

Stereotactic radiosurgery for haemorrhagic cerebral cavernous malformation: a multi-institutional, retrospective study

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ABSTRACT

Background Cerebral cavernous malformations (CCMs) frequently manifest with haemorrhages. Stereotactic radiosurgery (SRS) has been employed for CCM not suitable for resection. Its effect on reducing haemorrhage risk is still controversial. The aim of this study was to expand on the safety and efficacy of SRS for haemorrhagic CCM.

Methods This retrospective multicentric study included CCM with at least one haemorrhage treated with single-session SRS. The annual haemorrhagic rate (AHR) was calculated before and after SRS. Recurrent event analysis and Cox regression were used to evaluate factors associated with haemorrhage. Adverse radiation effects (AREs) and occurrence of new neurological deficits were recorded.

Results The study included 381 patients (median age: 37.5 years (Q1–Q3: 25.8–51.9) with 414 CCMs. The AHR from diagnosis to SRS excluding the first haemorrhage was 11.08 per 100 CCM-years and was reduced to 2.7 per 100 CCM-years after treatment. In recurrent event analysis, SRS, HR 0.27 (95% CI 0.17 to 0.44), $p < 0.0001$ was associated with a decreased risk of haemorrhage, and the presence of developmental venous anomaly (DVA) with an increased risk, HR 1.60 (95% CI 1.07 to 2.40), $p = 0.022$. The cumulative risk of first haemorrhage after SRS was 9.4% (95% CI 6% to 12.6%) at 5 years and 15.6% (95% CI 9 to 21.8%) at 10 years. Margin doses > 13 Gy, HR 2.27 (95% CI 1.20 to 4.32), $p = 0.012$ and the presence of DVA, HR 2.08 (95% CI 1.00 to 4.31), $p = 0.049$ were factors associated with higher probability of post-SRS haemorrhage. Post-SRS haemorrhage was symptomatic in 22 out of 381 (5.8%) patients, presenting with transient (15/381) or permanent (7/381) neurological deficit. ARE occurred in 11.1% (46/414) CCM and was responsible for transient neurological deficit in 3.9% (15/381) of the patients and permanent deficit in 1.1% (4/381) of the patients. Margin doses > 13 Gy and CCM volume > 0.7 cc were associated with increased risk of ARE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The radiosurgical treatment of cerebral cavernous malformation (CCM) is controversial.

WHAT THIS STUDY ADDS

⇒ This large, multicentric series shows that stereotactic radiosurgery is associated with haemorrhage risk reduction using recurrent analysis.
⇒ A dose > 13 Gy is associated with rebleeding and adverse radiation effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A margin dose of less than 13 Gy seems advisable to treat patient for haemorrhagic CCM.
⇒ Further analysis on haemorrhagic risk reduction should use recurrent analysis.

Conclusion Single-session SRS for haemorrhagic CCM is associated with a decrease in haemorrhage rate. Margin doses ≤ 13 Gy seem advisable.

INTRODUCTION

The prevalence of cerebral cavernous malformations (CCMs) is estimated between 0.2% and 0.5%.¹ Twenty-five per cent present with symptomatic, intracerebral haemorrhage (ICH).^{1,2} The 5-year risk of repeat haemorrhage is estimated to be as high as 30.8% in patients with brainstem CCM presenting with haemorrhage or focal neurological deficit (FND).² Resection is the primary treatment for haemorrhagic CCM, with an estimated permanent morbidity rate of approximately 3%.³ However, this rate is highly dependent

on the location; brainstem CCM resection carries significantly higher morbidity and mortality rate of 16% and 1.5%, respectively.⁴

Stereotactic radiosurgery (SRS) can be an alternative management option for patients with CCMs not amenable for resection.^{1 5} CCM radiosurgery remains a subject of controversy,⁶ despite several studies reporting a reduction in post-SRS haemorrhage rates.^{7–11} The major points of the contention include the lack of a distinct radiographic endpoint to evaluate the efficacy of SRS,^{7 8 10–12} and the high risk of SRS-related complications in the earlier reports.^{12–14} Since the efficacy of SRS seems to appear after a latency period of 2 years, one additional concern is that the observed effect might actually reflect the natural history of CCMs, as the haemorrhages occur in cluster.^{6 15 16}

The purpose of this study was to evaluate the safety and efficacy of single-session SRS for haemorrhagic CCM and to determine predictors of outcomes.

