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A Propensity Score–Matched Cohort Analysis of Outcomes After Stereotactic Radiosurgery in Older versus Younger Patients with Dural Arteriovenous Fistula: An International Multicenter Study

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Abstract

OBJECTIVE: This study aims to evaluate the outcomes of Gamma Knife stereotactic radiosurgery (SRS) for dural arteriovenous fistulas (dAVFs) in older patients (≥ 65 years) compared with younger patients (age <65 years).

METHODS: Two groups with a total of 96 patients were selected from a database of 133 patients with dAVF from 9 international medical centers with a minimum 6 months follow-up. A 1:2 propensity matching was performed by nearest-neighbor matching criteria based on sex, Borden grade, maximum radiation dose given, and location. The older cohort consisted of 32 patients and the younger cohort consisted of 64 patients. The mean overall follow-up in the combined cohort was 42.4 months (range, 6–210 months).

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RESULTS: In the older cohort, a transverse sinus location was found to significantly predict dAVF obliteration ($P=0.01$). The post-SRS actuarial 3-year and 5-year obliteration rates were 47.7% and 78%, respectively. There were no cases of post-SRS hemorrhage. In the younger cohort, the cavernous sinus location was found to significantly predict obliteration ($P=0.005$). The 3-year and 5-year actuarial obliteration rates were 56% and 70%, respectively. Five patients (7.8%) hemorrhaged after SRS. Margin dose 25 Gy was predictive of unfavorable outcome. The obliteration rate ($P=0.3$), post-SRS hemorrhage rate ($P=0.16$), and persistent symptoms after SRS ($P=0.83$) were not statistically different between the 2 groups.

CONCLUSIONS: SRS achieves obliteration in most older patients with dAVF, with an acceptable rate of complication. There was no increased risk of postradiosurgery complications in the older cohort compared with the younger patients.

Keywords

Arteriovenous; Dural; Fistula; Gamma Knife; Older; Radiosurgery; Stereotactic radiosurgery

INTRODUCTION

It is estimated by the U.S. Census Bureau report (2018) that by 2035 there will be 70.8 million older people (>65 years) and for the first time in the history, the older population is projected to outnumber the population of children.¹ Older patients present several challenges in the management of dural arteriovenous fistula (dAVF) compared with younger cohorts. The presence of medical comorbidities, difficult vascular access, and impaired renal function may limit the use of endovascular and surgical treatment options, and in patients with more comorbidities and/or frailty, stereotactic radiosurgery (SRS) has been advocated in the management of dAVF.²

SRS plays an important role in this patient population. SRS has been found useful in treating recurrences or residual dural arteriovenous malformations.^{3–5} In other instances, upfront SRS can be used in selected patients with dAVFs who are not candidates for embolization or surgery. This study aims to evaluate the outcomes of SRS of dAVFs in patients aged 65 years and make comparisons with the younger cohort aged <65 years.

METHODS

Patient Selection

This is a 9-center international multicenter retrospective institutional review board–approved study that reviewed patients who underwent SRS for dAVFs between 1988 and 2016. A common formatted data spreadsheet was formulated containing variables about clinical data. This spreadsheet was sent to all the participating medical centers. Verified de-identified data were collected from the institutions and combined. Any questions or inadequate data were queried back to the participating institutions and clarified. The final datasheet consisted of 133 patients with DAVF with a minimum of 6 months follow-up. The 9 participating centers and the number of patients from each center are University of Virginia (33 patients), University of Pennsylvania (9 patients), Charles University, Prague (16 patients), Université de Sherbrook (1 patient), University of Beaumont (1 patient), University of Manitoba (1

patient), University of Pittsburgh (29 patients), University of West Virginia (2 patients), and Yale University (4 patients). From this data set, 1:2 propensity score matching was performed and 32 older patients aged ≥ 65 years and 64 younger patients aged <65 years were selected and matched for sex, Borden grade, maximum radiation dose, presence of cortical venous reflux (CVR), and location (Figure 1). The cavernous sinus location was chosen as a matching criterion because such dAVFs have been shown to have superior obliteration rates compared with dAVFs in other locations.^{6,7} Failure to match for this variable introduces a potential bias toward better obliteration rate in the group having more dAVFs in the cavernous sinus.

Clinical Assessment, Details of Radiosurgery Treatment, and Follow-Up

Clinical characteristics such as age, sex, presenting symptoms, location, previous history of treatment if any, Borden grade, Cognard grade, angiographic characteristics, treatment details, obliteration rates, and complications were collected and analyzed. The radiosurgery technique has been previously described.³ Radiosurgery was performed using various Gamma Knife models (U, B, C, 4C, Perfexion, or Icon [Elekta, Stockholm, Sweden]) depending on the available technology at the time of treatment. A stereotactic frame was placed with the patient under local anesthesia and sedation. Magnetic resonance imaging (MRI) and cerebral angiography were performed for nidus definition and planning of dose. Treatment was planned by a team of neurosurgeons, a radiation oncologist, and a medical physicist. For clinical and radiologic assessments, patients were typically followed up in their respective medical centers at 6-monthly intervals for the first 2 years and thereafter at yearly intervals after SRS. The images were reviewed by the local treating team. During the follow-up, patients were evaluated with MRI or contrast computed tomography. If the MRI or contrast computed tomography showed evidence of obliteration of dAVF, then, patients underwent angiography for confirmation of obliteration. Long-term follow-up was carried out with MRI even after obliteration to look for radiation-induced changes.

