Contemporary radiosurgery of cerebral cavernous malformations: Part 1. Treatment outcome for critically located hemorrhagic lesions

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OBJECTIVE Long-term benefits of radiosurgery (RS) applying modern protocols to treat cavernous malformations (CMs) remain unclear as critics may consider the decrease in the rebleed rate generally observed 2 years after RS as a reflection of the lesion's natural history. The authors adopted an early intention-to-treat attitude since rehemorrhage from deep-seated CMs ultimately leads to stepwise neurological deterioration. The safety of this early policy was previously demonstrated. Here, the authors revisit their current practice in a larger population with a longer follow-up time to assess the long-term effects of RS in the context of current knowledge on the natural history of CMs.

METHODS The authors conducted a retrospective analysis of 210 patients with 210 hemorrhagic CMs located in the brainstem, thalamus, or basal ganglia and treated with Gamma Knife RS between 1995 and 2014. Two hundred six patients had available follow-up, which was a median of 5.5 years (range 1–20 years). The median age was 37 years (0.5–77 years) at presentation and 43 (2–78) at treatment. One hundred twenty-seven CMs had bled once and 83 had had multiple hemorrhages prior to treatment.

RESULTS The lifetime annual bleed rate of CMs having a single hemorrhage prior to treatment was 2.4% per lesion. The hemorrhage rate stabilized at 1.1% after a temporary increase of 4.3% within the first 2 years after RS. The annual pretreatment hemorrhage rate was 2.8% for the lesions having multiple bleeds prior to RS with a pretreatment rebleed rate of 20.7% and with a modest gradual decrease within the first 5 years and remaining stable at 11.55% thereafter. The rebleed rate fell to 7.9% for the first 2 years after RS and declined further to 1.3% thereafter, which was significantly lower than the long-term pretreatment rebleed risk. The rate of hemorrhage-free survival remained 86.4% and 75.1% (1 patient each) at 20 years after RS in the single- and multiple-bleed groups, respectively.

Pretreatment hemorrhages resulted in permanent deficits in 48.8% of the cases with a single bleed and in 77.1% of the cases with multiple bleeds. Both the rate and severity of deficits were significantly lower in the first group. Only mild and a low rate of permanent neurological deficits were caused either by posttreatment hemorrhages (7.4%) or by radiation (7.2%). The rate of persistent morbidity in the single-bleed group remained significantly lower at the end of the study than pretreatment morbidity in the multiple-bleed group (OR 2.9, 95% CI 1.6–5.3). Lesion-specific mortality was < 1%.

CONCLUSIONS The hemorrhage rate of CMs after RS remained low after the first 2 years during the longer follow-up period. The benefit of early treatment appears to be confirmed by the study results as repeated hemorrhages carry the risk of significantly higher cumulative morbidity than the morbidity associated with RS.

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KEYWORDS cavernous malformation; radiosurgery; brainstem; thalamus; basal ganglia; hemorrhage; vascular disorders; stereotactic radiosurgery

ABBREVIATIONS ARE = adverse radiation effect; AVM = arteriovenous malformation; CM = cavernous malformation; mRS = modified Rankin Scale; RHH = Royal Hallamshire Hospital; RS = radiosurgery; TRC = Thornbury Radiosurgery Centre.

