Stereotactic Radiosurgery for Dural Arteriovenous Fistulas: A Systematic Review and Meta-Analysis and International Stereotactic Radiosurgery Society Practice Guidelines

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BACKGROUND: Dural arteriovenous fistulas (dAVFs) are often treated with stereotactic radiosurgery (SRS) to achieve complete obliteration (CO), prevent future hemorrhages, and ameliorate neurological symptoms.

OBJECTIVE: To summarize outcomes after SRS for dAVFs and propose relevant practice recommendations.

METHODS: Using a PICOS/PRISMA/MOOSE protocol, we included patients with dAVFs treated with SRS and data for at least one of the outcomes of the study. Relevant outcomes were CO, symptom improvement and cure, and post-SRS hemorrhage or permanent neurological deficits (PNDs). Estimated outcome effect sizes were determined using weighted random-effects meta-analyses using DerSimonian and Laird methods. To assess potential relationships between patient and lesion characteristics and clinical outcomes, mixed-effects weighted regression models were used.

RESULTS: Across 21 published studies, we identified 705 patients with 721 dAVFs treated with SRS. The CO rate was 68.6% (95% CI 60.7%-76.5%) with symptom improvement and cure rates of 97.2% (95% CI 93.2%-100%) and 78.8% (95% CI 69.3%-88.2%), respectively. Estimated incidences of post-SRS hemorrhage and PNDs were 1.1% (95% CI 0.6%-1.6%) and 1.3% (95% CI 0.8%-1.8%), respectively. Noncavernous sinus (NCS) dAVFs were associated with lower CO ($P = .03$) and symptom cure rates ($P = .001$). Higher grade was also associated with lower symptom cure rates ($P = .04$), whereas previous embolization was associated with higher symptom cure rates ($P = .01$).

CONCLUSION: SRS for dAVFs results in CO in the majority of patients with excellent symptom improvement rates with minimal toxicity. Patients with NCS and/or higher-grade dAVFs have poorer symptom cure rates. Combined therapy with embolization and SRS is recommended when feasible for clinically aggressive dAVFs or those refractory to embolization to maximize the likelihood of symptom cure.

KEY WORDS: Stereotactic radiosurgery, SRS, Obliteration, Hemorrhage, Toxicity, Meta-analysis

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ABBREVIATIONS: AVM, arteriovenous malformation; **CO,** complete obliteration; **CS,** cavernous sinus; **CT/A,** computerized tomography/angiography; **CVD,** cortical venous drainage; **dAVF,** dural arteriovenous fistula; **ISRS,** International Stereotactic Radiosurgery Society; **MPD,** median prescription dose; **MRA,** magnetic resonance angiography; **NCS,** noncavernous sinus; **PND,** permanent neurological deficit; **SRS,** stereotactic radiosurgery.

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Dural arteriovenous fistulas (dAVFs) are rare arteriovenous shunts comprising abnormal connections between meningeal arteries and venous sinuses or meningeal/cortical veins, and represent approximately 10% to 15% of all intracranial vascular malformations.[1–3] The natural history and clinical course of dAVFs depend on their venous drainage pattern.[4,5] Cavernous sinus (CS) dAVFs are more benign, although may present with multiple refractory ophthalmological complaints and potentially progressive vision loss because of increased intraocular pressure and/or

reduced ocular perfusion.[6] Noncavernous sinus (NCS) dAVFs with direct cortical venous drainage (CVD; high-grade dAVFs) are more aggressive with both nonhemorrhagic neurological deficits and intracranial hemorrhage, and mortality rates of up to 35% and 45%, respectively, if left untreated.[7,8] Thus, prevention of hemorrhage/rehemorrhage and amelioration of venous congestion-related neurological symptoms are the primary goals of treatment.

Treatment options include endovascular embolization, microsurgical ligation, and stereotactic radiosurgery (SRS). Endovascular embolization is the most common treatment, which has a complete obliteration (CO) rate between 70% and 90%.[9,10] Microsurgical ligation is an alternative either standalone or in combination with embolization.[11] For patients with complex dAVFs who are unlikely to achieve CO with embolization alone and are not optimal surgical candidates, SRS is an effective minimally invasive treatment modality with low complication rates.[12,13] However, reported SRS experiences are limited to retrospective studies with variable follow-up and reported outcomes. As such, this meta-analysis aims to summarize clinical outcomes after SRS for dAVFs based on a critical review of the data in the published literature and provide practice guidelines on behalf of the International Stereotactic Radiosurgery Society (ISRS).

METHODS

Study Selection

A systematic literature search was performed using PubMed, EMBASE, and the Cochrane Library, for studies published through May 1, 2021, using various combinations (AND/OR) of the following keywords: radiosurgery, stereotactic, dural arteriovenous fistula, dAVF, SRS, obliteration, symptom cure, symptom improvement, hemorrhage, neurologic deficit, cortical venous drainage, CVD, low-flow, high-flow, Gamma Knife, LINAC, and CyberKnife. The Population, Intervention, Control, Outcomes, Study Design (PICOS) method (Reporting Guidelines Checklist) was used for definition of the inclusion criteria during the initial search.[14–16] In addition, this review was performed in accordance to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Reporting Guidelines Checklist) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocols (Reporting Guidelines Checklist).[17,18] Bibliographies of the included studies were also reviewed to identify additional studies. No registered review protocol number was associated with this study.

To be eligible for inclusion, studies were required to have (1) patients clinically/radiographically diagnosed with dAVFs (both CS and NCS) treated with SRS; and (2) available data for at least one of the outcomes of the study. The exclusion criteria were (1) studies that did not report on at least one outcome; (2) studies with ≤5 dAVFs treated with SRS; (3) studies with a median follow-up length of <1 year; (4) studies with overlapping data with the largest series of patients and single-institution reports preferred to minimize potential duplication of patients; (5) nonhuman studies; (6) studies published in languages other than English; and (7) abstract-only reports.

Data Extraction

The literature search and data extraction were performed by the first author (R. S.). Data extracted included CO rates, symptom cure and improvement rates, post-SRS hemorrhage/permanent neurological deficit (PND) rates, prescription dose, target volume, previous embolization/surgical ligation rates, patient age, Borden class and presence of CVD, and the proportion of patients with CS vs NCS dAVFs. CO was defined as no evidence of residual fistula after SRS on radiographic follow-up, either via angiogram or MRI/magnetic resonance angiography (MRA) or computerized tomography/angiography (CT/A) as per institutional standards. Symptom improvement was defined as patients who noted at final clinical follow-up either improvement or complete resolution of initial presenting symptoms after SRS. Symptom cure was defined as patients who only had complete resolution of initial presenting symptoms at final follow-up after SRS.

