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Significant Hemorrhage Rate Reduction after Gamma Knife Radiosurgery in Symptomatic Cavernous Malformations: Long-Term Outcome in 95 Case Series and Literature Review

Remedios López-Serrano[a] Nuria E. Martínez[b] M. Elena Kusak[b] Alicia Quirós[c] Roberto Martínez[b]

[a]Department of Neurological Surgery, Getafe University Hospital, Getafe, and [b]Department of Neurological Surgery and Gamma Knife Radiosurgery Unit, Ruber Internacional Hospital, and [c]Department of Mathemathics, León University, León, Spain

Keywords

Cavernous malformation · Gamma Knife radiosurgery · Hemorrhage rate reduction · Adverse radiation effects

Abstract

Background: The natural history of cavernous malformations (CMs) has remained unclear. This lack of knowledge has made treatment decisions difficult. Indeed, the use of stereotactic radiosurgery is nowadays controversial. The purpose of this paper is to throw light on the effectiveness of Gamma Knife radiosurgery (GKRS) therapy. ***Methods:*** The authors reviewed data collected from a prospectively maintained database. A total of 95 patients (57 female and 38 male) underwent GKRS for high-surgical-risk CMs. A total of 76 cavernomas were deeply located (64 lesions in the brainstem and 12 lesions in the thalamus). All of them were located in eloquent regions. The median malformation volume was 1,570 mm^3. The median tumor margin dose was 11.87 Gy, and the mean tumor maximum dose was 19.56 Gy. ***Results:*** Ninety-five cavernous CMs were managed from 1994 to 2014. All patients had experienced at least 1 symptomatic bleeding incident before treatment (only 1 hemorrhage event in 81%). The median length of follow-up review was 78 months. The pretreatment annual hemorrhage rate was 3.06% compared with 1.4% during the first 3-year latency interval, and 0.16% thereafter ($p = 0.004$). Four patients developed new location-dependent neurological deficits, and 3 patients had edema-related headache after radiosurgery. All of them presented full recovery. ***Conclusions:*** The best dosage range for preventing bleeding was identified as between 11 and 12 Gy in our series. Although the efficacy of radiosurgery in CMs remains impossible to quantify, a very significant reduction in the bleeding rate occurs after a 3-year latency interval. No permanent neurological morbidity is reported in our series. These results defend the safety of GKRS in surgical high-risk CM from the first bleeding event.

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E-Mail karger@karger.com
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Remedios López-Serrano, PhD, MD
Department of Neurological Surgery, Getafe University Hospital
Carretera de Toledo (A-42) Km 12,5
ES–28905 Getafe (Spain)
E-Mail lpz.serrano@gmail.com

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Introduction

Cerebral cavernous malformations (CMs) are vascular lesions that occur in approximately 0.37–0.5% of the general population [1]. CMs occur in sporadic or familial forms. The natural history of these lesions is still controversial. CMs located in highly eloquent areas seem to be more aggressive than superficial lesions. This may be the reason that bleeding is more likely to be symptomatic in these locations [2–4]. Bleeding risk seems to increase during the first months after a bleeding episode to 34% per patient-year [5]. This entity is angiographically occult. In 10–30% of patients it is associated with other vascular malformations such as developmental venous anomalies, which could increase the hemorrhage risk [6, 7]. The annual hemorrhage rate of CMs is estimated to be 0.1–2.5% per lesion-year and 0.25–16.5% per patient-year [8].

The most common clinical presentations of CMs are seizures and hemorrhages in superficial lesions and cranial nerve deficits in deep lesions, mainly in the brainstem.

Nowadays, management of CMs is based on observation in asymptomatic patients and microsurgical removal of symptomatic accessible lesions. In cases of microsurgical high-risk symptomatic malformations, radiosurgery management has been used in multiple centers around the world, obtaining unclear results in most cases because of radiation-related morbidity rates, but it seems that some reduction of bleeding rate occurs after this treatment [9, 10].

The purpose of this paper is to shed light on the effectiveness and safety of Gamma Knife radiosurgery (GKRS) in symptomatic patients with CMs in highly eloquent sites, who have bled only once or twice.

Methods

Patient Profile

We retrospectively reviewed our experience during the past 17 years with data collected from a prospectively maintained database. Ninety-five CMs were managed with GKRS from 1994 to 2014 at our institution. The CMs treated were situated in the brainstem (n = 64), thalamus/basal ganglia (n = 12), and hemispheric eloquent areas (n = 19). A total of 76 cavernomas were deeply located (80%). The mean age of patients was 40 years. Gender distribution was 57 females and 38 males.

Diagnostic Criteria, Follow-Up, and Statistical Analysis

Bleed or hemorrhage was defined as the detection of symptoms or new neurological deficits associated with evidence of newly discovered blood products in high-resolution magnetic resonance imaging (MRI) studies. Twenty-five patients had a single hemorrhage and 7 patients had multiple hemorrhages prior to treatment. All patients included in our study had experienced at least 1 symptomatic bleeding incident before treatment.