Favorable response was defined as 1) complete obliteration of dAVF, 2) no permanent radiation adverse effects, and 3) no episodes of post-SRS hemorrhage.

Unfavorable outcomes were defined as 1) failure of obliteration of dAVF, and/or 2) occurrence of permanent radiation adverse effect, and/or 3) occurrence of post-SRS hemorrhage.

Statistical Analysis

A Shapiro-Wilk test was used to assess the normality of data and nonparametric data were analyzed using median and range. Patients aged ≥ 65 years were identified and matched with younger patients using the propensity score matching using nearest-neighbor criterion with a 1:2 ratio and appropriate caliper settings.⁸ There was no statistically significant difference between the 2 groups in sex, Borden grade, maximum radiation dose, proportion of patients having CVR, and cavernous location (Table 1). The proportions and median values between the 2 groups were compared using the Mann-Whitney U test and χ^2 tests. The factors affecting the obliteration rates were analyzed using the Cox proportional hazards model. Univariate analysis was first performed. Factors that predicted obliteration with a P value

<0.15 were analyzed with multivariate analysis and hazard ratios were calculated. Unfavorable outcomes were evaluated with binary logistic regression analysis in univariate and multivariate settings. The statistical analysis was carried out with SPSS version 25 (IBM Corp., Armonk, New York, USA) with R essential package for SPSS (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and Clinical Features

After 1:2 propensity score-based matching, 2 groups were delineated. The older cohort group included 32 patients and the younger cohort consisted of 64 patients. In the older group, the median age of patients was 70 years (range, 66–80 years). There were 14 men and 18 women. The presenting symptoms were headaches in 9 patients (28.1%), tinnitus in 11 (34.4%), visual disturbance in 9 (28.1%), seizures in 2 (6.3%), neurologic deficit in 7 (21.9%), and intracerebral hemorrhage in 4 (12.5%).

In the younger cohort, there were 31 males and 33 females. The median age was 54 years (range, 12–65 years). There was a statistically significant difference between the mean age of the 2 cohorts ($P < 0.00001$). dAVF were found incidentally in 10 patients (15.6%). The presenting symptoms were headaches in 23 patients (35.9%), tinnitus in 18 (28.1%), visual disturbance in 16 (25%), and seizures in 9 (14.1%). Thirteen patients (20.3%) presented with intracerebral hemorrhage. Neurologic deficit was found in 16 (25%) at presentation (Table 1).

Angiographic Features and Treatment Details

In the older group, Borden grade I was the most common type of dAVF which was observed in 15 (46.9%) of the cases. Borden grades II and III were seen in 6 patients (18.8%) and 8 patients (25%), respectively. Using the Cognard classification, type I was the most common ($n = 15$, 51.7%) (Table 1). CVR drainage was seen in 10 patients (31.3%). Antegrade and retrograde venous drainage was seen in 18 patients (56.3%) and 7 patients (21.9%), respectively. Four patients (12.5%) had venous ectasia. Five patients (15.6%) had spinal drainage from the dAVF. No patient in the older group had associated aneurysm. The median maximum diameter of the lesion was 14.5 mm (range, 1.5–33 mm). Transverse sinus and tentorial were the most common location of dAVF and were seen in equal proportions (31.3%). Cavernous location was seen in 6 patients (18.8%). The median maximum dose given was 40 Gy (range, 18–50 Gy) and the median margin dose was 20.5 Gy (range, 14–25.6 Gy) delivered in a single fraction. Fifteen patients (46.9%) received SRS after a previous endovascular treatment. One patient had undergone surgical resection in addition to endovascular treatment before the SRS. Seventeen patients received upfront SRS in this cohort. In the age <65 years cohort, 23 patients (35.9%) had undergone a pre-SRS endovascular procedure and 2 patients had undergone a previous surgical resection in addition to endovascular treatment. A further 2 patients had undergone surgery only before undergoing SRS. Thirty-nine patients (60.9%) had undergone upfront SRS in this cohort.

In the younger group, Borden grades I, II, and III were seen in 26 patients (40.6%), 15 patients (23.4%) and 17 patients (26.6%), respectively. The median maximum diameter of the dAVF was 8.1 (range 0.5–60 mm). CVR was seen in 26 patients (40.6%). Anterograde and retrograde venous drainage were observed in 31 patients (48.4%) and 15 patients (23.4%), respectively. Ten patients (17.5%) had spinal drainage. Four (6.3%) had an associated aneurysm. The tentorium was the most common location (29.7%). The median margin dose given was 22 Gy (range, 9–33 Gy). Four patients had undergone pre-SRS surgical resection of dAVF and 23 (35.9%) had received a previous endovascular treatment. Upfront SRS was given to 39 patients (60.9%).

