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Radiosurgery for Cerebral Arteriovenous Malformation (AVM) : Current Treatment Strategy and Radiosurgical Technique for Large Cerebral AVM

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Arteriovenous malformations (AVMs) are congenital anomalies of the cerebrovascular system. AVM harbors 2.2% annual hemorrhage risk in unruptured cases and 4.5% annual hemorrhage risk of previously ruptured cases. Stereotactic radiosurgery (SRS) have been shown excellent treatment outcomes for patients with small- to moderated sized AVM which can be achieved in 80–90% complete obliteration rate with a 2–3 years latency period. The most important factors are associated with obliteration after SRS is the radiation dose to the AVM. In our institutional clinical practice, now 22 Gy (50% isodose line) dose of radiation has been used for treatment of cerebral AVM in single-session radiosurgery. However, dose-volume relationship can be unfavorable for large AVMs when treated in a single-session radiosurgery, resulting high complication rates for effective dose. Thus, various strategies should be considered to treat large AVM. The role of pre-SRS embolization is permanent volume reduction of the nidus and treat high-risk lesion such as AVM-related aneurysm and high-flow arteriovenous shunt. Various staging technique of radiosurgery including volume-staged radiosurgery, hypofractionated radiotherapy and dose-staged radiosurgery are possible option for large AVM. The incidence of post-radiosurgery complication is varied, the incidence rate of radiological post-radiosurgical complication has been reported 30–40% and symptomatic complication rate was reported from 8.1% to 11.8%. In the future, novel therapy which incorporate endovascular treatment using liquid embolic material and new radiosurgical technique such as gene or cytokine-targeted radio-sensitization should be needed.

Key Words : Arteriovenous malformations · Radiosurgery · Complication.

INTRODUCTION

Arteriovenous malformations (AVMs) are congenital anomalies of the cerebrovascular system with poorly formed blood vessels that shunt blood directly from the arterial to venous system bypassing the capillary network. AVM harbors 2.2% annual hemorrhage risk in unruptured cases and 4.5% annual hemorrhage risk of previously ruptured cases, deep location, deep venous drainage, associated aneurysm were proven risk factors of hemorrhage[22]. The highest individual rupture rate of AVM which harbored risk factors may be as high as 34%[54].

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The risks and benefits of AVM management must be weighed carefully in each patient. In the recent randomized prospective trial (ARUBA study), medical therapy alone showed superiority for outcome compared to interventional therapy in unruptured AVM[35]. However, ARUBA trial harbored several limitations[12,57]. For now, three treatment modalities, microsurgery, embolization and stereotactic radiosurgery (SRS) are available treatment modalities. Theoretically, microsurgical complete removal of AVM is ideal treatment. However, microsurgical removal harbored very high postoperative morbidity[52]. SRS have been shown excellent treatment outcomes for patients with small- to moderated sized AVM[15]. It is clear that angiographic nidus obliteration, which has been considered to eliminate the risk of hemorrhage as effectively as surgical resection, can be achieved in 80–90% of cases with a 2–3 years latency period[15]. Thus, SRS is widely accepted as an alternative to microsurgery in the treatment of AVMs, particularly in deep brain locations (i.e., brain stem, basal ganglia or thalamus) or critical lobar areas (i.e., sensorimotor, speech or visual cortex).

SRS has been shown favorable outcome for small to medium sized AVM. However, the efficacy of SRS for large volume AVM is still questionable. Large volume AVM are typically treated with reduced radiation doses which are associated with a lower chance of obliteration. Recently, various radiosurgical technique including staged-radiosurgery, hypofractionated radiotherapy (HfRT) and adjunctive endovascular therapy used to reduce radiation dose and to improve obliteration[15-17].

Herein, we will mention about current consensus and our institutional strategy of SRS (gamma knife radiosurgery, GKRS) for AVM which have been established by authors' (especially, D.H.K.) personal experiences during the more than three-decade period from 1990 through 2018. Also, this report will be summarized along with much of what we have learned from already published data.

METHOD

We summarized our institutional strategy for GKRS for AVM based on 30-year experience. In our institution, majority of GKRS for cerebral AVM have done by single experienced neurosurgeon (D.H.K.).

