Brainstem Cavernous Malformations: Surgical Results in 104 Patients and a Proposed Grading System to Predict Neurological Outcomes

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BACKGROUND: Once considered inoperable lesions in inviolable territory, brainstem cavernous malformations (BSCM) are now surgically curable with acceptable operative morbidity. Recommending surgery is a difficult decision that would be facilitated by a grading system designed specifically for BSCMs that predicted surgical outcomes.

OBJECTIVE: Informed by our efforts to develop a supplementary grading system for arteriovenous malformations, we hypothesized that a similar system might predict long-term outcomes and guide clinical decision-making.

METHODS: A consecutive, single-surgeon series of 104 patients was used to assess preoperative clinical and imaging predictors of microsurgical outcomes. Univariable logistic regression identified predictors and a multivariable logistic regression model tested the association of the combined predictors with final modified Rankin Scale scores. A grading system assigned points for lesion size, location crossing the brainstem's midpoint, presence of developmental venous anomaly, age, and time from last hemorrhage to surgery.

RESULTS: Average maximal diameter of BSCMs was 19.5 mm; 50% crossed the axial midpoint; 54.8% had developmental venous anomalies; mean age was 42.1 years; and median time from last hemorrhage to surgery was 60 days. One patient died (0.96%), and 15 patients (14.4%) experienced worsened cranial nerve or motor dysfunction, of which 10 increased their modified Rankin Scale scores (9.6%). BSCM grades ranged from 0 to 7 points and predicted outcomes with high accuracy (receiver operating characteristic = 0.86, 95% confidence interval: 0.78-0.94).

CONCLUSION: Rather than developing a grading system for all cerebral cavernous malformations that is weak with BSCMs, we propose a system for the patients who need it most. The BSCM grading system differentiates patients who might expect favorable surgical outcomes and offers guidance to neurosurgeons forced to select these patients.

KEY WORDS: Brainstem cavernous malformation, Cavernoma, Grading system, Surgical resection

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Cerebral cavernous malformations (CM) are clusters of abnormally enlarged blood vessels that, despite their low flow and absence of arteriovenous shunting, hemorrhage frequently and cause focal neurological deficits, seizures, and even death. They can occur in a solitary, sporadic form or in an autosomal dominant condition characterized by multiple lesions.[1,2] CMs in the cerebral and cerebellar hemispheres can be resected safely, and surgery is indicated when young age, neurological symptoms, mass effect, hemorrhagic behavior, accessible location, and low operative risk compare favorably to natural history risks. These decisions are straightforward and rarely require tools such as grading systems to advise patients. In contrast, treatment of patients with brainstem cavernous malformations (BSCM) is challenging due to the lesion's rarity, the technical difficulty of surgery next to critical anatomy, and significant associated operative risks.

ABBREVIATIONS: AVM, arteriovenous malformations; **BSCM,** brainstem cavernous malformations; **CM,** cavernous malformations; **DVAs,** developmental venous anomaly; **mRS,** modified Rankin Scale

However, BSCMs account for 15% to 18% of intracranial CMs, and their hemorrhage rates seem to be more than twice that associated with other intracranial CMs.[3,4] Neurosurgeons have been reluctant to operate on these lesions until only recently, but BSCMs are now aggressively managed. A recent systematic review of 68 surgical case series captured 1390 patients and found an early postoperative neurological morbidity rate of 45%, a long-term, permanent morbidity rate of 14%, and good outcomes (improved or unchanged) in 84% of patients.[3] The recommendation for surgery is a difficult decision that depends on patient presentation, lesion size, accessibility, distance to the pial or ependymal surface, hemorrhage history, and surgeon expertise, among other factors, and would be facilitated by a grading system.

Recently, Hernesniemi and colleagues[5] proposed the first such grading system, but the system applied to all CMs, including those in the spinal cord and not just those in the brainstem. BSCMs would all be characterized as high-risk Grade III lesions in this system with a 54% chance of long-term disability after surgery, thus failing to differentiate good surgical candidates from poor surgical candidates. A grading system designed specifically for BSCMs that predicted outcomes associated with microsurgical resection might be a valuable clinical tool for neurosurgeons wrestling with patient selection. Unfortunately, our current knowledge of clinical and anatomic predictors of long-term functional outcomes after surgical treatment remains limited to 2 recent retrospective reviews.[6,7] In a series of 260 patients, a multivariable logistic model found smaller lesion size ($P = .04$), younger age ($P = .11$), and fewer preoperative hemorrhages ($P = .12$) trended towards predicting good outcomes.[6] In the second series of 134 patients, age less than 40 years ($P = .02$), male sex ($P = .64$), surgery within 8 weeks of last hemorrhage ($P = .03$), and lateral surgical approach ($P = .32$) trended towards predicting good outcomes.[7] Further validation of outcome predictors is necessary, and the aim of our study is to identify important predictors in a 15-year experience with BSCMs in 104 patients, which represents the fourth largest experience in the literature. Informed by our large experience with arteriovenous malformations (AVM) and our efforts to develop a new grading system to predict outcomes for these surgical lesions, we hypothesized that a similar approach combining anatomic factors such as size, eloquence, and venous anatomy together with clinical factors such as age and hemorrhagic presentation might produce a meaningful new grading system for BSCM that predicts long-term functional outcomes and guides clinical decision-making.

METHODS

Study Population

This study was approved by the University of California, San Francisco (UCSF) Committee on Human Research and performed in compliance with Health Insurance Portability and Accountability Act regulations. A retrospective chart review was conducted for all patients undergoing surgical treatment for BSCM. During the 15-year period from October 1997 to November 2012, complete demographic, anatomic, and clinical data for 104 patients who underwent microsurgical resection by a single neurosurgeon (M.T.L.) were evaluated. There were no age limitations for inclusion. Patients with lesions located entirely in the basal ganglia or thalamus were excluded.

Data Collection

Data extraction was conducted by 2 investigators (R.M.G. and M.E.I.). Patient data was reconstructed based on clinical assessments (at admission, immediately postoperative period, and at last follow-up), radiographic films, operative notes, intraoperative imaging, and final pathology reports. The senior author (M.T.L.) reported all operative notes. All neuroimaging data were reviewed by an independent neuroradiologist and replicated for additional study variables. Operative notes and radiographic films were used to determine the presence of developmental venous anomalies (DVAs). No outside medical records were used. The modified Rankin Scale (mRS) score was used to assess patient outcomes.[8] The 9 patients that did not have any clinical follow-up evaluation after surgical resection documented in our system were contacted.

Study Variables

Patient demographics included sex and age (in years) at the time of surgery. The dates of surgery, admission, discharge, last follow-up evaluation, total number of hemorrhagic events, and time interval since last hemorrhagic event were recorded. The following definition was used to establish a history of discrete hemorrhagic event: a clear clinical history of an acute neurological deficit accompanied by intralesional or extralesional blood products present on magnetic resonance imaging (MRI). Patients with a slowly progressive clinical course, hemosiderin alone on MRI, or both were not considered to have a hemorrhagic event. Timing of a hemorrhagic event to surgical treatment was categorized accordingly: acute (<3 weeks), subacute (3-8 weeks), and chronic (>8 months). Data for comorbid medical conditions and at least 3 neurological examinations were collected at the dates indicated above. Neurological deficits were considered permanent if present beyond the 12-month postoperative follow-up visit.

The locations of each BSCM were classified as mesencephalic, pontine, or medullary. The 3-dimensional size and depth from the BSCM to pial or ependymal surface was measured on preoperative T1-weighted MR images. Intraoperative images were used to confirm lesion location as exophytic, superficial, or deep. Data on surgical approach, extent of resection, and perioperative complications were also collected.

Outcomes Variables

Outcomes were analyzed by 2 methods. The first method analyzed a relative change in mRS score compared to baseline. A relative improvement or no change was considered if the mRS score change was ≤ 0, while those with deteriorated outcome had mRS score change >0. The second method analyzed the absolute outcome with mRS score. The absolute outcome was considered favorable if the patient had a mRS score ≤ 2 at the last follow-up evaluation, and unfavorable if mRS score was >2. Univariable and multivariable analysis used the second method; the outcome variable was dichotomized into favorable (mRS $\leq$ 2, coded as 0) vs unfavorable (mRS score $>$ 2, coded as 1).

