Contemporary radiosurgery of cerebral cavernous malformations: Part 2. Treatment outcome for hemispheric lesions

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OBJECTIVE The role of radiosurgery (RS) in treating superficial cavernous malformations (CMs) is insufficiently studied in part because of the disappointing results of early experimental attempts as compared to the mostly safe and effective microsurgery. Nonetheless, because of lesion- or treatment-specific factors, a therapeutic alternative may be required. In this study, the authors aimed to assess the safety of RS in treating superficial CMs and to analyze its long-term effect on hemorrhage rates and epilepsy control.

METHODS The authors conducted a retrospective analysis of 96 patients with 109 CMs located in the cerebral or cerebellar hemispheres and treated with RS between 1995 and 2014. A median of 15 Gy (range 10–25 Gy) was given to the 50% prescription isodose level, lesion volume was 604 mm³ (4–8300 mm³), and the prescription isodose volume was 638.5 mm³ (4–9500 mm³). Outcomes were compared to those of 206 deep-seated lesions reported on in another study. Ninety-five patients had available follow-up, which was a median of 7 years (1–21 years). Median patient age was 42 years (0.5–77) at presentation and 45 (3–80) at treatment. Seventy-one CMs presented with symptomatic hemorrhage, and 52 caused seizures.

RESULTS In the nonhemorrhagic group (37 lesions), one bleed occurred during the follow-up period, for an annual bleed rate of 0.4% per lesion. The lifetime annual bleed rate of CMs having a single hemorrhage prior to treatment was 2.5%. The rebleed rate in the single-bleed group decreased from 1.8% within the first 2 years after RS to 0.7% thereafter. The pretreatment rebleed rate for lesions having multiple bleeds prior to RS was 14.15%, which fell to 3.85% for the first 2 years after RS and declined to 1.3% thereafter. Multivariate analysis showed younger age, deep lesion location, and multiple pretreatment hemorrhages as significant predictors of posttreatment hemorrhage.

Pretreatment hemorrhages led to permanent deficits in 41.4% of the cases with a single bleed and in 46.1% of cases with multiple bleeds. Only mild (modified Rankin Scale score 1) and a low rate of permanent neurological deficits were caused either by posttreatment hemorrhages (4.3%) or by radiation (2%).

The rate of improvement in epilepsy was 84.9% after RS in patients with at least one seizure prior to treatment, not depending on the presence of hemorrhage or the time interval between presentation and treatment. Favorable outcome occurred in 81% of patients whose seizures were not controlled with antiepileptic medication prior to RS.

CONCLUSIONS Radiosurgery for superficial CMs is safe and appears to be effective, offering a real treatment alternative to surgery for selected patients. Given their relatively benign natural history, superficial CMs require further study to verify the long-term benefit of RS over the lesions' natural history.

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KEYWORDS cavernous malformation; radiosurgery; hemispheric; epilepsy; hemorrhage; vascular disorders; stereotactic radiosurgery

ABBREVIATIONS AED = antiepileptic drug; ARE = adverse radiation effect; CM = cavernous malformation; ILAE = International League Against Epilepsy; mRS = modified Rankin Scale; RS = radiosurgery.

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RADIOSURGERY (RS) in the management of cerebral cavernous malformations (CMs) is mainly studied in the context of deep-seated lesions as both their natural history and their surgical intervention carry higher risks of morbidity, and therefore a treatment alternative to traditional microsurgery is more warranted.²⁵ Radiosurgery was introduced for the treatment of CMs based on the assumption that their pathological vessels would respond to RS with an obliterative response similar to that of arteriovenous malformations.³³ However, there is no radiological endpoint for RS of CMs; therefore, arguments for the use of RS can only rely on patient statistics based on clinical observations.²⁵ Therefore, most centers still follow a cautious policy, recommending RS only for surgically inaccessible CMs with repeated hemorrhages.¹⁹ Undoubtedly, there is no such pressure to seek a treatment alternative for superficial lesions as they can be safely removed in most cases. This is reflected in the current radiosurgical literature: detailed analysis of a large cohort of superficial CMs has not yet been published.²⁵ From time to time, however, we do encounter patients harboring CMs in an eloquent hemispheric location who choose not to undergo microsurgery or whose patient-specific factors contraindicate resection, raising the question of whether RS may be a potential alternative to microsurgery for symptomatic superficial CMs.

