HHS Public Access

Author manuscript

J Neurosurg. Author manuscript; available in PMC 2020 September 15.

Published in final edited form as:

J Neurosurg. ; : 1–9. doi:10.3171/2018.12.JNS182208.

Hemorrhage risk of cerebral dural arteriovenous fistulas following Gamma Knife radiosurgery in a multicenter international consortium

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Disclosures

Dr. Vargo reports receiving speaking honoraria from Brainlab. Dr. Lunsford reports stock ownership in Elekta and being a consultant for Insightec, DSMB. Dr. Kano reports he has an Elekta Research Grant and is an Elekta AB grant recipient.

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Abstract

OBJECTIVE—The authors performed a study to evaluate the hemorrhagic rates of cerebral dural arteriovenous fistulas (dAVFs) and the risk factors of hemorrhage following Gamma Knife radiosurgery (GKRS).

METHODS—Data from a cohort of patients undergoing GKRS for cerebral dAVFs were compiled from the International Radiosurgery Research Foundation. The annual posttreatment hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. Risk factors for dAVF hemorrhage prior to GKRS and during the latency period after radiosurgery were evaluated in a multivariate analysis.

RESULTS—A total of 147 patients with dAVFs were treated with GKRS. Thirty-six patients (24.5%) presented with hemorrhage. dAVFs that had any cortical venous drainage (CVD) (OR = 3.8, p = 0.003) or convexity or torcula location (OR = 3.3, p = 0.017) were more likely to present with hemorrhage in multivariate analysis. Half of the patients had prior treatment (49.7%). Post-GRKS hemorrhage occurred in 4 patients, with an overall annual risk of 0.84% during the latency period. The annual risks of post-GKRS hemorrhage for Borden type 2–3 dAVFs and Borden type 2–3 hemorrhagic dAVFs were 1.45% and 0.93%, respectively. No hemorrhage occurred after radiological confirmation of obliteration. Independent predictors of hemorrhage following GKRS included nonhemorrhagic neural deficit presentation (HR = 21.6, p = 0.027) and increasing number of past endovascular treatments (HR = 1.81, p = 0.036).

CONCLUSIONS—Patients have similar rates of hemorrhage before and after radiosurgery until obliteration is achieved. dAVFs that have any CVD or are located in the convexity or torcula were more likely to present with hemorrhage. Patients presenting with nonhemorrhagic neural deficits and a history of endovascular treatments had higher risks of post- GKRS hemorrhage.

Keywords

Gamma Knife; arteriovenous; fistula; dural; hemorrhage; embolization; surgery; radiation; grading; scale; complication; outcome; vascular disorders; stereotactic radiosurgery

Dural arteriovenous fistulas (dAVFs) are relatively uncommon lesions. The natural history of these lesions has been studied in relatively small series.[6,40,45] The overall hemorrhage rates reported in the literature vary significantly. Due to the overall small number of patients in the reported series, independent assessment of risk factors predicting hemorrhage has been challenging.

These lesions are commonly treated with endovascular embolization, microsurgery, or radiosurgery.[15] The optimal management remains unclear, and these lesions often require multiple treatments. Radiosurgery has been used to treat dAVFs, but the literature is fairly limited. Unlike embolization and microsurgery, the obliteration process following radiosurgery is delayed, and the patient remains at risk for hemorrhage during the latency period. The latency period for dAVFs has been extrapolated from the arteriovenous

malformation (AVM) literature and is estimated to occur between 1 to 5 years following radiosurgery. However, supporting literature is relatively sparse. It also remains unclear whether and how radiosurgery alters the natural history of a dAVF.[39]

The goals of the current study are to calculate the posttreatment hemorrhage rate in a large multicenter cohort of patients with dAVFs referred for Gamma Knife radiosurgery (GKRS). We assess the reported natural history course of dAVFs, comparing them to the hemorrhage rates in our cohort following GKRS. Independent risk factors for pre- and post-GKRS hemorrhage are determined.