Logistic Regression Modeling

A binary logistic regression model was developed based on an a priori hypothesis that predictors of unfavorable functional outcomes were analogous to those found in the Spetzler-Martin grading system[9] and the Lawton-Young supplementary grading system.[10] We hypothesized that the BSCM maximum axial diameter (in millimeters, mm), presence of DVA, and ventral lesion location were predictors most similar to size, venous drainage, and eloquence in the Spetzler-Martin grading system. Given all BSCM lesions reside in eloquent regions, we hypothesized that ventrally located lesions with more restricted surgical access may be associated with poorer long-term outcomes. In addition, lesion crossing the axial midpoint of the brainstem was also used to capture eloquence, with the idea that a lesion extending deeply to more critical structures would tolerate parenchymal dissection poorly. Predictors most similar to the factors in the supplementary AVM grading system included age (in years) and time between last hemorrhagic event and surgery (in days). CMs are not characterized as compact or diffuse, and therefore this predictor was not evaluated. Time since last hemorrhage was chosen because the presence and age of an associated hematoma influences the separation and delivery of the lesion from the brainstem. This hemorrhage predictor was made into a categorical variable with indicator values set based on our clinical judgment as the following: acute (<3 weeks), subacute (3-8 weeks), and chronic (>8 weeks). The chronic hemorrhage subgroup was used as the reference baseline in the model building.

Predictors included in the final model were selected based on the a priori hypothesis described above and results of the univariable analysis. We did not use a strict *P* value threshold (ie, $P < .20$) alone for inclusion of predictors because this method has been shown to inaccurately control for necessary confounders.[11] All multivariable models included only preoperative variables except adjustment for the duration of follow-up time in months. The likelihood ratio test was used to compare the fit between multivariable models to the data. A linear trend was assessed between the outcome variable and the categorical predictor for time since last hemorrhage using the χ-square test for linear trend. The multivariable model's predictive accuracy was assessed using (1) receiver operating characteristic (ROC) analysis and (2) 10-fold cross validation. The later method was selected because all the data was used to develop and fit the final model. Collinear diagnostic testing assessed the independence of variables included in the final multivariable regression model using variance inflation factor (VIF; an indicator of how much of the inflation of the standard error could be caused by collinearity), and statistical tolerance (an indicator of how much collinearity that a regression analysis can tolerate). Both are measures of the strength of the interrelationships among the variables within a multivariable model and were used to determine if the final statistical model could further be simplified.

Statistics Analysis

Descriptive statistics comparing relative change in mRS scores by deterioration (worse) vs unchanged or improved outcome was analyzed by *t* tests and χ^2 tests for continuous and categorical variables, respectively. When necessary, the Fisher exact test and Wilcoxon-Mann-Whitney test were used for small cell counts. Univariable analysis tested the association of the outcome of absolute binary mRS scores, described above, with preoperative predictors. Multivariable parametric regression models were constructed to test the association of combined predictors with the absolute mRS score outcome. Statistical tests were considered significant if $P < .05$ except for the final logistic regression models where statistical significance was considered for $P < .1$. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). Data were analyzed using Intercooled Stata, Version 12 (Stata Corp., College Station, Texas) and JMP Software (SAS Institute Inc., Cary, North Carolina).

Brainstem Cavernous Malformation Grading System

The β coefficient estimates from the final multivariable logistic regression model were used to develop a weighted point scoring system for clinical and BSCM characteristics for each patient. The points were added together across 5 predictor categories. Continuous variables (axial size [mm] and age per 5 years) were dichotomized for the purposes of developing the point grading system using clinical judgment.

RESULTS

Patient Demographics

A total of 104 patients were diagnosed with BSCMs and microsurgically treated, with a mean age of 42.1 years and a slight female

TABLE 1. Patient Demographics and Lesion Characteristics by Brainstem Cavernous Malformations Location[a]

	Location			
	Midbrain	Pontine	Medullary	Total
Total, n (%)	21 (20)	63 (61)	20 (19)	104 (100)
Age at admission (in years), mean ± SE	42.5 ± 3.8	41.5 ± 1.8	43.7 ± 4.3	42.1 ± 1.5
Female sex, n %	11 (52)	38 (60)	9 (45)	58 (56)
Lesion size (diameter in mm), mean ± SE	19.8 ± 6.9	20.1 ± 7.5	16.3 ± 8.1	19.5 (7.7)
Exophytic, n (%)	2 (10)	9 (14)	3 (15)	14 (13.5)
Deep, n (%)	12 (57)	34 (54)	10 (50)	56 (53.8)
Ventral, n (%)	10 (48)	25 (40)	8 (40)	43 (41)
Crossing midpoint, n (%)	7 (33)	31 (49)	14 (70)	52 (50)
Hemorrhagic presentation, n (%)	21 (100)	62 (98)	20 (100)	103 (99)
Preoperative hemorrhages, mean ± SE	2.2 ± 0.3	1.9 ± 0.1	1.7 ± 0.2	1.9 ± 0.1
Time from last hemorrhage to surgery (days), mean ± SE	46.1 ± 12.5	71.5 ± 11.7	33.2 ± 6.7	60.0 ± 7.8
Acute hemorrhage (≤3 weeks since last hemorrhage), n (%)	10 (48)	20 (32)	12 (60)	42 (40.8)
Follow-up time (days), mean ± SE	15.2 ± 4.4	21.2 ± 3.8	13.8 ± 3.1	18.5 ± 2.6
mRS on admission, mean ± SE	2.3 ± 0.3	2.2 ± 0.1	2.3 ± 0.2	2.2 ± 0.1

[a]mm, millimeter; mRS, modified Rankin Scale score; SE, standard error.

Lesions were clustered by predominance in the midbrain, pons, or medulla. Patient demographics, hemorrhage history, other brainstem characteristics, and preoperative functional evaluation are summarized according to predominant location.

predominance (Table 1). All but 1 patient presented with a clear history of hemorrhage. The majority of patients (74.0%) had 1 or 2 hemorrhagic events before undergoing microsurgical resection; 26 patients (25%) had 3 or more hemorrhages, and 4 of these patients (3.8%) had 5 hemorrhages. A total of 196 events during 4345 cumulative years of life were documented, yielding a retrospective annual hemorrhage rate of 4.5%, assuming all lesions were congenital except for 1 patient with documented de novo development.

Most patients presented with sudden symptom onset, with 40% presenting acutely (<3 weeks). The most common presenting symptoms were cranial neuropathy (72%), diplopia/blurred vision (47.6%), headache (42.2%), motor deficits (36.5%, excluding cranial neuropathy), sensory deficits (36.5%), ataxia (22.4%), vertigo/dizziness (32.0%), nausea/vomiting (17.5%), and dysarthria (13.6%). Two patients were obtunded, and 1 was comatose at admission. Ninety-four patients (90.4%) had a focal neurological deficit at admission.

Fifty-seven patients (53.0%) had at least 1 preexisting medical condition including hypertension (21.2%), hyperlipidemia (9.6%), diabetes mellitus (5.8%), thyroid dysfunction (7.7%), or remote cancer (10.6%). Additionally, 21 patients (20.2%) had a comorbid neurological condition.

BSCM Characteristics

A total of 114 BSCMs were diagnosed in these 104 patients, with 13 patients having multiple CMs and 3 patients having multiple BSCMs. Operative lesions were located in the pons in 63 patients (61.0%), midbrain in 21 (20.0%), and medulla in 20 (19.0%, Table 1). Thirteen lesions spanned the pontomesencephalic (2) or pontomedullary (11) junctions, but were classified as either pontine or medullary based on their predominant location. The average maximal diameter of the BSCMs was 19.5 mm. Only 14 (13.5%) were considered exophytic. Forty-three (41%) of the BSCMs were ventrally located, and 52 (50%) crossed the axial midpoint. Fifty-six patients (54.8%) had a DVA detectable on preoperative MRI.

Surgical Management

One patient with a temporal AVM was previously treated with radiosurgery and 2 courses of proton beam radiation before developing his midbrain cavernous malformation. Seven patients (6.7%) had prior craniotomies performed by other neurosurgeons and presented with recurrent BSCMs. Five patients had preoperative hydrocephalus, and 1 underwent shunt placement prior to BSCM resection.

The median time from last hemorrhagic event to surgical treatment was 28 days. The 2-point method[12] was used to guide the surgical approach and 10 distinct approaches were used (Table 2). In the midbrain, anterior lesions were exposed with an orbitozygomatic-transsylvian approach (8 patients, 7.7%), superior lesions were exposed with a transcallosal-transchoroidal approach (4 patients, 3.8%), posterolateral lesions were exposed with a lateral supracerebellar-infratentorial approach (10 patients, 9.6%), and posterior lesions were exposed with a midline or paramedian supracerebellar-infratentorial approach (4 patients, 3.8%). In the pons, the majority of lesions were exposed laterally with an extended retrosigmoid approach (25 patients, 24.0%), but a translabyrinthine approach was used early in the series (3 patients, 2.9%) and a subtemporal-medial transpetrous (Kawase) approach was used with 2 anterolateral lesions (1.9%). In the medulla, posterior lesions were exposed with a suboccipital-transventricular approach (27 patients, 26.0%) and anterolateral lesions were exposed with a far lateral approach (13 patients, 12.5%), with the telovelar approach used for lesions in the inferior cerebellar peduncle (7 patients, 6.7%).