Since the introduction of modern RS for CM, we have treated 345 CMs between 1995 and 2014 in Sheffield, 109 of which had a superficial/hemispheric location with the longest follow-up of 21 years. This group is the subject of the present study, which is the second part of our series on CM RS. We aimed to assess the safety of this technique and to analyze its long-term effect on hemorrhage rates and epilepsy control.

Methods

Patient Details

From among the 319 patients harboring 345 CMs treated with RS between 1995 and 2014 in Sheffield, we analyzed 109 CMs with a superficial/hemispheric location in 96 patients in this study (Table 1) and compared them to a deep-seated lesion cohort.²⁴ Twenty-seven patients had multiple lesions. Forty-nine CMs were treated in these 27 patients during the same radiosurgical session, hemispheric lesions only in 18 patients, and hemispheric lesions with a coexisting deep-seated lesion in 9 patients. There was a slight female preponderance (57%) among the patients included in this study. The median age was 42 years (range 0.5–77 years) at presentation and 45 years (range 3–80 years) at treatment. Sixty-six percent of the lesions presented with symptomatic hemorrhages, the others with epilepsy or a focal neurological deficit without hemorrhage, or they were incidental (accompanying other symptomatic lesions; Table 1). Of the 71 lesions that presented with symptomatic hemorrhage, 58 had bled only once and 13 had had multiple hemorrhages prior to treatment. Six patients (6.25%) underwent surgery (either clot evacuation or failed resection) before RS.

Treatment Details

Stereotactic MRI had been used for localization and

TABLE 1. Location and presentation of hemispheric CMs treated between 1995 and 2014 in Sheffield

Parameter	No.	%
Location		
Cerebellar	15	14
Middle cerebellar peduncle	8	7
Frontal	29	27
Precentral gyrus	6	5.5
Parietal	21	19.5
Temporal	23	21
Occipital	4	4
Centrum semiovale	1	1
Cingulate gyrus	1	1
Corpus callosum	1	1
Presentation*		
Hemorrhage	71	66
Single bleed	58	54
Multiple bleed	13	12
Epilepsy	15	14
Focal deficit	1	1
Incidental	21	19

* Data unavailable for 1 lesion.

target definition in all cases. Patients were treated at two RS centers in Sheffield, either the National Centre for Stereotactic Radiosurgery at the Royal Hallamshire Hospital (1995–2014) or the Thornbury Radiosurgery Centre (2008–2014). The annual number of treated patients gradually reached a median of 6 (range 1–17) by 2000. The median time between presentation and treatment was 2 years (0.5–41 years). Technical details of the treatment and definition of the lesion were similar to those described in the first part of this series.²⁴ A median dose of 15 Gy (range 10–25 Gy) was given to the 50% prescription isodose level, the median lesion volume was 604 mm³ (range 4–8300 mm³), and the prescription isodose volume was 638.5 mm³ (4–9500 mm³). Both prescription doses and lesion volumes were significantly larger than those in the deep-seated cohort ($p < 0.01$).²⁴

Follow-Up

We updated our follow-up database in 2016 by contacting patients or general practitioners. Details of our follow-up protocol are described elsewhere.²⁴ We obtained follow-up information from 95 patients (99%) with a median follow-up of 7 years (range 1–21 years).

In the whole cohort of 319 patients, which includes those with the deep-seated lesions,²⁴ we identified 61 patients (19%) with at least one seizure prior to treatment likely caused by the lesion to be treated. Thus, we excluded all patients with multiple CMs or with an identifiable potential reason for epilepsy that was not related to the treated CM. We were able to contact 53 (87%) of the 61 patients by telephone in early 2017 for supplementary information on their epilepsy. Of these patients, 11 (21%) had had only one seizure at presentation, but only 2 of them were not on antiepileptic drugs (AEDs). As the 5-year risk of epilepsy after the first-ever seizure in patients harbor-

FIG. 1. Bar graph showing bleed rates prior to and after RS. Error bars indicate the 95% confidence interval.

ing CM is 94%¹⁶ and since it is a general practice to put patients on AEDs after their first seizure, we considered patients with a history of seizures as epileptic patients. Those patients who suffered from multiple seizures prior to treatment despite the use of AEDs were considered as the treatment-refractory group.

