

Cavernomas: Outcomes after gamma-knife radiosurgery in Iran

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ABSTRACT

Background: Treatment of cavernomas remains a challenge in surgically inaccessible regions. The purpose of this study was to evaluate outcomes after gamma-knife surgery (GKS) for these patients.

Materials and Methods: A retrospective review of 100 patients treated between 2003 and 2011 was conducted in order to evaluate hemorrhage rates, complications, radiation effects after GKS. Dosage at the tumor margin was stratified into two groups: those that received ≤ 13 Gy; and those who received > 13 Gy. The demographic and clinical characteristics of patients including age, gender, and hemorrhage rates were extracted from care records.

Results: The median age was 32.5 years (ranging from 15 to 79). 44% were female. The median follow-up time was 42.2 months (ranging from 24 to 90). The median volume of the lesions was 1050.0 mm³ (ranging from 112.0 to 4100.0) before GKS. A reduction of 27.5% in median size of cavernomas was achieved at the last follow-up. There was 12% treatment-related morbidity after GKS. The hemorrhage rate in the first 2 years after GKS was 4.1% and 1.9% thereafter. There was no mortality due to GKS, and 93 patients were alive at the last follow-up. The radiation-related complication developed with marginal dose 13 Gy.

Conclusion: The GKS for cavernomas appears to be a safe and beneficial in carefully selected patients. Low-dose GKS may be effective for the management of cavernous malformations.

Key words: Cavernomas, outcomes, gamma-knife radiosurgery, Iran

Introduction

Cavernous malformations (CMs) are a rare type of vascular abnormality which constitute about 8–15% of all vascular malformations.^[1] They are a well-constrained, benign vascular hematoma, often small, and only become clinically significant when they present with seizures, hemorrhage, or neurological dysfunction.^[2]

Management and treatment of patients with CMs in surgically inaccessible regions are one of the challenges of a neurosurgeon.^[1,3] At present, different treatment modalities are available for CMs. Although the surgery is the preferred management for patients with symptomatic lesions,^[3] radiosurgery may be used to treat CMs.^[4,5] However, it should be stressed that gamma-knife is not by any means even generally considered in the standard of care options for the management of these lesions.^[4,5]

The basis for using gamma-knife surgery (GKS) in patients with CMs derives from arteriovenous malformations (AVMs) successfully treated with this method.^[6] However, There are several gaps in using GKS in CMs diseases including: (a) Efficacy of radiosurgery; (b) dosage at the tumor margin; (c) no careful imaging assessment after GKS compared to AVMs; (d) a good description the natural course of CMs; (e) directly comparing the results of microsurgery and GKS; (f) Well-known long-term outcome after GKS; (g) The pathology of radiation-induced CMs disease.^[5,7] Therefore, for optimal use of GKS in CMs patients, the issues listed above should be considered.

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The aim of this study was to evaluate hemorrhage rates, complications, radiation effects, CMs location, and 8-years outcomes in CMs patients treated with GKS and to compare patients' subgroups by dosage at the tumor margin.

Materials and Methods

Patients and data collection

During an 8-year (January 2003-March 2011) period 107 patients, with CMs, were treated in Iranian Gamma-knife Center, of which 100 were eligible to enter this study (patients with full follow-up). Patients were selected for treatment with GKS based on eloquent sites or surgically inaccessible for lesions presented with hemorrhages without or with epilepsy, and to cases without any or with only minor neurological deficits.^[2,4]

Four patients (4%) had undergone surgery before GKS, and in 96 cases (96%) GKS was offered primarily.

Treatment planning and radiosurgery

Treatment planning and radiation dosimetry for CMs were performed. After application of stereotactic frame under local infiltration of anesthetics, magnetic resonance imaging (MRI) scanning was performed with the goal of conformal and selective coverage of the nidus on the basis of T2-weighted MRIs. Images were transferred to planning workstation and treatment planning was done using GammaPlan version 5.34. GKS was performed using the Leksell Gamma-knife model C system (Elekta Instruments, Stockholm, Sweden).

Malformations were defined within the hemosiderin ring and were treated with an average of 5 isocenters and a prescription isodose of 50% depending on the lesion location.^[4] Treatment parameters are summarized in Table 1.

Dosage at the tumor margin was stratified into 2 groups: Those that received ≤ 13 Gy; and those received > 13 Gy. The decision to stratify into above or below 13 Gy was retrospectively.

Follow-up

The posttreatment observation period was the date of the initial GKS procedure. MRI studies and clinical assessment were performed at 6 months intervals until the occurrence of surgical intervention or death from another cause. The last MRI scan for all patients was recorded during the follow-up period. Side effects and any clues of hemorrhage, including new foci, volume expansion of irradiated lesions, and edematous changes after GKS were also observed during the follow-up period.

