

Hypofractionated Stereotactic Radiotherapy with CyberKnife for Large Arteriovenous Malformations and Arteriovenous Malformations Located in Eloquent Areas

Ryoko NIWA,^{1,2} Shunsuke ICHI,¹ Ryutaro NOMURA,^{1,3} and Kengo SATO¹

¹CyberKnife Center, Japanese Red Cross Medical Center, Tokyo, Japan

²Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan

³CyberKnife Center, Chigasaki Chuo Hospital, Kanagawa, Japan

Abstract

Literature has yet to establish an appropriate treatment strategy for large arteriovenous malformations (AVMs) and AVMs located in eloquent areas. In this study, the treatment outcomes of hypofractionated stereotactic radiotherapy (HSRT) with CyberKnife (CK) for large AVMs and AVMs in eloquent areas were evaluated. This study retrospectively evaluated 38 consecutive patients with AVMs treated with HSRT in the Japanese Red Cross Medical Center between August 2010 and July 2015. Obliteration rates and hemorrhage rates at 3- and 5-years of follow-up were calculated. Factors for hemorrhage and obliteration were analyzed with logistic regression analysis. Fourteen (36.8%) patients had a history of hemorrhage. Twenty (52.6%) AVMs were larger than 10 mL, and 34 (89.5%) AVMs were located in eloquent areas. The majority of the AVMs (84.2%) were classified into high grades (grades 3, 4, and 5) using the Spetzler-Martin grading scale. The median modified radiosurgery-based AVM score was 2.05, and the median Virginia Radiosurgery AVM Score was 3. The mean marginal dose was 24.5 ± 2.5 Gy. Twenty-three and 15 patients received three- and five-fraction stereotactic radiotherapy, respectively. At 3 and 5 years posttreatment, two (2.0%/year) and six (6.7%/year) patients had hemorrhage with obliteration rates of 15.2% and 16.7%, respectively. AVM localization in eloquent areas was a risk factor for obliteration failure. This study revealed that HSRT with CK for large AVMs and AVMs located in eloquent areas contributed to hemorrhage risk reduction and obliteration, at least in the early stages.

Keywords: arteriovenous malformation, CyberKnife, stereotactic radiotherapy, hypofraction, outcome

Introduction

CyberKnife (CK) is a relatively less-invasive modality among radiosurgical treatments. Hypofractionated stereotactic radiotherapy (HSRT) with CK can reduce radiation toxicity on the surrounding structures with short treatment duration and thus holds a distinguished efficacy for metastatic brain tumors,^{1,2)} meningiomas,³⁾ cavernous malformations,⁴⁾ and small arteriovenous malformations (AVMs).^{5,6)} However, it is believed that no reports exist regarding HSRT with CK for AVMs that are difficult to treat

(e.g., large AVMs and AVMs located in eloquent areas). Herein, the treatment outcomes of HSRT with CK for large AVMs and AVMs located in eloquent areas are reported.

Materials and Methods

Patients

This study included 38 consecutive patients with AVMs treated with HSRT in the Japanese Red Cross Medical Center between August 2010 and July 2015. Clinical information, including age, sex, onset, history of hemorrhage, du-

Received February 3, 2022; Accepted June 2, 2022

Copyright © 2022 The Japan Neurosurgical Society

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives International License.

ration between the last hemorrhage and treatment, and history of surgical resection or endovascular embolization for AVM, was extracted from medical charts. This study protocol will be approved by the Institutional Review Board at the authors' hospital (#1398). Written informed consent from patients was waived because this is a retrospective and noninvasive study.

AVM characteristics

AVM nidus volume, drainage pattern, and location were evaluated using angiography, computed tomography (CT), and magnetic resonance (MR) imaging. In cases where patients had a history of surgical resection or endovascular embolization for AVM, the initial images acquired before any treatment were used for assessment. Based on the radiological and clinical information, Spetzler-Martin grading scale,⁷ the modified radiosurgery-based AVM score (m-RBAS),⁸ and the median Virginia Radiosurgery AVM Score (VRAS)⁹ were evaluated.

