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Combined endovascular embolization and stereotactic radiosurgery in the treatment of large arteriovenous malformations

Clinical article

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Object. Large cerebral arteriovenous malformations (AVMs) are often not amenable to direct resection or stereotactic radiosurgery (SRS) treatment. An alternative treatment strategy is staged endovascular embolization followed by SRS (Embo/SRS). The object of this study was to examine the experience at Washington University in St. Louis with Embo/SRS for large AVMs and review the results in earlier case series.

Methods. Twenty-one cases involving patients with large AVMs treated with Embo/SRS between 1994 and 2006 were retrospectively evaluated. The AVM size (before and after embolization), procedural complications, radiological outcome, and neurological outcome were examined. Radiological success was defined as AVM obliteration as demonstrated by catheter angiography, CT angiography, or MR angiography. Radiological failure was defined as residual AVM as demonstrated by catheter angiography, CT angiography, or MR angiography performed at least 3 years after SRS.

Results. The maximum diameter of all AVMs in this series was > 3 cm (mean 4.2 cm); 12 (57%) were Spetzler-Martin Grade IV or V. Clinical follow-up was available in 20 of 21 cases; radiological follow-up was available in 19 of 21 cases (mean duration of follow-up 3.6 years). Forty-three embolization procedures were performed; 8 embolization-related complications occurred, leading to transient neurological deficits in 5 patients (24%), minor permanent neurological deficits in 3 patients (14%), and major permanent neurological deficits in none (0%). Twenty-one SRS procedures were performed; 1 radiation-induced complication occurred (5%), leading to a permanent minor neurological deficit. Of the 20 patients with clinical follow-up, none experienced cerebral hemorrhage. In the 19 patients with radiological follow-up, AVM obliteration was confirmed by catheter angiography in 13, MR angiography in 2, and CT angiography in 1. Residual nidus was found in 3 patients. In patients with follow-up catheter angiography, the AVM obliteration rate was 81% (13 of 16 cases).

Conclusions. Staged endovascular embolization followed by SRS provides an effective means of treating large AVMs not amenable to standard surgical or SRS treatment. The outcomes and complication rates reported in this series compare favorably to the results of other reported therapeutic strategies for this very challenging patient population. *(DOI: 10.3171/2011.1.JNS10571)*

Key Words • large arteriovenous malformation • embolization • stereotactic radiosurgery

Cerebral AVMs carry significant risk of morbidity and mortality related to intracerebral hemorrhage, seizure, and progressive ischemic neurological decline due to vascular steal or venous hypertension. For many AVMs, microsurgical resection is the treatment of choice. It offers immediate elimination of hemorrhage risk, treats the symptoms of vascular steal, and often improves seizure control for those patients presenting with a seizure disorder.[24] Certain AVMs, however, are inoperable due to their large size, eloquent location, deep venous drainage, and/or other anatomical considerations that are associated with unacceptably high rates of morbidity and mortality.[24,50] For these lesions, alternative therapies such as SRS and endovascular embolization are often considered. Small AVMs (≤ 3 cm in maximum diameter) are

Abbreviations used in this paper: AVM = arteriovenous malformation; Embo/SRS = staged endovascular embolization followed by SRS; GKS = Gamma Knife surgery; NBCA = n-butyl cyanoacrylate; PVA = polyvinyl alcohol; SRS = stereotactic radiosurgery.

effectively treated with SRS.[2,15,45] Arteriovenous malformations having favorable angiographic characteristics (for example, single arterial feeders) can be cured with endovascular embolization.[16] However, these alternative therapies have limited utility in the treatment of large AVMs (at least when used as stand-alone procedures). For SRS, this relates to its adjusted prescription dose–volume relationship, which leads to substantially lower cure rates and higher complication rates when employed for large AVMs (> 3 cm in diameter).[2,4,7,10,25,29,35,36,51] For endovascular therapy, this relates to its overall limitation as a curative procedure for AVMs (whether large or small).[14,26,34,38,53,55–57]

Given these limitations, large AVMs (if treated) generally require staged and often multimodal therapy. Several options have been described. Staged[46,48] or repeat[12,27] SRS is one approach. It involves 2 or more SRS treatments performed at prespecified time intervals (typically 6–9 months for staged SRS and 3–4 years for repeat SRS) in an effort to reduce radiation side effects and ultimately promote AVM obliteration. Endovascular embolization followed by SRS (Embo/SRS) is another approach.[5,17,37,38,40] It comprises one or more embolization procedures designed to reduce AVM size, followed by SRS to treat the remaining AVM nidus; this approach is highly effective and allows treatment of AVMs that are initially too large for stand-alone SRS. Finally, some have advocated a multimodal therapeutic approach that includes the use of surgical intervention.[3,9,40]

At Washington University in St. Louis, we primarily use Embo/SRS for lesions deemed too large for either resection or stand-alone SRS. Endovascular embolization reduces the size of the AVM nidus, which effectively decreases the target volume for subsequent SRS. This strategy capitalizes on the principle that decreased target volumes significantly improve obliteration rates with fewer radiosurgical complications.[3,17,18,23,37] Other centers have published their experience with embolization followed by SRS.[17,37,40] However, the reported experience with this technique is relatively small, and controversy remains due to the reported negative impact of prior embolization on SRS obliteration rates[1,39,45,47] and the availability of other treatment paradigms. Herein, we report our experience treating 21 large and otherwise untreatable AVMs with a strategy of Embo/SRS. The safety and efficacy of this approach for these complex lesions is evaluated, and our results are compared with those of other treatment strategies.

