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SHORT REVIEW

What is the best therapeutic approach to a pediatric patient with a deep-seated brain AVM?

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Abstract

Although brain arteriovenous malformations (bAVMs) account for a very small proportion of cerebral pathologies in the pediatric population, they are the cause of roughly 50% of spontaneous intracranial hemorrhages. Pediatric bAVMs tend to rupture more frequently and seem to have higher recurrence rates than bAVMs in adults. Thus, the management of pediatric bAVMs is particularly challenging. In general, the treatment options are conservative treatment, microsurgery, endovascular therapy (EVT), gamma knife radiosurgery (GKRS), proton-beam stereotactic radiosurgery (PSRS), or a combination of the above. In order to identify the best approach to deep-seated pediatric bAVMs, we performed a systematic review, according to the PRISMA guidelines. None of the options seem to offer a clear advantage over the others when used alone. Microsurgery provides the highest obliteration rate, but has higher incidence of neurological complications. EVT may play a role when used as adjuvant therapy, but as a stand-alone therapy, the efficacy is low and the long-term side effects of radiation from the multiple sessions required in deep-seated pediatric bAVMs are still unknown. GKRS has a low risk of complication, but the obliteration rates still leave much to be desired. Finally, PSRS offers promising results with a more accurate radiation that avoids the surrounding tissue, but data is limited due to its recent introduction. Overall, a multi-modal approach, or even an active surveillance, might be the most suitable when facing deep-seated bAVM, considering the difficulty of their management and the high risk of complications in the pediatric population.

Keywords Deep-seated arteriovenous malformations · Microsurgery · Endovascular treatment · Gamma knife radiation surgery · Proton beam stereotactic radiosurgery · Review

Introduction

Arteriovenous malformations (AVMs) are distinguished from other types of cerebral vascular malformations by their direct anastomosis between arterial and venous channels without any intervening capillaries and a cluster of tortuous, dilated vessels forming the AVM nidus [1]. Brain AVMs can be divided according to their anatomical location into superficial or deep, with the latter found mostly in the basal ganglia, the thalamus, or the brainstem.

Brain AVMs (bAVMs) are infrequent in the general population and even rarer in the pediatric population with prevalence estimated between 0.014 and 0.028% [2]. Pediatric bAVMs tend to rupture more frequently than in adults, with an estimated risk of hemorrhage of 2–4% per year [3]. This leads to an estimated morbidity and mortality rate for each hemorrhagic event of 50% and 5–10%, respectively, in children [4]. Among pediatric bAVMs, the small and deep-seated ones are at higher risk of hemorrhagic presentation [5]. Furthermore, pediatric bAVMs tend to have higher recurrence rates after treatment compared to adults, perhaps in part due to their longer life expectancy and the growth spurts [6].

The most common presenting symptoms of pediatric bAVMs are focal neurological deficit, headaches, and seizure. Often, these symptoms result from AVM ruptures or micro-hemorrhages. Therefore, the necessity of an early diagnosis

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and treatment is crucial for a patient population with a long-life expectancy. However, due to the frequent absence of symptoms, the diagnosis of bAVM tends to be made only after it has bled.

Different therapies exist and their aim is to prevent catastrophic intracranial hemorrhages and alleviate neurological symptoms. In deep-seated pediatric bAVMs, their location and the young patient age make treatment riskier; hence, the crucial importance of choosing is the right approach. Furthermore, since pediatric patients have longer life expectancies and higher rates of AVM recurrence than adults, treatment durability and efficacy is of paramount importance [7]. However, in contrast to adult bAVMs where a European consensus on treatment has been proposed [8], the best approach is yet to be defined in pediatric bAVMs (Table 1).

The aim of this systematic review was to compare the various advantages and drawbacks of each different treatment modalities for deep-seated pediatric bAVMs.

