DOI: 10.5137/1019-5149.JTN.21690-17.1
Received: 10.10.2017 / Accepted: 17.12.2017
Published Online: 25.01.2018

Turk Neurosurg, 2018

Original Investigation

Gamma Knife Radiosurgery for Hemorrhagic Brainstem Cavernomas

Aysegul UCUNCU KEFELI[1], Meric SENGOZ[2], Selcuk PEKER[3]

[1]Kocaeli State Hospital, Radiation Oncology Clinic, Izmit, Turkey
[2]Acibadem University, School of Medicine, Department of Radiation Oncology, Istanbul, Turkey
[3]Koc University Hospital, Department of Neurosurgery, Istanbul, Turkey

ABSTRACT

AIM: The effectiveness and safety of gamma knife radiosurgery (GKRS) for hemorrhagic brainstem cavernous malformations (BSCM) is still an unresolved issue. The purpose of this study was to assess treatment results of GKRS for hemorrhagic BSCMs.

MATERIAL and METHODS: A retrospective review of patients with hemorrhagic BSCMs, who were treated at the Acıbadem Kozyatağı Hospital GKRS unit from May 2007 to October 2015 was performed.

RESULTS: In total, 82 patients were identified. All patients had experienced at least one hemorrhagic event (range 1-3) and all of them presented with radiological evidence of hemorrhage. The median target volume was 0.3 ml, and the median marginal radiation dose was 12 Gy. The mean durations before and after surgery were 25.5 (range 1-204) months and 50.3 (range 13-113) months respectively. Pre-treatment hemorrhage rates were calculated from the date of first hemorrhage to the date of radiosurgery. There were 97 bleeds over 174.4 patient-years during the observation period, with an annual hemorrhage rate of 55.7%. If the first bleed is excluded, the annual hemorrhage rate was 8.6%. Only three patients demonstrated re-bleeding, which occurred at 3, 12 and 79 months after radiosurgery. Over a total follow up time of 344 patient-years the annual re-bleeding rate was therefore 0.87%, indicating that the risk of BSCM hemorrhage was significantly decreased by radiosurgery.

CONCLUSION: GKRS was a safe and effective treatment for symptomatic low volume BSCMs when a low marginal dose is used. A randomized controlled trial is needed that compares GKRS to observation if we want to establish the true efficacy of this treatment.

KEYWORDS: Brainstem, Cavernoma, Gamma–knife, Radiosurgery

INTRODUCTION

Cavernous malformations (CMs) are benign vascular abnormalities of the brain that are composed of thin-walled dilated capillaries surrounded by hemosiderin deposits. Brainstem CMs (BSCMs), which are subsets of CMs are rare lesions, and account for 20% of all CMs (7). Treatment of these lesions is quite challenging because their natural history is unpredictable. Some are only detected incidentally on magnetic resonance imaging (MRI). Some may remain clinically silent for many years. Others are only diagnosed when they become aggressive and have recurrent hemorrhages. BSCMs causing hemorrhages can lead to clinically important symptoms such as cranial nerve deficits, motor and sensory weakness and ataxia. Annual hemorrhage rates range from less than 1% to more than 5% (5).

Despite the fact that the surgical series reported good results for patients treated by experienced surgeons, surgery still remains debatable for BSCMs in deep seated and eloquent locations for many neurosurgeons (1-3,5,7,13,14,25,26,30,39). For such patients, gamma-knife radiosurgery (GKRS), which has reduced hemorrhage rates, is an option (23). Initially, it was thought that treating BSCMs with GKRS could severely worsen neurological status (19). However, this is no longer true with technological advances in imaging, now that microsurgery

qr code

Corresponding author: Selcuk PEKER
E-mail: peker@selcukpeker.com

is becoming the first-line treatment option for most BSCMs (4). Recent studies show reduced re-hemorrhage rates thus making the role of radiosurgery still important for patients at increased surgical risk (6,15,16,18,20,21,28,29,32).

In this study, our aim was to analyze the outcomes of patients with BSCMs who were treated with GKRS at our institution and to report the re-bleeding rates and radiation-related side effects.

MATERIAL and METHODS

Patient Details

We retrospectively analyzed the treatment details and clinical outcomes of 82 patients with BSCM who underwent GKRS in our unit between 2007 and 2015. All patients had an MRI before radiosurgery and hemorrhage was defined as imaging confirmation of acute blood accumulation on MRI associated with new neurological symptoms.