METHODS

Patient population and inclusion criteria

This retrospective, multicentre study follows the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). All patients with haemorrhagic CCM (sporadic or familial) treated with single-session SRS were included in the study. Patients lacking follow-up after SRS or presenting with progressive FND and seizures without evidence of clinical and radiological prior ICH were excluded (online supplemental figure 1).

This study included 381 patients treated between 1995 and 2021 at 11 centres of the International Radiosurgery Research Foundation. Each centre obtained approval for sharing deidentified data (IRB number: 17972). Data from each cohort were checked for internal consistency and any missing data or discrepancies were resolved by request to the collaborators.

SRS technique

SRS was delivered using the Leksell Gamma-Knife available at each participating centre. Stereotactic, high-resolution brain MRI and/or CT scanning were used for planning.

Follow-up and study endpoints

Clinical and imaging follow-up was performed by the participating centres according to local protocols, usually every 6 months after SRS for 2 years and annually thereafter. The Zabramski stage was defined before and after treatment.¹⁷ Outcome measures included pre-SRS and post-SRS symptomatic ICH rate as the primary endpoint, occurrence and evolution of neurological deficit, occurrence of adverse radiation effect (ARE) and epilepsy evolution.

The study adheres to the standards set by the Angioma Alliance Scientific Advisory Board that define haemorrhage as ‘a clinical event involving acute or subacute onset

symptoms (any headache, epileptic seizure, impaired consciousness or new/worsened focal neurological deficit referable to the anatomic location of the CCM) accompanied by radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intralesional hemorrhage. The definition includes neither an increase in CCM diameter without other evidence of recent hemorrhage, nor the existence of a hemosiderin halo’.¹⁸ Neurological symptoms were classified as improved, stable or worsening. A worsening condition was defined as the occurrence of a new permanent symptom and/or worsening of at least one neurological symptom. Neither epilepsy (new-onset or pre-existing) nor headache was included in this evaluation of neurological symptom evolution.

AREs were defined as perilesional T2 hyperintensity or cyst development. They were classified as symptomatic or asymptomatic. The CCM volume was contoured in the GammaPlan software for treatment purposes on T2 or T1 with gadolinium in function of where the CCM was more clearly visualised. The lesion was contoured in each slide, excluding the hemosiderin rim. The same sequences were used to compare the CCM at last follow-up. The lesion volume evolution was defined as enlarged if the lesion was more than 20% at last follow-up compared with SRS target volume, decrease if the volume decreased of more than 20% from baseline and stable otherwise.

Patients presenting with at least one epileptic seizure prior to SRS were classified in four categories: no additional seizures and no antiepileptic medication, no seizure with medication, improvement of at least 50% of the frequency and/or intensity of seizures with medication and seizure refractory to medication. Post-SRS seizure outcomes were defined using the Engel classification at last follow-up.¹⁹

Statistical analysis

The statistical analysis was performed using R (R Foundation for Statistical Computing). Normality of continuous variables was assessed graphically and with the Shapiro-Wilk test; with normality not verified, continuous variables are presented as median, first and third quartile (Q1–Q3). A p value <0.05 was considered significant.

No data were imputed. Analysis was performed per patient for relevant characteristics and per cavernoma for efficacy and adverse event. Patients treated for multiple CCM at different timepoints were handled as different patients (n=4 patients for 5 CCM).

The post-SRS annual haemorrhage rate (AHR) was calculated by dividing the cumulative number of haemorrhages by the cumulative number of contributed years of follow-up by each lesion. Each lesion contributed risk time from the date of SRS to the date of last follow-up, death or new procedure for CCM. Due to the discrepancy on the best method to calculate the pre-SRS AHR, all three methods previously reported in the literature were used: (1) CCMs are congenital lesions; the observation period is calculated from birth until SRS, all haemorrhages are

included, (2) CCMs are acquired lesions; the observation period is calculated from diagnosis to SRS, all haemorrhages are included, (3) the period is calculated from first haemorrhage to SRS but the first haemorrhage is excluded if this is the reason for diagnosis.^{10–12} The pre-SRS AHRs were compared with the overall and first 2-year post-SRS AHR using the methodology described by Sahai *et al.*²⁰

As haemorrhages occurred multiple times pre-SRS and post-SRS, univariate and multivariate recurrent event analysis was performed using the Prentice, William and Peterson Gap-Time (PWP-GT) model,²¹ using the third method of haemorrhagic rate calculation. This method was chosen since CCMs are not congenital lesions, can form during lifetime, with the risk of bleeding being non-constant since birth and increasing following a haemorrhage.^{2, 17} Optimal cut-off points for continuous variable were calculated with the Youden index. Statistically significant factors and clinically relevant ones with a *p* value <0.20 were included in the multivariate analysis.