Treatment

The institution of the current study recommends observation, surgical resection, endovascular embolization, stereotactic radiosurgery, or any combination of these treatment procedures for small AVMs in noneloquent areas, considering individual clinical and radiological characteristics. In contrast, HSRT with CK is employed as a treatment tool for large AVMs or AVMs in eloquent areas because high-grade AVMs with Spetzler-Martin grading scale left untreated have high risks of morbidity and mortality.¹⁰

For treatment planning, plain CT (1-mm slice), contrast-enhanced CT (Omnipark 350, 2 mL/kg iv, 1-mm slice), T2-weighted MR imaging (2-mm gapless), and MR angiogram were performed, and these images were fused with MutiPlan, version 4.6 (Accuray Inc., Madison, WI, USA). Radiation areas were manually depicted to exclude eloquent regions and were then completed using the inverse planning method. The prescription dose was decided according to dose-volume histogram 95% (DVH95). Considering the AVM target volume and location, a three- or five-fraction radiotherapy approach was chosen three to five consecutive days, depending on the number of the fractions. All treatment planning was conducted by two senior authors (RN and KS) who are well-experienced neurosurgeons in the CK field. Patients put soft-shell masks on their faces during irradiation with CK (Accuray Inc.), and intravenous sedation was added when patients were restless. Automatic adjustments were performed to ensure accurate irradiation using the X-ray tracking system.

Follow-up evaluations

Patients were followed up every 6 months at the outpatient clinic of the current study or by referral physicians using physical examinations and MR imaging. Posttreatment hemorrhage was defined as intracranial hemorrhage

confirmed by radiological investigations with acute-onset symptoms. Annual hemorrhage rates were calculated as the number of patients with hemorrhage divided by the number of patients under regular follow-ups and by post-treatment years. Angiography was then recommended for confirmation 3 years after treatment if MR imaging indicated complete obliteration. However, several patients refused angiography because of its invasiveness, and nidus disappearance with no draining veins on MR imaging was considered complete obliteration in such cases.

Statistical analysis

Statistical analysis was conducted using IBM SPSS statistics, version 23 (IBM Corp., Armonk, NY, USA). Logistic regression analyses were used to analyze the data collected to identify factors for hemorrhage and obliteration 5 years after treatment. For analysis, continuous and categorical variables were divided into two groups based on the median as follows: sex, age (>36 years), history of hemorrhage, history of endovascular embolization, nidus volume (>12 mL), eloquent area, Spetzler-Martin grading scale (grades 3, 4, and 5), m-RBAS (>1.5), VRAS (3 and 4), three-fraction radiotherapy, marginal dose (>25.0 Gy), maximum dose (>30.7 Gy), and minimum dose (>21.0 Gy). Moreover, $p < 0.05$ were considered statistically significant.

Results

Clinical and treatment characteristics

Patient and AVM characteristics are shown in Table 1. Twenty (53%) patients were men, and the mean age was 35 ± 18 years. Nine patients were children of <16 years old, with the youngest being 5 years old. Clinical onset included hemorrhage (9, 23.7%), headache (7, 18.4%), epilepsy (10, 26.3%), and incidental findings (12, 31.6%). Fourteen (36.8%) patients had a history of hemorrhage before CK, and the median interval period between the hemorrhagic event and HSRT was 5 months (range, 2-156 months). Eleven of these patients experienced a hemorrhagic event within 1 year before CK. Two (5.3%) and 20 (52.6%) patients had a history of surgical resection for AVMs and preceding endovascular embolization, respectively. None of the patients in the current study experienced radiosurgical treatment before HSRT. For endovascular treatment, coils (three AVMs), *n*-butyl cyanoacrylate (16 AVMs), and onyx (4 AVMs) were used as embolization tools. Multiple materials could be used for one AVM.

The median nidus volume was 12.0 mL (range, 0.6-91.1 mL). Twenty (52.6%) AVMs were large-sized (>10 mL), and 34 (89.5%) AVMs were located in eloquent areas. Using the Spetzler-Martin grading scale, 1 (2.6%) grade 1, 3 (7.9%) grade 2, 15 (39.5%) grade 3, 16 (42.1%) grade 4, and 1 (2.6%) grade 5 AVMs were identified. The drainage pattern could not be evaluated in two AVMs that were located in eloquent areas due to the lack of information from referral

