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Gamma Knife treatment strategies for paediatric AVMs: approaches to refractory cases

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Original Article

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Abstract

Introduction: While paediatric arteriovenous malformations (AVMs) often require aggressive therapeutic intervention due to their high bleeding incidence, choosing a course of treatment for deep and eloquent areas and asymptomatic cases is difficult. Sequelae are a concern in children, as they survive for longer after treatment. The authors have long recommended and implemented staged Gamma Knife radiosurgery (GKRS) in their treatment guidelines to maximise therapeutic effects.
Methods: Fifty-eight paediatric patients with AVM and ≤15 years old who underwent GKRS under general anesthesia from 2002 to 2020 were followed up for an average of 81·5 months. Obliteration dynamics and clinical outcomes were analysed.
Results: The mean patient age was 10·5 years. The mean nidus volume was 6·6 cm^3, the complete occlusion rate was 69%, the annual post-irradiation bleeding rate was 2·19% and nine (16%) cases had transient radiation-induced changes. One (1·7%) patient had sequela, and three (5·1%) developed encapsulated hematomas and cysts. Additionally, the 3- and 5-year cumulative occlusion rates were 39·0% and 53·3%, respectively. Multivariate analysis showed significantly higher occlusion rates in patients ≤12 years old and with a nidus volume of ≤4 cm^3.
Conclusions: GKRS is a useful treatment for paediatric AVM; however, its use poses some challenges.

Introduction

Arteriovenous malformations (AVMs) are known to have a variable and dynamic pathogenesis in the paediatric population, despite being a congenital disease. Moreover, their clinical presentation, especially through childhood, is often different from that of adults. While bleeding and rebleeding incidences are high, often requiring aggressive therapeutic intervention, a large number of de novo and diffuse types are believed to complicate the determination of the course of treatment.[1,2] Deciding on a course of treatment is extremely difficult, especially for eloquent and deep areas and asymptomatic cases, for which surgical intervention is complex. Treatment is also a concern in children, particularly regarding sequelae incidence, as children have longer survival periods after treatment. Frequently, follow-up is used as a management approach.[3]

Stereotactic radiosurgery (SRS) is a minimally invasive therapy aimed at achieving a radiological outcome of complete nidus obliteration and the disappearance of early draining veins. The therapy is aimed at reducing the hemorrhage risk to that of the general population.[4] SRS has become a standard management option for AVMs, and it is particularly useful for lesions located in deep or eloquent regions that have high surgical risks.[5,6] The authors have recommended and implemented staged Gamma Knife radiosurgery (GKRS) for paediatric AVMs in treatment guidelines to maximise risk avoidance and therapeutic effects. This study reports the results of GKRS for paediatric AVMs based on experience.

Methods

This retrospective study was conducted at a single institution from January 2002 to March 2020. Patients ≤15 years old who were treated with GKRS under general anesthesia for AVMs were eligible for inclusion. Patients followed up for more than 2 years after the initial treatment were included. To avoid complications, staged GKRS was performed on patients with a large nidus volume with an irradiated volume of ≤4·0 cm^3. The prescription dose was limited to 22 Gy.[9] The main short circuit in the main body of the AVM is located at the nidus of the transition area of the efferent vessel, which is a hemorrhagic site subject to hemodynamic stress. Therefore, this was defined as the most important target region in the treatment plan. An anesthesiologist had been administering non-intubated monitored anesthesia care, as described previously,[7] to all patients since 2017.

After treatment, magnetic resonance imaging evaluation was performed approximately every 6 months, and computed tomography angiography or angiography was performed when the nidus appeared to be occluded. If a residual nidus was found in the irradiated field or in the case of a second or subsequent staged GKRS, the treatment was performed under general anesthesia if the patient was ≤15 years old at the time of treatment.

Univariate and multivariate Cox proportional hazards analyses were used to determine the factors associated with obliteration, radiation-induced changes (RICs) and hemorrhage following radiosurgery.

