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Stereotactic Radiosurgery for Brain Arteriovenous Malformations

Radiocirurgia Estereotática para Malformações Arteriovenosas Cerebrais

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ABSTRACT

Stereotactic radiosurgery is an established treatment modality in the management of brain arteriovenous malformations (AVMs). Technological advances in radiation delivery systems associated with improvements in neuroimaging have recently changed radiosurgery indications and results. Besides this advances, and the association with microsurgery and embolization, the management of these benign lesions are still controversial. AVMs in eloquent areas and those with large volumes remain a challenge for all treatment modalities. This article discusses the modern approach of radiosurgery for brain AVMs including new options such as combined approaches and the use of hypofractionated stereotactic radiation for large and high flow lesions.

Key words: Arteriovenous malformations, Stereotactic radiosurgery, Fractionated stereotactic radiotherapy

RESUMO

A radiocirurgia estereotática é uma técnica estabelecida no manejo das malformações arteriovenosas cerebrais (MAVs). Os avanços tecnológicos nos equipamentos dedicados ao tratamento com radiação associados ao avanço das modalidades de neuroimagem, recentemente modificaram os resultados e as indicações da radiocirurgia. Apesar destes avanços e da associação com outras modalidades de tratamento, como a microcirurgia e a embolização, o manejo destas lesões benignas é ainda controverso. MAVs em áreas eloquentes e lesões de grande volume permanecem como um desafio para todas as modalidades de tratamento. Esta publicação discute a abordagem moderna da radiocirurgia para as malformações arteriovenosas cerebrais, incluindo novas opções como as abordagens combinadas e o uso da radiação estereotática hipofracionada para lesões de grande volume e alto fluxo.

Palavras-chave: Malformações arteriovenosas, Radiocirurgia estereotática, Radioterapia estereotática fracionada

INTRODUCTION

The decision making for brain AVMs treatment is still a challenge. Although there are many treatment options including microsurgery, embolization and stereotactic radiosurgery (SRS), the best management, considering the limited knowledge of the natural history of these benign lesions, is still a matter of content in the literature. Moreover, multidisciplinary management in specialized centers using combined approaches, commonly microsurgery and SRS, embolization and SRS, and embolization and microsurgery, probably is the most promising method for the achievement of better results for patients harboring these difficult lesions.

If the treatment of AVMs is controversial in a routine basis, special considerations should be taken regarding the large (giant) AVMs, those located in very eloquent areas (e.g. motor cortex and brainstem), lesions with high flow, arterial stenosis, harboring intranidal fistulas, deep venous drainage and those related to proximal, nidal and venous aneurysms.

In the last decades, the widespread use of linear accelerator (LINAC) SRS has made the technique available throughout the world. The field has gained many advances including improvements in software for dosimetry and the increase of mechanical accuracy of dedicated devices for SRS. Stereotactic image based on computerized tomography, magnetic resonance imaging and angiography have also improved bringing more detail and precision for planning the procedure. These changes

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have made SRS a very safe and precise procedure. Nowadays, SRS is the treatment option for the management of AVMs that offers the lower complication rates for the patients.

In the following sections, the authors will discuss the indications, limitations, results and complications of SRS for the management of AVMs. The applications of the technique in special situations will also be discussed.

Natural History of Brain Arteriovenous Malformations

AVMs are benign lesions carrying an unpredictable risk of massive intracranial bleeding causing definitive neurological deficits or death. While incidental findings of unruptured lesions in old patients can lead to a very indolent clinical course, repetitive bleeding in other cases have made these lesions to be treated in a more aggressive fashion.

After a 24 year follow-up assessment, Ondra et al prospectively followed 166 untreated symptomatic patients with brain AVM's, with a mean follow-up period of 23.7 years. The rate of major rebleeding was 4% per year and the mortality rate was 1% per year. At the end of the follow-up review, 23% of the patients died from AVM hemorrhage. The combined rate of major morbidity and mortality was 2.7% per year. There was no difference in the incidence of bleeding, rebleeding or death, regardless the presentation with or without evidence of hemorrhage. The mean interval between initial presentation and subsequent hemorrhage was 7.7 years³⁸.