All patients were studied with MRI special sequences – T1-weighted, T2-weighted, and gradient-echo T2-weighted postcontrast images – as the primary diagnostic tool, followed by a brain angiography study that was normal in every case.

The follow-up review was performed with consecutive MRIs and personal/telephonic interview every 6 months during the first year, yearly thereafter for 2 years, and then biennially, triennially, and every 5 years after 10 years of follow-up. The assessment of episodic clinical events was made with serial reviews of all available MRIs before and after treatment.

The following patient information was obtained prior to Gamma Knife treatment: familial or sporadic form of CM, number of CMs, other previous treatments (radiotherapy, microsurgical resection), and the development of new symptoms or new neurological deficits after bleeding.

After Gamma Knife treatment, the following information was obtained: Karnofsky functional scale, posttreatment bleeding rate, posttreatment complications (edema, headache, new neurological deficit), permanent and nonpermanent postradiation morbidity rate, percentage of lesion regression, and mean volume regression.

The pretreatment hemorrhage rate per patient/year was retrospectively calculated assuming that the lesion was present from birth to the date of treatment. The annual posttreatment hemorrhage rate was calculated using the following equation: total number of hemorrhages in all patients/total number of patient-years observed.

Qualitative variables were compared with the Fisher exact test or the McNemar χ^2 test, as appropriate. Continuous variables were compared using the Student t test or the Mann Whitney test, as indicated. Pearson (r) or Spearman (ρ) correlation coefficient and tests were used for evaluating the relation between continuous variables. The log-rank test for Kaplan-Meier analysis and Cox re-

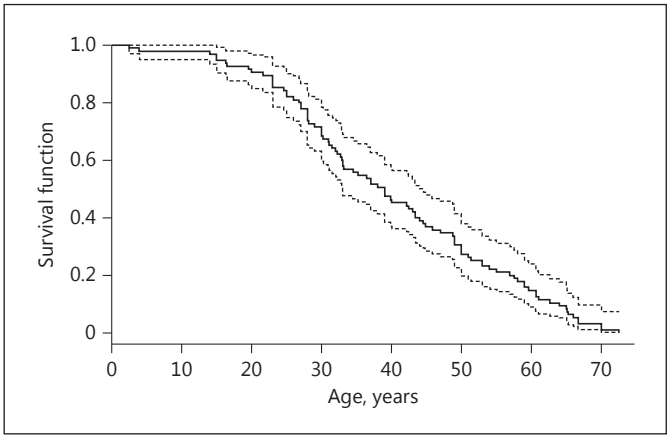

Fig. 1. Hemorrhage-free survival curve illustrating bleeding events (Kaplan-Meier estimate). Hemorrhage events show a most pronounced increase in patients from 30 to 50 years old.

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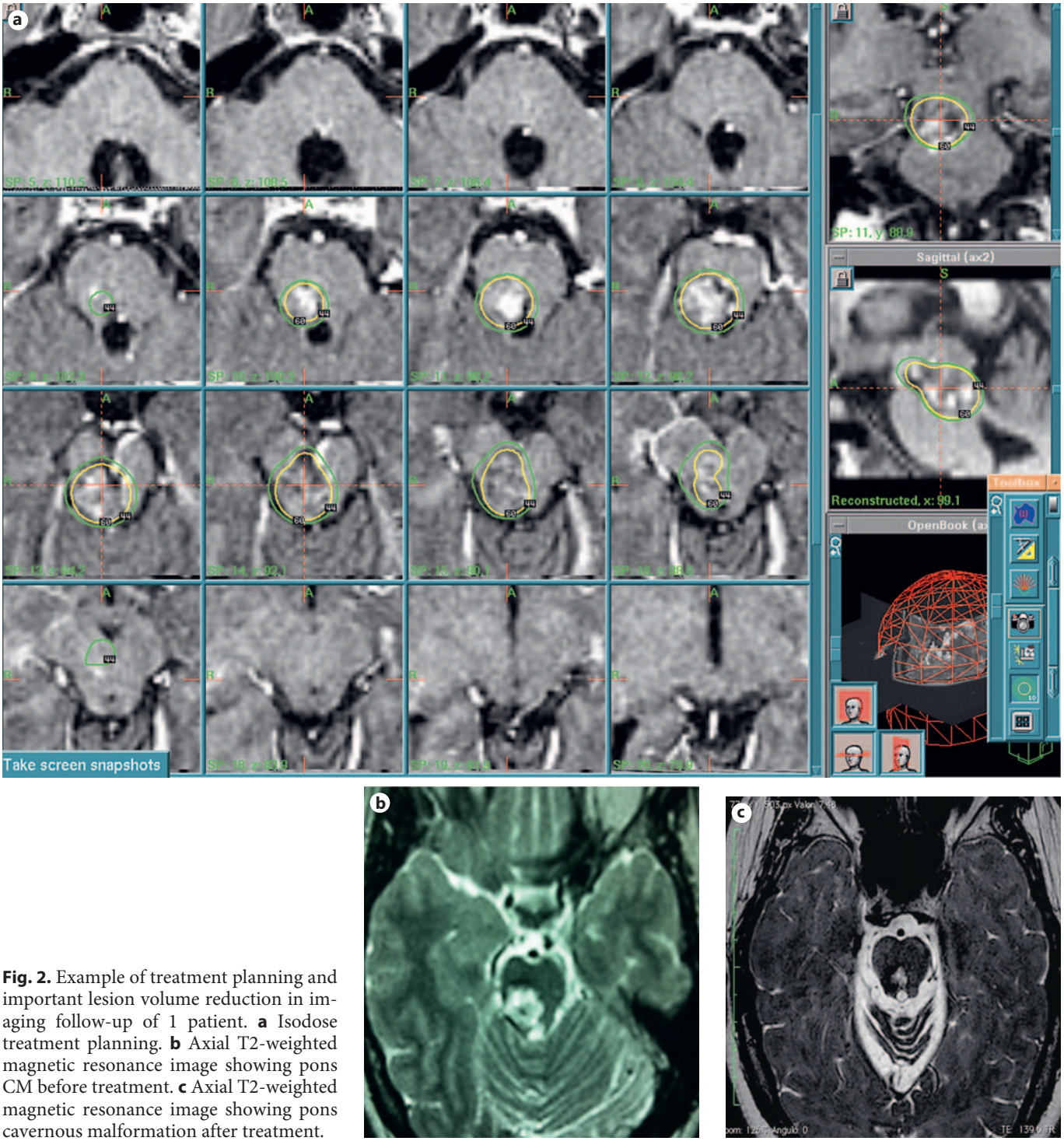