Results

Sixty-eight (18·6% of 387 total AVMs) patients ≤15 years old were treated for AVMs with GKRS under general anesthesia. Finally, 58 patients who were followed up for more than 2 years after the initial treatment were included. Patient background and treatment outcomes are shown in Tables 1 and 2, respectively. The mean follow-up duration was 81·5 months. Bleeding onset was observed in 30 cases. Of the 28 patients with no bleeding onset, 20 were asymptomatic and diagnosed incidentally, 5 had seizure onset, and 3 developed neurological-deficit symptoms. The average number of treatments was 1·34. The post-treatment occlusion rate was 40 (69%) cases, with 12 cases of occlusion confirmed by angiography, 12 by contrast-enhanced computed tomography and the remaining 16 by magnetic resonance angiography.

Typically, the interval between sessions was planned to be at least 3–4 years, the period for which the irradiation response may persist. However, the interval between treatment sessions was 28–116 months (mean, 49·6 months). This wide range of interval durations occurred for two reasons. First, in some patients, the subsequent treatment sessions were postponed until the latency period was completed. Second, one patient had a reappearance post-GKRS, and that session was included (Fig. 1). The median time from initial treatment to occlusion was 59·3 months, with occlusion occurring after the first GKRS session in 28 (48%) cases. The cumulative occlusion rate was calculated to be 39·0% at 3 years and 53·3% at 5 years (Fig. 2).

The log-rank test showed a significantly better occlusion rate in the group with a pre-treatment nidus volume of ≤4 cm^3 ($p = 0·005$) and a Pollock–Flickinger score of ≤1 ($p = 0·035$). After multivariate analysis using a Cox proportional hazards model with a stepwise approach to examine input variables, the following variables were significantly associated with occlusion after treatment: age <12 years (hazard ratio, 2·17; 95% confidence interval, 1·03–4·56; $p = 0·039$) and nidus volume <4 cm^3 (hazard ratio, 3·36; 95% confidence interval, 1·17–9·66; $p = 0·024$; Table 3).

Post-treatment bleeding was observed in ten (17%) patients, three of whom underwent surgical removal of the nidus, four of whom underwent re-irradiation and three of whom experienced spontaneous occlusions. The annual bleeding rate by person-years was 2·19%. In two patients, the modified Rankin Scale score decreased by one point or more due to AVM-related events after treatment, and one patient died; these outcomes were caused by post-treatment bleeding. No factor was found to be significantly associated with post-treatment bleeding, including prior bleeding or a single drainer.

Table 1. Summary of patients

Gender	Male: 34 Female: 24
Age (mean ± SD years)	10·5 ± 2·8
Size of nidus, cm^3 (mean ± SD)	6·6 ± 8·7
Spetzler–Martin grade	
1	0
2	12
3	29
4	13
5	4
Pollock–Flickinger AVM score (mean ± SD)	1·3 ± 0·9
≤1·00 (%)	37 (64)
1·01–1·50	9 (16)
1·51–2·00	2 (3·4)
≥2·00	10 (17)
AVM location	
Frontal (%)	19 (33)
Temporal	6 (10)
Parietal	2 (3·4)
Occipital	10 (17)
Thalamus	1 (1·7)
Basal ganglia	13 (22)
Brainstem	2 (3·4)
Cerebellum	4 (6·9)
Corpus callosum	1 (1·7)
Eloquent AVM location (%)	48 (83)
Deep drainage	44 (83)
Multiple drainages	22 (42)
AVM contact with ventricle	43 (81)

Table 2. Outcomes after GKRS. ($n = 58$)

Margin dose, Gy	22·2 ± 1·3
Maximum dose, Gy	43·0 ± 3·0
Isodose line, %	50·8 ± 2·5
Mean follow-up, months	81·5 ± 66·0
Staged GK, *n* (%)	13 (22)
The interval time of each session, months	49·6 ± 18·5
Post-GK obliteration, *n* (%)	40** (69)
Post-GK hemorrhage, *n* (%)	10 (17)
Radiologic RIC/permanent RIC, *n* (%)	9/1 (16/1·7)
Post-GK hematoma and cyst, *n* (%)	3 (5·1)
Favourable outcome*, *n* (%)	36 (62)
Time to obliteration from first GK, months	59·3 ± 57·1
Annual post-GK hemorrhage rate, %	2·19

*Favourable outcome: obliteration, no post-GK hemorrhage, no permanent RIC
**angiographically obliteration: 10/38 cases, CTA: 12/38, MRA: 16/23.