The annual hemorrhage rate pre and postGKS was recorded in patient-years based on definitions presented by Lee *et al.*, The preGKS hemorrhage rate in 100 patients who experienced >2 bleeding episodes was considered. The preGKS

observation period extended from the time of the patient's first symptomatic image-documented hemorrhage to the time of GKS. A total of 461.4 patient-years was documented. There were 258 episodes of hemorrhage through this period. After exclusion of the first hemorrhage ($258-100 = 158$ episodes), the calculated annual hemorrhage rate was 34.3% (158 episodes in 461.4 patient-years).^[5]

Statistical analysis

All statistical analyses were performed using the PASW statistics 18 version 18 (SPSS, Inc., 2009, Chicago, IL, USA). Data are given as mean, median, and standard deviation.

Ethics

In this center, at the beginning of treatment, all patients gave their informed consent to each study protocol. The Ethics Committee of Iranian Gamma-Knife Center approved the study protocol.

Results

The last MRI scan was achieved at median follow-up time 42.2 months (ranging from 24 to 90) from GKS. All of the cases participated in regularly scheduled follow-up for at least 2 years. Patient characteristics and outcomes are summarized in Tables 1 and 2, respectively.

During follow-up time, continuing improvement of neurological deficit (83%), conserved stationary state (5%), transient worsening (10%), and progressive neurological deterioration (2%) were observed. Temporary neurological events without radiological evidence of hemorrhage or edema occurred in 3 patients. In seven patients, the symptom got worse with growth of the lesions and increased surrounding edema indicative of radiation effect from 5 to 9 months after GKS (1 headache and focal neurological symptoms in 6). The prescribed marginal dose was ranging from 14 to 17 Gy in these cases. No significant difference in therapeutic effect was seen when comparing patients' subgroups by dosage at the tumor margin.

Ninety-nine patients with a single lesion and one with two lesions were treated. Overall, 101 CMs were seen, and 3.96% had surgery. The CMs locations were supratentorial 52% ($n = 52$) and infratentorial 48% ($n = 48$). A statistically significant decrease in the annual hemorrhage rate was found after GKS ($P < 0.0001$), and epilepsy was controlled in 32 of 42 (76.2%) at the last follow-up.

Local tumor control

The reduced-size image of the lesions after GKS was attained in 85 of 100 (85%) cases at last follow-up. Median volume of the lesions was 1050.0 mm³ (ranging from 112.0 to 4100.0) before GKS and 761.3 mm³ (ranging from 85.2 to 2422.1) at the last follow-up, which is a decrease of 27.5% in median size of cavernomas.

Table 1: Patient characteristics (n=100)

Parameter	Number of patients	Percentage	Median (±SD), range
Age, years			32.5±13.8 (15-79) years
Gender (female/male)	44/56	44/56	
Follow-up time			42.2±27 (24-90) months
Previous surgery	4	4.0	
Symptoms and signs			
Headache	48	48	
Epilepsy	42	42	
Sensory deficit	7	7	
Conscious disturbance	5	5	
Dizziness	24	24	
Diplopia	16	16	
Facial palsy	5	5	
Lower cranial nerves palsy	2	2	
Focal neurological deficits			
Ataxia	21	21	
Hemiparesis	59	59	
Speech disorder	5	5	
Impairment of vision	6	6	
Hearing loss	7	7	
Tremor	5	5	
Tumor site			
Supratentorial			
Parietal	7	7	
Occipital	6	6	
Temporal	7	7	
Frontal	1	1	
Thalamic	15	15	
Basal ganglia	16	16	
Infratentorial			
Cerebellar	5	5	
Brainstem	43	43	
Annual hemorrhage rate preGKS		34.30	
Tumor volume (mm ³)			1050.0±850.1 (112-4100)
Coverage of tumor margin (%)			100.0±2.7 (86-100)
Isodose level (%)			50.0±14.1 (35-96)
Number of isocenters			5.0±5.2 (1-17)
Maximal dose (Gy)			26.0±7.1 (12.3-40.0)
Dosage at the tumor margin			
≤13 (Gy)	33	33	12.0±1.4 (7.4-13.0)
>14 (Gy)	67	67	15.0±1.2 (14.0-18.0)
Total (Gy)	100	100	14.0±2.0 (7.4-18.0)

SD – Standard deviation; GKS – Gamma-knife surgery

Survival

Overall, the neurological status was either stable, transient worsening or improved in 98.0% of the patients after GKS. At the time of analysis, 93 out of 100 patients (93%) were alive and achieved improvement of neurological deficit: 90 patients had GKS as primary treatment, 3 had GKS after

Table 2: Patient outcomes (n=100)

Parameter	Number of patients	Percentage	Median (±SD), range
Tumor volume at last follow-up (mm ³)			761.3±614.2 (85.2-2422.1)
Increase/stable or decrease	0/100	0/100	
Clinical outcomes			
Stable or improved neurological status at last follow-up		93	
Annual hemorrhage rate			
<2 years after GKS (%)			4.1
>2 years after GKS (%)			1.9
Management of complication			
Conservative	99	99	
Surgery	1	1	
Repeat gamma knife	0	0	
Cause of death			
Neurological death	1	1	
Systemic death	6	6	
Living patients	93	93	

SD – Standard deviation; GKS – Gamma-knife surgery

a surgical resection, and 13 (13%) of patients have survived over 7 years.