Also, we reviewed literature for current radiosurgical strategies (volume-staged radiosurgery [VS-RS], dose-staged radiosurgery and HfRT) for large AVM (volume >10 cm^3). Studies for this study were selected based on the following criteria : 1) the study must include at least 10 patients with cerebral AVMs treated with SRS. 2) The study must include posttreatment outcomes data. And 3) the language of the study must be English. Studies pertaining to repeat SRS for AVMs or SRS for other types of cerebrovascular lesions were excluded (Fig. 1).

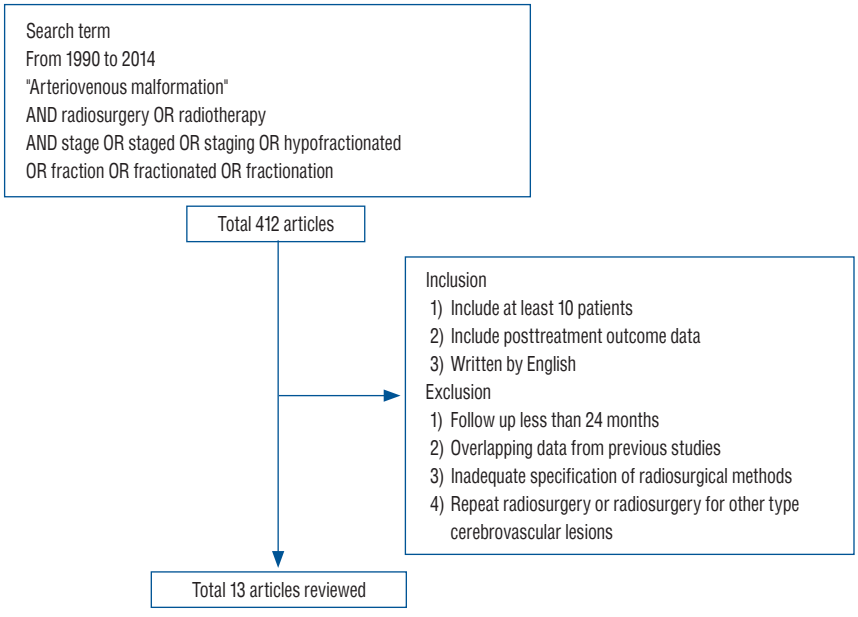

Fig. 1. Literature research for radiosurgery for large AVM. AVM : arteriovenous malformation.

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Literature research was performed using PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and the following search term "Arteriovenous malformation" AND radiosurgery OR radiotherapy AND stage OR staged OR staging OR hypofractionated OR fraction OR fractionated OR fractionation.

This search yielded 412 articles from 1990 to 2014, which were further screened based on the inclusion criteria above using the title and abstracts of the search results. With excluded articles from this study due to insufficient follow-up time (less than 24 months), overlapping data from previous studies, and inadequate specification of radiosurgical methods. A total of 13 articles' radiosurgical methods and outcomes for large AVM SRS were reviewed in tables.

CURRENT CONSENSUS OF CEREBRAL AVM RADIOSURGERY IN OUR INSTITUTE

Dose-volume guideline of cerebral AVM have been already reported[15,20,28]. The most important factors are associated with obliteration after SRS is the radiation dose to the AVM. In our institutional clinical practice, now 22 Gy (50% isodose line) dose of radiation has been used for treatment of cerebral AVM in single-session radiosurgery. In early 1990, 25 Gy dose of radiation was used for AVM radiosurgery, however, the dose of radiation gradually decreased to 22 Gy. Over dose of 25 Gy had been showed similar obliteration rate and higher complication rate[15]. The "12 Gy volume" has been known the most important factors of symptomatic radiation injury, we have tried to minimize irradiated normal brain area which received over 12 Gy[13,16].

In our institute, all of AVM radiosurgery was performed by the Leksell model G stereotactic frame and, after 2011 Leksell model Perfexion stereotactic frame (ELEKTA Instruments INC., Stockholm, Sweden) was used. Treatment plans were generated using the Elekta Gamma Plan system based on conventional cerebral angiography, gadolinium-enhanced axial 3-dimensional T1-magnetization-prepared rapid acquisition gradient echo magnetic resonance (MR) (1.25 mm slice thickness) and time of flight (TOF) MR images (1 mm slice thickness). The optimal plan was created by adjustment of the collimator and sectors so that the optimal dose coverage of the target can be achieved while minimizing the dose to the surrounding normal tissues. Until June 2005, the Leksell Gamma Knife unit model B type was used, replaced by the C type from July 2005 to January 2011. The Gamma Knife Perfexion unit has been adopted to treat patients from February 2011 onwards.

