Stereotactic radiosurgery for the treatment of symptomatic brainstem cavernous malformations

EDWARD A. MONACO III, M.D., PH.D., AFTAB A. KHAN, M.D., ΑJAY NIRANJAN, M.CH., M.B.A., HIDEYUKI KANO, M.D., PH.D., RAMESH GRANDHI, M.D., DOUGLAS KONDZIOLKA, M.D., F.R.C.S., JOHN C. FLICKINGER, M.D., AND L. DADE LUNSFORD, M.D.

Department of Neurological Surgery and the Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Object. The authors performed a retrospective review of prospectively collected data to evaluate the safety and efficacy of stereotactic radiosurgery (SRS) for the treatment of patients harboring symptomatic solitary cavernous malformations (CMs) of the brainstem that bleed repeatedly and are high risk for resection.

Methods. Between 1988 and 2005, 68 patients (34 males and 34 females) with solitary, symptomatic CMs of the brainstem underwent Gamma Knife surgery. The mean patient age was 41.2 years, and all patients had suffered at least 2 symptomatic hemorrhages (range 2–12 events) before radiosurgery. Prior to SRS, 15 patients (22.1%) had undergone attempted resection. The mean volume of the malformation treated was 1.19 ml, and the mean prescribed marginal radiation dose was 16 Gy.

Results. The mean follow-up period was 5.2 years (range 0.6–12.4 years). The pre-SRS annual hemorrhage rate was 32.38%, or 125 hemorrhages, excluding the first hemorrhage, over a total of 386 patient-years. Following SRS, 11 hemorrhages were observed within the first 2 years of follow-up (8.22% annual hemorrhage rate) and 3 hemorrhages were observed in the period after the first 2 years of follow-up (1.37% annual hemorrhage rate). A significant reduction (p < 0.0001) in the risk of brainstem CM hemorrhages was observed following radiosurgical treatment, as well as in latency period of 2 years after SRS (p < 0.0447). Eight patients (11.8%) experienced new neurological deficits as a result of adverse radiation effects following SRS.

Conclusions. The results of this study support a role for the use of SRS for symptomatic CMs of the brainstem, as it is relatively safe and appears to reduce rebleeding rates in this high-surgical-risk location.

(DOI: 10.3171/2010.7.FOCUS10151)

KEY WORDS • cavernous malformation • brainstem • Gamma Knife • cerebral hemorrhage • stereotactic radiosurgery

SYMPTOMATIC, multiply hemorrhagic CMs of the brainstem present a vexing clinical problem, as they are often not amenable to resection with acceptable risk. While CMs of the brain occur in 0.1%–4.0% of the population, they comprise 8%–15% of all its vascular lesions.3,18,23,27,38 These angiographically occult vascular abnormalities typically occur supratentorially; however, those isolated to the brainstem have been reported to account for 9%–35% of all CMs.7,16,26 A number of causes have been identified for CMs, including genetic, congenital, postsurgical, and postirradiation effects.5,13,29 Up to one-third of patients harboring CMs possess associated DVAs.17,20,26,27,31

The near ubiquity of MR imaging has increased the frequency with which CMs are diagnosed and has better elucidated the epidemiology and natural history of these lesions.1,9,18,21,24,28,33,34 Presentation symptoms correspond with lesion location, and while supratentorial CMs are often identified incidentally or after seizures, those in the brainstem typically produce focal neurological deficits. The annual hemorrhage risk has been estimated to be 0.1%–2.5% per lesion-year and 0.25%–16.5% per patient-year, but this risk is substantially higher (up to 34% annual risk) for patients with prior hemorrhagic events.4,12

Symptomatic CMs of the brainstem can be managed microsurgically, and several centers have documented
acceptable outcomes. However, microsurgery for CMs in this location carries with it high rates of morbidity (up to 35%), demands complete resection, and is only reasonably suited for those lesions that present to an ependymal or pial surface.

Methods

Patient Population

After receiving approval from the University of Pittsburgh institutional review board, we retrospectively analyzed our prospectively collected pre- and post-SRS data obtained in 68 patients (whose brainstem CMs were treated between 1988 and 2005). The average age of patients in this analysis was 41.2 years (range 5–79 years). All patients had previously experienced at least 2 hemorrhagic events, and 36.8% had suffered 3 or more hemorrhages (range 3–12). Bleeding events were defined as the development of a new neurological deficit with coexisting imaging evidence of new blood products in a newly discovered or previously identified CM. Information pertaining to clinical events was obtained via discussions with patients and/or their treating physicians combined with review of all available imaging studies. The diagnosis of CM was made by CT prior to 1990 and by MR imaging after 1990. Sixty-four patients (94.1%) presented with preexisting neurological deficits resulting from CM hemorrhages. Fifteen patients (22.1%) had previously undergone partial microsurgical resection. Half of the patients underwent angiography prior to SRS. These studies failed to identify a vascular abnormality. Only 1 patient (1.47%) was found to have an associated DVA. A summary of the patient characteristics is shown in Table 1.