TABLE 2. Summary of Surgical Approaches

	N	%
Midbrain		
Transcallosal-transchoroidal	4	3.8
Orbitozygomatic approach	8	7.7
Supracerebellar-infratentorial		
Midline/paramedian	4	3.8
Lateral	10	9.6
Pons		
Extended retrosigmoid	25	24.0
Translabyrinthine	3	2.9
Medial transpetrous (kawase)	2	1.9
Medulla		
Suboccipital-transventricular	27	26.0
Suboccipital-telovelar	7	6.7
Far lateral	13	12.5
Far lateral-retrosigmoid	1	1.0
Total	104	

Surgical approaches are summarized by location within midbrain, pons, or medulla. Frequencies and percentages are shown.

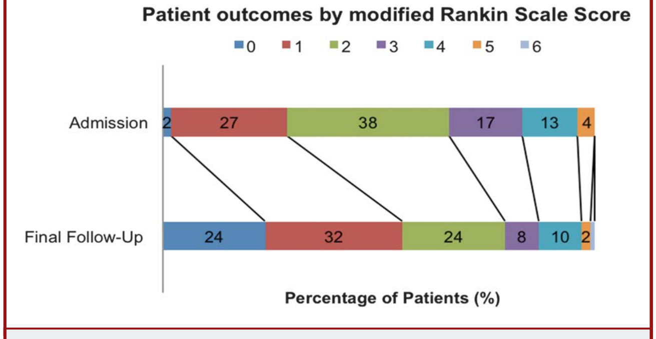

FIGURE 1. *Percentage of modified Rankin Scale scores at admission and at final follow-up clinical evaluation for 104 patients. The 1 perioperative death in the series is shown schematically (modified Rankin Scale score = 6), but the numerical value is not provided.*

Frameless stereotactic navigation and neurophysiological monitoring were used in all patients. Ninety-five patients underwent single-staged microsurgical resection and gross total resection was achieved in these patients (91.3%). Complete resection was confirmed radiographically with immediate postoperative and delayed (6 months to 1 year) MRI in these patients. Nine patients (8.7%) had residual/recurrent lesions, with a median time from surgical resection to re-hemorrhage of 2.1 years (range, 3 days to 5.9 years). The estimated retrospective recurrent hemorrhage rate was 7.0% per year. All 9 patients required an additional operation through the same craniotomy, and gross total resection was achieved in these patients after this second stage.

Patient Outcomes

Favorable outcomes after BCSM resection were observed in 83 of 104 patients (mRS score 0-2, 79.8%; Figure 1 and Table 3). Most patients (89.4%) showed relative improvements (54.8%) or were unchanged from their preoperative neurological baseline (34.6%). The majority of patients made good clinical recovery in all 4 categories (motor, sensory, cerebellar, and cranial nerve dysfunction) by the last postoperative follow-up evaluation (Figure 2). The largest improvement was observed in cranial neuropathy deficits, which was reduced by 20.6% from 77 (72.0%) at admission to 55 patients (51.4%) at final follow-up visit. Motor deficits improved by 13% from 39 (36.4%) at admission to 25 (23.4%) patients. Sensory

TABLE 3. Demographic, Clinical, and Anatomical Factors Associated With Their Relative Outcomes (Changes in mRS Between Admission and Final Clinical Evaluation)[a]

Predictor	Intact, Improved, or Same	Worse or Dead	*P* Value
Total, n	93	11	
Age (years), mean ± SE	41.3 ± 16.0	49.1 ± 12.2	.06[b]
Female sex, n (%)	52 (56)	6 (55)	.5[c]
Maximum BSCM diameter (mm), mean ± SE	19.6 ± 0.8	19.2 ± 2.17	.91[b]
Lesion location, n (%)			.13[c]
Mesencephalic	18 (19)	3 (27)	
Pontine	56 (60)	7 (64)	
Medullary	19 (20)	1 (9)	
Lesion located ventrally, n (%)	38 (41)	5 (45)	.76
Preoperative no. of hemorrhages, mean ± SE	1.9 ± 0.11	2.18 ± 0.30	.21[b]
Time from hemorrhage to surgery (days), mean ± SE	59.0 ± 8.3	69.1 ± 22.9	.23[b]
Acute hemorrhage <3 weeks, n (%)	40 (43)	2 (18)	.19[c]
Subacute hemorrhage 3-8 weeks, n (%)	22 (24)	3 (27)	.72[c]
Motor deficit at admission, n (%)	16 (17)	8 (73)	.63[c]
Sensory deficit at admission, n (%)	36 (39)	2 (18)	.16[c]
Cranial nerve at admission, n (%)	50 (54)	6 (55)	.61[c]
Developmental venous anomaly, n (%)	49 (53)	7 (64)	.54[c]
Hospitalization time (days), mean ± SE	9.1 ± 0.81	14.6 ± 3.2	.09[b]
Follow-up time (months), mean ± SE	16.8 ± 2.2	33.7 ± 14.8	.98[b]
mRS[d] score on admission, n (%)			.84[c]
0	2 (2)	0	
1	24 (26)	4 (36)	
2	36 (39)	3 (27)	
3	15 (16)	3 (27)	
4	12 (13)	1 (9)	
5	4 (5)	0	
mRS[d] score at last evaluation, n (%)			≤.001[c]
0	25 (27)	0	
1	33 (35)	0	
2	23 (25)	2 (18)	
3	6 (6.5)	2 (18)	
4	6 (6.5)	4 (36)	
5	0	2 (18)	
6	0	1 (9)	

[a]BCSM, brainstem cavernous malformations; mRS, modified Rankin Scale; no., number; SE, standard error.
[b]Wilcoxon-Mann-Whitney test.
[c]Fisher exact test.
[d]Modified Rankin Scale score.
The table compares patients who experienced a worse relative long-term outcome with those who improved or were unchanged, relative to neurological status at admission.

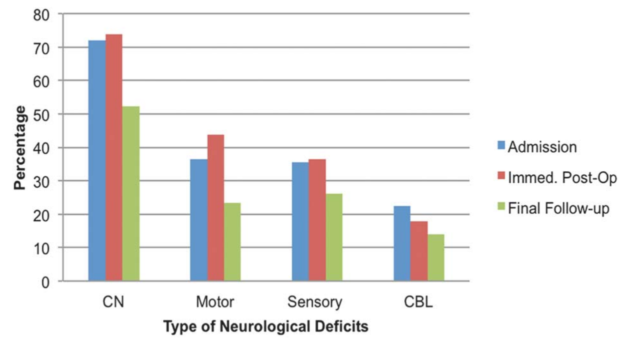

FIGURE 2. *Summary of total neurological deficits across 104 patients at 3 time periods (admission, immediate posterative period, and final follow-up clinical evaluation). CBL, cerebellar dysfuction; CN, cranial neuropathy; Immed. Post-Op, immediate postoperative period.*

deficits and cerebellar dysfunction also improved by 9.4% and 8.4%, respectively. By the last follow-up exam, 24 patients were neurologically intact. Among those patients with at least a 12-month follow-up observation, the proportion with no permanent deficits was 40%, and the proportion with a single deficit or intact was 66%.

Unfavorable outcomes were observed in 21 patients (mRS $>$ 2, 20.2%). There were 2 deaths in the follow-up period. The first death occurred within 48 hours of surgery in a 41-year-old woman who awoke intact after an uncomplicated resection of a pontine lesion, had an apneic event the night of surgery, experienced a global ischemic injury, and died of severe cerebral edema and elevated intracranial pressure (surgical mortality, 0.96%). The second death was due to pancreatic cancer 4 years after and unrelated to the BSCM resection; he had a dense hemiparesis and was wheelchair-bound at his last clinical evaluation (mRS 4, which, for the purposes of statistical outcome analysis, was used as the final mRS). Overall, 15 patients (14.4%) experienced cranial nerve or motor dysfunction that was worse at last follow-up relative to their preoperative baseline. These new deficits resulted in relative changes in mRS scores in 10 of these patients (permanent neurological morbidity, 9.6%).

A total of 29 patients (28%) had at least 1 postoperative complication in the perioperative period (Table 4). Seven patients required shunt placement for hydrocephalus, cerebrospinal fluid leakage, or pseudomeningocele; 5 patients required tracheostomy (1) or percutaneous endoscopic gastrostomy (4); and 4 patients required reoperation for bleeding in the resection cavity (3) or for epidural hematoma (1). The mean duration of follow-up was 18.6 months (range, 1-144 months). Sixty-eight patients (65.4%) had follow-up $>$6 months.