Hernesniemi et al performed a long-term follow-up study in an unselected, consecutive patient population with AVMs. Patients with untreated AVMs were followed from admission to death, the occurrence of AVM rupture or initiation of treatment. The authors included 238 patients with a mean follow-up period of 13.5 years (range from one month to 53.1 years). The average annual risk of hemorrhage from AVMs was 2.4%. The risk was higher during the first 5 years after diagnosis, decreasing thereafter. Risk factors predicting subsequent AVMs hemorrhage in univariate analysis were young age, previous rupture, deep and infratentorial locations, and exclusively deep venous drainage¹⁵.

Laakso et al performed a retrospective survival study in 623 consecutive patients harboring AVMs. Patient survival was estimated using the relative survival ratio, which provides a measure of the excess mortality, experienced by the patients

compared with the general population. Median follow-up was 11.9 years and total follow-up was 10,165 person-years. Treatment was conservative in 155 patients. Total AVMs occlusion was attained in 356 patients and partial occlusion in 94. Overall, 206 deaths were observed with 100 been related to the AVMs. Diagnosis of AVMs was associated with significant long-term excess mortality, with cumulative relative survival ratios of 0.85 (95% confidence interval, 0.81-0.88) and 0.69 (95% confidence interval, 0.62-0.75) at 10 and 30 years after admission, respectively. Men had higher excess mortality than women. The excess in mortality was higher in conservatively treated patients, intermediate in patients with partially occluded AVMs, and lower in those with totally occluded AVMs²⁷.

Therefore, the risk of bleeding at diagnosis can be widely different according to the presence of risk factors. According to the Columbia prospective AVMs database, the bleeding risk was 0.9% for patients with no risk factors, 2.4% for lesions with deep venous drainage, 3.1% for deep location and 4.5% for patients with hemorrhage at presentation. In patients with associated risk factors, such as hemorrhage at presentation, deep location and deep drainage, the risk is 34.4%⁴⁹.

Treatment Modalities

Treatment choices should be considered between many modalities regarding the management of brain AVMs, namely: observation, microsurgery, SRS (considering the possibility of fractionation) and embolization. Also, combined therapeutic methods should be considered for selected patients, as discussed later.

Although the histology of the lesions is the same, they present a different behavior considering its morphology, location, patient's age and clinical presentation. According to Stapf et al, ruptured AVMS have a 2.5 times higher risk of bleeding than unruptured AVMs⁵⁰.

Considering the risk of stroke or clinical impairment after SRS exclusively for ARUBA-eligible patients ("A Randomised Trial of Unruptured Brain Arteriovenous Malformations"), Pollock et al observed that the risk of stroke or death after SRS was approximately 2% per year for the first 5 years after the event. The risk declined to 0.2% annually in years 6 to 10. Patients with small volume brain AVMs (<5.6 cc) may benefit from SRS compared with the natural history of unruptured

AVMs over the planned follow-up interval of the ARUBA trial (5-10 years)^{34,44}.

Other interesting consideration regarding the treatment of AVMs is the possibility of seizure control after SRS. According to Yang et al., in 161 consecutive patients who underwent SRS for unruptured AVMs, and a mean follow-up of 89.8 months, 96.7% of the patients who achieved AVM obliteration (58/60) were seizure-free. Seizure control for those patients who did not achieved AVM obliteration was only 30.8% ($p=0.001$)⁵⁹.

Westphal et al. reported that aneurysms are related to AVM bleeding⁵⁴. Aneurysms associated to AVMs can be classified as follows: unrelated to AVM (type 1), flow related in a proximal feeding vessel (type 2), flow related in a distal feeding vessel (type 3) and intranidal (type 4). According to Mansmann et al., the presence of previous bleeding and aneurysms at distal feeding branch are related to high risk of bleeding. Venous ectasia and proximal aneurysms have no clear effect in AVM hemorrhage³¹.

Mechanism of Action of Stereotactic Radiosurgery

The advantages of SRS when compared to microsurgical or endovascular treatments are noninvasive characteristic, minimal risk of acute complications, and is performed as an outpatient procedure requiring no recovery time. Its major disadvantage is the latency period between the treatment and its results. SRS promotes occlusion of the small abnormal AVMs vessels through a radiation-induced fibrosis, which takes two to three years to occur. Reaction is probably mediated by changes involving the endothelial and muscular layers of the vessels. Histological differences in the constitution of the vessels walls explain why the results of SRS are poor in other vascular lesions such as cavernous angiomas.