Fig. 2. Example of treatment planning and important lesion volume reduction in imaging follow-up of 1 patient. **a** Isodose treatment planning. **b** Axial T2-weighted magnetic resonance image showing pons CM before treatment. **c** Axial T2-weighted magnetic resonance image showing pons cavernous malformation after treatment.

gression were used in the survival analysis for outcomes. The covariates for the linear and logistic regression models were chosen using the Akaike information criterion for all possible models. Statistical analysis was performed with IBM SPSS software version 20.0 and R Core Team software version 2013.

Treatment Strategy

GKRS was used as the primary treatment in 90 patients and as the secondary treatment after a failed microsurgery in 4 patients.

Initially, a Leksell Gamma Knife model B was used. Since 2000 to 2007, model 4C was introduced. Radiosurgery with Leksell

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Gamma Knife Perfexion was performed thereafter. Stereotactic localization of the CM was obtained with MRI using axial and coronal MRI thin-cut slice images with and without Gd-DTPA enhancement. Thereafter, images were transferred into the Leksell Gamma-Plan workstation for dose treatment planning through the local network using conformal and selective radiation. The target limit was considered as the region characterized by mixed signal change within the T2-defined hemosiderin ring [5]. A neurosurgeon and a radiation oncologist performed dose planning and target selection. The mean interval between the hemorrhage event and the date of stereotactic radiosurgery (SRS) was 6–12 months from bleeding or last bleeding (in cases of multiple episodes). After radiosurgery, all patients received a tapering dexamethasone dose and were generally discharged on the same day of treatment.

Results

Pre-SRS Hemorrhage Rate

Since these vascular malformations could be present at birth, the pre-SRS hemorrhage rate was calculated from the number of hemorrhages in the interval between birth and the date of SRS. Therefore, the observation period is assumed to be the patient's lifetime. A total of 117 hemorrhages occurred in 95 patients. The mean interval between birth and the date of SRS was 40 years. Bleeding episodes appeared most pronounced in patients from 30 to 50 years old (Fig. 1). However, we do not have enough statistical evidence and this fact could be due to overinterpretation of the curve. The occurrence of 117 bleeds in 40 years led to an annual hemorrhage rate of 3.06% (117 bleeds in 3,817 patient-years).

Treatment Details

Fifty to ninety-five percent prescription isodose was used for the margin with a multi-isocenter technique. Vital functional structures were carefully protected. The mean number of isocenters was 4.99 (range: 1–25). The average target volume was 1,570 mm^3 (range: 500–8,100 mm^3). The mean lesion margin dose was 11.87 Gy (range: 8–20 Gy), and the mean maximum dose was 19.56 Gy (range 9.5–32). The mean percentage target coverage (PTC) was 61.77 (range: 50–97). The mean homogeneity index (HI) was 1.65, and the mean conformity index (CI) was 0.95.

