Cavernous sinus cavernous hemangioma (CSCH) is a relatively rare benign lesion of the cavernous sinus. Despite its benign nature, it can manifest symptoms that can result from progressive mass growth and compression of cranial nerves. CSCHs could be misdiagnosed as meningioma or schwannomas. 1-5 Magnetic resonance image (MRI) and red blood cell (RBC) scan are commonly used for differential diagnosis of these lesions. 6 Surgical removal of CSCH can cause many morbidities or sometimes mortality due to increased mass vascularization; the surgical mortality rate associated with CSCH is reported to be 38%. 3 With advances in neurosurgical techniques, the risk is decreasing; however, surgical removal of CSCH is still challenging. Since its discovery, Gamma Knife surgery (GKS) has been widely used to manage CSCH and avoid the surgery-related risks. The purpose of this study was to evaluate the efficacy and safety of GKS treatment of CSCH with a specific focus on their relationship with radiological results and clinical outcomes.

This study included all adult patients (age >18 years) who underwent stereotactic radiosurgery for a radiologically suspected CSCH between 2001 and 2017 at the Department of Neurosurgery, Severance Hospital, Yonsei University. Patients with insufficient clinical data as well as patients with insufficient follow-up time (less than 12 months) were excluded from the final analysis.

All CSCHs were diagnosed based on radiologic findings, except for one case of histopathologic diagnosis at the previous surgery. The diagnosis was made by experienced neuroradiol-
ogists based on typical MRI findings, including 1) high signal intensities on T2-weighted images, 2) strong delayed enhancement after contrast injection, and 3) a round shape without a “dural tail” sign to exclude the possibility of meningioma. In cases where the diagnosis was difficult to confirm using MRI, labeled red blood cell pool scintigraphy (RBC scan) was used for differential diagnosis. This study showed progressive scan, establishing RBC scan as an effective method for the diagnosis of CSCH.

Single-session GKS was provided to all of the patients using the Leksell Gamma Knife (Elekta Instrument AB, Stockholm, Sweden), Model B, C, or Perfexion. Following the frame fixation, a T1-weighted, three-dimensional, multiplanar, rapid-acquisition, gradient-echo MRI and a T2-weighted sequence were obtained before and after gadolinium enhancement. Those images were exported to a computer workstation for dose planning using the Gamma Plan software (Elekta Instrument AB). The GKS dose was determined according to the proximity to the optic pathway and the mass volume calculated during the dose planning. Multiple isocenter planning method was applied to minimize the radiation exposure to the critical neuronal structures, such as the optic nerve.

All GKS were outpatient-based, and performed with a routine clinical follow-up schedule, as follows: clinical follow-up at 4 weeks after GKS, imaging follow-up at 6 and 12 months after GKS, and then annual follow-up. Specifically, in case of sustained symptoms, imaging follow-up was performed, regardless of the scheduled timeline.

We evaluated the changes in mass volume, symptom improvement, and adverse effects induced by GKS at regular follow-up. T1-weighted gadolinium-enhanced image and T2-weighted image were used for mass volume measurement. The mass volume change was defined as the ratio of the follow-up mass volume to the initial mass volume. “Remarkable response” was defined as the follow-up mass volume less than 1/3 of the initial mass volume, “moderate response” as the follow-up mass volume more than 1/3 and less than 2/3, and “minimal response” as the follow-up mass volume more than 2/3. As for the patient’s recovery, “complete recovery” was defined as the disappearance of symptoms before treatment, “partial recovery” as any improvement in clinical feature, and “no change” as no clinical deterioration or improvement observed after treatment.

We used the SPSS version 21.0 (IBM Corp., Armonk, NY, USA) for statistical analyses and the Wilcoxon paired t test to analyze the volume change data. P-value less than 0.05 was considered statistically significant.

Among the 29 patients who were treated by GKS, three patients missed a follow-up MRI due to general clinical improvement, as they personally declared. As a result, they were excluded from this study, and a final total of 26 CSCH patients were included in this study. Among the 26 patients, GKS was performed for 24 patients as a primary treatment, and a second-
temporal volume change after GKS during follow-up.

Then, we classified the 26 patients into two groups according to their radiologic results to identify the factors that influence mass volume change after GKS; 7 patients were classified as moderate remission group and 19 patients as remarkable remission group. We checked to see whether there were any significant differences between the two groups using the chi-square or Student’s t-test (Table 2). Naturally, the mass volume after GKS showed a significant difference between the two groups ($p=0.044$, $p<0.001$). The marginal dose tended to be higher in the remarkable remission group than in the moderate remission group, but it did not reach statistical significance. We expect that if more sample sizes are secured, the results would have statistical significance. Other variables did not show statistical difference.

Cavernous hemangioma in cavernous sinus is a rarely presented lesion, which shares similar histologic, but different clinical features with intracerebral lesions. Many well-known neurosurgeons have reported their clinical experience of surgical removal of CSCHs, and specifically, suggested a total removal rate of 40–92.3%. Even though these surgeries were performed by very experienced neurosurgeons, the reported postoperative morbidity and mortality rates were as high as 80% and 20%, respectively. The reasons for the poor surgical outcomes were the high mass vascularization and deep location.