Methods

Patient Population

At Washington University in St. Louis, patients with AVMs are evaluated by a multidisciplinary team including vascular neurosurgeons, endovascular specialists, and radiation oncologists. Patient cases are reviewed to determine treatment options. In the majority, resection (with or without preoperative embolization) or SRS is recommended. In others, observation is advised due to advanced patient age, significant comorbidities, or lesion complexity that prevents safe intervention of any kind. Patients presenting with large AVMs are often not suitable candidates for resection or stand-alone SRS. We have adopted a treatment strategy of Embo/SRS for these otherwise untreatable lesions. Between 1994 and 2006, 103 AVMs were treated with SRS—75 with SRS alone and 28 with Embo/SRS. Of those treated with Embo/SRS, 7 were excluded from analysis—4 who were treated before 1997 (the year our records were converted to electronic format) had missing records; 1 who underwent craniotomy for AVM resection at another institution due to dissatisfaction with seizure control (surgery occurred 1 year after Embo/SRS, thus precluding assessment as to the success or failure of Embo/SRS), 1 who suffered a hemorrhage during embolization requiring emergent clot evacuation and AVM resection, and 1 who died during a car accident 1 year after Embo/SRS (the car accident was determined to be the result of driver error). The remaining 21 cases are the subject of this report. All of the patients in these cases had single, large AVMs (defined as ≥ 3 cm in maximum diameter).

Following institutional review board approval, patient charts were retrospectively reviewed, including clinic notes, hospital records, and embolization and SRS procedure notes. Standard demographic and presenting clinical information was recorded. The results of pre- and posttreatment neuroimaging studies, including catheter cerebral angiography, MR imaging, MR angiography, and CT angiography, were reviewed. Procedural complications and neuroimaging-defined treatment success or failure was determined as described below.

Embolization Protocol

Embolization of AVMs was performed by one of 3 interventional neuroradiologists (D.T.C., C.P.D., C.J.M.). Procedures were usually performed under general anesthesia unless functional testing of eloquent cortex was anticipated. Nidus obliteration was performed primarily with liquid embolic agents, although embolization methods changed over the time period reviewed (see Table 3). Early in the series, PVA particles (Cook Medical) were used alone. For the majority of patients, however, NBCA (B. Braun Surgical, GmbH) was used, with adjunctive use of platinum coils (Boston Scientific) and/or PVA in select cases. Postembolization, all patients were observed overnight in the neurosurgical intensive care unit. The number of embolization procedures was dependent upon the success at reducing the volume of the residual nidus, technical limitations, or procedural related complications. Repeat embolizations of residual nidus were generally completed at 4 to 6–week intervals. The goal of embolization was to reduce the size of the residual nidus to a volume amenable to SRS (typically ≤ 10 cm^3). Ideally, this was achieved by targeting peripheral AVM compartments to attain a compact AVM volume that would facilitate SRS (for example, see Fig. 1). An endovascular strategy of AVM flow reduction, which is commonly used as a presurgical adjunct, was specifically avoided.

Size of AVM nidus before embolization was calculated by the following equation: volume = (D1 × D2 × D3)/2. In earlier cases, nidus diameters were measured