Methods

Patient Population

Most of the methods given here have been previously described.[10,11,38,41] Ten medical centers participating in the International Radiosurgery Research Foundation obtained individual IRB approvals to participate in this study. A total of 147 patients were identified with cerebral dAVFs treated with GKRS from 1988 to 2016. At each center, retrospective clinical outcome analysis of patients was performed. The following centers contributed data for this study: University of Virginia (60 patients), University of Pittsburgh (43 patients), Yale (14 patients), Na Homolce Hospital (Prague; 14 patients), University of Pennsylvania (9 patients), West Virginia University (2 patients), University of Sherbrooke (2 patients), University of Manitoba (1 patient), University of Puerto Rico (1 patient), Beaumont Health System (1 patient).

The records of dAVF patients who underwent GKRS (Elekta AB) between 1988 and 2016 were evaluated by clinicians at each center for study inclusion. A database with selected variables was created and sent to all participating centers. Participating centers reviewed the medical records of their patients, entered the data in the spreadsheet, and removed all patient identifiers from the database. Pooled and de-identified data were screened by an independent third party for errors. Any uncertainties or ambiguities in the data were addressed by the contributing center. Afterward, data were transmitted to the first and senior authors who, along with their coauthors, developed this report.

Patients were included in the study if they had a cerebral dAVF treated with GKRS. Patients who underwent volume-staged GKRS were excluded. To determine the risk of post-GKRS hemorrhage, patients were included if they had a minimum of 6 months of neuroimaging and clinical follow-up, although patients experiencing a complication within 6 months of treatment were also included. A dAVF presenting with hemorrhage or nonhemorrhagic neural deficits (NHNDs; seizures or neural deficits) was defined as an aggressive clinical presentation.

Radiosurgical Technique

The Gamma Knife models U, B, C, 4C, or Perfexion were used depending on the technology available at the time of the procedure for each participating center. The radiosurgery procedure began with the application of the Leksell model G stereotactic frame (Elekta AB) using a local anesthetic supplemented by additional sedation as needed. All radiosurgeries

were performed in a single fraction. After stereotactic frame placement, stereotactic high-resolution MRI was performed. In cases in which MRI was not feasible or in which MRI distortion was a concern, stereotactic computed tomography scanning was conducted. Thin-slice axial and/or coronal images were obtained after intravenous contrast administration. Stereotactic cerebral angiography was conducted and incorporated in treatment planning for nidus definition and dose planning. Radiosurgery dose planning was then performed by the neurosurgeon in conjunction with a radiation oncologist and medical physicist.

Clinical and Neuroimaging Follow-Up

Clinical and neuroimaging evaluations were generally performed at follow-up intervals of 6 months for the first 2 years after radiosurgery and yearly thereafter. When there was no dAVF visible on MRI and/or CT, the patient underwent angiography to confirm the obliteration of the nidus. All images were analyzed by both a neurosurgeon and a neuroradiologist. Patients were instructed to continue MRIs every 1–5 years to monitor for long-term complications, even after angiography demonstrated complete dAVF obliteration. For those patients for whom MRI was contraindicated (e.g., when a cardiac pacemaker was present), CT was performed instead of MRI. Whenever feasible, patients underwent follow-up neurological examination and neuroimaging at the respective treating center. However, since participating institutions represent tertiary referral centers, some patients underwent follow-up evaluations by their local physicians. For such patients, clinical notes and actual neuroimaging studies (i.e., not just the radiological reports) were received and reviewed by the treating clinicians who performed the GKRS procedure. The follow-up images were compared with the images obtained at the time of GKRS. The dimensions of the dAVF were assessed in the axial, sagittal, and coronal planes in relation to comparable measurements on the GKRS neuroimaging studies.

Statistical Analysis

Data are presented as median or mean and range for continuous variables and as the frequency and percentage for categorical variables. Calculations of normality were assessed graphically and statistically. Statistical analyses of categorical variables were carried out using chi-square and Fisher’s exact tests, as appropriate. Statistics of means were carried out using unpaired Student t-tests, both with and without equal variance (Levene’s test) as necessary, and Wilcoxon rank-sum tests when variables were not normally distributed. The pre-GKRS annual hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. To calculate the annual rebleed rate, the number of recurrent hemorrhages was divided by the total number of risk years from the dates of initial hemorrhage to the dates of GKRS. None of our patients had hemorrhage after the dAVF was declared obliterated based on MRI or angiography; therefore, the post-GKRS annual hemorrhage rate was calculated dividing the hemorrhagic events by the patient risk years from the dates of GKRS to the dates that the dAVFs were judged to be obliterated on neurovascular imaging or the dates of last follow-up if the dAVF remained patent. Patient and dAVF characteristics were assessed in a univariate analysis to test covariates predictive of hemorrhage. Clinically significant variables and interaction expansion covariates were further assessed in both multivariate analyses, as deemed relevant. Factors predictive in the univariate analysis ($p < 0.15$) were entered into multivariate logistic regression models with