Radiosurgical Technique

Radiosurgical treatment of CMs was performed as previously described in our reports. Briefly, the Leksell Model G stereotactic frame (Elekta Instruments) was applied to the patients head after the administration of loc

tal anesthetic and, as needed, conscious sedation. For the 3 patients under the age of 12 years, frame application and SRS were performed after induction of general anesthesia. Through 1990, CT scanning was used for dose planning (17 patients), whereas stereotactic MR imaging was used since 1991. Upon the administration of a single-dose of paramagnetic contrast medium (0.1 mmol/kg), we obtained a 3D volume acquisition spoiled gradient recalled in steady-state sequence (1- to 1.5-mm-thick slices). An additional variable echo multiplanar (3/0 thickness) sequence was obtained to identify the hemosiderin signal surrounding the CM. Images were exported to dose-planning workstations for the U, B, C, or 4C Gamma Knife instruments (Elekta Instruments). These immediate pretreatment dose-planning images served as the baseline for future comparison with follow-up images.

Radiosurgery dose plans, with single or multiple isocenters (range 1–9), were created to yield highly conformal (to the lesion’s 3D geometry) and selective (rapid dose fall-off outside the CM margin) dosing (Fig. 1). The targeted edge of the CM 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. In general, targeting of accumulated blood products was avoided because iron breakdown products are potential radiation sensitizers. Dose planning details are summarized in Table 2. Stereotactic radiosurgery was performed with a 201 60Co source Gamma Knife. Following completion of SRS, each patient received a single 40-mg dose of methylprednisolone. All patients were discharged from the hospital within 24 hours.

Follow-Up

Clinical follow-up data were obtained from patients, their caregivers, or referring physicians. Follow-up MR imaging was requested at 6-month intervals during the first 2 years after SRS, after which it was recommended on an annual basis. Sixty-six patients (97.1%) had follow-up of at least 2 years, 40 (58.8%) had follow-up from 2–5 years, 17 (25%) had follow-up from 5–10, and 9 (13.2%) had follow-up for more than 10 years.

Statistical Analysis

Hemorrhage was defined as imaging evidence of a new area of blood density corresponding to a new neurological sign or symptom. The annual hemorrhage rate was calculated using the following formula: total number of hemorrhages in all patients/total number of patient-years observed. Hemorrhage rates were compared before and after SRS using a paired t-test.

Results

Pretreatment Hemorrhage Rate

Pretreatment observation comprised the time from the first symptomatic, image-documented hemorrhage to the time of SRS. Thus, a total of 386 patient-years were observed with a mean pretreatment observation period of 5.68 years (range 1–38 years). There were 193 hemorrhages documented during this time (2.84 per patient). All
radiosurgery for brainstem cavernous malformations

patients had at least 2 hemorrhages prior to SRS (range 2–12). After exclusion of the first hemorrhage (193–68 = 125 hemorrhages), the calculated annual hemorrhage rate was 32.38% (125 hemorrhages in 386 patient-years observed).

Posttreatment Hemorrhage Rate

The observation period following radiosurgery was considered to be the time following treatment until either of the following: most recent clinical follow-up, surgical intervention, or death. Thus, postradiosurgical follow-up averaged 5.17 years per patient (range 0.58–12.41 years) with an overall observation period of 353 patient-years. During follow-up after SRS, 7 patients died (10.3%). Two patients died in the setting of subsequent microsurgical resection of lesions that rebled, and the remaining 5 died of either unknown causes or causes unrelated to their CMs (1 myocardial infarction, 3 cancer related, and 1 unknown). There were no deaths directly attributable to SRS.

