STAGED VOLUME RADIOSURGERY FOR LARGE ARTERIOVENOUS MALFORMATION - A CASE STUDY

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ABSTRACT

Introduction: *Large Arteriovenous malformations (AVMs) are challenges to manage because of outcomes and adverse affects. Volume Staged Radiosurgery has been an appropriate approach when removal resection and embolization are not recommended.*

Case presentation: *A 53 year old male was diagnosed with a large intracranial AVM with persistent headache and short-term seizure. Brain Magnetic Resonnace Imaging (MRI) and angiograph showed a bulky volume of AVM nidus. Removal resection and embolization were not recommended because of high risk of adverse affects. Patient was treated by Volume staged radiosurgery.*

Management and outcome: *Radiosurgery was divided into two stages. First stage was 15 Gy to the anterior half, and second stage was 13 Gy to the posterior half of whole AVM, interval time was 5 months. 5 months post-treatment, there was still remained shunts for right internal carotid artery (ICA), completely obliteration for right external carotid artery (ECA). One year post-treatment, Obliteration for right ICA was completed.*

Dicussion: *Staged Volume Radiosurgery is a potential treatment option for large AVM with controlled and obliteration efficacy, especially to AVMs which are not appropriate for removal surgery and embolization.*

Keywords: *radiosurgery, arteriovenous malformations*

I. INTRODUCTION

Arteriovenous malformations (AVMs) are congenital vascu- lar anomalies comprised of an abnormal number of blood vessels that are abnormally constructed. The blood vessels directly shunt blood from arterial input to the venous system without an intervening capillary network to dampen pressure. Both abnormal blood vessel construction and ab- normal blood flow lead to a risk of rupture and intracranial hemorrhage. In addition, patients with lobar vascular mal- formations may suffer from intractable vascular headaches or develop seizure disorders. The annual incidence of AVM recognition is thought to be 10,000 patients per year in the United States. However, the reliance on magnetic reso- nance imaging (MRI) has led to an increasing recognition of these vascular anomalies even in patients with minimal symptoms. The decision making relative to management of an AVM must be carefully evaluated based on several risk factors. The options for management include observation, endovascular embolization alone or in preparation for other adjuvant management, craniotomy and surgical removal, and stereotactic radiosurgery (SRS)[1]. All treatments may be done in one or more stages.

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In general, the following factors are evaluated when a patient is seen with an AVM: the patient's age, associated medical condition, history of a prior hemorrhagic event, prior management if any, overall volume and morphology, location of the AVM, initial presenting symptoms (headache, seizures, and local neurologic deficits), the AVM angioarchi- tecture (e.g., compact vs diffuse nidus), estimation of its sur- gical risks, presence of a proximal or intranidal aneurysm, and prior surgical experience in training. In making a deci- sion for management strategies, we often employ a decision tree algorithm as shown in Fig. 1.

Optimal care depends on careful weighing of each of the above factors and the estimated risk of subsequent hemor- rhage. The patient's clinical presentation and location are important issues as well as symptoms in each patient. Age, prior bleeding event, smaller AVM size, deep venous drainage, and high flow rates have been suggested by some as increasing the potential for subsequent bleeding

Surgical removal is an important option for patients with lobar vascular malformations of suitable size, especially at centers of excellence with extensive AVM experience. In- complete removal requires adjuvant management, perhaps including radiosurgery. Spetzler and Martin, among others, defined the relationship of AVM volume, pattern of venous drainage, and location within critical areas of the brain as important considerations that help to facilitate outcome prediction at the time of surgical resection at centers of ex-cellence. Outcomes after AVM radiosurgery do not correlate with the same predictions of the Spetzler-Martin scale when microsurgery is used [5]. Outcomes after radiosurgery may be predicted based on volume, location, age, angioar- chitecture, and dose delivered [6]. SRS is an excellent manage- ment strategy for patients with AVMs 30 mm in average diameter (for a single procedure). Staged procedures are used for larger vascular malformations or for those that were incompletely obliterated 3 years or more after an initial procedure.