We investigated the risk factors associated with new haemorrhage after SRS and ARE. As the number of recurrent events (second and third haemorrhage) after SRS was low, a Cox regression instead of a PWP-GT analysis was performed.²² Kaplan-Meier curves for first haemorrhage after SRS were plotted. A logistic regression model was employed to evaluate the risk factors for AREs after SRS.

RESULTS

Demographics

A total of 381 patients (211 (55.4%) female, median age of 37.5 years (Q1–Q3: 25.8–51.9) at SRS) were included. The presentation leading to the discovery of the CCM was haemorrhage in 94.5% of patients (360/381), seizure without evidence of haemorrhage in 2.4% (9/381) and progressive FND in 1.6% (6/381), and an incidental discovery in 1.6% (6/381). The 13 patients not presenting with haemorrhage on diagnosis experienced haemorrhagic events in the time interval between diagnosis and radiosurgery. Two patients had a genetic mutation identified (0.6%): one a CCM1/KRIT1 mutation, and the other a CCM2 mutation (table 1).

Twenty-four (6.3%) patients had more than one CCM treated in the same SRS session: 18 patients with two lesions, 4 patients with three CCMs, 1 patient with four CCMs and 1 patient had five CCMs treated; in total, 414 CCMs were treated and included. Nineteen patients (5%) had been previously managed surgically for 21 CCMs (5.1%); the median time from resection to SRS was 3 years (Q1–Q3: 1–6). Seven patients had bleeding events after surgery; the remaining 14 were treated for a recurrent/residual CCM. Most treated CCMs (171/414 (41.3%)) were located in either supratentorial lobar areas or the brainstem (155/414 (37.4%)); basal ganglia and thalamic CCM (60/414 (14.5%)) or cerebellar CCM (28/414 (6.8%)) were less common. A median margin

Table 1 Demographic characteristics of the 381 included patients

Demographics	n (%)
Age at diagnosis (years), median (Q1–Q3)	34.7 (24.3–48.6)
Age at SRS (years), median (Q1–Q3)	37.5 (25.8–51.9)
Sex	
Male	170 (44.6%)
Female	211 (55.4%)
Genetic mutation identified	2 (0.6%)
Initial presentation	
Incidental*	6 (1.6%)
Seizure*	9 (2.4%)
Haemorrhage	360 (94.5%)
Focal neurological deficit*	6 (1.6%)
Clinical symptoms pre-SRS†	
None	29 (7.6%)
Motor deficit	86 (22.6%)
Sensory deficit	62 (16.3%)
Cerebellar symptom	26 (6.8%)
Cranial nerve deficit	98 (25.7%)
Seizure	77 (20.2%)
Headaches	72 (18.9%)
Others‡	56 (14.7%)
Pre-SRS seizure control (n=77)	
No seizure without medication	2 (2.6%)
No seizure with medication	34 (44.2%)
Improvement of at least 50% in frequency or intensity under medication	14 (18.2%)
Improvement of less than 50% under medication	27 (35.1%)

*Not associated with acute or subacute haemorrhage; patients were included due to haemorrhagic events occurring in the time interval between diagnosis and radiosurgery.

†Patients may exhibit several symptoms pre-SRS. The percentages are calculated for each symptom per patient.

‡Speech disorder, memory loss, unspecified gait trouble. Q1–Q3, first to third quartiles; SRS, stereotactic radiosurgery.

dose of 12 Gy (Q1–Q3: 12.0–14.0) was employed and the median target volume was 0.6 cm³ (Q1–Q3: 0.2–1.5) (table 2).