Fourteen hemorrhages in 13 patients were documented during this period (0.21 hemorrhages per patient). Eleven of these hemorrhages occurred in 10 patients within a 2-year latency period after SRS, while only 3 were identified after 2 years. The annual hemorrhage rate during the first 2 years after SRS was calculated to be 8.22% (11 hemorrhages/133.75 patient-years). The annual hemorrhage rate after the initial 2-year follow-up was calculated to be 1.37% (3 hemorrhages/219.25 patient-years). Statistical analysis revealed a significant reduction (p < 0.0001) in the annual hemorrhage rate after SRS (32.38% before SRS compared with 8.22% after SRS, respectively; Fig. 2), as well as a reduction in the mean number of hemorrhages per patient (2.84 before compared with 0.21 after SRS, respectively; p < 0.0001). Furthermore, we confirmed a statistically significant reduction (p < 0.0447) in the annual hemorrhage rate following the 2-year latency after SRS treatment (8.22% compared with 1.37%, respectively).

Adverse Radiation Effects

Eight patients (11.8%) had new neurological symptoms following SRS in the absence of a new hemorrhage. In all but 1 of these patients, the neurological worsening was transient and responded fully to a short course of corticosteroids. The remaining patient suffered a permanent new neurological deficit and went on to undergo microsurgical resection. Two additional patients (2.94%) were discovered to have new T2 signal abnormality surrounding their CMs, but the patients were neurologically asymptomatic. Overall, at the most recent follow-up, the neurological condition was either stable or improved in 79.4% of the patients following SRS.

Discussion

It has been observed by our group, 10 and by others, 11,33,37 that symptomatic brainstem CMs have a high rate of rehemorrhage (up to a 60% annual risk) and corresponding neurological deficits. Indeed, brainstem CMs are of unique interest because even bleeding events too

TABLE 2: Summary of brainstem CM radiosurgery dose planning

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>malformation vol (ml)</td>
<td>1.19</td>
<td>0.12–6.8</td>
</tr>
<tr>
<td>no. of isocenters</td>
<td>3.38</td>
<td>1–9</td>
</tr>
<tr>
<td>margin dose (Gy)</td>
<td>15.84</td>
<td>12–32</td>
</tr>
<tr>
<td>maximum dose (Gy)</td>
<td>29.52</td>
<td>16–40</td>
</tr>
</tbody>
</table>

Fig. 1. Magnetic resonance imaging-based SRS dose plan obtained in a 14-year-old boy who had suffered 2 previous symptomatic hemorrhages of a CM of the midbrain and pons. A portion of the dose plan is shown on axial T2- (A) and T1-weighted (B) MR images illustrating the limited dosing to hemosiderin-stained adjacent brainstem parenchyma. Radiosurgery was performed, as shown in a midsagittal MR image (C), with a margin dose of 14 Gy, a maximal dose of 30 Gy, to a total volume of 2.3 ml.

Fig. 2. Bar graph showing the annual hemorrhage rates in the 68 patients with symptomatic multiple hemorrhagic brainstem CMs before SRS, during the first 2 years after SRS, and after a latency period of 2 or more years.
small to be detected with modern imaging can cause profound neurological sequelae. Multiply hemorrhagic, symptomatic CMs of the brainstem are admittedly a rare entity with only a few hundred patients presented in several retrospective series. As such, management of this neurologically devastating problem is not clearly defined. Herein, we have shown that in a highly selective group of patients with surgically high risk symptomatic CMs of the brainstem, SRS is a reasonable alternative treatment with a safety profile similar to or better than other treatment approaches.

Although the treatment of choice for most symptomatic CMs is microsurgical resection, when the lesions are discovered in locations like the brainstem the risks are not trivial. Porter et al.43 reviewed a series of 86 patients who underwent surgery for brainstem CMs. Fifty-two percent of the CMs in this series reached the pial surface. Following surgery, 33% of patients had new cranial nerve deficits, 30% exhibited cerebellar findings, and 29% had new-onset weakness. The overall rate of temporary and/or permanent morbidity and mortality was 35%. Overall mortality rate was 8% and all-cause 30-day mortality rate was 3.5%. Twelve percent of patients had permanent or severe deficits. Eleven patients required additional surgery to either retreat the target lesion or address a complication.