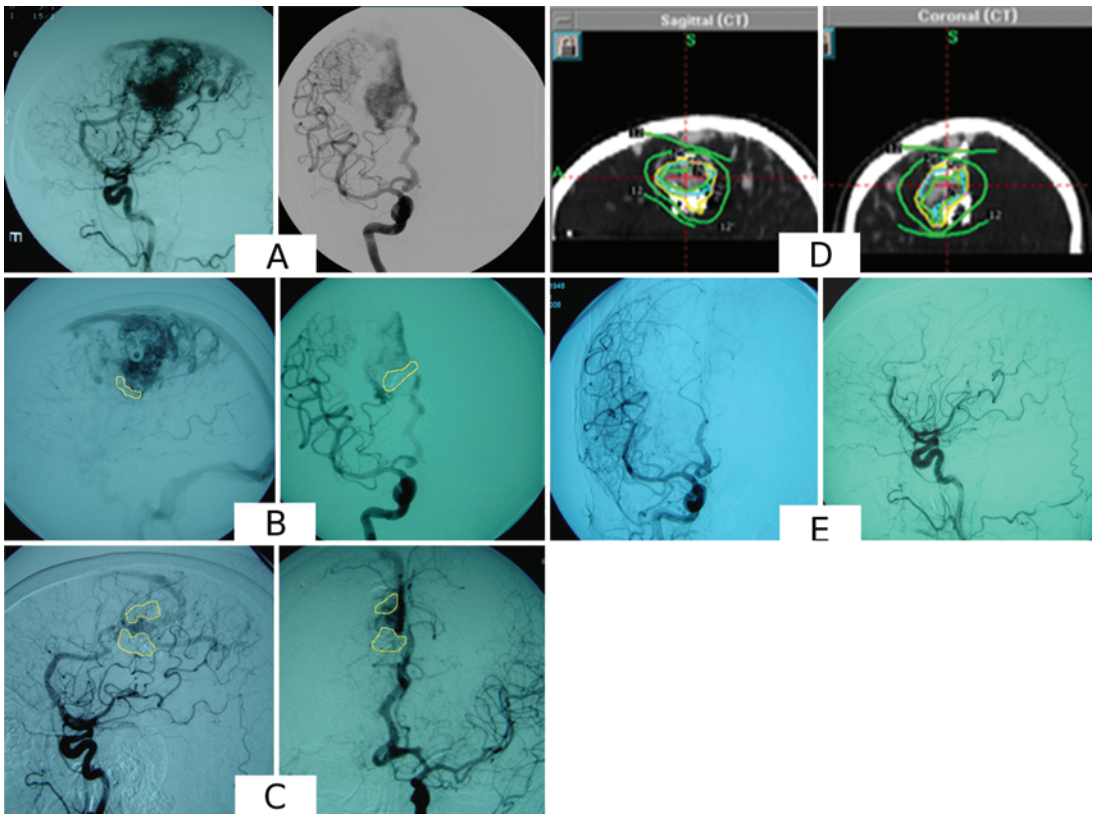

Fig. 1. Case 9. This 56-year-old woman presented with seizures and an unruptured Spetzler-Martin Grade III AVM. **A:** Pretreatment angiograms showing a large AVM nidus, feeding arteries that were primarily from the right ACA, and superficial venous drainage that drained into the superior sagittal sinus and vein of Labbé. **B:** Angiograms obtained immediately after the first embolization, which was performed via an ACA branch, showing reduction of the nidus size by the area *outlined in yellow*. **C:** Angiograms obtained immediately after the second embolization, which was performed via 2 ACA branches, showing further peripheral reduction of the AVM nidus. **D:** Gamma Knife treatment plan. The original AVM volume of 18 cm^3 was reduced to 10 cm^3 for radiosurgery. **E:** Follow-up angiograms obtained 1.5 years after GKS showing complete obliteration of the patient's AVM.

on hard films using correction factors derived from external fiducial markers. In later cases, nidus diameter measurements were obtained using correction software on the angiographic unit (Axiom Artis, Siemens Medical Systems) or from axial slices from a CT angiogram. The number of embolization sessions and procedural complications were identified in procedural reports and medical records. Postembolization AVM size was calculated during SRS planning.

Stereotactic Radiosurgery Protocol

Before June 1998, SRS treatment was performed in 6 patients with LINAC-based radiosurgery units (Varian Medical Systems). After June 1998, SRS treatment was performed in 15 patients with Leksell Gamma Knife units (Elekta AB). In all cases, SRS treatment was performed following AVM embolization (for example, see Fig. 1). The treatment target (residual AVM nidus) was defined with a combination of CT angiography, 3D stereotactic MR imaging, and catheter cerebral angiography. In certain cases, cerebral angiograms were not repeated on the day of treatment. Identification was completed with a consensus of input from the neurosurgeon (M.R.C., R.G.D., K.M.R., or G.J.Z.), neuroradiologist (D.T.C., C.P.D., or C.J.M.), and radiation oncologist (J.R.S.). Treatment planning goals required that the dose-volume histogram encompass at least 95% of the target volume with the prescribed isodose. All patients in the study were treated with a single course of SRS.

Follow-Up Evaluation

The following outcome measures were assessed: procedural complications, posttreatment cerebral hemorrhage, radiological success or failure, and neurological outcome. Data for procedural complications and hemorrhage were collected by review of charts and procedure notes by the authors. Radiological success was defined as AVM obliteration on cerebral angiography, CT angiography, or MR angiography. Our usual practice is to confirm all CT angiography and MR angiography studies with cerebral angiography. Radiological failure was defined as incomplete AVM obliteration on follow-up neuroimaging studies performed at least 3 years following SRS. Patients with insufficient radiological follow-up were defined as those with long-term clinical follow-up but lacking confirmation of AVM nidus obliteration on neuroimaging studies obtained at least 3 years after SRS. Patients lost to follow-up were those lacking long-term clinical or radio-

logical follow-up. Radiological information was extracted from the dictated reports at the time of the imaging study. Neurological outcome was collected from the attending neurosurgeon's outpatient clinic notes. Complications were categorized as minor if the patient remained independent and was able to carry out all previous activities. All other complications were considered major.