dAVF Obliteration

In the older cohort, obliteration of dAVF was achieved in 20 patients (62.5%) at last follow-up. The 3-year and 5-year obliteration rates were 47.7% and 78%, respectively. In the younger cohort, obliteration was confirmed in 34 patients (53.1%). The 3-year and 5-year cumulative obliteration rates in this group were 56% and 70%, respectively. Kaplan-Meier analysis showed no statistically significant difference in the obliteration rates seen in the 2 cohorts (log-rank $P = 0.30$) (Figure 2A). Several factors such as presence of CVR, presence of venous ectasia, previous intracerebral bleed, presence of spinal drainage, and margin dose were analyzed using the Cox proportional hazard model for predicting obliteration rate. In the older cohort, a transverse sinus location was found to significantly predict dAVF obliteration both in the univariate and in the multivariate setting (multivariate analysis: $P = 0.01$; hazard ratio [HR], 4.531; 95% confidence interval [CI], 1.296–15.84). The Borden grade, presence of CVR or spinal drainage, cavernous location, margin dose, and previous history of bleed did not predict obliteration rate in univariate analysis. Previous endovascular treatment did not adversely affect post-SRS obliteration rate in the older group ($P = 0.51$) (Figure 2B).

In the younger cohort, Borden grade, CVR, spinal drainage, and low Cognard grade were found to be significant in univariate analysis for obliteration but did not reach statistical significance in the multivariate analysis (Table 2). Cavernous location predicted obliteration in both univariate and multivariate analysis (multivariate $P = 0.005$; HR, 3.16; 95% CI, 1.416–7.063) for the younger cohort (Table 2).

Upfront SRS

In the elderly group, upfront SRS was delivered to 17 patients (53.1%). 64.3% were of Borden type I, 7.1% were type II and 28.6% were type III. Three patients (17.6%), 2 patients (11.7%), 2 patients (11.7%) and 4 patients (23.5%) had CVR, venous ectasia, spinal drainage, and neurodeficits, respectively, in this subcohort. The lesions were located in tentorium in 6 patients (35%), cavernous sinus in 5 patients (29.4%), and transverse sinus in 2 patients (11.7%). Ten patients (58.8%) achieved complete obliteration. The 3-year actuarial obliteration rate in this subgroup was 62%. No patient developed post-SRS bleed. The median time to obliteration was 32.5 months. Two patients (11.7%) developed permanent radiation injury and both these patients achieved dAVF obliteration. Logistic regression analysis showed that presence of low Borden grade (univariate $P = 0.94$; HR, 0.933; 95% CI, 0.111–7.820) and presence of CVR (univariate $P = 0.762$; HR, 1.5; 95% CI,

0.109–20.6) did not predict the obliteration rate of dAVFs when upfront SRS was given in the older patients.

In the younger cohort, 39 patients (60.9%) received upfront SRS. Of these patients, 22 (56.4%) achieved obliteration; 60.6%, 27.3%, and 12.1% patients were classified as Borden grade I, II, and III respectively. CVR was observed in 10 patients (25.6%). The tentorium was the most common location (33.3%) followed by cavernous location (25.6%). The 3-year actuarial obliteration rate in this cohort was 60%. No patient developed post-SRS hemorrhage. Median time to obliteration was 20 months. Three patients (7.69%) developed permanent radiation adverse effects. Logistic regression analysis showed cavernous location predicted obliteration (univariate $P = 0.032$; HR, 11.0; 95% CI, 1.237–99.1) in this subgroup.

SRS as a Salvage Procedure After Failed Endovascular or Surgical Treatment

In the older cohort, 15 patients (46.9%) had failed a previous endovascular treatment before SRS. Of these patients, 8 (53.3%) showed a transverse sinus location and 4 (27%) a tentorial location. Six patients (40%) were classified with Borden type I. CVR was seen in 9 patients, 3 patients had spinal drainage, and venous ectasia was present in 2 patients. Ten patients (66.6%) achieved obliteration of the dAVF after salvage SRS. The median time to obliteration was 35 months (range, 6–133 months). No cases of post-SRS hemorrhage or radiation adverse events were noted after salvage SRS.

In the younger cohort, 23 patients (35.9%) had previous endovascular treatment and 2 patients had undergone surgical resection before SRS in addition to endovascular treatment. A further 2 patients had surgical resection only before SRS. Six patients were classified with Borden grade III. Eleven patients (47.8%) achieved complete obliteration after salvage SRS. No patient developed permanent radiation injury, and 4 (16%) developed post-SRS hemorrhage. Persistent symptoms were noted in 6 patients (26.1%).

Favorable Versus Unfavorable Outcomes

In the older cohort, no patients developed post-SRS hemorrhage or underwent repeat SRS. One patient underwent additional post-SRS embolization. Two patients (6.7%) developed permanent radiation-induced injury. Persistent symptoms at last follow-up were noted in 6 patients (18.8%). Twenty patients (62.5%) achieved post-SRS dAVF obliteration. An unfavorable outcome was seen in 14 patients (43.7%). Logistic regression analysis showed that presence of CVR, venous ectasia, spinal drainage, and margin dose ≥ 25 Gy did not predict unfavorable outcome.

In the younger group, cortical venous drainage and margin dose ≥ 25 Gy were predictive of unfavorable outcome in both univariate and multivariate analysis (Table 3). Five patients (7.8%) developed post-SRS hemorrhage. The median time to hemorrhage was 9 months (range, 9–35 months). Persistent symptoms were noted in 11 patients (17.1%). An unfavorable response was seen in 35 patients (54.6%) (Table 4).

