

Strategy Determines Outcome After Embolization of Brain Arteriovenous Malformations: A Strategy-Stratified Analysis

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Abstract

BACKGROUND AND OBJECTIVES: Comparative studies of brain arteriovenous malformation (AVM) embolization have concentrated on the liquid embolic agent, although embolization is undertaken with goals that differ fundamentally between patients. We tested whether the treatment goal set before the procedure, rather than the embolic agent, determines angiographic and clinical outcome.

METHODS: We reviewed 493 consecutive patients who underwent AVM embolization at our centres. Each patient was assigned before treatment to one of five strategies: curative, volume reduction before radiosurgery, targeted embolization of an aneurysm, targeted embolization combined with volume reduction, or fistula-directed embolization. Predictors were examined with multivariable logistic regression, and haemorrhage during follow-up with Kaplan-Meier and Aalen-Johansen estimators treating death as a competing risk.

RESULTS: Complete obliteration was achieved in 108 patients (21.9%). Obliteration differed 14-fold across strategies (60.0% with curative intent versus 4.2%-25.7% with other goals, $P < .001$). Independent predictors of obliteration were a nidus of 3 cm or smaller (odds ratio [OR] 11.71, 95% CI 6.43-21.33), a single feeding artery (OR 1.95, 95% CI 1.12-3.39) and curative intent (OR 10.37, 95% CI 5.85-18.37). Higher Onyx volume conferred no obliteration benefit in AVMs larger than 6 cm (no obliteration at any volume tier) or in grade IV-V lesions ($P = .97$), with a non-significant increase in complications ($P = .19$).

CONCLUSION: Outcome after AVM embolization is governed by the treatment goal and by whether obliteration is achieved. In large or high-grade AVMs, escalating embolic volume offers no obliteration benefit and carries a possible complication signal.

INTRODUCTION

Endovascular embolization occupies an unsettled position in the management of brain arteriovenous malformations (AVMs). It is used as a stand-alone treatment intended to cure, as an adjunct that reduces nidus volume before stereotactic radiosurgery (SRS) or resection, and as a targeted procedure that secures a bleeding point without addressing the malformation as a whole. Because these are different clinical undertakings, an aggregate obliteration or complication rate calculated across an unselected embolization series describes no patient in particular.

Most comparative work has nevertheless been organized around the embolic agent. Series comparing ethylene vinyl alcohol copolymer (Onyx) with n-butyl cyanoacrylate (NBCA) report obliteration rates that range from under 10% to more than 90%, a spread that far exceeds any plausible difference between two liquid agents and that instead reflects differences in patient selection and in what the operator was trying to achieve. Reported complete obliteration after Onyx embolization has ranged from 16% in early unselected experience to 93% in cohorts explicitly selected for curative treatment, and complication rates have varied in parallel.

A second unresolved question concerns the quantity of embolic agent. Injecting more material fills more of the nidus, and larger injected volumes have been linked to delayed intracerebral haemorrhage after otherwise

uneventful procedures. Whether escalating the injected volume actually improves the chance of obliteration in the lesions where obliteration is hardest to achieve, and at what cost, has not been examined in a series large enough to stratify by both nidus size and Spetzler-Martin (S-M) grade.

We therefore analysed 493 consecutive embolization patients, stratified a priori by the treatment goal recorded before the procedure rather than by the agent used. Our hypotheses were that the treatment goal, not the embolic agent, would determine angiographic and clinical outcome; that high-grade AVMs would serve as a negative control in which no strategy achieves obliteration; and that increasing embolic volume in those lesions would add risk without adding benefit.

METHODS

Study Design and Patients

This was a retrospective analysis of prospective enrolled consecutive patients who underwent endovascular embolization of a brain AVM at our centres between January of 2015 and December of 2018; no patient was excluded on the basis of AVM grade, location, presentation or outcome. The final cohort comprised 493 patients, of whom 387 (78.5%) were treated with Onyx and 106 (21.5%) with NBCA or Glubran. The institutional review board approved the study and waived individual informed consent. Reporting follows the STROBE recommendations for observational research.

Every patient was discussed at a multidisciplinary neurovascular conference attended by cerebrovascular neurosurgeons, interventional neuroradiologists and radiation oncologists. Patients were referred for embolization rather than primary radiosurgery when the malformation was accessible through an arterial pedicle that could be catheterized safely and when at least one of the following applied: an angioarchitectural feature carrying an immediate rupture risk, such as a flow-related or intranidal aneurysm or a high-flow fistulous compartment; a nidus judged small and compact enough that complete obliteration was realistically attainable in one or a small number of sessions; or a nidus too large for radiosurgery at an effective marginal dose, in which case embolization was undertaken to reduce the target volume. Primary radiosurgery without embolization was preferred for compact deep or eloquent niduses smaller than 3 cm without accessible pedicles and for patients who declined an endovascular procedure; those patients are not part of this cohort.

Definition of Treatment Strategy

The goal of each procedure was recorded in the pre-procedural plan before the patient entered the angiography suite and was extracted from that plan rather than being inferred from the result achieved. Five mutually exclusive strategies were distinguished. Curative embolization denoted an intention to obliterate the entire nidus with embolization alone, in a single session or in planned stages. Volume-reduction embolization denoted an intention to reduce nidus volume to bring the lesion within a favourable radiosurgical target volume, with no expectation of cure. Targeted aneurysm embolization denoted occlusion of a flow-related or intranidal aneurysm, or of an identified bleeding compartment, without an attempt on the remainder of the nidus. Targeted embolization combined with volume reduction denoted both aneurysm and AVM objectives in the same session. Fistula-directed embolization denoted occlusion of a high-flow arteriovenous fistulous

component. Five patients had no goal documented and were excluded from strategy-stratified analyses but retained in all other analyses.

Angioarchitecture and the Definition of Eloquence

Nidus maximum diameter was measured on the pre-treatment angiogram. Venous drainage was classified as superficial, deep or mixed, and any deep component was scored as deep venous drainage. The number of arterial feeders and the number of pedicles actually embolized were recorded separately, since the two differ whenever a subset of feeders is treated.

Regions classified as eloquent followed the original Spetzler-Martin definition and comprised the sensorimotor cortex, the language cortex of the dominant hemisphere, the visual cortex, the thalamus and hypothalamus, the internal capsule, the brainstem, the cerebellar peduncles and the deep cerebellar nuclei. The superficial cerebellar hemisphere and vermis, the corpus callosum, and frontal or parietal convexity outside the central region were classified as non-eloquent. Two investigators applied this rule to the pre-treatment imaging independently; disagreements were resolved by consensus with a third senior reviewer. Spetzler-Martin grade was computed from nidus size, eloquence and deep venous drainage using the standard thresholds of less than 3 cm, 3 to 6 cm and more than 6 cm. High-risk AVM was defined as hemorrhagic, inferior tentorial and Spetzler-Martin grade IV and V.

Embolization Technique and Choice of Embolic Agent

All procedures were performed under general anaesthesia with systemic heparinization through a transfemoral approach and biplane angiography. Onyx 18 or Onyx 34 was delivered through a dimethyl sulfoxide-compatible microcatheter using a “plug-and-push” technique with a proximal reflux plug; NBCA or Glubran was diluted with iodized oil to concentrations of 18% to 33% according to the flow characteristics of the target pedicle. The injected volume of Onyx was recorded prospectively in millilitres; equivalent volumetric records were not available for the cyanoacrylate group, so volume analyses are confined to Onyx-treated patients.

The choice of agent was not randomized and was not governed by a written protocol. It reflected operator preference, the era of treatment, and pedicle characteristics, and it is therefore subject to selection bias that no statistical adjustment can fully remove.

Outcomes and Their Adjudication

The angiographic endpoint was obliteration on the immediate post-embolization angiogram, graded as complete when no nidus opacification remained in the venous phase, near-complete when more than 90% of the nidus volume had been obliterated with a small residual shunt, and partial otherwise. The 90% threshold is not arbitrary: it corresponds to the degree of devascularization that earlier Onyx series adopted as the benchmark of a technically high-yield injection, and it is also the point beyond which residual nidus volume falls within the range treatable by radiosurgery at an effective marginal dose. We report complete obliteration

separately throughout so that readers who regard only angiographic cure as meaningful can read the stricter endpoint.