Results

Descriptive Findings

Twenty-one patients with large AVMs were treated with Embo/SRS. Patient characteristics are shown in Table 1. There were 10 male and 11 female patients; their mean age at presentation was 45 years (range 24–72 years). Hemorrhagic presentation was noted in 8 patients; nonhemorrhagic presentation was noted in 13. The AVM characteristics are shown in Table 2. The mean maximum diameter of the AVM nidus was 4.2 cm (range 3.0–6.0 cm). The mean volume of the AVM nidus was 20.1 cm^3 (range 7.5–60 cm^3).

Embolization Technique and Complications

Seventeen patients were treated with NBCA embolization (without PVA), 3 patients were treated with PVA (without NBCA), and 1 patient was treated with PVA and NBCA. Platinum coils were used as an adjunct in 4 patients. A total of 43 embolization procedures were performed with a mean of 2.1 embolization procedures per patient (range 1–5 procedures). There were no AVM cures with embolization alone. The mean preembolization AVM volume was 20.1 cm^3 (range 7.5–60.0 cm^3). The mean postembolization residual AVM volume was 8.9 cm^3 (range 2.4–23.5 cm^3). The mean reduction in AVM volume was 56%.

All 21 patients were included in the analysis of procedural complications. There were 8 complications related to the 43 embolization procedures performed (19% of procedures; 38% of patients). These led to transient neurological deficits in 5 patients (24% of patients), minor permanent neurological deficits in 3 patients (14% of patients), and major permanent neurological deficits in none (0%). There was a 7% (3/43) permanent morbidity rate per procedure. There were no mortalities. Specific transient complications were as follows: visual changes in 2 patients, contrast extravasation and small subarachnoid hemorrhage in 2 patients who developed headaches and transient confusion, and a vessel perforation in 1 patient who developed intraventricular hemorrhage and hydrocephalus requiring an external ventricular drain. Permanent deficits included a basal ganglia infarct and left hemiparesis in 1 patient (independent and ambulatory), a small permanent visual field deficit in 1 patient, and a cerebellar infarct and gait instability in 1 patient (independent and ambulatory). There were a total of 4 instances of vessel perforation documented by contrast extravasation in 43 embolization procedures (9% risk per procedure)—3 resulted in transient neurological deficits and 1 resulted in the aforementioned permanent gait ataxia (see Table 3).

TABLE 1: Summary of demographic characteristics and presenting symptoms in 21 patients*

Characteristic	Value
sex	
M	10
F	11
age	
18–30 yrs	4
30–45 yrs	8
45–60 yrs	6
60–72 yrs	3
mean (yrs)	45
presenting Sx	
rupture	8
seizure	5
headache (w/o AVM rupture)	5
sensorimotor deficit	2

* Values represent numbers of patients unless otherwise indicated.

TABLE 2: Characteristics of AVMs in 21 cases

Characteristic	No. of Cases
location	
frontal	4
frontal-parietal	3
parietal	2
parietal-occipital	3
occipital	3
temporal	3
temporal-parietal	1
periventricular	1
cerebellar	1
left hemisphere	11
right hemisphere	10
Spetzler-Martin grade	
II	2
III	7
IV	10
V	2
volume	
7.5–9.9 cm^3	3
10–14.9 cm^3	4
15–19.9 cm^3	6
20–24.9 cm^3	5
>25 cm^3	3

Stereotactic Radiosurgery Technique and Complications

Stereotactic radiosurgery was performed using LINAC in 6 patients and Gamma Knife in 15 patients. Of those treated with LINAC, 2 received 20 Gy at the 50% isodose line, 1 received 20 Gy at the 87% isodose line, 1