Treatment Details

Until August 2012, radiosurgical treatment was performed using a Leksell Gamma Knife 4C with a 201-source cobalt-60 gamma unit. After August 2012, it replaced with a Gamma Knife Perfexion (Elekta AB, Sweden). All patients had undergone MRI after applying frames; non-contrast T1- weighted and T2-weighted images were taken at slice thickness of 1.5 mm.

The target was defined as the site of mixed signal change surrounded by an outer hemosiderin ring. Hematoma eccentric from the malformations was excluded. Radiotherapy dose plans were created with single or multiple isocenters (range 1-12), at the 50% isodose line in 62.2% of cases and a highly conformal dose distribution was achieved. The details of dose planning are summarized in Table I. After radiosurgery, all patients received 40 mg intravenous methylprednisolone and were discharged from hospital within a few hours.

Follow-up and Statistical Analyses

The mean clinical follow-up time was 50 months (range 13-113 months), so the minimum follow-up was 13 months. Imaging studies were initially requested 3 months after radiosurgery and yearly thereafter. Clinical follow-up data were obtained from patients (or their referring physicians) either by telephone conversation, outpatient clinic visit, or both. Patients were asked if they were “the same, better, or worse” compared to their pre-treatment status.

Pre-treatment hemorrhage rates were calculated from the date of first hemorrhage to the date of radiosurgery. Hemorrhage was defined as the presence of new signs of hemorrhage on MRI with associated neurological symptoms and radiation-induced adverse effects were defined as a signal change around the BSCM, but without hemorrhage. The annual hemorrhage rate was then calculated by dividing the total number of hemorrhages in all patients by the total number of patient-years for which they were observed. Statistical analyses were done by the Wilcoxon signed-rank test to compare hemorrhage rates before and after stereotactic radiosurgery. All analyses were performed with PASW Statistics for Windows-Version 18.0 (SPSS, Inc, Chicago, IL, USA) and p values less than 0.05 were accepted as statistically significant.

RESULTS

The median Karnofsky performance score was 90 (range 70-100). We included 47 males (57%) and 35 females (43%) with a median age of 41.5 years (range 6-69 years). Although only 34 patients (41.4%) presented with neurological deficits, all had previously experienced at least one hemorrhagic event (range 1-3) and all presented with radiological evidence of hemorrhage. Only 8 patients underwent surgery before GKRS. All identified cavernomas were in the brainstem, with the specific locations shown in Table II. Six patients had additional intracerebral cavernomas that were also treated by GKRS. In the brainstems 68.2% of the lesions were presented as intraparenchymal, whereas only 30.4% were presented on pial surface. A summary of the patient characteristics is shown in Table II.

Table I: Summary of Radiosurgery Dose Planning for the BSCMs

Parameter	Mean	Median	Range
Lesion volume (cm^3)	0.53	0.3	0.1-3.6
No. of isocenters	2.91	2	1-12
Marginal dose (Gy)	11.79	12	10-13
Maximum dose (Gy)	23.63	24	17-29

Table II: Characteristics of 81 Patients with BSCMs

Patient Characteristics	Number of Patients
Age (median) (years)	41.5
Sex, (%)	
Male	56.1
Female	43.9
Dominant presenting neurological symptoms (%)	
Headache	65.9
Cranial nerve deficit	26.8
Diplopia	19.5
Hemiparesis	15.9
Dizziness	17.1
Seizure	1.2
No. of bleeding episodes	
1	82.7%
2	15.9%
3	1.2%
Lesion location in brainstem	
Pons	47.5%
Medulla Oblongata	33%
Mesencephalon	19.5%

Re-hemorrhage Rates

The mean observation period before radiosurgery was 25 months (range 1-204 months) and there were 97 bleeds in the 174.4 patient-years of observation. This yielded an annual hemorrhage rate of 55.7% in the BSCM observed at our institution. If we excluded the first bleed, the annual hemorrhage rate was 8.6%.

The mean follow-up period after radiosurgery was 50 months (range 13-113 months). During this time, only three patients re-bled, which occurred after 3, 12 and 79 months. Over the total follow-up time of 344-patient-years the annual re-bleeding rate was only 0.87% (i.e., 3 episodes in 344- patient-years) indicating that the risk of BSCM hemorrhage was significantly decreased by radiosurgery ($p<0.0001$).