Angiographic outcomes were adjudicated by two neurointerventionalists who had not performed the index procedure, working from the archived angiographic runs and blinded to the clinical course; the degree of obliteration was agreed by consensus and, where the two disagreed by one category, a third senior neurointerventionalist arbitrated. Periprocedural complications were any adverse event occurring during the procedure or the index admission and were classified as haemorrhagic, ischaemic or neurological, or technical, the last comprising retained microcatheter. Follow-up haemorrhage was any new intracranial haemorrhage attributable to the AVM after discharge, confirmed on cross-sectional imaging. Functional status was scored with the mRS before treatment and at last clinical follow-up; poor outcome was defined as mRS above 2 and functional deterioration as any increase in mRS from baseline.

Statistical Analysis

Continuous variables are summarized as median and interquartile range and compared with the Kruskal-Wallis or Mann-Whitney test; categorical variables are summarized as counts and percentages and compared with the chi-square test, or the Fisher exact test where expected cell counts fell below five. Binomial proportions are reported with Wilson score intervals. Annualized haemorrhage rates were calculated as events divided by accrued patient-years, with exact Poisson confidence intervals.

Multivariable logistic regression models were fitted for complete or near-complete obliteration, for periprocedural complication and for poor outcome. Covariates were specified in advance on clinical grounds: nidus 3 cm or smaller, eloquent location, deep venous drainage, single feeding artery, infratentorial location, embolic agent, and curative intent. The obliteration model was also fitted without the strategy term so that the anatomical predictors could be read independently of treatment goal. Results are reported as odds ratios with 95% confidence intervals.

Freedom from haemorrhage after treatment was estimated with the Kaplan-Meier method and compared with the log-rank test. Because a patient who dies can no longer bleed, we repeated the analysis with the Aalen-Johansen estimator, treating death from any cause as a competing risk, and report the cumulative incidence of haemorrhage from that model. Two-sided P values below .05 were considered significant. No correction for multiplicity was applied, and secondary comparisons should be read as hypothesis-generating. Analyses were performed in Python 3.12 with SciPy 1.17.

RESULTS

Cohort Characteristics

The cohort comprised 493 patients with a median age of 28 years (Fig. 1). Baseline characteristics stratified by treatment strategy are given in Table 1. The strategy groups differed markedly in the lesions they contained: patients treated with curative intent had substantially smaller niduses and lower S-M grades than those treated for volume reduction, which is the expected consequence of a goal chosen to match the lesion. 333 patients (67.5%) met the a priori definition of a high-risk AVM and 111 (22.5%) had an S-M grade IV or V

malformation. Adjunctive Gamma Knife radiosurgery was delivered to 213 patients (43.2%). Median follow-up was 28 months, accruing 1560 patient-years.

Table 1
Baseline Characteristics of 493 Patients, Stratified by Treatment Strategy

Characteristic	Overall (n = 493)	Curative (n = 190)	Volume reduction (n = 196)	Targeted (aneurysm) (n = 43)	Targeted + volume (n = 35)	Fistula- directed (n = 24)	P
Age, y, median (IQR)	28.0 (19.0– 38.0)	29.0 (20.0– 39.8)	26.5 (18.0– 36.2)	30.0 (23.5– 39.5)	34.0 (25.0– 45.0)	25.0 (17.0– 38.2)	0.028
Male sex, n (%)	277 (56.2)	118 (62.1)	109 (55.6)	20 (46.5)	17 (48.6)	11 (45.8)	0.472
Hemorrhagic presentation, n (%)	274 (55.6)	111 (58.4)	89 (45.4)	34 (79.1)	29 (82.9)	7 (29.2)	< 0.001
Seizure at presentation, n (%)	92 (18.7)	31 (16.3)	46 (23.5)	4 (9.3)	3 (8.6)	8 (33.3)	0.019
Nidus diameter, cm, median (IQR)	4.0 (3.0– 5.0)	3.0 (2.0– 4.0)	4.0 (4.0– 6.0)	4.0 (3.0– 5.0)	4.0 (3.0– 5.0)	4.0 (4.0– 6.0)	< 0.001
Nidus < 3 cm, n (%)	156 (31.6)	96 (50.5)	28 (14.3)	12 (27.9)	10 (28.6)	5 (20.8)	< 0.001
Nidus 3–6 cm, n (%)	271 (55.0)	80 (42.1)	134 (68.4)	23 (53.5)	19 (54.3)	15 (62.5)	< 0.001
Nidus > 6 cm, n (%)	63 (12.8)	13 (6.8)	33 (16.8)	8 (18.6)	5 (14.3)	4 (16.7)	< 0.001
Eloquent location, n (%)	238 (48.3)	79 (41.6)	101 (51.5)	24 (55.8)	21 (60.0)	12 (50.0)	0.128
Deep venous drainage, n (%)	177 (35.9)	50 (26.3)	75 (38.3)	27 (62.8)	17 (48.6)	6 (25.0)	< 0.001
Infratentorial, n (%)	75 (15.2)	32 (16.8)	24 (12.2)	10 (23.3)	8 (22.9)	1 (4.2)	0.105
Associated aneurysm, n (%)	122 (24.7)	20 (10.5)	9 (4.6)	40 (93.0)	35 (100.0)	17 (70.8)	< 0.001
Spetzler-Martin grade I, n (%)	36 (7.3)	28 (14.7)	2 (1.0)	1 (2.3)	2 (5.7)	1 (4.2)	< 0.001
Spetzler-Martin grade II, n (%)	172 (34.9)	85 (44.7)	63 (32.1)	10 (23.3)	7 (20.0)	7 (29.2)	< 0.001
Spetzler-Martin grade III, n (%)	171 (34.7)	53 (27.9)	73 (37.2)	15 (34.9)	15 (42.9)	12 (50.0)	< 0.001

Data are n (%) unless stated. *High-risk AVM was defined a priori as haemorrhagic presentation, infratentorial location, or Spetzler-Martin grade IV-V. P values compare the five strategy groups (chi-square, Fisher exact, or Kruskal-Wallis as appropriate).

Characteristic	Overall (n = 493)	Curative (n = 190)	Volume reduction (n = 196)	Targeted (aneurysm) (n = 43)	Targeted + volume (n = 35)	Fistula- directed (n = 24)	P
Spetzler-Martin grade IV, n (%)	92 (18.7)	20 (10.5)	48 (24.5)	14 (32.6)	7 (20.0)	3 (12.5)	< 0.001
Spetzler-Martin grade V, n (%)	19 (3.9)	3 (1.6)	9 (4.6)	3 (7.0)	3 (8.6)	1 (4.2)	< 0.001
Spetzler-Martin IV-V, n (%)	111 (22.5)	23 (12.1)	57 (29.1)	17 (39.5)	10 (28.6)	4 (16.7)	< 0.001
High-risk AVM*, n (%)	333 (67.5)	127 (66.8)	122 (62.2)	37 (86.0)	31 (88.6)	12 (50.0)	< 0.001
Number of feeders, median (IQR)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.5)	2.0 (1.0–3.0)	< 0.001
Onyx (EVOH), n (%)	387 (78.5)	161 (84.7)	147 (75.0)	31 (72.1)	30 (85.7)	18 (75.0)	0.087
Adjunctive GKS, n (%)	213 (43.2)	72 (37.9)	96 (49.0)	18 (41.9)	17 (48.6)	8 (33.3)	0.182
Pre-treatment mRS, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	0.018
Follow-up, months, median (IQR)	28.0 (18.0–48.0)	35.0 (21.0–48.0)	26.5 (18.0–60.0)	20.0 (12.0–43.5)	26.0 (17.5–39.0)	24.0 (15.0–35.2)	0.047
<i>Data are n (%) unless stated. *High-risk AVM was defined a priori as haemorrhagic presentation, infratentorial location, or Spetzler-Martin grade IV-V. P values compare the five strategy groups (chi-square, Fisher exact, or Kruskal-Wallis as appropriate).</i>							

Obliteration, Complications and Functional Outcome by Strategy

Across the whole cohort, complete obliteration was achieved in 108 patients (21.9%) and complete or near-complete obliteration in 146 (29.6%). Periprocedural complications occurred in 76 patients (15.4%), comprising ischaemic or neurological events in 12.4% and retained microcatheter in 13 (2.6%). Poor outcome was recorded in 66 patients (13.4%) and death in 7 (1.4%).