Definitions and Statistical Analysis

“Symptomatic hemorrhage” is defined as a sudden neurological event with concurrent radiological evidence of a bleed,³ and rates of first hemorrhage were calculated based on the assumption of lesion presence since birth.²⁵ Morbidity was assessed with the modified Rankin Scale (mRS).³⁶ Both hemorrhage and morbidity rates were calculated for

treated lesions. Events unrelated to hemorrhage were classified as transient adverse radiation effects (AREs), permanent AREs, and transient neurological events unrelated to the treatment, as described elsewhere.²⁶ Postradiosurgical seizure outcome was assessed at least 2 years after RS and was classified using the International League Against Epilepsy (ILAE) classification.³⁸ The Mann-Whitney U-test, Fisher’s exact two-sided test, and log-rank test were used for statistical comparisons, and the odds ratio or hazard ratio and 95% confidence intervals are given, as appropriate. For predictors of posttreatment hemorrhage, a binary logistic regression model was used for multivariate analysis. A p value < 0.05 was considered statistically significant.

Results

Rate of Hemorrhage Before RS

Assuming that the malformations were present from birth, the pretreatment hemorrhage rate was calculated as 2.5% per treated lesion per year in the single-bleed group (Fig. 1 and Table 2). The median time between the presenting bleed and RS was 1 year (range 0.5–12 years). In the multiple-bleed group, the annual bleed rate was 2.1% until the first hemorrhage, and the rebleed rate was 14.15% until treatment. The median time between the first bleed and treatment was 4 years (range 1–21 years) in this group, and the median time between the first and second bleeds was 2 years (range 0.3–20 years).

Rate of Hemorrhage After RS

No bleed occurred in the nonhemorrhagic group within the first 2 years after RS, and only 1 occurred thereafter (Fig. 1 and Table 2). The annual bleed rate was 0.4% for the whole follow-up period (95% CI 0–1.2). The annual rebleed rate in the single-bleed group was 1.8% within the first 2 years after RS, which fell further to 0.7% thereafter. In the multiple-bleed group, the rebleed rate was

TABLE 2. Annual hemorrhage rates before and after RS

Group	Hemispheric CM				Deep-Seated CM			
	Before RS		After RS		Before RS		After RS	
	1st bleed	Rebleed	w/in 2 Years	After 2 Years	1st Bleed	Rebleed	w/in 2 Years	After 2 Years
Nonhemorrhagic	—	—	0%, —, 0 bleeds in 75 lesion-yrs	0.4%, 0–1.2, 1 bleed in 241 lesion-yrs	—	—	—	—
Single bleed	2.5%, 1.85–3.1, 57 bleeds in 2291 lesion-yrs	—	1.8%, 0–4.3, 2 bleeds in 110 lesion-yrs	0.7%, 0–1.5, 3 bleeds in 413 lesion-yrs	2.4%, 2.0–2.8, 125 bleeds in 5196 lesion-yrs	—	4.3%, 1.7–6.9, 10 bleeds in 235 lesion-yrs	1.1%, 0.2–2.0, 6 bleeds in 557 lesion-yrs
Multiple bleed	2.1%, 0.9–3.15, 13 bleeds in 635 lesion-yrs	14.15%, 7.4–20.9, 15 bleeds in 106 lesion-yrs	3.85%, 0–11.8, 1 bleed in 26 lesion-yrs	1.3%, 0–3.9, 1 bleed in 76 lesion-yrs	2.8%, 2.2–3.4, 80 bleeds in 2891 lesion-yrs	20.7%, 7.3–24.1, 113 bleeds in 547 lesion-yrs	7.9%, 3.6–12.3, 12 bleeds in 151 lesion-yrs	1.3%, 0.2–2.4, 5 bleeds in 381 lesion-yrs

— = not applicable.