Before the era of GKS, radiotherapy was considered as an alternative treatment modality for avoiding the surgical risk. A number of studies have reported good clinical outcomes after radiotherapy, with a relatively high dose of radiation (>3 Gy) in fractions considered as an effective dose for CSCH management. Radiation therapy can cause complications in the central nervous system, especially after high-dose radiation.

According to Iwai, et al., CSCH was firstly treated with GKS in 1999. The patient was surgically treated at first, and then, GKS was performed for the residual lesion, resulting in good clinical outcome. Following that case, many studies suggested that GKS could be an alternative to surgery or conventional radiotherapy.

Wang, et al. published the meta-analysis results of GKS for 59 CSCH patients. Their study reported a remarkable mass shrinkage (more than 50%) in 40 patients (67.8%), partial shrinkage (25–50%) in 15 patients (25.4%), and no change (less than 25%) in 4 patients (6.8%). They also reported that there was no significant correlation between lesion volume and mass shrinkage. However, patients with remarkable mass shrinkage were associated with higher prescription radiation dose (14 Gy vs. 13.5 Gy, $p=0.031$).

Our study also demonstrated remarkable mass shrinkage during relatively early follow-up. Specifically, significant shrinkage was observed in 19 patients (73.1%), clinical symptoms were relieved within a short period after GKS for about half of the patients (53.8%), and no complication related to GKS was noted. These results were consistent with previous studies, and the rapid clinical improvement could be a result of rapid volume reduction (Fig. 2).

The optimal radiation dose for mass control and symptom relief still remains debatable. The exposure to higher radiation doses facilitates higher rates of mass control, but it can negatively affect critical structures around the cavernous sinus, such as the optic apparatus or cranial nerves. Therefore, the possibility of this complication usually limits the exposure to high radiation doses. Our results showed that a higher radiation dose tended to induce earlier and greater volume reduction.

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Our study had several limitations. First, CSCHs were not diagnosed according to pathologic findings, but imaging findings. Therefore, there was a small possibility of misdiagnosis, and we tried to minimize the risk of misdiagnosis by performing RBC scan in case of difficult differentiation from other pathology.

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**Table 2. Comparisons between Moderate Remission Group and Remarkable Remission Group**

| Variables     | Moderate remission (n=7) | Remarkable remission (n=19) | $p$ value |
|---------------|--------------------------|-----------------------------|-----------|
| Sex (%)       |                          |                             | 0.904     |
| Male          | 1 (14.3)                 | 5 (26.3)                    |           |
| Female        | 6 (85.7)                 | 14 (73.7)                   |           |
| Age (yr)      | 60.5±10.7                | 52.8±13.8                   | 0.201     |
| Side (%)      |                          |                             | 1.000     |
| Left          | 5 (71.4)                 | 12 (63.2)                   |           |
| Right         | 2 (28.6)                 | 7 (36.8)                    |           |
| Marginal dose (Gy) | 13.3±0.5                  | 13.8±0.6                    | 0.069     |
| Mass volume before GKS (mL) | 10.2±10.2                 | 8.9±6.2                     | 0.698     |
| Mass volume after GKS (mL) (%) | 4.7±4.0                  | 8.0±1.3                     |           |
| GKS, Gamma Knife surgery. |                  |                             |           |

**Fig. 1. Temporal volume changes after GKS in 26 patients. The graph shows rapid mass decrease (within 6–12 months after GKS). The mass volume gradually decreased over 2 years, and no volume re-expansion was observed. GKS, Gamma Knife surgery.**
Second, as about half of the patients in our series were incidentally diagnosed or had no cranial nerve deficit, the rationality of upfront GKS for these lesions could be controversial. Nevertheless, the minimal invasiveness and higher safety of GKS could be a rationale for treating CSCHs that are incidentally found, as well.

Although surgical resection for CSCH is a curative treatment, it is not always easy and safe. Due to the highly radiosensitive nature of CSCH, GKS could be an effective and safe primary treatment modality for CSCH to prevent possible surgical complications. Further studies should be performed to define the natural history of and optimal treatment guidelines for CSCH.

**AUTHOR CONTRIBUTIONS**

Conceptualization: Jin Mo Cho, Won Seok Chang, Hyun Ho Jung, and Jong Hee Chang. Data curation: Jin Mo Cho and Kyoung Su Sung. Formal analysis: Jin Mo Cho and In-Ho Jung. Funding acquisition: Jong Hee Chang. Investigation: Jin Mo Cho and In-Ho Jung. Methodology: Jin Mo Cho and Jong Hee Chang. Project administration: Jong Hee Chang. Resources: Won Seok Chang, Hyun Ho Jung, and Jong Hee Chang. Software: Jin Mo Cho and In-Ho Jung. Supervision: Jong Hee Chang. Validation: Won Seok Chang, Hyun Ho Jung, and Jong Hee Chang. Visualization: Jin Mo Cho, In-Ho Jung, and Jong Hee Chang. Writing—original draft: Jin Mo Cho and Jong Hee Chang. Writing—review & editing: Jin Mo Cho, In-Ho Jung, and Jong Hee Chang. Approval of final manuscript: all authors.

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