Logistic Regression Analysis

Univariable binary logistic regression identified associations with age (P = .002), presence of DVA (P = .03), chronic hemorrhage time (P = .08), and lesion crossing the brainstem midpoint (P = .09), with the ORs of these predictors trending towards increased odds of unfavorable outcomes (Table 5).

TABLE 4. Perioperative Complications[a]

Complication (n)	Cause
Death (1)	Postoperative apnea, global ischemia (1)
Cerebrospinal fluid (13)	Cerebrospinal fluid leak (4)
	Pseudomeningocele (4)
	Hydrocephalus (5)
	Shunts placed (7): 4 VPS, 3 LPS
Infection (10)	Pneumonia (2)
	Meningitis/ventriculitis (3)
	Sepsis (3)
	Wound infection (1)
Vascular (8)	Hematoma evacuation resection site (3)
	Internal capsule hemorrhage (1)
	Pontine hemorrhage, delayed (1)
	Epidural hematoma (1)
	Transverse sigmoid sinus thrombosis (1)
	Vasospasm requiring angioplasty (1)
Lower cranial nerves (5)	Tracheostomy (1)
	PEG (4)
Miscellaneous (4)	Respiratory failure (1)
	Pneumocephalus requiring EVD (1)
	Atypical facial pain (2)

[a]No., number; EVD, external ventricular drain; LPS, lumboperitoneal shunt; PEG, percutaneous endoscopic gastrostomy; VPS, ventriculoperitoneal shunt.
The table summarizes perioperative complications among 29 patients after microsurgical resection of brainstem cavernous malformations.

Ventral lesion location (OR = 1.75, 95% CI: 0.69-4.60, P = .25) and maximum axial diameter (OR 1.04, 95% CI: 0.98-1.10, P = .23) predicted increased odds of unfavorable outcomes. Acute (OR = 0.52, 95% CI: 0.18-1.48, P = .22) and subacute (OR = 0.69, 95% CI: 0.21-2.29, P = .55) hemorrhage, compared to chronic hemorrhage, were potentially protective, suggesting that earlier timing of surgical resection from last hemorrhagic event increased the odds of favorable outcomes in the long-term.

The multivariable logistic regression model, adjusted for follow-up observation time, identified age, maximum axial diameter, DVA, acute and subacute hemorrhage time, and lesion crossing the midpoint of the brainstem to be significant predictors (P values $\leq$ .10; Table 6). The test for trend did not find a linear relationship between hemorrhagic subgroups and unfavorable functional outcomes (χ^2 = 2.82, P = .09). A full logistic multivariable model was constructed as follows: logit (mRS outcome) = $\beta0$ + $\beta1$ (developmental venous anomaly) + $\beta2$ (maximum axial diameter per mm) + $\beta3$ (ventral location) + $\beta4$ (time since last hemorrhage $<$3 weeks) + $\beta5$ (time since last hemorrhage $\geq$3-8 weeks) + $\beta6$ (age per 5 years) + $\beta7$ (lesion crossing midpoint of brainstem) + $\beta8$ (time since last surgery in months). Ventral lesion location was not predictive of outcome (P = .68) and was actually found to have a protective trend in the full model (OR = 0.77, 95% CI: 0.22-2.73). Given this finding, a logistic multivariable model was constructed excluding ventral location, and this restricted final model was no worse statistically than the full model (likelihood ratio test, degrees of freedom = 1, χ^2 = 0.17, P value = .69).

TABLE 5. Univariable Analysis of Demographic and Surgical Predictors in 104 Patients[a]

Predictor	OR	95% CI	*P* Value
Preoperative			
Age, per 5 years	1.06	1.02-1.09	.002
Female sex	1.37	0.51-3.66	.527
Admission motor deficit present	2.92	1.10-7.80	.032
Admission cranial nerve deficit present	2.74	0.74-10.11	.131
Developmental venous anomaly present	3.44	1.15-10.26	.027
Location and size			
Lesion located ventrally	1.75	0.69-4.60	.254
Lesion located in pons	0.84	0.32-2.21	.719
Lesion located in midbrain	1.30	0.42-4.10	.645
Lesion located in medulla	0.99	0.29-3.33	.981
Lesion crossing axial midpoint	2.37	0.87-6.47	.093
Distance to pial surface, mm	0.73	0.46-1.17	.192
Maximal axial diameter, per mm	1.04	0.98-1.10	.233
Hemorrhage events and timing			
Total no. of hemorrhage events, per event	1.29	0.85-1.94	.231
Time since last hemorrhage, per day	1.00	0.99-1.01	.363
Acute hemorrhage time (<3 weeks)	0.52	0.18-1.48	.222
Subacute hemorrhage time (≥3-8 weeks)	0.69	0.21-2.29	.551
Chronic hemorrhage time (≥8 weeks)	2.41	0.91-6.38	.076
Intraoperative/postoperative			
Adhesions present intraoperative	2.12	0.79-5.66	.133
Deep lesion by intraoperative evaluation	0.93	0.35-2.42	.880
Superficial lesion by intraoperative evaluation	1.04	0.38-2.87	.944
Exophytic lesion by intraoperative evaluation	1.09	0.28-4.42	.901
Cranial nerve deficit (at final clinical evaluation)	1.95	0.72-5.33	.192
Motor deficit (at final clinical evaluation)	20.56	6.36-66.40	<.001
Hospitalization time, days	1.11	1.04-1.18	.001
Follow-up time last surgery, per month	1.00	1.00-1.04	.013

[a]CI, confidence interval; OR, odds ratio.
The table summarizes the univariable binary logistic analysis, which included a priori demographic, preoperative, and postoperative factors. Each predictor was tested against unfavorable functional status (mRS ≥ 3, n = 21) vs favorable functional status (modified Rankin Scale score < 3, n = 83) as the dependent variable at last clinical follow-up evaluation.

The area under the ROC curve, indicating the predictive accuracy of the model, was identical for the full and the restricted models (ROC = 0.86, 95% CI: 0.78-0.94; Table 6). Prediction of functional outcomes using 5 variables was as accurate as using 6 variables: for the full model, the sensitivity and specificity were 47.6% and 95.2%, respectively, while for the restricted model they were 42.9% and 95.2%, respectively. A 10-fold cross validation of the full model with all 6 variables had a misclassification rate of 17.1% (95% CI: 17.0-17.2). The VIF for variables included in the multivariable model ranged from 1.11 to 1.62 and the tolerance of variables ranged from 0.62 to 0.90. A lesion crossing the midpoint was statistically independent of an axial lesion that measured greater than 20 mm (χ^2 = 1.15, *P* value = .28).

Proposed BSCM Grading System

A BSCM grading system was constructed using the 5 significant variables identified in the multivariable model. Analogous to the Spetzler-Martin and supplementary grading systems for AVMs, points were assigned for maximum axial diameter, presence of DVA, lesion crossing the brainstem midpoint, age, and time between last hemorrhagic event and surgery (Table 7). Predictors were weighted by the β coefficient estimates in the final multivariable model, points were added, and grades were assigned that ranged from 0 to 7 points (Figures 3, 4, and 5). Neurological outcomes were predicted by BSCM grade, with all good outcomes in Grade 0 and I patients, all poor outcomes in Grade VI and VII patients, and decreasing rates of favorable outcome in between (Table 8). The absolute numbers of patients in subgroups at the extremes are small and could be affected by sampling variability.