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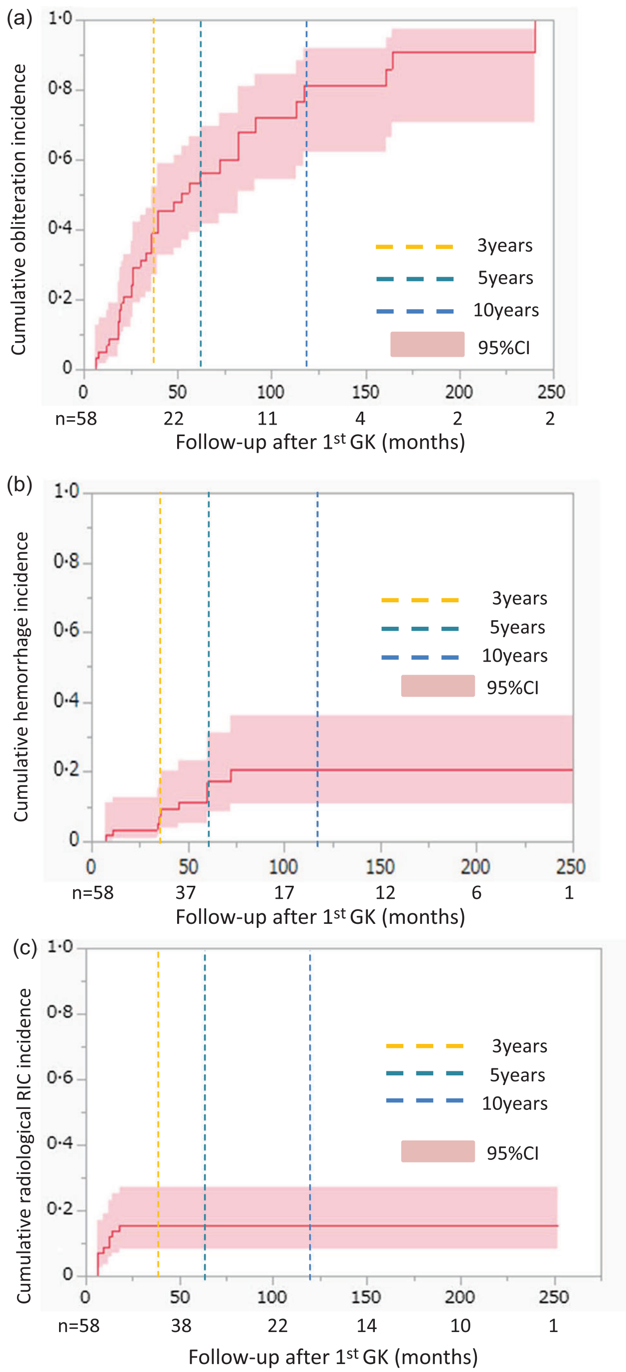

Figure 1. A 7-year-old girl with progressive left upper and lower extremity paralysis (SMG, 5; PFS, 2.18). (a) The first GKRS to reduce flow to the drainer (irradiated volume, 4 cm^3; 22 Gy 50%). (b) The second GKRS to obliterate the residual nidus is performed 3 years later (thick line, first GKRS). The fourth GKRS to achieve complete occlusion of the residual nidus was performed 11 years after the initial surgery. GKRS, Gamma Knife radiosurgery; SMG, Spetzler–Martin Grade; PFS, Pollock–Flickinger score.

Nine (16%) patients had MRI-detectable RICs during the post-irradiation course; only one showed persistent RICs, but they remained asymptomatic. Late RICs included cyst and encapsulated hematoma formation in three (5%) patients, two of whom were asymptomatic and one of whom developed intraventricular hemorrhage during the course of treatment, which required nidus removal. Fortunately, the lesion closed without worsening of neurological aspects. GKRS treatment led to occlusion without RIC or bleeding in 36 (62%) patients with a favourable outcome.