Different models have been studied to clarify the mechanisms of AVMs obliteration after SRS. Using the rete mirabile model in the swine, Jahan et al. studied the histopathological changes of SRS. In this model, immunohistochemical analysis showed intimal cells to be proliferating smooth muscle cells with surrounding extracellular collagen type IV. Adventitial fibrosis composed of collagen type IV was also seen with smooth muscle cells interspersed with the collagen matrix. The radiation action in these cell leads to the production of collagen type IV due to a repair reaction¹⁸.

The ultrastructural changes in AVMs vary along the time since the procedure performed. About 30 months post-SRS, partial vaso-occlusion occurs through regulation of cytoplasmatic debris and proteinaceous material leaking from the endothelium. After 50 months occurs a heterogeneous thrombus formation with fibrinoid and proteinaceous materials. After 65 months, complex luminal closure by a fibrin thrombus is observed in vessels with diameter up to 5.5 mm⁵². Endothelial destruction is followed by spindle-shaped cell proliferation in the sub endothelial region and in the connective tissue stroma of AVMs vessels. These modified fibroblasts might contribute to the volume reduction and final obliteration of AVM's vessels after SRS⁵¹.

Massoud et al. applied a biomathematical brain AVM model to investigate the potential role of intranidal hemodynamic perturbations in elevating the risk of rupture after simulated SRS. It was found that the theoretical occurrence of AVMs hemorrhage after SRS was low, particularly when radiation-induced fibrosis of the nidus was modeled during the latency period³².

TECHNICAL CONSIDERATIONS

The fundamental principle of SRS is the delivery of focal, high dose radiation to a designated intracranial target while sparing the surrounding normal brain tissue. Therefore, this principle is based on conformity. SRS for AVMs was first described by Steiner et al using the Gamma-Knife system (GK)⁵¹. Modern SRS using advanced neuroimaging has also been developed with the GK^{10,30,43}. SRS performed with the GK is characterized by the use of multiple isocenters, which uses circular collimators to deliver a conformal target dose prescribed to the 50% isodose line. This conformity is achieved at the cost of dose heterogeneity with multiple "hot spots" inside of the target.

The advent of micro-multileaf collimators has introduced the capability of beam-shaping according to the anatomical architecture of the lesion. This allows the achievement of a conformational plan prescribed to the 90% isodose line in a very homogeneous fashion. While dose homogeneity may not be important in the treatment of malignant lesions, the concept seems to be important in the treatment of benign lesions such

as AVMs, where the target volume is embedded in the normal tissue.

Using the technique of shaped beam radiosurgery with a single isocenter, Pedroso et al. described the treatment results in 83 patients after a mean follow-up period of 54 months. Patients were treated with a mean dose of 15 Gy. A peripheral dose of 18 Gy was shown to be the most important predictor for occlusion in this series. A transient complication was noticed in one case (2.3%) but no permanent deficits due to SRS have been detected. The authors concluded that a homogeneous dose distribution permitted no permanent complications⁴⁰.

When SRS is applied to AVMs, an inflammatory cascade is initiated in the tissue and blood vessels. That response depends on the total dose of radiation, but the volume of normal tissue that receive 12 Gy or more is a significant predictor of permanent late sequelae after SRS¹⁰. In small lesions we find a fast fall off of the peripheral dose, which happens since the gradient dose varies inversely with the target volume¹. The nidus volume and the applied radiation dose are the most important factors for those patients²⁹.

APPLICATIONS AND RESULTS

SRS for AVMs has been classically applied for lesions up to 3 cm in diameter. The results of many series in the literature have demonstrated a significantly higher obliteration rate especially for lesions smaller than 10 cm³ in volume. Lower incidences of complications and better technical feasibility have also been reported in these smaller lesions. Besides the size of the AVM, the dose delivered to the lesions is also related to the occlusion rate and incidence of complications^{5,63}.

The most important information when deciding for the appropriate method for each patient should be the risk-benefit of each method and the natural course of the disease. A history of prior hemorrhage, a deep AVM location, exclusively deep venous drainage, and associated aneurysms were statistically significant risk factors for bleeding¹³. Thus, SRS is an accepted alternative to microsurgery for patients with small AVM's, especially when such lesions are located in eloquent areas, such as the basal ganglia or brainstem, or for inaccessible lesions³⁷.