The obliteration rate ($P = 0.30$), favorable outcome ($P = 0.3$), unfavorable outcome ($P = 0.31$), post-SRS hemorrhage rate ($P = 0.16$), and persistent symptoms at follow-up ($P = 0.83$) were not found to be statistically different between the 2 cohorts.

DISCUSSION

The clinical spectrum of dAVF is highly variable. dAVFs can be completely asymptomatic and undergo spontaneous obliteration or present with a life-threatening intracerebral hemorrhage. They can manifest with nonhemorrhagic neurologic deficits such as parkinsonism, dementia, or seizures.^{9,10} The older patient cohort presents with several issues with respect to management of dAVF. Significant advances in endovascular, surgical, and radiosurgical management have resulted in reasonable results in older patients. Embolization is a frequent treatment in many cases. Several studies have shown the safety of endovascular treatment of vascular diseases in older patients.^{11,12} Risks specifically related to age such as diffuse atherosclerosis, vessel tortuosity, coexistence of peripheral vascular disease, and renal failure may preclude the use of endovascular treatment in some patients. SRS is effective both in the setting of failed endovascular or surgical treatment and as an upfront treatment in selected cases. The multimodal treatment strategy for the treatment of dAVF is being increasingly accepted.^{4,13,14}

Factors Affecting Obliteration of dAVF

Classifying the patients into low risk and high risk based on the presence of CVR was reported to be a significant factor in deciding SRS treatment.^{15,16} Tonetti et al.¹⁶ suggested classifying the dAVF with CVR into aggressive and nonaggressive based on the presence of neurologic deficits and previous hemorrhage. The risk of hemorrhage is less with nonaggressive dAVFs.^{15,17} Van Dijk et al. in their study of 118 dAVFs with CVR followed up for a mean of 4.3 years found an annual mortality, annual hemorrhage rate, and annual nonhemorrhagic neurologic deficits rate of 10.4%, 8.1%, and 6.9%, respectively, giving an overall annual event rate of up to 15%.¹⁸ Söderman et al.¹⁹ found annual risk of hemorrhage from unruptured dAVF to be 1.5% and this increased to 7.4% per year in cases of dAVF that had previously bled. Gross et al.¹⁷ studied the natural history of dAVF with 409 lesion years of follow-up and found an annual bleeding rate of 0% in Borden grade I dAVFs. The annual hemorrhage risk increased to 6% and 10% for Borden grade II and III dAVFs. We classified the patients into low Borden grade, which included Borden grade I without CVR, and high Borden grade, consisting of grade II and grade III cases.

In the older cohort, using the Cox proportional hazards model, low Borden grade (without CVR) did not affect obliteration in this cohort. Older patients may have a favorable response to SRS, even those with CVR and aggressive disease. Further studies with more cases are required to validate this outcome in older patients. Other factors such as margin dose, history of previous bleed, spinal drainage, low Cognard grade, and venous ectasia were not predictive of obliteration in the older cohort. In the younger group, low Borden grade, presence of CVR, and spinal drainage predicted obliteration in the univariate setting but failed to reach statistical significance in the multivariate analysis.

Location of dAVF and its Implications on Clinical Outcome

Our study found that in the older cohort, the transverse sinus location of dAVF positively predicted obliteration (Figure 3). We wanted to verify if a selection bias could be introduced by disproportionately more cases of dAVF in the transverse sinus location present in this cohort. However, the number of dAVFs in the transverse sinus location was equal to the number of lesions in the tentorial location in the older cohort (Table 1). Of patients with dAVF in the transverse sinus location, 70% were females, and 7/10 patients (70%) had tinnitus. We considered the possible reasons why the transverse sinus location had a favorable outcome. The size of the dAVF and margin dose were not different in this subgroup compared with other patients in the study. Of the patients with dAVF in the transverse sinus location, 50% had CVR and belonged to high Borden grade (grade II and III). Of the patients, 80% had previous endovascular treatment. Only 1 patient had a history of previous bleed. Symptom resolution was seen in 7 patients (70%) and no patient developed radiation adverse effects. Thus, female patients older than 65 years with dAVF in a transverse sinus location, no history of previous bleed, and a failed previous attempt of endovascular treatment had a favorable outcome with respect to obliteration of dAVF and symptom relief after SRS in the present study. Houser et al.²⁰ showed in their series of transverse sinus dAVFs that female patients older than 40 years were most often affected. Transverse sinus thrombosis/occlusion was shown to be responsible for formation of dAVFs by opening small arteriovenous connections present within the wall of the sinus.^{20,21} Whether these connections are physiologic and have opened up because of sinus hypertension or other cerebrovascular pathophysiology remains the subject of debate.^{22,23} Hamada et al.²² studied the histopathologic aspects of dAVFs in the transverse-sigmoid sinus region in 9 patients. These investigators found the small vessels averaging 30 μ m in the wall of the sinus that were the connecting vessels. They were unable to find normal physiologic connections in the sinus wall in 5 control patients. These investigators also showed in their rat model of dAVF creation that venous hypertension rather than thrombosis itself is important in the pathogenesis. The details of previous thrombosis or sinus occlusion are not available for the patients in the present study. Cavernous sinus location did not predict favorable outcome for obliteration in the older cohort treated with SRS. The obliteration rate in the cavernous location has been observed to be higher than in other locations.^{6,7}

In the younger cohort, a cavernous sinus location predicted dAVF obliteration both in univariate and in multivariate analysis (multivariate $P=0.005$). The difference in obliteration rate between the older and younger cohort based on the location of dAVF warrants further investigation. dAVFs in the tentorium and anterior cranial fossa locations are more prone to bleeding than are dAVFs in other locations.^{4,10,24} In our study, 50% of the hemorrhage events were from these 2 locations.