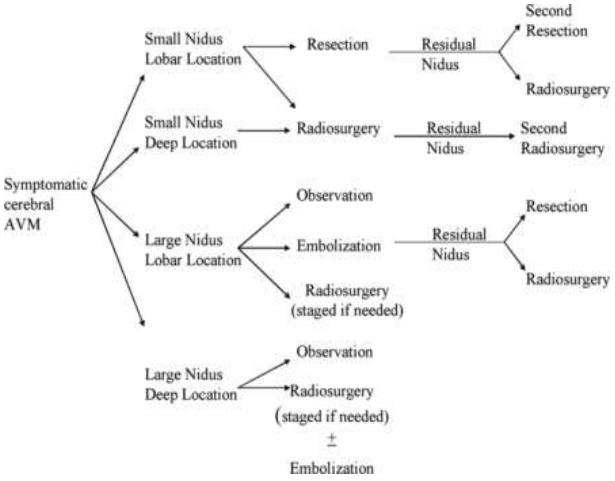


Figure 1. Treatment strategy for AVM

The chief benefit of radiosurgery management is risk reduction; the chief deficit of radiosurgery is the latency interval that is required to achieve complete obliteration of the AVM [7], [8]. The latency interval is generally 2 to 3 years, but in selected patients it may be longer. AVM radiosurgery has been used for children not suitable for other management strategies, as well as for older patients who have significant medical risk factors for surgical removal.

Surgical removal is arguably the best option for small- to medium- sized lesions, defined as Spetzler-Martin (SM) **(table 1)** Grades I– III, occurring in noneloquent an d superficial regions of the brain, particularly those with a history of hemorrhage[11]. Complete resection is curative and eliminates the risk of hemorrhage without a latent period. Large lesions, usually SM Grades IV and V, have substantially higher surgical complication rates and remain a therapeutic challenge. The overall prevalence or natural history of large AVMs is not well known, but such lesions have also been associated with increased rates of hemorrhage.38 In most reports, lesion size is defined by the greatest maximal dimension of the AVM nidus, and the incidence of AVMs larger than 2.5–3 cm varies from 30% to 62% in natural history stud- ies [10].

For larger volume AVM (average diameter 4–5 cm), observation may be the only reasonable strategy in view of the risks of even multimodality management [2]. This may be especially true

for patients who have never bled previously. Endovas- cular embolization employing a variety of particulate, glue, or coil methods may be used as an adjunct prior to cran- iotomy and surgical removal. [3,4] It has also been performed in preparation for SRS, although its role prior to radio- surgery has declined with the realization that embolization rarely leads to significant volumetric reduction. Although the flow within the AVM may change after embolization, SRS must include the original volume. In contrast, before surgical removal, embolization may provide major benefit, either by reducing flow or eliminating deep-seated feeders that would otherwise be a significant problem during AVM resection. Recanalization of embolized AVM components over time may require repeat SRS.

Comparing clinical reports of SRS treatment for AVMs to surgical series is not straightforward, as total AVM vol- ume rather than SM grade is the most important factor for SRS risk stratification [5]. Select small AVMs (< 10 ml) have a 3-year obliteration rate of 70%–95%. Single- session SRS for the treatment of SM Grade I–II AVMs using a median radiation dose of 22 Gy can have an oblit- eration rate as high as 90% at 5 years[16]. Radiation dose and treatment volume play important roles in the rates of AVM obliteration; Pan et al. reported only a 25% overall obliteration rate at 40 months for single-stage SRS to treat AVM volumes larger than 15 ml using doses less than 17.5Gy. SRS results by SM grade are exceptionally limited for large or higher-risk lesions; one report showed no oblit- erations in 4 patients with SM Grade V AVM treated in a single session.

Different treatment paradigms for large inoperable AVMs include single-stage SRS, embolization (definitive- ly, pre-SRS, or post-SRS), SRS with planned salvage of sur- gery or repeat SRS, proton-based SRS, fractionated SRS, dose-staged SRS, and volume-staged (VS)-SRS, which is an alternative approach where the nidus is divided into separate volumes and treated in separate sessions while minimizing overlap between stages [2,4].