Haemorrhagic risk

The cumulative number of pre-SRS haemorrhages was 528; 324 out of 414 (78.3%) CCM had a single haemorrhagic event, 71 out of 414 (17.1%) CCM bled twice, 16 out of 414 (3.9%) had three haemorrhages, 1 out of 414 (0.2%) bled four times and finally 2 out of 414 CCM (0.5%) bled five times. The calculated pre-SRS AHR varied based on the methodology used; 3.31 per 100 CCM-years (follow-up from birth: 15931.2 years; 528 haemorrhages), 43.35 per 100 CCM-years (follow-up

Table 2 Clinical, radiological and treatment characteristics of 414 CCMs

Clinical and radiological data per CCM	n (%)
Previous surgery	21 (5.1%)
Location characteristics	
Adjacent to the cortex	253 (61.1%)
Adjacent to ependymal plane	100 (24.2%)
Location (anatomic)	
Brainstem	155 (37.4%)
Basal ganglia and thalamus	60 (14.5%)
Supratentorial lobar area	171 (41.3%)
Cerebellum	28 (6.8%)
Associated developmental venous anomaly	50 (12.1%)
Number of pre-SRS haemorrhages	
1	324 (78.3%)
2	71 (17.1%)
3	16 (3.9%)
4	1 (0.2%)
5	2 (0.5%)
Median (Q1–Q3) time from diagnosis to SRS, years	0.9 (0.3–3.1)
Zabramski classification	
1	78 (19.0%)
2	307 (74.7%)
3	25 (6.1%)
4	1 (0.2%)
Unknown	3
Dosimetric parameter per CCM, median (Q1–Q3)	
Target volume, cm ³ , median (Q1–Q3)	0.6 (0.2–1.5)
Margin dose, Gy, median (Q1–Q3)	12 (12c14)
Isocentres, median (Q1–Q3)	4 (2–8)
Isodose line %, median (Q1–Q3)	50 (50–51.5)
CCM, cerebral cavernous malformation; Q1–Q3, first to third quartiles; SRS, stereotactic radiosurgery.	

from diagnosis: 1218 years; 528 haemorrhages) and 11.08 per 100 CCM-years (follow-up from diagnosis: 1218 years; 135 haemorrhages after the exclusion of haemorrhages leading to CCM diagnosis).

The post-SRS AHR was 2.7 per 100 CCM-years, with a total of 50 haemorrhages occurring over 1850.9 years of follow-up. Specifically, 34 out of 414 (8.2%) CCM had a single post-SRS haemorrhagic event, 5 out of 414 (1.2%) bled twice and 2 out of 414 (0.5%) bled three times. Of these, 34 occurred in the first 2 years after SRS. With a cumulative follow-up of 750.2 years, this led to an AHR of 4.53 per 100-CCM years in the first 2 years after SRS. Sixteen haemorrhages occurred after 2 years over 1108.3 years of follow-up, which led to an AHR after 2 years of 1.44 per 100 CCM-years. There was a statistically significant reduction in haemorrhage rate post-SRS (–8.33

per 100 CCM-years, 95% CI 6.67 to 10, $p < 0.0001$), when comparing pre-SRS (from diagnosis after the exclusion of first haemorrhages) and post-SRS. The different calculated AHR can be found (table 3, figure 1A).

In the multivariate recurrent event analysis, SRS (HR 0.27, 95% CI 0.17 to 0.44, $p < 0.0001$) was associated with a significant reduction in haemorrhage rate. The presence of a DVA was associated with an increased risk of haemorrhage (HR 1.60, 95% CI 1.07 to 2.40, $p = 0.022$) (table 4).

The 2-year, 5-year and 10-year cumulative probability of a new, post-SRS, first haemorrhage was 7.2% (95% CI 4.4% to 9.7%), 9.4% (95% CI 6% to 12.6%) and 15.6% (95% CI 9% to 21.8%), respectively (figure 1B). In the multivariate Cox regression analysis, a margin dose > 13 Gy (HR 2.27, 95% CI 1.20 to 4.32, $p = 0.012$) and the presence of a DVA (HR 2.08, 95% CI 1.00 to 4.31, $p = 0.049$) were associated with a higher probability of bleeding after SRS (table 5, figure 1C).

Imaging outcomes

With a median imaging follow-up of 3.1 years from SRS (Q1–Q3: 1.8–6.1), the CCM volume was stable in 232 out of 412 (56.3%), decreased in 171 out of 412 (41.5%) and increased in 9 out of 412 (2.2%). Among the nine patients with an increased CCM volume, eight had a rebleed of their CCM. The pre-SRS and post-SRS Zabramski scale was available in 378 CCMs. At last follow-up, in 288 of them (76.2%), it was unchanged (table 2).

Adverse radiation effects

ARE occurred in 42 patients and 46 CCM (11.1%), with 95.6% (44/46) presenting as T2 perilesional hyperintensity. Of these 42, 25 patients were managed with observation, 13 required a corticosteroids regimen, 1 was treated with corticosteroid and bevacizumab, and in 1 case, the treatment was unknown. Two CCMs developed delayed cysts. One cyst was managed conservatively, and one required stereotactic aspiration.