Posttreatment Follow-Up

Follow-up imaging after SRS revealed a regression in targeted volume in 39 CMs (Fig. 2). There were no size changes in 30 CMs and unknown imaging status in 26 CMs. As the follow-up extended beyond a mean period of 5 years, the mean regression volume was 50% of the previous total lesion volume. In the multiple regression model, size reduction seemed to relate with patient age ($p = 0.042$) and maximum dose levels ($p = 0.028$).

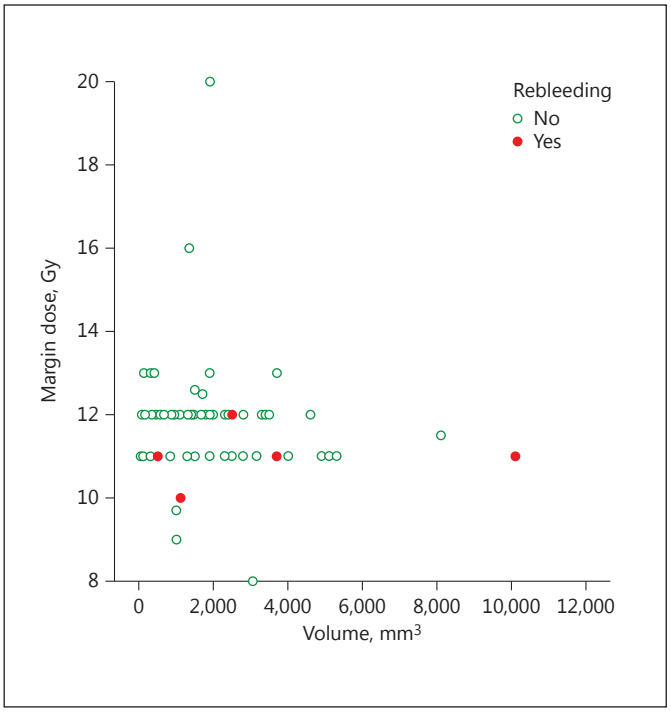

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Fig. 3. Dispersion graph illustrating the relation between rebleeding, margin dose, and target volume. Patients treated with 12 Gy or higher did not present rebleeding.

The posttreatment observation period was from the time of SRS until the last follow-up examination or death. The mean follow-up period was 78 months (range: 6–216 months). After treatment, only 5 bleedings were observed in total. All of them received less than the margin dose of 12 Gy. In our outcomes, Figure 3 shows a trend towards relating posttreatment bleeding with lower margin doses. The Cox regression model did not find a statistically significant association ($p = 0.18$) but the multiple regression model did ($p = 0.03$). Finally, we could identify 11.25 Gy as the best margin dose for preventing bleeding in an ROC curve (Fig. 4), maintaining the same sensitivity and specificity in the dosage range between 11 and 12 Gy. Sensitivity was 80% and specificity was 70%.

Target volume showed a significant influence on treatment outcomes in the Cox regression model ($p = 0.010$). However, the multiple regression model did not find a statistically significant association ($p = 0.13$). These results could be biased by the scarce number of bleeding events (Fig. 3).

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Table 1. Summary of main series

Study	Patients, *n*	SRS type	Mean FU, months	Main margin dose, Gy	AREs, %	Annual hemorrhage rate, %			LI, years
						pre-SRS	post-SRS LI	post-SRS after LI	
Kondziolka et al. [9], 1995	44	GKRS	43.2	16.00	26.00	56.50	NA	1.10	2
Amin-Hanjani et al. [15], 1998	95	PBR	65.0	15.00	20.60	17.30	NA	4.50	2
Chang et al. [16], 1998	57	HI/LINAC	90.0	13.5–20	7.00	9.40	9.40	1.60	3
Karlsson et al. [17], 1998	22	GKRS	78.0	18.00	27.00	NA	10–12	5.00	4
Pollock et al. [14], 2000	17	NA	51.0	18.00	59.00	24.80	8.80	2.90	2
Liu et al. [19], 2005	125	GKRS	64.0	12.10	13.10	NA	10.30	3.30	2
Lunsford et al. [5], 2010	103	GKRS	67.8	16.00	11.65	32.48	10.80	1.06	2
Nagy et al. [2], 2010	113	GKRS	48.0	12–15	7.30	30.50; 2.20	15.00; 5.10	2.40; 1.30	2
Lee et al. [10], 2012	49	GKRS	49.0	11.00	4.10	31.30	10.74	3.33	2
Liscák et al. [18], 2013	112	GKRS	85.0	16.00	15.50	6.50	NA	0.50	2
Kim et al. [29], 2014	39	GKRS	48.0[a]	13.00	10.30	33.60	NA	2.04	2
Azimi et al. [21], 2015	100	GKRS	42.2	13.00	12.00	4.10	NA	1.90	2
Sager et al. [41], 2014	52	LINAC	60.0	15.00	NA	39.00	NA	1.21	NA
Ferdorcsák et al. [42], 2015	51	GKRS	NA	NA	NA	21,70	4.00	0.00[b]	2
López-Serrano et al., this study	95	GKRS	78.0	11.87	7.00	3.06	1.40	0.16	3

AREs, adverse radiation effects; SRS, stereotactic radiosurgery; FU, follow-up; LI, latency interval; GKRS, Gamma Knife radiosurgery; PBR, proton beam radiosurgery; HI/LINAC, linear accelerator radiosurgery; NA, not applicable. [a] Follow-up from diagnosis. [b] Unknown follow-up period.