Material and methods

A search of PubMed databases through the last 10 years (from 2008 to 2018) and using the following criteria: "cerebral" [All Fields] AND "children" [All Fields] OR "pediatric" [All Fields] AND ("arteriovenous malformations" [MeSH Terms] was performed. Basic inclusion filters were: English language and articles providing information on type of treatment and clinical outcomes. Articles not related to pediatric AVMs, cerebral locations or deeply seated AVMs were excluded. A PRISMA flow diagram was created in order to analyze the recent literature (Fig. 1) [24].

Results

The literature search identified 261 articles. Two hundred forty-five of them were excluded due to the bAVM not being deep-seated, not being in English, or not giving information about the type of treatment and the outcomes (Fig. 1). The final 16 articles were compared with respect to treatment modalities, study design, number of patients involved, obliteration rates, time from treatment to obliteration, complications, and their rates (Table 1). Based on the final 16 articles selected for this review, the results found according to the treatment options are as follows:

1. Regarding conservative treatment, no clinical study was found respecting our inclusion and exclusion criteria.
2. Two clinical studies on microsurgery, comprising a total of 130 pediatric patients with 30 of the bAVMs being deep-seated, were identified. The obliteration rate ranged between 94 and 100%. Obliteration was immediate after treatment. The temporary and permanent complications were 5.6–13% and 4–8.4%, respectively.
3. Two clinical studies on EVT, comprising a total of 73 pediatric patients with 20 of the bAVMs being deep-seated, were identified. The obliteration rate ranged between 12 and 22%. The mean number of sessions needed varied between 1.5 and 3.4. The temporary and permanent complications were 5.5–26.3% and 0.0–1.2%, respectively.
4. Eight clinical studies on GKRS, comprising a total of 1063 pediatric patients with 427 of the bAVMs being deep-seated, were identified. The obliteration rate ranges between 34% and 81%. The median time from treatment to obliteration varied between 24 and 51 months. The temporary and permanent complications rates were 2.9–48.0% and 0.0–7.0%, respectively.
5. One clinical study on PSRS, comprising a total of 80 pediatric patients with 37 of the bAVM being deep-seated, was identified. The obliteration rate was 41%. The median time from treatment to obliteration was 49 months. The temporary and permanent complications were 13.7% and 2.3%, respectively.
6. Three clinical studies on multimodality management, comprising a total of 223 pediatric patients with 61 of the bAVM being deep-seated, were identified. The obliteration rate ranged between 18 and 93%. The median time from treatment to obliteration was either not specified or of 1.8 years. The temporary and permanent complications were 5.4–13% and 0–13%, respectively.

Discussion

Conservative treatment

Although the role of conservative management of pediatric bAVMs was emphasized in earlier series, it has largely been abandoned except for situations where therapy carries more risks than benefits [3]. When facing pediatric patients with a high-grade bAVM or in a deep-seated anatomical location, an aggressive management philosophy may be indicated and recommended [21]. Indeed, these patients are at higher risk of recurrent hemorrhage, incapacitating symptoms, or progressive neurological deficits.

In our systematic review, we failed to identify any articles describing the natural history of pediatric bAVMs. Recently, the ARUBA study suggested that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in adult patients with unruptured bAVMs followed up for 33 months [25]. Although this study did not include pediatric patients and important

Table 1 Treatment options characteristics of deep-seated brain AVM in pediatric patients