and without treatment characteristics.[1] Additionally, competing risk survival analysis of dAVF-free hemorrhage was calculated using the modified Kaplan-Meier method and Gray's method.[18] After confirmation of the assumption of proportional hazards, factors predictive of hemorrhage ($p < 0.15$) were entered into a modified multivariate Cox regression analysis to assess hazard ratios in the presence of competing mortality risk.[16] Patients were censored from the postradiosurgery bleeding risk group when the dAVF was obliterated. In addition, patients were censored in competing risks analysis if they underwent further treatment, were lost to follow-up, or died. Due to similar outcomes, cortical venous drainage (CVD) with concomitant retrograde drainage into a normal vein was analyzed as one entity for post-GKRS hemorrhage risk analysis. A p value of less than or equal to 0.05 was considered statistically significant. Statistical analysis was carried out with Stata 14.0 and SAS 9.4.

Results

Patient and dAVF Characteristics

A total of 147 patients were treated with GKRS from 1988 to 2016 at the participating institutions, 61 of whom were female (41.8%). Patient demographics are shown in Table 1. The mean age was 56 years (SD 14). Patients most commonly presented with headaches (51.7%), subjective tinnitus (32%), hemorrhage (24.5%), and neurological deficits (21.1%). Half of the patients had received prior treatment (49.7%); 66 had prior endovascular treatment (44.9%), 8 had prior resections (5.4), and 5 had prior stereotactic radiosurgery (3.4%). Of the patients who received prior endovascular treatment, 39.4% had more than two endovascular attempts (n = 26).

The location, size, Borden grades, Cognard classification, and additional dAVF characteristics are also detailed in Table 1 (only 137 and 136 patients had Cognard classifications and Borden grades available, respectively). The majority of treated dAVFs were Borden grade 1 (n = 49) or Cognard class I (n = 42). Most dAVFs were located in the transverse/sigmoid sinus. Spinal drainage was observed in 27 dAVFs (19.9%). CVD was present in 77 dAVFs (52.4%), and venous ectasia was documented in 36 (24.5%).

Patient Demographics and dAVF Characteristics in Hemorrhagic Presentation

Patient and dAVF characteristics stratified by hemorrhagic presentation are shown in Table 1. A total of 36 patients (24.5%) presented with hemorrhage. Twenty-seven patients (18.4%) had intracerebral hemorrhage, 7 (4.8%) had intraventricular hemorrhage, and 16 patients (10.9%) demonstrated subarachnoid hemorrhage. Most patients with hemorrhagic presentation had CVD detected on imaging (77.8%).

Patients presenting with hemorrhage were more likely to have a chief complaint of "headache" ($p < 0.0001$) and less likely to note tinnitus ($p < 0.0001$) compared to those presenting without hemorrhage. Predictors of hemorrhagic dAVF presentation are shown in Table 2. Higher Borden, modified Borden,[48] and Cognard grades were predictive of hemorrhagic presentation. In the univariate analysis, any CVD, spinal drainage, associated edema, venous ectasia, and a convexity or torcula location were predictive of hemorrhagic presentation. In the multivariate analysis, dAVFs with any CVD and convexity or torcula

location remained predictive of hemorrhagic presentation. Past treatment was not predictive of hemorrhagic presentation.

GKRS Parameters and Follow-Up

Pre-GKRS CT or MRI studies were available for all patients. The mean dose to the periphery was 21.5 Gy (SD 3.2), with a mean maximum dose of 40.3 Gy (SD 6.4) and a mean isodose line of 53.8% (SD 10.7%). The mean number of isocenters was 4.8 (SD 6.4).