Follow-up MR digital subtraction angiography (DSA) images including angiography were performed at 1 year, 2 years, and 3 years after GKRS. If complete obliteration was demonstrated in MR DSA, cerebral angiography was performed in 2 or 3 years after GKRS to identify residual AVM or complete obliteration. If there was persistent lesion, follow up MR DSA is checked annually or considering additional treatment.

REPEATED RADIOSURGERY FOR RESIDUAL AVM

This residual or persistent AVM after SRS could be treated by microsurgical resection or embolization. However, microsurgical resection of residual AVM still harbors higher treatment related-complications. Considering invasiveness of microsurgical resection of AVM, surgical decision making of previously irradiated nidus is complicated. Also, embolization for residual AVM nidus is complicated because selection of small serpentine feeding arteries is technically difficult and embolization alone therapy have been shown poor obliteration rate[48].

Thus, repeated radiosurgery can be a viable option for residual AVM after latent period of first radiosurgery. In the recent systematic review of Awad et al.[4], median obliteration rate of repeated radiosurgery was 61.5%. Also, Maesawa et al.[35] reported 70% complete obliteration rate after second radiosurgery for AVM, they reported that dose-response curve of second radiosurgery was not significantly different from first radiosurgery.

The factors associated with obliteration after repeated radiosurgery have been reported, marginal dose was the most important factor for obliteration[35]. Stahl et al.[53] reported that volume of AVM, prescription dose and pretreatment hemorrhage were significant factors for obliteration after second radiosurgery. Third radiosurgery for residual nidus after second radiosurgery were also reported, the reported obliteration rate of third radiosurgery was 54%[53].

In our institute, if the persistent AVM nidus is located in the area of previous irradiation field, AVM nidus could be ob-

served for 2–4 years. However, if the residual AVM is located outside of previous irradiation field, early repeat radiosurgery could be applied.

In repeated radiosurgery, radiation-induced complication such as brain edema, radiation necrosis and cyst formation should be closely monitored. The rate of radiation induced complication after repeated radiosurgery for AVM reported that range from 4.9% and 7.4%[4,35,53].

RADIOSURGERY FOR LARGE CEREBRAL AVM

Dose-volume relationship can be unfavorable for large AVMs when treated in a single-session radiosurgery, resulting high complication rates for effective dose[15,17]. In large AVM, reported obliteration rate is low (less than 50%) and large area of irradiated normal tissue adjacent AVM could increase radiation-induced complication[10,11,16]. For this reason, single-session radiosurgery could not be a good treatment option of higher grade AVM (Spetzler-Martin grade III–V). There has been relentless endeavor to improve complete obliteration rate with minimizing post-treatment complication of high-grade AVM radiosurgery. Adjunctive embolization and several radiosurgical strategies have been introduced to treat large AVM.

Radiosurgery after embolization of AVM

Embolization alone could be used sole curing modality of cerebral AVM, however, embolization alone treatment has not been shown favorable complete obliteration rate[46]. Embolization still have played important role in multimodality treatment of cerebral AVM and embolization has been used as an adjunct before SRS for large volume AVM[36]. The role of pre-SRS embolization is permanent volume reduction of the nidus and treat high-risk lesion such as AVM-related aneurysm and high-flow arteriovenous shunt[9,25,36]. Several drawbacks of this approach include the morbidity associated with embolization, the potential for recanalization and the fact that embolization may divide the nidus into multiple compartments without reducing the nidus size for SRS[24,30,48,60].

In previous report, embolization of AVM nidus before radiosurgery decrease the obliteration rate compared to radiosurgery alone[52]. There were proposed reasons of decreased obliteration rate of embolized nidus, embolized nidus can increased the difficulty of defining or delineation of nidus during planning of radiosurgery[44]. Embolization can compartmentalize compact nidus into noncontiguous or diffuse one, it can make the difficulty of deciding target area of AVM nidus[50]. Furthermore, the embolized nidus may recanalize and recruit feeding vessels during latency period after radiosurgery[21,47]. Furthermore, Andrade-Souza et al.[2] reported embolic agents may absorb or scatter radiation, the overall dose to nidus could be reduce in AVM radiosurgery.

Despite the lower obliteration rates of embolized AVM, embolization has its clear strength of AVM volume reduction and eradicate high risk angiographical lesions. Volume reduction of AVM can improve probability of total obliteration and reduce radiation-induced complication[29,31]. Although there is periprocedural risk of AVM embolization, for now, embolization has been considered important adjunctive tool of AVM radiosurgery.