Reference	Type of study	Treatment type	No. pts.	Obliteration rate	Time from treatment to obliteration	Complications	Complication rates
Gross et al., 2015 [9]	Clinical study	Microsurgery	94 (10 dsBAVM or eloquent)	94%	Immediate	Neurological deficits New onset seizures	Temporary: 13% Permanent: 4.0% dsBAVM: 29% Superficial BAVM: 3.0%
Nair et al., 2012 [10]	Clinical study	Microsurgery	36 (20 dsBAVM or eloquent)	100%	Immediate	Homonymous hemianopia Bone flap osteomyelitis Death	Temporary: 5.6% Permanent: 8.4%
Soltanolkotabi et al., 2013 [11]	Clinical study	EVT	25 (3 dsBAVM)	12%	Mean of 1.5 sessions (range NS.)	Clinically silent Neurological deficits Procedure related	Temporary: 26.3% Permanent: 0.0%
Berenstein et al., 2010 [12]	Clinical study	EVT	48 (17 dsBAVM)	22%	Mean of 3.4 sessions (range NS.)	Neurological deficits Procedure related	Temporary: 5.5% Permanent: 1.2%
Kano et al., 2012 [13]	Clinical study	GKRS	135 (56 dsBAVM)	81%	Median 49 months (range 41–58)	Neurological deficits	Temporary: 4.4% Permanent: 1.5%
Hanakita et al., 2015 [14]	Clinical study	GKRS	116 (36 dsBAVM)	76%	Median 24 months (range 8–65)	Hemorrhages Neurological deficits Seizures	Temporary: 6.9% Permanent: 3.4%
Yen et al., 2010 [15]	Clinical study	GKRS	186 (79 dsBAVM)	58%	NS.	Hemorrhages Neurological deficits Seizures	Temporary: 9.1% Permanent: 7.0%
Capitanio et al., 2018 [1]	Clinical study	GKRS	33 (10 dsBAVM)	61%	NS.	Gliosis and edema Cyst development Radionecrosis	Temporary: 12.1% Permanent: 0%
Starke et al., 2016 [16]	Clinical study	GKRS	357 (150 dsBAVM)	63%	NS.	Hemorrhages Neurological deficits Death	Temporary: 8.4% Permanent: 5.3%
Ding et al., 2014 [17]	Clinical study	GKRS	51 (16 dsBAVM)	59%	Median 51 months (range 19–82)	Hemorrhages Cyst formation	Temporary: 13.7% Permanent: 2.0%
Pan et al., 2008 [18]	Clinical study	GKRS	105 (43 dsBAVM)	61%	Median 48 months range NS.)	Hemorrhages Cerebral edema Cyst formation Neurological deficits	Temporary: 2.9% Permanent: 4.7%
Potts et al., 2014 [19]	Clinical study	GKRS	80 (37 dsBAVM)	34%	Mean of 36 months (range NS.)	Hemorrhages Seizures Neurological deficits	Temporary: 48% Permanent: 2%
Walcott et al., 2014 [20]	Clinical study	PSRS	44 (24 dsBAVM)	41%	Median 49 months (range 12–92)	Hemorrhages New onset seizures Neurological deficits	Temporary: 13.7% Permanent: 2.3%
Darsaut et al., 2011 [21]	Clinical study	Multimodality (microsurgery, EVT and GKRS)	120 (47 dsBAVM)	18–63%	Mean of 1.8 years and 2.2 procedures (low grade) Mean of 6.4 years and 6.1 procedures (high grade)	Neurological deficits Procedure related	Temporary: 13% Permanent: 13%
Shtaya et al., 2017 [22]	Clinical study	Multimodality (microsurgery, EVT and GKRS)	47 (5 dsBAVM)	83%	NS.	Hematomas Seizures Increased ICP	Temporary: 7% Permanent: 4.3%
Dorfer et al., 2009 [23]	Clinical study	Multimodality (microsurgery, EVT and GKRS)	56 (9 dsBAVM)	93%	NS.	Procedure related Neurological deficits	Temporary: 5.4% Permanent: 0.0%