Salvage SRS After Failed Endovascular and Surgical Management: A Multimodality Approach

The treatment of dAVF has become multimodal and often achieves a reasonable success rate.^{4,14} SRS has been advocated for residual dAVF after embolization or surgery. Several series have described the sequential use of Gamma Knife with embolization to achieve

symptom relief and obliteration rates.^{4,6,25,26} The consideration of endovascular treatment in conjunction with radiosurgery lessens the risk of hemorrhage and provides early symptomatic relief, while the effects of radiation take effect.⁵ Radiosurgery aims to obliterate small vessels that cannot be embolized without risk of infarction or that are too small to be embolized.⁴ This study confirms the role of SRS in management of residual/recurrent disease after embolization or surgery in both younger and older cohorts. Such use of SRS after previous treatment may have been initially planned or unplanned in patients with dAVF. Multimodal treatment may be suited for older patients (Figure 4) particularly as a means of mitigating procedural risks. We also compared the outcomes between patients who received embolization before SRS and those who did not receive embolization. No difference was noted in the obliteration rates between the 2 groups ($P = 0.51$).

Upfront SRS

Endovascular or surgical treatment is the first-line option for treating dAVF. SRS may not be the initial treatment in some cases because early obliteration is essential to achieve symptom relief and reduce the risk of hemorrhage or nonhemorrhagic neurologic deficits.^{18,27} The reasons for giving upfront SRS include difficult vascular access for embolization, renal failure, medical comorbidities, and patient preference. Upfront SRS has been shown to achieve reasonable obliteration rates. Pan et al.⁶ described 11 of 20 patients with transverse sinus dAVF treated with upfront SRS and observed an overall obliteration rate of 58%. Guo et al.²⁸ described patients with low-flow dAVF in the cavernous location treated with SRS alone and showed an obliteration rate of 80%. Although upfront SRS is able to achieve obliteration in many patients, it does not reduce the risk of hemorrhage and cause symptom alleviation immediately. Therefore, the ideal candidates for upfront SRS are those without CVR with a low Borden grade and whose symptoms are negligible. Larger multicenter trials are required to characterize the important role of upfront SRS.

Justification and Limitations of the Study

This international multicenter study incorporates patients from varied geographic locations and helps to include more patients to increase the generalizability of the study. A multicenter study also helps to dilute confounding factors created because of genetic composition and environmental and other demographic factors. To our knowledge, this study is one of the largest series that addresses the outcomes of SRS in older patients with dAVFs. A matched multicenter analysis is hoped to reduce the effect of selection bias created as a result of unequal distribution of variables between the 2 groups and give a meaningful direction in management of this difficult disease in the aging population. The limitations of any retrospective study apply to this study. The low number of patients in the older cohort is an important limitation. However, the rarity of this disease requires that a meaningful conclusion be drawn from the available data. The median age of the younger group is 54 years and the median age of the older cohort is 70 years. The effect of age on the outcomes would be more appreciated if the median age difference between the 2 groups were wider. The follow-up period may not be sufficient to determine latent side effects from SRS or hemorrhages in patients with unobliterated dAVF. We have not matched the size of dAVF between the groups because these data were not consistently available in all cases. This factor could introduce a selection bias. The presence of CVR has been observed to be

important for the SRS outcomes in many studies.^{15,16} Variations in management algorithms and radiosurgical technologies between centers and within centers as function of time could introduce study bias. In the present study, both groups were matched for this variable and we do not expect this to bias the overall results.

CONCLUSIONS

The outcomes of SRS for comparable dAVFs in the older versus younger patients were not found to be significantly different. Thus, older age is not a contraindication to dAVF management with SRS. SRS achieves obliteration in most older patients with dAVF with an acceptable rate of complication. There was no increased risk of post-SRS complications in the older cohort compared with the younger patients.

