy]		
Mean (median)	21.4	(22)
Standard deviation (range)	± 2.6	(16.5–25)
Maximum dose [Gy]		
Mean (median)	47.2	(44)
Standard deviation (range)	± 5.3	(33–51)
No. of isocenters		
Mean (median)	13	(14)
Standard deviation (range)	± 5	(3–25)
V12 [cc]		
Mean (median)	13.68	(11.80)
Standard deviation (range)	± 9.66	(1–39)
V10 [cc]		
Mean (median)	17.90	(15.60)
Standard deviation (range)	± 12.57	(1.70–51.40)
% coverage		
Mean (median)	97	(98)
Standard deviation (range)	± 3	(84–100)
Conformity Index		
Mean (median)	0.65	(0.65)
Standard deviation (range)	± 0.14	(0.34–0.95)
Gradient Index		
Mean (median)	2.89	(2.86)
Standard deviation (range)	± 0.23	(2.52–3.36)

Radiological outcome

The radiological follow-up has been completed in 20 patients (60.6%) with DSA and in almost all (32/33) with MRI (97%). Volume fractioned GK treatment has been performed on 4/33 (12.1%) patients with a volume larger than 7 cc. A complete AVMs obliteration rate at first GK treatment was achieved in 17/33 (51.5%) patients; (15 single fraction and 2 volume-fractioned). Retreatment has been performed in 5 patients (15.1%) after an observation time of at least 42 months. 3/5 (60%) of retreated patients experienced complete obliteration. Subtotal obliteration was observed in 5/7 remaining patients (71.4%). Overall obliteration rate of the studied population was 60.6% (20/33).

Clinical outcome

No hemorrhages were detected during the follow-up (0%). No new permanent neurological deficits developed after GK treatment (0%); temporary symptoms related to GK treatment that required a medical therapy and an eventual hospitalization shorter than 5 days have been observed in 4 patients (12.1%). Ten patients reported an improvement of neurologic signs/symptoms (55%), 3 reported a complete resolution (16.7%) and a persistence of presenting symptoms was noted in 5 patients (27.8%). We observed a complete resolution of seizures after GKRS (Engel class I) in 4 patients (30%), Engel class II improvement was observed in 8 patients (61.6%). Temporary worsening was observed in 4 patients (30.8%). All patients who experienced a complete resolution of seizures achieved a complete obliteration of their AVM at last FU. Obliteration rate of the retreatment group is 50%, with

subtotal obliteration achieved in 50% of the cases (see Table 3 for Resume).

Results of univariate analysis/statistical analysis

Prescription doses (PD) of respectively 22 and 23 Gy were statistically associated with OR, $p = 0.05$ and $p = 0.02$. The mean mPFS was associated with OR ($p = 0.01$), and a cut-off value lower than of 0.57 of the PCI was associated with obliteration rate ($p = 0.02$). Detailed results are presented in Table 4.

Table 3 Descriptive statistical results

Follow-up	Months	Months
Mean (median)	78.5	(65)
Standard deviation (range)	± 43.5	(27–174)
Radiological FU	No. of patients	%
DSA	20	60.6
MRI	32	96.97
Outcome	No. of patients	%
Obliteration rate	20	60.6
Obliteration at 1st treatment	17	51
Volume reduced	13	100
Volume reduced at 1st treatment	15	93.8
Hemorrhage post treatment	No. of patients	%
	0	0
Adverse radiation effects (ARE)	No. of patients	%
No ARE	29	87.9
Gliosis and edema	2	6.1
Cyst development	1	3.0
Cyst and radionecrosis	1	3.0
Neurological deficit after SRS GK	No. of patients	%
New	0	0
Temporary	4	12.1
Unchanged	5	27.8
Improved	10	55.6
Cured	3	16.7
Seizure after SRS GK	No. of patients	%
New/Worsened	0	0
Temporary	4	30.8
Unchanged	5	38.5
Improved	4	30.8
Cured	4	30.8
Volume staged GK	No. of patients	%
	4	12.1
Re-treatment group	No. of patients	%
	5	15.1
Outcome re-treatment	No. of patients	%
Obliteration	3	50
Volume reduced	3	50