TABLE 3: Clinical and demographic characteristics*

Case No.	Age (yrs), Sex	AVM Location	SM Grade	AVM Vol (cm^3)	Embo	Embolisate	SRS Vol (cm^3)	GKS vs LINAC	SRS Dose†	Complications	Imaging	
											Last FU (yrs)/ Study Type	Findings
1	43, F	rt parietal	4	21	1	PVA	6	LINAC	18 at 53%	SRS—minor worsening of lt hemiparesis	2.1/A	AVM oblit
2	37, F	lt parietal	5	60	3	NBCA	14	GKS	18		2.4/A	AVM oblit
3	32, F	lt periventricular	4	28	1	NBCA, coils	15	LINAC	18 at 44%	Embo—temp vision change	2.9/MRA	AVM oblit
4	66, F	rt parietooccipital	4	18	1	PVA	13	GKS	16		2.5/A	AVM oblit
5	40, M	rt frontal	3	8	2	NBCA	4	GKS	18	Embo—basal ganglia infarct w/ perm lt hemiparesis	1.7/CTA	AVM oblit
6	44, M	rt parietooccipital	4	9	2	NBCA	9	GKS	16		2.5/A	AVM oblit
7	40, M	rt frontoparietal	2	14	1	NBCA, coil	24	GKS	18		2.6/A	AVM oblit
8	24, M	rt parietooccipital	3	22	5	NBCA, PVA, coils	7	LINAC	20		2.9/A	AVM oblit
9	56, F	rt frontoparietal	3	18	2	NBCA	10	GKS	18		1.5/A	AVM oblit
10	62, M	lt occipital	3	19	3	NBCA	6	GKS	18	Embo—IPH & IVH w/ temp vision changes	2.5/A	AVM oblit
11	25, M	lt occipital	4	16	2	NBCA	9	LINAC	18 at 42%	Embo—perm vision deficit	2.7/A	AVM oblit
12	59, F	lt temporoparietal	5	21	1	NBCA	9	GKS	18		6.9/A	AVM oblit
13	47, M	lt occipital	4	18	2	NBCA	3	GKS	18	Embo—perf w/ cerebellar infarct & SAH; perm gait ataxia	4.7/A	AVM oblit
14	72, F	cerebellar	3	10	1	NBCA	4	GKS	20		2.0/A	AVM oblit
15	55, F	lt frontoparietal	4	13	1	NBCA, coils	9	GKS	18		5.3/A	AVM oblit
16	28, M	lt temporal	4	38	2	PVA	8	LINAC	20		15/MRA	AVM oblit
17	38, F	lt temporoparietal	4	18	3	NBCA	8	LINAC	20 at 87%	Embo—perf w/ IVH & EVD, no perm deficit	4.9/CTA	nidus obliterated, but early draining vein present
18	29, F	rt frontal	3	25	3	NBCA	6	GKS	18		3.5/A	residual nidus (two 0.5-cm stains)
19	50, F	rt parietal	3	25	3	NBCA	8	GKS	14		6.1/CTA	residual nidus (0.7 × 1 cm)
20	45, M	lt temporoparietal	4	9	2	NBCA	2	GKS	20	Embo—perf w/ transient confusion	insuff FU	—
21	52, M	lt frontal	2	14	2	NBCA	10	GKS	20	Embo—perf w/ transient confusion	insuff FU	—

* A = catheter angiography; Embo = Endovascular Embolization; EVD = external ventricular drain; FU = follow-up; insuff = insufficient; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; oblit = obliteration; perf = perforation; perm = permanent; SM = Spetzler-Martin; temp = temporary.
† Dose is at the 50% isodose curve unless otherwise noted.

received 18 Gy at the 53% isodose line, 1 received 18 Gy at the 44% isodose line, and 1 received 18 Gy at the 42% isodose line. Of those treated with Gamma Knife, the mean margin dose was 17.9 Gy at the 50% isodose line (range 14–20, mode 18 in 9 patients). The mean volume of residual AVM treated with SRS was 8.7 cm^3 (range 2.4–23.5 cm^3), slightly less than the actual mean residual AVM volume of 8.9 cm^3. Mean time to SRS following last embolization procedure was 2.6 months (range 1–11.5 months).

Of the 21 SRS procedures performed, 1 (5%) led to a permanent complication. This included a patient with a minor worsening of a preprocedural left hemiparesis. The patient's AVM was right frontoparietal in location with an SRS volume of 6 cm^3, and it treated with LINAC, 18 Gy at the 80% isodose.

Obliteration Rates and Long-Term Patient Outcome

Long-term clinical follow-up was obtained in 20 of 21 patients. One patient was lost to clinical follow-up after treatment and could not be located. A Social Security database search showed that the number was still valid and the patient had not died. The mean length of follow-up after SRS treatment to the last clinical evaluation was 3.6 years (range 1.5–15 years). No posttreatment AVM hemorrhages were noted. The long-term patient outcome was as follows: 20% permanent minor neurological morbidity (4/20), 0% major permanent neurological morbidity (0/20), and 0% mortality (0/21).

Long-term radiological follow-up was obtained in 19 of 21 patients. One patient was lost to follow-up (same as above). The second patient refused follow-up imaging at 3 years posttreatment due to poor renal function although he still maintained clinical follow-up. Of the 19 patients with radiological follow-up, 13 patients had AVM obliteration confirmed on catheter angiography, 2 on MR angiography, and 1 on CT angiography. Treatment success as defined by cerebral angiography was 81% (13/16). Treatment success as defined by cerebral angiography, CT angiography, or MR angiography was 84% (16/19). The cause of the treatment failures could be evaluated in 2 of 3 patients (1 treatment plan could not be reviewed due to change in software). The SRS treatment plan for these 2 patients included the residual nidus within the 50% isodose curve, indicating that targeting error and AVM recanalization did not account for the treatment failures.