Primary and Secondary Outcomes

The primary outcomes defined for this study were CO rates and symptom cure/improvement rates after SRS at final follow-up. Secondary outcomes were post-SRS hemorrhage and PNDs either secondary to SRS-related toxicities or failure of treatment at final follow-up. Although the majority of studies assessed CO based on angiography, some studies examined potential CO using noninvasive imaging modalities such as CT/CTA or MRI/A with either radiographic approach generally performed 2 to 3 years after SRS. The time elapsed after SRS to final clinical follow-up for assessment of symptom cure/improvement and post-SRS hemorrhage/PNDs varied across studies.

Statistical Analysis

All analyses were performed using the Meta-Analysis for R (metafor) package version 2.0-0 of R Studio Version 1.1.383 (Boston, MA).[19,20] Variances were determined via the DerSimonian and Laird method with proportions for primary and secondary outcomes calculated for each study.[21] The summary effect sizes for each outcome were then determined with a weighted random-effects model based on the sample size of each study with forest plots created.[22,23] The I^2 statistic and Cochran Q-test were calculated to determine heterogeneity for each outcome.[24,25] Significant heterogeneity was recognized if both $I^2 > 50\%$ and P-value $< .10$ were present. Egger's test was used to assess for the risk of publication bias.[26] Statistical significance was defined as a $P \leq .05$ on two-tailed t-test.

For outcomes with significant heterogeneity, mixed-effects meta-regression models using an ordinary least square approach were used to explore potential contributors of heterogeneity, including median prescription dose (MPD), median target volume, previous embolization or surgery, presence of CVD, proportion of patients with NCS vs CS dAVFs, proportion with high-grade (ie, Borden grades II and III) dAVFs, and hemorrhage before SRS. Relevant weighting was performed by taking the number of patients or lesions in each study and dividing this by the total number across all studies included in each meta-regression to estimate potential linear relationships.[22]

Ethics

The procedures followed for the purposes of this study were in accordance with the ethical standards of the responsible committee on

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human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996, and 2000) of the World Medical Association.

RESULTS

Patient, Study, and Lesion Characteristics

Across a total of 21 published studies meeting our inclusion criteria, we identified 706 patients with 721 dAVFs treated with SRS.[12,13,27–45] Patients were treated between 1994 and 2021 at institutions in the United States, Sweden, Canada, the United Kingdom, South Korea, Taiwan, Japan, Spain, and India. Data on both outcomes as well as patient age, median clinical and angiographic follow-up, proportion of patients who received previous surgery and/or embolization, the proportion of patients with previous hemorrhage or CVD, target volume size and Borden Class, and MPD are detailed in Table 1. The median age of the studied cohort was 59 years (range: 13-90 years). The median/mean treatment volume was 2.45 cc (range: 0.04-37.5 cc). The MPD was 19.1 Gy (range: 13-33 Gy) with a median isodose of 50%. The median clinical follow-up across all studies was 2.75 years (range: 3.8 months-15.5 years). The proportion of patients who had previous surgery ranged from 0% to 22.2%, and the proportion of patients who had previous embolization ranged from 0% to 71.4%. The proportion of patients with CVD across all studies ranged from 0% to 72.3%.

Complete Obliteration, Symptom Cure, and Symptom Improvement Rates

There were 19 studies with 688 lesions with data on CO rates.[12,13,27–39,42–45] At final radiological follow-up, the pooled CO rate after SRS was 68.6% (95% CI 60.7%-76.5%; Figure 1). There was significant heterogeneity among the included studies. Higher proportions of NCS dAVFs were associated with lower CO rates (Figure 2; $P = .03$). Differences in MPD, nidus size, previous surgery or embolization, presence of CVD, higher grade, and hemorrhage before SRS did not explain the observed heterogeneity. Egger's test with respect to CO rates was nonsignificant.

There were 13 studies with 452 patients with data on symptom improvement rates.[13,29–35,37,40,41,44,45] At final clinical follow-up, the pooled symptom improvement rate after SRS was 97.2% (95% CI 93.2%-100%; Figure 3A). There was significant heterogeneity among the included studies, and differences in MPD, nidus size, proportion of NCS dAVFs or higher grade, previous surgery or embolization, presence of CVD, and hemorrhage before SRS did not explain the observed heterogeneity. Egger's test with respect to symptom improvement rates was nonsignificant.

There were 8 studies with 390 patients with data on symptom cure rates.[12,13,29,31,33,35,44,45] At final clinical follow-up, the pooled symptom cure rate after SRS was 78.8% (95% CI 69.3%-88.2%; Figure 3B). There was significant heterogeneity among the included studies. Higher grade ($P = .04$) and higher proportion of NCS dAVFs ($P = .001$) were associated with lower symptom cure rates, and embolization prior to SRS was associated with higher symptom cure rates ($P = .01$; Figure 4). Additional heterogeneity could not be explained by differences in proportions of patients with hemorrhage before SRS, nidus size, MPD, previous surgery, or presence of CVD. Egger's test with respect to symptom cure rates was nonsignificant.

Post-SRS Hemorrhage and Permanent Neurological Deficit Rates

There were 12 studies with 283 patients with data on PND rates.[12,27,29,30,32–36,38,41,42] At final clinical follow-up, the pooled PND rate after SRS was 1.3% (95% CI 0.8%-1.8%; Figure 5A). There was no significant heterogeneity among the included studies. Differences in previous surgery or embolization, MPD, nidus sizes, proportion of NCS dAVFs or higher-grade dAVFs, previous hemorrhage, and CVD were not associated with incidence of PNDs. Egger's test with respect to PND rates was nonsignificant.

There were 14 studies with 605 patients with data on post-SRS hemorrhage rates.[12,13,27–33,35,37,41,42,45] At final clinical follow-up, the pooled post-SRS hemorrhage rate after SRS was 1.1% (95% CI 0.6%-1.6%; Figure 5B). There was no significant heterogeneity among the included studies. There was a positive correlation between patients with previous hemorrhage and experiencing post-SRS hemorrhage rates ($P = .007$; **Supplementary Figure 1**, http://links.lww.com/NEU/D64). Differences in MPD, previous surgery or embolization, nidus size, and proportion of NCS dAVFs or higher-grade dAVFs were not associated with post-SRS hemorrhage. Egger's test with respect to post-SRS hemorrhage rates was nonsignificant.