Table 1 Patient and AVM characteristics

Variable	Value
Sex, <i>n</i> (%)	
Male	20 (52.6)
Female	18 (47.4)
Age (years), median (range)	36 (5-63)
Clinical onset, <i>n</i> (%)	
Hemorrhage	9 (23.7)
Headache	7 (18.4)
Epilepsy	10 (26.3)
Incidental findings	12 (31.6)
Hemorrhage before CK, <i>n</i> (%)	14 (36.8)
Treatment before CK, <i>n</i> (%)	
Resection	2 (5.3)
Embolization	20 (52.6)
Radiosurgery	0 (0)
Nidus volume (mL)	
range	0.6-91.1
median	12.0
mean ± SD	16.8 ± 17.9
Eloquent area, <i>n</i> (%)	34 (89.5)
Spetzler-Martin grading scale, <i>n</i> (%)	
I	1 (2.6)
II	3 (7.9)
III	15 (39.5)
IV	16 (42.1)
V	1 (2.6)
m-RBAS, median (range)	2.05 (0.33-10.21)
m-RBAS distribution, <i>n</i> (%)	
<1	3 (7.9)
1-1.5	8 (21.1)
1.5-2	8 (21.1)
>2	19 (50.0)
VRAS, <i>n</i> (%)	
1	1 (2.6)
2	9 (23.7)
3	16 (42.1)
4	12 (31.6)

AVM arteriovenous malformation, *CK* CyberKnife, *m-RBAS* modified radiosurgery-based AVM score, *VRAS* Virginia radiosurgery AVM score

Table 2 Treatment characteristics

Variable	Value
Marginal dose (Gy)	
Range	20.0-30.0
Median	25.0
Mean ± SD	24.5 ± 2.5
Maximum dose (Gy)	
Range	25.0-38.7
Median	30.7
Mean ± SD	30.7 ± 3.0
Minimum dose (Gy)	
Range	14.5-26.2
Median	21.0
Mean ± SD	20.8 ± 2.6
Conformity index, median (range)	1.3 (1.2-2.0)
Fraction, <i>n</i> (%)	
3	23 (60.5)
5	15 (39.5)

three- and five-fraction radiotherapies, respectively.

Adverse effect

MR images of regular follow-ups could be assessed in 28 patients for 3 years. The rest of the evaluation was performed only by physician referrals. Among the 28 patients, six (21.4%), one (3.6%), and one (3.6%) presented with mild perifocal edema, severe perifocal edema treated with steroids, and edema along the corticospinal tract, respectively. In addition, asymptomatic microbleeding with preceding perifocal edema occurred in two (7.1%) patients. No radionecrosis or cyst formation was observed.

Hemorrhage

Among the 33 patients with a follow-up duration longer than 3 years, two suffered from posttreatment hemorrhage within 3 years (2.0%/year). Both did not have a history of hemorrhage. For patients with large AVMs, one of 20 developed hemorrhage (2.0%/year). At 5 years posttreatment, six of 18 AVMs and five of 12 large AVMs caused hemorrhage (6.7%/year and 8.3%/year, respectively). Half of them had a history of hemorrhage. None of the hemorrhage cases occurred after complete obliteration. Statistical analysis did not find any risk factor for hemorrhage at 5 years.

Obliteration

At 3 years posttreatment, five (15.2%) patients showed complete obliteration, three (9.1%) suggested no change, and the remaining patients demonstrated partial obliteration. At 5 years posttreatment, three (16.7%) patients demonstrated complete obliteration. Among the three patients with unchanged AVMs at 3 years, one patient had a hem-

physicians. The median value of m-RBAS was 2.05 (range, 0.33-10.21) and that of VRAS was 3 (range, 1-4).

Table 2 summarizes the HSRT treatment methods with CK used in this study. The marginal, maximum, and minimum doses were 24.5 ± 2.5, 30.7 ± 3.0, and 21.0 ± 2.6 Gy, respectively, as mean values. The mean conformity index was 1.4 ± 0.2, which indicated good adaptations of target areas for AVM shapes. Twenty-three and 15 patients received

Table 3 Summary of HSRT for large AVMs and AVMs located eloquent areas in the literature