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DESPITE increasing numbers of publications with positive results²⁷ and our better understanding of the natural history of cerebral cavernous malformations (CMs),^{13,16,38} the role of radiosurgery (RS) in the management of these lesions remains controversial¹⁴ given the heterogeneity of available data and the lack of quality evidence.³³ Radiosurgery was introduced for the treatment of CMs based on the assumption that their pathological vessels would have a post-RS obliterative response similar to that of arteriovenous malformations (AVMs).^{21,37} However, unlike for AVMs, there is no radiological endpoint for RS of CMs; therefore, arguments for the use of RS rely solely on patient statistics.²⁷ Therefore, most centers generally follow the original cautious policy of recommending RS only for surgically inaccessible CMs with repeated hemorrhages.²⁰ Our policy has been intuitively more proactive from the beginning, treating CMs even after their first hemorrhage. If left untreated, repeated hemorrhages can lead to stepwise neurological deterioration especially from deep-seated lesions (located deep to the brainstem, thalamus, or basal ganglia); therefore, a minimally invasive treatment with low morbidity such as RS should have been considered even if the long-term benefits had yet to be confirmed.²⁸ When reviewing our practice of treating deep-seated CMs up to 2008, we, like other authors,^{15,18} found RS to be not only safe but also apparently effective, dramatically reducing annual rebleed rates after a latency period of 2 years.²⁹ These results reassured us to continue our proactive practice,²⁸ which has also been adopted by others.^{3,23,32}

Since the publication of that earlier report,²⁹ several studies have provided data confirming the reproducibility of good outcomes after contemporary CM RS.²⁷ Thus, the most important remaining question is whether the clinical course of CMs following RS is truly better than their natural history. Given that several good-quality natural history studies with large patient cohorts have recently been published,^{16,24,38} we believed it would be worthwhile to revisit our current practice in the context of recent knowledge. The number of deep-seated CMs treated with modern RS in Sheffield reached 236 by the end of 2014 with the longest follow-up of 20 years, allowing us to perform an in-depth analysis of the effect of different presentations on long-term outcome. The results of our analysis of 210 critically located hemorrhagic CMs are presented here.

Methods

Patient Details

Three hundred thirty-four patients harboring CMs were treated with RS between 1986 and 2014 in Sheffield at either of two RS centers, the National Centre for Stereotactic Radiosurgery at the Royal Hallamshire Hospital (RHH) and the Thornbury Radiosurgery Centre (TRC; Fig. 1). We excluded 15 patients treated during the early experimental phase due to poor treatment definition as treatment planning had been based only on CT scans.²⁶ This left 345 lesions in the remaining 319 patients since 1995. Of these, we analyzed 210 CMs located in the brain-

FIG. 1. Flowchart indicating the number of CMs and patients treated with RS at both centers in Sheffield. Two hundred ten patients with 210 lesions harboring deep-seated CMs were included in this study; 206 patients had available follow-up data (black). Twenty-one patients with 26 nonhemorrhagic CMs, 96 patients with 109 hemispheric/superficial CMs,³⁰ and 7 lesions in 7 patients with repeat RS are subjects of separate analyses (gray).³¹

TABLE 1. Location and presentation of deep-seated CMs treated between 1995 and 2014 in Sheffield

Parameter	No.	%
Lesion location		
Brainstem	155	74
Medullary	16	10.3
Pontomedullary	18	11.6
Pontine	70	45.2
Pontomesencephalic	12	8
Midbrain	32	20.6
Mesencephalo-thalamic	7	4.5
Thalamus/basal ganglia	55	26
Thalamomesencephalic	8	14.5
Thalamic	26	47
Basal ganglia	8	14.5
Paraventricular	6	11
Internal capsule	1	2
Subinsular	6	11
Presentation		
Brainstem		
Single bleed	91	59
Multiple bleed	64	41
Thalamic/basal ganglia		
Single bleed	36	65.5
Multiple bleed	19	34.5

stem, thalamus, or basal ganglia in 210 patients who had presented with hemorrhage (Table 1), among which were 103 lesions in 103 patients who had been reported on in our earlier study with a shorter follow-up.²⁹ Forty-two patients had multiple lesions, and hemispheric lesions in addition to the deep-seated CM were treated in 8 patients during the same session. There was a slight female preponderance (54%) among the patients. The median age was 37 years (range 0.5–77 years) at presentation and 43

(range 2–78) at treatment. One hundred twenty-seven CMs had bled only once and 83 had had multiple hemorrhages prior to treatment (Table 1). Before RS, 21 patients (10%) underwent surgery—either clot evacuation, with or without partial resection, or shunt insertion.