Discussion

The treatment of large AVMs is a challenging task. Microsurgery remains an option for selected high-grade AVMs, since it generally provides immediate angiographic cure and eliminates the risk of hemorrhage.[24] However, it is clear that as AVM size and grade increases, so does operative morbidity and mortality.[20,24,50,52] As a result, the treatment of many large, complex AVMs has shifted away from surgery and toward treatment strategies such as single-stage SRS,[7,39,43] Embo/SRS,[17,37,40] repeat SRS,[12,27] volume-staged SRS,[46,48] and multimodal therapy that includes surgical intervention.[3,9,40]

Single-stage SRS is the most popular treatment for nonsurgical AVMs due to high cure rates and low morbidity in appropriately selected lesions. However, the efficacy and safety of SRS decreases substantially as AVM size increases.[2,7,15,19,35,42,51] Miyawaki et al.[39] reported a 23% obliteration rate in their series of 30 large AVMs (defined as > 14 cm^3 in volume) treated with LINAC (mean SRS dose 16 Gy). Ellis et al.[7] noted a 44% obliteration rate in their series of 25 large AVMs (defined as > 10 cm^3 in volume) treated with LINAC (mean SRS dose > 10 Gy). Colombo et al.[4] reported a 33% obliteration rate in their series of 22 large AVMs (defined as > 2.5 cm in diameter) treated with LINAC (mean SRS dose 27 Gy). Results from centers utilizing Gamma Knife are similar, with the obliteration rate decreasing as AVM volume increases.[2,35,43] Pan et al.[43] calculated a 50% obliteration rate by the Kaplan-Meier method in their series of 76 large AVMs (defined as > 10 cm^3 in volume) treated with Gamma Knife (mean SRS dose 17 Gy). In addition, complication rates for single-stage SRS are known to worsen with increasing AVM size.[25,35,36] In the series of Miyawaki et al., 72% of patients had postradiosurgical T2 signal abnormalities on MR images, with surgical intervention being required in 22% of these cases.[39] In the series of Colombo et al., 22% of patients developed neurological deficits due to radionecrosis.[4] In the series of Pan et al., 49% of patients developed moderate to severe radiation-induced edema as demonstrated by MR imaging, with 3.9% of patients suffering permanent neurological deficits.

Given these unsatisfactory results with single-stage SRS, we have opted to treat large, inoperable AVMs with Embo/SRS. In our series, 21 patients with large AVMs (mean diameter 4.2 cm, mean volume 20.1 cm^3) were treated with this strategy. A margin dose of 16–20 Gy was used in all but 1 case (1 patient received 14 Gy due to eloquent location). Arteriovenous malformation obliteration was achieved in 81% of patients (13/16) as assessed by catheter angiography and in 84% of patients (16/19) as assessed by catheter angiography, MR angiography, or CT angiography. Though our complication rates were relatively high—endovascular procedural complication rate of 19% (8/43 procedures), SRS procedural complication rate of 5% (1/21 procedures), overall complication rate of 43% (9/21 patients)—the majority of resulting neurological deficits were transient, and all permanent neurological deficits were minor and nondisabling. Overall, permanent minor neurological deficits occurred in 20% of patients (4/20), permanent major neurological deficits occurred in 0% (0/20), and the mortality rate was 0% (0/21). No posttreatment hemorrhages occurred.

Others have reported their experience with Embo/SRS for the treatment of large AVMs (see Table 4). Mathis et al.[37] treated 24 patients with very large AVMs with NBCA embolization (primarily) followed by GKS. The average initial AVM volume was 37 cm^3; the average SRS treatment volume was 10.3 cm^3; SRS treatment dosing was not provided. They reported 0% permanent morbidity due to endovascular therapy, 4% permanent morbidity due to SRS, and AVM obliteration in 50% of patients. Mizoi et al.[40] treated 29 patients with large AVMs with PVA embolization followed by GKS. All AVMs were > 3 cm in diameter, average SRS treatment volume was 11