Mathiesen et al.24 reported on a series of patients with deep-seated CMs, including 40 patients with CMs confined to the brainstem, 17 of whom underwent microsurgical resection. They reported a 69% incidence of transient and an 8% risk of permanent neurological deterioration. There was a 15% rate of rehemorrhage after surgery, in each case attributed to subtotal resection. From these data it was concluded that microsurgery for symptomatic lesions was feasible as long as a radical resection could be confidently and safely achieved. In a retrospective series of 137 patients with brainstem CMs treated by microsurgery, Wang et al.32 reported that 4.6% of patients harbored residual CM after surgery and 27.7% experienced deterioration after surgery or developed new neurological deficits. Hauck et al.11 reported on 44 microsurgically treated patients with brainstem CMs, all of whom had symptomatic hemorrhages. Postoperatively, 1 patient was found to have residual a CM and went on to suffer a subsequent hemorrhage. Fourteen percent of the patients experienced increased cranial nerve deficits, 7% had worsened hemiparesis, and 4% had new deafness. In a series of 45 patients with brainstem CMs treated surgically via a supracerebellar infratentorial approach, de Oliveira et al.4 found that 44% of patients had new postoperative deficits with almost half of these being permanent. Twenty-nine percent of patients experienced treatment-related complications including hydrocephalus, CSF leakage, meningitis, and a pseudomeningocele. Four patients required placement of a tracheostomy and feeding tube. Despite postoperative MR imaging that confirmed gross-total resection in 100% of the patients, 7 presented with recurrence, 4 of whom underwent reoperation.

We have previously reported our data on the treatment of surgically high-risk cavernomas6-8,15,22 but never exclusively on lesions localized to the brainstem (midbrain, pons, and medulla). With the continued evolution of imaging techniques, treatment planning, and dose selection we wished to test the hypothesis that SRS for surgically high-risk symptomatic CMs of the brainstem is efficacious and safe. We first identified SRS as being associated with a significant reduction on hemorrhage rates for symptomatic CMs in 1995.14 In our most up-to-date report,22 we showed that in 103 patients with surgically high-risk CMs the rate of rehemorrhage significantly declined from a pre-SRS annual rate of 32.5% to 10.8% in the 2 years following treatment, and to an annual rate of 1.06% thereafter. Adverse radiation effects were observed in 13.5% of patients, with most being transient and most occurring early in the experience. The data presented herein are in good agreement with our previous observations, showing a decrease in the annual hemorrhage rates of symptomatic CMs located exclusively in the brainstem from 32.38% before SRS to 8.22% in the first 2 years after treatment, and 1.37% thereafter. Similar reductions in annual hemorrhage rates have been documented in the literature.

In 57 patients harboring surgically inaccessible CMs, Chang et al.3 observed a pre-SRS hemorrhage annual rate of 9.4% that declined to 1.6% 36 months after treatment. Only 7% of these patients suffered AREs. Using stereotactic Bragg-peak proton beam therapy, Amin-Hanjani et al.2 treated 95 patients with 98 CMs. They observed a reduction in the hemorrhage rate from a pretreatment annual rate of 17.5% to 4.5% after a 2-year latency period. They did, however, have 16% of patients suffer permanent neurological dysfunction and 3% die. Liu et al.21 treated 125 patients with a reduction in the annual hemorrhage rate from 10.3% pretreatment to 3.3% posttreatment. Seventeen (13.1%) of these patients experienced AREs. In a smaller study of 22 patients with CMs treated by SRS, Kim et al.14 documented an annual hemorrhage rate reduction of 35.5%–3.55%, with 6 patients demonstrating AREs. Finally, García-Muñoz et al.8 reported 15 patients treated with SRS and showed that the annual hemorrhage rate decreased from 34.45% to 7.17%. Other reports have failed to reproduce similar reductions in hemorrhage risk but are limited by either their size, details of treatment, and/or limited follow-up.24,31,35

Although Pollock and colleagues31 treated 17 patients and showed a reduction in annual hemorrhage rates from 40% pre-SRS to 2.9% after a 2-year latency period post-SRS, they did not conclude that radiosurgery was protective against hemorrhage. Indeed, 59% of these patients had evidence of AREs, a finding possibly attributable to a high median target dose of 18 Gy causing toxicity in the radiation-sensitized adjacent hemosiderin-containing brain. Some other authors have expressed concerns related to the high risk of reactive edema around treated CMs.9,24 However, this may be the result of adverse effects on coexistent DVAs, as many of the patients in these reports harbored DVAs. Far fewer patients in the current series experienced AREs, with only 11.8% of patients being symptomatic. Surrounding a CM is parenchyma containing hemosiderin, a potential radiation sensitizers. We have previously proposed that radiation dosing to the tissue surrounding the CM may injure this adjacent tis-
sue, causing AREs. Using multiple small isocenters to deliver a highly conformal dose with greater selectivity to the CM target within the T2-defined hemosiderin-stained brain appears to be critical. With such a strategy, we have shown before a decrease in the rate of ARE risk from 18.5% to 8%. In the current study, the mean marginal dose was limited to 15.84 Gy and the mean number of isocenters was 3.38.