VS-RS for large AVM

VS-RS is one option of large volume AVM radiosurgery, it permits a higher radiation dose to be delivered to the AVM nidus and reduce radiation exposure to the adjacent normal brain. VS-RS compartmentalize the AVM nidus into geometrically distinct, smaller volume targets, each subdivided nidi are treated sequentially in a separate radiosurgical session[26]. The interval of each radiosurgery sessions are usually from 3 to 6 months[26,40].

The each session volume is decided on the chance of developing a radiation-induced complication based on the 12-Gy volume[43]. AVM usually fed by multiple arteries, volume staging can be based on different feeding arterial area on planning angiogram and major draining veins is treated last session[43]. Recommended minimum marginal dose is typically 16 Gy because the 3-year obliteration rate were approximately 70%[17,37].

In the report of Seymour et al.[49], they treated 31 patients of large AVM (largest diameter >3 cm) using VS-RS and followed up for 4.8 years. They divided treatment sessions from 2 to 4 stages (2 stages, 71%; 3 stages, 26%; and 4 stages, 3%), they applied marginal dose was 17 Gy for 6.8 mL volume (median session interval, 3.7 months). Near or complete obliteration rate was 42% and complication rate was 13%. In addition, they compared treatment outcomes of VS-RS for large AVM between marginal dose of ≥17 Gy and <17 Gy group, ≥17 Gy group showed better obliteration rate than <17 Gy group (42%

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vs. 22%). However, the complication rate was not significantly different (<17Gy group, 27% and ≥17Gy group, 15%)[47]. They proposed at least 17 Gy marginal dose for VS-RS for AVM.

Also, in the recent report of Pollock et al.[45], they treated 34 AVM (mean volume, 22.2 cm^3) using GKRS and followed-up for 8.2 years. In their report, they used marginal dose of 16 Gy for 2 stages (6 months interval) of VS-RS. They reported overall 71% nidus obliteration rate and 6% rate of adverse radiation effect. Despite of relatively large volume over 22 cm^3, they showed high obliteration rate and favorable functional outcome (65% showed excellent outcome). However, six of 34 (18%) patients experienced bleeding from AVM after completion of VS-RS and one patient experienced bleeding between stages[45].

The strategy of the surgical resection after downgrading of large AVM after VS-RS was reported. Abla et al.[1] reported 93.8% (15 of 16 patients) cure rate of surgical resection after VS-RS for large AVM. In their report, mean number of VS-RS sessions was 2.7 (volume per stage, 8–10 cm^3; dose per stage, >17 Gy) and interval of first session to surgery was 5.7 years[1]. This treatment strategy may be a viable surgical adjunction of VS-RS for large AVM.

To author's personal experience, nidus usually divided two portions (two sessions), and nidus division was performed based on different feeding arterial area (anterior circulation and posterior circulation). The interval of each session was 3 to 6 months, usually. However, in our institution, second-stage radiosurgery could be applied after 2–4 years first-stage radiosurgery (after firstly-irradiated area nidus obliteration). In this long-term staging method, second irradiation field delineation becomes easier than short-term staging method; it may lead better outcome of VS-RS for large AVM.

Complete obliteration rate of VS-RS was reported from 33% to 53% and the rate of complication was from 4% to 67% (Table 1)[31,40,45,52]. The rate of latent period hemorrhage of VS-RS was from 10–74%. Seymour et al.[49] reported the most important factors for higher obliteration was radiation dose (over 17 Gy).

HfRT for large AVM

The benefit of hypofractionation in radiation therapy may be achieved by the difference in the α/β ratio which is tissue's intrinsic characteristics between AVM nidus and normal brain. Hypofractionation make deliver higher dose to AVM nidus than single-session radiosurgery and minimize biologic equivalent dose (BED) to normal brain tissue. As fractionation increase, the obliteration rates become less favorable. In early report, fraction size of 2 to 4 Gy (a total 50 Gy) showed poor obliteration rates of 8%[33]. Thus, modern HfRT for large AVM delivers dose of over 4 Gy per fraction is recommended and proposed the fraction strategies are 7 Gy×4, 5.6 Gy×6, 4.7 Gy×8, and 4.2 Gy×10 which is the BED to a single-session radiosurgery 15 Gy[61]. In the previous report, the obliteration rates of HfRT were reported from 5% to 74% and the complication rate of HfRT rate were reported from 3% to 41% (Table 2)[3,6-8,39,56,58,61].