DISCUSSION

BSCM Grading and Similarities to AVM Grading

The management of brainstem cavernous malformations has evolved dramatically in the past 20 years. Once considered inoperable lesions in inviolable territory, BSCMs are now surgically curable with acceptable operative morbidity and established exposures, brainstem entry zones, and resection

TABLE 6. Multivariable Binary Logistic Regression Models With the Dependent Outcome Variable is Unfavorable (mRS > 2) Vs Favorable (mRS ≤ 2) Functional Status at Last Clinical Evaluation[a]

	Final Model		Full Model	
Predictor	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age, per 5 years	1.07 (1.03-1.11)	.001	1.07 (1.02-1.12)	.001
Maximum axial size, per 1 mm	1.09 (0.99-1.18)	.080	1.09 (0.99-1.19)	.078
Developmental venous anomaly	4.01 (1.04-15.40)	.043	4.15 (1.06-16.21)	.041
Acute hemorrhage time (<3 weeks)[b]	0.18 (0.04-0.82)	.027	0.18 (0.04-0.82)	.027
Subacute hemorrhage time (≥3-8 weeks)[b]	0.24 (0.05-1.38)	.110	0.23 (0.05-1.45)	.100
Lesion located ventrally	—	—	0.77 (0.22-2.73)	.681
Lesion crossing axial midpoint	3.40 (0.93-12.42)	.075	3.60 (0.95-13.46)	.060
Follow-up time from last surgery, per month	1.02 (1.00-1.04)	.030	1.02 (1.00-1.04)	.027
Area under ROC curve	0.86 (0.78-0.94)		0.86 (0.78-0.94)	

[a]mm, millimeter; mRS, modified Rankin Scale score; ROC, receiver operating characteristic.
[b]The baseline reference group includes those presenting with posthemorrhage time of ≥8 weeks.
Two multivariable binary logistic parametric regression models were included in the final analysis. The full model included 6 predictors adjusted for total follow-up time since brainstem cavernous malformation surgery. The likelihood ratio test was used to determine the fit between the final and full models to the data.

techniques. Published reports on BSCMs focus on these surgical principles and outcomes, but patient selection remains a critical determinant of results and has been inadequately addressed in these reports. Rational patient selection is derived from the identification of measurable preoperative factors that correlate with operative morbidity and neurological outcome. These clinical or anatomic factors are often packaged in grading scales that simplify this difficult task of patient selection and make surgical risk assessment formulaic. To our knowledge, only 1 grading system has been proposed for CMs which is based on: (1) location supratentorially vs infratentorially or in the basal ganglia and spinal cord; and (2) focal neurological deficits.[5] While this grading system recognizes less favorable outcomes associated with BSCM, it does not differentiate patients with BSCMs who might expect more favorable surgical outcomes and offers no guidance to neurosurgeons forced to select these patients. Rather than considering all CMs and developing a broadly applicable grading system that is weak with BSCMs, we instead focused our efforts on BSCMs and the patients who need a grading system most of all.

TABLE 7. Proposed Brainstem Cavernous Malformations Grading Scale[a]

Predictor	Criteria	Points
Size (cm)	≤2	0
	>2	1
Crossing axial midpoint	No	0
	Yes	1
Developmental venous anomaly	No	0
	Yes	1
Age (years)	≤40	0
	>40	2
Hemorrhage	Acute (0-3 weeks ago)	0
	Subacute (3-8 weeks ago)	1
	Chronic (>8 weeks ago)	2
Total		7

[a]cm, centimeter.
Detailed description of the predictors included in the proposed brainstem cavernous malformations grading system. Point values were determined using weights from final regression model based on β coefficient estimates.

In the literature's largest experience with BSCMs, Abla et al[6] found that small size, young age, and fewer hemorrhages predicted good surgical outcomes. In the next largest experience, Pandey et al[7] confirmed the importance of age and added early surgery after last hemorrhage, male sex, and lateral surgical approach as positive predictors. Our study again confirmed the predictive power of age and early surgery after last hemorrhage, and also found the presence of a DVA to be predictive as well. Although not strictly significant statistically, size and location crossing the axial midpoint trended towards significance on multivariable analysis. We were struck by the similarity of outcome predictors for BSCMs and AVMs, although their pathobiology and pathophysiology are so different. The predictors used in the Spetzler-Martin and Lawton-Young grading systems include size, eloquence, plus venous drainage, and age, hemorrhagic presentation, plus compactness, respectively. We routinely combine these 6 variables into a supplemented Spetzler-Martin score for AVMs. With the exception of compactness or diffuseness that applies the AVMs and not to CMs, predictors that seem to impact BSCM outcomes are remarkably similar and indicate that many of the same surgical factors impacting AVM outcomes also impact BSCM outcomes. This insight might offer new, analogous methodology for preoperative risk assessment.

Elements of the BSCM Grading System

Size is an obvious factor in resecting brain AVMs and BSCMs, but does not always emerge as statistically significant because conservative biases may influence patient selection with brainstem

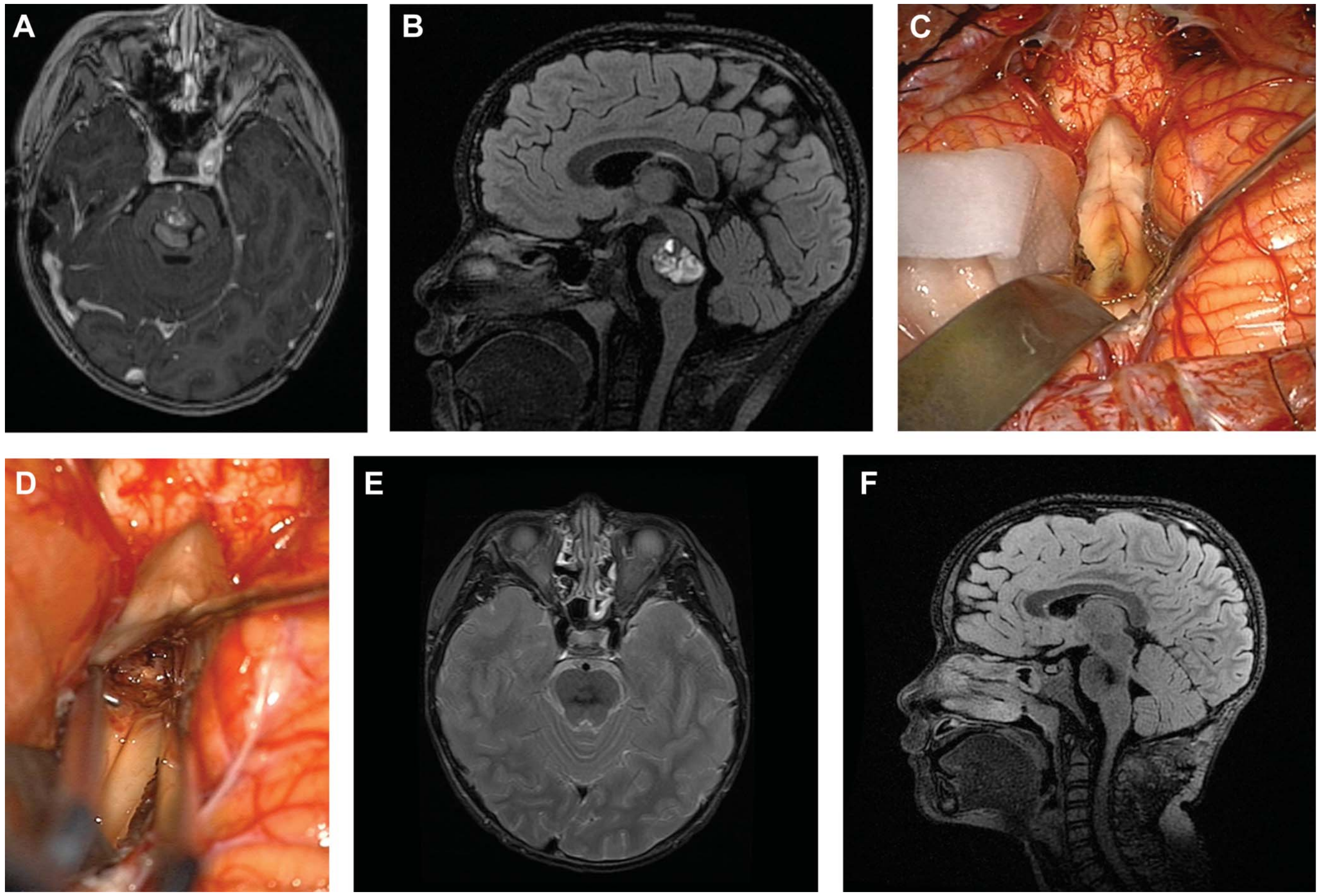

FIGURE 3. *Case 1. A 7-year-old boy presented with somnolence, unsteady gait, diplopia, and slurred speech. Preoperative magnetic resonance imaging (MRI) demonstrated a brainstem cavernous malformation in the pons that came to the floor of the fourth ventricle (***A***, axial T1-weighted MRI with gadolinium, and* **B***, sagittal T2-weighted MRI). The brainstem cavernous malformations grade was 5 (size = 1, crossing the midpoint = 1, developmental venous anomaly = 1, age = 0, hemorrhage timing = 2).* **C***, suboccipital-transventricular approach exposed the lesion on the ventricular floor (hemosiderin stain) and (***D***) the lesion was resected completely. Postoperative MRI confirmed complete resection (***E***, axial T2-weighted, and* **F***, sagittal fluid attenuation inversion recovery images). The patient was intact at last follow-up exam.*

lesions at either size extreme. Maximal axial diameter was not significant in our univariable analysis, but approached significance in our multivariable analysis ($P = .08$). Larger lesions might not be associated with worse outcomes due to exophytic pial presentation or at least shorter distances beneath pial surfaces, larger operative cavities, more associated hematoma, and greater splay of fiber tracts through which to work. As with AVMs, lesion size remains an important consideration intuitively, if not statistically, and was built into our BSCM grading system. Larger lesions have more contact area with the surrounding brainstem, which inevitably increases circumferential dissection, tissue manipulation, risk to perforators, bleeding, likelihood of residual lesion, and need for reoperation.

