Cavernous malformations (CMs) are a subgroup of benign vascular malformations of low-flow sinusoidal origin. Cavernous malformations are associated with hemorrhage and epilepsy. Their estimated prevalence in the general population is 0.4%–4%, and CMs comprise 5%–10% of all intracranial vascular lesions. Approximately 20% of cerebral CMs are located in the brainstem. The annual rate of clinical hemorrhagic events with neurological symptoms of brainstem CMs has been estimated at 2.7%–5% per year, which is much higher than that for CMs in other locations. Repeated hemorrhages may result in severe and irreversible neurological deficits as a consequence of the critical functions of the brainstem. Therefore, symptomatic brainstem CMs should be considered as critical diseases that warrant aggressive management.

The optimal treatment strategy for brainstem CMs remains controversial. Surgery was the first technique developed for the management of CMs. With the improvement of microsurgery and other advances, including modern neuroanesthesia, intraoperative neuronavigation with diffusion tensor imaging, and white matter tractography, in addition to postoperative care techniques, many centers have reported satisfactory outcomes. Although surgically accessible lesions can be managed with excision, the microsurgical resection of brainstem CMs often carries considerable risks of mortality and significant morbidity, including CSF leak, hemiplegia, paraplegia, and lower cranial nerve deficits. Therefore, the approach to aggressive CMs of the brainstem remains a vexing challenge.

During the past two decades, stereotactic radiosurgery (SRS) has arisen as an alternative approach to conventional surgical management for high-risk CMs in the brainstem. Stereotactic radiosurgery can provide a high degree of accuracy, and a rapid radiation dose fall-off at the periphery of target lesions, enabling the clinician to de-
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liver a high radiation dose to CMs and spare healthy brain tissue.\textsuperscript{20} However, despite the theoretical benefits of SRS, only a few studies have reported the use of this treatment modality for brainstem CMs. Those studies that have been published have been limited by their small sample sizes, short follow-up durations, and lack of control groups. All of the published studies have been retrospective observational case series. In particular, no randomized controlled trials comparing SRS and other management options for brainstem CMs have been published.

Given the paucity of available data, we performed a systematic review and meta-analysis of the available data from the published literature to determine the efficacy and safety of SRS for brainstem CMs.

Methods

Data Source and Search Strategy

To identify eligible studies, a literature search was conducted by two of the authors (X. Y. L. and H. S.) in the PubMed, Web of Science, and EMBASE electronic databases, for all reports of brainstem CMs treated with SRS. The following keywords were used: “brainstem,” “radiosurgery,” “radiotherapy,” “gamma knife,” “LINAC” (linear accelerator), “cavernous malformation,” “cavernoma,” and “cavernous hemangioma.” We resolved all differences of opinion through discussion.

Inclusion and Exclusion Criteria

Inclusion criteria comprised original research studies that reported the results of SRS for brainstem CMs exclusively between January 1990 and September 2013. If a study mentioned the treatment of brainstem CMs by SRS, but the patient data were included with the treatment of CMs in other locations, then the study was excluded. No language limitations were applied. If an institution or author had published multiple studies, only the report with the largest sample size was included for the analysis. No limits were set regarding the date of publication or the duration of follow-up. After potential articles were reviewed, reference lists were hand-searched. No records were identified from other sources, such as conference notes or personal bibliographies.

Meta-Analysis

Through this method, 196 studies were initially identified, and 45 duplicate citations were excluded. Of the remaining 151 studies, 146 of records were excluded. The search produced 5 publications that described outcomes for patients treated with SRS for brainstem CMs, and data on 178 patients with brainstem CMs were extracted (Fig. 1).