Five hemorrhages were documented after treatment (0.8% of bleeding events per patient per year) (Table 2). Four of them occurred within the 3-year latency interval after SRS, which led to an annual hemorrhage rate of 1.4% during this period. One hemorrhage was documented after the 3-year latency interval, which led to an annual hemorrhage rate of 0.16% after the latency interval. (Fig. 5). The Fisher exact test of bleeding after and before treatment (divided by the time in years) revealed a significant difference ($p = 0.004$), showing a decrease from 3.06 to 0.16% of bleeding events per patient per year after the latency period (with respect to the whole history of the population). Additionally, the paired comparison between the individual rates (number of bleedings divided by number of years for each patient) is also significant ($p < 0.001$). In 86.5% of patients the posttreatment Karnofsky functional scale performance scores remained between 90 and 100. A summary of the main series is outlined in Table 1.

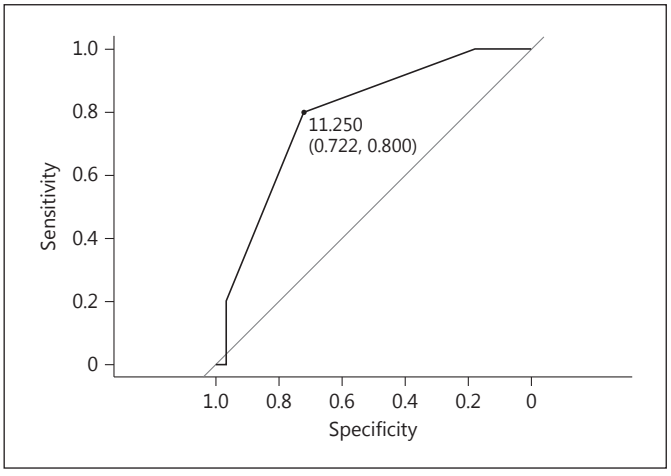

Fig. 4. ROC curve for margin dose, showing 11.25 Gy as the best margin dose for preventing bleeding episodes, maintaining the same sensitivity and specificity in the dosage range between 11 and 12 Gy.

Adverse Radiation Effects

Seven patients developed new non-bleeding-related symptoms after treatment (Table 2). Four patients had temporary neurological deficits approximately 6 months after radiosurgery. Three patients presented edema-related headache. They received a dexamethasone tapering dose with good clinical response, presenting full recovery of symptoms.

One patient with a thalamic CM suffered hemiparesis secondary to a rebleeding event during the posttreatment

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Table 2. Posttreatment bleeding and nonbleeding complications

Complications	Target volume, mm^3	Main margin dose, Gy	Main maximum dose, Gy	Recovery
Non-bleeding-related symptoms (n = 7)				
Headache	1,346	16	32	Yes
Headache	330	12	24	Yes
Headache	164	12	20	Yes
Hemiparesis	4,900	11	18	Yes
VI CN	750	12	20	Yes
Mass effect	3,400	12	20	Yes
VI CN	2,800	11	20	Yes
Bleeding symptoms after LI (n = 1)				
Hemiparesis	1,120	10	12.5	Yes (part)
Bleeding symptoms during LI (n = 4)				
LCN	500	11	16.9	Yes
Hemiparesis	10,100	11	20	No
Hemiparesis	3,700	11	18.3	Yes
Hydrocephalus	2,500	12	21.8	Yes

VI CN, cranial nerve deficit; LI, latency interval; LCN, lower cranial nerve deficits.

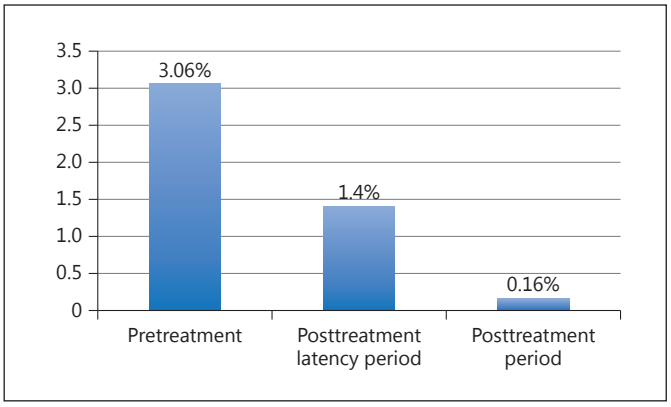

Fig. 5. Bar graph illustrating the annual hemorrhage rates of 95 cavernous malformations before radiosurgery, within 3 years after radiosurgery, and after the 3-year latency interval.