Treatment Details

As an inclusion criterion for this study, stereotactic MRI had been used for localization and target definition. Our standard protocol is to perform T2-weighted and proton density imaging using 1.5-mm slices, TE 80 msec, TR 3000 msec, 256 matrix, number of signal averages 1. GammaPlan (Elekta AB) was used for dose planning. Treatments were delivered with the Gamma Knife model RBS 5000 (Nucletec) until 2001, Gamma Knife Model C (Elekta AB) until 2011, and Gamma Knife Perfexion (Elekta AB) thereafter in the RHH and all with Perfexion in the TRC. The number of treated patients gradually increased from 3 in 1995 to an annual average of 20 more recently (Fig. 2A). The median time between presentation and treatment was 1 year (0.1–34 years). Cavernous malformations were defined within the hemosiderin ring and were treated after complete resolution of the last hematoma, and a median dose of 12–13 Gy (depending on location) was given to the 50% prescription isodose level, excluding co-existing developmental venous anomalies.²⁷ Our standard treatment protocol has not changed essentially since 1995, apart from a significant reduction in the prescription dose from 15 to 12 Gy after 2000 ($p < 0.001$; Table 2).

Follow-Up

Treated patients are assessed primarily clinically in the referring neurosurgical unit, supplemented with reimaging as indicated. We recommend clinical follow-up in 6 months' time within the 1st year after RS and annually thereafter in an uneventful clinical course. As there is no radiological endpoint to demonstrate the effect of RS, and without new symptoms there is no therapeutic reason for

FIG. 2. A: Bar graph showing the number of patients treated each year. **B:** Follow-up times for our previous study²⁹ (median 4 years, range 0.5–13 years; 99 patients) and our current study (median 5.5 years, range 1–20; 206 patients).

TABLE 2. Summary of radiosurgical parameters

Parameter	Lesion Location		Median (range)		
	Brainstem	Thalamus/BG	Treatment Period		
			1995–2000	2001–2009	2010–2014
TV (mm ³)	240* (10–8400)	537 (3.5–5200)	442† (25–3142)	303 (22–8400)	208 (3.5–4470)
PIV (mm ³)	260‡ (11–6100)	620 (83–5000)	503† (43–3800)	372 (11–6100)	233 (31–4810)
Prescription isodose (%)	50 (41–81)	50 (41–84)	50 (45–75)	50 (41–90)	50 (41–84)
Prescription dose (Gy)	12 (10–18)	13 (12–20)	15‡ (10–20)	12 (10–17.5)	12 (11–16)
Max dose (Gy)	24 (12–35.6)	26 (15.5–40)	28‡ (18–40)	24 (17.1–36.7)	24 (12–32)

BG = basal ganglia; PIV = prescription isodose volume; TV = target volume.

Treatment periods reflect on the utilization of developing equipment: Gamma Knife model RBS 5000, Model C, and Perfexion.

* $p < 0.01$.

† Not significant.

‡ $p < 0.001$.

imaging, we continue our earlier practice of recommending reimaging only in cases of clinically significant events.^{21,29} We updated our follow-up database in 2016 by contacting patients or general practitioners. In cases with clinically significant events reported, we requested detailed clinical information and scans from local hospitals. For deceased patients, information on the cause of death was obtained from either general practitioners or local hospitals. We obtained follow-up information for 206 patients (98%) with a median follow-up of 5.5 years (range 1–20 years; Fig. 2).