To standardize the appraisal of study results, pre- and post-SRS hemorrhage rates were calculated. The annual hemorrhagic rates were calculated with the following formula: rate = total number of bleeds in all patients/total number of patient-years in the observation period.\textsuperscript{20}

The observation period comprised the time from the first symptomatic, image-documented hemorrhage to the time of SRS. A meta-analysis was performed for each study. The pre- and post-SRS hemorrhages were counted, the annual hemorrhagic rates were computed, and the risk ratio (RR) was calculated. An RR < 1 indicated that SRS decreased the risk of hemorrhage. The overall RR was computed with the Comprehensive Meta-Analysis software (version 2.0, Biostat). Differences with p values < 0.05 were considered statistically significant.

Results

Systematic Literature Review

The 5 included studies were retrospective case series representing Class III data.\textsuperscript{4,27} A total of 178 patients (91 males, 51.1%) met our criteria and were analyzed in this study. The ages of patients ranged from 5 to 77 years. Overall, 180 brainstem CMs were diagnosed in 178 patients, ranging in size from 0.04 cm\textsuperscript{3} to 14.6 cm\textsuperscript{3}. Five patients had no history of hemorrhage prior to SRS, 119 patients had 1 or 2 episodes of hemorrhage, and 53 patients had 3 or more hemorrhages. All patients had neurodeficits, and the most common symptoms and signs were cranial nerve deficits, hemiparesis, hemisensory deficits, headaches, and coma. Four studies used Gamma Knife surgery (GKS; n = 164 patients), and 1 used LINAC-based SRS (n = 14)\textsuperscript{9,16,17,19,20}

In all patients, the targeted edge of the CM was considered to be the region characterized by mixed signal change within the T2-weighted signal, which was defined as a hemosiderin ring. The surrounding hemosiderin ring was not the CM itself. In general, the targeting of accumulated blood products was avoided because iron breakdown products are potential radiation sensitizers. The mean marginal doses varied between 11 and 15.84 Gy, and the maximal radiation doses ranged from 13 to 47 Gy. Of the 5 studies, 4 had a mean or median follow-up time greater than 24 months. The demographic characteristics of the included patients are summarized in Table 1.

Hemorrhage Rate

The criterion for a post-SRS hemorrhage was the presence of a new hemorrhage in the CM or adjacent brainstem parenchyma on CT or MRI with any new or worsening neurological deficits. The posttreatment observation period extended from the time of treatment until any of the following occurred: the most recent clinical or imaging follow-up, surgical intervention, or death from another cause.\textsuperscript{16} Among the 5 studies, 4 found SRS to be effective in the treatment of brainstem CMs, and 1 study documented no statistical benefit. Four studies reported the postradiosurgical annual hemorrhage rate for the first 2 years of follow-up, and the annual hemorrhage rate after 2 years. Four studies showed a statistically significant reduction in the annual hemorrhage rate from 2 years after SRS treatment. One study reported a pooled post-SRS annual hemorrhage rate rather than using 2 years as a cut-off (Table 1). That study found that there was no statistically significant difference between the pre-SRS and annual hemorrhage rates.

When all of the studies were analyzed, the overall RR was 0.161 (95% CI 0.052–0.493; p = 0.001), which demonstrated that SRS decreased the risk of hemorrhage from.
brainstem CMs 6-fold. There was evidence of some heterogeneity when all 5 studies were analyzed together (Q = 26.099; p = 0.00003; I² = 84.674). However, the p value was < 0.05 for the heterogeneity test; thus, the assumptions made for using a random model to perform the analysis were accurate, although there was no difference when the random model was changed to a fixed model (Fig. 2).

Adverse Radiation Effects

A radiation-induced complication was regarded as a clinical deterioration when there was a signal change around the CMs with no evidence of a new hemorrhage on CT or MRI. During follow-up after SRS, 10 patients died (5.61%). Four patients died because of rebleeding, and the remaining 6 died of either unknown causes or causes unrelated to their CM (1 myocardial infarction, 3 cancer-related, 1 suicide, and 1 unknown). There were no deaths directly attributable to SRS.