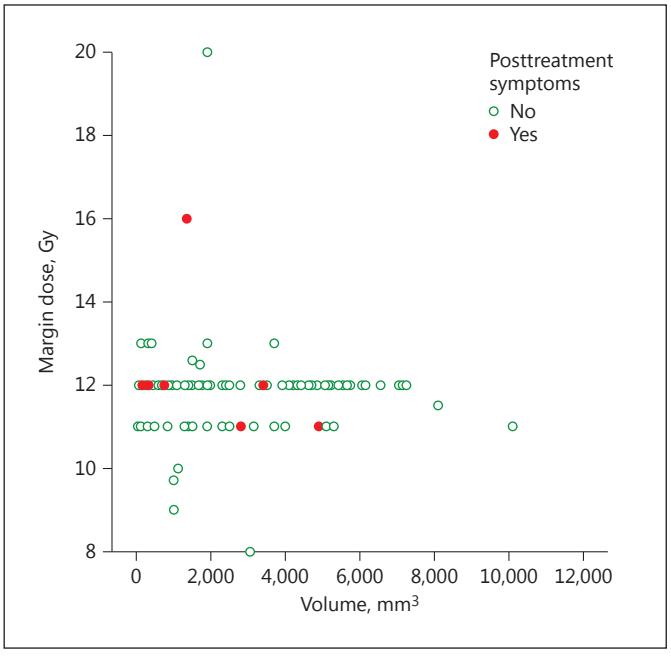

Fig. 6. Dispersion graph illustrating the relation between adverse radiation effects, margin dose, and isodose volume. Posttreatment adverse effects appeared mainly over 12 Gy.

latency period. She underwent microsurgical resection with no recovery and persistence of symptoms. Two patients died of unrelated causes (hepatitis C virus and lung cancer). One patient with familial multiple cavernomatosis presented 2 new CMs after SRS.

Adverse radiation effects (AREs) could be related to higher doses (Fig. 6), although there is no statistically significant association in our study. Volume and coverture dose show a weak negative correlation with AREs (ρ = –0.260, p = 0.011). Using multiple regression analysis, neither posttreatment rebleeding (Fig. 3) nor AREs (Fig. 6) could be related to the prescribed radiation dose, brainstem location, or multiple pretreatment hemorrhages. This could be due to the scarce number of AREs and posttreatment bleeding events in our series.

Discussion

Hemorrhage Rate

The specific indications for treating CMs with SRS remain unclear nowadays. The annual hemorrhage rate of untreated CMs can vary significantly from 0.25 to 32.48% depending on factors such as study design, hemorrhage definition, or prior bleeding incidents [3–5, 11–15].

The rebleeding rate can be significantly reduced after the latency period in arteriovenous malformations (it is typically 2–3 years after radiosurgery to allow thrombo-obliteration to occur). In the case of CMs, different latency periods have been chosen in the literature, from 2 to 4 years [2, 5, 10, 14–19]. There is no way of confirming thrombo-obliteration response by imaging studies, al-

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though it is possible to evidence a decrease in volume with MRI in many cases. This fact also could be due to the natural history of the disease since the size of the CM could spontaneously increase or decrease without treatment.

In our study we presumed that the lesions were present from birth [2, 13, 20]. The bleeding risk could be underestimated, but our intention was to avoid overestimation of the pretreatment hemorrhage rate in order to further validate SRS posttreatment results. Other authors have employed this equation before [16, 21, 22].

In our study, we observed 5 bleedings after treatment in a maximum follow-up of 216 months (18 years), with a mean follow-up of 78 months (6.5 years). In this period, only 1 patient sustained 1 hemorrhage after a latency period of 3 years. The annual hemorrhage rate before treatment was 3.06% per year per patient (calculated from the number of hemorrhages divided by the risk years from the day of birth). The annual hemorrhage rate after treatment was 1.4% per year for the first 3 years followed by 0.16% per year from 3 to 18 years.

In our major series of patients with hemorrhagic CMs located in deep and eloquent areas, we observed a reduction in the annual rate of hemorrhage after the 3-year latency interval from 3.06 to 0.16% ($p = 0.004$). This protection cannot be measured by comparing SRS results with the natural history of the disease because to date this course is unknown, and the hemorrhage risk could vary significantly during follow-up without any treatment. The hemorrhage rate from untreated CMs is described to be high initially (cluster effect), and it could decrease 2–3 years after the hemorrhage event without any treatment [23]. Comparing our results with the natural history series, the hemorrhage rate after treatment is remarkably lower in our series [24–26]. Thus, we can presume some radiosurgery effect.