Definitions and Statistical Analysis

“Symptomatic hemorrhage” is defined as a sudden neurological event with concurrent radiological evidence of a bleed.⁵ Rates of first hemorrhage were calculated based on the assumption of lesion presence since birth.²⁷ Morbidity was assessed with the modified Rankin Scale (mRS).⁴³ Scores were assigned by the first author based on reported neurological deficits and individual patient questionnaires addressing their daily activity. Both hemorrhage and morbidity rates were calculated for treated lesions, as opposed to patients. Any clinical deterioration after RS was investigated with reimaging to exclude hemorrhage. Events unrelated to hemorrhage were classified as transient adverse radiation effects (AREs) with perilesional edema developing within 12 months after treatment, permanent AREs developing typically more than 12 months after treatment, and transient neurological events without radiological evidence of perilesional edema (considered unrelated to treatment), as described previously.²⁹ The Mann-Whitney U-test, Fisher’s

er’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. A p value < 0.05 was considered statistically significant.

No significant difference was found between the different treatment eras in terms of pretreatment and posttreatment hemorrhages or morbidity (data not shown). Likewise, the outcomes of the brainstem and thalamic/basal ganglia groups were not significantly different (data not shown) despite smaller brainstem lesions; therefore, we pooled data from these two subgroups.

Results

Risk of Hemorrhage Before RS

In the single-hemorrhage group, the annual pretreatment hemorrhage rate was 2.4%. In the multiple-bleed group it was 2.8%, and the rebleed rate was 20.7% before treatment (Table 3). Rates of the first bleed in the single- and multiple-bleed groups were not significantly different (OR 1.16, 95% CI 0.88–1.54, $p = 0.31$). The median time between the presenting bleed and RS was 1 year (0.1–34 years) in the single-bleed group and 3 years (0.3–35 years) in the multiple-bleed group. The median time between the first and second bleed was 2 years (0.2–23 years) in the latter group. The annual rebleed rate modestly decreased from 46.15% (95% CI 34.8%–57.5%) in the 1st year to 32.15% (95% CI 13.7%–50.6%) in the 5th year after the first bleed and thereafter remained 11.55% before RS (95% CI 6.3%–16.8%; Fig. 3A).

TABLE 3. Annual hemorrhage rates before and after RS

Group	Before RS		After RS	
	1st Bleed	Rebleed	w/in 2 Years	After 2 Years
Single-bleed	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	2.8%, 2.2–3.4, 80 bleeds in 2891 lesion-yrs	20.7%, 17.3–24.1, 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.

FIG. 3. A: Rebled rates in the multiple-bleed group only modestly decreased within 5 years after the first bleed and remained 11.6% thereafter prior to RS (black). In contrast, within 2 years after RS, the rebled rates in this group decreased to 1.3% (gray). **B:** Kaplan-Meier curves estimating hemorrhage-free survival of the pooled hemorrhagic group before ($n = 210$ patients, black) and after RS ($n = 206$ patients, gray). The difference was significant. **** $p < 0.0001$.

Risk of Hemorrhage After RS

In the single-bleed group, the rebled rate was 4.3% within the first 2 years after RS, falling to 1.1% thereafter (Fig. 4 and Table 3); the risk of rebleeding after 2 years was significantly lower (OR 4.1, 95% CI 1.4–11.1, $p < 0.01$). In the multiple-bleed group, the rebled rate was 7.9% within the first 2 years after RS and fell to 1.3% thereafter; the risk of rebleeding after 2 years was significantly lower (OR 6.5, 95% CI 2.3–16.8, $p < 0.001$). Moreover, the long-term posttreatment rebleeding risk in the multiple-bleed group was significantly lower than the long-term rebleeding risk prior to treatment (OR 9.8, 95% CI 3.6–24.6, $p < 0.0001$; Figs. 3A and 4).

The median hemorrhage-free survival time prior to treatment was estimated to be 42 months after hemorrhagic presentation, whereas 78% of the patients (1 patient) would remain hemorrhage free 20 years after RS (HR 5.54, 95% CI 3.91–7.85, $p < 0.0001$; Fig. 3B). In the single- and multiple-bleed groups, 86.4% and 75.1% of patients (1 patient each), respectively, would remain hemorrhage free 20 years after RS (Fig. 5). The difference

FIG. 4. Bar graph showing bleeding rates prior to and after RS. Error bars indicate the 95% confidence interval. ** $p < 0.01$; *** $p < 0.001$.

in hemorrhage-free survival between the two groups was not significant.