However, theoretically, the α/β ratio of AVM vasculature is similar to late responding tissue, therapeutic advantage of HfRT is still questionable. Previously published reports for HfRT for large AVM were small sample size study, thus, cautious interpretation should be needed for efficacy of HfRT for large AVM.

Dose-staged radiosurgery for large AVM

The definition of dose-staged radiosurgery is confusing. Conventional radiotherapy or HfRT could be considered 'dose-staged' treatment. However, in this report, dose-staged radiosurgery for AVM is defined as repeated radiosurgery of the whole nidus using low doses for each single session over an interval period of 3–4 years[41]. In general, suboptimal radiation dose (under 18 Gy) is given in each radiosurgical session. In systematic review, complete obliteration rate of dose-staged radiosurgery for large AVM were reported from 0% to 70% and radiation induced complication rate was reported from 0% to 20%, However, most of studies including this systematic review used linear accelerator (LINAC) instead of GKRS[52]. According to this systematic review, dose-staged radiosurgery for large AVM showed less favorable outcome in terms of complete obliteration rate and compared to VS-RS[38]. The optimal dose and time interval have not been defined.

Inoue et al reported that lower dose of irradiation (mean marginal dose, 19.5 Gy) showed over 85% obliteration rate in AVM[47]. Also, Foote et al.[18] reported 66% of size reduction of low-prescribed dose radiosurgery (median marginal dose, 12.5 Gy) for large AVM. Salvage radiosurgery (median marginal dose, 15 Gy; medial interval from 1st treatment, 41 months) was performed, they reported 60% cure rate after salvage re-treatment and 1.9% of radiation-induced complication. Al-

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Table 1. Summary of patient and treatment characteristics in series using volume staged radiosurgery for large AVMs

Study	Number of enrolled patients	Median age (years)	Median total AVM volume (cm^3)	Treatment modality	Dose of each session	Mean volume of each session (cm^3)	No. of stages	Time interval of stages (months)	S-M grade	Previous hemorrhage	Pre-radiosurgery embolization	Rate of complete obliteration	Rate of radiation induced complication	Latent period hemorrhage	FU period (median, years)
Sirin et al.[51] (2006)	28	37	24.9	GKRS	13–18 Gy/ 13–18 Gy	Median 12.3/11.5	2 : 26 (93%) 3 : 2 (7%)	Median 5	III : 2 (7%) IV : 11 (39%) V : 15 (54%)	13/28 (46%)	13/28 (46%)	7/14(50%)	4/28 (14%)	4/28 (14%)	4.2
Kano et al.[31] (2012)	47	33	22.0	GKRS	13–18 Gy / 13–18 Gy	11.5/9.5	2 : 32 (89%) 3 : 4 (11%)	Mean 4.9	III : 5 (11%) IV : 28 (60%) V : 14 (30%)	18/47 (38%)	21/47 (45%)	17/47 (36%)	3/47 (6%)	8/47 (17%)	7.3
Franzin et al.[19] (2016)	20	Mean 38	Mean 15.9	GKRS	18–25 Gy / 13–24 Gy	7.8/4.7	2	Mean 13	III : 10 (50%) IV : 7 (35%) V : 3 (6%)	6/30 (25%)	11/20 (55%)	8/20 (40%)	5/20 (25%)	2/20 (10%)	3.8
Seymour et al.[49] (2016)	31	35	18.9	GKRS	16–18 Gy	Median 6.8/6.8	2 : 22 (71%) 3 : 8 (26%) 4 : 1 (3%)	Median 3.7	III : 10 (32%) IV : 16 (52%) V : 5 (16%)	11/31 (35%)	5/31 (16%)	13/31 (42%)	13/31 (37%)	23/31 (74%)	4.8
Hanakita et al.[23] (2016)	18	Mean 37	38	GKRS	16 Gy/ 16 Gy/ 16 Gy	NA	2 : 10 (56%) 3 : 8 (44%)	Median 6	III : 4 (22%) IV : 7 (39%) V : 7 (39%)	12/18 (67%)	3/18 (17%)	6/18 (33%)	12/18 (67%)	4/18 (22%)	4.4
Pollock et al.[45] (2017)	34	31	22.2	GKRS	14–18 Gy	10.7	2–4	Median 5	III : 8 (34%) IV : 19 (56%) V : 5 (15%)	12/34 (35%)	4/34 (12%)	18/34 (53%)	2/34(6%)	6/34 (18%)	8.2