The most important factor in reducing the risk of hemorrhage

after SRS is the complete obliteration of the lesion. Although controversial, some studies suggest that partially treated AVMs have a higher risk of bleeding, even when compared with patients not treated⁶³. Since the total obliteration rate is inversely related to the AVM volume, reports have shown that after SRS, AVMs larger than 4 cm have a higher bleeding risk^{61,63}. Other authors have found a better obliteration rate for lesions treated with one isocenter, and for lesions not previously embolized^{7,11,46}.

Some authors have also suggested that small AVMs (<3mL) are more frequently associated with bleeding as the clinical presentation, although this concept is being reviewed^{8,12,48}.

AVMs classification was classically based on the "Spetzler-Martin AVM grading system", which includes the diameter of the AVM nidus, the type of venous drainage and its location. Although a valid and interesting prognostic grading system for patient selection for surgical treatment, it has limited relevance for the prognosis and results after SRS²⁹.

The "Radiosurgery-based arteriovenous malformation score (RBAS)", first described by Pollock et al, which takes into account the patient's age, AVM size and location, permits an accurate prediction of the outcome after SRS, leading to a better patient selection for this therapeutic modality⁴³. The RBAS has been recently validated in a series of 80 patients with a mean AVM volume of 2.3 cm³. In this study, an occlusion rate of 92% in 3 years with RBAS score ≤ 1 was observed with no hemorrhage or radiation-related complications⁵.

The largest series in the literature for AVMs treated with SRS found an angiographic cure rate from 56 to 92% of the patients, independently of the AVM size or location. The complication rate (radiation induced sequelae or hemorrhage) varied from 2 to 10%^{7,11,24,42,50,58}.

Lunsford et al. reported an obliteration rate of 76.5% in 227 AVM patients treated with a mean marginal dose of 21.2 Gy. Treatment success was strongly correlated with AVM size, ranging from 100% obliteration rate for AVMs less than 1cc to 58% for AVMs from 4 to 10 mL³⁰. Modern doses for the treatment of Brain AVMs range usually from 15 to 22 Gy (Table 1).

Table 1. Radiosurgery treatment for brain AVMs: analysis of the major trials.

Author	Year	Nr of patients	Radiosurgery device	Location	Margin Dose (Gy)	AVM nidus volume (mL)	Obliteration rate (3rd year %)	Hemorrhage (% total / year)	AREs (% symptomatic)
Koga	2010	48	Gamma Knife	Thalamus	21	3.3	65	0.36	21
Kemeny	2011	356/160	Gamma Knife	Basal ganglia and Thalamus / Brainstem	17.5-25	2	41 – midbrain 42.5 – peritumoral 65 – pons/medulla 69 – thalamus	2.2 (exception: thalamic >8ml – 8.2%)	50 – infratentorial 35 – supratentorial (lesion > 8 ml)
Sheehan	2012	182	Gamma Knife	Basal ganglia and Thalamus	21.3	<3 vs >3	50.5	11.5/2.6	9.9
Lunsford	2012	113	Gamma Knife	Basal ganglia and Thalamus	20	2.7	57	11/2.7	4.5
Lunsford	2012	67	Gamma Knife	Brainstem	20	1.4	41	6/1.9	10
Sheehan	2013	134	Gamma Knife	Primary motor and sensory cortex	---	3.4	28	---/2.5	12.8
Karlsson	1997	945	Gamma Knife	- multiple -	18.6 *	3.6	56	5.8	5
Friedman	2003	617	LINAC	- multiple -	17.5	6.9	367 follow-up at 3 yrs **	---	2
Colombo	1994	180	LINAC	- multiple -	---	2	80	8.3/7.4-9.4	3.3
Yamamoto	1996	40	Gamma Knife	- multiple -	22	3.7	65	0	7.5
Pollock	1998	313	Gamma Knife	- multiple -	21	4.1	61	2.5	9

* (23 Gy in obliterated cases and 13 Gy in nonobliterated cases)

** (93% for < 1mL, 83% for 1-4mL, 63% for 4-10mL, 35 for > 10mL)

Gy: Gray

AREs: Adverse radiation effects

In a study of 97 patients treated with a LINAC system, a one-year and two-year thrombosis rate of 76% and 90% respectively was observed. Radiation doses varied from 18.7 to 40 Gy, with the margins of the target volume encompassed by the 70 to 90% isodose line, for lesions lesser than 15mL⁷. Friedman et al reported an overall 77% complete obliteration rate for 192 patients treated with a LINAC system. A complete obliteration rate was reported in 84% of the cases for lesions between 4 to 10 cm³, 93% for lesions between 1 to 4 cm³ and 100% for lesions lesser than 1mL¹⁴.