The factors associated with obliteration following SRS in- clude size and location of the AVM, margin dose, patient age, and prior embolization; pre-SRS embolization may obscure targeting and lower rates of successful obliteration with SRS.2,7,30 Delayed recanalization following emboliza- tion may leave up to 15% of patients susceptible to repeat hemorrhage. In addition, embolization-related neurologi-cal complications can occur in 4%–40% of patients[9] .

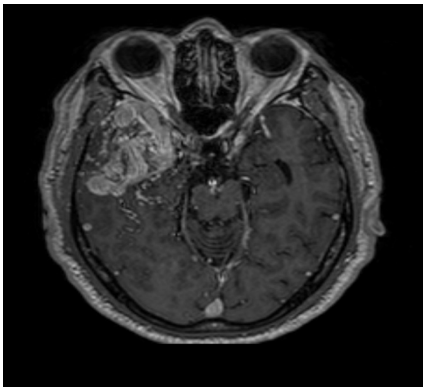
VS-SRS has been described as a way to potentially improve rates of obliteration and decrease the normal tissue 12-Gy volume by 27.3% and the overall 12-Gy volume by 11% compared with a hypothetical single session of SRS.32 Volume staging also allows for potentially sublethal damage in normal tissue within the low-dose range to be repaired, theoretically further decreasing the risk of a symptomatic adverse radiation effect (ARE). The rates of obliteration in the VS setting have varied, and predictors of response, such as volume per stage, dose per stage, and AVM architecture, have not been fully defined[2,4]. Multi- ple scales have been developed to estimate appropriateness of SRS for the treatment of AVMs, such as the modified radiosurgery-based AVM grading system and the Virginia Radiosurgery AVM Scale (VRAS) [11]. Some or all of these grading systems may be reasonable predictors of outcome, but none have been validated in the VS setting.

In this study, we introduce a 55 years old male with large AVM diagnosis, AVM at eloquent site, affected functionally. Removal surgery and endovascular intervention were not available.

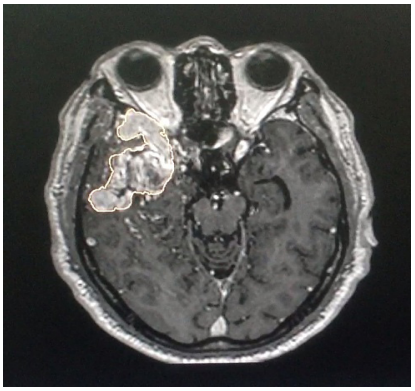
II. CASE REPORT

A 55 year old man presented persistent headache in 2 years. He had previously hypertension history, treated permantly by Calcium blocker, without history of vision blur and seizure. He came to Neurosurgery Department because of increasing headache and short-term seizure. Brain MRI showed a large AVM

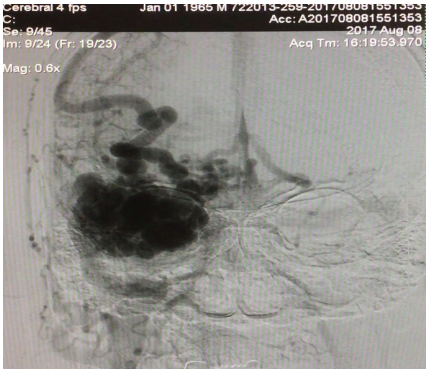
at right brain lobular, maximum diameter of AVM's nidus was 6.48 cm. In DSA, there were many large and high flow supplying arteries (the largest was right internal carotid artery-ICA). The diagnosis was inoperative large AVM, SM V, inappropriate for embolization. We decided to use Staged Volume Radiosurgery with interval time was 3-6 months. The AVM had been divided into two halves (anterior and posterior) based on a land mark as posterior edge of anterior clinoid. Dose to anterior half was 15 Gy and posterior half was 15 Gy after calculated doses for coverage and organs at risk. PTVs were defined as GTV + 2mm. Simulation was performed by using specific radiosurgery thermomask, CT simulation and MRI were recorded by slices of 1mm thickness; plans were calculated by dosimetrists and software Monaco 5.1. MRIs and DSA were taken before treatment, between 2 stages and 3, 6, 12, 18 months after second stage. Following up time was 24 months at time of report.