Table 4 Mann–Whitney *U* test: obliteration results

Factors	*p* value
Volume (< 2.2 cc vs > 2.2 cc)	0.05
Modified P-F score (< 0.96 vs > 0.96)	0.01
Prescription dose (> 23 Gy vs < 23 Gy)	0.02
Prescription dose (> 22 Gy vs < 22 Gy)	0.05
Paddick C.I. (< 0.57 vs > 0.57)	0.02

Discussion

Reported obliteration rates (OR) for radiosurgically treated pediatric AVMs range from 34 up to 82.7% in the literature. As well, neurological morbidity, i.e., side effects like gliosis, delayed cyst formation, radiation-induced necrosis, or late-onset neoplasia are reported within a broad range [3, 24–26]. Our overall OR is in line with previously reported results with DSA-confirmed obliteration of 60.6% with a median follow-up of 65 months; besides, we observed MRI near complete in 15/16 (94%) of remaining patients. Kano et al. recently reported that only 3% of MRI-obliterated AVMs are still patent at DSA [26]; still we decided to consider "true" obliteration only those confirmed by ways of DSA even though this could potentially lower the actual overall OR of the studied population. To the best of our knowledge, our reported follow-up is one of the longest available in literature; nevertheless, considering the young age of the patients, we deem is of paramount importance to keep following them up to get even more precise results about long-term OR, de novo AVM formation, adverse radiation effects, cysts formation, and bleeding rates after obliteration. Prescription dose (PD) and its relation to overall OR has been debated in literature. Dinca et al. [2] in their 2012 seminal paper showed that obliteration rate was independent from PD variations within the 20–25 Gy range while they correspondingly confirmed that a reduction to a dose below 20 Gy was deleterious to the final goal of a complete obliteration. Kano et al. [26] clearly showed that a higher PD was associated with higher OR although higher rates of adverse radiation effects (AREs) occurred with higher PD and higher value of mPFs. Potts and colleagues [24], in 2014, proved that a PD higher than 18 Gy was one of the main factors needed in order to achieve obliteration and minimize hemorrhage and subsequent neurological deficit further proving at the same time that lower doses led to cure in a minority of patients (16%). Starke et al. [27] in the first multicentric study on pediatric AVM treated by means of SRS GK, in 2016, observed a $\geq$ 22-Gy prescription dose to be associated with AVM obliteration and improved outcome in multivariate analysis. The aforementioned results highlight the importance of a minimal and maximal PD. We showed, that both a PD of 23 Gy and 22 Gy did impact OR, respectively ($p = 0.02$) and ($p = 0.05$). Besides, we found a cutoff value close to 1 (0.96)

of the modified Pollock-Flickinger being positively correlated with obliteration rate and with low AREs, confirming the importance of this score in predicting radiosurgical outcome even in the pediatric population.

References of Table 5: [2, 3, 5, 25, 28–32] Our OR is slightly lower than those presented by Dinca and the other groups (51.5% for the first radiosurgical treatment and 61% overall). In our opinion, OR is similar although not identical not only because we considered exclusively DSA-verified children; supporting the hypothesis that there must be other important factors different from the PD that are implicated in the final outcome. The effect of previous endovascular embolization, for example, among other treatment modalities, though debated, has been reported to actually decrease the obliteration rate [27].

Unfortunately, we are not able to find a correlation between previous treatment and AVM obliteration rates in our population likely because the small size of the reported population underpowered the study from a statistical point of view needed to detect such difference".