Amin-Hanjani et al. [15] reported, in a study of 95 patients, a drop in the annual hemorrhage rate from a pretreatment rate of 17.3% per year to a posttreatment rate of 4.5% after 2 years. Chang et al. [16] described 57 treated patients with a pretreatment hemorrhage rate of 9.4%, which was reduced to 1.6% posttreatment after 3 years. Pollock et al. [14] noted a reduction in the annual hemorrhage rate to 2.9% in 17 treated patients. Karlsson et al. [17] described 22 patients treated with SRS with a hemorrhage rate of 5% after a 4-year latency period. Liu et al. [27], in a study of 125 patients, reported a posttreatment hemorrhage rate per year of 3.30% after a 2-year latency period.

Liscák et al. [18] followed up 107 treated patients. The pretreatment hemorrhage rate was 3% (calculated from the number of hemorrhages divided by the risk years from the day of birth) and the posttreatment hemorrhage rate was 1.60% per year after a 2-year latency period. Nagy et al. [2] used the same equation in 113 stratified patients. In the low-risk group there were 62 bleeds in 2,893 patient-years before treatment, with a pretreatment hemorrhage rate of 2.2% per treated lesion per year. The posttreatment hemorrhage rate was 1.3%. In the high-risk group the annual bleeding rate was 2.9% until the first hemorrhage. Thereafter, the annual rebleed rate was 30.5% until treatment. The post-treatment hemorrhage rate was 2.4%. Lunsford et al. [5] reported 103 treated patients with an annual hemorrhage rate before treatment of 32.48% (calculated as the number of hemorrhages in the interval between the first bleeding event and the day of SRS). The reduction in the hemorrhage rate after treatment was 1.06% after a 2-year latency period.

The wide range of results in the pretreatment estimated hemorrhage rate is due to two different equations employed on the final calculation. Some series estimated the risk period starting at birth, while other studies estimated this interval from the first bleeding episode to the rebleeding date in order to avoid overestimation. However, this fact does not affect the posttreatment hemorrhage rate equation, as the rates remained quite similar in the series.

Imaging techniques, treatment planning, and dose conformational selection have evolved throughout the past years, and these are important issues to be taken into account. Recent reports from other reference centers have also demonstrated favorable outcomes after SRS employing remarkably lower margin doses (Table 1). Lee et al. [28] reported 49 patients with brainstem CMs treated with GKRS. The mean marginal dose of radiation was 13.1 Gy (12.8 Gy in group A and 13.7 Gy in group B). The mean follow-up period was 64.0 months. In group A, the annual hemorrhage rate following GKRS was 2.03% after 2 years. In group B, the annual hemorrhage rate was 38.36% prior to GKRS and 1.50% after 2 years. There was no statistically significant difference in the annual hemorrhage rates at each follow-up period after GKRS between the 2 groups. Kim et al. [29] retrospectively analyzed the outcome of 39 patients. The median prescribed marginal dose was 13 Gy. The pretreatment annual hemorrhage rate was 33.6%. Following GKRS, there were 2 hemorrhagic events after the first 2 years (2.4%/year). A significant volume reduction after GKRS was observed in 24 patients (61.5%). Azimi et al. [21] reported a retrospective review of 100 patients. The radiation-related complication developed with a marginal dose of 13 Gy. The hemorrhage rate was 4.1% in the first 2 years after GKRS and

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1.9% thereafter. Finally, Kida et al. [30] collected 298 cases from 23 different Gamma Knife centers across Japan. After the latency period, the posttreatment hemorrhage rate was 2.8% per year. No significant difference in dose-dependent response was seen for 3 different ranges of marginal doses, suggesting that lower margin doses are effective.

Adverse Radiation Effects

In our study of 95 patients, 3 patients suffered symptomatic brain edema with good response to dexamethasone after SRS, and 4 patients suffered new non-bleeding-related cranial nerve damage approximately 6 months after treatment. Only 7.36% of the patients presented worsening of their pretreatment neurological symptoms. All of them fully recovered. Therefore, there is no permanent morbidity without hemorrhage in this series.

AREs are suspected to be related to the radiation dose delivered to the brain tissue immediately surrounding the CM, which may be more likely to release vasoactive cytokines from the iron-impregnated gliotic brain [5]. Preliminary studies observed a higher incidence of complications in the treatment of CMs because of the higher doses used, similar to those used in the treatment of arteriovenous malformations and in similarly critical locations [15, 31, 32]. On account of this, SRS centers expressed reservations because of the high rate of AREs [14, 17]. Margin dose and a central location of the CM were predictors of radiation-related problems in previous reports [14, 17]. These facts seem to be related to higher margin doses. On the other hand, recent studies showed an important reduction in CM rebleeding rates [2, 5, 10, 16], such as the series from Lee et al. [28] of 49 brainstem CMs with a mean follow-up of 49 months and a mean margin dose of 11 Gy, which showed an important reduction of AREs to 4.1%, with an annual hemorrhage rate of 1.74% at 2 years posttreatment.