Complications and death

Complications of transient and progressive neurological deficit were 12%. In the present study, complications due to radiation developed with marginal dose as low as 13 Gy. Two patients developed hemorrhage after GKS. One patient with rebleeding and acute hydrocephaly underwent ventriculoperitoneal shunt insertion 2 months after GKS. He had been treated with marginal dose of 14 Gy for lesion volume of 1800.0 mm³ in brainstem, and the other case died 3 years after GKS due to rebleeding from an untreated CMs. Six patients died unrelated to the treated CMs.

Adverse radiation effects

Adverse radiation effects (AREs) followed the GKS was not seriously affected by the treatment in cases. Late-delayed AREs is needed for assessment over longer time periods.

Discussion

Our findings were promising in treating patients with cavernomas. However, the favorable results could possibly be explained by selection of patients with well-established favorable prognostic factors such as “often single lesion”, without any or with only minor neurological deficits, and “small tumors.” In addition, one might argue that the use of MRI for dose planning and targeting the nidus itself could improve the outcomes.^[3]

One might wonder why so many lesions were deemed unresectable, and patients received Gamma-knife. One explanation for such practice was due to the fact that

there were patients with eloquent cortex ($n = 4$), medical comorbidity ($n = 10$), unwilling to receive surgery ($n = 12$), and for thalamic ($n = 15$), basal ganglia ($n = 16$), and brainstem ($n = 43$) lesions maximal safe resection was not feasible. However, as a guide, it should be noted that gamma-knife for CM should be subject to scrutiny as it is generally not accepted as a treatment modality for these lesions.

Several studies of GKS for the treatment of CMs have been reported in the English literature.^[4,5,8-17] Overall results of our patients are compatible with other reports of GKS for cavernomas. Some authors have found that there was no difference in the hemorrhage rate before and after GKS.^[18] However, other authors suggested that it could be performed for eloquent sites.^[14-16] At present, the successful treatment of GKS for CMs is evaluated with reduction annual hemorrhage rate and tumor volume. Hasegawa *et al.* reported that the annual hemorrhage rate was 12.3% for the first 2 years after radiosurgery and 0.8% thereafter.^[8] Another study by Kida and Hasegawa has reported that the bleeding rate was 8% at 1st year after radiosurgery, 5% in the 2nd year and 0% by year 7.^[9] Other studies have shown annual hemorrhage rates of 3.3–9.4% for the first several years after GKS and then lower hemorrhage rates in later years of follow-up.^[4-5,10-14] The current study found that patients with such surgically inaccessible lesions showed a reduced hemorrhage rate. However, at present, there is no way to predict the behavior of CMs for hemorrhage.

Previously reported mean rates of the volume reduction after radiosurgery for CMs varied from 37.3%^[17] to 81%.^[19] These are similar to our findings. However, it is unclear whether shrinkage of the bulk is really induced by radiation or other factors and needs to be investigated in the future.

The optimal dose of CMs for a positive response and minimum side effects is controversial. Liscák *et al.* showed statistically significant increases in the collateral edema by marginal dose exceeding 15 Gy.^[18] Lee *et al.* reported that radiation-related complication developed with marginal dose 13 Gy, and they suggested that lower radiosurgical doses are required for CMs in specific sites such as brainstem.^[17] Similar finding was reported by Amin-Hanjani *et al.* and Karlsson and Tsai.^[20,21] As suggested, we also recommend low-dose radiosurgery using on average a 13 Gy marginal dose. The radiation-related complication in our cases confirmed the value of such a treatment strategy. As in a study by Lee *et al.*,^[17] we were not able to show any significant differences in therapeutic effect compared with the higher marginal dose based on available data. The optimal dose and threshold for radiation-related complication for CMs have not been defined up till now. It seems that there is a need to explore the issue further particularly for specific sites such as the brain stem.

The CMs lesion is considered as a factor in decision-making using GKS and outcomes. Gross *et al.* evaluated CM location in 1055 patients and reported that 76% of the lesions were supratentorial, 23% were infratentorial, and 1% was both.^[22] This is in line with our findings. However, the natural history of benign lesions should be considered for better outcomes.^[21]

A neurological complication after GKS was not rare, particularly within 1-year after GKS.^[17] Karlsson and Tsai by analyzing of 15 papers reported that complication rates between different centers ranged from 7% to 62% and the average was 26%,^[21] which is in line with our findings. However, we were not able to explain differences in complication rates and future studies are recommended.

Finally, although surgical resection is the first option for CMs patients,^[3] GKS is an alternative to conservative therapy in cases at a surgically inaccessible site and is recommended.

There are several principle weaknesses in this study. The first is the retrospective nature and the inherent limitations of this methodology. Second, due to a limited number of patients with prior surgery, we cannot compare these outcomes. Third, there were differences in treatment and variation in tumor location for patients prior to entering to the study. Thus, the findings should be interpreted with caution.

Conclusion

The GKS for cavernomas appears to be a safe and beneficial treatment in carefully selected patients. Low-dose GKS may be effective for the management of CMs.

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