Finally, treatment outcome is also important when deciding the choice of the treatment modality. Nataf et al, in a series of 78 AVMs treated with microsurgery or SRS have found a similar cure rate but with the cost of a significantly higher rate of neurological deficits after microsurgery³⁶.

Arteriovenous Malformations in Eloquent Areas

AVMs located in eloquent brain areas account for a small percentage of the cases. Around 10% of them are located in the thalamus and basal ganglia, 2 to 6% in the brain stem and a small amount are located in primary sensory and motor cortex. Although uncommon, these lesions have a more aggressive natural history with up to 90% of the cases presenting with hemorrhage, causing permanent neurologic deficits in 85% of the patients^{6,22,23}.

Because of their critical location, AVMs in eloquent areas are often considered intractable by microsurgery or endovascular technique. Thus, SRS has been increasingly indicated over the past 20 years and appears as an alternative technique for management, as it can reach cure in a significant number of cases.

Kano et al. evaluated 133 patients with AVMs of the thalamus and lenticular nucleus with an average volume of 2.7 cm³ and

an average diameter of 2.2 cm. Using the GK, with an average margin dose of 20 Gy, they reached obliteration rates of 52% in 3 years and 72% in a 5-year period. During the latency period the risk of bleeding was 4.6% per year, similar to that of untreated patients²³. In another series, Koga et al achieved 72% obliteration at the end of the third year, with similar complication rates, which demonstrates the good applicability of SRS in the treatment of these AVMs²⁵.

The results of GK SRS were evaluated in 67 patients harboring brainstem AVMs. At least one bleeding event was observed in 76% of the patients. Radiation treatment consisted in the delivery of a mean total dose of 36 Gy with a marginal dose of 20 Gy, for AVMs with an average volume of 1.4 cm³. The obliteration rate in this series was 41% in three years and 70% at the end of the fifth year. The annual rate of hemorrhage after treatment was 1.9%²². The occurrence of adverse events was slightly higher than the literature, close to 16%, with a recovery rate near to half of the cases^{6,9,22,23}. Also in this series, 38% of the patients undergoing SRS and a previous neurologic deficit presented improvement after treatment²².

Sheehan et al. described the treatment of AVMs located in the primary motor and sensory cortex in 134 patients. Treated lesions had an average volume of 4.1cm³ and an average diameter of 2.5cm. Using an average dose of 20 Gy, they reached 28% obliteration in three years and 53% at five years. The obliteration rate was 80% in AVMs smaller than 3 cm³ and 55% for lesions with larger volumes. The risk of bleeding was 2.5% per year and the occurrence of radiation adverse effects was 16%⁹.

When properly indicated, SRS reaches obliteration rates close to 70% at the end of the third year in difficult lesions. The predictors of a higher cure rate are lesion size (less than 3 cm³), absence of prior embolization, low number of isocenters, margin dose of at least 20 Gy and the presence of a single draining vein^{6,22,23,60}.

Despite the good results and safety for AVMs located in eloquent areas, SRS carries a risk of permanent neurologic deficits in 14% and transient deficits in 6% of the cases. Complications tends to appear between 6 months and 2 years after the treatment^{22,23,25,35}. The main factors associated with the occurrence of complications are a larger lesion size, higher Spetzler-Martin classification grade, radiation doses greater than 12 Gy, a greater number of isocenters and lesion

localization, being the thalamus at the highest risk. The bleeding risk does not change with the SRS treatment, and there is no report of hemorrhage after confirmed obliteration^{6,22,23}.

Thus, in cases of AVMs with high surgical risk, or for small lesions in young patients in whom the cumulative lifetime risk is greater than the one presented by the treatment, SRS appears a feasible option with satisfactory results and acceptable complication rates.