DISCUSSION

dAVFs are associated with significant morbidity and potentially mortality owing to their risks of neurological deficits and intracranial hemorrhage.[7,8] Certain clinical and radiographic features distinguish benign vs aggressive dAVFs, including presence of clinical symptoms, CVD, and venous drainage patterns, as detailed by the Borden and Cognard classifications for NCS dAVFs.[46,47] For benign dAVFs with low risk of serious sequelae, initial conservative management is a viable option, although close clinical and radiographic follow-up may be indicated because of a small risk of CVD development.[48] For complex dAVFs with high-grade features, definitive treatment is often recommended. Previous meta-analysis have reported a favorable overall CO rate of 82% after embolization with PND, morbidity, and mortality rates of 4%, 3%, and 0%, respectively.[49] However, embolization with or without surgical ligation may not result in CO or long-term cure.[50] As such, SRS is often used after planned or previous unsuccessful embolization with the goal of achieving CO (although with a delay expected after SRS before achieving this) to abate symptoms and prevent future potential neurological complications. SRS has been established as an effective option in management for patients with arteriovenous malformations

TABLE 1. Studies Examining Clinical Outcomes After SRS for dAVFs

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Cifarelli et al [12]	55 (55) CS dAVFs: 4/55 (7.3%) (37/18)	50 (N/A)	Clinical: 11.4 years (3.8-19)	Previous surgery: 11/55 patients (20%) Previous embolization: 36/55 patients (65%)	ICH: 20/55 patients (36%) SAH: 7/55 patients (12%) CVD: 39/55 patients (71%)	Small (1-10 mm): 14 patients Medium (10-20 mm): 26 patients Large (>20 mm): 15 patients Borden I: 16 patients Borden II: 12 patients Borden III: 27 patients	MPD: 21 Gy (12-33 Gy) All treated with GK-SRS Mean Maximum Dose: 38 Gy (18-50 Gy)	CO: 30/46 patients (65.2%) with angiographic follow-up	Symptom cure: 17/23 patients (74%)	Post-SRS hemorrhage: 3/55 patients (5.5%) No new permanent neurological deficits after SRS
Gross et al [27]	8 (9) All NCS dAVFs (5/3)	56.8 (44-69)	2.9 years (1.6-4.7)	Previous surgery: 1/8 patients (12.5%) Previous embolization: 4/8 patients (50%)	Previous hemorrhage: 0 patients CVD: N/A	Median treatment volume: 1.0 cc (0.1-2.93 cc) Borden I: 3 patients Borden II: 3 patients Borden III: 3 patients	MPD: 17.7 Gy (15-20 Gy) All treated with single-fraction LINAC-SRS	CO: 8/9 patients (89%)	N/A	No cases of post-SRS hemorrhage or new permanent neurological deficits
Soderman et al [28]	65 (67) Sphenoid and CS dAVFs: 10 lesions N/A	N/A	N/A	Previous surgery: 3/65 patients (4.6%) Previous embolization: 10/65 patients (15.4%)	Previous hemorrhage: 22/65 patients (33.8%) CVD: 47/65 patients (72.3%)	Mean target volume (by location): 0.62-4.4 cc Borden I: 20 patients Borden II: 19 patients Borden III: 28 patients Note: Missing treatment data for 21 patients	MPD: 20-25 Gy (after 1990) All treated with single-fraction GK-SRS Isodose line: 40%-60%	CO: 37/63 patients with angiographic follow-up (59%)	N/A	Post-SRS hemorrhage: 2/73 patients (2.7%) No new permanent neurological deficits after SRS

TABLE 1. Continued.

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Dmytriw et al [29]	14 (16) CS dAVFs: 1/16 lesions (6/8)	57.2 (44-71)	Clinical and angiographic follow-up 3 years after SRS	Previous surgery: 3/14 patients (21.4%) Previous embolization: 10/14 patients (71.4%)	Previous ICH: 3 patients (21.4%) CVD: 7/16 lesions (43.8%)	Target volume range: 0.04-4.47 cc Borden I: 5 patients Borden II: 4 patients Borden III: 7 patients	MPD 20 Gy (15-25 Gy) All treated with single-fraction GK-SRS	CO: 8/16 treated dAVFs (50%)	Symptom improvement: 14/14 patients (100%) Symptom cure: 11/14 patients (78.6%)	No cases of post-SRS hemorrhage or new permanent neurological deficits
Yang et al [30]	40 (44) CS dAVFs: 17 patients, 19 lesions 28/40 patients with upfront SRS before or after embolization (22/18)	60 (29-90)	45 months (23-116 months)	Previous surgery: 0 patients (0%) Previous embolization: 12/40 patients (30%)	Previous ICH: 6/44 patients (13.6%) CVD: 20/44 lesions (45.4%)	Median target volume: 2.0 cc (0.2-8.2 cc) Borden I: 24 lesions Borden II: 20 lesions Borden III: 0 lesions	MPD: 20 Gy (15-25 Gy) All treated with single-fraction GK-SRS Isodose: 50% in 42 fistulas, 60% in 2 fistulas	CO: 32/44 patients with angiographic follow-up (72.3%) Upfront SRS and embolization: 83% SRS alone: 67%	Symptom improvement: 19/22 patients (86.4%) in low-bleeding-risk dAVFs	No cases of hemorrhage related to SRS or new permanent neurological deficits
Park et al [31]	30 (30) CS dAVFs: 18/30 lesions (8/22)	64 (39-89)	33 months (6-82 months)	Previous surgery: 0 patients (0%) Previous embolization: 7/30 patients (23.3%)	Previous hemorrhage: 4/30 patients (13%) CVD: 19/30 patients (63.3%)	Median target volume: 2.9 cc (0.8-13.6 cc) Borden I: 11 patients (36%) Borden II: 17 patients (57%) Borden III: 2 patients (7%)	MPD: 17 Gy (12-20 Gy) All single-fraction GK-based SRS	CO: 23/30 patients with angiographic follow-up (77%)	Symptom cure: 21/30 patients (70%) Symptom improvement: 30/30 patients (100%)	No cases of post-SRS hemorrhage or new permanent neurological deficits

TABLE 1. Continued.

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Pollock et al [32]	20 (20) All symptomatic CS dAVFs (3/17)	67 (34-80)	Clinical: 36 months (4-59 months) Annual angiographic follow-up until obliteration confirmed (median: 1 year after SRS)	Previous surgery: 0 patients (0%) Previous embolization: 13/20 patients (65%)	CVD: 4/20 patients (20%)	Median target volume: 2.8 cc (0.7-7.5 cc)	MPD: 20 Gy (18-20 Gy) Median maximum dose: 40 Gy (22.2-40 Gy) All single-fraction GK-based SRS	CO: 13/15 patients (87%)	Symptom improvement: 19/20 patients (95%)	Two cases of new neurological deficits related to embolization; none related to SRS No cases of post-SRS hemorrhage after SRS
Friedman, et al [33]	23 (23) All NCS dAVFs 2 of 25 initial identified patients lost to follow-up (5/18)	57 (33-79)	Clinical: 50 months (20-99 months) 16/23 patients with angiographic follow-up Angiographic: 21 months (11-38 months)	Previous surgery: 1 patient (4.3%) Previous embolization: 20/23 patients (86.7%)	Previous ICH: 2/23 (8.7%) CVD: 4/23 (17.4%)	Median target volume: 9.6 cc (2.7-29.6 cc)	MPD: 18 Gy (16-20 Gy) Median maximum dose: 36 Gy (32-40 Gy) All single-fraction GK-based SRS	CO: 7/17 patients (41.2%)	Symptom cure: 20/23 patients (87.0%) Symptom improvement: 22/23 patients (95.7%)	No cases of post-SRS hemorrhage or new permanent neurological deficits
O'Leary et al [34]	16 (17) CS dAVFs: 3/17 lesions (6/10)	59 (36-88)	Clinical follow-up: 8-96 months 2-year angiographic follow-up	Previous surgery: N/A Previous embolization: N/A	Previous hemorrhage: N/A CVD: 7/17 patients (41.2%)	N/A Borden I: 10 patients Borden II: 4 patients Borden III: 3 patients	MPD: 25 Gy (all patients received this except 1 patient with 20.83 Gy) All single-fraction GK-based SRS Isodose: 50%	CO: 10/13 patients with angiographic follow-up (76.9%)	Symptom improvement: 6/14 patients (42.6%)	No cases of post-SRS hemorrhage Permanent hearing loss 2/2 SRS: 1/14 patients with clinical follow-up (7.2%)