TABLE 4: Literature comparison*

Author & Year/ Treatment	N	Average AVM Vol	Embo Material/Avg Embos per Pt	Average SRS Tx Vol	Average Tx Dose	Re-Tx Volume/ Dose	Permanent Complication Rate	Obliteration Rate w/ Confirmatory Modality
Embo/SRS								
Gobin et al., 1996	30	22 cm^3	NBCA/2.8	9 cm^3	25 Gy at 60–70% id	—	embo: 12.6% SRS: 0% PTH: ~3.6%/yr	18/30 (60%) 18 A
Mathis et al., 1995	24	37 cm^3	PVA/NR	10.5 cm^3	NR	—	embo: 0% SRS: 4% PTH: none	12/24 (50%) 12 A
Mizoi et al., 1998	29	>3 cm diam	PVA/2.8	10.9 cm^3	19.2 Gy at 30–70% id	—	embo: 11% SRS: 0% PTH: 1/32 pts	11/29 (38%) 11 A
present study	19	20.1 cm^3	NBCA/2.1	8.7 cm^3	17.9 Gy at 50% id	—	embo: 14% SRS: 5% PTH: none	16/19 (84%) 13 A, 2 MRA, 1 CTA
repeat SRS								
Karlsson et al., 2007	19	16 cm^3	—	16 cm^3	16 Gy at 50% id	NR/18 Gy at 50% id	SRS: 7% PTH: 7%/yr	13/19 (68%) 13 A
salvage SRS								
Foote et al., 2003	41	13.8 cm^3	—	13.8 cm^3	12.5 Gy	4.7 cm^3/15 Gy	SRS: 2% PTH: 2/47 pts (1.5%/yr)	24/41 (59%) 15 A, 9 MRA
volume-staged SRS								
Sirin et al., 2006	14	24.9 cm^3	—	12.3 cm^3 Stage I 11.5 cm^3 Stage II	16 Gy at 50% id	—	SRS: 4% PTH: 4/28 pts	7/21 (33%) 3 A, 4 MRA

* diam = diameter; id = isodose; NR = not reported; PTH = post-treatment hemorrhage.

cm^3, and average SRS treatment dose was 19.2 Gy. They reported 11% permanent morbidity due to endovascular therapy, 0% permanent morbidity due to SRS, and AVM obliteration in 38% of patients. Gobin et al.[17] treated 30 patients with large AVMs with NBCA embolization followed by LINAC SRS. The average initial AVM volume was 22 cm^3, the average SRS treatment volume was 9 cm^3, and the average SRS treatment dose was 25 Gy. They reported 12.6% permanent morbidity due to endovascular therapy, 0% permanent morbidity due to SRS, and AVM obliteration in 60% of patients.

The results of the present study compare favorably to these published reports. In our series, the rate of permanent neurological morbidity was higher than rates previously reported (19% vs 4%–12.6%); however, all of the deficits in our series were minor and nondisabling in nature. Our rate of radiological success, on the other hand, was substantially higher (81% vs 38%–60%). Although it is difficult to directly compare these 4 studies given that the case material is small and likely heterogeneous, some conclusions can be drawn. First, use of liquid embolic agents (for example, NBCA) for endovascular embolization is associated with increased rates of complete AVM obliteration following Embo/SRS (38%–50% success rate when using PVA[37,40] vs 60%–84% success rate when using primarily NBCA [present study and Gobin et al.[17]]) (see Table 4). This conclusion is supported by the overall AVM literature, which documents recanalization rates of 12%–43% for AVMs treated with particulate embolization[37,45,49] versus recanalization rates as low as 0% for AVMs treated with acrylic glue embolization.[57] Second, Embo/SRS is associated with higher cure rates when endovascular therapy is pursued until residual AVM volume ≤ 10 cm^3. For example, cure rates of 60%–84% were achieved in the 2 case series in which average SRS treatment volume was ≤ 10 cm^3 (present study and Gobin et al.[17]) versus cure rates of 38%–50% in the 2 case series where average SRS treatment volume was > 10 cm^3[37,40] (see Table 4). Subgroup analyses provided within 2 of these case series lend further support to this conclusion. Mizoi et al.[40] documented AVM obliteration in 56% (9/16) of cases where residual AVM volume was < 10 cm^3 versus 14% (2/14) of cases where residual volume was > 10 cm^3. We noted AVM obliteration in 87% (13/15) of cases where residual AVM volume was ≤ 10 cm^3 versus 75% (3/4) of cases where average residual AVM volume was > 10 cm^3.

Other strategies have been employed to treat large, inoperable AVMs (Table 4). Repeat SRS is a strategy in which a large AVM is treated with SRS in 2 or more stages. The initial SRS treatment is often at a lower dose (< 16 Gy) with the intent of achieving AVM size reduction

(rather than cure), and it is followed by a second planned SRS treatment 3 or more years later. Karlsson et al.[27] were the first to report this strategy. They treated 19 patients with large AVMs (average volume 16 cm^3) and reported a relatively high overall obliteration rate (68%). Permanent SRS morbidity was 7%, and a 7% annual risk of hemorrhage following SRS was noted. Foote et al.[12] reported on a similar treatment strategy in which multiple SRS sessions were employed to treat (mostly) large AVMs. In their study, 41 AVM patients who had been treated with SRS (average initial AVM volume 13.8 cm^3) and had radiological evidence of residual nidus at late follow-up (average residual AVM volume 4.7 cm^3) were treated with "salvage" SRS. The authors documented an obliteration rate of 59% (24/41). Permanent SRS morbidity was 2%, and 2 posttreatment hemorrhages occurred (1.5% annual risk of hemorrhage following SRS). These results are difficult to compare with those of other large AVM series, however, given that repeat SRS was not the intent of the initial SRS treatment, and that many of the AVMs included in their series were small in size at outset. Volume-staged SRS has also been employed for the treatment of large, inoperable AVMs.[46,48] This strategy involves treating separate portions of the large AVM with SRS at discrete stages. Generally, standard SRS doses are used at each stage (16–20 Gy), and the stages are approximately 6 months apart. Sirin et al.[48] were the first to report on this strategy. They treated 28 patients with large AVMs (average volume 24.9 cm^3), 21 of whom had follow up more than 36 months. Of these, 33% (7/21) had total AVM obliteration, 33% (7/21) had residual AVM that was treated with repeat SRS, and 33% (7/21) had residual AVM that was not retreated. The rate of permanent SRS morbidity was 4%, and posttreatment hemorrhages occurred in 4 patients.