NS, not Specified; dsBAVM, deep-seated brain arterio-venous malformation

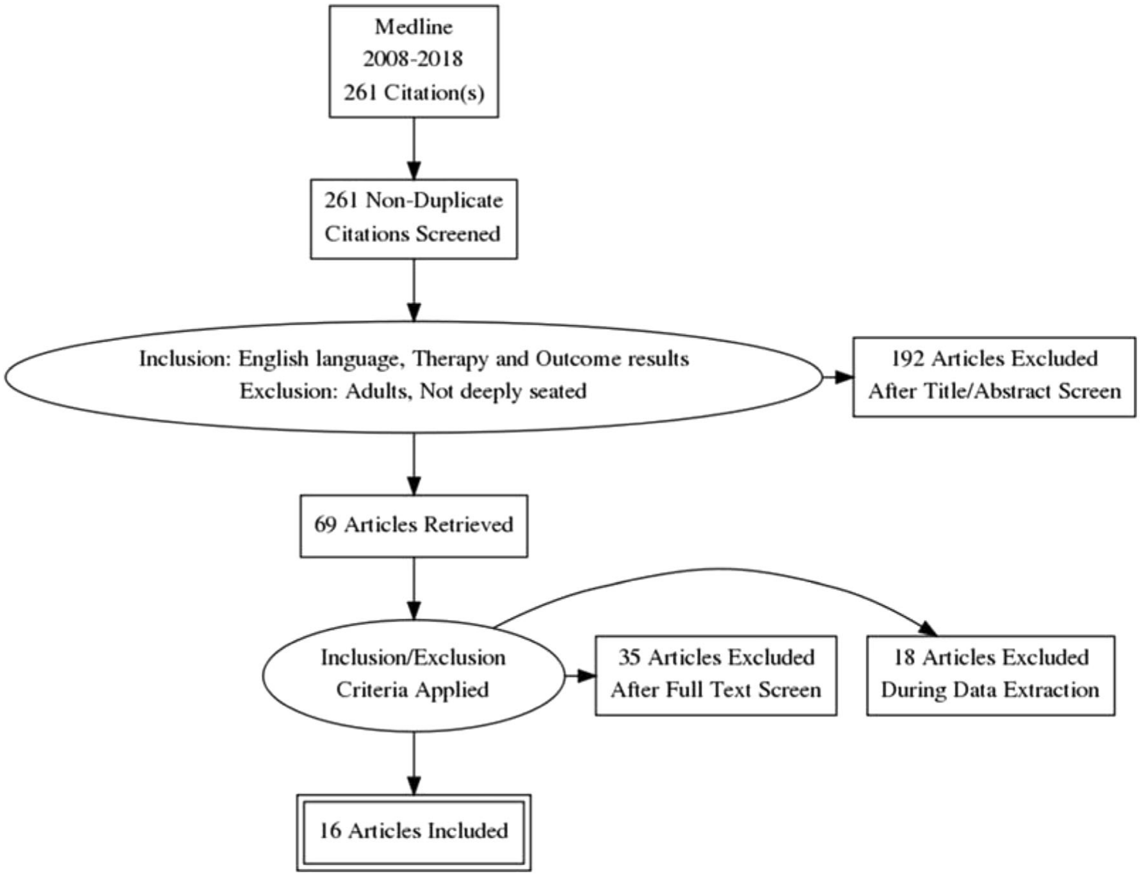

Fig. 1 PRISMA flow diagram

criticisms has been raised related to study design, outcome measures, and even data reporting [26], considering the high risks related to the treatment of deep-seated bAVMs, lending some consideration to the ARUBA study seems prudent.

Microsurgery

Microsurgery offers the advantages of immediate therapeutic cure and obliteration rates of pediatric bAVMs that can reach up to 100% [10]. This approach is particularly advantageous in cases of ruptured AVMs, which are at greater risk of a possible re-rupture, especially within the first year [9]. However, it is important to weigh the risk of complications related to the procedure, given that permanent neurological risks can be in a high range of 4.0 to 8.4% [9, 10].

In a single-center retrospective series, Gross et al. [9] identified a total of 94 pediatric patients who underwent microsurgical resection for bAVMs. Based on their analysis, the obliteration rate was 94%, confirmed by postoperative angiography, and obliteration took effect immediately following surgery. However, only 11% of the bAVMs were located in a deep area of the brain and the authors noticed a higher risk of neurological complications in the presence of deep-seated bAVM or eloquent-region bAVMs compared to other locations (29 vs 3%; $p < 0.01$). The complication rate for temporary and permanent neurological deficit was of 13 and 4.0%, respectively. Those neurological complications were mainly visual field deficits, hemiparesis, and new onset of seizures with relative rates of 13%, 3%, and 3%, respectively.