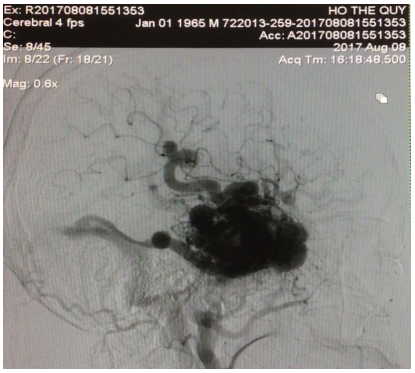


Pre-treatment MRI

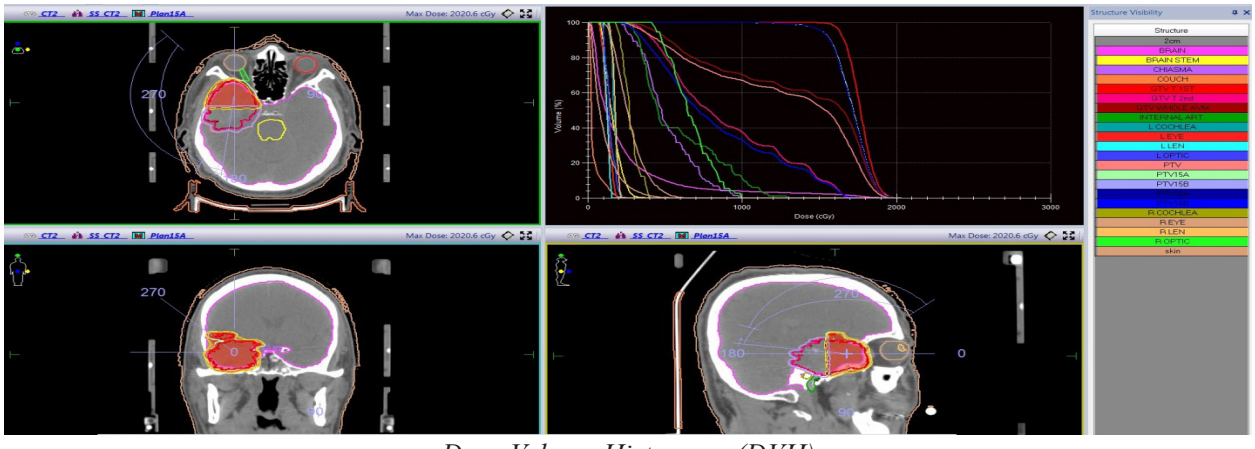


Whole AVM nidus Contouring





Pre-treatment DSA



Dose Volume Histogram (DVH)

Statistics | Display

Structure	Volume (...	Min. Dose (c...	Max. Dose (...	Mean Dose ...	Cold Ref. (...	Volume < (...	Volume < (...	Hot Ref. (c...	Volume > (...	Volume > (...	% in Vol...	Is in ...	Heterogeneity Ind...	Conformity Index
GTV T 1ST	30.544	1335.2	2020.6	1760.8				**1500.0**	30.496	99.84	100.00	yes	1.16	0.61
PTV15A	46.888	988.7	2020.6	1704.4				**1500.0**	44.988	95.95	100.00	yes	1.24	0.85
R OPTIC	0.600	410.7	988.7	657.9				**800.0**	0.120	20.00	100.00	yes	2.07	0.00
CHIASMA	0.584	219.0	976.3	509.2				**800.0**	0.048	8.22	100.00	yes	3.41	0.00
skin(Unsp.Tiss.)	3539.416	2.3	634.8	99.5							100.00	no	15.29	
BRAIN	1447.832	8.7	2015.2	221.9							100.00	yes	25.89	
BRAIN STEM	27.152	67.5	415.4	155.5							100.00	yes	2.96	
L COCHLEA	0.344	124.6	216.1	166.0							100.00	yes	1.51	
L EYE	6.864	59.8	195.7	119.5							100.00	yes	2.16	
L LEN	0.144	94.0	143.5	117.7							100.00	yes	1.48	
L OPTIC	0.592	80.5	215.6	136.4							100.00	yes	2.02	
R COCHLEA	0.328	175.7	387.9	269.7							100.00	yes	1.97	
R EYE	7.184	90.8	618.7	265.8							100.00	yes	3.41	
R LEN	0.208	131.2	208.3	171.9							100.00	yes	1.40	