Outcomes stratified by strategy are shown in Table 2 and Fig. 2. Complete or near-complete obliteration ranged from 60.0% under a curative goal to 4.2% under a fistula-directed goal ($P < .001$), a 14-fold spread. Complete obliteration showed the same pattern (46.3% versus 3.6%–22.9%, $P < .001$). Periprocedural complications, by contrast, did not differ significantly across the five strategies (8.3% to 22.9%, $P = .36$), and neither did neurological complications (8.3% to 14.3%, $P = .89$). Follow-up haemorrhage ($P = .010$) and poor outcome ($P < .001$) did differ, being lowest after curative embolization and highest after targeted or targeted-plus-volume procedures, which is consistent with the residual nidus that those strategies leave behind.

Functional status improved overall: median mRS fell from 2 before treatment to 1 at last follow-up ($P < .001$), with 89.5% of patients stable or improved.

Table 2
Angiographic and Clinical Outcomes by Treatment Strategy

Outcome	Overall	Curative	Volume reduction	Targeted (aneurysm)	Targeted + volume	Fistula-directed	P
Complete obliteration	108 (21.9)	88 (46.3)	7 (3.6)	2 (4.7)	8 (22.9)	1 (4.2)	< 0.001
Complete or near-complete (> 90%)	146 (29.6)	114 (60.0)	18 (9.2)	2 (4.7)	9 (25.7)	1 (4.2)	< 0.001
Any periprocedural complication	76 (15.4)	34 (17.9)	25 (12.8)	7 (16.3)	8 (22.9)	2 (8.3)	0.361
Hemorrhagic	27 (5.5)	12 (6.3)	10 (5.1)	0 (0.0)	4 (11.4)	1 (4.2)	0.265
Ischemic/neurological	34 (6.9)	14 (7.4)	12 (6.1)	6 (14.0)	1 (2.9)	1 (4.2)	0.319
Retained microcatheter	13 (2.6)	7 (3.7)	2 (1.0)	1 (2.3)	3 (8.6)	0 (0.0)	0.085
Neurological complication (hemorrhagic + ischemic)	61 (12.4)	26 (13.7)	22 (11.2)	6 (14.0)	5 (14.3)	2 (8.3)	0.894
Follow-up hemorrhage	78 (15.8)	18 (9.5)	37 (18.9)	12 (27.9)	8 (22.9)	3 (12.5)	0.010
Poor outcome (mRS > 2)	66 (13.4)	13 (6.8)	35 (17.9)	10 (23.3)	8 (22.9)	0 (0.0)	< 0.001
mRS deterioration	52 (10.5)	14 (7.4)	27 (13.8)	6 (14.0)	3 (8.6)	2 (8.3)	0.293
Death	7 (1.4)	3 (1.6)	2 (1.0)	1 (2.3)	1 (2.9)	0 (0.0)	0.852
Annual hemorrhage rate, %/y (95% CI)	5.00 (3.95–6.24)	2.99 (1.77–4.73)	5.68 (4.00–7.83)	9.81 (5.07–17.13)	8.22 (3.55–16.20)	4.10 (0.85–12.00)	—
Complete obliteration denotes absence of nidus opacification on the immediate post-embolization angiogram; near-complete denotes more than 90% nidus obliteration. Poor outcome denotes modified Rankin Scale score above 2 at last follow-up. Annual haemorrhage rates are per patient-year with exact Poisson 95% confidence intervals.							

The annual haemorrhage rate for the whole cohort was 5.00% per year (95% CI 3.95–6.24), and it tracked the residual nidus rather than the agent: 2.99% per year after curative embolization compared with 5.68% after volume reduction and 9.81% after targeted aneurysm embolization.

Outcome Across Spetzler-Martin Grades

Outcomes by S-M grade are given in Table 3 and Fig. 3. Complete or near-complete obliteration fell monotonically from grade I to grade V, while complication and poor-outcome rates rose. Freedom from haemorrhage during follow-up favoured patients in whom complete or near-complete obliteration had been achieved (annual haemorrhage 3.62% versus 5.60% per year), although the difference did not reach significance over the available follow-up (log-rank $P = 0.09$; Fig. 6). Because seven patients died during follow-up, we repeated the analysis with death as a competing risk; the Aalen-Johansen cumulative incidence curves were superimposable on the Kaplan-Meier estimates, indicating that competing mortality did not materially bias the haemorrhage estimates in this cohort.

Table 3
Outcomes Across Spetzler-Martin Grades

Spetzler-Martin grade	n	Complete, n (%)	CNC, n (%)	Complication, n (%)	Follow-up hemorrhage, n (%)	Poor outcome, n (%)	Annual hemorrhage, %/y
I	36	30 (83.3)	34 (94.4)	3 (8.3)	2 (5.6)	2 (5.6)	2.00
II	172	47 (27.3)	60 (34.9)	21 (12.2)	17 (9.9)	15 (8.7)	3.06
III	171	24 (14.0)	37 (21.6)	30 (17.5)	30 (17.5)	20 (11.7)	5.39
IV	92	6 (6.5)	14 (15.2)	18 (19.6)	25 (27.2)	26 (28.3)	9.58
V	19	0 (0.0)	0 (0.0)	4 (21.1)	4 (21.1)	3 (15.8)	4.81
<i>CNC, complete or near-complete obliteration. Grades were computed from nidus size, eloquence coded as an independent covariate, and deep venous drainage.</i>							

Predictors of Obliteration, Complications and Poor Outcome

Independent predictors of complete or near-complete obliteration are shown in Table 4 and Fig. 4. A nidus of 3 cm or smaller (OR 11.71, 95% CI 6.43–21.33, $P < .001$), a single feeding artery (OR 1.95, 95% CI 1.12–3.39, $P = .018$) and curative intent (OR 10.37, 95% CI 5.85–18.37, $P < .001$) were independently associated with obliteration. The embolic agent was not (OR 0.88 for Onyx versus NBCA, $P = .73$). When the strategy term was removed so that anatomy alone was modelled, nidus 3 cm or smaller (OR 14.78, $P < .001$), absence of deep venous drainage (OR 0.49 for its presence, $P = .010$) and a single feeding artery (OR 1.92, $P = .010$) remained independent predictors, whereas eloquent location did not reach significance ($P = .34$), most likely because eloquence is correlated with both deep drainage and nidus size in this cohort.

Table 4
Multivariable Predictors of Complete or Near-Complete Obliteration

Variable	OR (95% CI)	P value
Nidus $\leq$ 3 cm	11.71 (6.43–21.33)	< .001
Eloquent location	0.95 (0.54–1.69)	0.872
Deep venous drainage	0.66 (0.35–1.24)	0.197
Single feeding artery	1.95 (1.12–3.39)	0.018
Infratentorial	0.54 (0.24–1.21)	0.135
Onyx (vs NBCA)	0.88 (0.44–1.76)	0.725
Curative intent (vs other)	10.37 (5.85–18.37)	< .001
<i>Odds ratios from a multivariable logistic regression model including all listed covariates. An anatomy-only model that omitted curative intent is reported in the text.</i>		

For periprocedural complications (Table 5), a single feeding artery was protective (OR 0.53, 95% CI 0.29–0.94, $P = .031$) and curative intent carried increased risk (OR 1.80, 95% CI 1.04–3.12, $P = .035$); the embolic agent was again not predictive ($P = .25$). The number of pedicles actually embolized was associated with complications when substituted for the single-feeder term (OR 1.61 per additional pedicle, 95% CI 1.10–2.34, $P = .014$), consistent with cumulative exposure to catheterization risk. For poor outcome, haemorrhagic presentation was the dominant determinant (OR 3.10, 95% CI 1.65–5.82, $P < .001$) and a small nidus was protective (OR 0.36, $P = .010$).

Table 5
Multivariable Predictors of Periprocedural Complication

Variable	OR (95% CI)	P value
Nidus $\leq$ 3 cm	0.62 (0.32–1.18)	0.144
Eloquent location	1.28 (0.75–2.20)	0.364
Deep venous drainage	1.56 (0.90–2.68)	0.111
Single feeding artery	0.53 (0.29–0.94)	0.031
Infratentorial	1.39 (0.72–2.70)	0.327
Onyx (vs NBCA)	1.49 (0.75–2.96)	0.250
Curative intent (vs other)	1.80 (1.04–3.12)	0.035
<i>Odds ratios from a multivariable logistic regression model including all listed covariates.</i>		

Volume of Embolic Agent

Onyx volume, available for 387 patients, ranged from 0.2 to more than 10 mL. Across the whole Onyx group, larger injected volumes were associated with a higher chance of obliteration after adjustment for nidus diameter (adjusted OR 1.54 per additional millilitre, 95% CI 1.25–1.88, $P < .001$; Table 6). This association is

partly definitional, because injecting more material and filling more of the nidus are close to the same event, and it should not be read as evidence that volume can be escalated at will.