TABLE 1. Continued.

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Hanakita et al [35]	22 (22) CS dAVFs: 3/22 lesions (14/8)	60 (31-73)	33 months (12-100 months)	Previous surgery: 2/22 patients (2%) Previous embolization: 8/22 patients (36%)	Previous hemorrhage: 6/22 patients (27.3%) CVD: 15/22 patients (68.2%)	Median target volume: 1.5 cc (0.1-9.5 cc) Borden I: 4 patients Borden II: 11 patients Borden III: 3 patients	MPD: 25 Gy (18-25 Gy) All single-fraction GK-based SRS	CO: 12/22 patients (55%) CO without vs with CVD: 86% vs 47%	Symptom improvement: 9/9 patients with symptoms at presentation (100%) Symptom cure: 7/9 patients (77.8%)	No cases of post-SRS hemorrhage or new permanent neurological deficits
Pan et al [13]	264 (264) patients with follow-up CS dAVFs with follow-up: 156 (64.2%) (141/180) (of all patients, no specific sex data on patients with follow-up data)	57.8 (17-81)	CS dAVFs: 20.8 months (1-149 months) NCS dAVFs: 28 months (2-141 months)	Previous surgery: 13/264 patients (4.9%) Previous embolization: 41/264 patients (15.5%)	Previous ICH: 23/321 patients (7.2%) CVD: 19.7%	Mean treatment volume (CS dAVFs): 4.7 cc (range: 0.2-28.4 cc) Mean treatment volume (NCS dAVFs): 16.9 cc (0.8-52 cc) Borden type among patients with NCS: Borden I: 63 patients Borden II: 35 patients Borden III: 17 patients	MPD: 17.2 Gy Maximum dose for CS dAVFs: 25 Gy Maximum dose for NCS dAVFs: 30 Gy All single-fraction GK-based SRS	CO: 173/264 patients with angiographic follow-up (65.5%) CS dAVFs: 70% NCS dAVFs: 59%	Symptom cure: Analogous numbers to obliteration rate Symptom improvement: 260/264 patients (98.9%) CS dAVFs: 156/156 patients 100% NCS dAVFs: 104/108 patients (96%)	Post-SRS hemorrhage: 2/321 patients (0.62%) No permanent neurological deficits

TABLE 1. Continued.

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Oh et al [36]	43 (43) 30 treated with embolization and SRS 13 treated with SRS alone N/A for SRS ± embolization cohort	59.2 (16-82)	22 months (embolization and SRS)	N/A	N/A	Mean treatment volume: 6.9 cc (0.35-37.5 cc) Borden type for SRS cohort alone not available	MPD: 19 Gy (15-25 Gy) Mean maximum dose: 38 Gy (22-50 Gy) All single-fraction GK-based SRS	CO with SRS and embolization: 25/30 patients (83%) CO with SRS alone: 7/13 patients (54%)	N/A	1/43 patients with post-SRS hemorrhage (2.3%) 1/43 patients with facial palsy (2.3%)
Seo et al [37]	16 (16) CS dAVFs: 6/16 lesions 12 treated with embolization before SRS (9/7)	54 (13-77)	Clinical: 87.5 months (24-186 months) Angiographic: 44.5 months (14-174 months)	Previous surgery: 0 patients (0%) Previous embolization: 12/16 (75%)	Previous hemorrhage: N/A CVD: 14/16 patients (75%)	Median target volume: 0.55 cc (0.04-10.3 cc) Borden I: 2 patients Borden II: 3 patients Borden III: 11 patients	MPD: 19 Gy (13-23 Gy) All single-fraction GK-based SRS Median isodose: 50% (50%-60%)	CO: 10/16 patients (62.5%) CS vs NCS dAVFs: 100% vs 40% (P = .034)	Symptom improvement: 13/16 patients (81.3%)	Post-SRS hemorrhage: 1/16 patients (6.3%)
Barcia-Solorio et al [38]	25 (25) All CS dAVFs N/A	N/A	49.76 months (15 months-14 years)	N/A	N/A	N/A	"Total dose": 30-40 Gy (except in one post-traumatic case, 20 Gy)	CO: 21/25 of all fistulae (84%) 20/22 of low-flow dAVFs (90.9%)	N/A	No new permanent neurological deficits after SRS
Lewis et al [39]	7 (7) (9 in series, 2 did not receive SRS) All NCS dAVFs All received embolization and SRS N/A	61 (52-72)	N/A	Previous surgery: 2/9 patients (22.2%) 5/9 (55.6%) required VP shunting	Previous ICH or SAH: 5/9 patients (55.6%)	N/A	Prescription dose: 8-20 Gy All single-fraction GK-based SRS	CO: 5/7 patients (71.4%)	N/A	N/A
Chung et al [40]	8 (8) treated with SRS 3/8 also received embolization N/A specific to SRS cohort	N/A	N/A	N/A	N/A	N/A	MPD: 20 Gy (15-25 Gy) Mean isodose: 70% (50%-90%)	N/A	Symptom improvement: 6/8 patients (75%) Symptom cure: 1/8 patients (12.5%)	1/8 patients developed permanent neurological deficit (decrease in visual acuity) 2/2 SRS

TABLE 1. Continued.