Clinical Outcome

During follow-up, 49 patients (60%) showed improvement, 30 (36%) stabilized, and 3 (4%) experienced progression of neurological symptoms. MRI showed reduced lesion size in 49 patients (60%), and no change in the other cases. Although 3 patients experienced progression of neurological symptoms, we did not see adverse radiation effects (defined as perilesional edema on T2 -weighted MRI) in any of the patients.

DISCUSSION

Natural History of CMs

Radiosurgery was established in the 1980s as an effective management strategy for arteriovenous malformations (AVMs) (12). With the favorable results obtained with these malformations it was hypothesized that the vessels of angiographically occult vascular malformations, such as CMs, could respond to GKRS similarly (24). However, the actual response depends more on the unique biology and natural history of these lesions, which is still poorly understood. Indeed, CMs typically exhibit an unpredictable biologic behavior. They have a different structure from AVMs, being devoid of muscular and elastic tissue, and lined by endothelial cells without tight junctions. In a recent study, it was shown that the structural and cellular differences of CMs and AVMs affected the radiosurgery treatment responses (38). Because the exact incidence of these lesions remains uncertain and the reported hemorrhage rates and risk factors for hemorrhage vary significantly, interpreting findings from studies on the natural history of CMs is difficult (10,11).

One of the key determinants of lesion behavior and symptomatology is location. Some authors have stated that CMs in eloquent areas, such as the speech cortex, motor cortex, or brainstem, may hemorrhage with higher frequency (27,35). In one study, indirect comparisons between a cohort of patients with BSCMs and CMs in other brain regions were studied and the risk of recurrent intracranial hemorrhage in the BSCM cohort was found to be 21.0% to 60.2% higher (37).

Hemorrhage Rate

In a recent systematic review by Gross et al., annual bleeding rates for brainstem CMs ranged from 2.3% to 4.1% per patient-year in observational studies of the natural history and ranged from 2.7% to 6.8% per patient-year in surgical series before intervention (9).

Porte et al. identified CM location as the primary factor affecting hemorrhage risk, and noted a 4.1% per patient-year annual hemorrhage rate for deep lesions (deep hemispheric or brainstem) (35).

In patients with brainstem CMs, repeated hemorrhage at the lesion site leads to permanent neurologic deficits. It was shown that greater number of cranial nerve deficits (81.2%) occur if

Table III: Summary of Published Studies Results of RSs for BSCMs

Authors (year)	No. of patients	Mean follow up time (mo/yrs)	Mean marginal dose (Gy)	Mean maximal dose (Gy)	Mean target volume (ml)	Annual Hemorrhage Rate (%)			
						Before SRS	After SRS	ARE (%)	Modality
Liscák et al., 2000	26	24	*14.7	0.8	*0.8	4	6.4	-	GK
Monaco et al., 2010	68	5.2 yrs	15.84	29.52	1.19	32.38	α8.22/ϒ1.37	11.8	GK
Fuetsch et al., 2012	14	*7.1 yrs	*13.9	*25.4	*1.6	-	α12.5/ϒ4.8	25	LINAC
Lee et al., 2012	49	40.6 mo	11	-	3.2	31.3	α4.29/ϒ3.64	4.1	GK
Park et al., 2013	21	38.9 mo	*13	*20-34	1.27	39.5	α8.2/ϒ0	5	GK
Kim et al., 2014	39	4.1 yrs	*13	-	1.09	33.6	α8.1/ϒ2.4	5.1	GK
Lee et al., 2014	49	64 mo	13.1	-	0.74	38.36	α8.3/ϒ1.81	0	GK
Frischer et al., 2014	38	5.2 yrs	*12	*24	-	47.6	α2.6/ϒ0.6	-	GK
Present study	81	50 mo	11.79	23.63	0.53	55.7	0.87	0	GK

GK: *gamma knife,* ***RS:*** *radiosurgery,* ***AHR:*** *annual hemorrhage rate,* ***ARE:*** *adverse radiation effect,* ***LINAC:*** *Linear accelerator,* ***SRS:*** *Stereotactic radiosurgery,* ***mo:*** *Month,* ***yrs:*** *Years.* *******median values, α within the first 2 years after radiosurgery, ϒ 2 years after radiosurgery.*

patients had multiple hemorrhages (81.2%) when compared with patients who had experienced a single hemorrhagic event (65%) (27).