Stereotactic Radiosurgery and Embolization

The association of embolization and SRS has been used for the management of AVMs not amenable to microsurgical treatment. The association is also useful for those lesions larger than 3 cm that cannot be treated by SRS alone, since the complete cure of AVMs by embolization is not the rule³. The concept of nidus volume reduction by endovascular treatment, making the lesion ideal for SRS, has been the only treatment option for many AVMs^{3,17,20,56,63}. Although the unquestionable advantages of this association, some pitfalls have already been demonstrated in the literature. Embolization has limited curative potential besides the management morbidity. The possibility of partial nidus embolization without the full occlusion of a whole AVM compartment has sometimes turned a large AVM into two or more small residual nidus. Instead of facilitating SRS, this result can difficult the SRS treatment or even make it not possible. Moreover, some studies have already shown that embolic material produce a shielding effect for the effects of radiation, jeopardizing its final results^{2,20}.

One study tested the hypothesis that the glue/contrast mixture used for embolization reduces the dose delivered to some compartments of the AVM. Using an experimental model, the authors confirmed a reduction of 10-15% in the dose delivered by clinical photon beams used for SRS at the glue/tissue interface².

This combined approach may be used either after planned partial embolization of large or complex AVMs or after failed attempt of endovascular complete obliteration⁶². Endovascular embolization reduces the size of the AVMs nidus, which effectively decreases the target volume for subsequent SRS. This strategy capitalizes on the principle that decreasing the target volume significantly improves obliteration rates with fewer radiosurgical complications³.

According to Kano et al., the obliteration rates after the association of embolization and SRS were 35%, 53%, 55% and 59% at 3, 4, 5 and 10 years, respectively. In the same period obliteration rates for SRS alone were 47%, 71%, 76% and 76%. Factors associated with a higher rate of total obliteration were smaller target volume ($< 8\text{cm}^3$) and higher margin dose ($> 18\text{Gy}$)²⁰. In other study, higher cure rates were observed when endovascular therapy was pursued until residual AVMs volumes were smaller than 10cm^3 . A total obliteration of 87% was achieved in this group of patients while 75% was obtained when the average residual AVMs volumes were more than 10mL^3 .

A meta-analysis including 10 studies with a total of 1,988 patients demonstrated that the obliteration rate was significantly lower in patients who had undergone embolization followed by SRS comparing to patients who had undergone SRS alone (41% vs 59%). The relative higher hemorrhage rate after combined treatment in this report may be partially explained by fact that nidus size and AVMs volumes were larger in the embolization group than in the nonembolized group⁵⁶.

Using LINAC-based SRS, the documented obliteration rate in AVMs treated after prior embolization was 76% after a median follow-up of 3.1 years. The obliteration rate was significantly higher in AVMs smaller than 3 cm in diameter (92% vs 60%), Spetzler-Martin grades I and II, compared with grades III/IV (90% vs 59%), and AVMs with a single feeder, compared with those with multiple feeders (82% vs 65%)⁶².

Another study showed higher complete obliteration in AVMs treated with initial embolization (using liquid embolic agents – nBCA) and subsequent GK SRS compared with only GK. According to Izawa et al, poorer results of SRS after initial nidus embolization can be caused by several factors. First, selection bias probably plays a significant role since larger AVMs with more complex angioarchitecture are usually chosen for combined management. Second, embolization can be potentially helpful for SRS only if specific anatomical compartments of the lesions, preferably located on its periphery, are obliterated. Third, recanalization of the embolized part of the AVM can be met in 2% to 19% of the cases, especially if polyvinyl alcohol particles are used¹⁷.

In the majority of the studies related to the combination therapy of embolization followed by SRS, particles or glue were used as the embolization agent⁴⁷. The advent of Onix®, which is

a copolymer that precipitates when coming into contact with blood and is not associated with the risk of gluing the distal portion of the microcatheter, might improve the results of embolization. Pierro et al reported 58.8% complete obliteration with Onix® embolization followed by SRS. Better results were also reported in Spetzler-Martin grades I-II and lesions until 3cm diameter⁴¹.

When two treatment modalities are used the inherent risks associated with each treatment are also added¹⁷. However, it is still unclear whether the risk of intracranial hemorrhage is increased post-SRS of an AVM after prior embolization⁶².

Blackburn et al described a rate of permanent morbidity of 7% for embolization and 5% for SRS. There were no mortalities or hemorrhage after treatment³. Kano et al. found no difference in the risk of hemorrhage after SRS in patients who had or who had not undergone embolization. The hemorrhage rate after embolization followed by SRS for AVMs of 8 cm³ or larger (n=46) was 2.2%, 11.8% and 17.6% at 1, 3 and 5 years, respectively. In AVMs smaller than 8 cm³ (n=74), the rate was 0%, 1.4% and 1.4% in the same period. Ten patients (8.3%) developed symptomatic adverse radiation effects and permanent neurologic deficits occurred in 3 (2.5%)²⁰.

