Clinical Neurology and Neurosurgery 151 (2016) 55–60

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Gamma knife radiosurgery for brainstem cavernous malformations☆

Hong Bin Liu (MS), Yi Wang (MS), Sen Yang (MS), Fei Long Gong (MS), Yang Yang Xu (MS), Wei Wang (MD)*

Department of Neurosurgery, West China Hospital, Sichuan University, China

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form
19 September 2016
Accepted 24 September 2016
Available online 11 October 2016

Keywords:
Cavernous malformation
Gamma knife surgery
Annual hemorrhage rate
Stereotactic radiosurgery
Brainstem

ABSTRACT

Objective: The goal of this retrospective study was to evaluate the efficacy and safety of gamma knife radiosurgery (GKS) for the treatment of brainstem cavernous malformations (CMs).
Methods: Between January of 2009 and December of 2014, 43 patients (20 males and 23 females) with brainstem CMs were treated at the West China Hospital, Sichuan University, Gamma Knife Center. The mean age of these patients was 41.7 years. All of the patients experienced 1 or more episodes of symptomatic bleeding (range 1–4) before undergoing GKS. The mean volume of the malformations at the time of GKS was 442.1 mm^3, and the mean prescribed marginal radiation dose was 11.9 Gy. The mean follow-up period after radiosurgery was 36 months (range 12–120 months).
Results: Before GKS, 50 hemorrhages (1.2 per patient) were observed (25.0% annual hemorrhage rate). Three hemorrhages following GKS were observed within the first 2 years (3.92% annual hemorrhage rate), and 1 hemorrhage was observed in the period after the first 2 years (1.85% annual hemorrhage rate). In this study of 43 patients, new neurological deficits developed in only 1 patient (2.32%; permanent paresthesia on the left side of the face and the right lower limb of the patient). There were no deaths in this study.
Conclusion: GKS is a favorable alternative treatment for brainstem CMs. Using a low marginal dose treatment might reduce the rate of hemorrhage and radiation-induced complications.

1. Introduction

Cavernous malformations (CMs) are benign vascular malformations, accounting for 5%–10% of all intracranial vascular angiomas [1–3]. Approximately 20% of intracranial cavernous malformations occur in the brainstem [4]. The annual hemorrhagic rate of brainstem CMs has been estimated at 0.1%–2.5% per lesion per year and 0.25%–16.5% per patient per year, but this rate obviously increases (up to 34% the annual risk) in patients with prior hemorrhagic events [4,5]. For brainstem CMs, the goal of any treatment method is to control rebleeding and avoid complications from recurrence. The optimal management of intracranial CMs is microsurgical resection. Surgical resection of brainstem CMs, especially intra-axial CMs, remains difficult, and the morbidity and mortality are especially high. Therefore, gamma knife radiosurgery has been regarded as a favorable alternative treatment method. Although large numbers of studies have reported that using a low marginal dose could decrease the risk of radiation-induced injuries, [6–8] the optimal marginal dose has not yet been confirmed. The purpose of this article was to analyze the annual hemorrhage rates and radiation-induced complications of GKS using a low marginal dose.

2. Materials and methods

2.1. Patient population

Forty-four patients (20 males and 23 females) with a single brainstem CM underwent GKS at our center between January of 2009 and December of 2014. The criteria for choosing radiosurgery as follows: (i) All patients have hemorrhage and neurological deficit. (ii) Each patient is assessed by the surgeon and not suitable for open surgical intervention. (iii) The risk of surgery is very high and may lead to new neurological deficits and after surgery, the lesion may be residual and bleeding again. (iv) Patients and their families were unwilling to bear the risk of surgery and refuse to surgery. The mean age of the patients in this analysis was 41.7 years, ranging from 22 to 66. Hemorrhage events were defined as the occurrence of a new neurological deficit and MRI findings of a recently developed hemorrhage. In other words, the information

☆This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. There are no portion of the contents of the paper have been present.
* Corresponding author at: Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China.
E-mail address: wcnscn@163.com (W. Wang).

http://dx.doi.org/10.1016/j.clineuro.2016.09.018
0303-8467/

Table 1
Characteristics of 43 patients with 43 brainstem CMs treated with GKS between 2009.1 and 2015.1.

Characteristic	No. (%)[a]
Age in yrs (range)	41.7 (22–66)
Total no. of CMs	43
Location	
Midbrain	6 (14%)
Pons	26 (60.4%)
Medulla	
No. of pre-GKS hemorrhagic events (% of – total)	
1	38 (88.4%)
≥2	5 (11.6%)
Patients w/pre-GKS neurological deficit	43 (100%)
Follow-up after GKS (yrs)	
<2	12 (27.9%)
≥2	31 (72.1%)

[a] Unless otherwise indicated.

Table 2
Summary of brainstem CM radiosurgery dose planning: parameter, mean and range.

Parameter	Mean	Range
Malformation vol. (mm^3)	442.1	13.7–2670
No. of isocenters	3.8	1–10
Margin dose (Gy)	11.9	9–14
Maximum dose (Gy)	24.0	18–28.8
Isodose level (%)	24.0	45%–50%

Table 3
The dominant presenting neurological deficits pre-GKS in 43 patients with brainstem CMs.