Nonetheless, Umansky et al. [33] recently reported the largest experience on multimodal (endovascular Onyx+ radiosurgical) treatment for pediatric bAVMs. The authors clearly showed a significant nidus volume reduction after endovascular treatment (average "virgin" AVM volume 3.48 mL and average radiosurgery volume 1.2 mL) allowing for a smaller focus of stereotactic radiosurgery obtaining brilliant results in terms of both safety and overall obliteration rates. Nonetheless, it should be noted that multimodal treatment does not necessarily equal to different treatment modalities added in series in order to complete what left by the preceding one. As clearly stressed by Pierre Lasjaunias and coworkers in the 3rd volume of Surgical Neuroangiography devoted to the evaluation and treatment of pediatric vascular diseases, in the ideal scenario, there is more than a semantic difference between staged, partial, and palliative treatment. Partial targeted treatment is an incomplete exclusion motivated by a clinical concern requiring improvement and directed toward a specific portion of the lesion when complete exclusion cannot be offered with an acceptable level of risk [34].

Still, as evidenced by others, [27] a longer follow-up (e.g., 10 years) could potentially detect even higher OR, further evidencing the importance of a continuous follow-up in the pediatric population. Statistical analysis did not significantly correlate OR to other parameters, such as lesion volume, Spetzler-Martin grade, patients' age, number of arteries feeding the AVM, and most angioarchitectural features. These results are in contrast with adults' literature, in which radiation dose, lesion volume, and AVM angioarchitecture (diffuse vs compact nidus) have been observed as prognostic factors for the response to radiosurgical treatment, while the scant pediatric literature reveals no such correlations. Reviewing the larger pediatric series, we have not found any study that showed a factor consistently associated with OR in the pediatric literature. Although, larger series do not reveal significant correlations. The only multicenter-based paper published by Starke et Al. in 2016, underlined the importance of a high PD ($\geq$ 22 Gy) for AVM obliteration and favorable outcome. Even though considering the inherent limitation of every single center study, i.e., selection bias, we did find that both the mFPS $\leq$ 1 as outlined before and the PCI strongly correlated with OR. The low cut-off of the Paddick Conformity Index (PCI) result correlated with the OR. Our study shows that a low PCI should not be considered as a negative prognostic factor since a lower conformation means that a larger portion at the periphery of the AVM, where angiographically occult microfeeders coming from transit-vessels reside, receive the same

Table 5 Series of at least 30 patients with a maximum age of 19 years

Authors year	SRS form	No. of pts	Peripheral dose (Gy)	Obliteration rate (%)		Complication rate (%)	Bleed rate (%)
				1-time treatment	Overall		
Shin et al. 2002	GK	82	20	71	71	4	4
Smyth et al. 2002	GK	31	18	27	35	6	25
Cohen-Gadol 2006	GK	38	20	54	55	0	3
Pan et al. 2008	GK	100	18.5	65	81	5	4
Yen et al. 2010	GK	186	21.9	49.5	58	3.2	9
Yeon et al. 2011	GK	39	20	44	51	7.7	10.2
Kano et al. 2012	GK	135	20	43	54	2.2	6
Dinca et al. 2012	GK	363	22.7	71.3	82,7	3.6	2.1
Nataf et al. 2003	LINAC	49	25	61	61	0	8
Reyns et al. 2007	LINAC	100	23	65	70	5	2
Starke et al. 2016	GK	357	21	52–68	63	2.7–3.3	4.5–10.2
Present Study	GK	33	22	51.5	61	0	0