The volume of tissue included in the 12 Gy isodose line was associated with a higher rate of symptomatic adverse radiation effects^{10,20}. According to a meta-analysis including 1,699 patients, there was no difference in the rate of hemorrhage at 3 years after SRS between patients who had undergone embolization followed by SRS and those who had undergone SRS alone (7.3% vs 5.6%). There was also no difference in permanent neurologic deficits related to radiation-induced changes between the two groups (3.3% vs 3.4%). The use of Onix® for embolization prior to SRS was quite satisfactory in the global clinical outcome. A worsening of the prior clinical status, with a modified Rankin Scale (mRS) > 2 , was observed permanently in only one case (5%). No deaths or intracranial hemorrhages were observed during the follow up period⁵⁶.

The bleeding risk after partial embolization followed by Linac SRS was significantly associated with AVM diameter $\geq 3\text{cm}$ (29% vs 0% for AVMs $< 3\text{cm}$), AVM volume $\geq 4\text{cm}^3$ (29% vs 0% for those $< 4\text{cm}^3$), AVM with multiples feeders (24% vs 6% for those with single feeder) and dose $< 18\text{Gy}$ (33% vs 7% for dose $> 18\text{Gy}$)⁶³. Saatci et al also reported low morbidity and mortality rates (7.1% and 1.4%, respectively), in a large series

of patients treated with Onix® embolization⁴⁵.

Radiosurgery for Large Brain Arteriovenous Malformations

The management of large AVMs remains a medical challenge due to their complexity and large amount of involved adjacent normal brain tissue. The conventional treatment of large and complex AVMs is associated with low efficacy and high rate of morbidity and mortality. Patients harboring large AVMs are usually not considered candidates for any form of treatment. In symptomatic cases, of surgically untreatable lesions, the use of stereotactic radiation might again be the only treatment option.

The risk of post SRS radiation-related injury is higher in patients with large AVMs. Single stage SRS of large volume AVMs was associated with a low rate of obliteration and unacceptable adverse radiation effects. Pan et al reported that the obliteration rate after GK SRS was 25% for AVMs with volumes greater than 15 cm³, within 40 months of follow-up³⁹. Miyawaki et al., using LINAC SRS, reported an obliteration rate of 22% in patients with AVMs larger than 14 cm³³³.

Because of the impossibility of administering a single dose SRS to achieve acceptable results in the treatment of large AVMs, two alternatives of stereotactic radiation were developed for these lesions: staged volume SRS and hypofractionated stereotactic radiotherapy (HSRT).

Multistage volumetric management of large AVMs was the initial method for obtaining higher AVMs obliteration rates with a reduction in normal tissue damage. In staged-volume SRS, the AVM is divided into two or more volumes and each of them is treated in a separate single session. The time between sessions usually range from 2 to 36 months^{16,21,47,57}.

There are no specific studies related to the natural history of AVMs larger than 10 to 15 cm³. However, in studies which included Spetzler-Martin grade 4 or 5 AVMs, the annual hemorrhage risk was 1.5% to 10.4% in patients without a previous history of hemorrhage, and 6% to 13.9% in patients with a previous hemorrhage^{14,19,26}.

Huang et al. reported a total obliteration rate of 29% and 89% in 5 and 10 years, respectively, after two or more stages. AVMs volumes were greater than 15 cm³ in symptomatic patients, with a minimum delivered dose of 15Gy, while the mean

separate anatomic volumes were 22.9 cm³ (range from 15.7 to 50 cm³)¹⁶.

Kano et al. used two or more stages of SRS for symptomatic large-volumes lesions (>10 cm³) unsuitable for surgery. In this study, 47 patients underwent prospectively staged-volume SRS with a median margin dose of 16 Gy (range 13-18Gy) for both stages. The obliteration rates after the initial 2-stage volumetric SRS were 7%, 20%, 28% and 36% after 3, 4, 5 and 10 years, respectively. A higher marginal dose was associated with a higher rate of total obliteration, and a marginal dose of 17 Gy or more been related with a total obliteration rate of 11%, 43% and 62% after 3, 4 and 5 years, respectively²¹.