On multivariate logistic regression, CCM volume > 0.7 cc (OR 5.19, 95% CI 2.41 to 12.5, $p < 0.001$) and margin dose > 13 Gy (OR 5.17, 95% CI 2.55 to 11.2, $p < 0.001$) were associated with the occurrence of ARE (online supplemental table 2).

Clinical outcomes

At a median clinical follow-up of 3.78 from SRS (Q1–Q3: 1.71–6.54) years, 60 (15.7%) patients developed new or worsening neurological deficits. Post-SRS haemorrhages were responsible for 15 (3.9%) cases of transient neurological deficits, 7 (1.9%) cases of permanent neurological deficits, 16 (4.2%) cases of headache and 1 (0.3%) case of seizures. AREs were responsible for 15 cases (3.9%) of transient deficits, 2 (0.5%) cases of new seizures and 4 cases (1.1%) of permanent deficits. Twenty-one (5.5%) patients were asymptomatic.

In four (1.1%) patients, the neurological deterioration (two transient and two permanent) was linked to the CCM without evidence of new haemorrhage or ARE

Table 3 Annual haemorrhage rate per 100 CCM-years

	Annual haemorrhage rate per 100 CCM-years			
	Pre-SRS	Post-SRS		Overall
		<2-year post-SRS	≥2-year post-SRS	
Overall cohort				
From birth	3.31	4.53	1.44	2.7
From diagnosis with first haemorrhage included	43.35			
From diagnosis with first haemorrhage excluded*	11.08			
Single haemorrhage before SRS (n=324)				
From birth	2.66	3.6	1.48	2.38
From diagnosis with first haemorrhage included	47.86			
From diagnosis with first haemorrhage excluded*	3.1			
Multiple haemorrhages before SRS (n=90)				
From birth	5.45	7.78	1.36	3.68
From diagnosis with first haemorrhage included	37.71			
From diagnosis with first haemorrhage excluded*	21.07			

*Except when the diagnosis was before the first haemorrhage (n=21 cases for overall series and single bleed patients). CCM, cerebral cavernous malformations; SRS, stereotactic radiosurgery.

on MRI. Two (0.5%) patients developed Todd's paresis. Eight (2.1%) more patients developed neurological deficits (4 (1.1%) of them transient and 4 (1.1%) permanent) with no clear aetiology. In three (0.9%) patients, new neurological symptoms (one transient, two permanent) developed following a first-ever haemorrhage of coexisting, non-haemorrhagic CCM. Furthermore, one (0.3%) patient developed normal-pressure hydrocephalus, and one (0.3%) patient presented with ischaemic stroke. Overall, accounting for all post-SRS events, 119 out of 371 (32.1%) patients had improved neurological function at a last follow-up, 83 out of 371 (22.4%) patients remained stable and 20 out of 371 (5.4%) deteriorated, 149 out of 371 (40.1%) had no symptoms prior SRS and did not develop new symptoms. Six patients (1.6%) died during the follow-up, with repeat CCM haemorrhage being the cause in one patient. The cause of death was either unrelated to the CCM (three cases) or unknown (two cases) in the other five patients.

Seizure

Seventy-seven patients (20.2%) presented with at least one seizure prior to SRS. Of these 77 patients, 2 (2.6%) had no further seizure and required no medication, 34 (44.2%) had no more seizure under medication, 14 (18.2%) had an improvement of at least 50% in the frequency/intensity of seizures under medication and 27 (35.1%) had an improvement of less than 50% in the frequency/intensity of epileptic activity under medication or had medically refractory seizures (table 1).

New-onset, post-SRS seizure occurred in three patients; in two of them due to ARE. Overall, at a last clinical follow-up, 46 patients (57.5%) were Engel class I, 11 (13.75%) were Engel class 2, 8 (10%) were Engel class 3,

12 (15%) showed no improvement (Engel class 4A and B) and 3 (3.75%) had worse symptoms (Engel class 4C). In 14 (17.5%) patients, seizure medications were completely withdrawn (online supplemental table 1).

Additional management

Further treatment was required in eight patients, with three undergoing CCM resection and four repeat SRS. One patient underwent a stereotactic aspiration of a cyst and a thalamotomy for tremor. The median time from SRS to new treatment was 3.1 years (Q1–Q3: 1.3–6.5).