Values expressed as hemorrhage rate, 95% CI, no. of bleeds in lesion-years. Deep-seated data are from Nagy et al., 2018.

FIG. 2. Kaplan-Meier curves of hemorrhage-free survival after RS. **A:** Comparison of nonhemorrhagic (light gray), single-bleed (dark gray), and multiple-bleed (black) groups. **B:** Comparison of hemispheric (light gray) and deep-seated (black) lesion groups. No. at risk (%) refers to lesions.

TABLE 3. Binary logistic regression model for predictors of posttreatment hemorrhage

Parameter	OR	95% CI	p Value
Age in yrs			
0–10	11.6	3.8–57.7	0.002
11–30	1.2	1.0–10.2	0.745
31–50	0.84	0.8–7.0	0.645
>50*	1	—	0.01
Location			
Brainstem*	1	—	0.013
Thalamus/basal ganglia	0.41	0.17–0.94	0.038
Hemispheric	0.33	0.34–0.72	0.006
Presentation			
Hemorrhagic*	1	—	0.001
Epilepsy	0.147	0.056–0.385	0.001
Incidental	0.035	0.006–0.207	0.001
No. of pre-RS hemorrhages (single vs multiple)	1.9	1.22–2.96	0.008
Sex (female)	1.06	0.54–2.05	0.862
Greater lesion vol	1.0	1.0–1.0	0.567

— = not applicable.

Boldface type indicates statistical significance.

* Reference variable.

FIG. 3. Bar graph showing permanent morbidity before and after RS in patients with single and multiple hemorrhages. Overall permanent morbidity as measured with the mRS changed significantly in neither group after RS. Post = persistent neurological deficit at the endpoint of post-treatment follow-up; Pre = morbidity before treatment.

3.85% within the first 2 years after RS, falling to 1.3% thereafter.

The rate of hemorrhage-free lesions was 100%, 96.4%, and 92.3% for nonhemorrhagic, single-bleed, and multiple-bleed groups, respectively, at 2 years after RS and 97.2%, 96.4%, and 92.3% at 5 years after RS (Fig. 2A). The difference between hemorrhage-free survival rates for these subgroups was not significant. The rate of hemorrhage-free lesions for the hemispheric and deep-seated lesion groups was estimated to be 96.1% and 90.7%, respectively, at 5 years after RS (Fig. 2B). Although there was a trend toward a lower chance of hemorrhage-free survival in the deep-seated lesion group in the follow-up period (HR 0.53, 95% CI 0.27–1.06), the difference between the two groups was not significant ($p = 0.075$, log-rank test).

The 9 lesions in pediatric patients (age < 14 years) had a higher hemorrhage rate after treatment (33% vs 5% of the 99 lesions in adults); given the low patient numbers, however, conclusive comparison with adults is not yet feasible.

Multivariate analysis revealed that younger age, hemorrhagic presentation, and deep lesion location were significant predictors for posttreatment hemorrhages (Table 3).

Pretreatment Morbidity

Before treatment, 41.4% of the lesions (95% CI 28.3–54.4) caused permanent neurological deficits after a single original bleed, which was not significantly different from the multiple-bleed group (46.1%, 95% CI 14.8–77.5; Fig. 3 and Table 4). In contrast to the deep-seated lesions with single and multiple bleeds,²⁴ superficial lesions with multiple hemorrhages did not cause a significantly higher proportion of more severe (mRS score > 1) neurological deficits (37.5% vs 50% in the single- and multiple-bleeds group, respectively). There was also no significant difference in persistent morbidity after a single bleed between the hemispheric and deep-seated (48.8%) groups (OR 0.77, 95% CI 0.41–1.43).²⁴

TABLE 4. Pre- and post-treatment mRS in percentage of lesions having more than 1 year of follow-up