Authors & year	Modality	Cases	Pretreatment hemorrhage	Pretreatment embolization	Nidus volume	SM grade III, IV, and V	Treatment dose (Gy)	Obliteration rate	Posttreatment hemorrhage
Aoyama et al., 2001	LINAC	26	12 (46%)	1 (4%)	2.26 cm (mean)	14 (54%)	33.4 (mean)	53% at 3 years	3
Lindvall et al., 2003	LINAC	29	14 (48%)	13 (45%)	11.5 mL (mean)	11 (38%)	32.6 (median)	48% at 2 years	2
Veznedaroglu et al., 2004	LINAC	7	2 (29%)	6 (86%)	23.8 mL (mean)	7 (100%)	42	83% at 5 years	NA
		23	10 (43%)	13 (57%)	14.5 mL (mean)	22 (96%)	30	22% at 5 years	NA
Zabel-du et al., 2006	LINAC	15	8 (53%)	4 (27%)	27 mL (median)	15 (100%)	26 (median)	17% at 3 years	3
Xiao et al., 2010	LINAC	20	11 (55%)	10 (50%)	46.8 mL (median)	20 (100%)	30 (median)	0%	1
Lindvall et al., 2015	LINAC	24	9 (38%)	16 (67%)	18.5 mL (mean)	NA	32.9 (mean)	70% at 3 years	3
Present study	CK	38	14 (37%)	20 (53%)	16.8 mL (mean)	32 (84%)	25 (median)	15% at 3 years	2

The numbers above indicate the numbers of the patients otherwise indicated.

AVM arteriovenous malformation, CK CyberKnife, NA not available, SM grade Spetzler-Martin grading scale

orrhage, one patient did not exhibit any changes, and the last one was lost to follow-up at 5 years.

A significant negative relationship between the eloquent area and obliteration at 5 years (OR, 0.036; 95% CI, 0.002-0.828; p value = 0.038) was noted. High scores with m-RBAS or VRAS were also related to obliteration failure (OR, 0.036; 95% CI, 0.002-0.828; p value = 0.038, in both).

Discussion

This study evaluated HSRT with CK treatment outcomes for challenging AVM cases. Current literature emphasizes various methods (e.g., surgical resection, endovascular treatment, radiosurgery, or any combination of them), but their outcomes have not reached a satisfactory level. When it comes to radiosurgical treatment, stereotactic radiosurgery (SRS) was initially confronted with high comorbidity risks, including surrounding brain edema.¹¹⁻¹⁴ Consequently, dose-¹⁵ and volume-staged SRS¹⁶⁻¹⁹ commenced despite these treatment strategies suffering from distinct disadvantages (i.e., each radiosurgery required sufficient time intervals and every radiosurgery after intervals required new radiological investigations for the development of efficient treatment plans). HSRT is a promising method because it can reduce radiation toxicity on surrounding structures with short treatment duration while delivering sufficient radiation doses to the target areas.²⁰⁻²⁶

Hemorrhage

Literature reports that the annual hemorrhage rate of AVMs and that of recently ruptured AVMs are 2%-4%/year and 6%-15%/year, respectively.²⁷⁻²⁹ In this study, the hemorrhage rate was calculated as 2.0%/year at 3 years. Compared to the natural history of AVMs, this result demonstrates a relatively low hemorrhage risk, especially when considering that 28.9% of the AVMs in the current study had already ruptured within 1 year before CK treatment.

The findings of the current study exhibit a similar efficiency with the treatment outcomes of HSRT with LINAC (Table 3).^{20-24,26} However, the hemorrhage rate of the current study at 5 years was 6.7%/year, which is higher than expected. This may be due to the AVM characteristics in the current study under high hemorrhage risks (e.g., history of hemorrhage and large-sized AVMs). However, the statistical analysis of the current study does not suggest that these characteristics were indeed risk factors for hemorrhage—perhaps due to the small number of patients included. The results of the current study may indicate that additional treatment is necessary for AVMs that are not obliterated at 3 years after HSRT with CK.

Obliteration

Complete obliteration was achieved in 15.2% and 16.7% of the patients in the current study at 3 and 5 years, respectively. Current literature outlines that the obliteration rates can vary from 18% at 5 years to 65% at 3 years after gamma knife^{11,12,14-17} and vary from 0% to 83% at 5 years after HSRT with LINAC (Table 3).^{20-24,26} The results of the current study are not excellent, but they are certainly satisfactory. The relatively low obliteration rates may be related to the high proportion of high-grade AVMs with the Spetzler-Martin grading scale because they are difficult to be treated even with radiosurgery. An additional possibility may involve the high proportion of patients with paradoxical preceding endovascular embolization. Preceding embolization may decrease complete obliteration rates because embolization materials cause artifacts to undermine accurate treatment planning, and recanalization may occur.³⁰⁻³³ Recent studies have suggested that postradiosurgical embolization is more favorable than preradiosurgical embolization.^{34,35} The low radiation dose may also have affected the obliteration rates. In the future, dose escalation and increase of the maximal dose while carefully evaluating potential complications will be considered.