We have hypothesized that the radiobiological effect of SRS on CMs is similar to that for arteriovenous malformations: progressive endothelial cell proliferation and hyalinization yielding luminal closure. Gewirtz et al. reviewed the histopathological changes in 8 CMs in a patient who underwent resection after failed SRS treatment (with 18–26-Gy equivalents). These lesions demonstrated fibrinoid necrosis compared with untreated controls but still possessed patent vascular channels. Nyáry et al. identified endothelial cell destruction and marked fibrosis in the connective tissue stroma of a thalamic CM 1 year after 40-Gy irradiation. Taken together with clinical data, these reports suggest that CMs may respond to SRS in a fashion similar to other vascular lesions via delayed luminal closure of vascular channels.

Our study, as with previously published reports on this topic, is limited by its retrospective nature and by the relative rarity of brainstem CMs. Selection bias is likely to contribute to the results of such studies. In this instance, only patients with brainstem CMs who had 2 or more hemorrhages confirmed by the observation of new neurological findings and new MR imaging evidence were evaluated. At our multidisciplinary conference, all patients were judged to have excessive risks for a microsurgical resection based on CM location, size, and lack of contact with a pial or ependymal surface. Unlike the ability one has to observe arteriovenous malformation obliteration with imaging, no such imaging correlate has been identified for CMs. As such, only clinical outcomes serve as the measure of effectiveness. Importantly, the natural history of brainstem CMs has not been fully elucidated. As such, our data, and those of others, cannot refute the possibility that some CMs may bleed repeatedly and then cease to bleed. If such a phenomenon were identified, it would certainly call into question our observations.

Conclusions

The current study lends further support to the role of SRS in the management of a selective group of patients with surgically high-risk symptomatic CMs that repeatedly bleed as an alternative to observation alone. In particular, when these CMs are within the brainstem, highly conformal SRS may reduce the annual hemorrhage rates substantially with an acceptable safety profile and few permanent AREs.

Disclosure

Drs. Lunsford, Kondziolka, and Niranjan are consultants with AB Elekta. Dr. Lunsford is also a stockholder in AB Elekta.

Conception and design: Lunsford, Monaco, Kano, Kondziolka, Flickinger. Acquisition of data: Lunsford, Niranjan, Kano, Kondziolka, Flickinger. Analysis and interpretation of data: Lunsford, Monaco, Kano, Kondziolka. Drafting the article: Monaco, Kano, Grandhi. Critically revising the article: Lunsford, Monaco, Niranjan, Kano, Grandhi. Reviewed final version of the manuscript and approved it for submission: Lunsford, Monaco, Niranjan, Kano, Grandhi, Kondziolka, Flickinger. Statistical analysis: Monaco, Kano, Grandhi. Administrative/technical/material support: Lunsford, Kano, Niranjan, Kano, Grandhi, Kondziolka, Flickinger. Study supervision: Lunsford, Niranjan, Kondziolka, Flickinger.

References

The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. 
**Neuroradiology 42:**327–332, 2000

**J Neurosurg 88:**51–56, 1998

**J Neurosurg 87:**531–536, 1993

**J Neurosurg 102 (Suppl):**207–213, 2005

**J Neurosurg 102 (Suppl):**81–86, 2005

**J Neurosurg 113:**23–29, 2010

**Neurosurgery 37:**591–605, 1995

**J Neurosurg 99:**31–37, 2003

**Neurosurgery 43:**195–201, 1998

**Br J Neurosurg 14:**96–100, 2000

**J Neuroradiol 20:**34–41, 1993

**J Neurosurg 102 Suppl:**56–58, 2005

**Prog Neurol Surg 20:**231–234, 2007

30. Otten P, Pizzolato GP, Rilliet B, Berney J: [131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,553 autopsies.] 
**Neurochirurgie 35:**82–83, 128–131, 1989 (Fr)

**J Neurosurg 93:**987–991, 2000

**J Neurosurg 87:**190–197, 1997

**J Neurosurg 90:**50–58, 1999

**J Neurosurg 67:**518–524, 1987

**Stereotact Funct Neurosurg 64 (Suppl 1):**98–109, 1995

**Neurosurgery 18:**162–172, 1986

**Surg Neurol 59:**444–454, 2003

**J Neurosurg 75:**32–39, 1991


Address correspondence to: L. Dade Lunsford, M.D., Department of Neurological Surgery, UPMC Presbyterian, Suite B-400, 200 Lothrop Street, Pittsburgh, Pennsylvania 15213. email: lunsfordld@upmc.edu.