PD. Of note, a lower PCI did not result as expected in a higher rate of adverse radiation effects. Despite these encouraging results, the identification of other prognostic factors that can predict OR in the pediatric population is far away from being clarified as compared to the adult population [16, 28]. Besides OR, hemorrhage prevention, seizures control, and prevention of neurological deficits progression are key objectives of the SRS GK treatment of brain AVMs. Reported hemorrhagic events after SRS cover a wide range between 0 and 25% [2, 5, 35, 36]. We did not record any bleeding in the therapeutic window between SRS and obliteration at last FU. To the best of our knowledge, this is the lowest rate reported in GK literature along with the one reported by Zeiler et Al. in 2016 [36]. The clinical evolution of presenting neurological symptoms represents a poorly debated topic [2, 3, 26, 37]. Hemorrhagic presentation ranges between 50 and 80%, higher than the adult population one highlighting AVM obliteration with the resultant rebleeding prevention as the primary endpoint in most of the published experiences. Still, 50% of the reported patients presented because of seizures or associated deficits. Even though a preliminary result considering the young age of the subjects, we observed a significant clinical amelioration in a large proportion of treated patients. Complete seizures resolution was associated with total AVM obliteration [38]. Nonetheless, 61.6% experienced seizure amelioration (both attacks frequency and severity), and 55% of patients reported improvement of clinical presenting symptoms (16.7% resolution). We do acknowledge that GK radiosurgery poses some risks to the developing brain, particularly considering the long-term rate of secondary malignancies. Even though, its reported incidence seems rare (rate of secondary malignancies after SRS 0.04% according to Patel TR et al. [39] and Xhumari et al [40]. Even though considering that the PCI has not been validated for AVMs treatment as a surrogate for safety and/or efficacy of the treatment provided, is one of the key elements defining GK treatment plan quality. By providing information regarding selectivity, we were surprised by noticing that a low conformity index was not associated with an increased rate of side effects, both immediate and long-term. At the same time, we found it statistically significantly associated to AVM obliterations rate. We acknowledge this observation raises more questions than answers and we hope for future studies better delineating its relationship with outcome after GK treatment for such a challenging disease."

Conclusions

GK SRS can be considered safe and effective in children with AVMs as there is evidence of high OR associated with low morbidity and mortality rates. The overall complication rate is comparable to the complication rates reported in studies of grade III AVMs treated with microsurgical and multimodality approaches [41]. The substantially unaffected post-radiosurgical hemorrhagic rate makes this treatment an appropriate strategy in such a delicate population. A PD of 23 Gy and 22 Gy did impact OR, respectively ($p = 0.02$) and ($p = 0.05$). Our personal experience indicates that the mFPS is a valuable prognostic tool for the pediatric population too; a score ≤ 1 is associated with a high rate of excellent outcome and a low rate of modified ranking scale decline. A PCI < 0.57 should not be regarded as a negative prognostic factor while planning GK treatment, but as a beneficial factor strongly correlated to the outcome. ($p = 0.02$). This last element, never described before to the best of our knowledge, deserves further evaluation with much larger patient populations.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliationswith or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Kiris T, Sencer A, Sahinbas M, Sencer S, Imer M, Izgi N (2005) Surgical results in pediatric Spetzler-Martin grades I-III intracranial arteriovenous malformations. Childs Nerv Syst 21:69–74 discussion 75-66
2. Dinca EB, de Lacy P, Yianni J, Rowe J, Radatz MW, Preotiuc-Pietro D, Kemeny AA (2012) Gamma knife surgery for pediatric arteriovenous malformations: a 25-year retrospective study. J Neurosurg Pediatr 10:445–450
3. Pan DH, Kuo YH, Guo WY, Chung WY, Wu HM, Liu KD, Chang YC, Wang LW, Wong TT (2008) Gamma Knife surgery for cerebral arteriovenous malformations in children: a 13-year experience. J Neurosurg Pediatr 1:296–304
4. Chung WY, Shiau CY, Wu HM, Liu KD, Guo WY, Wang LW, Pan DH (2008) Staged radiosurgery for extra-large cerebral arteriovenous malformations: method, implementation, and results. J Neurosurg 109(Suppl):65–72
5. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, Niranjan A, Novotny J, Lunsford LD (2012) Stereotactic radiosurgery for arteriovenous malformations, part 2: management of pediatric patients. J Neurosurg Pediatr 9:1–10
6. Iizuka Y, Rodesch G, Garcia-Monaco R, Alvarez H, Burrows P, Hui F, Lasjaunias P (1992) Multiple cerebral arteriovenous shunts in children: report of 13 cases. Childs Nerv Syst 8:437–444