Table 6
Multivariable Predictors of Poor Functional Outcome (mRS > 2)

Variable	OR (95% CI)	P value
Nidus ≤ 3 cm	0.36 (0.17–0.78)	0.010
Eloquent location	1.55 (0.87–2.76)	0.135
Deep venous drainage	1.29 (0.73–2.29)	0.383
Infratentorial	1.21 (0.59–2.46)	0.605
Onyx (vs NBCA)	0.62 (0.34–1.14)	0.121
Curative intent (vs other)	0.46 (0.22–1.00)	0.050
Hemorrhagic presentation	3.10 (1.65–5.82)	< .001
Complete/near-complete obliteration	1.11 (0.47–2.64)	0.805
<i>Odds ratios from a multivariable logistic regression model including all listed covariates.</i>		

Stratification by lesion size dissolves the apparent benefit precisely where it would matter (Table 6, Fig. 5). In AVMs of 3 to 6 cm the obliteration rate rose from 14.0% at volumes of 1 mL or less to 29.1% above 3 mL ($P = .001$). In AVMs larger than 6 cm, no patient in any volume tier achieved complete or near-complete obliteration (0 of 55), while complications ran between 17.9% and 25.0%. In S-M grade IV-V lesions the pattern was the same: obliteration was 15.2%, 15.4% and 9.1% across ascending volume tiers ($P = .97$), with complications of 24.2%, 30.8% and 13.6%.

Across the full Onyx cohort, complication risk rose with injected volume but the association did not reach significance after adjustment (OR 1.09 per additional millilitre, 95% CI 0.96–1.22, $P = .19$), with unadjusted rates of 14.8%, 17.0% and 20.5% across ascending tiers. We therefore describe the volume-complication relationship as a signal that warrants caution rather than as a demonstrated hazard.

High-Grade AVMs as a Negative Control

The 111 patients with S-M grade IV-V AVMs behaved as a natural negative control (Table 7, Fig. 7). Complete obliteration was achieved in only 5.4%, while complications occurred in 19.8%, poor outcome in 26.1% and haemorrhage at 8.43% per year (95% CI 5.65–12.11), a rate that exceeds most published natural-history estimates for untreated lesions. Neither complete obliteration ($P = .43$) nor follow-up haemorrhage ($P = .68$) nor poor outcome ($P = .13$) differed significantly among the five strategies in this subgroup, confirming that when the lesion cannot be obliterated, the choice of goal cannot rescue the angiographic result.

Table 7

Onyx Volume, Obliteration and Complications, Overall and by Nidus Size and Spetzler-Martin Grade

Subgroup	Onyx volume (mL)	n	CNC, n (%)	Complication, n (%)	Follow-up hemorrhage, n (%)	Poor outcome, n (%)
All Onyx patients	≤ 1.0	190	61 (32.1)	28 (14.7)	24 (12.6)	23 (12.1)
All Onyx patients	1.1-3.0	112	36 (32.1)	19 (17.0)	16 (14.3)	15 (13.4)
All Onyx patients	> 3.0	85	17 (20.0)	17 (20.0)	15 (17.6)	7 (8.2)
All Onyx patients	P (volume vs outcome)	387	0.122	0.322		
Nidus < 3 cm	≤ 1.0	64	45 (70.3)	9 (14.1)	2 (3.1)	3 (4.7)
Nidus < 3 cm	1.1-3.0	13	11 (84.6)	2 (15.4)	1 (7.7)	1 (7.7)
Nidus < 3 cm	> 3.0	1	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)
Nidus < 3 cm	P (volume vs outcome)	78	0.192	0.813		
Nidus 3–6 cm	≤ 1.0	114	16 (14.0)	17 (14.9)	21 (18.4)	17 (14.9)
Nidus 3–6 cm	1.1-3.0	82	24 (29.3)	13 (15.9)	10 (12.2)	9 (11.0)
Nidus 3–6 cm	> 3.0	55	16 (29.1)	11 (20.0)	11 (20.0)	5 (9.1)
Nidus 3–6 cm	P (volume vs outcome)	251	0.001	0.394		
Nidus > 6 cm	≤ 1.0	11	0 (0.0)	2 (18.2)	1 (9.1)	3 (27.3)
Nidus > 6 cm	1.1-3.0	16	0 (0.0)	4 (25.0)	5 (31.2)	5 (31.2)
Nidus > 6 cm	> 3.0	28	0 (0.0)	5 (17.9)	3 (10.7)	2 (7.1)
Nidus > 6 cm	P (volume vs outcome)	55	no events	0.983		
S-M I-III	≤ 1.0	157	56 (35.7)	20 (12.7)	17 (10.8)	13 (8.3)
<i>Restricted to the 387 patients treated with Onyx, for whom injected volume was recorded. P values compare injected volume between patients with and without the outcome (Mann-Whitney).</i>						

Subgroup	Onyx volume (mL)	n	CNC, n (%)	Complication, n (%)	Follow-up hemorrhage, n (%)	Poor outcome, n (%)
S-M I-III	1.1-3.0	86	32 (37.2)	11 (12.8)	10 (11.6)	7 (8.1)
S-M I-III	> 3.0	63	15 (23.8)	14 (22.2)	10 (15.9)	5 (7.9)
S-M I-III	P (volume vs outcome)	306	0.205	0.099		
S-M IV-V	≤ 1.0	33	5 (15.2)	8 (24.2)	7 (21.2)	10 (30.3)
S-M IV-V	1.1-3.0	26	4 (15.4)	8 (30.8)	6 (23.1)	8 (30.8)
S-M IV-V	> 3.0	22	2 (9.1)	3 (13.6)	5 (22.7)	2 (9.1)
S-M IV-V	P (volume vs outcome)	81	0.967	0.277		
<i>Restricted to the 387 patients treated with Onyx, for whom injected volume was recorded. P values compare injected volume between patients with and without the outcome (Mann-Whitney).</i>						

The safety consequences of that choice were nonetheless substantial. Patients in whom a curative goal was pursued despite a grade IV-V lesion had a complication rate of 39.1% compared with 10.5% among those treated for volume reduction ($P = 0.009$), for a complete obliteration rate of 13.0% versus 3.5% ($P = .14$). The same curative strategy applied to grade I-III lesions produced complete obliteration in 50.9% with complications in 15.0%. The strategy is therefore not intrinsically hazardous; it becomes hazardous when it is applied to a lesion that cannot deliver the benefit that justifies its risk. Poor outcome was, paradoxically, lower in the high-grade curative group (8.7%) than in the volume-reduction group (29.8%, $P = .079$), which we interpret as selection of better-baseline patients for a curative attempt rather than as evidence of benefit.

Embolic Agent and Adjunctive Radiosurgery

Onyx and NBCA were compared directly in Table 8. Complete or near-complete obliteration was 29.5% with Onyx and 30.2% with NBCA ($P = .98$); complete obliteration was 22.7% versus 18.9% ($P = .47$); any complication 16.5% versus 11.3% ($P = .24$); and retained microcatheter 3.1% versus 0.9% ($P = .32$). Poor outcome was more frequent in the NBCA group (19.8% versus 11.6%, $P = .042$), but this group also contained a higher proportion of deep and high-grade lesions, and the difference did not persist after adjustment (Table 5). Adjunctive Gamma Knife radiosurgery was delivered to 213 patients, more often after partial embolization, and outcomes in the combined-modality group did not differ significantly from embolization alone within the available follow-up (Table 9).