DISCUSSION

Haemorrhage risk reduction

This multicentric study included 381 patients harbouring 414 haemorrhagic CCMs. Only CCMs with at least one haemorrhagic episode were included to ensure a more homogeneous population. To the best of our knowledge, this is the largest report on SRS-managed haemorrhagic CCM to date.

Using recurrent event analysis, SRS appears to significantly reduce the risk of haemorrhage (HR 0.29, $p<0.001$). Several publications have underlined the importance of using specific statistical methodology for recurrent events.^{21 23} With the number of haemorrhages being the main outcome used to evaluate SRS efficacy for CCM and also a proven risk factor of subsequent haemorrhages, we believe that the PWP-GT model was more suitable.^{21 22} While a reduction of the AHR after SRS treatment has been previously reported in the literature,^{10 11 15} it is the first time that a recurrent event analysis model is used to evaluate the efficacy of SRS. The advantage of this method is that it takes into consideration the natural

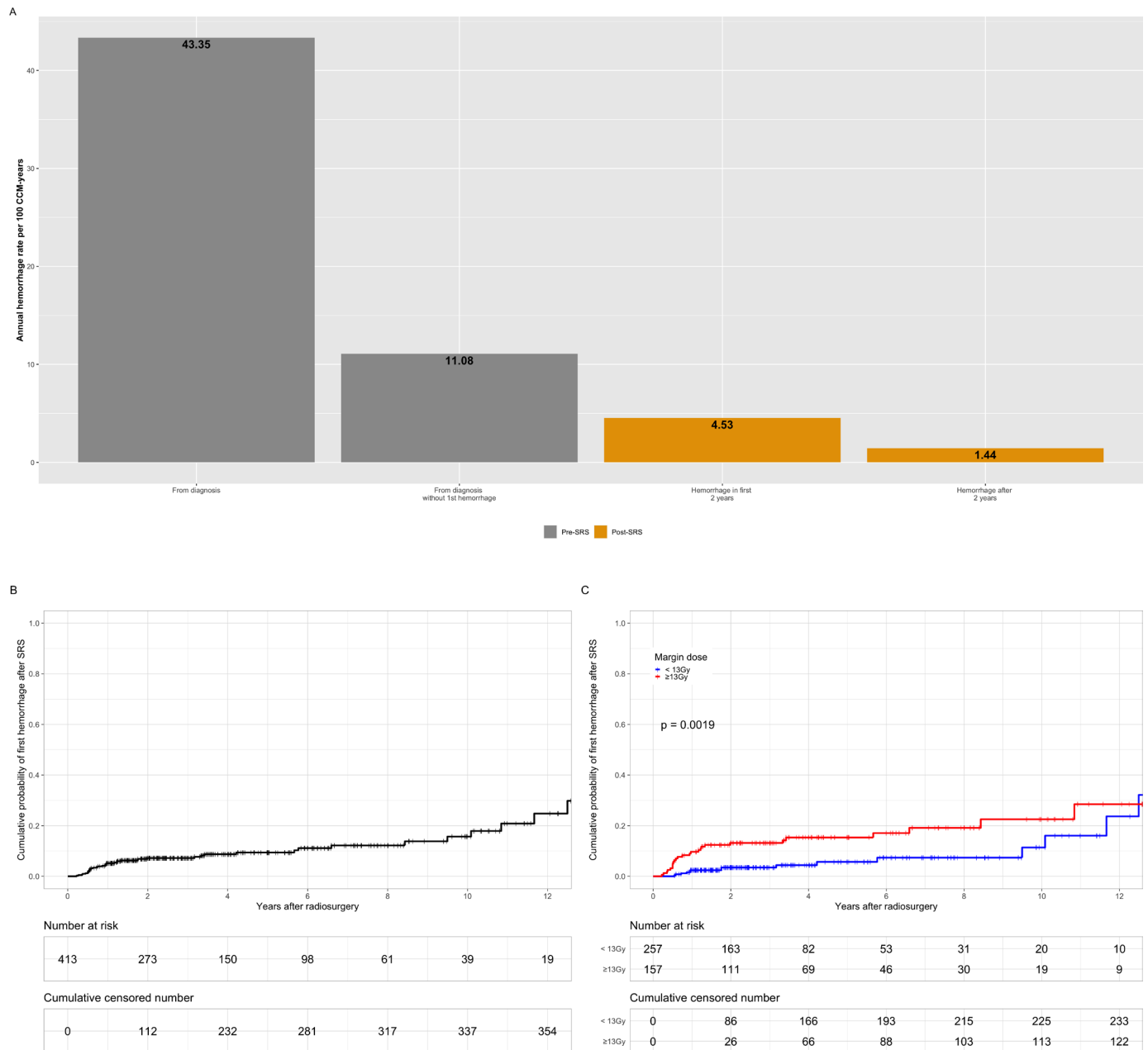


Figure 1 Bar plot of annual haemorrhage rate per 100 CCM-years in the overall cohort (A). Kaplan-Meier curve for first new haemorrhage after SRS (B) in function of margin dose (C). CCM, cerebral cavernous malformation; SRS, stereotactic radiosurgery.