Statistical analysis revealed that anatomical localization in eloquent areas was a risk factor for obliteration failure. For AVMs in noneloquent areas, adequate irradiation to the marginal region was feasible, and it may contribute to obliteration. Minimum dose,^{36,37} marginal dose,^{38,39} and nidus volume^{37,39} were reported as factors related to obliteration, but no significant difference was suggested in this study. This may be simply due to the relatively small number of patients included. In contrast, m-RBAS^{8,40} and VRAS^{9,32} demonstrated a distinct relationship with obliteration, although these scales were originally proposed to predict treatment outcomes with gamma knife, and, thus, may also be feasible for HSRT with CK.

The majority of the AVMs treated by HSRT with CK in this study resulted in partial obliteration. Patients with partially obliterated AVMs may have lower hemorrhage risks than the natural course based on a report by Maruyama *et al.* that showed that radiosurgical treatment could reduce hemorrhage risk in the latency period.⁴¹ Moreover, in terms of partially obliterated AVMs, subsequent complete obliteration with additional treatment can be achieved more safely.^{24,42} Therefore, the majority of the patients in the current study with partial obliteration were considered to reap the benefits of using HSRT with CK. However, additional treatment procedures should be considered after 3 years from treatment to achieve the best result because the obliteration rate at 5 years did not significantly improve. In that case, volume-staged SRS is considered to be more favorable than dose-staged SRS regarding obliteration rates.⁴³⁻⁴⁵ Marginal doses ranging from 15 to 20 Gy in two to four stages should be delivered to achieve obliteration,^{44,45} although caution should be focused on adverse effects.

Limitations

The limitations of the findings of the current study stem from the retrospective nature of this study and the relatively small number of patients examined in a single institution. Complications were not adequately evaluated because of insufficient information on patients followed up by referral physicians. Despite these limitations, the findings of the current study are believed to contribute to treatment options for high-risk AVMs because reports on such AVMs are very limited in the current literature.

Conclusions

This report summarized the treatment strategies of HSRT with CK for AVMs performed in the institution of the current study. The treatment outcomes of HSRT with CK for large AVMs and AVMs located in eloquent areas were satisfactory when compared to the literature results of HSRT with LINAC. More specifically, the hemorrhage rate was 2.0%/year at 3 years and increased to 6.7%/year at 5 years, whereas the obliteration rate was 15.2% and

16.7% at 3 and at 5 years, respectively. Additional treatment should be considered when obliteration is not achieved within 3 years after HSRT with CK.

Abbreviations

CyberKnife (CK); hypofractionated stereotactic radiotherapy (HSRT); arteriovenous malformation (AVM); computed tomography (CT); magnetic resonance (MR); the modified radiosurgery-based AVM score (m-RBAS); the median Virginia Radiosurgery AVM Score (VRAS); stereotactic radiosurgery (SRS).

Conflicts of Interest Disclosure

All authors have no conflict of interest associated with this manuscript.