Table 8
Outcomes by Treatment Strategy Within Spetzler-Martin Grade IV-V AVMs (n = 111)

Strategy	n	Complete, n (%)	CNC, n (%)	Complication, n (%)	Follow-up hemorrhage, n (%)	Poor outcome, n (%)
Curative	23	3 (13.0)	6 (26.1)	9 (39.1)	6 (26.1)	2 (8.7)
Volume reduction	57	2 (3.5)	7 (12.3)	6 (10.5)	14 (24.6)	17 (29.8)
Targeted (aneurysm)	17	1 (5.9)	1 (5.9)	4 (23.5)	6 (35.3)	6 (35.3)
Targeted + volume	10	0 (0.0)	0 (0.0)	3 (30.0)	3 (30.0)	4 (40.0)
Fistula-directed	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
P value	111	0.429	0.164	0.036	0.680	0.127
<i>P values compare the five strategies. The direct comparison of curative intent with volume reduction gave a complication rate of 39.1% versus 10.5% (Fisher exact $P = .009$).</i>						

Table 9
Direct Comparison of Onyx and n-Butyl Cyanoacrylate

Outcome	Onyx (n = 387)	NBCA (n = 106)	P
Complete obliteration	88 (22.7)	20 (18.9)	0.471
CNC obliteration	114 (29.5)	32 (30.2)	0.979
Any complication	64 (16.5)	12 (11.3)	0.244
Retained microcatheter	12 (3.1)	1 (0.9)	0.316
Neurological complication	51 (13.2)	10 (9.4)	0.384
Follow-up hemorrhage	55 (14.2)	23 (21.7)	0.085
Poor outcome	45 (11.6)	21 (19.8)	0.042
<i>Complications in the cyanoacrylate group were recorded as free text; an absent entry was treated as no complication.</i>			

DISCUSSION

In 493 consecutive patients, the pre-procedural treatment goal explained a 14-fold difference in obliteration while the embolic agent explained essentially none. Complete or near-complete obliteration was 29.5% with Onyx and 30.2% with NBCA, a difference of less than one percentage point, whereas the same endpoint moved from 4.2% to 60.0% according to what the operator set out to do. Once the goal and the anatomy were accounted for, the agent added no independent information about obliteration, complications or functional

outcome. The clinically actionable variable is therefore the decision taken before the catheter is advanced, not the material advanced through it.

This reading reconciles a literature that has looked inconsistent. Early unselected Onyx experience reported 16% total obliteration with complications in 13.6% of patients, whereas cohorts explicitly selected for curative embolization have reported complete obliteration in every treated patient without haemorrhagic or ischaemic complications. Both are accurate accounts of different undertakings. Our curative subgroup, at 46.3% complete and 60.0% complete or near-complete obliteration, sits between them, as would be expected of a consecutive series in which curative intent was applied across a broader anatomical range than a hand-picked cohort. Systematic reviews of primary embolization with intention to cure and of embolization before radiosurgery reach the same conclusion from the opposite direction, namely that pooled estimates are dominated by case selection rather than by technique.

The volume analysis deserves careful statement because it is easy to overread in either direction. Larger Onyx volumes were associated with obliteration overall and within intermediate-sized niduses, and we do not argue against adequate injection where cure is achievable. What the stratified data show is that this benefit does not extend to the lesions where the temptation to inject more is greatest: in AVMs larger than 6 cm, not one of 55 patients achieved complete or near-complete obliteration at any volume tier, and in grade IV-V lesions the obliteration rate was flat across tiers. Meanwhile complication rates rose modestly and non-significantly with volume. Ovalle and colleagues found that the volume of embolic agent injected per procedure was an independent predictor of delayed intracerebral haemorrhage after otherwise uneventful embolization, with a mean of 4.5 mL in patients who bled versus 1.7 mL in those who did not, even after controlling for AVM size; Strauss and colleagues reached a similar conclusion in their critical appraisal of 92 consecutive Onyx cases. Our data are compatible with those reports without independently establishing the hazard: there is no obliteration benefit from higher dose in large or high-grade lesions, and there is a possible complication signal.

The high-grade subgroup is the sharpest statement in the dataset. Complete obliteration of 5.4%, complications of 19.8%, poor outcome of 26.1% and an annual haemorrhage rate of 8.43% describe a group in which embolization did not alter the natural trajectory and may have added to it. That no strategy outperformed the others on angiographic outcome is not a negative finding but the point: when the lesion cannot be obliterated, the goal cannot be met by any route. What differed was the price paid for trying. A curative attempt in a grade IV-V AVM tripled the complication rate relative to volume reduction while leaving 87% of patients with residual nidus. The contrast with the same strategy in grade I-III lesions, where it yielded complete obliteration in 50.9% for a 15.0% complication rate, isolates the error as one of indication rather than of technique. Contemporary series of grade IV-V malformations report that intervention can be justified in properly selected patients, and current practice guidelines for intermediate and high-grade lesions emphasize the same qualification.

These findings bear directly on how embolization is combined with radiosurgery. Meta-analyses of pre-radiosurgical embolization have found lower obliteration after SRS in embolized patients, an effect usually attributed to nidus recanalization, target delineation through the embolic cast, and case-mix. Our data suggest a complementary explanation: series that pool curative and volume-reduction embolization are pooling

procedures with different objectives and different residual anatomy, so the embolized arm is systematically enriched for lesions that were never obliterable. Reporting embolization outcome without reporting embolization intent will continue to generate contradictory pooled estimates.

Finally, the pattern of follow-up haemorrhage supports the second half of our thesis. Annual haemorrhage was 2.99% after curative embolization, 5.68% after volume reduction and 9.81% after targeted aneurysm embolization, tracking the residual nidus rather than the agent. Patients in whom complete or near-complete obliteration was achieved bled at 3.62% per year compared with 5.60% among those left partially treated. The difference did not reach significance over a median 28 months, and we present it as directionally consistent rather than as proof, but it aligns with registry evidence that partially treated malformations retain, and may transiently increase, their haemorrhagic risk.

Limitations

This is a retrospective two-centre analysis and inherits the biases of that design. Assignment to a treatment strategy was clinical, not random, and strategy is strongly confounded with lesion anatomy; the comparison between strategies within the grade IV-V subgroup partly addresses this by holding grade constant, but residual confounding by indication certainly remains. The choice of embolic agent was likewise non-random and era-dependent, so the null comparison between Onyx and NBCA should be read as an absence of a large agent effect within this case-mix rather than as formal equivalence.

CONCLUSION

Curative intent produced a 14-fold higher obliteration rate than other goals without a significant excess of complications when it was applied to lesions in which cure was attainable, but tripled the complication rate for negligible angiographic gain when applied to Spetzler-Martin grade IV-V malformations. Increasing the volume of embolic agent conferred no obliteration benefit in AVMs larger than 6 cm or of grade IV-V and carried a possible complication signal. The decision that matters in AVM embolization is the choice of objective, matched to a lesion that can deliver it.

ABBREVIATIONS

AVM, arteriovenous malformation; CI, confidence interval; EVOH, ethylene vinyl alcohol copolymer; GKS, Gamma Knife stereotactic radiosurgery; mRS, modified Rankin Scale; NBCA, n-butyl cyanoacrylate; OR, odds ratio; S-M, Spetzler-Martin; SRS, stereotactic radiosurgery

Declarations

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Ethics: The institutional review board approved this retrospective study and waived the requirement for individual informed consent.

Data availability: The de-identified analytic dataset is available from the corresponding author on reasonable request.