history of CCM with multiple haemorrhages and their effect on the risk of future bleeding events. These results are in accordance with a recent meta-analysis showing that SRS showed high efficacy in preventing future haemorrhage (86%, 95% CI 81% to 90%) with a low risk of long-term morbidity (10%, 95% CI 7 to 13%), while the rates were 77% (95% CI 75% to 83%) and 21% (95% CI 16% to 28%) for observation, respectively.²⁴

Some uncertainty concerning the efficacy of SRS is that the observed risk reduction stems from the tendency of CCM to present with closely spaced clusters of haemorrhage interspersed with long haemorrhage-free intervals.¹⁶ It is currently unknown if and when the bleeding

risk returns to baseline levels.^{2 25} Unfortunately, only prospective clinical trials with a control group could completely elucidate the effect of SRS on haemorrhage risk. The difficulty of performing such a clinical trial was previously demonstrated by the inability to recruit enough patients.⁶ However, in a retrospective study by Lee *et al*, no significant difference in the haemorrhage rate during the first 2 years after SRS was observed when comparing patients that were treated after multiple haemorrhages to patients treated after a single haemorrhage.²⁶ It should be noted though, that the risk factors linked to an aggressive behaviour with repeat haemorrhages are not well understood,²⁷ and that comparisons with natural history studies

Table 4 Recurrent event analysis using the Prentice, Williams and Peterson Gap-Time model for risk factors associated with haemorrhage in 411 CCMs

Factor	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Gender female	0.243	1.21 (0.88 to 1.67)		
Familial form	0.821	0.77 (0.06 to 9.43)		
Developmental venous anomaly	0.014	1.69 (1.11 to 2.57)	0.022	1.60 (1.07 to 2.40)
Location brainstem vs others	0.022	1.44 (1.05 to 1.96)	0.072	1.31 (0.98 to 1.75)
Prior surgery	0.559	1.18 (0.68 to 2.04)		
Stereotactic radiosurgery	<0.0001	0.25 (0.15 to 0.41)	<0.0001	0.27 (0.17 to 0.44)

CCM, cerebral cavernous malformation.

would be biased, as most of them only include the first haemorrhage.² A better understanding of the natural history and the development of imaging protocols or plasma biomarkers could help to better define the efficacy of SRS.^{28 29}

Interestingly, we found margin dose >13 Gy (HR 2.27, $p=0.012$) to be associated with an increased risk of new post-SRS haemorrhage. This association might initially seem counterintuitive. Shin *et al* demonstrated the presence of vascular endothelial growth factor (VEGF)-staining small capillaries and venules in irradiated CCM that were resected after a new bleeding. They formulated the hypotheses that these vessels are foci of neovascularisation, which may progress to the characteristic thin-walled large lumen vessel responsible for subsequent haemorrhage.³⁰ Kim *et al* showed in vivo that endothelial cell irradiation with more than 20 or 30 Gy in single fraction was responsible for increasing vascular endothelial growth factor A (VEGF-A) production.³¹ Given that usually a 50% isodose line is used in Gamma Knife radiosurgery, maximum doses >26 Gy would have frequently been delivered with prescription doses > 13 Gy. While this radiobiological mechanism could support our results, there is paucity of data regarding the optimal radiation dose that would adequately reduce the risk of haemorrhage, while at the same time not inducing overexpression of VEGF. In

the same way, the reason for rebleeding in the first 2 years after SRS or later could be attributed to different pathophysiological phenomenon. This association has never been described before, with most studies either reporting no differences in haemorrhage rate after SRS in function of the dose^{7 11 32} or not investigating for associated risk factors.^{8 12}