Forty percent (95% CI 3.0–76.9) of the pediatric group (10 patients, age ≤ 14 years) and only 11.7% (95% CI 7.2–16.3) of the adult population (196 patients) suffered from a bleed after RS (OR 5.0, 95% CI 1.5–17.6, $p < 0.05$).

Pretreatment Morbidity

Before treatment, permanent neurological deficits occurred in 48.8% of cases (95% CI 39.9–57.7) in the single-

FIG. 5. Kaplan-Meier curves for hemorrhage-free survival after RS. The patients at risk and the percentage of hemorrhage-free survivals are given for each group at 2, 5, 10, and 20 years after RS. Gray line and text, single-bleed group; black line and text, multiple-bleed group (Mx bleeds).

FIG. 6. Bar graph showing permanent morbidity before and after RS in patients with single ($n = 122$ patients) and multiple hemorrhages ($n = 79$ patients). Overall permanent morbidity did not significantly change in the two groups, but the rate of score 3+ morbidity was significantly increased after RS ($p < 0.01$). Persistent morbidity was significantly higher in the multiple-bleed group before RS than in the single-bleed group before and after RS. Post = persistent neurological deficit at the endpoint of posttreatment follow-up; Pre = morbidity before treatment. ** $p < 0.01$; *** $p < 0.001$.

bleed group. The rate of permanent deficits was significantly higher in the multiple-bleed group at 77.1% (95% CI 67.9–86.3; $p < 0.001$; Fig. 6 and Table 4). Repeated bleeds were associated with increased risks of new deficits (OR 3.4, 95% CI 1.8–6.2, $p < 0.001$) and with more severe disabilities (mRS score > 1 ; OR 2.5, 95% CI 1.2–4.8, $p < 0.01$).

Posttreatment Morbidity

Twenty-seven (13.1%) of 206 lesions with follow-up bled 33 times after RS, and the chance of suffering from permanent disability after the bleed was 45.5% (15 of 33 bleeds; Table 4). Posttreatment hemorrhage-related morbidity was 7.4% (95% CI 3.8–11.1) for the whole cohort (5.9% with an increase of 1 mRS score and 1.5% with an increase of 2 mRS scores). The rate of transient and permanent AREs was 8.3% (17/206) and 7.2% (14/194 with 2-year follow-up; 95% CI 3.5–10.9), respectively (all an increase of 1 mRS score). Transient neurological events without radiological evidence of hemorrhage or perilesional edema occurred 12 times in 10 patients after RS. The rate of persistent neurological deficits was significantly lower in the single-bleed group after RS (53.3%, 95% CI 44.7–62.6) than in the multiple-bleed group prior to RS (77.1%; $p < 0.01$; Fig. 6). This refers to a significantly higher risk of permanent deficits in the multiple-bleed group prior to RS than the overall morbidity of the single-bleed group after RS (OR 2.9, 95% CI 1.6–5.3, $p < 0.001$).

Treatments After RS

Five lesions were surgically removed after a post-RS bleed, and 6 lesions were treated with RS twice. This second group is the subject of another study addressing the results of multiple RS treatments.³¹

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

Group	mRS Score			
	0	1	2	3–4
Single-bleed ($n = 125$)				
Pre-RS mRS	51	33	14.5	1.5
Morbidity of posttreatment hemorrhage (+mRS)	92.3	5.7	2	0
Morbidity of AREs (+mRS)	94.3	5.7	0	0
Posttreatment end state (mRS)	46.7	31.2	19.7	2.4
Multiple-bleed ($n = 81$)				
Pre-RS mRS	24	45	28.5	2.5
Morbidity of posttreatment hemorrhage (+mRS)	93	3.5	3.5	0
Morbidity of AREs (+mRS)	90	10	0	0
Posttreatment end state (mRS)	22	40.2	26.8	11

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.