The mean overall follow-up duration was 42 months (SD 38.6). Post-GKRS angiographic follow-up was available for 89 patients (60.5%); MRI follow-up was available for 46 patients (31.3%). Ten patients (6.8%) were lost to follow-up. Of the 133 dAVF treated with GKRS with sufficient follow-up for post-GKRS hemorrhage analysis, 87 (65%) had angiography follow-up and 44 (33%) had MRI follow-up. The obliteration rate at last follow-up in these 133 patients was 62% (n = 82) with a mean time to obliteration of 44.9 months (SD 36 months).

Post-GKRS Hemorrhage Rate

After angiographically confirmed obliteration, no dAVFs were noted to have hemorrhaged. Post-GKRS hemorrhage rates are displayed in Table 3. Following GKRS, 4 dAVFs (2.7%) hemorrhaged. With 474 patient-years of follow-up, the overall annual post-GKRS hemorrhage rate was 0.84%. The annual risk of post-GKRS hemorrhage was 1.45% for dAVFs with CVD; 2.58% for dAVFs with CVD and aggressive presentation; and 0% for dAVFs with CVD and benign presentation. The post-GKRS hemorrhage rate for dAVFs with CVD and hemorrhagic or NHND presentations were 0.93% and 6.36%, respectively. Of patients who presented with NHND, post-GKRS hemorrhage rates for those with seizures or neurological deficits were 40% and 2.38%, respectively. Of the 4 patients who suffered post-GKRS hemorrhage, only 1 initially presented with hemorrhage. Borden grades and Cognard classes for the post-GKRS hemorrhagic dAVFs were 2, 2, 2, and 3 and IIa+b, IIa+b, IIa+b, and III, respectively. Times from GKRS to hemorrhage were 9, 10, 11, and 35 months. The locations of the dAVFs that bled were all different (anterior fossa, middle fossa, tentorial, and torcula).

Predictors of post-GKRS hemorrhage are shown in Table 4. In the univariate analysis, younger age, NHND presentation, history of seizures, and dAVF with CVD and retrograde drainage into a normal vein were predictive of post-GKRS hemorrhage. In the multivariate analysis, NHND presentation and increasing number of past endovascular treatments were significant independent predictors of post-GKRS hemorrhage (i.e., with each additional past endovascular treatment, the risk of post-GKRS hemorrhage increased). Three of 4 post-GKRS hemorrhagic dAVFs had past endovascular treatments, 2 of which had multiple past treatments. The annual rates of post-GKRS hemorrhage for patients with and without prior endovascular treatments were 1.25% and 0.42% over 238 and 235 years, respectively. None of the post-GKRS hemorrhagic dAVFs had venous ectasia; therefore, hazard ratios for venous ectasia could not be calculated.

Discussion

In our retrospective review of 147 GKRS-treated DAVFs, we intended to assess pre-GKRS hemorrhage incidence and post-GKRS hemorrhage rates while identifying associated risk factors. A quarter of our cohort presented with hemorrhage. dAVFs with any CVD or located in the convexity or torcula were more likely to present with hemorrhage. Only 4 patients suffered post-GKRS hemorrhage, resulting in an annual post-GKRS hemorrhage rate of 0.84%. NHND presentation and increasing number of past endovascular treatments were predictive of post-GKRS hemorrhage.

We found that dAVFs with any CVD were more likely to present with hemorrhage, which is concordant with the literature.[2,4,5,12,34] Additional previously identified hemorrhage risk factors include variceal or aneurysmal venous dilations and galenic drainage.[2] Diverging from the literature, venous ectasia was not a predictor of hemorrhagic presentation in our cohort.[2,6] Della Pepa et al. performed a detailed analysis of dAVF angioarchitecture with regard to clinical presentation. Similar to other studies, they observed that dAVFs with CVD had 3 equally distributed clinical presentations: benign, hemorrhagic, and NHND.[13,42,48] They postulated that commonly used dAVF-classification hemorrhage risk factors, CVD and venous ectasia, are insufficient due to their inconsistent determination of venous leptomeningeal hypertension and the variability of venous anastomotic networks.[47] Among dAVFs with CVD, they found that dAVFs with a double-thrombosed dural sinus and venous aneurysms were most likely to present with hemorrhage, concluding that these pathological features were concurrent with higher venous strain. In our cohort, we observed that dAVFs with CVD presented similarly: 41% benign, 23% aggressive, and 35% hemorrhagic. These variable venous drainage patterns may explain why the literature reports different hemorrhagic risks associated with venous ectasia.[6] Unfortunately, the angioarchitecture variables assessed by Della Pepa et al. were unavailable by centers participating in our study.