The presence of a DVA (HR 1.60, $p=0.022$ with PWP-GT) as a risk factor for new haemorrhage after SRS is in accordance with the literature.^{33 34} The implications for the radiosurgical management of CCM are unknown, other than that targeting the DVA is not recommended due to an increased risk of complications.³⁵ CCMs located in the brainstem reportedly have a worse natural history² and are associated with higher rebleeding risk after SRS,⁸ a finding that was not validated in our model. Similarly, no increased risk of post-SRS haemorrhage in patients with multiple pre-SRS haemorrhages as compared with patients with a single haemorrhage was observed.^{7 8}

Adverse radiation effects

AREs occurred in 46 CCMs (11.1%) and were associated with transient neurological symptoms in 15 patients, permanent in 4 and seizures in 2 cases. A recent meta-analysis reported a 4% risk of permanent deficit due to ARE.³⁶ A volume >0.7 cc (OR 5.19, $p<0.001$) and a

Table 5 Cox analysis for factor associated with new haemorrhage after SRS in 413 CCMs*

Factor	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Gender female	0.68	1.14 (0.61 to 2.13)		
Developmental venous anomaly	0.037	2.15 (1.05 to 4.40)	0.049	2.08 (1.00 to 4.31)
Age at SRS >65	0.037	3.02 (1.07 to 8.52)	0.052	2.81 (0.99 to 7.95)
Volume >0.7 cc	0.042	1.94 (1.02 to 3.66)	0.064	1.85 (0.96 to 3.53)
Margin >13 Gy	0.003	2.63 (1.39 to 4.98)	0.012	2.27 (1.20 to 4.32)
Location brainstem vs others	0.65	1.16 (0.62 to 2.15)		
Multiple haemorrhages pre-SRS	0.048	1.90 (1.00 to 3.60)	0.071	1.80 (0.95 to 3.42)

*The analysis was performed on 413 CCM, as volumetric measurements on one CCM were missing CCM, cerebral cavernous malformation; SRS, stereotactic radiosurgery.

margin dose >13 Gy (OR 5.17, $p < 0.001$) were associated with increased risk of ARE. This is concordant with other literature reports.³⁷ The haemosiderin ring has been hypothesised to act as a radiosensitiser due to its elevated iron content.^{12 38} This characteristic could explain the higher risk of ARE with similar doses, volume and location compared with arteriovenous malformation.¹³ It is currently recommended to avoid the inclusion of haemosiderin in the treatment plan.³⁸

Limitations

Even though the multicentric design can partially mitigate the effect of individual centre biases, its retrospective nature makes it subject to selection bias, institutional treatment practices and reporting bias. The reason for treating patient with SRS over surgery could not be reliably captured.

As seizure control was not the primary goal of treatment, the complete Engel classification was not employed to report outcomes.

The imaging was not centrally reviewed. New haemorrhage was defined in this study as evidence of acute or subacute bleeding and new symptoms as recommended.¹⁸ Asymptomatic haemorrhage was not captured and the haemorrhage rate could be underestimated. Due to the long-time interval in which patients were treated, various MRI sequences and/or CT scan were used. This could have introduced bias in the evaluation of haemorrhage, DVA and ARE; however, the direction of this bias could not be ascertained, and careful description of new symptom onset was performed. Moreover, despite the fact that the median follow-up time in this study is comparable to a recent meta-analysis study evaluating the natural history of CCM, it is conceivable that delayed complications, such as adverse radiation effects or de novo CCM, could be missed.²

Of the included CCM in the study, 5.1% were surgically managed before SRS. This rate is in accordance with rate of remnant or recurrence (4.3% to 6.6%) found in the open surgery reports.^{39 40} The differences between residual or recurrent CCM after surgery could not be reliably captured, as imaging availability and techniques evolved with time.

Genetic mutations were confirmed in 0.6% of the patients. Patients were not uniformly tested for genetic mutations in all participating centres due to the differences in genetic testing availability and the inclusion of patients treated over a long period. As such, the number of patients harbouring gene mutations associated with CCM formation is probably underestimated.

We made the choice to have broad inclusion criteria, rather than exclude specific patient subgroups (with a familial form, a previous surgery) to be closer to clinical practice. This choice can increase heterogeneity in the cohort.

Generalisability

Due to the multicentric nature of the study, the results can apply to haemorrhagic CCM treated with radiosurgery

but not to the group with progressive FND without clear evidence of new haemorrhage.

CONCLUSION

Single-session SRS decreases the risk of repeat haemorrhage in haemorrhagic CCM. Further evidence is needed to confirm the efficacy of SRS and improve case selection. Prescription doses ≤ 13 Gy could reduce SRS-related complications and the risk of repeat haemorrhage.

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