The concept that some areas are more critical and inviolable than others is important in AVM surgery and is captured by eloquence. However, the entire brainstem is considered eloquent, making eloquence meaningless in a BSCM grading system. We captured this concept with BSCMs by their crossing the axial midpoint, with the idea that such lesions are more deeply embedded in the brainstem than those on the periphery, might require more parenchymal transgression, are closer to more vital central tracts and nuclei, and can incur bilateral brainstem morbidity. Furthermore, central BSCMs have greater technical challenges associated with longer corridors, reduced visualization, more blind spots in the resection cavity, and limited maneuverability of instruments. Crossing the axial midpoint and axial size were important confounders in determining long-term patient outcomes and were statistically independent of each other ($P = .28$). These variables, although related, did not demonstrate statistical evidence of collinearity, suggesting that each contributes significantly and independently to the final multivariable model. These variables were included in our final statistical model to fully classify our

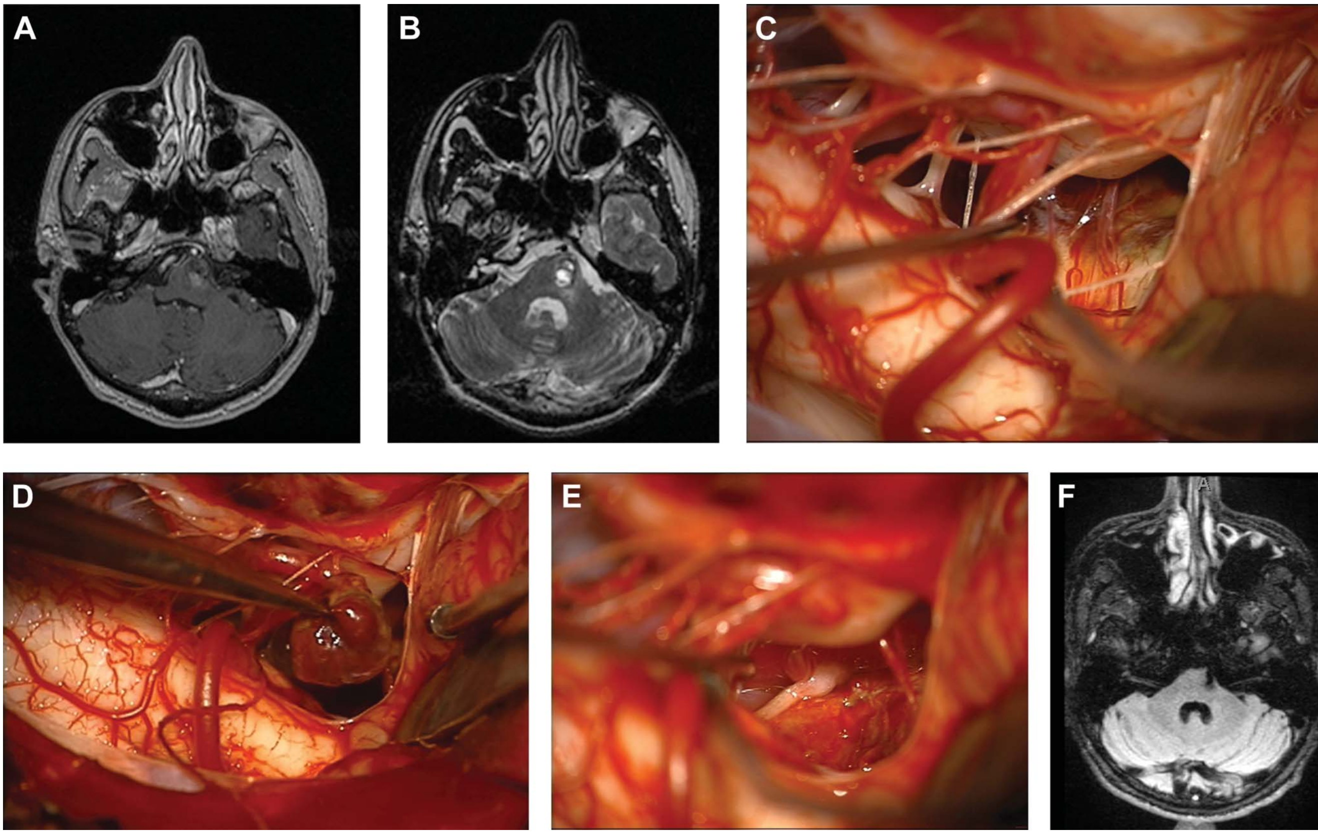

FIGURE 4. *Case 2. A 22-year-old man presented with headaches, diplopia, and left facial weakness. Preoperative magnetic resonance imaging demonstrated a brainstem cavernous malformation in the medulla (***A***, axial T1-weighted image with gadolinium, and* **B***, axial fast spin echo image). His brainstem cavernous malformations grade was 1 (size = 1, crossing the midpoint = 0, DVA = 0, age = 0, hemorrhage timing = 0).* **C***, left far lateral craniotomy exposed the brainstem cavernous malformations in the vagoaccessory triangle and (***D***) the lesion was removed.* **E***, resection cavity contained no residual lesion. Postoperative magnetic resonance imaging confirmed complete resection (***F***, axial extended echo-train acquisition fluid attenuation inversion recovery magnetic resonance imaging). He was neurologically intact at last follow-up exam.*

patient population and theoretically delineate between mid-level grades. Other measures of brainstem eloquence were considered, such as depth below the pial or ependymal surface, ventral location, or crossing the midline, but crossing the midpoint proved to be simple, reproducible, and approached significance in univariable and multivariable analysis (P = .09 and .06, respectively).

Although some authors observe DVAs with all BSCMs, we found them radiographically and intraoperatively in just over half of patients in our series. Surprisingly and for the first time, we found an association between DVAs and neurological outcome (univariable analysis, P = .03; multivariable analysis, OR = 4.01; 95% CI: 1.04-15.40; P = .04). Preservation of DVAs is an established practice because they are part of normal venous circulation and their compromise can cause venous ischemia or infarction.[6] DVAs were meticulously preserved in this experience, and therefore their association with outcome was not due to their sacrifice or venous complications. We speculate that DVAs increase the overall complexity of BSCM resection, often creating obstacles in the surgical corridor, bleeding during resection, or generating satellite lesions in the brainstem. In the Spetzler-Martin grading system, deep venous drainage is a surrogate measure of deep AVM location and does not relate directly to venous physiology. In this BSCM grading system, DVAs have no relation to lesion depth and can course in many directions, deep or superficial to the lesion. Points are assigned based on preoperative MR imaging and therefore apply only to those large enough to be visible radiographically.

Age is the only factor identified in all major BSCM experiences that predicts outcome, including ours (P = .002 and P = .001 in uni- and multivariable analysis). Age was also identified as a significant factor predicting outcome after AVM surgery and is incorporated into the Lawton-Young supplementary grading system.[10] As in that grading system, this BSCM grading system used 40 years somewhat arbitrarily as a dividing line between young and old. These findings indicate the importance of neural plasticity in recovery, rehabilitation, and general resilience after BSCM resection, particularly in the pediatric patients (<20 years). These findings also indicate the negative effects of increasing comorbidities