Mortality

Six deaths occurred during the follow-up period. Four were unrelated to the treated CM, and the cause of death was unknown in one case. One patient died of hemorrhage from one of her treated brainstem CMs. This gives an estimate of treatment-specific mortality of 0.49%–0.99%.

Discussion

Natural History of CMs

Understanding the natural history of CMs is fundamental in therapeutic decision-making. However, as these lesions are rare and heterogeneous in terms of both presentation and location,¹³ substantial variability among earlier studies has often led to confusion. Recent developments focusing on standardization and data accumulation may bring us closer to consensus. First, it has become widely accepted that hemorrhage is considered as a clinical event of acute or subacute onset of symptoms with evidence of concurrent hemorrhage in order to avoid earlier confusion due to the presence of a hemosiderin ring even in asymptomatic cases.⁵ Second, despite evidence of de novo CM formation, both retrospective studies assuming lesion presence since birth and prospective studies have provided similar estimates (1.4%–2.5%) for annual hemorrhage rates.¹³ Third, hemorrhagic presentation was found to be the most significant risk factor for further bleeding, indicating the destabilization of CMs by the first bleed.^{6,13,38} While the annual bleed rate was found to be 0.4%–0.6% after nonhemorrhagic presentation,¹³ the annual rebleed rate was estimated between 4.5% and 33.77%,^{17,22} giving rise to a cumulative rebleeding incidence of 16%–57% at 5 years and up to 72% at 10 years after hemorrhagic presentation.^{7,16} Last, a brainstem location was found to be a significant risk factor for rebleeding with an annual rebleed rate of 32.3% as compared to 6.3% for other lesion locations,³⁸ and the estimat-

ed risk of a first hemorrhage within 5 years of diagnosis was 30.8% and 8% with or without hemorrhagic presentation, respectively.¹⁶ Another study found even lower 5-year hemorrhage-free survival with brainstem CMs, estimating 53% with median hemorrhage-free survival times of 5–6 and 9 years for cases of hemorrhagic and nonhemorrhagic presentation, respectively.²⁴ Similarly, the annual rebleed rate of deep supratentorial CMs was found to be higher (14.1%) with a 55.3% 5-year overall hemorrhage-free survival.³⁹ The risk of morbidity due to a single bleed from a brainstem CM is also increased. Up to 40%–60% of cases are left with persistent morbidity, and the risk of death is also substantial.^{10,35} Moreover, each subsequent bleeding episode carries the chance of cumulatively increasing permanent disability.⁴¹ Pretreatment behavior of CMs in our study was consistent with these results.

Several studies have suggested that the elevated rebleed risk decreases a few years after the first hemorrhage (“temporal clustering”), a matter of intensive debate since its first description.⁷ In the original study, a 2.4-fold decline in the annual rebleed rate from 25.2% to 9.6% was found 2.5 years after hemorrhagic presentation. While such 1.65- to 2.3-fold declines in the rebleed rate after 2 years have been confirmed by several subsequent observational studies, in all but one of these studies the rebleed rate did not return to baseline (defined as the annual rate of first hemorrhage) even 5 years after the first bleed.^{16,38}