Study	n (patients/ lesions) (male/ female)	Mean/ median age (years) (range)	Median Follow-up (range)	Previous treatments	Previous hemorrhage and CVD rate	Mean/ median target size (cc) (range) and Borden class	Mean/median prescription doses (range)	CO rate	Symptom improvement and symptom cure	Post-SRS hemorrhage and additional toxicities/ comments
Jung et al [41]	5 (5) All low-flow CS dAVFs 2/5 also received embolization (1/4)	67 (50-69)	Clinical: 30 months (9-59 months)	Previous embolization: 2/5 patients (40%)	Previous hemorrhage: 0% CVD: 0%	Median target volume: 1.7 cc (0.24-4.7 cc)	MPD: 20 Gy (16-20 Gy) All single-fraction GK-based SRS Isodose: 50%	N/A	Symptom improvement: 5/5 patients (100%)	No cases of post-SRS hemorrhage
Kida et al [42]	13 (13) CS dAVFs: 4/13 lesions (9/4)	54.3 (39-74)	24 months	Previous surgery: 0% Previous embolization: 7/13 patients (53.8%)	N/A	Mean diameter: 14.9 mm	Mean MPD: 18.9 Gy (15-24 Gy) All single-fraction GK-based SRS	CO: 5/13 patients (38.5%)	N/A	No cases of post-SRS hemorrhage or new permanent neurological deficits
Maglinger et al [43]	10 (14) All NCS dAVFs (5/5)	63 (40-74)	19.5 months Angiographic follow-up: 10-49 months	Previous surgery: 0% Previous embolization: 7/14 lesions (50%)	Previous hemorrhage: 0% CVD: 50%	Mean treatment size: 1.7 cc (0.041-5.6 cc) Borden I: 2 patients Borden II: 7 patients Borden III: 5 patients	MPD: 18 Gy (16-25 Gy) All single-fraction GK-based SRS Isodose: 50%	CO: 8/14 patients (57%)	N/A	N/A
Sardana et al [44]	5 (5) (4/1)	44.8	N/A	N/A	CVD: 0%	N/A	N/A	CO: 5/5 patients (100%)	Symptom improvement/ cure: 5/5 patients (100%)	N/A
Wang et al [45]	21 (21) 5 patients had embolization (2 after SRS) CS dAVFs: 13/21 lesions (10/11)	56.3 (14-79)	70.5 months (3-136 months)	Previous embolization: 3/21 patients (14.3%) (planned; 2 with embolization after SRS)	Previous hemorrhage: 1/21 patients (4.8%) CVD: 8/21 patients (38.1%)	Mean treatment volume: 9.76 cc (1.9-30.5 cc) Borden I: 13 patients Borden II: 7 patients Borden III: 1 patients	Mean MPD: 15.8 Gy (13-18 Gy) All single-fraction GK-based SRS Isodose: 50%	CO: 8/17 patients (47%) Borden I vs II/III: 66.7% vs 25%	Symptom cure: 77% Symptom improvement: 100% No difference in symptom improvement/ cure by Borden class	Post-SRS hemorrhage: 1/21 patients (4.8%)

Abbreviations: CO, complete obliteration; CS, cavernous sinus; CVD, cortical venous drainage; dAVF, dural arteriovenous fistula; GK, Gamma Knife; ICH, intracranial hemorrhage; LINAC, linear accelerator; MPD, mean/median prescription dose; NCS, noncavernous sinus; SAH, subarachnoid hemorrhage; SRS, stereotactic radiosurgery; VP, ventriculoperitoneal.

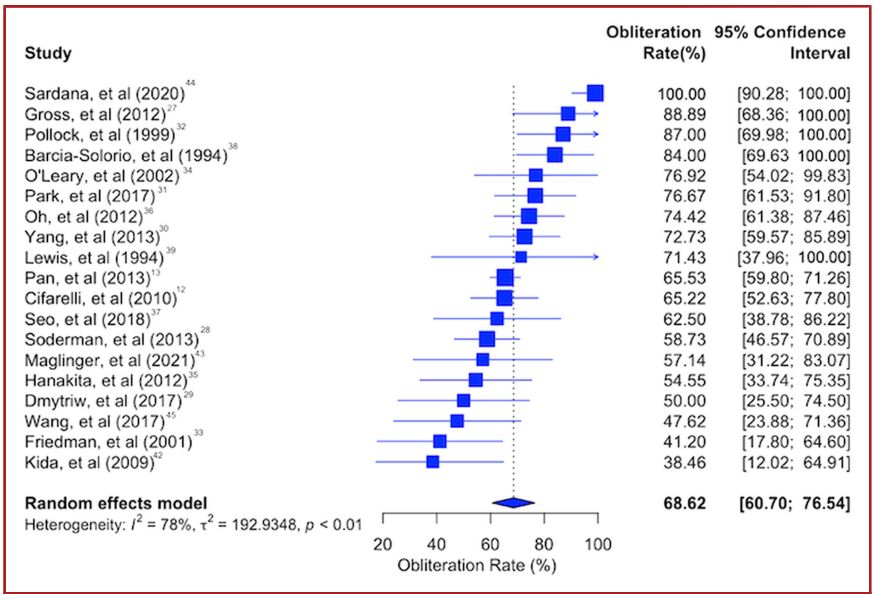

FIGURE 1. *Forest plot of complete obliteration (CO) rate after stereotactic radiosurgery (SRS).*

(AVMs) with reductions in risk of roughly 50% and 90% during the latency period after SRS before achieving CO and at the time of achieving CO, respectively.[51] Previous meta-analyses have examined CO outcomes after SRS, with no additional studies examining updated CO rates or providing estimates of outcomes relevant to patients' quality of life, including symptom