Twenty-one patients (11.8%) had new neurological symptoms after SRS in the absence of new hemorrhage. One patient exhibited a new permanent deficit of a painful paresthesia without hemorrhage that occurred 8 months after SRS. Ventriculoperitoneal shunt placement was necessary in 2 patients due to occlusive hydrocephalus. Five patients had collateral edema. In addition, 5 additional patients (2.8%) were discovered to have new T2 signal abnormalities surrounding their CM, but the patients were neurologically asymptomatic. The wide variation that existed in the detail of reporting acute and long-term complications across the 5 studies prevented statistical analysis of these features, but the available information from these studies is provided in Table 2.
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Bleeding from brainstem cavernomas may cause severe deficits due to destruction of critical nerve tissue and the critical ascending and descending white matter tracts and neuronal nuclei. The natural history of brainstem CMs is different from those at other locations, and they have a high rate of bleeding and permanent neurological deficits. After the first hemorrhage, CMs become destabilized, and the risk of further bleeding is increased. Although microsurgical resection represents the treatment of choice in accessible CMs located under the pial or ependymal surfaces, a significant risk remains for the microsurgical intervention of CMs located in the brainstem.

In a systematic review of the literature, Gross and colleagues identified 821 patients with brainstem CMs across 52 surgical series with long-term follow-up data. They reported early postoperative morbidity that ranged from 29% to 67% due to the intraoperative manipulation of neural tissues, changes in microcirculation, and transient postoperative brainstem edema. Long-term follow-up data revealed morbidity and mortality rates of 14% and 1.9%, respectively. Sixteen patients died due to operation-related or other causes. Abla et al. reported the complete obliteration of brainstem CMs in 231 (89%) of 260 patients. Postoperatively, 137 patients (53%) developed new or worsening neurological symptoms. Permanent new deficits remained in 93 patients (36%). There were perioperative complications in 74 patients (28%), and 18 patients (6.9%) experienced 20 repeated hemorrhages. Twelve patients required a repeat operation for residual/recurrent CMs.

In contrast to arteriovenous malformations (AVMs), it is difficult to define what constitutes treatment efficacy for CMs because CMs are angiographically occult malformations. The obliteration of diseased vascular channels cannot be demonstrated by conventional imaging or angiography studies, and a decrease in lesion size is an unreliable measure. Clatterbuck et al. reported a mean volume decrease of 991 mm$^3$ over a 26-month period for 76 observed CMs, which included 55% of cases that decreased in size and 35% that increased in size. The authors of that study claimed that the decrease in size likely reflected the maturation and resorption of blood products. Therefore, postradiosurgical bleeding rates were chosen as an indirect measure of treatment in clinical practice.

The results from the present meta-analysis suggest that SRS is a highly efficacious modality in the management of brainstem CMs. The significant decrease in the hemorrhage rate from 6.8% to 2.0% is a strong indication of the effectiveness of SRS in treating brainstem CMs. The table below summarizes the data from the 5 included studies of SRS for brainstem CMs:

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Mean Marginal Dose (Gy)</th>
<th>Follow-Up (mos)</th>
<th>Hemorrhage Rate (%) Before SRS</th>
<th>Hemorrhage Rate (%) After SRS</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liscák et al., 2000</td>
<td>26</td>
<td>14.76 (median)</td>
<td>24 (median)</td>
<td>4</td>
<td>6.8</td>
<td>GKS</td>
</tr>
<tr>
<td>Monaco et al., 2010</td>
<td>68</td>
<td>15.84</td>
<td>62</td>
<td>32.38</td>
<td>8.22*$1.37†</td>
<td>GKS</td>
</tr>
<tr>
<td>Lee et al., 2012</td>
<td>49</td>
<td>11</td>
<td>40.6</td>
<td>31.3</td>
<td>4.29*$3.64†</td>
<td>GKS</td>
</tr>
<tr>
<td>Fuetsch et al., 2012</td>
<td>14</td>
<td>13.9</td>
<td>85.2</td>
<td>121.8</td>
<td>12.5*$1.8†</td>
<td>LINAC</td>
</tr>
<tr>
<td>Park &amp; Hwang, 2012</td>
<td>21</td>
<td>13</td>
<td>38.9</td>
<td>39.5</td>
<td>8.2*$0†</td>
<td>GKS</td>
</tr>
</tbody>
</table>

* Initial 2 years.
† After 2 years.