Abbreviations and Acronyms

CI	Confidence interval
CVR	Cortical venous reflux
dAVF	Dural arteriovenous fistula
HR	Hazard ratio
ICH	Intracerebral hemorrhage
MRI	Magnetic resonance imaging
SRS	Stereotactic radiosurgery

REFERENCES

1. Vespa J Older People Projected to Outnumber Children. The United States Census Bureau Available at: <https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html>. Accessed September 17, 2018.
2. Zipfel GJ, Shah MN, Refai D, Dacey RG, Derdeyn CP. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. *Neurosurg Focus* 2009;26:E14. [PubMed: 19408992]
3. Cifarelli CP, Kaptain G, Yen C-P, Schlesinger D, Sheehan JP. Gamma Knife radiosurgery for dural arteriovenous fistulas. *Neurosurgery* 2010;67: 1230–1235 [discussion: 1235]. [PubMed: 20871448]
4. Lewis AI, Tomsick TA, Tew JM. Management of tentorial dural arteriovenous malformations: transarterial embolization combined with stereo-tactic radiation or surgery. *J Neurosurg* 1994;81: 851–859. [PubMed: 7965115]
5. Link MJ, Coffey RJ, Nichols DA, Gorman DA. The role of radiosurgery and particulate embolization in the treatment of dural arteriovenous fistulas. *J Neurosurg* 1996;84:804–809. [PubMed: 8622154]
6. Pan DH, Chung WY, Guo WY, et al. Stereotactic radiosurgery for the treatment of dural arteriovenous fistulas involving the transverse-sigmoid sinus. *J Neurosurg* 2002;96:823–829. [PubMed: 12005389]
7. Wu H-M, Pan DH, Chung WY, et al. Gamma Knife surgery for the management of intracranial dural arteriovenous fistulas. *J Neurosurg* 2006; 105(suppl):43–51. [PubMed: 18503329]
8. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci* 2010;25:1–21. [PubMed: 20871802]

9. Hurst RW, Bagley LJ, Galetta S, et al. Dementia resulting from dural arteriovenous fistulas: the pathologic findings of venous hypertensive encephalopathy. *AJNR Am J Neuroradiol* 1998;19: 1267–1273. [PubMed: 9726465]
10. Lasjaunias P, Chiu M, terBrugge K, Tolia A, Hurth M, Bernstein M. Neurological manifestations of intracranial dural arteriovenous malformations. *J Neurosurg* 1986;64:724–730. [PubMed: 3701421]
11. Falero RA, Piloto OL. Endovascular procedures in elderly patients. *AJNR Am J Neuroradiol* 2012;33: E129 [author reply E130]. [PubMed: 23019175]
12. Sturiale CL, Brinjikji W, Murad MH, Lanzino G. Endovascular treatment of intracranial aneurysms in elderly patients: a systematic review and meta-analysis. *Stroke* 2013;44:1897–1902. [PubMed: 23686977]
13. Lucas CP, Zabramski JM, Spetzler RF, Jacobowitz R. Treatment for intracranial dural arteriovenous malformations: a meta-analysis from the English language literature. *Neurosurgery* 1997;40:1119–1130 [discussion: 1130–1132]. [PubMed: 9179884]
14. Natarajan SK, Ghodke B, Kim LJ, Hallam DK, Britz GW, Sekhar LN. Multimodality treatment of intracranial dural arteriovenous fistulas in the Onyx era: a single center experience. *World Neurosurg* 2010;73:365–379. [PubMed: 20849795]
15. Strom RG, Botros JA, Refai D, et al. Cranial dural arteriovenous fistulae: asymptomatic cortical venous drainage portends less aggressive clinical course. *Neurosurgery* 2009;64:241–247 [discussion: 247–248].
16. Tonetti DA, Gross BA, Jankowitz BT, et al. Reconsidering an important subclass of high-risk dural arteriovenous fistulas for stereotactic radio-surgery [e-pub ahead of print]. *J Neurosurg* 2018: 1–5. 10.3171/2017.10.JNS171802.
17. Gross BA, Du R. The natural history of cerebral dural arteriovenous fistulae. *Neurosurgery* 2012;71: 594–602 [discussion: 602–603]. [PubMed: 22610384]
18. van Dijk JMC, terBrugge KG, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. *Stroke* 2002;33:1233–1236. [PubMed: 11988596]
19. Söderman M, Pavic L, Edner G, Holmin S, Andersson T. Natural history of dural arteriovenous shunts. *Stroke* 2008;39:1735–1739. [PubMed: 18388337]
20. Houser OW, Campbell JK, Campbell RJ, Sundt TM. Arteriovenous malformation affecting the transverse dural venous sinuses: acquired lesion. *Mayo Clin Proc* 1979;54:651–661. [PubMed: 480990]
21. Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. *Radiology* 1995;194:671–680. [PubMed: 7862961]
22. Hamada Y, Goto K, Inoue T, et al. Histopathological aspects of dural arteriovenous fistulas in the transverse-sigmoid sinus region in nine patients. *Neurosurgery* 1997;40:452–456 [discussion: 456–458]. [PubMed: 9055283]
23. Kerber CW, Newton TH. The macro and micro-vasculature of the dura mater. *Neuroradiology* 1973; 6:175–179. [PubMed: 4772438]
24. Awad IA, Little JR, Akrawi WP, Ahl J. Intracranial dural arteriovenous malformations: factors predisposing to an aggressive neurological course. *J Neurosurg* 1990;72:839–850. [PubMed: 2140125]
25. Friedman JA, Pollock BE, Nichols DA, Gorman DA, Foote RL, Stafford SL. Results of combined stereotactic radiosurgery and transarterial embolization for dural arteriovenous fistulas of the transverse and sigmoid sinuses. *J Neurosurg* 2001;94:886–891. [PubMed: 11409515]
26. Koebbe CJ, Singhal D, Sheehan J, et al. Radio-surgery for dural arteriovenous fistulas. *Surg Neurol* 2005;64:392–398 [discussion 398–399]. [PubMed: 16253680]
27. Duffau H, Lopes M, Janosevic V, et al. Early rebleeding from intracranial dural arteriovenous fistulas: report of 20 cases and review of the literature. *J Neurosurg* 1999;90:78–84. [PubMed: 10413159]
28. Guo WY, Pan DH, Wu HM, et al. Radiosurgery as a treatment alternative for dural arteriovenous fistulas of the cavernous sinus. *AJNR Am J Neuroradiol* 1998;19:1081–1087. [PubMed: 9672015]

Figure 1.