We also observed that dAVFs located in the convexity or torcula were more likely to present with hemorrhage compared to those in other locations. There have been inconsistent reports regarding dAVF location and hemorrhage risk. In a retrospective review of 236 dAVFs, Li et al. found that convexity-based dAVFs were associated with hemorrhagic presentation in their univariate model ($p = 0.0001$); however, significance disappeared in the multivariate model.[28] Similar univariate-to-multivariate elimination of lesion location significance has occurred in other studies; however, few studies included detailed dAVF locations, such as the torcula.[33]

Unlike cerebral AVMs, which are likely present since birth, dAVFs may more commonly arise during one's life-time.[8] Popular theories regarding dAVF formation include venous stasis or angiogenic growth.[2,8,23] Since the timing of dAVF formation is uncertain, knowledge concerning their natural history remains limited. van Dijk et al. followed 20 patients with persistent dAVFs with CVD, 6 who underwent partial treatment and 14 who refused treatment, and they observed an annual risk of hemorrhage of 8.1% over 86.9 patient-years.[45] Attempting to circumvent small sample size limitations, Söderman et al. analyzed the risk of hemorrhage in patients from angiographic diagnosis until treatment, observing an annual risk of hemorrhage of 7.4% for patients who previously presented with

hemorrhage and 1.5% for those without a hemorrhagic presentation; however, their analysis was limited by the short average diagnosis-to-treatment time of 0.6 years.[40,46] In a meta-analysis of the literature, Borden grades 1, 2, and 3 were reported to have an annual hemorrhage risk of 0%, 6%, and 10% respectively.[21] More recently, Gross et al. retrospectively aggregated multiinstitutional data of dAVF patients with at least 1 month of untreated follow-up. They found that Cognard class I, asymptomatic Cognard class II–IV, NHND presenting Cognard class II–IV status, and hemorrhagic Cognard class II–IV dAVFs had 0%, 2.9%, 3.3%, and 46.2% annual hemorrhage rates, respectively.[19] These studies show that the natural dAVF hemorrhage risk is lowest for Borden grade 1 dAVFs and highest for Borden class II/III dAVFs with history of hemorrhage.[37] Similar to reported rates, 36 patients (24.5%) in our cohort presented with hemorrhage.[28,33] However, since over half our patients had prior treatment and the date of initial angiography-confirmed diagnosis was unknown, we were unable to calculate the natural annual risk of dAVF hemorrhage. The Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) investigators have compiled a 1000-patient dAVF database, aiming to expand the current knowledge regarding dAVF natural history while avoiding the limitations that exist in the current literature.

In past dAVF radiosurgical series (Table 5),[3,7,8,14,17, 22,24–27,29–32,35,39,43,44] investigators have observed a posttreatment hemorrhage risk similar to the natural risk of hemorrhage, often assuming that posttreatment risk is synonymous with the natural risk until GKRS obliteration is achieved.[39] As previously discussed, Söderman et al. reported a distinct pretreatment risk of hemorrhage for unruptured (1.5%) and ruptured (7.4%) dAVFs with CVD.[40] Our annual post-GKRS hemorrhage rate for unruptured dAVFs with CVD (1.5%) was similar to the pretreatment risk of these lesions reported by Söderman et al. However, our annual post-GKRS hemorrhage rate for ruptured dAVFs with CVD was significantly less (0.93%) than the reported rates (7.4%–42.6%).[37] This discrepancy between the reported pretreatment hemorrhage risk and our observed post-GKRS hemorrhage risk suggests that post-GKRS hemorrhage risk factors may differ from natural hemorrhage risk factors. To our knowledge, this is the first study to assess for predictors of post-GKRS dAVF hemorrhage. Compared to reported natural history Borden grade 2–3 rebleed rates, our post-GKRS hemorrhage rate was lower (0.93% vs 7.4%, 46.2%, and 46%) implying that GKRS may have a protective effect on hemorrhagic dAVFs.[19,20,40] This effect was not observed in dAVFs with NHND presentation, with an observed post-GKRS hemorrhage rate of 6.4%, which is higher than the reported pretreatment hemorrhage rates (3.3%).[37] We found that NHND presentation was an independent predictor of post-GKRS hemorrhage. Interestingly, when stratified by type of NHND, seizure, or neurological deficit, patients presenting with seizure had a high annual post-GKRS hemorrhage rate compared to those presenting with NHNH–neurological deficits (40% vs 2.3%). This suggests that there may be unequal venous strain or venous compliance between patients with varying NHND presentations, warranting further investigation.