Sirin et al. analyzed 28 patients who underwent prospectively staged volume SRS for large AVMs (>15 cm³). In a group of 14 patients followed for more than 36 months, total obliteration was obtained in 7 patients⁴⁷.

Large AVMs (Spetzler-Martin grade 4 and 5) are probably associated with a greater risk of hemorrhage in its natural history. According to Kano et al the incidence of hemorrhage after volumetric staged SRS was 21%, corresponding to an annual hemorrhage rate of 5.1% in the latency period after treatment. In univariate and multivariate analyses, the number of prior hemorrhages was the only factor associated with an increased hemorrhage rate after staged volume SRS²¹.

Because of the high dose heterogeneity and the large cumulative treatment volume, the treatment of large AVMs in separate volumes may be related to radiation-induced complications. In the series of Sirin et al., 14% of the patients developed peri-AVM imaging changes requiring steroid use. One patient experienced severe adverse radiation effects with worsening of an existing neurological deficit⁴⁷.

A low incidence of adverse effects was observed using a margin dose of 16 Gy in AVMs larger than 10 cm³. Only one patient (2%) developed transitory symptomatic adverse radiation effects after the first-stage, and 2 patients (4%) after the second-stage. Three out of 17 patients who underwent repeated SRS, after failed staged SRS, developed symptomatic adverse radiation effects²¹.

HSRT may be an alternative in the treatment of large AVMs because it combines the advantage of spatial precision of SRS with the radiobiological advantages of better sparing of late-responding tissues. Thus, HSRT allows the application of a

higher total dose in a large volume than it would be possible to deliver in a single fraction⁶². Instead of using a rigid stereotactic frame attached to the skull as in GK SRS, HSRT uses a relocatable stereotactic mask system.

Lindvall et al. described the use of HSRT for the management of large AVMs with the obliteration rate of 48% and 83% after 2 and 8 years, respectively²⁸. In other study, two different fractionation schemes were compared. One used 7 Gy in 6 fractions in alternate days for 2 weeks, with a total of 42 Gy, and other used 5 Gy in 6 fractions, also in alternate days for 2 weeks, totalizing 30 Gy. Because of a higher incidence of complications, namely the high incidence of radiation induced symptomatic edema, the lower dose scheme was more effective⁵³.

The efficacy and safety of HSRT to decrease AVMs volume opened the possibility of the application of this technique, instead of the use of endovascular embolization to reduce the volume of large AVMs before a single dose SRS treatment. Xiao et al. described the treatment of giant AVMs with HSRT as the first stage. Using an exponential model of response, the authors suggest that the patients may be retreated with SRS in 3 years. Patients who responded better had received a significant higher dose ($p < 0.04$)⁵⁵.

However, the use of HSRT is still controversial in the literature because of the variability in the treatment results among various studies. Treating AVMs larger than 4 cm in diameter, Zabel-du Bois et al reported a complete obliteration rate of 17% and 33% using HSRT, and 47% and 60% applying SRS, after 3 and 4 years follow-up, respectively⁶².

CONCLUSIONS

SRS has already proved its role in the management of AVMs. Its safety and good results have been demonstrated in a large number of patients after a long-term follow-up period. Unquestionably, it is the safer method of treatment with the cost of a delayed treatment result. Moreover, SRS and sometimes HSRT can treat lesions not amenable to any other treatment method.

Although the management of AVMs is still a matter of content in the literature, advances in the three treatment options for

these lesions, namely microsurgery, endovascular embolization and stereotactic radiosurgery allow the definition of some treatment strategies.

Therefore, microsurgery has been used for patients with acute symptomatic bleeding and those harboring Grade I, II and selected Grade III patients (Martin-Spetzler Grading Scale). Microsurgery is also the best approach when the lesion is felt to be at high risk for hemorrhage during the latency period between SRS treatment and AVM obliteration (e.g. associated aneurysm, venous outflow obstruction).

SRS is the treatment of choice in small lesions, included those unruptured. The option of using SRT or staged treatment for large AVMs should be considered and further studies are needed to define the results of these techniques. Endovascular embolization has been used for volume reduction and for the management of AVMs related to aneurysms and arteriovenous fistulas. If SRS can be used alone, embolization should be avoided because embolic material typically makes SRS targeting much more difficult and almost certainly reduces the success rate.

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