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Figures

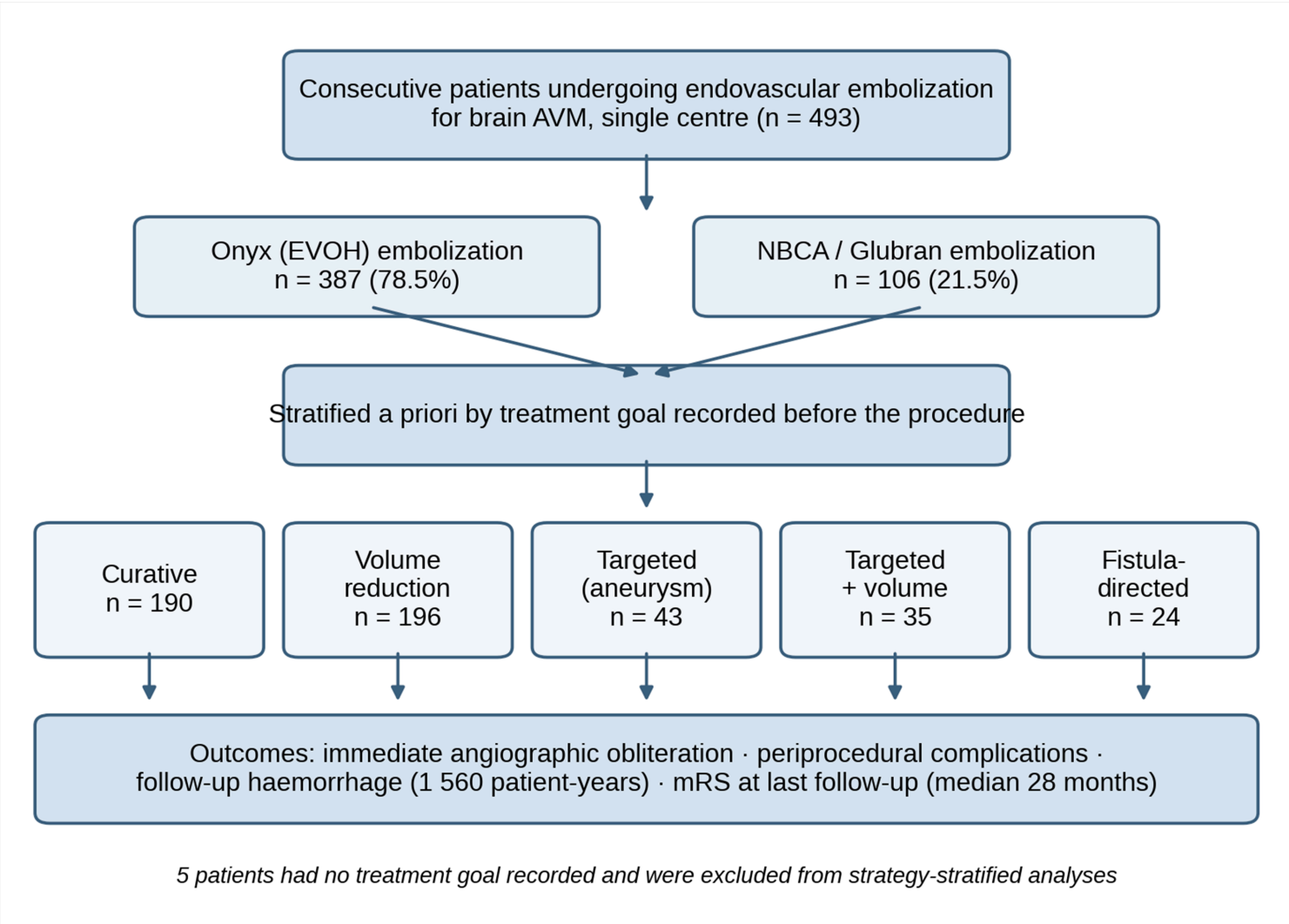


Figure 1

Cohort composition. Consecutive patients undergoing brain AVM embolization, showing the distribution of embolic agents and the a priori assignment to one of five treatment strategies. Five patients had no documented treatment goal and were excluded from strategy-stratified analyses only.

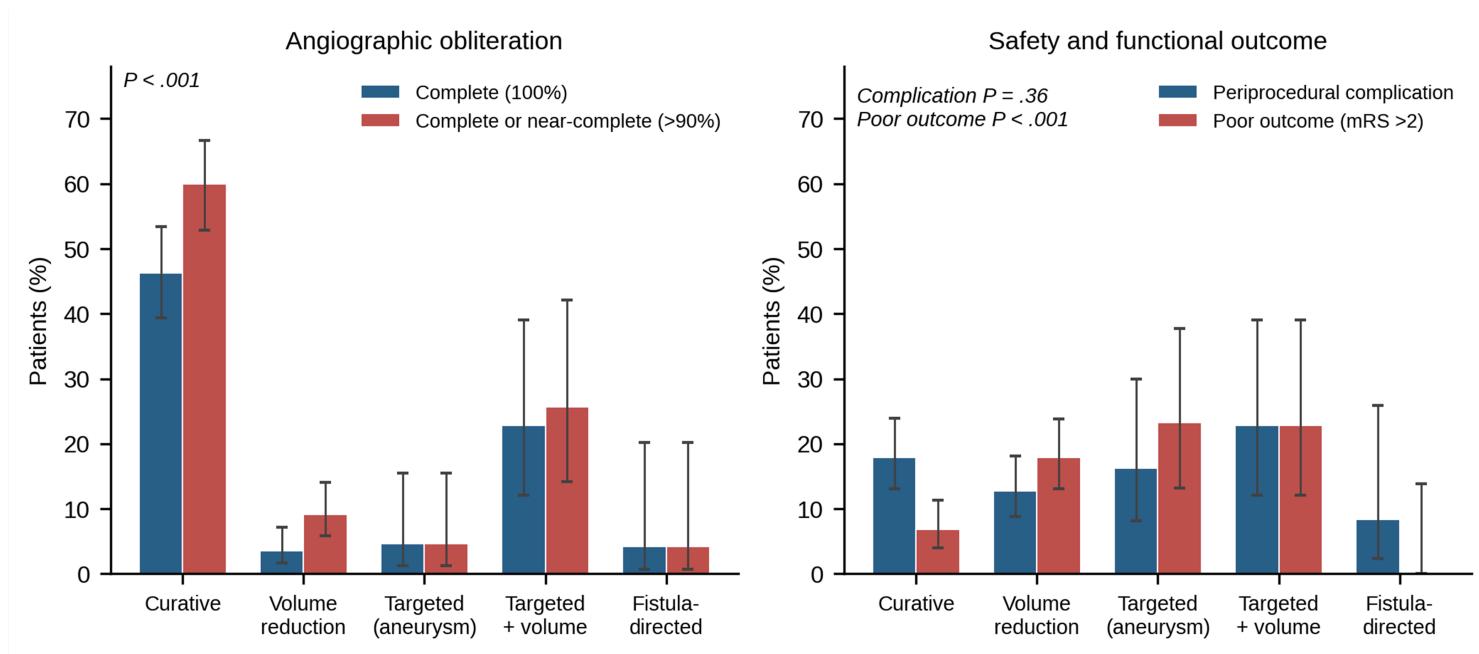


Figure 2

Angiographic obliteration (left) and safety and functional outcome (right) by treatment strategy. Bars show percentages with Wilson score 95% confidence intervals. Obliteration differed 14-fold across strategies ($P < .001$) whereas periprocedural complications did not ($P = .36$).