Discussion

Several studies on GKRS treatment for paediatric AVMs have reported occlusion rates of approximately 60–80%.[8–13] However, few studies have focused on cases requiring multiple treatment sessions of SRS; the occlusion rate for such multiple sessions, including that in adults, is estimated to be 30–60%.[3,14] The post-treatment occlusion rate in this study was 69%, which is good considering that the patients had an average nidus volume of 6·6 cm^3 and that about 80% of the patients had a Spetzler–Martin classification of grade 3 or higher. Treatment dose has been associated with post-treatment occlusion, but the dosing rationales in each study vary widely from institution to institution, ranging from nidus volume to history of bleeding. Many of the rationales remain unclear.[10,15] The novelty of the present study lies in the transition area between the nidus and efferent vessel being used as the main target region and the almost uniform irradiation plan, with a maximum irradiated volume of 4 cm^3 and a treatment dose of 22 Gy. This is 50% of the dose required for vascular occlusion and the tolerable dose for normal tissues.[16–20] The 4 cm^3 volume was derived from dose–volume isoeffect curves for a 3% risk of brain necrosis from a single fraction of radiosurgery, as described by Flickinger et al.[9] It is believed that, by limiting the use of this method in paediatric patients and keeping the course of treatment consistent, the nidus volume and Pollock–Flickinger score can be used more simply in actual clinical practice as factors associated with post-treatment occlusion and bleeding. Nidus volume may be an important factor in post-treatment bleeding due to the prolonged waiting period required to achieve occlusion.[12] By establishing a maximum irradiated volume, predicting that a larger nidus requires more division and that the risk of bleeding will persist during the extended treatment time is easy. Moreover, using the efferent vessel–nidus transition area as the main target in the usual AVM treatment strategy may be reminiscent of how bleeding tends to be further encouraged during the waiting period. However, post-irradiation intranidal reflux slowly decreases over a period of 6 months to 1 year and hemodynamic changes proceed as blood flow adapts to the surrounding normal brain tissue reflux.[18] The annual hemorrhage rate of 2·19% reported in the current study suggests that this method is as effective as other methods. The advantages of GKRS for paediatric AVMs include the presence of de novo forms and the possibility of new feeders appearing during the procedure.[21,22] Moreover, the authors believe that this method, which can reliably induce a decrease in nidal afference and reflux from the drainer side, will ultimately contribute to a shorter time until occlusion is achieved. Ischemic symptoms due to vascular steal and nidal compression are frequent in children due to enlargement with growth.[23] However, emphasising that GKRS is expected to improve symptoms through the early reduction of nidus compression due to decreased blood flow, even without occlusion, based on progressive disease (Fig. 1) is important.

Edematous changes after GKRS were observed in 13% of the patients, but all such changes improved within 2 years after irradiation and were considered to have occlusive hyperemia due to impaired venous return.[24] No cases of prolonged neurological symptoms were observed. Post-treatment oedema occurs in 20–30% of patients and dose-staged radiosurgery, in which the target is the entire AVM and the dose is lowered according to the irradiated