Neurological Sign	No. of Patients	Percentage (%)
Cranial nerve deficits	29	67.4
Hemiparesis or asthenia	11	25.6
Hemisensory deficits	23	53.5
Conscious disturbance	3	7.0
Headache and Vertigo	1	2.3

pertaining to bleeding events had to be compatible with the timing of the patient's symptoms. No patients were found to have an associated developmental venous anomaly (DVA), and the computation of the hemorrhage rate before GKS presumes that the CM occurred de novo at the time of symptomatic hemorrhage. The method of calculation of the annual hemorrhage rate was as follows: the numbers of hemorrhage events/total patient-years. Before treatment, neurological deficits were observed in 43 patients, and one of the 43 patients had undergone partial microsurgical resection. Before GKS, 38 patients (86.3%) had suffered 1 hemorrhage, and 5 patients had suffered 2 or more hemorrhages (range 2–4) (11.4%) (Table 1). The dominant neurological deficits included cranial nerve deficits (67.4%), hemiparesis or asthenia (25.6%), hemisensory deficits (53.5%), conscious disturbances (7.0%), and headaches and vertigo (2.3%) (Table 3).

2.2. Gamma knife surgery

Stereotactic radiosurgery was performed using the Leksell Gamma Knife (Elekta C Elekta Instruments, Sweden). The mean volume was 442.1 mm^3 (range 13.7–2670 mm^3). The number of isocenters ranged from 1 to 10 (mean 3.8), and the isodose line was 45–50% (mean 49.5%). The mean marginal dose was 11.9 Gy (range 9–14 Gy), and the mean maximal radiation dose was 24.0 Gy (range 18–28.8 Gy) (Table 2), using multiple small shots to achieve a highly conformal dose to the CM. The targeted edge of the CM, according to findings on T2-weighted MR images, was considered to be the region characterized by a mixed signal change within the T2-weighted signal–defined hemosiderin ring. After GKS, each patient received a 40-mg dose of methylprednisolone and 250-ml mannitol to reduce the single high-dose radiation which may cause brain edema. All of the patients were discharged from the hospital after being carefully observed for 24 h.

2.3. Follow-up imaging and clinical evaluation

After GKS, follow-up MR imaging and clinical evaluations were performed at 6-month intervals during the first years and then annually. The mean follow-up time was 36 months, ranging from 12 to 120 months. Thirty-one patients (72.1%) had follow-ups of at least 2 years, and 12 patients (27.9%) had follow-ups shorter than 2 years. Any signs of hemorrhage, including the occurrence of a new neurological deficit and MRI findings of a recently developed hemorrhage, were carefully assessed. Information pertaining to bleeding events had to be compatible with the timing of the patient's symptoms. Hemorrhage rates were compared before and after GKS using Wilcoxon's signed-rank test. The statistical analysis was performed with the Statistical Package for the Social Sciences software (SPSS version 22.0, IBM Corporation, Chicago, Illinois, USA), GraphPad Prism (GraphPad, Version 6.0) and the level of statistical significance (*p*-value) was set to less than 0.05.

3. Results

3.1. Hemorrhage rate before GKS

Before GKS, 43 patients had experienced 1 or more hemorrhagic events, with 1 hemorrhage in 38 patients, and 2 or more hemorrhages in 5 patients. The first hemorrhage in the 38 patients was excluded based on the calculation of the hemorrhage rate. The observation time before GKS occurred between the time of the first symptomatic, imaging-confirmed bleeding to the time of GKS. A total of 28 patient-years were observed. Before GKS, there were 7 hemorrhage events during this period, and the calculated annual hemorrhage rate was 25.0% (7 hemorrhage events in 28 patient-years). The annual preoperative hemorrhage rate, assuming that the CM was present at birth, was 2.91% (50 hemorrhage events in 1713 patient-years).

3.2. Hemorrhage rate after GKS

The mean follow-up time after GKS was 36 months, ranging from 12 to 120 months, with an overall observation period of 130.5 patient-years. There were 3 bleeding events within 2 years, and 1 bleeding event occurred >2 years after GKS. During the follow-up after GKS, no patients died. Post-radiosurgery, the annual bleeding rate during the first 2 years was calculated to be 3.92% [(3 hemorrhage events/76.5 patient-years); initial 2 years post-GKS: 76.5 patient-years = (31 patients × 2 years) + (12 patients × various follow-up periods)], and the annual bleeding rate after the initial 2-year follow-up was calculated to be 1.85% [(1 hemorrhage events/54 patient-years); after the initial 2 years post-GKS: 54 patient-years = (31 patients × various follow-up periods) – (31 patients × 2 years)] Statistical analysis revealed that the risk of brainstem CM hemorrhages was significantly reduced after GKS ($P < 0.013$), as shown in Fig. 2. The Kaplan Meir investigation of the fraction of patients with heorrhages is shown in Fig. 3.

3.3. Adverse radiation effects

One patient (2.32%) had new neurological symptoms following GKS without a new hemorrhage (Fig. 1), consisting of numbness of the left side of the face and the right lower limb of the patient. This neurological deterioration persisted at the latest follow-up. No