Surgery Outcomes

There is no established consensus on the optimal management strategy of BSCMs due to their unpredictable behaviours. However, it is widely agreed that surgical resection is the most efficacious treatment for these lesions. Especially since the advent of (1.5T or 3.0T) MRI, intraoperative electrophysiological monitoring and advanced skull-base techniques have enabled safer resection of even high-risk BSCMs. The literature contains many reports on surgical outcomes among patients with BSCMs, but significant morbidity rates have led to disagreement about the indications for surgery in these cases (1-3,5,14,27,30,36). In inappropriately selected patients (with deep-seated surgically inaccessible lesions), intervention can lead to further morbidity. The goal of surgery for any patient with a BSCM must be radical excision, because partial excision will probably increase the risk of recurrence (8). Ferroli et al., in 2005, investigated 52 patients with BSCM who were treated by microsurgical resection and revealed re-bleeding and mortality rates of 34.7% and 1.9%, respectively (5). In addition, 19% of the patients who were treated with microsurgical resection showed clinical deterioration from before to after surgery (e.g., permanent neurological morbidity) and worse outcome in patients with deep-seated lesions compared to superficial ones.

In a systematic review of 78 studies with 745 cases of BSCM, complete resection was documented in 684 cases (92%)(9). At long term follow up, although the clinical status of the 85% patients stayed either the same or improved, approximately 14% deteriorated and 1.9% died from surgery-related complications. Recently, another 710 patients with BSCMs were added to this meta-analysis (68 surgical series), of which 92% were completely resected (11). After re-calculation including these additional cases, 45% of the 944 patients exhibited neurological morbidity in the early-postoperative period, which was considered relatively high compared to natural history studies. Also, 16% of the patients (n=151) showed clinical deterioration after surgical resection of the CM.

Decisions about whether BSCM should be treated surgically must therefore be made based on the lesion's location and its accessibility. Concerning the indications for surgery, Abla et al. stated that BSCMs should be excised if they are symptomatic, cause a mass effect, or are located on the pial surface (1).

Role of Radiosurgery

Table III summarizes the studies to date, including ours, that have documented the treatment outcomes for patients with BSCMs treated radiosurgically. In our study, we showed that the annual hemorrhage rate before GKRS (8.7%) declined significantly within the first two years after treatment (0.87%), with no radiation-related adverse events. We think that the low marginal dose (mean 11.79) and low treatment volume (mean 0.53) were responsible for these improvements seen with our data. Consistent with this, Kim et al., recently showed similar results, suggesting that an adequate marginal dose as low as 11 Gy may be needed to avoid serious adverse events (18).

Considering the significant surgical morbidity associated with brainstem CMs, especially for high-risk lesions, stereotactic radiosurgery certainly appears valid. In 1995, Kondziolka et al. reported their experience of stereotactic radiosurgery for 47 patients with CMs, 27 of whom had brainstem lesions (19). They observed an annual hemorrhage rate of 8.8% in the first 2 years after stereotactic radiosurgery reducing to 1.1% thereafter (4% overall morbidity). Although this showed the effectiveness of radiosurgery for the first time, the data was considered inadequate, so they did not recommend radiosurgery for minimally symptomatic lesions or for patients who may be better managed with open surgical resection.

In 1998, Karlsson et al. reported 22 cases in which CMs were treated with radiosurgery (6 were located in the brainstem) (17). The authors observed post-treatment hemorrhage in 9 patients over 155 risk years, yielding an 8% annual post-treatment incidence of hemorrhage. They also documented 27% radiation-related complications, which was unacceptably high. This was because some treatments were performed with computed tomography guidance and treatment doses were high compared to today's standards (range, 18-33 Gy).

Pollack et al. also investigated the outcomes of stereotactic radiosurgery in 17 patients with high-surgical-risk CMs and they also observed a high rate of radiation-related morbidity (41%) (34). Like Karlsson et al., they had also used a high marginal dose of 18 Gy.