References

- 1) Martinage G, Geffrelet J, Stefan D, et al.: Efficacy and tolerance of post-operative hypo-fractionated stereotactic radiotherapy in a large series of patients with brain metastases. *Front Oncol* 9: 184, 2019
- 2) Mengue L, Bertaut A, Ngo Mbus L, et al.: Brain metastases treated with hypofractionated stereotactic radiotherapy: 8 years experience after Cyberknife installation. *Radiat Oncol* 15: 82, 2020
- 3) Oh HJ, Cho YH, Kim JH, et al.: Hypofractionated stereotactic radiosurgery for large-sized skull base meningiomas. *J Neurooncol* 149: 87-93, 2020
- 4) Huang L, Sun L, Wang W, et al.: Therapeutic effect of hypofractionated stereotactic radiotherapy using cyberknife for high volume cavernous sinus cavernous hemangiomas. *Technol Cancer Res Treat* 18: 1533033819876981, 2019
- 5) Colombo F, Cavedon C, Casentini L, Francescon P, Causin F, Pinna V: Early results of CyberKnife radiosurgery for arteriovenous malformations. *J Neurosurg* 111: 807-819, 2009
- 6) Feutren T, Huertas A, Salleron J, et al.: Modern robot-assisted radiosurgery of cerebral angiomas-own experiences, system comparisons, and comprehensive literature overview. *Neurosurg Rev* 41: 787-797, 2018
- 7) Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. *J Neurol Surg* 65: 476-483, 1986
- 8) Pollock BE, Flickinger JC: Modification of the radiosurgery-based arteriovenous malformation grading system. *Neurosurgery* 63: 239-243, 2008
- 9) Starke RM, Yen CP, Ding D, Sheehan JP: A practical grading scale for predicting outcome after radiosurgery for arteriovenous malformations: analysis of 1012 treated patients. *J Neurosurg* 119: 981-987, 2013
- 10) Laakso A, Dashti R, Juvela S, Isarakul P, Niemelä M, Hernesniemi J: Risk of hemorrhage in patients with untreated Spetzler-Martin grade IV and V arteriovenous malformations: a long-term follow-up study in 63 patients. *Neurosurgery* 68: 372-377, 2011
- 11) Miyawaki L, Dowd C, Wara W, et al.: Five year results of LINAC radiosurgery for arteriovenous malformations: outcome for large AVMS. *Int J Radiat Oncol Biol Phys* 44: 1089-1106, 1999
- 12) Pan DH, Guo WY, Chung WY, Shiau CY, Chang YC, Wang LW: Gamma knife radiosurgery as a single treatment modality for