FIG. 2. Forest plots of all studies with their respective RRs, events (hemorrhages), and cumulative RRs.
TABLE 2: Documented adverse radiation effects in the 5 studies used in the meta-analysis

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Documented Adverse Radiation Effects (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liscák et al., 2000</td>
<td>hydrocephalus (1), rebleeding (2), collateral edema (5)</td>
</tr>
<tr>
<td>Monaco et al., 2010</td>
<td>neurological deficit (8)</td>
</tr>
<tr>
<td>Lee et al., 2012</td>
<td>cyst developed (1), neurological deficit (1)</td>
</tr>
<tr>
<td>Fuetsch et al., 2012</td>
<td>neurological deficit (2), hydrocephalus (1)</td>
</tr>
<tr>
<td>Park &amp; Hwang, 2012</td>
<td>painful paresthesia (1)</td>
</tr>
</tbody>
</table>

The incidence of radiation-induced complications after SRS for CMs is higher than it is in SRS for AVMs in similar locations with comparable doses. For example, Pollock et al. demonstrated a 59% rate of complications after treatment for CMs compared with 10% for AVMs. Parenchyma surrounds the CM, which contains hemosiderin, a potential radiation sensitizer. The hemosiderin ring may explain the increase in complications. Complication rates of SRS are also related to the radiation dosage. In the review by Pham et al., the application of mean doses of 15–16.2 Gy had low radiation-induced complication rates (0%–9.1%), whereas doses greater than or equal to 16.5 Gy were associated with higher radiation-induced morbidity rates (> 17%). The 5 studies included in our meta-analysis had mean marginal doses of less than 16 Gy. However, the optimal radiation dose, which delivered a therapeutic effect while minimizing radiation-induced injury, remains ambiguous. Although 21 patients had radiation-induced complications, most of the complications were transient and responsive to methylprednisolone treatment. The benefit of the significant decrease in the hemorrhage rate far outweighs the risk of complications.

Despite the best efforts of the authors of the eligible studies, the possibility of selection bias cannot be fully excluded. At present, in the majority of patients, SRS is reserved for patients with contraindications for microsurgery or with recurrent or residual CMs after resection. On the other hand, there were source study biases due to limitations of the quality and accuracy of included studies, as it is impossible for us to control for the quality of the data reported in the articles.

To date, studies regarding the radiosurgical management of brainstem CMs have been flawed by their limited sample size, relatively short follow-up period, and lack of possible comparison of the results with untreated brainstem CMs. These issues highlight the inherent limitations in any meta-analysis that is based on observational data. However, we believe that pooling of the individual series according to a systematic review and meta-analysis enables an improved understanding of the role of SRS in treating CMs in the brainstem. As a next step in the analysis of this treatment, a prospective study with larger numbers of patients who are treated with SRS as the primary treatment modality with longer follow-up periods is needed. Nevertheless, our results suggest that SRS is effective and should be considered as an alternative treatment for brainstem CMs that are inoperable or carry a high operative risk.
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Conclusions

The present study reports the results of a systematic review and meta-analysis of the radiosurgical management of brainstem CMs. Although there are no randomized controlled trials that have evaluated the effectiveness of this approach, the results of our meta-analysis of 5 studies comprising 178 patients with brainstem CMs revealed a decreased rehemorrhage rate after SRS. Additionally, the results appear to be improving with recent advances in technology and care. Based upon the limited available evidence and the findings of the meta-analysis, SRS may confer a benefit to patients with brainstem cavernomas and should be considered for the management of brainstem CMs in cases with high operative risk.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Acquisition of data: Lu, Sun. Analysis and interpretation of data: Lu, Xu. Drafting the article: Lu, Xu. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: Li. Study supervision: Li.

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