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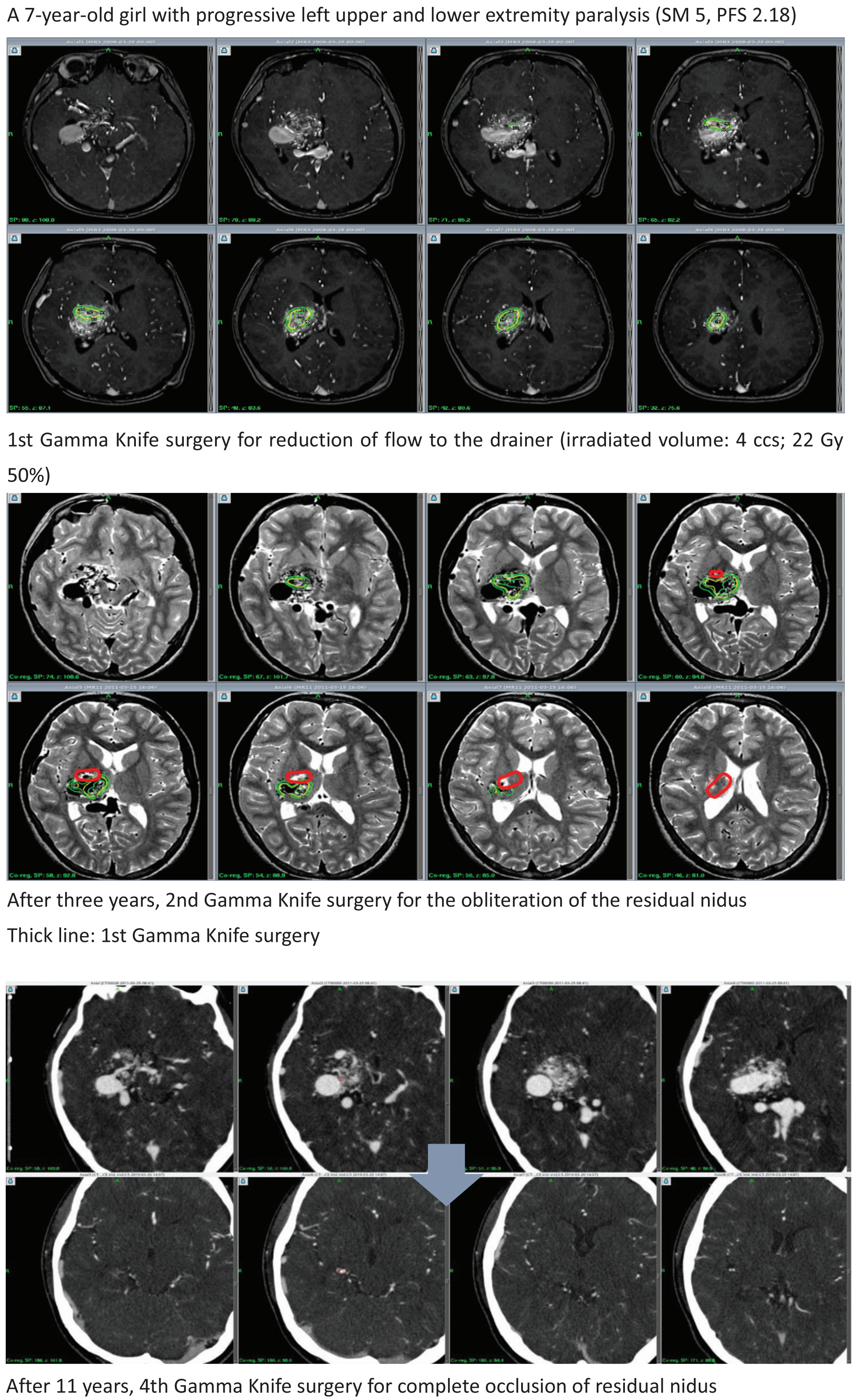

Figure 2. The Kaplan–Meier curve for the (a) actuarial obliteration rate, (b) hemorrhage incidence after GKRS and (c) radiological RIC rate. GKRS, Gamma Knife radiosurgery; RIC, radiation-induced changes.

volume, is often conducted.[11,25] Since the low-dose region volume increases proportionally with the treatment volume in stereotactic radiotherapy, a lower treatment dose can be said to reduce the occlusion rate and, simultaneously, increase the possibility of requiring repeated irradiation. This will further increase the incidence of radiation injury and compromise the flexibility of the surrounding brain tissue for later hemodynamic changes.[26] Karlsson et al. showed that the α/β of AVMs is very low, that the dose from a single irradiation is important for the occlusion rate, and that increasing the number of irradiations and the total dose do not increase the occlusion rate.[27] Pollock et al. also reported that dividing the nidus can reduce the volume of the

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Table 3. Result of univariate and multivariate Cox proportional hazards analyses for factors associated with nidus obliteration