Group	mRS Score			
	0	1	2	3–4
Single-bleed group (n = 58)				
Pre-RS mRS	58.6	25.9	13.8	1.7
Morbidity of posttreatment hemorrhage (+mRS)	94.5	5.5	0	0
Morbidity of AREs (+mRS)	98.2	1.8	0	0
Posttreatment end state (mRS)	55.2	27.6	13.8	3.4
Multiple-bleed group (n = 13)				
Pre-RS mRS	53.8	23.1	23.1	0
Morbidity of posttreatment hemorrhage (+mRS)	100	0	0	0
Morbidity of AREs (+mRS)	100	0	0	0
Posttreatment end state (mRS)	53.8	23.1	23.1	0

Posttreatment morbidity is expressed as the percentage of lesions for which scores increased posttreatment to the mRS score shown (+mRS), and other values are expressed as the percentage of lesions for which the mRS score shown was obtained at the time of assessment.

Posttreatment Morbidity

Eight bleeds occurred from 8 lesions after RS, and 3 of them caused permanent disability (37.5%), resulting in an increase of 1 mRS score. Thus, posttreatment hemorrhage-related morbidity was 4.3% (95% CI 0–9.3; Fig. 3 and Table 4).
The rate of transient AREs was 9.3% and the rate of permanent AREs was 1.95% (95% CI 0–4.65; all mRS score 1; Fig. 3 and Table 4). These rates are not significantly different from those in the deep-seated cohort.²⁴ The rate of transient neurological events (focal neurological deficit or headache, excluding epilepsy) without radiological evidence of hemorrhage or perilesional edema was 1.95% after RS.

Epileptic Seizures and RS

All 61 lesions associated with seizures prior to treat-

ment were supratentorial. The rate of epileptogenic lesions was 13% (9/68) in the deep-seated group (thalamic/basal ganglia) and 55% (52/94) in the supratentorial hemispheric group (excluding cerebellar). Sixty-six percent of lesions in the frontal lobe were associated with seizures, which is a higher rate than in other hemispheric locations (50%). Twenty (38%) of the 53 lesions with follow-up presented with seizures; in the other cases (62%) seizures were the consequence of hemorrhage. Five lesions originally presenting with epilepsy bled prior to RS (Table 5), which gives a prospective annual bleed rate of 6.4% (95% CI 0.8–11.9) between presentation and RS.
The seizure rate increased temporarily in 9.4% of the patients within the 1st year after treatment. Using the ILAE classification for posttreatment outcome assessment, we considered class 1–3 as improvement, class 4 as moderate improvement, and class 5–6 or subsequent removal of the treated CM as treatment failure (Table 5). The overall rate of improvement was 84.9% (95% CI 74.9–94.9)—87.2% (95% CI 76.2–98.2) in the hemorrhagic group and 78.6% (95% CI 54.0–100.0) in the nonhemorrhagic group (no significant difference). Favorable outcome did not depend on the time interval between presentation and RS: 85% when CM was treated within 3 years after presentation and 82% when treated later. In the hemorrhagic group, epilepsy improved at the same rate (87%) whether the treatment was performed within 3 years of seizure onset or later. There was no significant difference in this outcome measure in the nonhemorrhagic group either (80% improved after early treatment, 71% improved after later RS). In the ILAE class 1 group (both superficial and deep lesion groups), 33% of the patients (14/42) were off AEDs at the end of the follow-up, which was 26.4% of the entire epileptic cohort. Only one patient in the class 1 group was on a combination of two AEDs; the others were seizure free with AED monotherapy, and 4 patients (9.5%) were able to reduce their AED dose. For patients with seizures refractory to antiepileptic therapy prior to RS, a favorable outcome occurred in 81% (34/42).