Hasegawa et al. examined the outcomes of radiosurgery in a cohort comparable to ours in 2002 (13). Among 82 symptomatic patients with CMs (45 in the brainstem) and imaging-confirmed hemorrhages, who were considered high risk for surgical resection, the annual hemorrhage rate was 12.3% for the first 2 years dropping to 0.76% in years 3 to 12. After radiosurgery, 11 patients (13.4%) in their study had new neurological symptoms without hemorrhage. However, these were minor in 6 cases and temporary in 5. The authors found that all patients with radiation-related complications had received higher marginal doses than those without complications (17.45 vs. 16.06 Gy, $p<0.03$), had doses delivered at a lower number of isocenters (1.64 vs 3.06, $p<0.03$), and tended to have more previous hemorrhages (3.18 vs 2.32, $p<0.001$). They also observed more radiosurgery-related complications in their patients with BSCMs or lesions in the diencephalon than in those with lesions at other sites.

Supporting this in 2005, Liu et al. reported on 125 patients with CMs, of which 49 of them were in the brainstem (22). After treatment by GKRS, the annual hemorrhage rate was 10.3% for the first 2 years, declining to 3.3% thereafter. Consistent with the findings of higher complication rates with higher doses, Liu et al, reported fewer radiation-related complications (3 patients; 2.4%), when using a lower mean marginal dose (12.1 Gy) compared with higher doses.

Treatment in Cases of Single Bleed Brainstem CMs

In our study, 82.7% of patients were treated after only a single

bleed. The benefits of treating patients with BSCMs after a single hemorrhage event have not been established, but there are some encouraging results in the literature. Nagy et al. documented 113 patients treated with GKRS (79 of were in the brainstem) and stratified the CMs into two groups; low-risk CMs were those with no more than one symptomatic bleed before GKRS, and high-risk CMs were those with multiple symptomatic hemorrhages before treatment (29). In the low-risk group (77 CMs), the observed hemorrhage rate in the first two years after radiosurgery was 5.1%, falling to 1.3% thereafter. Permanent adverse radiation effects occurred in 7.3%, but were minor in both the high- and low-risk groups. Similarly, Park et al. reported radiosurgical treatment results for 31 patients with BSCMs, 10 of whom had been treated after their first hemorrhage (31). The median marginal dose was 13 Gy in that study, and the authors observed no hemorrhage during the first two years after radiosurgery; moreover, only one patient developed permanent paresthesia. In addition, Lee et al. recently published a study of the effectiveness of GKRS for 49 patients with BSCMs, with 31 undergoing GKRS after a single bleed and 18 undergoing GKRS after two or more bleeds (21). There was no statistically significant difference between the groups and GKRS was considered an effective treatment.

Adverse Radiation Effects

A major concern of radiosurgery for BSCMs is the significantly higher rate of radiation-related side effects compared with radiosurgery for AVMs (17,34). In the studies of radiosurgery for CMs the reported complication rates vary, with permanent radiation-related complications ranging from 1.5 to 41% (19,22,24,28,29,32). We think that the most important reason for the large inter-study variation is the difference in marginal doses prescribed. In 2009, Pham et al. reviewed the literature for angiographically occult vascular malformations, of which most were CMs (96%), and reported on the rates of postoperative hemorrhage, seizure control and radiation-induced morbidity (33). They found that authors using mean radiation doses of 15-16.2 Gy at the tumor margin reported permanent radiation-induced morbidity rates of 0-9.1%, while researchers delivering mean radiation doses to the tumor margin of ≥16.5 Gy and higher reported total morbidity rates of more than 17%.

In our study, none of the 82 patients with BSCMs treated by GKRS experienced adverse radiation effects. As stated, this may be because of the low radiation doses used (median 12 Gy).

Limitations

The most important limitation of our study is that it lacked a control group of patients who were managed conservatively. Unfortunately, there were also no definitive criteria for patient selection, and because the choice depended on discussions about the treatment between the referring physicians and patients, we cannot deny that selection bias may have occurred. Despite this, however, most of the lesions (68.2%) were deep-seated and intraparenchymal tumors with high surgical risk.

Finally, we had to depend on clinical outcomes to evaluate treatment efficacy because the radiobiological effect of radiosurgery on CMs is unpredictable and the relevance assessed by currently available neuroimaging modalities is not adequate for now.