AVM : arteriovenous malformation, S-M grade : Spetzler-Martin grade, GKRS : gamma knife radiosurgery, FU : follow-up, NA : not applicable

Table 2. Summary of hypofractionated radiotherapy for large AVM

Study	Number of enrolled patients	Median age (years)	Mean AVM volume (cm^3)	Treatment modality	Total dose (Gy)/ Fraction (Fr)	S-M grade	Previous hemorrhage	Pre-radiosurgery embolization	Rate of complete obliteration	Rate of radiation induced complication	Latent period hemorrhage	FU period (median, years)
Aoyama et al.[3] (2001)	26	NA	NA	LINAC	35/4	NA	12/26 (46%)	1/26 (4%)	53% (3-year actuarial rate)	0%	2/26 (8%)	3
Chang et al.[7] (2004)	33	NA	NA	LINAC	35/4	Grade 3≥17 (52%)	15/33 (45%)	3/30 (10%)	32% (3-year actuarial rate)	1/33 (3%)	6/33 (18%)	3.1
Xiao et al.[58] (2010)	20	34	46.8	LINAC	30/5 30/6 25/5	IV : 7 (35%) V : 13 (65%)	11/20 (55%)	10/20 (50%)	1/20 (5%)	1/20 (5%)	1/20 (5%)	2.7
Murray et al.[39] (2014)	10	Mean 43.2	22.4	LINAC	55/11	NA	4/10 (40%)	NA	5/10 (50%)	NA	NA	3.5
Chen et al.[8] (2016)	34	Mean 43.8	11.4	LINAC	35/5	mRBAS : 2.01	17/34 (50%)	8/34 (23%)	26/34(74%)	14/34 (41%)	2/34 (6%)	8
Boström et al.[6] (2016)	14	37	11.4	LINAC	30–55/5–11	III : 5 (36%) IV : 4 (29%) V : 3 (21%)	8/15 (53%)	5/14 (36%)	4/14 (29%)	1/14 (7%)	2/14 (14%)	3.6

AVM : arteriovenous malformation, S-M grade : Spetzler-Martin grade, FU : follow-up, NA : not applicable, LINAC : linear accelerator, mRBAS : modified Radiosurgery-Based Arteriovenous Malformation Score

though, they did not intend dose-staging radiosurgery, they reviewed the volume reduction rate of low dose radiosurgery and indirectly showed favorable outcome of dose-staging radiosurgery.

In the representative study of Park et al.[41], they reported favorable outcome of dose-staged radiosurgery for large AVM (mean volume, 20.42 cm^3) (Table 3). They treated 37 patients of AVM by dose-staged (2 stages) radiosurgery (GKRS) and followed-up after completion of session for 3.1 years. In first session, marginal dose of 13 Gy was given for mean nidus volume 19.6 cm^3, and in second session, marginal dose of 17 Gy was given for mean nidus volume 6.9 cm^3 (interval of session, 39 months). In first session, they treated larger volume of nidus using lower dose of radiation compared to second session of radiosurgery and reported 62.5% complete obliteration rate with no symptomatic radiation necrosis[41].

There has been debate of superiority between VS-RS and dose-staged radiosurgery for AVM. In the systematic review of Moosa et al.[38], dose-staged SRS for AVM showed lower obliteration and similar complication rates compared with volume staged SRS for AVM. They preferred VS-RS to dose-staged SRS for large AVM. However, in their study, the definition of dose-staged RS included HfRT[52]. For now, in our institution, we also prefer VS-RS to dose-staged radiosurgery for large AVM. Future comparative study for dose-staged and VS-RS will be needed to evaluate superiority between two methods.

COMPLICATION OF RS FOR CEREBRAL AVM

Dose prescription of AVM radiosurgery must take into account not only the chance of obliteration but also the risk of radiation induced complication. Post-radiosurgery complications include brain edema, radiation necrosis, arterial stenosis, delated cyst formation and organizing hematoma[16,28,42].