Treatments After RS

Five lesions were surgically removed after a post-RS

TABLE 5. Seizure outcome in epileptic patients using ILAE classification

Group	Improved (%)				Mod Improvement (%)	Unchanged (%)	Worse (%)
	Class 1		Class 2	Class 3	Class 4	Class 5	Class 6 or CM Removed
	–AED	+AED					
Deep (no.)							
Epi only (2)	0	0	0	0	0	1 (50)	1 (50)
+Bleed (7)	2 (29)	3 (43)	0	0	1 (14)	0	1 (14)
Hemispheric (no.)							
Epi only (12)	2 (17)	6 (50)	0	3 (25)	0	0	1 (8)
+Bleed (32)	10 (31.3)	19 (59.4)	0	0	0	1 (3)	2 (6.3)
Total							
Epi only	2 (14)	6 (43)	0	3 (21)	0	1 (7)	2 (14)
+Bleed	12 (31)	22 (56)	0	1 (2.5)	1 (2.5)	1 (2.5)	3 (7.5)

Epi = epilepsy; mod = moderate; +Bleed = epilepsy + bleed.

bleed, and one lesion was treated with RS twice. The results of multiple RS treatments is the subject of another study.²⁷

Mortality

Eight deaths occurred during the follow-up period, 5 of which were unrelated to the treated CMs and 2 for which the cause was unknown. One patient died after surgical removal of a hemorrhagic lesion that had been treated with RS earlier. Thus, estimated treatment-specific mortality was 0.9%–2.7%.

Discussion

Natural History of Hemispheric CMs

Six CMs are detected per million population per year, and approximately three-quarters are located superficially (lobar supratentorial and cerebellar).^{2,13} Nearly half of them are asymptomatic at detection, 32% of the symptomatic cases present with seizures, and only 19% present with hemorrhage or focal neurological deficits. Hemorrhagic presentation of superficial CMs is markedly lower than that of deep-seated lesions, which can be as high as 55%–70%.⁴ When treatment is considered, hemorrhage and seizures are the two major clinical factors carrying the risk of long-term morbidity. In order to avoid the earlier confusion caused by the presence of a hemosiderin ring even in asymptomatic cases, we now define hemorrhage as a clinical event of acute or subacute onset symptoms with evidence of concurrent hemorrhage, which has become widely accepted.³ Thus, among recent natural history studies, there is agreement that hemorrhagic presentation and brainstem location are the most significant risk factors for bleeding. The annual bleed rate for CMs in a nonbrainstem location was estimated to be 6.3% and 0.3% with or without hemorrhagic presentation, respectively,^{12,34} and the 5-year risk of intracerebral hemorrhage was 18.4% for ruptured CMs and 3.8% for unruptured CMs in a nonbrainstem location.¹⁵ These are significantly lower estimates than those for deep-seated lesions. Some have suggested that the elevated rebleed risk decreases a few years after the first hemorrhage (“temporal clustering”).⁷ However, in most studies, the rebleed rate did not return to baseline (defined as the annual rate of first hemorrhage) even 5 years after the first bleed.^{15,34} Although hemorrhage from CMs is less severe than hemorrhage caused by other vascular malformations, the risk of morbidity is not negligible.⁸ Five-year morbidity for unselected cases was found to be 37%²³ and can reach as high as 60% for cases in the brainstem.³¹ However, it is not clear whether subsequent bleeding episodes cumulatively increase permanent disability in superficial lesions as they do in deep-seated CMs.^{26,35}

Seizures related to CMs are thought to be induced by surrounding hemosiderin deposition, perilesional gliosis, and inflammation.⁶ The 5-year risk of a first unprovoked seizure has been reported to be relatively low: 6% in CMs presenting with hemorrhage or focal neurological deficit and 4% in incidental lesions.¹⁶ In contrast, the 5-year risk of developing epilepsy after a single seizure reaches 94%. In one study, despite the fact that 97% of the patients were

prescribed AEDs and 46% were receiving polytherapy, only 53% of them achieved 2-year seizure freedom.¹⁶

In the present study, 66% of the lesions presented with hemorrhage, 12% bled repeatedly, and the annual rate of first hemorrhage was approximately 2% with a rebleed rate of 14%, in line with findings in other studies. Forty-one percent of the single-bleed lesions and 46% of the multiple-bleed lesions caused persistent morbidity; the difference between the two groups was not significant, reflecting a more benign natural history, in contrast to the deep-seated lesions, in which subsequent bleeds caused significant neurological deterioration.²⁶ All lesions causing seizures prior to treatment were supratentorial, and the rate was 13% in the thalamic/basal ganglia group and 55% in the lobar group. Forty-two percent of the hemorrhagic supratentorial lobar lesions caused seizures after a bleed, and CMs with nonhemorrhagic epileptic presentation had a higher risk of a later bleed than that estimated in population-based studies,⁴ with a prospective annual bleed rate of 6.4%.