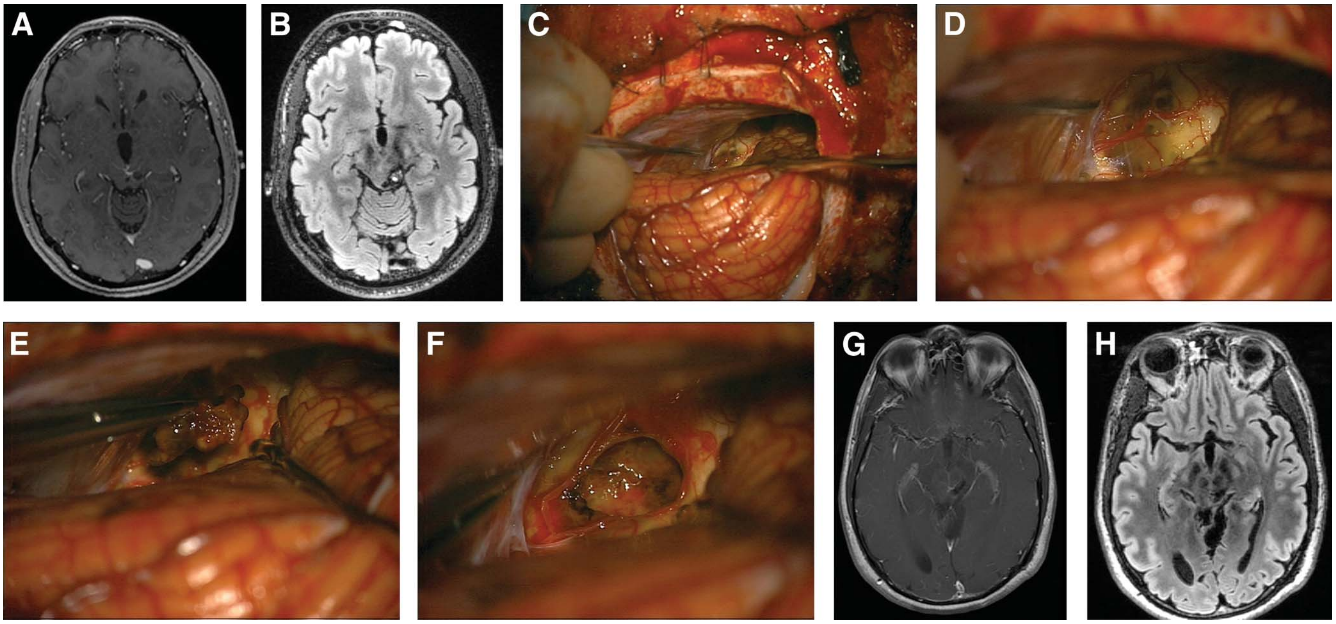

FIGURE 5. *Case 3. A 28-year-old man presented after his second hemorrhage from a brainstem cavernous malformations (BSCM) with left fourth nerve palsy and right-sided hemisensory loss. Preoperative magnetic resonance imaging demonstrated a BSCM in the midbrain (***A***, axial T1-weighted image with gadolinium showing superior developmental venous anomaly, and* **B***, axial T2-weighted fast spin echo image showing its location on the lateral midbrain surface). His BSCM grade was 3 (size = 0, crossing the midpoint = 0, developmental venous anomaly = 1, age = 0, hemorrhage timing = 2).* **C***, left lateral supracerebellar-infratentorial approach in the sitting position allowed gravity to open the infratentorial plane and (***D***) expose the lateral midbrain.* **E***, BSCM was removed and (***F***) the resection cavity was clean. Postoperative magnetic resonance imaging showed no residual lesion (***G***, axial T1-weighted image with gadolinium showing preserved developmental venous anomaly, and* **H***, axial extended echo-train acquisition fluid attenuation inversion recovery image). At his last postoperative examination, his cranial nerve exam returned to normal but his hemisensory loss persisted at his preoperative baseline.*

beyond 40 years on general anesthetic and surgical risks, recoverability, and overall outcome.

The supplementary grading system for AVMs recognizes the surgical advantages of hemorrhage by scoring a point for patients presenting with unruptured AVMs. Hemorrhage facilitates surgery by separating the AVM from adjacent brain, and hematoma evacuation creates working space around the nidus that can minimize brain transgression or access deep nidus that might otherwise have been unreachable. These same advantages apply to BSCMs, which explains the predictive power of early surgery after last hemorrhage. Early surgery allows time for stabilizing the patient's condition and reducing edema around the lesion, while

TABLE 8. **Neurologic Outcomes According to Proposed Brainstem Cavernous Malformations Grading System**[a]

	Favorable Outcome (mRS 0-2)		Unfavorable Outcome (mRS 3-6)		Relative Outcomes	
Grade	n	Patients With Assigned Grade, %	n	Patients With Assigned Grade, %	Same/Improved n (%)	Worse n (%)
0	2	100	0	0	1 (50)	1 (50)
I	12	100	0	0	12 (100)	0
II	18	94.7	1	5.3	19 (100)	0
III	25	86.2	4	13.8	28 (100)	0
IV	13	76.5	4	23.5	15 (88)	2 (12)
V	13	68.4	6	31.6	15 (79)	4 (21)
VI	0	0	4	100	2 (50)	2 (50)
VII	0	0	2	100	1 (50)	1 (50)
Total	83	—	21	—	93 (89)	11 (11)

[a]CI, confidence interval; mRS, modified Rankin Scale score; OR, odds ratio.
The table shows the absolute and relative outcomes in 104 patients according to brainstem cavernous malformations grade in the proposed grading system.

still capitalizing the liquefied hematoma around or within the BSCM.[13-15] Although not rigorously studied, this liquefied hematoma remains for approximately 8 weeks, which is why we chose this endpoint for the subacute time window in our grading system. In the chronic phase, liquid hematoma is absorbed and the BSCM adheres to surrounding parenchyma with gliosis, scar tissue, and hematoma organization, making it more difficult to remove safely and cleanly.[16] A BSCM's ease of separation from the brainstem is so critically important from a technical standpoint, and acute/subacute hematoma helps the neurosurgeon peel the lesion gently away. Therefore, this hemorrhage variable measuring the time interval from hemorrhage to surgery is capturing this surgical nuance. Forty percent of our patients underwent surgery acutely, with 64% within 8 weeks, and others reported similar percentiles (42.3% and 69.3% of patients undergoing resection within 4 and 8 weeks, respectively).[7] The number of hemorrhagic events experienced by a patient has been shown by others to influence outcome, but it was not significant in our experience and was excluded from the BSCM grading system. The number of BSCM hemorrhages is beyond the surgeon's control as well as difficult to assess, as some events are likely not captured by the patient or physician, whereas timing of surgery relative to hemorrhage can be orchestrated by the neurosurgeon and used in the selection process.

Compact or diffuse nidus is the final element of the supplementary AVM grading system, but these anatomic descriptors do not apply to BSCMs or CMs generally. CMs have a discrete capsule and clear demarcation from parenchyma, so this variable was not included in the BSCM grading system.

The grading system can be easily applied at the bedside by assigning points to the 5 predictors and generating scores from 0 to 7 (Table 7). The chances of an unfavorable outcome increase with increasing grade, as do the chances of surgical morbidity (Table 8). There is no clear dividing line defining operative thresholds, but clearly Grades VI and VII BSCMs are associated with significant risks. Remembering the 5 predictive variables may seem cumbersome, but they are analogous to the supplemented Spetzler-Martin system for AVMs, which is familiar to many clinicians.

Limitations

Our study has several important limitations. Categories for age, axial size, and time since last hemorrhagic event were chosen somewhat arbitrarily based on our clinical experience. Follow-up time for patients in this analysis was heterogeneous and wide ranging, although the majority of patients were observed for at least 6 months. Referrals and transfers from distant hospitals make consecutive clinical follow-up a significant challenge that likely influences our findings. Most retrospective data analyses are susceptible to information and selection bias, and this one is no exception. Although it is the fourth largest surgical series in the literature,[6,7,14] the sample size was small and statistical significance was not definitively established for all variables in the BSCM grading system.

This study is a retrospective review of a single vascular neurosurgeon's experience with a rare disease during a 15-year period, and nearly all patient and surgical outcomes (ie, complete resection rate, morbidity rate, long-term outcomes, etc.) are similar to other large surgical series.[6,7,14,17-19] However, these results may not be generalizable to other neurosurgeons with less specialized practices or outside tertiary centers. The external validity of the proposed BSCM grading system will need further evaluation and validation. The purpose of a grading system is to guide the analysis of a particular patient's condition, but we must stress the need to individualize treatment recommendations. No grading system can replace a thorough and thoughtful assessment of the patient clinically, the lesion anatomically, and the neurosurgeon technically. We offer this BSCM as a basic tool for patient selection that can serve as an initial screening. BSCMs are exceptionally rare and technically challenging for even the most experienced specialists. Therefore, management planning should consider not only careful patient selection, but also referral to high-volume specialists, particularly with high-grade BSCMs.

CONCLUSION

Rather than developing a broadly applicable grading system for all CMs that is weak with BSCMs, we propose a system for the patients who need it most of all. The BSCM grading system differentiates patients who might expect favorable surgical outcomes and offers guidance to neurosurgeons forced to select these patients. Except for compactness, the same surgical factors affecting AVM outcomes also affect BSCM outcomes. Like eloquent AVMs, BSCMs crossing the axial midpoint are deeply embedded in the brainstem, require more parenchymal transgression, are closer to central tracts and nuclei, and can incur bilateral morbidity. Like hemorrhagic presentation with AVMs, acute/subacute hematoma helps separate a BSCM from the brainstem and is important technically. By predicting and stratifying outcomes after resection, the BSCM grading system might be a valuable clinical tool for neurosurgeons wrestling with patient selection.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Portions of this work were presented in a poster form at the Congress of Neurological Surgeons Annual Meeting, San Francisco, California, in October 21, 2013.