7. Garcia-Monaco R, De Victor D, Mann C, Hannedouche A, Terbrugge K, Lasjaunias P (1991) Congestive cardiac manifestations from cerebrocranial arteriovenous shunts. Endovascular management in 30 children. Childs Nerv Syst 7:48–52
8. Willinsky RA, Lasjaunias P, Terbrugge K, Burrows P (1990) Multiple cerebral arteriovenous malformations (AVMs). Review of our experience from 203 patients with cerebral vascular lesions. Neuroradiology 32:207–210
9. Cumming GR (1980) Circulation in neonates with intracranial arteriovenous fistula and cardiac failure. Am J Cardiol 45:1019–1024
10. Cronqvist S, Granholm L, Lundstrom NR (1972) Hydrocephalus and congestive heart failure caused by intracranial arteriovenous malformations in infants. J Neurosurg 36:249–254
11. Lasjaunias P, Piske R, Terbrugge K, Willinsky R (1988) Cerebral arteriovenous malformations (C. AVM) and associated arterial aneurysms (AA). Analysis of 101 C. AVM cases, with 37 AA in 23 patients. Acta Neurochir 91:29–36
12. Lasjaunias P, Berenstein A, Ter Brugge K (2012) Surgical Neuroangiography: 1 clinical vascular anatomy and variations. Springer, New York
13. Al-Shahi R, Warlow C (2001) A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain 124:1900–1926
14. Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML (2005) Natural history, evaluation, and management of intracranial vascular malformations. Mayo Clin Proc 80:269–281
15. Al-Jarallah A, Al-Rifai MT, Riela AR, Roach ES (2000) Nontraumatic brain hemorrhage in children: etiology and presentation. J Child Neurol 15:284–289
16. Smyth MD, Sneed PK, Ciricillo SF, Edwards MS, Wara WM, Larson DA, Lawton MT, Gutin PH, McDermott MW (2002) Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. J Neurosurg 97:48–55
17. Valavanis A, Yasargil MG (1998) The endovascular treatment of brain arteriovenous malformations. Adv Tech Stand Neurosurg 24:131–214
18. Taeshineetanakul P, Krings T, Geibprasert S, Menezes R, Agid R, Terbrugge KG, Schwartz ML (2012) Angioarchitecture determines obliteration rate after radiosurgery in brain arteriovenous malformations. Neurosurgery 71:1071–1078 discussion 1079
19. Franzin A, Panni P, Spatola G, Vecchio AD, Gallotti AL, Gigliotti CR, Cavalli A, Donofrio CA, Mortini P (2016) Results of volume-staged fractionated Gamma Knife radiosurgery for large complex arteriovenous malformations: obliteration rates and clinical outcomes of an evolving treatment paradigm. J Neurosurg 125:104–113
20. Engel J Jr, Burchfiel J, Ebersole J, Gates J, Gotman J, Homan R, Ives J, King D, Lieb J, Sato S, Wilkus R (1993) Long-term monitoring for epilepsy. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 87:437–458
21. Spetzler RF, Martin NA (1986) A proposed grading system for arteriovenous malformations. J Neurosurg 65:476–483
22. Pollock BE, Flickinger JC (2008) Modification of the radiosurgery-based arteriovenous malformation grading system. Neurosurgery 63:239–243 discussion 243
23. Paddick I (2000) A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. J Neurosurg 93(Suppl 3):219–222
24. Potts MB, Sheth SA, Louie J, Smyth MD, Sneed PK, McDermott MW, Lawton MT, Young WL, Hetts SW, Fullerton HJ, Gupta N (2014) Stereotactic radiosurgery at a low marginal dose for the treatment of pediatric arteriovenous malformations: obliteration, complications, and functional outcomes. J Neurosurg Pediatr 14:1–11