	Univariate		Multivariate	
Variables	P	OR(95%CI)	P	HR(95%CI)
Age <12	0.0145*	0.18(0.05-0.71)	0.039*	2.17(1.03-4.56)
SM ≦2	0.34	0.53(0.15-1.88)	N/A	N/A
PFS ≦1	0.005*	6.44(1.74-23.8)	0.912	1.06(0.37-3.01)
Nidus volume＜4㎤	0.0014*	0.11(0.02-0.44)	0.024*	3.36(1.17-9.66)
Male sex	0.75	0.74(0.22-2.48)	N/A	N/A
Single deep drainer	0.54	0.60(0.17-2.01)	N/A	N/A
Single drainer	0.35	0.51(0.15-1.71)	N/A	N/A
Exposed to ventricle wall	0.71	0.73(0.32-9.31)	N/A	N/A
Previous hemorrhage	0.377	0.57(0.17-1.90)	N/A	N/A
Post GK hemorrhage	0.022*	0.17(0.04-0.76)	N/A	N/A

*Indicates a statistically significant with a P-value < 0.05.

surrounding brain tissue irradiated with ≥12 Gy, which is considered to be associated with radiation injury, by at least 50%.[28] Furthermore, paediatric AVMs are highly radiosensitive, and the nidus and dilated vessels leading out of the target area commonly disappear or shrink after stereotactic radiotherapy.[15] In the present study, among the 27 patients with a nidus larger than 4 cm^3 at the time of initial GKRS, five (19%) achieved complete occlusion after only a single GKRS treatment. The authors believe that staged treatment with an upper irradiated volume limit is a useful method for maximising therapeutic effect with minimal risk of radiation injury in sensitive paediatric normal brain tissue.

Avoiding residual nidus bleeding after treatment

When bleeding is observed after treatment, the main concern is whether the residual nidus can be removed, rather than whether additional irradiation therapy is required. Shimizu et al. reported the advantage of prior GKRS in reducing the size of the nidus in AVMs that are considered difficult to remove, thus reducing the difficulty of subsequent removal and allowing for easier bleeding control during removal.[29] Regarding the origin of bleeding after treatment, especially when spatially divided irradiation is performed on a large nidus, an imbalance of reflux pressure in the nidus is expected, resulting in hemorrhage from the most vulnerable part of the nidus. Deep drainer, single drainer and ventricular side are reportedly hemorrhage factors of the nidus[1,30]; these were not significant in the current study. This observation might be explained by the presumptions that removal may be necessary during the long-term waiting period and that the irradiated area was designed to reduce the nidus size on the functionally dominant region side, which would otherwise be difficult to remove, and to eliminate afferent vessels from deep inside the brain. In paediatric AVMs, where changes can be observed from time to time, developing a multidisciplinary strategy that is not limited to radiotherapy, with the ultimate goal of safely eliminating the nidus, is essential.

GKRS treatment for non-hemorrhagic AVMs

Among the patients with non-hemorrhagic AVM, 20 were asymptomatic and 8 were symptomatic. The asymptomatic patients included those found to have a headache upon thorough examination. Additionally, among the symptomatic patients, five had seizure onset, two had progressive paralysis and one had symptoms of hydrocephalus. Comparing the three groups of hemorrhagic, non-hemorrhagic symptomatic and asymptomatic cases, the nidus size was significantly larger in the symptomatic group and the RIC was higher in the asymptomatic group. The annual bleeding rate was 1·68%, 2·56% and 3·4% in the hemorrhagic, asymptomatic and symptomatic groups, respectively, although these were not significantly different. However, only one of the five patients with post-treatment hemorrhage showed a decrease in modified Rankin Scale score in the final evaluation. In one of the two patients with pre-treatment progressive paralysis, the progression of paralysis stopped after treatment, and the condition improved in the other patient. This suggests the importance of early therapeutic intervention during childhood when brain plasticity is high. Starke et al. reported lower occlusion rates, RIC, post-treatment hemorrhage and favourable outcomes in pre-treatment of non-hemorrhagic patients[12]; this finding may result from an attenuated radiation dose to the surrounding unaffected brain parenchyma due to hematoma degradation products and gliosis adjacent to the lesion. Comparing pre-treatment hemorrhagic and non-hemorrhagic cases, Chen et al. reported a similar incidence of post-treatment hemorrhage, while Ding et al. found lower post-treatment hemorrhage but higher RIC in non-hemorrhagic cases.[31,32] In the present study, the size of the nidus in the symptomatic group was remarkably large (11·2 cm^3). In addition to the time to occlusion and occlusion rate, the large size may have caused blood flow imbalance in the nidus due to local irradiation. Recently, image sharing between Brainlab Elements and GammaPlan has become possible at the authors' hospital, and the dominant area for each feeder by angiography can be easily considered in the treatment plan, as shown in Fig. 3. The authors hope that visualising the changes over time in irradiated and non-irradiated areas and creating treatment plans and strategies that consider changes in reflux within the nidus will both improve treatment outcomes and help elucidate the bleeding mechanism of AVMs.