Thirty-two older patients aged 65 years and 64 younger patients aged <65 years were selected and matched for sex, Borden grade, maximum radiation dose, presence of cortical venous reflux, and location. dAVF, dural arteriovenous fistula; SRS, stereotactic radiosurgery.

Figure 2.

(A) Kaplan-Meier analysis showing no statistically significant difference in the obliteration rates seen in the 2 cohorts (log-rank $P = 0.30$). (B) The Borden grade, presence of cortical venous reflux or spinal drainage, cavernous location, margin dose, and previous history of bleed did not predict obliteration rate in univariate analysis. Previous endovascular treatment did not adversely affect poststereotactic radiosurgery obliteration rate in the older group ($P = 0.51$). GKRS, Gamma Knife radiosurgery.

Figure 3.
In the older cohort, the transverse sinus location of dural arteriovenous fistula positively predicted obliteration. GKRS, Gamma Knife radiosurgery.

Figure 4.

Multimodal treatment may be suited for older patients, particularly as a means of mitigating procedural risks. CVR, cortical venous reflux; dAVF, dural arteriovenous fistula; GKRS, Gamma Knife radiosurgery.

Table 1.

Comparison of Demographic Characteristics, Symptoms, Angiographic Characteristics, Location of Dural Arteriovenous Fistula, and Details of Treatment in the Age <65 Years Group and Age ≥ 65 Years Groups

Characteristics	Age <65 Years Group	Age ≥65 Years Group	P Value
Number of patients	32	64	—
Age (years), median (range)	70 (66–80)	54 (12–65)	<0.00001
Variables used in matching			
Sex, male/female (% male)	14:18 (43.8)	31:33 (51.6)	0.47
Borden grade I	15 (46.9)	26 (40.6)	0.55
Borden grade II	6 (18.8)	15 (23.4)	0.60
Borden grade III	8 (25)	17 (26.6)	0.86
Cavernous location	6 (18.8)	12 (18.8)	1.00
Maximum dose (Gy), mean ± standard deviation	40.3 ± 7.2	40.8 ± 6.3	0.72
Cortical venous reflux	10 (31.3)	26 (40.6)	0.37
Symptoms			
Headache	9 (28.1)	23 (35.9)	—
Tinnitus	11 (34.4)	18 (28.1)	—
Visual changes	9 (28.1)	16 (25)	—
Seizures	2 (6.3)	9 (14.1)	—
Neurologic deficit	7 (21.9)	16 (25)	—
Asymptomatic presentation	1 (3.1)	10 (15.6)	—
Presentation with intracerebral hemorrhage	4 (12.5)	13 (20.3)	—
Presence of intraventricular hemorrhage	0 (0)	5 (7.8)	—
Presence of subarachnoid hemorrhage	3 (9.4)	4 (6.3)	—
Angiogram characteristics			
Anterograde venous drainage	18 (56.35)	31 (48.4)	—
Retrograde venous drainage	7 (21.9)	15 (23.4)	—
Venous ectasia	4 (12.5)	12 (18.8)	—
Spinal drainage	5 (15.6)	10 (17.5)	—
Presence of aneurysm	0 (0)	4 (6.3)	—

Characteristics	Age	65 Years Group	Age <65 Years Group	P Value
Maximum diameter (mm), median (range)	14.5 (1.5—33)		8.1 (0.5—60)	—
Single hole	23 (71.9)		42 (65.6)	—
Multihole	9 (28.1)		22 (34.4)	—
Cognard type I	15 (51.7)		24 (42.1)	—
Cognard type IIa	1 (3.4)		7 (12.3)	—
Cognard type IIb	0 (0)		4 (7)	—
Cognard type IIa+b	4 (13.8)		2 (3.5)	—
Cognard type III	1 (3.4)		3 (5.3)	—
Cognard type IV	3 (10.3)		7 (12.3)	—
Cognard type V	5 (15.6)		10 (17.5)	—
Location				
Transverse sinus location	10 (31.3)		18 (28.1)	—
Cavernous location	6 (18.8)		12 (18.8)	—
Tentorial location	10 (31.3)		19 (29.7)	—
Torcula	2 (6.3)		3 (4.7)	—
Anterior fossa	1 (3.1)		6 (9.4)	—
Middle fossa	1 (3.1)		4 (6.3)	—
Convexity	1 (3.1)		6 (9.4)	—
Treatment characteristics				
Maximum dose (Gy), median (range)	40 (18–50)		40 (28–50)	—
Margin dose (Gy), median (range)	20.5 (14–25.6)		22 (9–33)	—
Previous resection	1 (3.1) [*]		4 (6.3) [†]	—
Previous Gamma Knife radiosurgery treatment	0		3 (4.7)	—
Previous endovascular treatment	15 (46.9)		23 (35.9)	—
Upfront Gamma Knife radiosurgery	17 (53.1)		39 (60.9)	

Values are number (%) except where indicated otherwise.