Management Options for CMs

Given CMs’ relatively benign natural history and considerable risk with intervention, the role of the three management options—microsurgical removal, RS, and observation—in the treatment of deep-seated CMs is yet to be defined.^{33,34} For such lesions, surgical removal remains a salvage treatment generally recommended in only limited circumstances.² Although the risk of microsurgery has decreased over the decades with increasing experience and safer techniques,^{2,42} it is still substantial, resulting in 10%–14% persistent morbidity and 1.5%–1.9% mortality.^{11,12} Although the procedure offers a definitive cure, the rate of complete resection is only 89%–91%, and the rebleed rate never goes to zero: 62% of residual lesions rebleed with an annual rebleed rate of 0.5%–2% and mortality rate of 6%.^{11,12} The outcome of microsurgical resection is worse in the pediatric population, with 25% being left with persisting morbidity and 15% developing a recurrence with an annual rebleed rate of 5.25%.¹ Thus, prophylactic surgical removal of deep-seated CMs in patients with no or minimal neurological deficit is not a common practice⁹ and remains an option only for those lesions that behave aggressively and are resectable with acceptable morbidity. From this perspective, we consider RS not as a competitive but as a complementary intervention since the question about these lesions is whether to observe them or to treat them with RS. Moreover, RS can also be an alternative intervention when surgery is technically feasible but medically contraindicated or declined by the patient.²⁸

Outcome After RS

The first paper on modern CM RS was published in 1995 by the Pittsburgh group,²¹ who found a dramatic de-

crease in the annual rebleed rate from 32% pretreatment to 1.1% within 2 years after RS, as well as low treatment-related persistent morbidity. Numerous contemporary studies adopting their strict planning, patient selection, and follow-up criteria have confirmed the reproducibility of these results (see review article in Nagy and Kemeny, 2015²⁷), and our current results are in line with these earlier findings.

Specifically, highly conformal treatment planning, lesion definition strictly within the hemosiderin ring, the avoidance of associated developmental venous anomalies, the application of a lower prescription dose, and the treatment of lesions after resolution of the last hemorrhage led to about 5% mild, persistent AREs.^{27,28} The poor outcomes often cited by critics of RS are from an earlier era representing our collective learning curve with inaccurate target definition, unnecessarily high radiation dose, and confusion over the lesion’s natural history.^{8,26,36} It was found in a recent study that the rate of AREs increased if CMs were treated with a prescription dose > 15 Gy without the benefit of a reduction in posttreatment bleed rates.¹⁹ The effect of a further dose reduction, however, is not known as we did not find a correlation between outcome and dose within the range applied in the present study. Nevertheless, the current practice of the radiosurgical community is to treat these lesions with a lower prescription dose than was previously chosen based on AVM RS.²⁸ Thus, critical voices regarding morbidity have been quieted recently.

In contrast to the initial cautious policy of treating lesions after at least two hemorrhages,²⁰ our stance has been more proactive from the beginning, treating CMs with no more than one prior bleed. This group represents two-thirds of our patients, and our analysis of earlier results has reassured us to continue this practice.²⁹ In agreement with our previous results, data in the present study indicated that the rates of both permanent AREs (7.2%) and posttreatment bleed-related morbidity (7.4%) were low and their effects were mild (AREs: all an increase of 1 mRS score; posttreatment hemorrhage-related morbidity: 80% an increase of 1 mRS score and 20% an increase of 2 mRS scores), and treatment-specific mortality was < 1%, all related to bleeds. Moreover, not only were the rate (77.1% vs 48.8%) and severity of pretreatment morbidity significantly higher in the multiple-bleed group, but the morbidity rate remained significantly lower in the single-bleed group even after RS (53.3%). Thus, a second bleed carries a greater risk for persistent neurological deficits than that with early RS (Fig. 6 and Table 4). Similar results have been published by another group,²³ and it appears that a proactive policy has recently been starting to gain wider acceptance.⁴