REFERENCES

1. Dubovsky J, Zabramski JM, Kurth J, et al. A gene responsible for cavernous malformations of the brain maps to chromosome 7q. *Hum Mol Genet.* 1995;4(3): 453-458.
2. Campeau NG, Lane JI. De novo development of a lesion with the appearance of a cavernous malformation adjacent to an existing developmental venous anomaly. *AJNR Am J Neuroradiol.* 2005;26(1):156-159.
3. Gross BA, Batjer HH, Awad IA, Bendok BR, Du R. Brainstem cavernous malformations: 1390 surgical cases from the literature. *World Neurosurg.* 2013;80 (1-2):89-93.

4. Gross BA, Lin N, Du R, Day AL. The natural history of intracranial cavernous malformations. *Neurosurg Focus.* 2001;30(6):E24.
5. Kivelev J, Laakso A, Niemelä M, Hernesniemi J. A proposed grading system of brain and spinal cavernomas. *Neurosurgery*. 2001;69(4):807-813; discussion 813-814.
6. Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF. Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. *Neurosurgery*. 2011;68 (2):403-414; discussion 414-415.
7. Pandey P, Westbroek EM, Gooderham PA, Steinberg GK. Cavernous malformation of brainstem, thalamus and basal ganglia: a series of 176 patients. *Neurosurgery*. 2013;72(4):573-589; discussion 588-589.
8. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5): 604-607.
9. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg.* 1986;65(4):476-483.
10. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. *Neurosurgery*. 2010;66(4):702-713; discussion 713.
11. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. *J Clin Epidemiol.* 1996;49(8):907-916.
12. Brown AP, Thompson BG, Spetzler RF. The two point method: evaluating brain stem lesions. *BNI Q.* 1996;12:20-24.
13. Bruneau M, Bijlenga P, Reverdin A, et al. Early surgery for brainstem cavernomas. *Acta Neurochir (Wien).* 2006;148(4):405-414.
14. Wang C, Liu A, Zhang J, Sun B, Zhao Y. Surgical management of brain-stem cavernous malformations: report of 137 cases. *Surg Neurol.* 2003;59(6):444-454; discussion 454.
15. Fahlbusch R, Strauss C, Huk W. Pontine-mesencephalic cavernomas: indications for surgery and operative results. *Acta Neurochir Suppl (Wien).* 1991;53:37-41.
16. Cenzato M, Stefini R, Ambrosi C, Giovanelli M. Post-operative remnants of brainstem cavernomas: incidence, risk factors and management. *Acta Neurochir (Wien).* 2008;150(9):879-886; discussion 887.
17. Ferroli P, Sinisi M, Franzini A, Giombini S, Soler CL, Broggi G. Brainstem cavernomas: long-term results of microsurgical resection in 52 patients. *Neurosurgery*. 2005;56(6):1203-1212; discussion 1212-1214.
18. Dukatz T, Sarnthein J, Sitter H, et al. Quality of life after brainstem cavernoma surgery in 71 patients. *Neurosurgery*. 2011;69(3):689-695.
19. Chen L, Zhao Y, Zhou L, Zhu W, Pan Z, Mao Y. Surgical strategies in treating brainstem cavernous malformations. *Neurosurgery*. 2011;68(3):609-620; discussion 620-621.

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COMMENTS

The authors provide an excellent discussion and rationale for the creation of a grading system to predict surgical outcome after surgical resection of brainstem cavernous malformations. The management of brainstem cavernous malformations presents a unique set of challenges to the cerebrovascular surgeon. Their system using the 5 factors of age, timing of surgery relative to hemorrhage, developmental venous anomaly, size, and crossing of the midpoint may contribute to improved outcomes for the management of these often difficult lesions. Prospective data collection going forward should help validate the grading system.

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Brainstem cavernous malformations are formidable lesions that were previously thought to be inoperable due to their location. Although these lesions are now aggressively managed with relatively good outcomes, the management continues to present considerable challenges.[1-3] Appropriate surgical planning as well as patient counseling on the expected transient morbidity and the potential for permanent worsening is crucial when microsurgical management is considered. Brainstem cavernous malformations are considered as clinically more aggressive lesions due to the sensitivity of their location to more subtle lesional changes and are also thought to have a higher bleeding rate.[3] The aim of this retrospective study was to identify significant outcome predictors in a large cohort of 104 patients. The authors developed a binary logistic regression model and hypothesized that the lesions maximum axial diameter (in millimeters, mm), presence of developmental venous anomaly, and ventral lesion location were predictors most similar to size, venous drainage, and eloquence in the Spetzler-Martin grading system. Outcomes were analyzed applying the modified Rankin Scale score and measuring absolute outcomes and changes from baseline. Unfavorable outcomes were observed in 21 patients. The proposed grading system then determined size, crossing of axial midpoint, presence of developmental venous anomaly, age, and presence of acute vs chronic hemorrhage (time between last hemorrhagic event and surgery) to be predictors of outcome. Predictors were weighted by the β coefficient estimates in the final multivariable model, points were added, and grades were assigned that ranged from 0 to 7 points. Indeed, as outlined in Table 8 of their presentation all good outcomes were in Grades 0 and I and conversely all poor outcomes in Grade VI and VII patients. This is a simple grading system that can be applied to clinical practice and is based on meticulous, empirical data collection of the authors' experience with these lesions. Although the study is conducted retrospectively (similar to the original Spetzler-Martin Grading study) and hence its applicability may be limited, the data may help further our understanding of the management and outcome of these lesions and can be tested further in future studies.

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1. Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF. Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. *Neurosurgery*. 2011;68 (2):403-414; discussion 414-415.
2. Lu XY, Sun H, Xu JG, Li QY. Stereotactic radiosurgery of brainstem cavernous malformations: a systematic review and meta-analysis. *J Neurosurg.* 2014;120(4):982-987.
3. Gross BA, Lin N, Du R, Day AL. The natural history of intracranial cavernous malformations. *Neurosurg Focus.* 2011;30(6):E24.

Risk assessment and management are concepts that pervade nearly all aspects of societal endeavor and our lives personally. From the financial sector to aviation, from the military to healthcare, organizations and individuals seek to identify hazards related to their pursuits and mitigate the consequences of identified pitfalls. In few disciplines are the stakes as high as in neurosurgery. As such, we continually seek to develop tools to weigh the risks of the natural history of the conditions we treat against those of surgical intervention. Put simply, the benefits of an operation must outweigh the risks of surgery for a procedure to be justified. Often, classification schemes are used to weigh various patient, disease, and procedurally related characteristics to decide if surgical intervention is the most appropriate course of treatment for a given pathology. Surprisingly, a grading system has yet to be devised to guide decision-making in the management of brain stem cavernous malformations (BSCMs), despite the fact that the natural history of BSCMs is often grave and the surgery to extirpate these lesions is among the most technically demanding and fraught with risk that neurosurgeons undertake.

Commendably, the authors of this manuscript have begun to fill this obvious void by presenting a novel grading system for BSCMs that accurately predicts post-operative morbidity. The cohort consisted of 104 patients who harbored 114 BSCMs operated upon by a single, highly experienced vascular neurosurgeon. The authors applied logistic regression techniques to determine that application of their new grading system accurately predicted surgical outcome as measured by dichotomized modified Rankin scale following surgery. The grading scale is scored from zero to seven and points are assigned for size, presence of an associated developmental venous anomaly, patient age, time from most recent hemorrhage and whether the BSCM "crosses the axial midpoint". Ultimately, the data reveal that BSCM grade and outcome are inversely related.

The strengths of this study are obvious. The statistics are robust and the data clearly demonstrate that a large proportion of BSCMs, in the hands of experienced cerebrovascular neurosurgeons, can be safely removed to immediately eliminate the risk of hemorrhage with acceptable morbidity. The scale is easy to remember and calculate, which is the sine qua non for any novel grading scale to be widely accepted into clinical practice.

The weaknesses of this report are minor. The analysis is retrospective and subject to associated intrinsic bias. Validation that the BSCM grading scale accurately predicts surgical outcome in a prospective study will be necessary prior to adoption into neurosurgical practice broadly.

Lastly, but perhaps most importantly, no grading system can supplant the doctor-patient relationship. Our role is to provide accurate information to the patient to empower the individual to make the best decision for him or her. However, these minor criticisms should not overshadow such laudable and timely work.

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