^{*} 1 patient had undergone previous endovascular treatment and surgery.

[†] 2 cases had previous endovascular treatment + surgical resection and 2 other patients had previous Gamma Knife radiosurgery + endovascular treatment.

Factors Predicting the Obliteration Rate in Dural Arteriovenous Fistula Treated with Gamma Knife Stereotactic Radiosurgery in Age 65 Years and 65 Years Groups Using the Cox Proportional Hazard Model

Table 2.

Variable	Univariate		Multivariate	
	P Value/Hazard Ratio/95% Confidence Interval	P Value/Hazard Ratio/95% Confidence Interval	P Value/Hazard Ratio/95% Confidence Interval	P Value/Hazard Ratio/95% Confidence Interval
Age 65 years group				
Low Borden grade (I)	0.62/0.792/0.312–2.015		—	
Presence of cortical venous reflux	0.34/0.864/0.421–2.804		—	
Previous intracerebral hemorrhage	0.13/0.194/0.026–1.475		NS	
Presence of spinal drainage	0.09/0.280/0.062–1.263		NS	
Cavernous location	0.81/0.885/0.314–2.495		—	
Margin dose	0.53/1.350/0.526–3.467		—	
Transverse sinus location	0.02/3.963/1.222–12.85		0.01/4.531/1.296–15.84	
Low Cognard grade (I and IIa)	0.59/0.751/0.265–2.128		—	
Age 65 years group				
Low Borden grade (I)	0.001/3.354/1.627–6.915		NS	
Presence of cortical venous reflux	0.01/0.383/0.175–0.840		—	
Previous intracerebral hemorrhage	0.09/0.437/0.167–1.144		—	
Presence of spinal drainage	0.05/0.352/0.121–1.028		—	
Cavernous location	0.011/3.608/1.635–7.960		0.005 3.16 1.416–7.063	
Margin dose	0.78/1.104/0.545–2.237		—	
Transverse sinus location	0.73/1.134/0.551–2.333		—	
Low Cognard grade (I and IIa)	0.004/3.154/1.457–6.825		NS	

Bold values denotes $P < 0.05$.

NS, not significant.

Table 3.

Factors Predicting Unfavorable Outcome in Dural Arteriovenous Fistula Treated with Gamma Knife Stereotactic Radiosurgery in the Age <65 Years Group, Age 65 Years Group, and the Combined Group Using Logistic Regression Analysis

Variable	Univariate		Multivariate	
	P Value/Hazard Ratio/95% Confidence Interval		P Value/Hazard Ratio/95% Confidence Interval	
Age 65 years group				
Presence of cortical venous reflux	0.66/0.696/0.139–3.498		—	
Presence of venous ectasia	0.11/7.125/0.640–79.2		—	
Previous intracerebral hemorrhage	0.52/2.000/0.241–16.61		—	
Presence of spinal drainage	0.16/4.250/0.566–31.9		—	
Margin dose 25 Gy	0.75/0.786/0.170–3.62		—	
Age <65 years				
Presence of cortical venous reflux	0.007/4.327/1.486–12.602		0.02/4.243/1.217–14.79	
Presence of venous ectasia	0.44/1.633/0.458–5.819		—	
Previous intracerebral hemorrhage	0.29/1.948/0.560–6.772		—	
Presence of spinal drainage	0.05/0.352/0.121–1.028		Not significant	
Margin dose 25 Gy	0.02/0.272/0.088–0.842		0.035/0.245/0.877–13.29	
Previous endovascular treatment	0.33/1.661/0.593–4.651		—	

Unfavorable outcome was defined as failure of obliteration of dural arteriovenous fistula or permanent radiation injury or post-Gamma Knife stereotactic radiosurgery hemorrhage.

Table 4.

Obliteration Rate, Complications, and Additional PostGamma Knife Stereotactic Radiosurgery Treatments in the Two Cohorts

Complication	Age 65 Years	Age 65 Years
Obliteration	20 (62.5)	34 (53.1)
Post-GK SRS hemorrhage	0 (0)	5 (7.8)
Time for post-GK SRS hemorrhage (months), median (range)	Not applicable	9 (9–35)
Persistent symptoms	6 (18.8)	11 (17.1)
Post-GK SRS endovascular treatment	1 (3.1)	8 (12.5)
Post-GK SRS surgical resection	0 (0)	0 (0)
Repeat GK SRS	0 (0)	1 (1.6)
Temporary radiation-induced change	0 (0)	1 (1.6)
Permanent radiation-induced change	2 (6.7)	4 (6.3)
Favorable outcome	18 (56.2)	29 (45.3)
Unfavorable outcome	14 (43.7)	35 (54.6)

Values are number (%) except where indicated otherwise.

GK SRS, Gamma Knife stereotactic radiosurgery.