The most pertinent question currently is whether RS brings any benefit over the CM’s natural history. Our understanding of natural history has significantly improved since 2010, when we presented our earlier results²⁹ and the results of another large cohort from Pittsburgh were published.²⁵ Opponents at that time argued with a virtual patient model obtained by a simulation based on available natural history data of heterogeneous quality;³⁶ therefore, that debate was merely speculative. Since then, several good-quality natural history studies analyzing large patient populations have been published, and we felt it ap-

appropriate to reflect on them. In the present study we distinguished between two presentation forms: single-bleed and multiple-bleed groups. While in the single-bleed group the annual rebleed rate fell to 1.1% after a 2-year temporary increase to 4.3%, in the multiple-bleed group it fell from 20.7% pretreatment to 7.9% within the first 2 years after treatment and to 1.3% thereafter (Fig. 4 and Table 3). Importantly, the time course of a decay of the rebleed rates parallels the histological changes after RS found by a recent histopathological study.⁴⁰ Kaplan-Meier analysis showed that the hemorrhage-free survival rate was 93.2% and 88.9% at 2 years, 91.7% and 88.9% at 5 years, and 86.4% and 75.1% at 20 years after RS in the single- and multiple-bleed groups, respectively (Fig. 5). Moreover, while we found a tendency for a spontaneous decline in annual bleed rates in the multiple-bleed group prior to treatment—in agreement with most previous studies—the rate remained as high as 11.5% even after 5 years, which is significantly higher than the long-term annual rebleed rate in the same cohort after RS (Fig. 3A). Comparing estimates of hemorrhage-free survival of the cohort before and after treatment (Fig. 3B), we found that the median hemorrhage-free survival was 42 months without treatment, and hemorrhage-free survival was estimated to be as high as 76% even at 20 years after treatment, which is a significant difference from the untreated course. In the context of recent natural history studies, our results compare favorably to those for an untreated course, suggesting that the reduction in the rebleed rate 2 years after RS is unlikely to be accounted for merely by “temporal clustering.”

Study Limitations

Although our results strongly suggest the benefit of early radiosurgical intervention, we admit that the weakest points of our study are its retrospective design and lack of a matched control group, which are common to all of the published radiosurgical papers.^{19,27} Critics of this method advocate a prospective randomized controlled trial to clarify the conflicting issues surrounding different management options for CMs.³³ As we pointed out above, we consider RS as a complementary rather than a competing intervention to resection, and we think that the ultimate question is whether to observe these lesions once they become symptomatic or to treat them with RS early after the first bleed. Thus, a prospective randomized trial or prospective case control study to compare conservative and early radiosurgical management after the first hemorrhage would be welcome, but the chances of conducting such trials are low.²⁸ Even if such a study became a reality in the near future, it would take years to collect reliable long-term results. Therefore, as a next step forward, a more realistic, close goal would be to conduct a multicentric retrospective case control study inviting both investigators of published large observational cohorts¹⁶ and RS centers.²⁷

Conclusions

Rebleed rates of deep-seated CMs are stabilized at around 1% following an initial 2-year latency interval after RS. This decrease was more dramatic than the gradual decay observed in untreated cases that had bled multiple

times prior to RS. Moreover, estimated long-term hemorrhage-free survival of CMs with hemorrhagic presentation after RS is significantly higher than hemorrhage-free survival prior to treatment in the same group. Treatment-related permanent morbidity was rare and mild. Cumulative morbidity after RS performed after the first bleed (53%) was significantly lower than pretreatment morbidity after multiple hemorrhages (77%). Thus, the very low radiation-induced morbidity seems to be an acceptable compromise for the potential long-term protective effect of RS as compared to the morbidity of potential future hemorrhages. These observations reassured us in our practice of treating CMs with early RS, but comparative studies are needed to verify our approach.

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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: Nagy, Kemeny. Acquisition of data: Burkitt, Stokes, Kemeny. Analysis and interpretation of data: Nagy. Drafting the article: Nagy. Critically revising the article: Radatz, Bhattacharyya, Yianni, Rowe, Kemeny. Reviewed submitted version of manuscript: Radatz, Bhattacharyya, Yianni, Rowe, Kemeny. Statistical analysis: Nagy. Administrative/technical/material support: Burkitt. Study supervision: Radatz.

Supplemental Information

Companion Papers

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