Two possible mechanism of postradiosurgery complication have been suggested. First, direct radiation injury of adjacent parenchyma, and another mechanism is the hemodynamic change after irradiation[34]. Radiation injury of adjacent white matter seems to be damage to oligodendrocytes following reactions of other glial cells such as microglia and astrocytes, which may be related to brain edema, necrosis, and delayed cyst formation. Radiation effects on arteries or draining veins seem to involve damage to endothelial cells followed by reac-

Table 3. Summary of dose-staged radiosurgery for large AVMs

Study	Number of patients	Mean age (years)	Mean volume (cm^3)	Treatment modality	Mean dose of each session (Gy)	Number of stages	Time interval of stages (months)	S-M grade	previous hemorrhage	Pre-radiosurgery embolization	Rate of complete obliteration	Rate of radiation induced complication	Latent period hemorrhage	Mean FU period (years)
Park et al.[41] (2016)	45	29	20.4	GKRS	2 stages : 13 Gy/ 17 Gy 3 stages : 12.25 Gy/ 13.5 Gy/ 15.5 Gy	2 stages : 37 (82%) 3 stages : 8 (18%)	Median : 39	III : 17 (38%) IV : 11 (24%) V : 2 (4%)	10/45 (22%)	6/45 (13%)	29/45 (64%)	0%	5/45 (11.1%)	8.7

AVM : arteriovenous malformation, S-M grade : Spetzler-Martin grade, FU : follow-up, GKRS : gamma-knife radiosurgery

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tions of the microscopic and macroscopic vascular wall, which may cause arterial stenosis, encapsulated hematoma, and hemorrhage after nidus obliteration[27].

The incidence of post-radiosurgery complication is varied, the incidence rate of radiological post-radiosurgical complication has been reported 30–40%[11,14,16]. However, symptomatic complication rate was reported from 8.1 to 11.8%[11,14]. Izawa et al.[28] reported long-term complication of GKRS for AVM, they reported 3.4% of delayed cyst formation, 1.7% of increasing seizure activity and 0.4% of white matter signal change in MRI. Also, there was report of new nidus development around the obliterated nidus after GKRS, Yun et al.[59] reported successfully treated redo GKRS for new nidus development around obliterated nidus and new nidi were detected after 31, 132, and 36 months after initial GKRS.

Management of post-radiosurgical complication should be performed individually. Corticosteroid showed favorable symptom resolution of post-radiosurgical complication, corticosteroid showed 34% of complete resolution of symptoms and 49% of partial improvement of symptoms[14].

The risk factors of post-radiosurgical complication also has been reported. Flickinger et al.[16] suggested "The 12-Gy volume" which is normal brain area received over 12 Gy adjacent of lesion was associated symptomatic post-radiosurgical image changing. Friedman et al.[20] reported 12-Gy volume and eloquent location were predictive factors for radiation-induced complication. Also, Izawa et al.[28] reported large nidus volume and lobar location were risk factors for long-term complication. In addition, they also reported higher dose of GKRS, large volume, complete nidus obliteration and lobar location of AVM were associated with delayed cyst formation[28].

The rate of latent period hemorrhage after SRS for AVM were reported 2.6% to 10%[5,11,20,28]. In meta-analysis of van Beijnum et al.[55], the rate of hemorrhage after SRS was 5.8% which showed higher than hemorrhage rate after microsurgery and embolization (0% and 1.9%, respectively). The risk of latent period hemorrhage was higher in older age, larger AVM and lower when used higher radiation dose[32]. However, prior rupture of AVM before SRS was not a predictor of post-radiosurgery hemorrhage[11].

The relatively non-invasiveness of treatment itself of SRS is strong advantage in AVM treatment. However, there has been potential risk of radiation induced complication and risk of latent period hemorrhage. It should be informed to patient and their caretaker, moreover, clinicians should keep in their mind of this complications.

CONCLUSION

SRS plays major role in treatment of brain AVM. SRS showed excellent obliteration rate in small AVM. Although SRS showed favorable outcome in large AVM in some studies, the radiosurgical treatment of large AVM still have challenges which including low obliteration rate and radiation-induced complications. We should keep in mind of posttreatment complication and relatively higher latent period hemorrhage after SRS of AVM. To author's personal experience, long-term staging method of VS-RS (interval of session, >2 years) is the most suitable strategy for large AVM. In the future, novel therapy which incorporate endovascular treatment using liquid embolic material and new radiosurgical technique such as gene or cytokine-targeted radio-sensitization should be needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : JB, DHK
Data curation : JB
Formal analysis : JB, DHL, WP, JSA
Methodology : JB, JCP, JSA
Project administration : JB, DHK
Visualization : JB
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