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First fraction (1st stage) was on 28/09/2017, delivered 15 Gy to the anterior half of whole AVM. Coverage were >95% prescriptive dose to 100% of volume, maximum dose was 1847 cGy (<140% prescriptive dose).

48 hours after first fraction, he felt mild headache, without seizure or dizzy, symptom disappeared after 24 hours treated by steroid (dexamethasone 8mg BID).

After 4 months, he came for continous treatment. MRI before second stage showed reduction of whole AVM toward treated half by 20% (figure 3). We decided to make some modifications:

- Alleated borderline between two halves anteriorly (toward treated half) by 2mm.

- Decreased dose for second stage at posterior half to 13 Gy, due to assure protection to organs at risk (chiasm, right optic nerve).

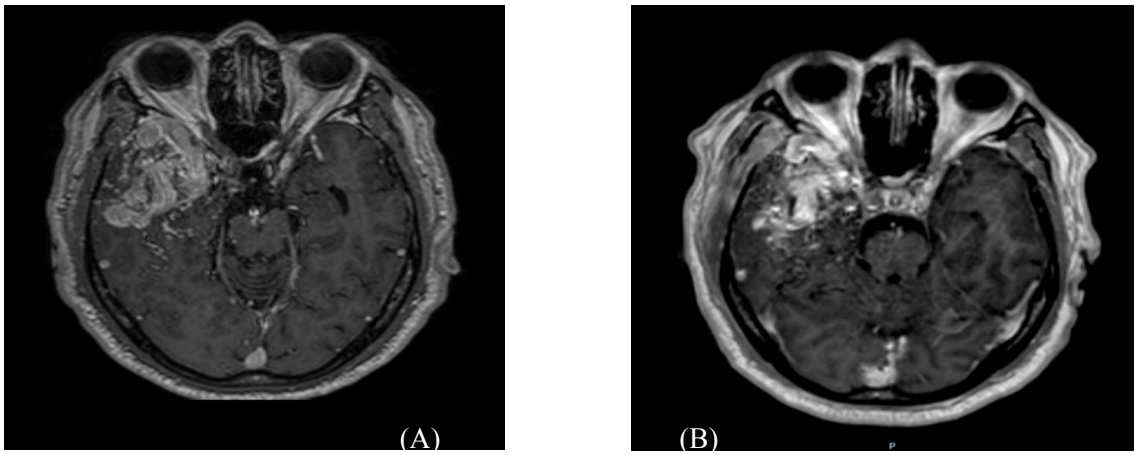
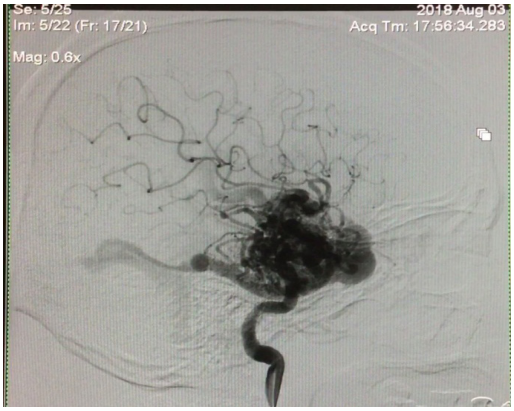


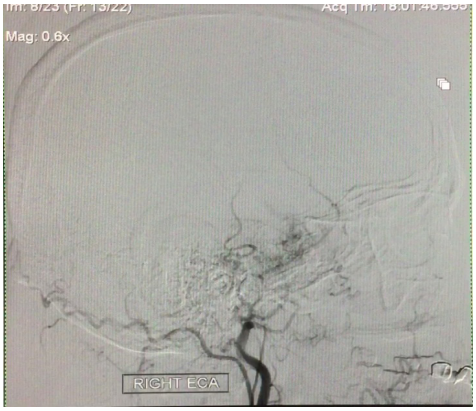
Figure 3. pre-treatment MRI (A), and before second stage (B)

The second stage was performed on 26 Feb 2018 (5 months apart).