Management of Hemispheric CMs

Because of the relatively benign natural history of hemispheric lesions, intervention is generally only advocated for symptomatic lesions.¹ Surgery is the treatment of choice in most cases given its low morbidity combined with high effectiveness.³⁰ In large series the rate of surgical morbidity for hemispheric lesions is around 5%, mortality is negligible, and the rate of complete resection is 98%.^{5,14,28} Outcome is best for noneloquent lesions, but a poor visual outcome was reported in 31% of occipital CMs after resection,¹⁷ and surgical removal in highly eloquent lesion locations such as a speech area sometimes cannot be safely performed even with the help of the most advanced techniques.¹⁰ Surgery is also generally recommended for CMs causing epilepsy resistant to conservative management.⁹ A favorable outcome is achieved in 71% of cases after resection of a single lesion, with the best chance if seizures are already medically controlled (81%). If the CM is resected within 1 year after presentation, the rate of a favorable outcome is 81%; if gross-total resection is performed, the rate is 77%; if there is resection of hemosiderin in addition to lesionectomy, the rate is 76%; and if using intraoperative electrophysiology, the rate is 78%.⁹ Knowing that nearly all patients harboring CMs who present with seizures go on to develop epilepsy within 5 years and that only half of these cases can be controlled medically, some surgeons advocate early surgical intervention.¹⁸

Thus, with a safe and effective surgical option in hand, the question becomes whether RS is a treatment alternative to microsurgical resection in selected patients under some circumstances, such as an eloquent lesion location, certain medical conditions, or patient preference.

Role of RS in the Management of Hemispheric CMs

The role of RS in the management of surgically inaccessible deep-seated CMs is well studied, but less is known about the benefit of RS for superficial hemispheric lesions as the need rarely arises.²⁵ Therefore, our knowledge is based on the pioneering paper published on modern RS for deep-seated CMs with multiple prior hemor-

rhages.²⁰ The authors' findings of a dramatic decrease in the annual rebleed rate from 32% pretreatment to 1.1% within 2 years after RS and low treatment-related morbidity have been confirmed by numerous contemporary studies adopting highly conformal planning and modern definitions regarding patient selection and follow-up criteria.²⁵ Specifically, the target is defined strictly within the hemosiderin ring while avoiding associated developmental venous anomalies, and a lower prescription dose (< 20 Gy) is used. Treatment is delivered after resolution of the last hemorrhage. These measures led to a low rate and minimal degree of persistent AREs when treating deep-seated CMs.²⁵ Reflecting the fact that most centers focus their attention on deep-seated lesions, we found only three papers providing sufficient information on the morbidity of superficial lesions when we recently reviewed the contemporary radiosurgical literature.^{11,21,22} According to data in these studies, the rate of persistent AREs is about 1%. Morbidity related to posttreatment hemorrhages can be estimated to be similar to that in deep-seated lesions, but hemorrhage rates were not usually calculated in this subgroup separately.