25. Reyns N, Blond S, Gauvrit JY, Touzet G, Coche B, Pruvo JP, Dhellemmes P (2007) Role of radiosurgery in the management of cerebral arteriovenous malformations in the pediatric age group: data from a 100-patient series. Neurosurgery 60:268–276 discussion 276
26. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, Niranjan A, Novotny J Jr, Lunsford LD (2012) Stereotactic radiosurgery for arteriovenous malformations, Part 3: outcome predictors and risks after repeat radiosurgery. J Neurosurg 116:21–32
27. Starke RM, Ding D, Kano H, Mathieu D, Huang PP, Feliciano C, Rodriguez-Mercado R, Almodovar L, Grills IS, Silva D, Abbassy M, Missios S, Kondziolka D, Barnett GH, Dade Lunsford L, Sheehan JP (2016) International multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: outcomes after stereotactic radiosurgery. J Neurosurg Pediatr 19(2):136–148. https://doi.org/10.3171/2016.9.PEDS16284
28. Cohen-Gadol AA, Pollock BE (2006) Radiosurgery for arteriovenous malformations in children. J Neurosurg 104:388–391
29. Shin M (2002) [Gamma knife radiosurgery for arteriovenous malformations: anatomy, techniques, and avoidance]. No shinkei geka. Neurol Surg 30:703–714
30. Nataf F, Schlienger M, Lefkopoulos D, Merienne L, Ghossoub M, Foulquier JN, Deniaud-Alexandre E, Mammar H, Meder JF, Turak B, Huart J, Touboul E, Roux FX (2003) Radiosurgery of cerebral arteriovenous malformations in children: a series of 57 cases. Int J Radiat Oncol Biol Phys 57:184–195
31. Yen CP, Monteith SJ, Nguyen JH, Rainey J, Schlesinger DJ, Sheehan JP (2010) Gamma Knife surgery for arteriovenous malformations in children. J Neurosurg Pediatr 6:426–434
32. Yeon JY, Shin HJ, Kim JS, Hong SC, Lee JI (2011) Clinico-radiological outcomes following gamma knife radiosurgery for pediatric arteriovenous malformations. Childs Nerv Syst 27:1109–1119
33. Umansky D, Corn BW, Strauss I, Shtraus N, Constantini S, Frolov V, Maimon S, Kanner AA (2018) Combined treatment approach to cerebral arteriovenous malformation in pediatric patients: stereotactic radiosurgery to partially Onyx-embolized AVM. Childs Nerv Syst 34:2269–2274
34. Lasjaunias PtB KG, Berenstein A (2006) Surgical Neuroangiography: Vol. 3: Clinical and Interventional Aspects in Children. Springer, Berlin
35. Pollock BE (2013) Arteriovenous malformations and radiosurgery. J Neurosurg 119:532–534
36. Zeiler FA, Janik MK, McDonald PJ, Kaufmann AM, Fewer D, Butler J, Schroeder G, West M (2016) Gamma Knife radiosurgery for pediatric arteriovenous malformations: a Canadian experience. Can J Neurol Sci 43:82–86
37. Yen CP, Jain S, Haq IU, Jagannathan J, Schlesinger D, Sheehan J, Steiner L (2010) Repeat Gamma Knife surgery for incompletely obliterated cerebral arteriovenous malformations. Neurosurgery 67:55–64 discussion 64
38. Ditty BJ, Omar NB, Foreman PM, Miller JH, Kicielinski KP, Fisher WS 3rd, Harrigan MR (2016) Seizure outcomes after stereotactic radiosurgery for the treatment of cerebral arteriovenous malformations. J Neurosurg 1–7
39. Patel TR, Chiang VL (2014) Secondary neoplasms after stereotactic radiosurgery. World Neurosurg 81:594–599
40. Xhumari A, Rroji A, Enesi E, Bushati T, Sallabanda Diaz K, Petrela M (2015) Glioblastoma after AVM radiosurgery. Case report and review of the literature. Acta Neurochir 157:889–895
41. Pandey P, Marks MP, Harraher CD, Westbroek EM, Chang SD, Do HM, Levy RP, Dodd RL, Steinberg GK (2012) Multimodality management of Spetzler-Martin grade III arteriovenous malformations. J Neurosurg 116:1279–1288