In deep-seated bAVMs, microsurgery is better suited for the insula and basal ganglia, where parenchymal dissection is most tolerable and rates of complete resection are higher, than in the thalamus [20]. However, microsurgery carries a risk of complications even when performed by experienced neurosurgeons. Indeed, deep-seated bAVMs are considered to be more complex than other supra-tentorial AVMs, given the corridor that the surgeon has to create into the brain parenchyma in order to approach them and the vicinity to vital structures. In some series, the rate of permanent neurological complications related to surgery was as high as 28.5% [12].

In a pediatric patient presenting with a large AVM located in an eloquent area such as motor or functional speech cortex, basal ganglia, thalamus, or brainstem, the role of microsurgery is still debated due to the high risks of complications [9]. It has been observed that children fare better than adults following microsurgery for bAVMs, a phenomenon that could not be explained by differences in AVM anatomy, rupture rates, neurological condition at presentation, or treatment techniques

[6]. Regardless of the cause, this indicates a better neural plasticity in pediatric patients and a need to recalibrate the surgical risk assessment. If pediatric bAVM patients indeed have increased surgical tolerance and better recovery, a more aggressive microsurgical management than in adult bAVM might be warranted.

Endovascular treatment

The development of more performant endovascular embolization agents and catheters has led to an increased use of EVT in pediatric deep-seated bAVMs. According to Akin et al. [27], the use of Onyx makes the embolized vessels less fragile than those filled with other embolic agents. However, catheters required for Onyx embolization are stiffer, have less flexible tips, and require micro-guidewires for navigation, factors that presumably increase the risk of vessel injury during catheterization.

However, the cure rates are still quite low and there is a high risk of partial embolization (Table 1). El-Ghanem et al. [3] identified three studies comprising a total of 139 pediatric bAVMs patients treated with EVT. An average of 2.1 treatment sessions per patient over the 3 studies were needed. The complete obliteration rates ranged from only 12% to 22%, and the treatment-related complication rates were between 7% and 26%. The complications were either adverse event related to the procedure itself or temporary or permanent neurological complications with rates of 12.2%, 24.5%, and 3.6%, respectively. Furthermore, in a series of 48 pediatric bAVM, 35% of which were deep-seated, Berenstein et al. [12] reported an angiographic cure rate of 21.7% and a complications rate of 6.7% after EVT. Lastly, Blauwblomme et al. [28] found that patients who underwent partial embolization of a bAVM had an annual bleeding risk of 4.7% compared to 1.6% per year for AVMs not submitted to partial embolization (surgery or complete embolization).

EVT also carries a risk associated with radiation in the pediatric population, as multiple sessions are often required. Due to their increased sensitivity and life expectancy, the window of opportunity for expressing radiation damage is greater [29]. It is widely suggested to stage embolization of complex lesions, especially in pediatric patients to limit both the contrast agent dose and the radiation exposure [30]. Additionally, it is believed that less dramatic alterations in cerebral hemodynamic, achieved through staged embolization, results in lower potential for morbidity [7]. However, there is little data to back up the lower risk of radiation when performing multiple repeated staged embolization in complex and deep-seated bAVM in pediatric patients [31] and the risk-benefit balance has to be carefully considered when facing pediatric deep-seated bAVMs.

Lastly, endovascular pre-operative embolization may be indicated as an adjunctive therapy to microsurgery in order to deeply penetrate the nidus to reduce its active size and to eliminate deep feeding arteries [32]. In fact, embolization can reduce intraoperative blood loss and facilitate safe resection, ideally by achieving hemostasis of deep, inaccessible feeding vessels. Onyx can be injected to penetrate and/or to devascularize the nidus directly or it can be targeted to occlude specific arterial branches feeding the nidus that would not be exposed until late in surgery.