The recognition of limited information prompted us to review our current practice of RS for CMs located superficially. As in most other centers, our practice is dominated by the treatment of deep-seated lesions;²⁴ only about one-third of the lesions treated at our institutions were located superficially. After being reassured by our early experience on the safety of RS for CMs, we have treated an average of 6 superficial CMs annually. The main indications were symptomatic hemorrhage or epilepsy (80%), and we also treated incidental lesions in patients with multiple CMs together with the main symptomatic target. The principles of treatment planning were similar to those for deep-seated CMs apart from a significantly higher prescribed dose (15 Gy). The rates of both persistent AREs (2%) and posttreatment bleed-related morbidity (4.3%) were low and mild (all an increase of 1 mRS score), and the only fatality related to the treated CM occurred after a bleed and subsequent surgery. Only 8 bleeds occurred during the whole follow-up period in the entire cohort, 5 during 730 lesion-years of observation after the 2-year latency period following RS, giving an annual bleed rate of 0.7%. The long-term hemorrhage rate was even lower when considering only adults, 0.3% (5 bleeds in 662 lesion-years). Importantly, the annual rebleed rate was 14.15% until treatment in the multiple-bleed group, which fell to 3.9% within the first 2 years after RS and to 1.3% thereafter. Moreover, the annual rebleed rate in the single-bleed group was not higher within the first 2 years after RS (1.8%) than the rate of the first bleed (2.5%), which fell further to 0.7% thereafter. In comparison, the deep-seated lesion posttreatment bleed rates were not significantly different. Multivariate analysis showed a deep lesion location besides multiple pretreatment hemorrhages as a significant predictor of posttreatment hemorrhages (Table 3).

The role of RS in the treatment of epilepsy caused by CM was first investigated in 2000 in a retrospective multicenter study analyzing 49 patients without any prior bleeding.³² It was demonstrated that 53% of the patients suffering from epilepsy refractory to medical therapy for

more than 1 year became seizure free, and 20% showed significant improvement (73% overall improvement rate). Similar results were found in more recent studies,^{21,37} although the outcome appeared to be better in the sporadic seizure group than in the chronic epilepsy group.²¹ A better radiosurgical outcome was reported with a short history of epilepsy (≤ 3 years), with 90% of patients experiencing improvement.³⁷ In the present study, the overall rate of improvement was 85%–87% in the hemorrhagic group and 78.6% in the nonhemorrhagic group (not significant). Moreover, in the seizure-free group, 33% of the patients were off AEDs, and 9.5% were able to reduce their AED dose. Favorable outcome in our study did not appear to depend on the timing of the intervention. Favorable outcome occurred in 81% of patients whose seizures had not been controlled with antiepileptic medication prior to RS.

Study Limitations

Although our results demonstrate the safety of RS for superficial CMs and the procedure's effectiveness appears to be compatible with microsurgery in terms of both bleeding prevention (especially in the adult population) and seizure control, the weakest points of our study are its retrospective design and lack of a matched control group. Skeptics advocate a prospective randomized controlled trial to clarify the conflicting issues surrounding the different management options for CM.²⁹ For deep-seated lesions without or with only minimal morbidity, we consider RS to be more favorable than resection, and we think that the decisive question is between observation and RS once such lesions become symptomatic.²⁵ As regards superficial lesions, we agree with recent recommendations that microsurgery is the treatment of choice for the symptomatic ones in eloquent locations.¹ However, for symptomatic CMs in eloquent locations, which carry a higher surgical risk, it is reasonable to ask which treatment modality is better. As superficial CMs are more common, it would be an optimal group for a prospective randomized trial or a prospective case control study in order to address these questions, especially compared to the rarer and more aggressive deep-seated lesion group.

Conclusions

While surgery is the treatment of choice for most symptomatic superficial CMs, under some circumstances such as an eloquent lesion location, certain medical conditions, or patient choice, an alternative treatment may be needed. Radiosurgery appears to stabilize the rebleed risk at a very low rate after a 2-year latency period, especially in the adult population, with a very low treatment-specific morbidity. Moreover, we can achieve good seizure control in the majority of epileptic cases. Thus, it can be an attractive alternative for selected superficial lesions.

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Disclosures

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

Conception and design: Radatz, Nagy, Kemeny. Acquisition of data: Nagy, Stokes, Bhattacharyya, Yianni, Rowe, Kemeny. Analysis and interpretation of data: Nagy. Drafting the article: Nagy. Critically revising the article: Radatz, Erőss, Bhattacharyya, Yianni, Rowe, Kemeny. Reviewed submitted version of manuscript:

Radatz, Erőss, Bhattacharyya, Yianni, Rowe, Kemeny. Approved the final version of the manuscript on behalf of all authors:

Radatz. Statistical analysis: Nagy. Administrative/technical/material support: Stokes. Study supervision: Radatz.

Supplemental Information

Companion Papers

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