We also observed post-GKRS that increasing number of past endovascular treatments was an independent predictor of post-GKRS hemorrhage. The mechanism behind GKRS and dAVF obliteration is likely similar to AVM GKRS obliteration: endothelial cell damage followed intimal layer thickening, hyaline transformation, and eventual luminal closure.[36] We

hypothesize that during GKRS-induced luminal narrowing, increasing amounts of past embolic material may temporarily heighten venous strain, increasing the risk of hemorrhage during the latent period. All 4 post-GKRS hemorrhagic dAVFs initially presented with CVD, which has been identified as a pretreatment hemorrhage risk factor.[9] We were unable to assess the hazards associated with venous ectasia due to statistical limitations. Interestingly, we observed that none of the dAVFs with venous ectasia hemorrhaged following GKRS. Perhaps during the obliteration process, the pre-existing venous ectasia, normally subjected to higher flow and increased strain, acts as a venous reserve and protects against hemorrhage. Additionally, the fistulous point may also be easier to target in these lesions. It would be interesting to see if these observations remain true in other dAVF series that report post-GKRS hemorrhage (Table 5).[24] Of the studies listed in Table 5, only 1 reported an annual post-GKRS hemorrhage risk of 3.3% for Borden grade 2–3 dAVFs.[7]

A total of 4 patients suffered post-GKRS hemorrhage, averaging an overall annual post-GKRS hemorrhage rate of 0.84% and 1.45% for those with CVD. Tonetti et al. reported a 0% incidence of post-GKRS hemorrhage in dAVFs with CVD and a nonaggressive presentation (no neurological deficit, seizure, or hemorrhage).[44] All 4 of our post-GKRS hemorrhages presented aggressively, further validating their conclusion that dAVFs with CVD and nonaggressive presentation are safe to treat with radiosurgery.

Limitations

Our study has the limitations inherent to retrospective analysis and multicenter collaboration, including selection and follow-up biases. Obliteration was determined by a nonblinded radiologist at the central site. The date of original diagnosis was not available for many patients; thus, we were unable to precisely calculate the annual risk of hemorrhage prior to treatment. Additionally, we used the time until image confirmed obliteration to calculate annual post-GKRS hemorrhage rates. Since the nidi should have been obliterated before the final imaging studies, our post-GKRS hemorrhage rates may be underestimated. Many patients had follow-up MRI rather than standard angiography. Ten patients (6.8%) were lost to follow-up and may have experienced treatment-related hemorrhage.

GKRS for dAVFs is often pursued in patients who cannot tolerate other treatment modalities or as adjunctive therapy to endovascular embolization; therefore, our cohort may not accurately represent all dAVFs.[22] The calculated predictors for hemorrhagic presentation apply to patients recommended for GKRS. It is important to note that many of our patients had received prior treatment; therefore, these predictors may not agree with the natural dAVF hemorrhage predictors prior to treatment. Select patient data contained herein were published in prior single-center studies, but all data were updated as part of the current study.[7,8,26,43,44]

Conclusions

Until obliteration is achieved, dAVF patients have a similar rate of hemorrhage before and after GKRS. dAVFs with any CVD or those located in the convexity or torcula were more

likely to present with hemorrhage. Patients presenting with NHNDs and a history of endovascular treatments had higher risks of post-GKRS hemorrhage.

ABBREVIATIONS

AVM	arteriovenous malformation
CVD	cortical venous drainage
dAVF	dural arteriovenous fistula
GKRS	Gamma Knife radiosurgery
NHND	nonhemorrhagic neural deficit

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TABLE 1.