Outcome at 5 months after second stage

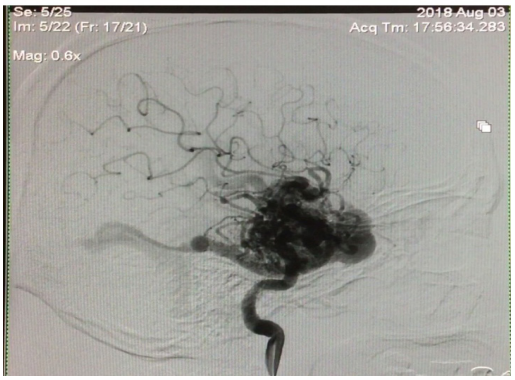


Remained shunts for right internal carotid artery

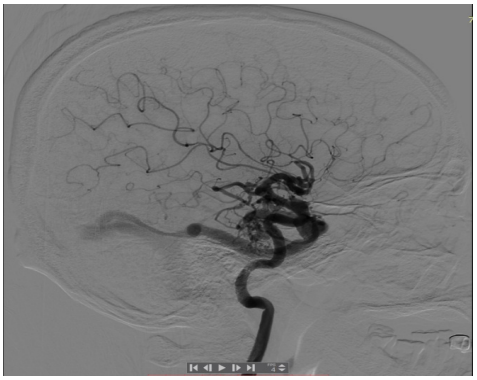


Completely obliteration for right external carotid artery

1 year after treatment



(A) Before treatment



(B) 1 year after treatment

III. DICUSSIONS

Adverse effects of radiosurgery include short term problems such as headache from the frame, nausea from pain sedative paom killer medication, and perhaps a small increased risk of seizure in patients with cortical lobar AVMs, particularly if a prior history of episodic seizures is present.

The probability of developing post radiosurgery imaging changes depends on marginal dose and treatment volume. The volume of tissue receiving 12 Gy or more (the 12-Gy volume) is the single factor that seems to have the closest correlation with the probability of developing imaging changes. Location does not seem to affect the risk of developing imaging changes but has a marked effect on whether or not these changes are associated with symptoms. Post- radiosurgery imaging changes (new areas of high T2 signal in brain surrounding the irradiated AVM nidus) develop in approximately 30 % of patients 1-24 months after radiosurgery.

Most such patients (2/3) are asymptomatic, leaving only about 9-10 % of all patients developing symptomatic post-radiosurgery imaging changes. A multi- institutional study analyzed 102 of 1255 AVM patients who developed neurological sequelae after radiosurgery. The median marginal dose was 19 Gy (range: 10-35) and the median treatment volume was 5.7 cc (range: 0.26-143). The median follow-up after the onset of complications was 34 months (range: 9-

140). Complications consisted of 80 patients with evidence of radiation related changes in the brain parenchyma. Seven also had with cranial nerve deficits, 12 developed seizures, and 5 had delayed cyst formation. Symptom severity was classified as minimal in 39 patients, mild in 40, disabling in 21, and fatal in 2 patients. Symptoms resolved completely in 42/105 patients with an actuarial complete resolution rate of 54+7% at 3 years post-onset.

In the present case, post radiosurgery imaging change was at 4 months after first stage treatment (whole volume reduced 20%) without symptoms. This is appropriate due to dose of 15 Gy at anterior half.

Delayed complications of radiosurgery include the risk of hemorrhage despite angiographically documented completely obliteration AVMs, the risk of temporary or permanent radiation injury to the brain such as persistent edema, radiation necrosis, and cyst formation, and the risk of radiation-induced tumors. Cyst formation after AVM radiosurgery was first reported by Japanese investigators who reviewed the outcomes of patients initially treated in Sweden. Delayed cyst formation has been reported in other recent long-term follow-up studies.