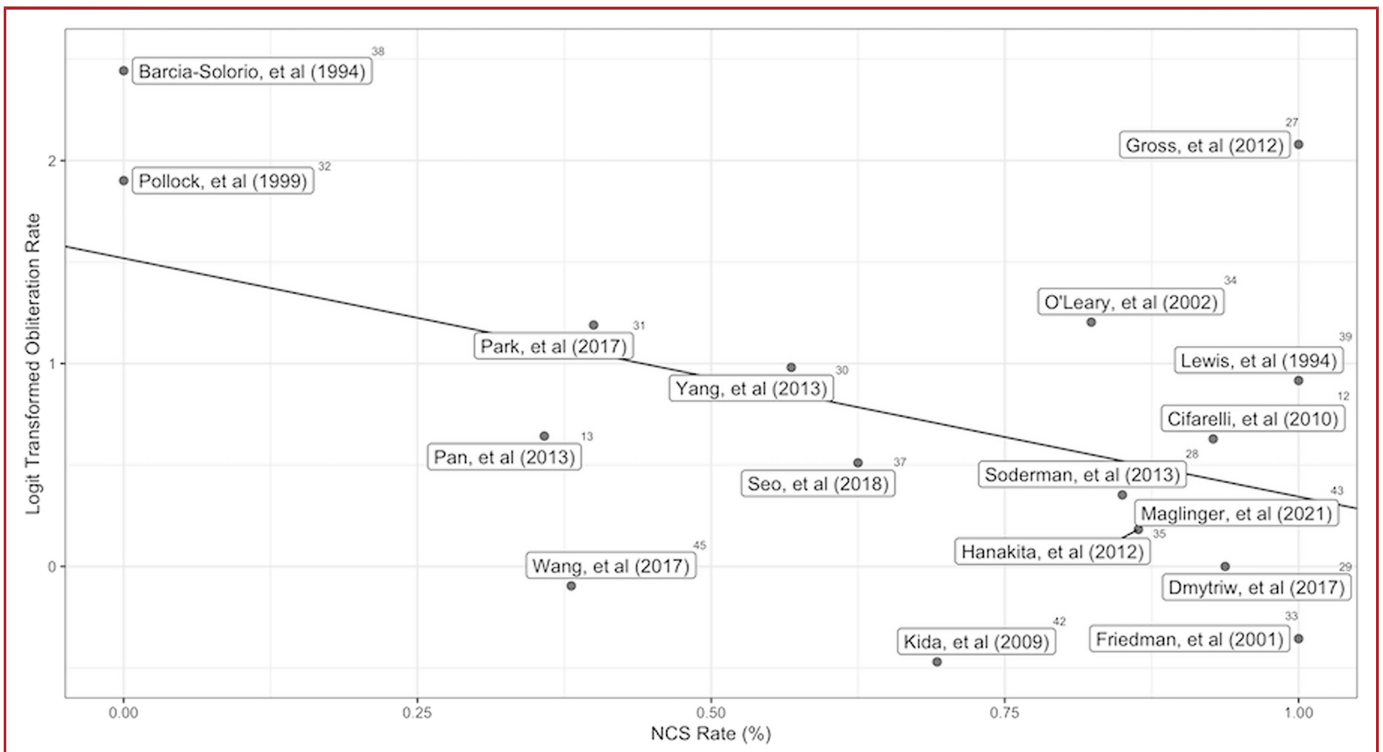

FIGURE 2. *Meta-regression examining correlation between proportion of NCS dural arteriovenous fistulas (dAVFs) and complete obliteration (CO).*

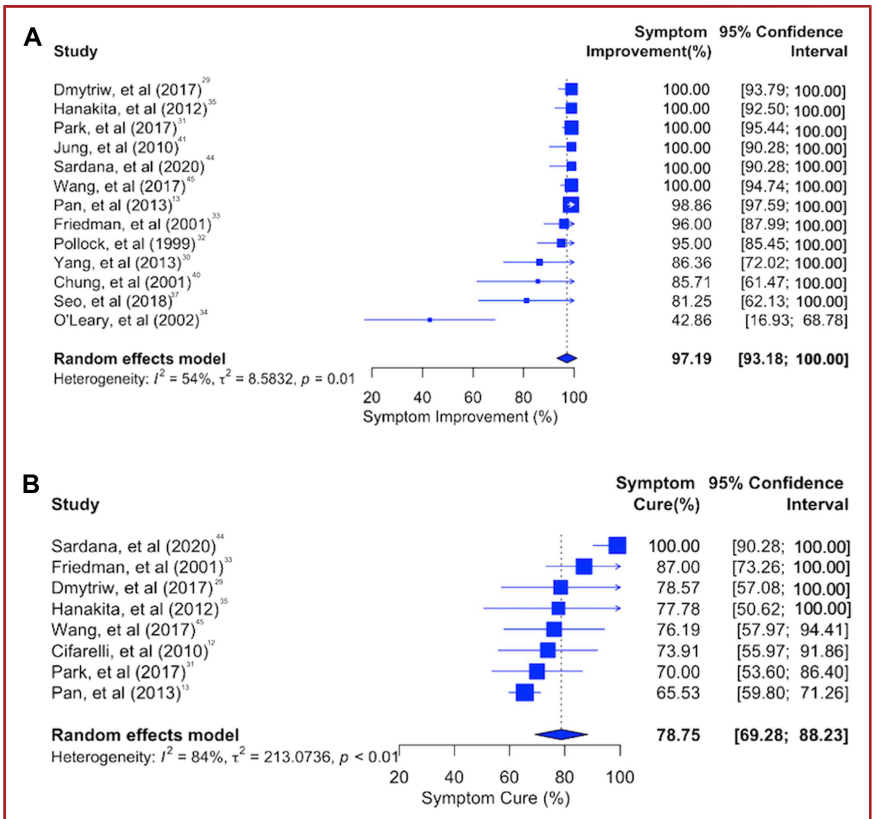

FIGURE 3. *Forest plots of* **A**, *symptom improvement and* **B**, *symptom cure rates after stereotactic radiosurgery (SRS).*

improvement, symptom cure, post-SRS hemorrhage rates, and PND rates.[52] The results of our analysis suggest that SRS is an effective treatment modality with a pooled CO rate of approximately 70%, with the proportion of patients reporting either symptom improvement or cure of approximately 97% and 80%, respectively. Rates of PND and hemorrhage after SRS were low (approximately 1%). Compared with outcomes after SRS for AVMs, hemorrhage rates were extremely low after SRS for dAVFs without a significant latency period (although with the limitation that our analysis did not have temporal information on when CO was achieved relative to SRS). Relatively higher CO rates compared with previous systematic reviews may be due to additional series with longer follow-up, given the latency period of SRS in achieving CO. Also, improved target delineation may also have contributed to higher CO rates using a combination of angiography with digital subtraction, thin-slice MRI/A, and CT compared with previous studies that used primarily angiography alone.[52]

Previous studies have noted the prognostic importance of dAVF location (CS vs NCS), CVD, and embolization before SRS. In the largest single-center study, Pan et al[13] noted a higher CO rate for CS (70%) vs NCS dAVFs (59%) after SRS. A smaller study found a larger difference in CO rates after SRS between CS dAVFs (100%) vs NCS dAVFs (40%; P = .034).[37] A previous systematic review noted a nonsignificant difference in CO rates between CS and NCS dAVFs (73% vs 58%; P = .27).[51] Regarding CVD, both Hanakita et al (86% vs 47%) and Wang et al (66.7% vs 25%) have noted more favorable CO rates in patients without CVD vs with CVD.[35,45] Chen et al,[52] in their previously-reported systematic review, did find CVD to be significantly correlated with lower CO rates (75% vs 56%; P = .03). Similarly, we found in our analysis that series with higher proportions of NCS dAVFs had significantly poorer CO and symptom cure rates. Embolization before SRS has been observed in the series of both Yang et al (83% vs 67%) and Oh et al (83% vs 54%) to result in higher CO rates.[30,36] We also noted that previous embolization was associated with significantly improved symptom cure rates. However, we did not find that CVD rates or dose escalation beyond MPDs used in contemporary SRS practice affected CO rates.

