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Gamma knife radiosurgery of the symptomatic brain stem cavernous angioma with low marginal dose

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ABSTRACT

Objective: To analyze the outcome of gamma knife radiosurgery (GKS) using low marginal dose for the symptomatic brain stem cavernous angioma (BSCA).
Methods: 39 patients (16 males, 23 females) were treated with GKS for BSCA from January 1997 to September 2012. Clinical data were analyzed retrospectively. The mean age was 41.5 years. All patients had a history of symptomatic bleeding once or more before performing GKS. Mean volume of BSCA was 1095.3 mm^3 and median prescribed marginal dose was 13 Gy.
Results: Mean follow-up period since diagnosis was 4.1 years. The number of hemorrhagic events between initial diagnosis and GKS was 5 over a total of 14.9 patients-years with annual hemorrhagic rate of 33.6%. Following GKS, there were five hemorrhagic events within the first 2 years (8.1%/year) and two after the first 2 years (2.4%/year). The difference was not statistically significant. Neurologic status improved in 24 patients (61.5%), and stationary in eleven (28.2%). 4 patients (10.3%) experienced the exacerbation of symptoms at the last follow-up and none of them were related to the radiation injury. Significant volume reduction after GKS was observed in 24 patients (61.5%). Surgical excision was performed in one patient due to swelling and rebleeding after GKS. Age at presentation, sex, mass size of BSCA, and location, GKS dose did not affect post-GKS hemorrhage.
Conclusions: GKS for BSCA using relatively low marginal dose is safe and effective. Long-term prospective study is needed to confirm the optimal dose for BSCA.

1. Introduction

Cavernous angioma or cavernoma is a benign vascular malformation, which can be found at any region within the brain [1]. Cavernous angioma accounts for 5%–15% of all central nervous system vascular malformations [2,3]. Brain stem cavernous angioma (BSCA) is rare, affecting only 0.4%–0.9% of the population [4–9] and representing 9%–35% of intracranial cavernomas [10–14]. BSCA is most frequently found in the pons. The current treatment of choice for most symptomatic cavernous angioma is microsurgical resection [15]; however, morbidity and mortality associated with the operation are especially high in a surgically inaccessible lesions such as brain stem. Therefore, radiosurgery has been used as an alternative method of treatment and the primary goal of the radiosurgery is the same as in the case of AVMs; the prevention of repeated hemorrhage. Though the natural history of BSCA and the use of radiosurgery in the management are still controversial issues recent studies reported reduction of recurrent hemorrhage after radiosurgery. Marginal dose used in radiosurgery, however, varies according to authors or institutions and optimal dose is not yet clearly determined. The purpose of this study is to investigate the outcome of GKS with low marginal dose for BSCA.

2. Materials and methods

2.1. Patient population

For this study, an Institutional Review Board approved retrospective chart of 39 patients undergoing gamma knife radiosurgery for brain stem cavernous angioma from January 1997 to September 2012 at Samsung Medical Center was reviewed. Mean age of the patients was 41.5 years ranging from 18 to 64. The ratio of men to women was 1:1.4. The most common location of BSCA was pons (30 patients, 76.9%) followed by medulla (4 patients, 10.3%), midbrain (3 patients, 7.7%), and pontomedullary junction (2 patients, 5.1%). Four patients (10.3%) had undergone previous partial microsurgical

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resection before GKS. Abnormal neurological symptom or sign was present in all patients. Most patients (64.1%) were presented with complex neurological deficit. Initial neurological manifestation was vertigo (15 patients), sensory deficit (12), diplopia (10), dysarthria (9), hemiparesis (7), headache (7), facial palsy (6), 6th nerve palsy (5), general weakness (1), and tinnitus (1). Bleeding events were defined as the development of hemorrhage in follow-up imaging associated with new neurological deficit. There were 44 bleeding events in 39 patients reported before GKS. All patients had a history of symptomatic bleeding once or more before performing GKS and bleeding happened repeatedly in 5 patients. Mean volume of BSCA at the time of GKS was 1095.3 mm^3 (range 31.5–5400). Additional lesions outside the brain stem were found in 3 patients. Adjacent venous anomalies were seen through MRI in 10 patients (25.6%).

2.2. Radiosurgical technique

GKS was performed in the following procedure. After application of Leksell stereotactic frame type G under local anesthesia, MRI scanning was done. Stereotactic MR imaging including T2-weighted images and postcontrast FLASH (Fast Low Angle SHot) sequences were used for dose planning. Upon administrating double dose contrast medium, we obtained a Fast Low Angle Shot images (FLASH, 1 mm-thick slices with no gap, 512 × 512 pixel). Images were transferred to planning workstations for Leksell Gamma Knife (Elekta Instruments) and dose planning was performed using GammaPlan versions 5.31, 5.32, 5.34, and 9.0. Radiosurgery dose plans, with single or multiple isocenters (range 1–9), were created and the targeted edge of the BSCA was considered to be the region characterized by mixed signal change within the T2-weighted signal-defined hemosiderin ring. This margin served as the 50% or greater isodose line. The median marginal dose was 13 Gy (range 11–18 Gy) and median isodose 50%. Irradiation was performed with Leksell Gamma Knife type B, C or Perfexion. Each patient received a 10 mg loading dose of dexamethasone in the morning on the day of GKS followed by 5 mg after completion. All patients were discharged from the hospital within 24 h.