Patients who developed delayed cyst formation were more likely to have had prior bleeds.

Various surgical approaches ranging from surgical fenestration to cyst shunting were needed to manage these patients. Patients with T2 signal change without additional neurological problems generally do not need any active intervention. Chang et al in a recent report suggested that hypofractionated stereotactic radiotherapy (HSRT) may have a lower frequency of cyst formation than the SRS. However the oveall nidus obliteration rates at 5 year was 61% for HSRT and 81% for SRS.

Large AVMs pose a challenge for surgical resection, embolization, and radiosurgery. Some may be treated using multimodality management but a population of patients with large AVMs remains "untreatable". Although AVM embolization prior to radiosurgery has been used for patients with large AVMs, recanalization was observed in 14 to 15% of patients. Single-stage radiosurgery of large volume AVM either results in unacceptable radiation-related risks due to large volumes of normal surrounding tissue or low obliteration efficacy.

The obliteration rate after fractionated radiotherapy (2 to 4 Gy per fraction to a total dose of up to 50 Gy) is low and associated with significant side effects. Kjellberg et al. used stereotactic Bragg peak proton beam therapy for the management of large AVMs, and found a complete obliteration rate at best 19% in patients. However, they postulated that some protection from further hemorrhage was achieved. In a subgroup of 48 patients with AVMs larger than 15 ml Pan et al found an obliteration rate of 25% after 40 months. In their single radiosurgery strategy, the average margin dose was 17.7 Gy and 16.5 Gy for AVMs with volumes 10 to 20 ml and more than 20 ml, respectively. In their follow-up examinations, they observed 37% moderate and 12% severe adverse radiation effect in patients with AVMs larger than 10 ml. Miyawaki et al. reported that the obliteration rate in patients with AVMs larger than 14 ml treated using Linear accelerator radiosurgery was 22%. Inoue et al. reported an obliteration rate of 36.4% and hemorrhage rate of 35.7% in the subgroup of AVMs larger than 10 ml treated by radiosurgery. It is clear that in the narrow corridor between dose response and complication, the chances to achieving a high obliteration rate with a low complication rate for large AVM radiosurgery are slim. For this reason, radiosurgical volume staging was developed as an option to manage large AVMs.

In this approach is employed if the total volume is expected to be more than 15 cc. Usually after outlining the total volume of the AVM nidus on the MRI, the malformation is divided into volumes (medial or lateral, superior or inferior components) using certain identified landmarks such as major vessel blood supply, the ventricles, or other anatomic structures such as the internal capsule. Using the computer dose planning system, the AVM is divided into approximately equal volumes. Each stage is defined at the first procedure, and then recreated at subsequent stages using internal anatomic landmarks. The second stage radiosurgery procedure is performed 3-6 months after the first procedure.

Pittsburgh group reported an obliteration rate of 50% (7 of 14) after 36 months without new deficits, with an additional 29% showing near total obliteration. Other reports have also documented the potential role of staged radiosurgery for large AVMs. Longer follow-up duration is needed to assess the final outcome in these patients as some may take up to 5 years for nidus obliteration. The concept of volume staging with margin dose selection at a minimum of 16 Gy seems reasonably safe and effective

In our case, other indications such as removal surgery and embolization were not available, because high risk of hemorhage and Spetzler Martin score V. Decision on staged volume radiosurgery was appropriate. Volume and maximum diameter of AVM nidus were massive, unsafe to adjacent organs at risk if using neither single fraction radiosurgery

or fractionated routine radiotherapy.

Time was a factor contributing to response and obliteration capacity evaluation. Though two stages of treatment had been accomplished, DSA at 6 months still remained shunts , while MRI showed completely response. Obliteration evidence presented in DSA only at 12 months after treatment.

IV. CONCLUSION

Staged Volume Radiosurgery is a potential treatment option for large AVM with controlled and obliteration efficacy. However, indication should be made after very careful discussion by neuro-surgeons, endovascular specialists and radio-oncologists, requires high amount of experiences before applying to treatment.

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