Conclusion

The staged GKRS approach used by the authors was defined by a maximum irradiated volume of 4 cm^3 and a treatment dose of 22 Gy, 50% isodose. This approach was based on the notion that early

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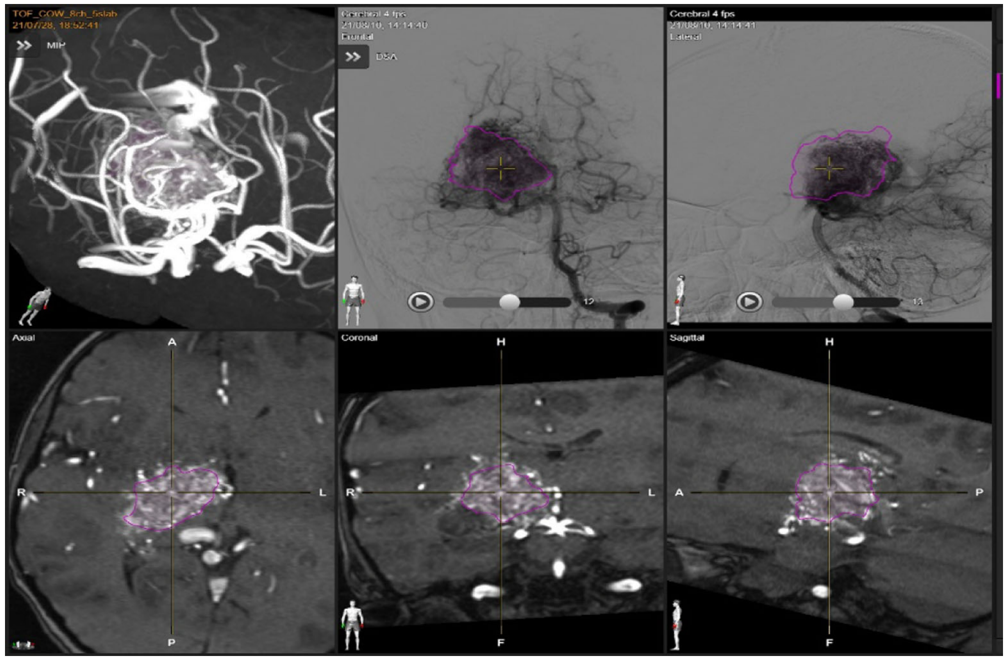

Figure 3. Brainlab Elements workstation. Simple understanding of the supply region for each feeder from the entire nidus enclosed by the line. Red arrow; defective area surrounding by purple line indicates nidus part which feeding from anterior circulation.

complete occlusion is not the only treatment goal, but that the most important consideration of a treatment regimen be avoiding that delayed radiation injury. The current study shows that an adequate treatment strategy exists even for AVMs considered to be high grade due to the nidus size. The annual post-treatment bleeding rate tended to be higher in non-hemorrhagic AVMs than in AVMs as a whole; therefore, developing a treatment strategy for non-hemorrhagic symptomatic AVMs in which early intervention is expected to maximise functional preservation and symptom improvement is necessary. In addition to the number of cases and follow-up period, new evaluation methods, such as hemodynamics, should be considered.

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Competing interests. The authors declare none.

Study approval statement. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Public Notice of the Ministry of Health, Labour and Welfare No. 415 of 2008) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committee (Tokyo Women's Medical University Ethics and Department of Neurosurgery, approval number 5247).

Consent to participate statement. The authors ensured that patients and their parent/legal guardian/next of kin provided written informed consent for participation.

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