Summary of patient and dAVF features overall and by hemorrhagic presentation

Variable	All (n = 147)	Hemorrhagic (n = 36)	Nonhemorrhagic (n = 111)
Age (mean ± SD)	56 ± 14	55 ± 12	56 ± 14
Female	61 (41.5)	11 (30.6)	50 (45.1)
Prior treatment for dAVF	73 (49.7)	18 (50.0)	55 (49.6)
Any endovascular	66 (44.9)	15 (41.7)	51 (46.0)
Endovasc ≥2 times	26 (17.7)	8 (22.2)	18 (16.2)
Craniotomy	8 (5.4)	4 (11.1)	4 (3.6)
SRS *	5 (3.7)	2 (5.6)	3 (2.7)
Patient presenting Sxs			
Headache	76 (51.7)	32 (88.9)	44 (39.6)
Tinnitus	47 (32.0)	1 (2.8)	46 (41.4)
Visual changes	29 (19.7)	5 (13.9)	24 (21.6)
Asymptomatic	14 (9.5)	2 (5.6)	12 (10.8)
NHNDs	29 (19.7)	0 (0.0)	29 (19.7)
Neurological deficit	31 (21.1)	10 (27.8)	21 (18.9)
Seizures	10 (6.8)	2 (5.6)	8 (7.2)
Spinal drainage	27 (19.9)	11 (30.6)	16 (14.4)
Associated edema	14 (8.8)	7 (19.4)	7 (6.3)
Multihole dAVF	55 (37.4)	13 (36.1)	42 (37.8)
Any cort venous drainage	78 (53.1)	28 (77.8)	50 (45.1)
Venous ectasia	36 (24.5)	13 (36.1)	16 (14.4)
Maximum dAVF diameter *			
Small (≤10 mm)	24 (24.0)	6 (16.7)	18 (16.2)
Medium (11–20 mm)	45 (45.0)	11 (30.6)	34 (30.6)
Large (>20 mm)	31 (31.0)	8 (22.2)	23 (20.7)
Location of dAVF			
Transverse/sigmoid	52 (35.4)	9 (25.0)	43 (38.7)
Tentorial	40 (27.2)	12 (33.3)	28 (25.2)
Carotid cavernous	21 (14.3)	3 (8.3)	18 (16.2)
Torcular	12 (8.2)	6 (16.7)	6 (5.4)
Anterior fossa	12 (8.2)	3 (8.3)	9 (8.1)
Convexity	10 (6.8)	5 (13.8)	5 (4.5)
Sagittal	8 (5.4)	3 (8.3)	5 (4.5)
Middle fossa	7 (4.8)	1 (2.8)	6 (5.4)
Borden grade *			
1	49 (35.8)	5 (15.2)	44 (42.3)
2	32 (23.4)	8 (24.3)	24 (23.1)

Variable	All (n = 147)	Hemorrhagic (n = 36)	Nonhemorrhagic (n = 111)
3	56 (40.9)	20 (60.6)	26 (34.6)
Cognard classification *			
I	42 (30.9)	4 (12.1)	38 (36.9)
IIa	10 (7.4)	1 (3.0)	9 (8.7)
IIb	11 (8.1)	2 (6.1)	9 (8.7)
IIab	10 (7.4)	3 (9.1)	7 (6.8)
III	8 (5.9)	3 (9.1)	5 (4.9)
IV	28 (20.6)	9 (27.3)	19 (18.5)
V	27 (19.9)	11 (33.3)	16 (15.5)

Cort = cortical; endovasc = endovascular; SRS = stereotactic radiosurgery; Sxs = symptoms.

Unless stated otherwise, data are presented as the number (%) of patients.

* Data only available for a portion of total patients (percentage of available patients shown).

TABLE 2.