Another goal of SRS is palliation of venous congestion–related symptoms. Initial series found that improvement of symptoms was achieved in approximately half of the patients, although more modern series have reported symptom improvement to be much higher (90%-100% of patients).[13,33,34] The location of dAVFs has not been shown to be associated with symptom improvement

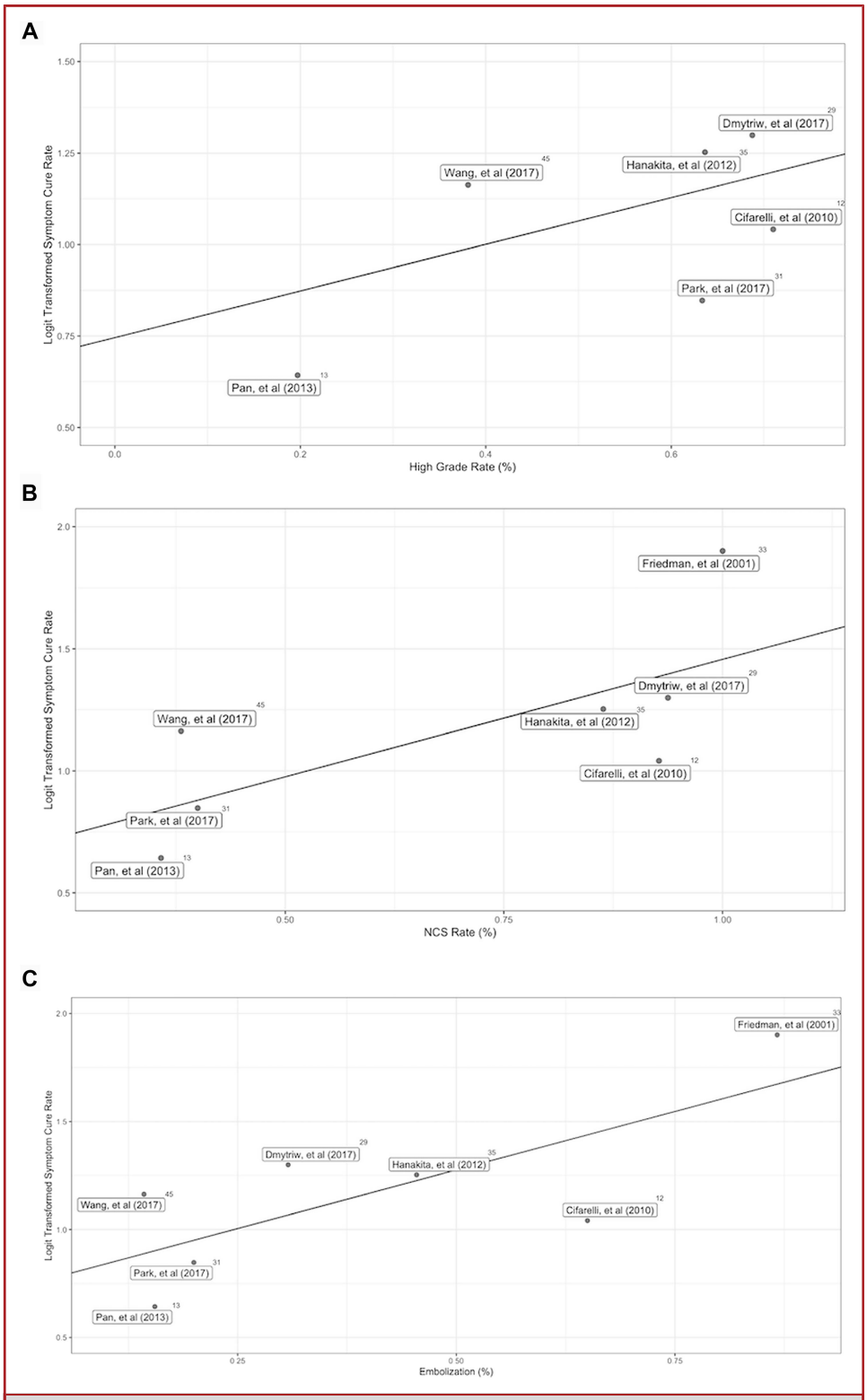

FIGURE 4. *Meta-regression examining correlation between symptom cure rates and* **A**, *grade,* **B**, *proportion of NCS dural arteriovenous fistulas (dAVFs), and* **C**, *receipt of embolization.*

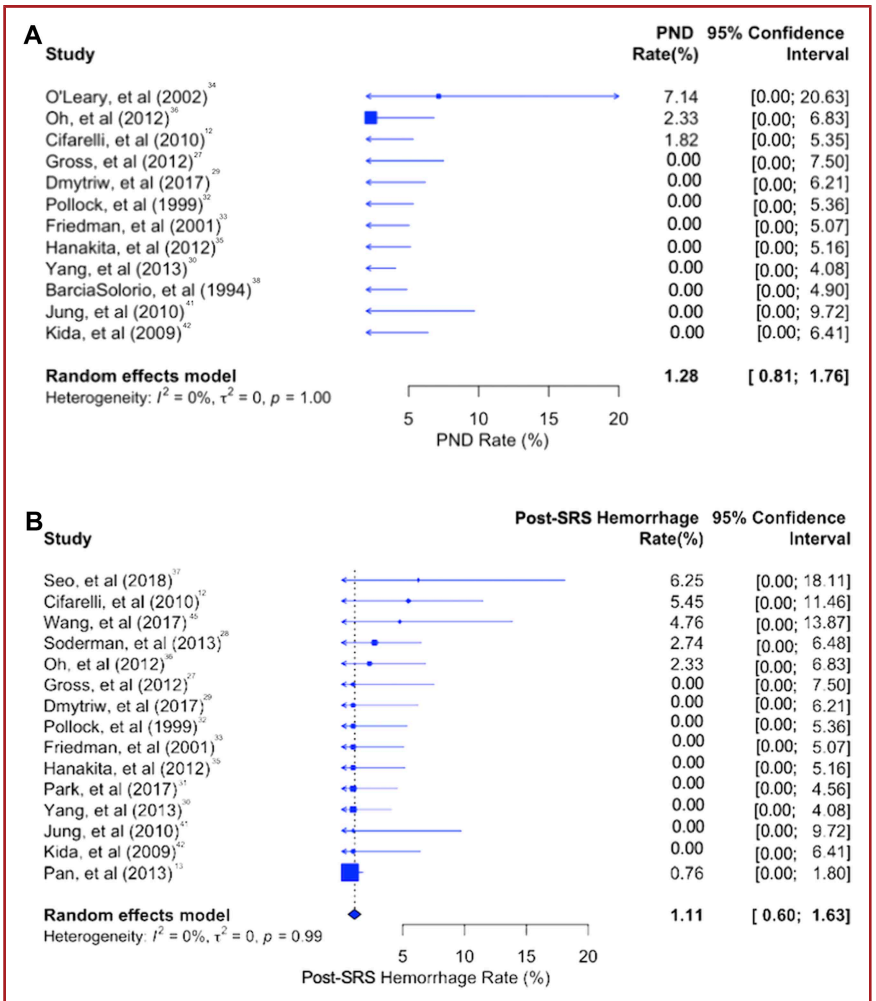

FIGURE 5. *Forest plots of* **A**, *permanent neurological deficit (PND) and* **B**, *hemorrhage after stereotactic radiosurgery (SRS).*

with excellent palliation achieved for both CS (100%) and NCS dAVFs (96%).[13] Similarly, Borden class and CVD have not previously been shown to correlate with symptom improvement or cure.[45] However, our analysis did reveal that higher proportion of patients treated with NCS dAVFs or higher Borden grade dAVF were associated with lower rates of symptom cure but not lower rates of symptom improvement. Although appropriate dAVF patient selection for SRS remains incompletely defined, CVD, previous intracerebral hemorrhage, and NCS location likely represent important factors to guide clinical decision-making.[53]