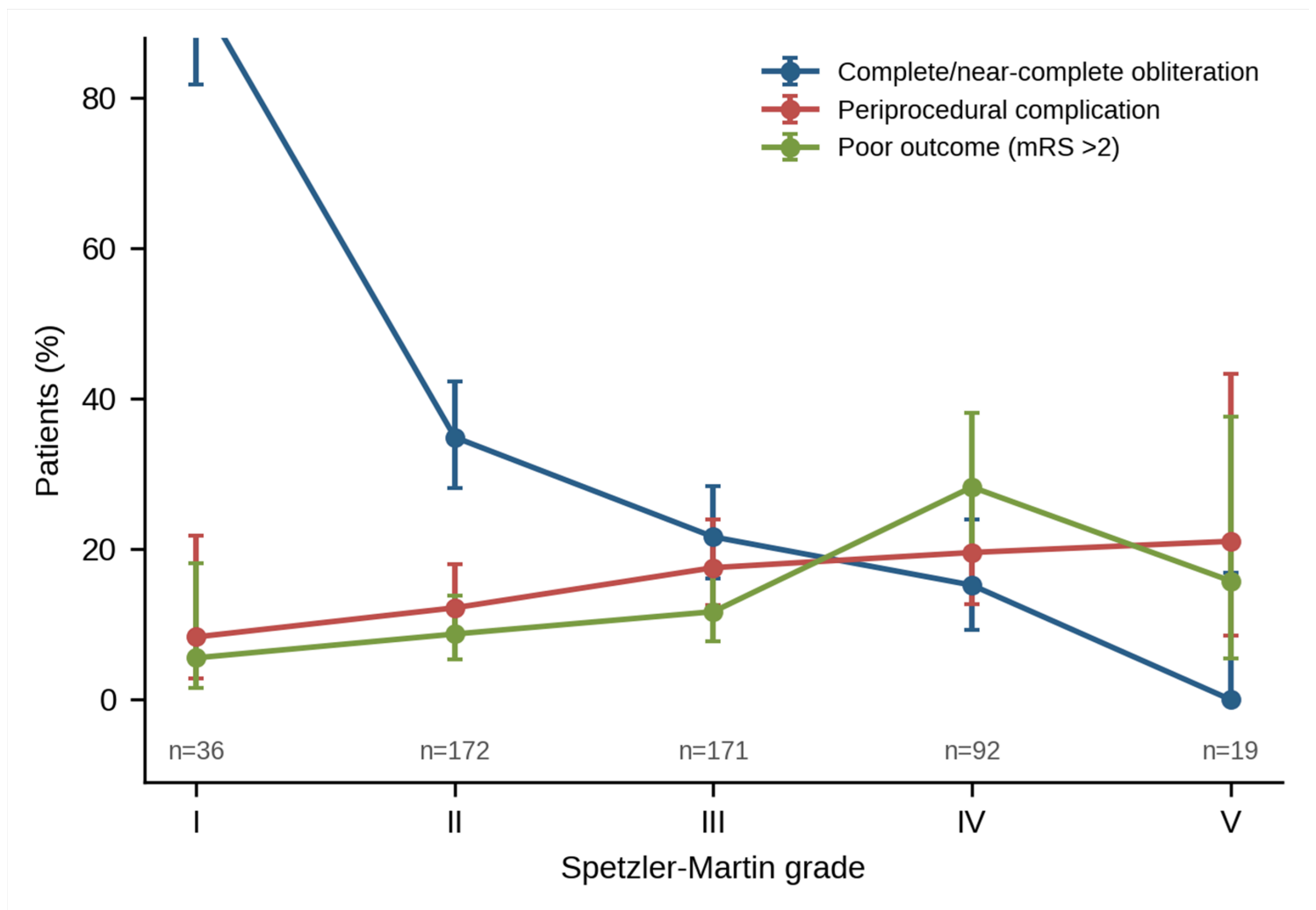


Figure 3

Complete or near-complete obliteration, periprocedural complication and poor functional outcome across Spetzler-Martin grades I to V, with Wilson score 95% confidence intervals. Group sizes are shown beneath each grade.

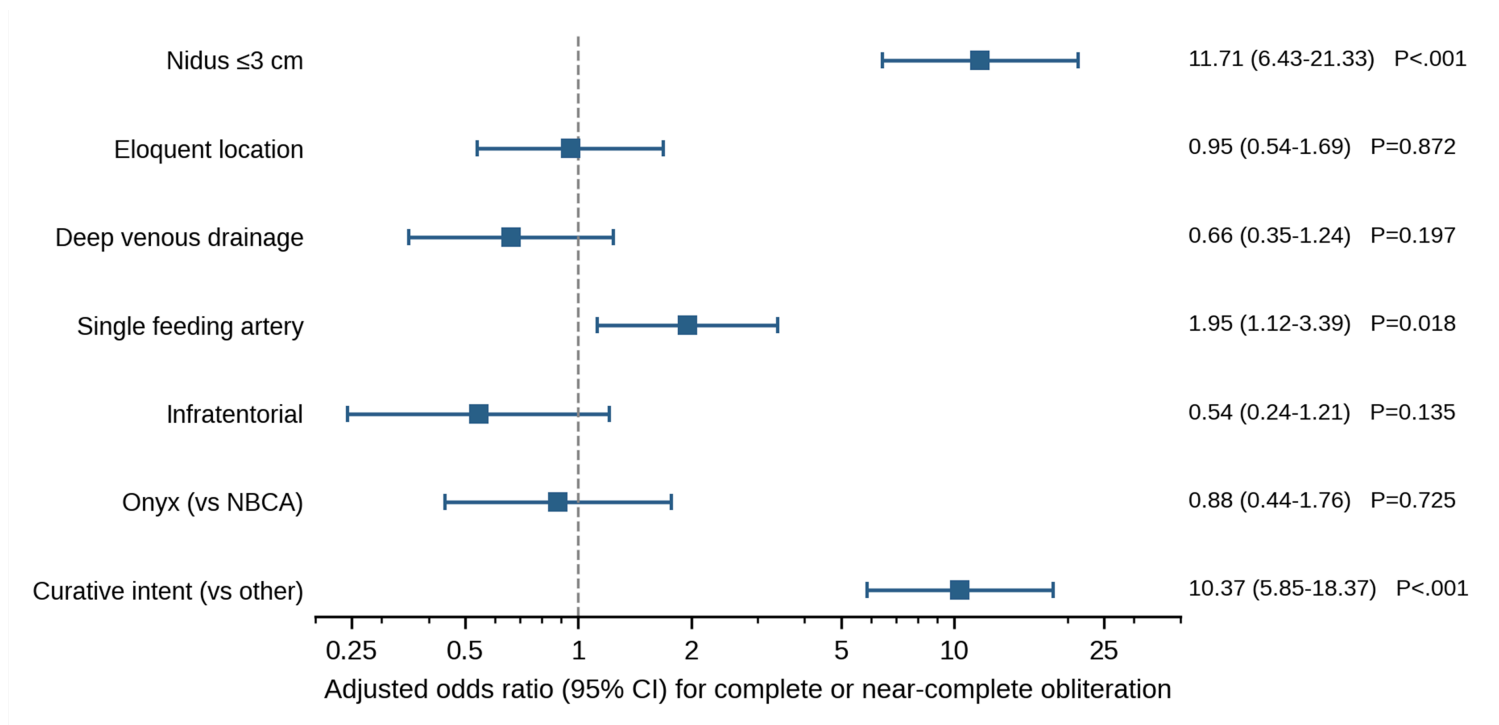


Figure 4

Forest plot of adjusted odds ratios for complete or near-complete obliteration from the multivariable logistic model. Nidus 3 cm or smaller, single feeding artery and curative intent were independently associated with obliteration; the embolic agent was not.

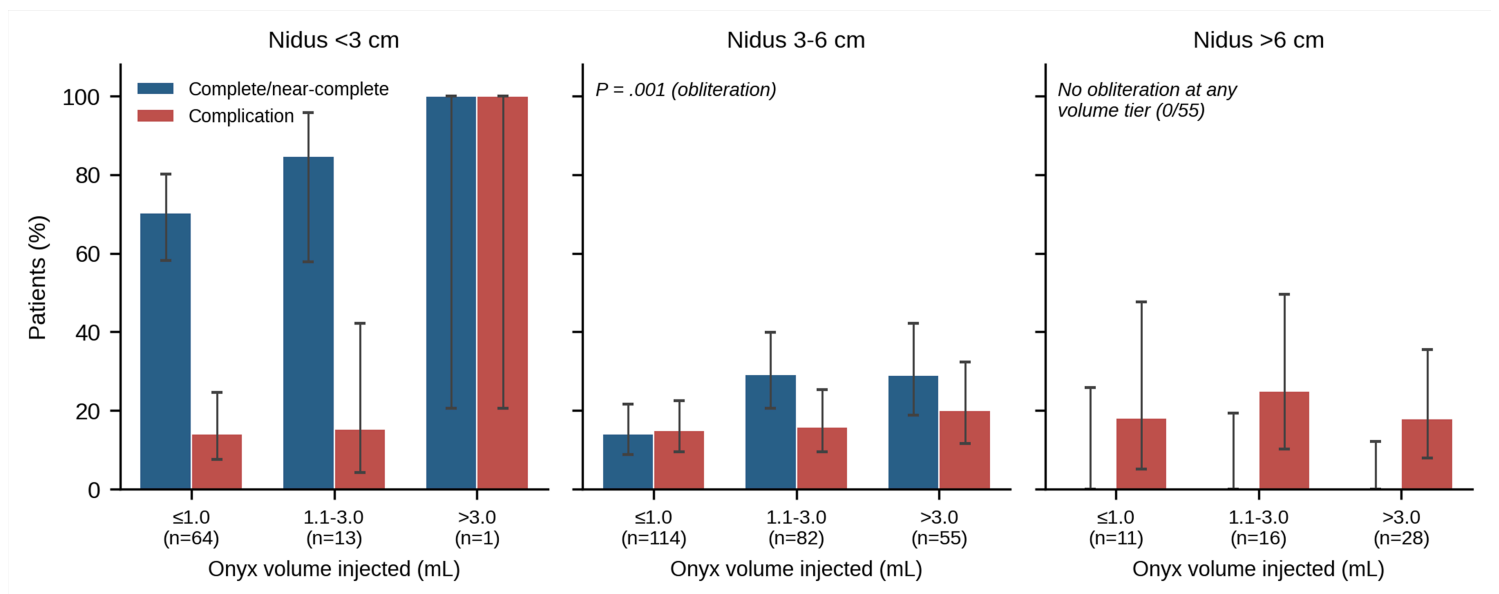


Figure 5

Onyx volume against obliteration and complications, stratified by nidus diameter. Higher volume was associated with obliteration in 3 to 6 cm niduses ($P = .001$) but conferred no benefit in niduses larger than 6 cm, where no patient in any volume tier achieved obliteration.