Stereotactic radiosurgery

While the “non-invasive” nature of SRS is an attractive attribute, the treatment effect is late-onset and not infrequently incomplete (Table 1). SRS requires between 36 and 51 months (Table 1) in order to achieve lesion obliteration and during this latency period, the patient remains at risk for hemorrhage at a rate similar to one in untreated AVMs [33]. Strake et al. [16] studied a total of 357 pediatric bAVMs who underwent GKRS treatment, 150 of which were classified as deep-seated. The overall obliteration rate was of 63%. No information was given on the median time to complete angiographically documented obliteration. However, the actuarial obliteration rates at 3, 5, 7, and 10 years were 37.6%, 70.2%, 75.6%, and 77.4%, respectively. The complications following the GKRS were temporary or permanent neurological deficits with rates of 8.4% and 5.3%, respectively. The mean prescription dose delivered to the nidus margin was 21 ± 3.6 Gy (range 5–35 Gy).

The reported occlusion rates of bAVMs vary widely, depending on AVM size, location, and patient age. In the current literature, the obliteration rates of bAVMs with GKRS range between 34% and 81% (Table 1). With an unfavorable anatomical location, radiation doses lower than 16 Gy are often recommended for deep-seated bAVMs in order to decrease the risk of permanent complications [34]. Consequently, the risk of non-obliteration is increased in deep-seated or eloquent-area AVMs compared to AVMs in non-eloquent brain areas (47% and 20%, respectively) [35].

Despite being a proven modality for small residual nidus or deeply located surgically intractable lesions [15], GKRS still carries important complication risks (Table 1). Fortunately, they are mainly temporary rather than permanent complications with rates of 2.9–48.0% and 0.0–7.0%, respectively (Table 1). It remains controversial if the high radiosensitivity of the brain tissue in pediatric patients increases chances of nidus obliteration or makes it more resistant [36]. For instance, Ding et al. [17] found an increase of post-radiosurgery hemorrhages for deep-seated bAVM. Furthermore, the optimal balance between the lowest-possible dosage to avoid side effects and a prescription-dosage high enough to be effective in deep-seated bAVM is yet to be defined. Lately, a margin dose of 22 Gy was determined to be the optimum cutoff for GKRS in bAVMs [16].

However, there is no solid data supporting the best prescription dosage when dealing with deep-seated bAVMs, as the basal ganglia and thalamus are among the areas of the brain most sensitive to radiation [37]. Thus, the prescription dosage has to be considered carefully.

Lastly, the concern regarding exposing developing brains to radiation therapy was the main reason behind delayed use of this modality in the pediatric population. Negative long-term effects of ionizing radiation on the nervous system have not been fully evaluated and related complications such as intracranial malignancy or neuropsychological retardation have been reported, but as of yet not well-studied [15]. Due to the still developing neuronal tissues, the pediatric brain is more at risk and sensitive to develop possible long-term side-effects of the ionizing radiation [15]. The long-term build-up of radiation-induced adverse effects can occur more than 20 years after the GKRS, which makes it often underestimated and challenging to consider when neurosurgeons have to decide the dosage of the radiation [14].

Proton radiotherapy

PSRS offers the advantages of deposing energy far more selectively than X-rays and thereby more effectively target deep-seated bAVM, while significantly reducing the radiation dose to the normal and critical perilesional tissue. These characteristics seem particularly important when applied to a pediatric population with deep-seated bAVMs.

Even though its use as a treatment modality for bAVMs has increased over the years, the literature regarding pediatric bAVMs treated with PSRS remains sparse (Table 1). Walcott et al. [21] was the only series reporting on pediatric bAVMs treated by PSRS. They studied the clinical outcomes of 44 patients, among whom 24 had deep-seated bAVMs. Despite an overall modest rate of total obliteration of 41%, the long-term overall complication rate was 14%, which is not negligible when dealing with deep-seated bAVM that are particularly hazardous to treat. The median time to obliteration was 49 ± 26 months (range 12–92 months), including 17 patients who underwent a second course of PSRS.