The possibility of CMs being associated with developmental venous anomalies is another factor to consider in order to avoid potential venous ischemic events and brain reactive edema [33–35].

Microsurgery as the Primary Option

As with every surgical procedure, the risks and benefits should be weighed. Nowadays, there is no consensus about resection indications in brainstem CMs. Most authors agree that symptomatic lesions with a pial or ependymal surface should be considered for resection [36]. However, the indication of surgery in asymptomatic lesions surrounded by deep eloquent tissue is still arguable depending on lesion location, clinical history, and the surgeon's technical expertise [1].

Hauck et al. [37] noted that after the first neurological event, the median event-free interval was 2 years, with an annual event rate of 42%. After 2 events, the median event-free interval was only 5 months, with a monthly event rate of 8%. In 95% of cases surgery successfully prevented further episodes during a median follow-up of 11 months. The postoperative event rate was 5% per year in the first 2 years and 0% thereafter.

Menon et al. [38] reported 23 patients with brainstem CMs who underwent surgical excision using standard skull base approaches. Outcomes were correlated to the number of preoperative hemorrhages, location of the cavernoma, timing of surgery in relation to the hemorrhage, and the preoperative neurological status. Nine patients improved after surgery, 12 deteriorated, and 2 died. In the conservatively managed group, 15 patients had a good outcome, 11 deteriorated, and 1 died. Multiple hemorrhages, poor preoperative neurological status, and surgery during the acute phase were predictive of the surgical outcome.

Most reports conclude that microsurgery of cavernomas must be considered as the primary option in patients with symptomatic hemorrhages whose lesions are in non-critical regions or approaching the pial surface in brainstem and thalamic lesions.

Study Weaknesses

Incomplete knowledge of the natural history of the disease makes it impossible to know which CMs may bleed repeatedly for some time and then cease independently whether treated or not. Unlike angiographic obliteration for arteriovenous malformations, there are no radiographic criteria for therapeutic success in the treatment of CMs [15].

The results of these carefully selected patients with microsurgical high-risk lesions could be affected by selection bias. Our study was retrospectively analyzed, although data were collected from a prospectively maintained database.

Conclusions

In our major series of patients with hemorrhagic CMs located in deep and eloquent areas, radiosurgery reduced the rate of hemorrhage after the 3-year latency interval from 3.06 to 0.16% ($p = 0.004$). This protection cannot be measured by comparing SRS results with the natural his-

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tory of the disease because to date this course is unknown and the hemorrhage risk could vary significantly during follow-up without any treatment. However, we can presume, at least, that there is no risk increase after treatment.

In this study, the results show an important reduction of AREs compared with previous literature [14, 17, 18, 39]. Highly conformal GKRS with a lower margin dose average (margin dose average: 11.3 Gy, range: 8–16 Gy) could be related to the safety of this treatment in recent series. Although no statistically significant difference has been found in this study, the scarce number of bleeding events in our series could bias this result.

Our patients did not present posttreatment permanent complications unrelated to hemorrhage. Rebleeding was remarkably low after the 3-year latency period compared with the rate in other previous series. The dosage range between 11 and 12 Gy was identified as the most adequate for preventing bleeding in our series.

Lee and Lim [40] recently reported that the annual hemorrhage rates in groups of patients with a history of a single or multiple symptomatic hemorrhages were not significantly different. Nagy et al. [2] suggested treating these patients after good results evidenced in his series. Considering that 81% of the studied CMs bled only once in our series, we also defend the safety of GKRS and, thus, intervention in surgical high-risk CM after the first bleeding event.

The pretreatment annual hemorrhage rate was 3.06% compared with 1.4% during the latency interval, and 0.16% thereafter ($p = 0.004$). Our patients are considered as a selected population because almost everyone suffered 1 documented symptomatic hemorrhage with evidence of acute bleeding in MRI. Our results cannot be extrapolated to the entire population. SRS protection cannot be measured by comparing SRS results with the natural history of disease because to date this course is unknown and the hemorrhage risk could vary significantly during untreated patient follow-up. However, we can presume, at least, that a reduction of hemorrhage events is likely. A prospective multicenter randomized trial of conservative treatment versus radiosurgery should be performed in order to verify their real efficacy and related side effects.

Disclosure Statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript. No funding was received for this research.

Author Contributions

R. López-Serrano, N.E. Martínez, M.E. Kusak, R. Martínez, and A. Quirós contributed to the preparation of the paper. R. López Serrano conceived and designed the study. N.E. Martínez was responsible for the acquisition of data. A. Quirós and R. López-Serrano carried out the analysis and interpretation of data. A. Quirós and R. López-Serrano performed the statistical analysis. R. López-Serrano drafted the article. All authors critically revised the article. M.E. Kusak and R. Martínez supervised the study.

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