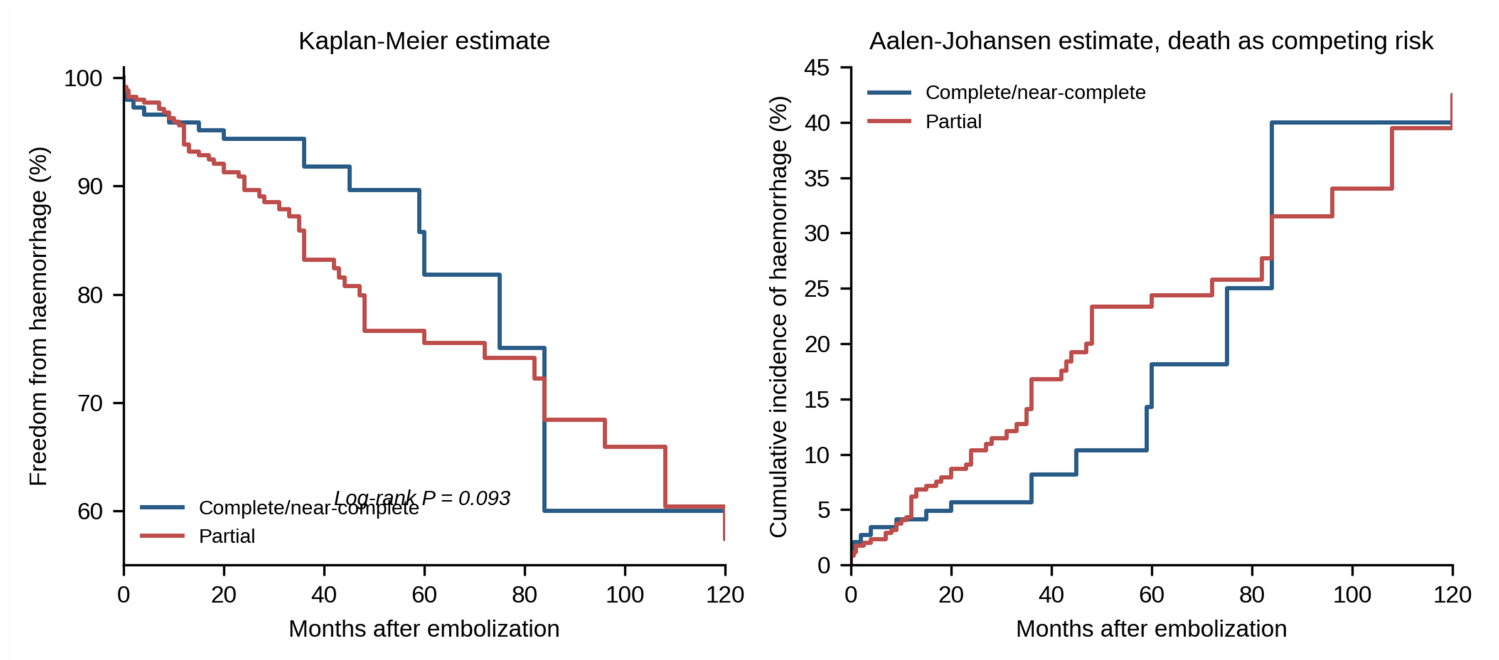


Figure 6

Freedom from haemorrhage after embolization by obliteration status. Left, Kaplan-Meier estimate; right, Aalen-Johansen cumulative incidence treating death as a competing risk. The two estimators were superimposable, indicating negligible competing-risk bias.

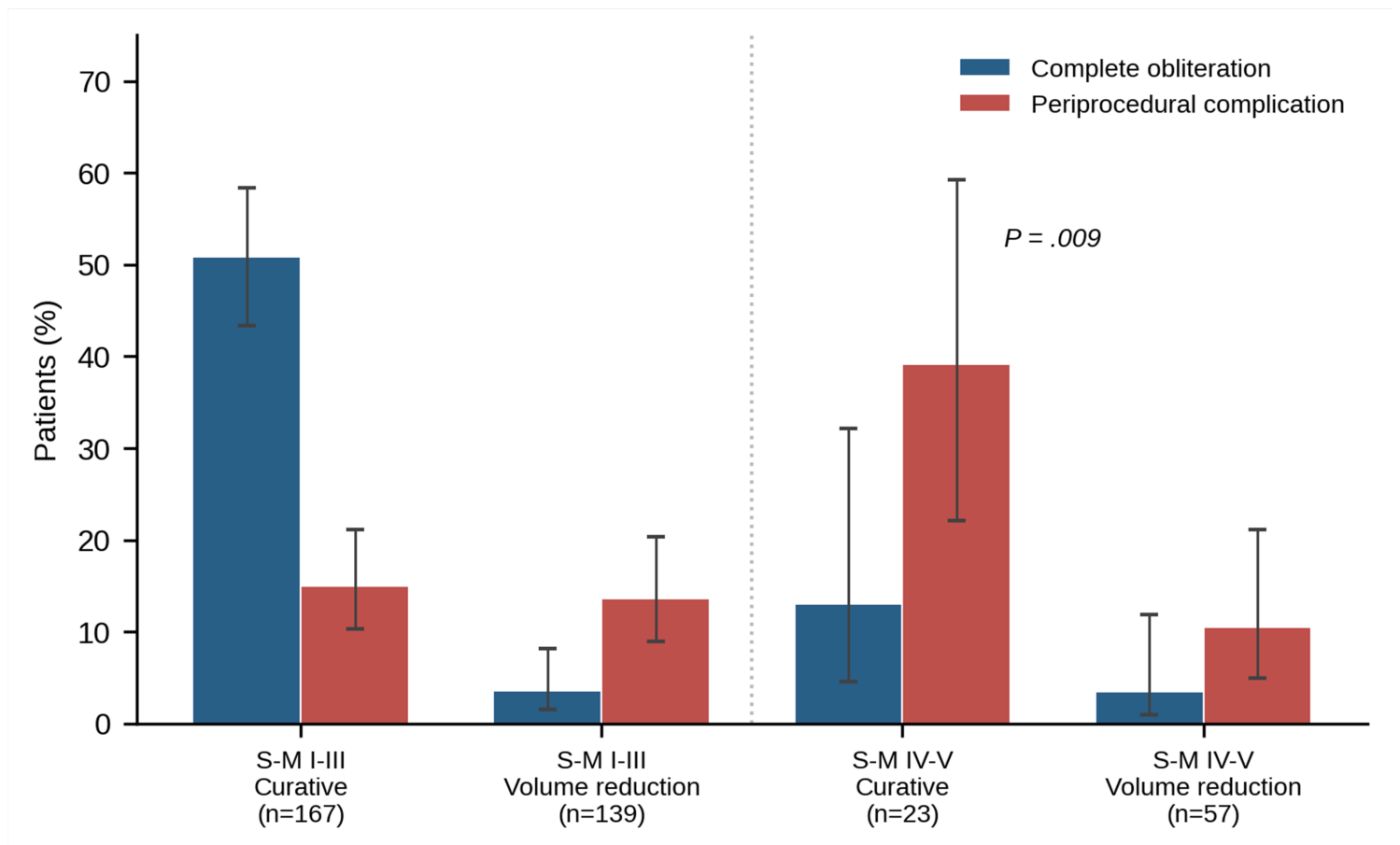


Figure 7

Complete obliteration and periprocedural complications for curative versus volume-reduction strategies, separately in Spetzler-Martin grade I-III and grade IV-V AVMs. The same strategy that yielded 50.9% complete obliteration for a 15.0% complication rate in low-grade lesions yielded 13.0% obliteration for a 39.1% complication rate in high-grade lesions.