Univariate and multivariate analyses for predictors of dAVFs presenting with hemorrhage

	Univariate			Multivariate		
Factor	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Male sex	1.89	0.56–4.23	0.119	NS	NS	NS
Borden grade	2.13	1.29–3.52	0.003	—	—	—
Modified Borden grade	1.84	1.38–2.46	<0.001	—	—	—
Cognard classification	1.36	1.13–1.64	0.001	—	—	—
Cortical venous reflux	2.58	1.16–5.75	0.020	NS	NS	NS
Any CVD	4.27	1.79–10.2	0.001	3.81	1.57–9.25	0.003
Spinal drainage	2.71	1.11–6.68	0.029	NS	NS	NS
Associated edema	3.59	1.16–11.1	0.026	NS	NS	NS
Venous ectasia	2.16	0.95–4.91	0.065	NS	NS	NS
Not transverse/sigmoid location	1.90	0.81–4.42	0.138	NS	NS	NS
Convexity or torcula location	4.00	1.56–10.3	0.004	3.29	1.23–8.81	0.017

NS = not significant in multivariate analysis; — = ranking classifications not entered in multivariate analyses.

Univariate factors with $p < 0.15$ are listed in the multivariate analysis.

TABLE 3.

Post-GKRS dAVF hemorrhage rates

dAVF Feature	Post-GKRS Hemorrhage Rate	Yrs at Risk
All dAVFs	0.84%	474
All dAVFs presenting w/ hemorrhage	0.69%	144
Borden grade 2–3 (CVD) dAVF	1.45%	275
Borden grade 2–3 w/ aggressive presentation	2.58%	155
Borden grade 2–3 w/ hemorrhagic presentation	0.93%	107
Borden grade 2–3 w/ NHND presentation	6.36%	47
NHND as seizure	40.0%	5
NHND as only neurological deficits	2.38%	42
Borden grade 2–3 w/ benign presentation	0%	131

TABLE 4.

Univariate and multivariate analyses for predictors of post-GKRS dAVF hemorrhage

	Univariate			Multivariate		
Factor	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Younger age	1.06	1.00–1.12	0.047	NS	NS	NS
Presenting w/ NHND	11.3	1.18–109	0.036	21.6	1.19–110	0.027
Presenting w/ seizure*	11.5	1.61–81.5	0.015	*	*	*
CVD & retrograde sinus drainage	10.7	1.11–102	0.040	—	—	—
Borden grade	1.34	0.42–4.28	0.621	—	—	—
Modified Borden grade	1.32	0.71–2.48	0.384	—	—	—
Cognard classification	0.85	0.47–1.30	0.470	—	—	—
Middle fossa location	5.61	0.58–54.0	0.136	NS	NS	NS
Increasing past endovascular treatments	1.42	0.92–2.23	0.116	1.81	1.04–3.15	0.036
Prior surgery	6.35	0.66–61.1	0.109	NS	NS	NS

Univariate factors with $p < 0.15$ are listed in the multivariate analysis.

*Excluded from multivariate due to inclusion in NHND.

TABLE 5.

Single-institution series of radiosurgery-treated dAVFs

Authors & Year	No. of dAVFs	Type of dAVF	Hemorrhagic Presentation	Post-GKRS Hemorrhage
Lewis et al., 1994	9	Tentorial	5 (55)	0 (0)
Barcia-Salorio et al., 1994	25	CCF	0 (0)	0 (0)
Link et al., 1996	29	All	5 (17)	0 (0)
Pollock et al., 1999	20	CCF	0 (0)	0 (0)
Friedman et al., 2001	25	Transverse/sigmoid sinus	2 (8)	0 (0)
O'Leary et al., 2002	17	All	10 (59)	0 (0)
Koebbe et al., 2005	23	All	3 (13)	0 (0)
Söderman et al., 2006	58	All	22 (38)	2 (3)
Cifarelli et al., 2010	55	All	20 (36)	3 (5)
Jung et al., 2010	5	CCF	0 (0)	0 (0)
Hanakita et al., 2012	22	All	6 (27)	0 (0)
Gross et al., 2012	9	All	4 (44)	0 (0)
Pan et al., 2013	321	All	23 (7)	1 (0.3)
Park et al., 2016	20	All	1 (5)	0 (0)
Dmytriw et al., 2017	16	All	3 (19)	0 (0)
Tonetti et al., 2017	19	dAVF w/o CVR	0 (0)	0 (0)
Chen et al., 2018	21	dAVF w/ CVR	8 (38)	3 (14)
Tonetti et al., 2018	42	dAVF w/ CVR	23 (55)	1 (2)

CCF = carotid cavernous fistula; CVR = cortical venous reflux.

Values are presented as the number (%) of cases.