CONCLUSION

It remains true that decisions about the optimal management of BSCMs should be made by experienced neurosurgeons. We add to the knowledge base supporting such decisions by showing, that although microsurgical resection remains the treatment of choice for these lesions, GKRS may be a better option for certain patients. These include patients who have had at least one lesion-related hemorrhage and patients who have lesions that put them at increased surgical risk for neurological deficits. Together with the literature to date, our results also indicate that low radiation doses are safe and effective in GKRS for BSCMs. However, prospective randomized controlled trials are now needed that compare GKRS to simple observation. This will help to establish optimal radiation dosages, and clarify the associated side effects and should help validate the efficacy of GKRS as a method for reducing intracranial hemorrhage rates.

REFERENCES

1. Abla AA, Lekovic GP, Garrett M, Wilson DA, Nakaji P, Bristol R, Spetzler RF: Cavernous malformations of the brainstem presenting in childhood: Surgical experience in 40 patients. Neurosurgery 67: 1589-1598, 2010
2. Abla AA, Turner JD, Mitha AP, Lekovic G, Spetzler RF: Surgical approaches to brainstem cavernous malformations. Neurosurg Focus 29: E8, 2010
3. Chen L, Zhao Y, Zhou L, Zhu W, Pan Z, Mao Y: Surgical strategies in treating brainstem cavernous malformations. Neurosurgery 68: 609-620, 2011
4. Duckworth EA: Modern management of brainstem cavernous malformations. Neurol Clin 28: 887-898, 2010
5. Ferroli P, Sinisi M, Franzini A, Giombini S, Solero CL, Broggi G: Brainstem cavernomas: Long-term results of microsurgical resection in 52 patients. Neurosurgery 56: 1203-1212, 2005
6. Frischer JM, Gatterbauer B, Holzer S, Stavrou I, Gruber A, Novak K, Wang WT, Reinprecht A, Mert A, Trattnig S, Mallouhi A, Kitz K, Knosp E: Microsurgery and radiosurgery for brainstem cavernomas: Effective and complementary treatment options. World Neurosurg 81: 520-528, 2014
7. Garrett M, Spetzler RF: Surgical treatment of brainstem cavernous malformations. Surg Neurol 72 Suppl 2: S3-9, 2009
8. Giliberto G, Lanzino DJ, Diehn FE, Factor D, Flemming KD, Lanzino G: Brainstem cavernous malformations: Anatomical, clinical, and surgical considerations. Neurosurg Focus 29: E9, 2010
9. Gross BA, Batjer HH, Awad IA, Bendok BR: Brainstem cavernous malformations. Neurosurgery 64: E805-818, 2009
10. Gross BA, Lin N, Du R, Day AL: The natural history of intracranial cavernous malformations. Neurosurg Focus 30: E24, 2011