Our analysis also found low rates of PNDs and hemorrhage after SRS, with pooled rates of approximately 1% for both. With respect to PNDs after SRS, these included decline in visual acuity and hearing loss with both limited to earlier studies.[34,40] Given the low rate of PNDs and hemorrhage after SRS, reviewed published studies did not note any dAVF or patient characteristics associated with either complication. We did find that patients with previous hemorrhage had higher rates of hemorrhage after SRS. However, we did not note that any examined independent variable was associated with PND rates.

Based on the findings of this study, proposed practice guidelines and recommendations for treatment of dAVFs with SRS can be found in Table 2. Initial observation and conservative management is a viable option for CS dAVFs and low-grade intracranial dAVFs.[54] Given the risk of potential morbidity and mortality associated with high-grade NCS dAVFs (ie, Borden types II and III), definitive treatment is recommended. Similarly, definitive treatment is recommended for patients with CS or low-risk NCS dAVFs with refractory or progressive symptoms after initial conservative management, given low morbidity associated with SRS. Embolization is recommended as first-line treatment for initial management of high-grade and/or symptomatic dAVFs. For complex fistulas, in which the likelihood of achieving CO is low with embolization alone, patients who have previously

TABLE 2. Practice Guidelines and Recommendations on Role of SRS for dAVFs

Recommendations on	
1. Patient selection	(a) Patients with complex dAVFs who are planned for embolization and are at high risk for not achieving CO with embolization alone (b) Patients with dAVFs who have received previous embolization without CO and have refractory symptoms (c) Patients with high-risk NCS dAVFs (ie, Borden type II or III or those with previous hemorrhage) or symptomatic CS dAVFs who are not candidates for or have refused both embolization or microsurgery
2. Treatment	(a) Pretreatment cerebral angiography and thin-slice (1 mm or less) MRI/A (or CT/A if not feasible) with T1 sequences with pregadolinium and postgadolinium (b) MRI is particularly recommended if feasible for targets adjacent to at-risk normal structures (ie, brain stem, cochlea, and optic apparatus) (c) If embolization is planned before SRS, pretreatment imaging should be performed after embolization to allow for improved target delineation to the residual fistula (d) Single-fraction SRS is recommended dependent on both fistula size and proximity to at-risk normal structures in definitive, adjuvant, or salvage settings with a 1-mm PTV expansion as needed
3. Outcomes and follow-up	(a) Patients should be followed with serial MRI/As (or CT/A if not feasible) every 6 months after SRS until obliteration is thought to be achieved (b) Cerebral angiogram is recommended to definitively confirm CO if suspected on serial imaging

Abbreviations: CO, complete obliteration; CS, cavernous sinus; CT/A, computed tomography/angiogram; dAVF, dural arteriovenous fistula; MRA, magnetic resonance angiography; NCS, noncavernous sinus; PTV, planning target volume; SRS, stereotactic radiosurgery.

experienced hemorrhage before definitive treatment, or those who have had embolization alone without CO and/or recurrence of symptoms, SRS is recommended as an adjuvant or salvage treatment option, especially if surgical ligation is not feasible or if patients refuse surgical ligation. Embolization may reduce the size of fistulas allowing for safer delivery of SRS but possibly introducing a risk of obscuring the dAVF on stereotactic targeted imaging.[55] If either surgical ligation or embolization is not feasible, then SRS is recommended, given that the majority of patients experience CO and symptom palliation with low rates of adverse events. Patients should be counseled appropriately regarding the delay from time of SRS to potential achievement of CO.

Single-fraction SRS is recommended with contemporary MPDs of approximately 17-25 Gy in definitive, adjuvant, or salvage settings depending on the size of the fistula and surrounding normal tissue tolerances. For SRS planning, both catheter cerebral angiography and thin-slice (ie, 1 mm slice or less) MRI, particularly with T1 pregadolinium and postgadolinium sequences (or CT if MRI is not feasible), are recommended for target delineation and critical structure avoidance. The target should generally comprise the fistula alone without inclusion of the feeding artery or draining vein, with a 1-mm expansion (if needed and based on technology platform) to comprise the planning target volume to account for set-up error after delineation of the initial target. Follow-up should comprise MRI/A (or CT/A if MRI is not feasible) every 6 months to monitor for obliteration. If angiographic obliteration is suggested on follow-up CT or MRI, then a subsequent cerebral angiogram is recommended to confirm CO. When a cerebral angiogram is not able to be performed to confirm obliteration, MRI/A or CT/CTA may be used to determine CO with a high degree of confidence.

Limitations

It is important to recognize the limitations of this study. All studies included in this study were retrospective analyses with heterogeneous follow-up and attrition rates that both introduce a significant risk of bias in our estimates. As we used study-level data rather than patient-level data, we were unable to control for specific patient and treatment characteristics, including Borden/Cognard type, target size, hemorrhage or symptoms before SRS, previous embolization or microsurgery, time elapsed between previous treatments and SRS, CVD or leptomeningeal drainage, dAVF location, and retrograde or anterograde flow. CO was generally determined by angiography, but CO based on MRI or CT alone and variable follow-up may introduce bias in this end point. As this analysis included patients treated across a variety of institutions and time periods, there were variations in patient selection, treatment planning, and follow-up that led to significant heterogeneity for a number of our summary effect estimates. Also, given the small number of series that reported on outcomes specifically after SRS alone vs SRS and embolization or surgery, we were unable to compare CO or symptom palliation rates between SRS alone vs multimodality therapy.

CONCLUSION

SRS is an effective and safe treatment option for patients with dAVFs. Treatment confers CO in the majority of dAVF-treated patients with excellent results with respect to symptom palliation, with multimodality treatment with embolization noted to result in superior symptom cure rates. Previous hemorrhage should be considered when counseling patients on the risk of hemorrhage after SRS.

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Supplementary Figure 1. Meta-regression examining correlation between hemorrhage before SRS and post-SRS hemorrhages.