- large cerebral arteriovenous malformations. *J Neurosurg* 93: 113-119, 2000
- 13) Yang SY, Kim DG, Chung HT, Paek SH, Park JH, Han DH: Radiosurgery for large cerebral arteriovenous malformations. *Acta Neurochir (Wien)* 151: 113-124, 2009
 - 14) Hanakita S, Koga T, Shin M, Igaki H, Saito N: Application of single-stage stereotactic radiosurgery for cerebral arteriovenous malformations >10 cm³. *Stroke* 45: 3543-3548, 2014
 - 15) Yamamoto M, Akabane A, Matsumaru Y, Higuchi Y, Kasuya H, Urakawa Y: Long-term follow-up results of intentional 2-stage gamma knife surgery with an interval of at least 3 years for arteriovenous malformations larger than 10 cm³. *J Neurosurg* 117: 126-134, 2012
 - 16) Kano H, Kondziolka D, Flickinger JC, et al.: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. *J Neurosurg* 116: 54-65, 2012
 - 17) Huang PP, Rush SC, Donahue B, et al.: Long-term outcomes after staged-volume stereotactic radiosurgery for large arteriovenous malformations. *Neurosurgery* 71: 632-643, 2012
 - 18) Ding C, Solberg TD, Hrycushko B, Medin P, Whitworth L, Timmerman RD: Multi-staged robotic stereotactic radiosurgery for large cerebral arteriovenous malformations. *Radiother Oncol* 109: 452-456, 2013
 - 19) Ding C, Hrycushko B, Whitworth L, et al.: Multistage stereotactic radiosurgery for large cerebral arteriovenous malformations using the gamma knife platform. *Med Phys* 44: 5010-5019, 2017
 - 20) Aoyama H, Shirato H, Nishioka T, et al.: Treatment outcome of single or hypofractionated single-isocentric stereotactic irradiation (STI) using a linear accelerator for intracranial arteriovenous malformation. *Radiother Oncol* 59: 323-328, 2001
 - 21) Lindvall P, Bergström P, Löfroth PO, et al.: Hypofractionated conformal stereotactic radiotherapy for arteriovenous malformations. *Neurosurgery* 53: 1036-1043, 2003
 - 22) Veznedaroglu E, Andrews DW, Benitez RP, et al.: Fractionated stereotactic radiotherapy for the treatment of large arteriovenous malformations with or without previous partial embolization. *Neurosurgery* 55: 519-530, 2004
 - 23) Zabel-du Bois A, Milker-Zabel S, Huber P, Schlegel W, Debus J: Linac-based radiosurgery or hypofractionated stereotactic radiotherapy in the treatment of large cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys* 64: 1049-1054, 2006
 - 24) Xiao F, Gorgulho AA, Lin CS, et al.: Treatment of giant cerebral arteriovenous malformation: hypofractionated stereotactic radiation as the first stage. *Neurosurgery* 67: 1253-1259, 2010
 - 25) Wang HC, Chang RJ, Xiao F: Hypofractionated stereotactic radiotherapy for large arteriovenous malformations. *Surg Neurol Int* 3: S105-S110, 2012
 - 26) Lindvall P, Grayson D, Bergström P, Bergenheim AT: Hypofractionated stereotactic radiotherapy in medium-sized to large arteriovenous malformations. *J Clin Neurosci* 22: 955-958, 2015
 - 27) Gross BA, Du R: Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg* 118: 437-443, 2013
 - 28) Abecassis IJ, Xu DS, Batjer HH, Bendok BR: Natural history of brain arteriovenous malformations: a systematic review. *Neurosurg Focus* 37: E7, 2014
 - 29) Rubin BA, Brunswick A, Riina H, Kondziolka D: Advances in radiosurgery for arteriovenous malformations of the brain. *Neurosurgery* 74: S50-S59, 2014
 - 30) Oermann EK, Murthy N, Chen V, et al.: A multicenter retrospective study of frameless robotic radiosurgery for intracranial arteriovenous malformation. *Front Oncol* 4: 298, 2014
 - 31) Ding D, Starke RM, Kano H, et al.: Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations: an international multicenter study. *J Neurosurg* 126: 859-871, 2017
 - 32) Starke RM, Kano H, Ding D, et al.: Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. *J Neurosurg* 126: 36-44, 2017
 - 33) Patibandla MR, Ding D, Kano H, et al.: Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study. *J Neurosurg* 129: 498-507, 2018
 - 34) Kim MJ, Park SH, Park KY, et al.: Gamma knife radiosurgery followed by flow-reductive embolization for ruptured arteriovenous malformation. *J Clin Med* 9, 2020
 - 35) Jiang X, Zhao Z, Zhang Y, Wang Y, Lai L: Preradiosurgery embolization in reducing the postoperative hemorrhage rate for patients with cerebral arteriovenous malformations: a systematic review and meta-analysis. *Neurosurg Rev* 44: 3197-3207, 2021
 - 36) Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD: A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. *Int J Radiat Oncol Biol Phys* 36: 873-879, 1996
 - 37) Karlsson B, Lindquist C, Steiner L: Prediction of obliteration after gamma knife surgery for cerebral arteriovenous malformations. *Neurosurgery* 40: 425-430; discussion 30-31, 1997
 - 38) Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD: An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. *Radiother Oncol* 63: 347-354, 2002
 - 39) Shin M, Maruyama K, Kurita H, et al.: Analysis of nidus obliteration rates after gamma knife surgery for arteriovenous malformations based on long-term follow-up data: the University of Tokyo experience. *J Neurosurg* 101: 18-24, 2004
 - 40) Wegner RE, Oysul K, Pollock BE, et al.: A modified radiosurgery-based arteriovenous malformation grading scale and its correlation with outcomes. *Int J Radiat Oncol Biol Phys* 79: 1147-1150, 2011
 - 41) Maruyama K, Kawahara N, Shin M, et al.: The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. *N Engl J Med* 352: 146-153, 2005
 - 42) Sanchez-Mejia RO, McDermott MW, Tan J, Kim H, Young WL, Lawton MT: Radiosurgery facilitates resection of brain arteriovenous malformations and reduces surgical morbidity. *Neurosurgery* 64: 231-238, 2009
 - 43) Moosa S, Chen CJ, Ding D, et al.: Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. *Neurosurg Focus* 37: E18, 2014
 - 44) Ilyas A, Chen CJ, Ding D, et al.: Volume-staged versus dose-staged stereotactic radiosurgery outcomes for large brain arteriovenous malformations: a systematic review. *J Neurosurg* 128: 154-164, 2018
 - 45) Shuto T, Matsunaga S: Volume-staged radiosurgery for large arteriovenous malformation: retrospective analysis of 19 cases. *Cureus* 13: e16901, 2021

Corresponding author: Ryoko Niwa, M.D.

CyberKnife Center, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935, Japan.

e-mail: NIWAR-NSU@h.u-tokyo.ac.jp