2.3. Follow-up

Follow-up MR imaging was performed at 6-month intervals during the first year after GKS. It was recommended on an annual basis after the first year. Mean clinical follow-up period since diagnosis was 4.1 years (range 0.4–16 years). 23 patients (59%) had follow-up period longer than 2 years and 11 (28.5%) longer than 5 years. Mean follow-up duration till the last MRI was 3.4 years (range 0.5–16).

2.4. Statistical analysis

We analyzed for variables which might affect the rebleeding of BSCA such as location, sex, age at presentation, mass size, and marginal dose using Cox-regression analysis. Tied time was considered using Efron method. We analyzed using Stata 13.0 (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845-4512, USA). Bleeding events was defined as imaging evidence corresponding to a newly developing neurological sign or symptom. We calculated the annual rate of recurrent hemorrhage between diagnosis and treatment using the following formula: total number of hemorrhages (excluding the first hemorrhage at diagnosis) in all patients/total number of patient-years between diagnosis and GKS. Post-treatment annual hemorrhage rate was calculated as a total number of hemorrhages after GKS in all patients/total number of patient-years after GKS. Hemorrhage rates were analyzed before and after GKS using Poisson distribution. Exact Poisson 95% confidence intervals were calculated and 95% confidence intervals (95% CI) were corrected using Bonferroni's method due to multiple testing. Finally, we statistically analyzed the difference of an annual hemorrhage rates after GKS between marginal doses below 13 Gy and higher than 14 Gy using Poisson distribution. Exact Poisson 95% confidence intervals were calculated.

3. Results

3.1. Pretreatment hemorrhage rate

Observation periods before GKS comprised of the time from hemorrhage in MRI associated with the first symptom to the time of GKS. Total of 14.9 patient-years were observed with a mean pretreatment observation period of 0.4 years (range 0–5.6 years). All patients had at least one hemorrhagic event prior to GKS. Because of the five patients presented with a recurrent hemorrhage before GKS, there were 44 hemorrhagic events documented during this time (1.1 hemorrhagic events per patient). After exclusion of the first hemorrhage, the calculated annual rate of recurrent hemorrhage was 33.6% (95% CI: 8.26–89.80).

3.2. Post-treatment hemorrhage rate

The observation period following GKS was considered to be the time following the treatment until the most recent clinical follow-up. Thus, the mean follow-up period after GKS was 3.7 years (range 0.3–15.9 years) with an overall observation period of 145.9 person-years. During the follow-up after GKS, no patients died. Seven hemorrhagic events in six patients were documented during this period. Only two hemorrhagic events developed after 2 years in each patient. The annual hemorrhage rate during the first 2 years after GKS was calculated to be 8.1%. (5 hemorrhages/61.4 person-years, 95% CI: 2.64–19.00) and the annual hemorrhage rate after the initial 2 year was calculated to be 2.4% (2 hemorrhages/84.5 person-years, 95% CI: 0.29–8.55). However, statistical analysis using 95% confidence interval did not reveal a significant reduction in the annual hemorrhage rate within 2 year after GKS (8.1%, 95% CI: 2.64–19.00) compared to before GKS (33.6%, 95% CI: 8.26–89.80). Also, statistical analysis did not reveal a significant reduction in the annual hemorrhage rate within a 2-year period (8.1%, 95% CI: 2.64–19.00) compared to following the 2-year latency period after GKS (2.4%, 95% CI: 0.29–8.55).

3.3. Factors associated with rebleeding

Univariate analysis using the Cox-regression proportional hazard model did not reveal statistically significant association of factors including age at presentation ($p = 0.1428$), sex ($p = 0.5926$), GKS dose ($p = 0.3319$), and mass size ($p = 0.4182$) with rebleeding after GKS. When we compared the annual hemorrhage rates between the marginal doses below 13 Gy (3.64%, 95% CI: 0.75–10.64) and higher than 14 Gy (9.75%, 95% CI: 3.58–21.21) using 95% confidence interval calculated by Poisson distribution, there was no statistically significant difference.

3.4. Mass shrinkage (Fig. 1)

Volume of the cavernous angioma before and after the treatment was measured on MR FLASH images using Gamma plan. We defined significant mass shrinkage or increment as change of total volume of more than 20% from the baseline. In all patients, follow-up MRI was available. Mass shrinkage was revealed in 24 patients