It is difficult to directly compare outcome after Embo/SRS with outcome after repeat or staged SRS given the small number of reported cases for each treatment approach, the varied embolic agents and SRS dosimetry employed, and the heterogenous nature of these complex lesions. Most importantly, a substantial difference in AVM size exists between the Embo/SRS case series and the repeat or staged SRS case series (average AVM volume for the former was 20.1–37 cm^3, average AVM volume for the latter was 13.8–24.9 cm^3).[12,17,27,37,40,48] Given this disparity, it is perhaps not surprising that the SRS series reported obliteration rates (50%–68%) comparable to those achieved with Embo/SRS (50%–80% in series using primarily NBCA), with lower permanent procedural morbidity (2%–7% vs 4%–19%) (present study and elsewhere[12,17,27,48]). Whether this apparent superiority in safety and equivalence in efficacy remains when treating similarly sized AVMs is unknown. But given the importance of AVM volume on SRS outcome,[11,28,36] some decrement in safety and efficacy would be expected if larger lesions were treated with repeat or staged SRS.

Embo/SRS has several advantages when compared with repeat or volume-staged SRS. First, it is designed to obliterate the offending AVM in a relatively short time period—that is, over 2–3 years. By comparison, AVM cure following repeat SRS takes considerably longer due to multiple SRS sessions performed at intervals of approximately 3–4 years.[12,27] Second, the endovascular portion of Embo/SRS affords an opportunity to treat "high-risk" components of an AVM such as feeding artery or nidal aneurysms. Third, the endovascular portion of Embo/SRS can ameliorate the symptoms of vascular steal if present.[8,13,31,33] Finally, improvements in microcatheters, microwires, and angiographic imaging equipment and the introduction of new embolic agents such as Onyx (ev3 Neurovascular) have occurred since 1994, the starting point for data collection in this study. These developments may be associated with improved embolization obliteration and complication rates.[22,30,41,44,54,56]

Embo/SRS also has certain disadvantages when compared with repeat or volume-staged SRS. First, endovascular therapy is associated with significant permanent morbidity (5%–19% per patient) and mortality (0.0%–3.7% per patient) (present study and elsewhere[6,8,16,17,21,53,55]). This is particularly important when considering Embo/SRS for large AVMs, as multiple embolization sessions are often required to achieve a residual AVM volume ≤ 10 cm^3 (for example, two-thirds of our cases required 2 or more endovascular treatments). Second, embolic material (particularly platinum coils) may obscure residual AVM nidus on imaging studies obtained for SRS treatment planning, which can adversely affect SRS targeting. This disadvantage may be minimized with the increased use of Onyx as an embolic agent, as we have found that time-of-flight MR angiography after Onyx embolization yields excellent characterization of residual AVM for SRS targeting.[32] In addition, some have reported that prior embolization is a significant predictor of radiological failure following SRS treatment of AVMs.[1,39,45,47] Even with these concerns, a high cure rate was achieved in the present series despite the universal presence of embolic material (primarily NBCA). Moreover, targeting error was not identified as a cause of radiological failure in our series.

Conclusions

Embo/SRS is an effective and relatively safe means of treating large, complex AVMs that are not amenable to surgery or single-stage SRS. Its rate of radiological success can be high; and its rates of major permanent neurological deficit, posttreatment hemorrhage, and death are relatively low. These results compare favorably to those reported for alternative therapeutic strategies including single-stage, repeat, or staged SRS. Further studies examining the safety and efficacy of Embo/SRS for large AVMs are warranted, especially in light of the widespread use of newer and more advanced endovascular techniques that may reduce procedural complication rates and improve efficacy of AVM volume reduction.

Disclosure

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Author contributions to the study and manuscript preparation

include the following. Conception and design: Zipfel. Acquisition of data: Blackburn, Ray. Analysis and interpretation of data: Zipfel, Blackburn, Ashley, Rich, Simpson, Moran, Cross, Chicoine, Dacey, Derdeyn. Drafting the article: Zipfel, Blackburn, Ashley, Drzymala, Derdeyn. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Zipfel.

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