11. Gross BA, Batjer HH, Awad IA, Bendok BR, Du R: Brainstem cavernous malformations: 1390 surgical cases from the literature. World Neurosurg 80: 89-93, 2012
12. Gross BA, Du R: Natural history of cerebral arteriovenous malformations: A meta-analysis. J Neurosurg 118: 437-443, 2013.
13. Hasegawa T, McInerney J, Kondziolka D, Lee JY, Flickinger JC, Lunsford LD: Long-term results after stereotactic radiosurgery for patients with cavernous malformations. Neurosurgery 50: 1190-1197, 2002
14. Hauck EF, Barnett SL, White JA, Samson D: Symptomatic brainstem cavernomas. Neurosurgery 64: 61-70, 2009
15. Huang YC, Tseng CK, Chang CN, Wei KC, Liao CC, Hsu PW: LINAC radiosurgery for intracranial cavernous malformation: 10-year experience. Clin Neurol Neurosurg 108: 750-756, 2006
16. Jay SM, Chandran H, Blackburn TP: Gamma knife stereotactic radiosurgery for thalamic & brainstem cavernous angiomas. Br J Neurosurg 26: 367-370, 2012
17. Karlsson B, Kihlström L, Lindquist C, Ericson K, Steiner L: Radiosurgery for cavernous malformations. J Neurosurg 88: 293–297, 1998
18. Kim BS, Yeon JY, Kim JS, Hong SC, Lee JI : Gamma knife radiosurgery of the symptomatic brain stem cavernous angioma with low marginal dose. Clin Neurol Neurosurg 126:110-114, 2014
19. Kondziolka D, Lunsford LD, Flickinger JC, Kestle JR: Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations. J Neurosurg 83: 825–831, 1995
20. Lee CC, Pan DH, Chung WY, Liu KD, Yang HC, Wu HM, Guo WY, Shih YH: Brainstem cavernous malformations: The role of Gamma Knife surgery. J Neurosurg 117 Suppl: 164-169, 2012
21. Lee SH, Choi HJ, Shin HS, Choi SK, Oh IH, Lim YJ: Gamma Knife radiosurgery for brainstem cavernous malformations: Should a patient wait for the rebleed? Acta Neurochir (Wien) 156: 1937-1946, 2014
22. Liu KD, Chung WY, Wu HM, Shiau CY, Wang LW, Guo WY, Pan DH: Gamma knife surgery for cavernous hemangiomas: An analysis of 125 patients. J Neurosurg 102 Suppl: 81–86, 2005
23. Lu XY, Sun H, Xu JG, Li QY: Stereotactic radiosurgery of brainstem cavernous malformations: A systematic review and meta-analysis. J Neurosurg 120: 982-987, 2014
24. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette DJ, Jungreis CA, Maitz AH, Horton JA, Coffey RJ: Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 75: 512-524, 1991
25. Lunsford LD, Khan AA, Niranjan A, Kano H, Flickinger JC, Kondziolka D: Stereotactic radiosurgery for symptomatic solitary cerebral cavernous malformations considered high risk for resection. J Neurosurg 113: 23-29, 2010
26. Mathiesen T, Edner G, Kihlström L: Deep and brainstem cavernomas: A consecutive 8-year series. J Neurosurg 99: 31-37, 2003
27. Menon G, Gopalakrishnan CV, Rao BR, Nair S, Sudhir J, Sharma M: A single institution series of cavernomas of the brainstem. J Clin Neurosci 18: 1210-1214, 2011
28. Monaco EA, Khan AA, Niranjan A, Kano H, Grandhi R, Kondziolka D, Flickinger JC, Lunsford LD: Stereotactic radiosurgery for the treatment of symptomatic brainstem cavernous malformations. Neurosurg Focus 29: E11, 2010
29. Nagy G, Razak A, Rowe JG, Hodgson TJ, Coley SC, Radatz MW, Patel UJ, Kemeny AA: Stereotactic radiosurgery for deep-seated cavernous malformations: A move toward more active, early intervention. J Neurosurg 113: 691-699, 2010
30. Ohue S, Fukushima T, Kumon Y, Ohnishi T, Friedman AH: Surgical management of brainstem cavernomas: Selection of approaches and microsurgical techniques. Neurosurg Rev 33: 315-324, 2010
31. Park YS, Kim SH, Chang JH, Chang JW, Park YG: Radiosurgery for radiosurgery-induced cavernous malformation. World Neurosurg 75: 94-98, 2011
32. Park SH, Hwang SK: Gamma knife radiosurgery for symptomatic brainstem intra-axial cavernous malformations. World Neurosurg 80: e261-266, 2013
33. Pham M, Gross BA, Bendok BR, Awad IA, Batier HH: Radiosurgery for angiographically occult vascular malformations. Neurosurg Focus 26: E16, 2009
34. Pollock BE, Garces YI, Stafford SL, Foote RL, Schomberg PJ, Link MJ: Stereotactic radiosurgery for cavernous malformations. J Neurosurg 93: 987-991, 2000
35. Porter PJ, Willinsky RA, Harper W, Wallace MC: Cerebral cavernous malformations: Natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg 87: 190-197, 1997
36. Ramina R, Mattei TA, de Aguiar PH, Meneses MS, Ferraz VR, Aires R, Kirchhoff DF, de Carvalho Kirchhoff D: Surgical management of brainstem cavernous malformations. Neurol Sci 32: 1013-1028, 2011
37. Salman RAS, Hall JM, Horne MA, Moultrie F, Josephson CB, Bhattacharya JJ, Counsell CE, Murray GD, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP: Untreated clinical course of cerebral cavernous malformations: A prospective, population-based cohort study. Lancet Neurol 11: 150-156, 2012
38. Tu J, Stoodley MA, Morgan MK, Storer KP, Smee R: Different responses of cavernous malformations and arteriovenous malformations to radiosurgery. J Clin Neurosci 16: 945-946, 2009
39. Wang CC, Liu A, Zhang JT, Sun B, Zhao YL: Surgical management of brain-stem cavernous malformations: Report of 137 cases. Surg Neurol 59: 444-454, 2003