Multimodality therapy

In deep-seated bAVMs, achieving a high permanent angiographic nidus obliteration rate often requires the combination of either microsurgical resection, or endovascular nidus casting with a variety of embolic agents, or radiosurgical nidus obliteration [23]. The obliteration rates in case of multimodal therapy range between 18% and 93%, but the main advantage of this treatment strategy is the low risk of temporary and permanent complications, ranging between 5–13% and 0–13%, respectively [21–23].

Current clinical practice

In clinical series published during our inclusion period over the last 10 years (from 2008 to 2018), patients with bAVMs were most commonly treated with GKRS (69%). In case of deep-seated bAVM, GKRS was used in 76%, microsurgery in 5%, and multimodal therapy in 11%. It is difficult to assess the number of pediatric patient treated conservatively, since this is probably under-reported. Although there may be a publication bias behind the abovementioned figures as various neurosurgical subspecialties may have different propensities to publish or perform multicenter studies, it seems unlikely that they do not somehow reflect our current clinical practice.

Post-therapy surveillance

Active surveillance after therapy of pediatric bAVMs is crucial. Although the recurrence rate is not well defined, Morgenstern et al. [38] found that bAVMs recurred after a median of 33.6 months. They suggested a surveillance strategy that utilizes digital subtraction angiography (DSA) at predefined intervals, so as to maximize the sensitivity of follow-up studies while sparing the child exposure to excessive ionizing radiation, anesthesia, and the risks of conventional angiography. Insufficient follow-up has been demonstrated to lead to delayed recurrence-detection and a greater likelihood of patients presenting with rupture of a recurrent bAVM [39].

Conclusions

Deep-seated brain AVMs in the pediatric population are rare, challenging and not well understood. The current literature rarely addresses the pediatric population alone and rarely even differentiates between deep-seated bAVMs and AVMs located in cortical and non-eloquent region of the brain. However, analyzing only AVMs located in deep brain region is warranted to better document the treatment outcomes.

The increased brain plasticity of pediatric patients may indicate that they are better suited to undergo treatment than adults [6]. Furthermore, given their higher propensity to rupture [3], pediatric patients may even benefit from early intervention, leading to a better outcome. The treatment goal is to lower the risk of hemorrhage by achieving a high permanent angiographic nidus obliteration rate. However, the most appropriate therapeutic management for deep-seated bAVMs is still uncertain.

Different treatment modalities are available, such as microsurgery, EVT, GKRS, PSRS, a combination of these, or conservative treatment. Microsurgery offers the highest obliteration rate for this pathology, either as stand-alone technique or as part of a multimodal therapy. However, microsurgery is associated with the highest rate of permanent neurological deficits and thus should be used cautiously when facing deep-seated bAVMs (Table 1). Due to its low obliteration rate, EVT alone is often not the most suitable technique, but have a role to play in small bAVMs with single feeders or as adjunctive therapy to microsurgery in order to facilitate safe resection of deep, inaccessible feeders. GKRS and PSRS have shown promising results in terms of lower risk of neurological complications, but the obliteration rates are mid-range, the effect-onset is delayed, and the long-term effects of radiation in vulnerable pediatric patients are unknown. Lastly, the cure-rates in case of dual-modal therapy, either with EVT followed by microsurgery or microsurgery followed by GKRS, or a multimodal combination of all three, were 63%, 43%, and 57%, respectively [40]. The use of a balanced multimodal approach might reduce procedure-related morbidities and mortalities while at the same time retain treatment efficacy.

Lastly, the high risk of recurrence in children, due to their long residual life expectancy and perhaps yet not understood underlying patho-biological mechanisms, supports the recommendation for long-term follow-up, regardless of treatment modality.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approved Not applicable as no new patients were involved in this research.

Informed consent Not applicable as no new patients were involved in this research.

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