Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part I

Endovascular Embolization of Cerebral Arteriovenous Malformations: Results of the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

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Abstract

This retrospective study constitutes a part of the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2. Its purpose is to evaluate the feasibility, safety, and outcome of endovascular embolization for cerebral arteriovenous malformations (AVMs) in Japan. Nine hundred and eighty-seven embolization procedures were registered with JR-NET 1 and 2 (424 procedures in 122 institutions with JRNET 1 and 563 procedures in 150 institutions with JRNET 2). In total, 790 patients (80.1%) had favourable clinical outcomes defined as modified Rankin Scale (mRS) scores 0–2 at 30 days after embolization. Complete AVM obliteration by embolization alone was achieved in 90 procedures (9.1%). The procedural morbidity and mortality rate was 2.5% and 0.3% per procedure, respectively. In the multivariate logistic regression models, deep venous drainage and embolization of four or more feeding pedicles per session were significantly associated with any treatment-related complications (P = 0.02 and P = 0.003, respectively). About 6 cm or more in maximum nidus diameter had a negative correlation with complications (P = 0.003). Our study shows that embolization of cerebral AVMs was performed with a high degree of safety and a low rate of symptomatic complications in Japan.

Key words: cerebral arteriovenous malformation, endovascular embolization, outcome, complication

Introduction

Cerebral arteriovenous malformations (AVMs) are complex vascular lesions with an annual associated haemorrhage risk of 2–4% in symptomatic patients.¹⁾ The primary goal of treatment for cerebral AVMs is to prevent bleeding. For this purpose, complete exclusion of the AVM should be achieved. Treatment methods are highly variable, depending on AVM characteristics and the complete obliteration of cerebral AVMs often requires a multidisciplinary approach, including endovascular embolization, microsurgical resection, and stereotactic radiosurgery.²⁻⁶⁾ Endovascular embolization plays an essential role in the treatment of cerebral AVMs. In multimodal treatments, endovascular embolization is generally the first step of treatment. Furthermore, the role of endovascular embolization as a stand-alone curative treatment has been expanded after the introduction of Onyx embolic system (ev3; Irvine, California, USA).⁷⁻¹⁰ Although considerable foreign data support its safety and efficacy, the actual outcome of endovascular embolization for cerebral AVMs in Japan has not been investigated.

Received May 27, 2013; Accepted July 8, 2013

This retrospective study constitutes a part of the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2 conducted by the JR-NET Study Group in the Japanese Society for Neuroendovascular Therapy (JSNET). The purpose of this study was to evaluate the outcome, feasibility, and safety of endovascular embolization for cerebral AVMs in Japan.

Materials and Methods

I. Patient selection

JR-NET is a retrospective database collecting data on any type of neuroendovascular therapy at the institutions with which board certified instructors and specialists of neurointervention by JSNET are assigned to work. In total, 11,114 procedures at 122 institutions were registered in JR-NET 1 between January 2005 and December 2006, and 20,854 procedures at 150 institutions were enrolled in JR-NET 2 between January 2007 and December 2009. We performed a retrospective search for cerebral AVM embolizations included in JR-NET 1 and 2. The local Ethics Committees approved the retrospective collection of clinical information from databases and submission of the data to our central office.

It should be added that the registration was based on the number of embolization sessions (procedures). Namely, patients receiving multistage embolization were repeatedly registered depending on the number of sessions (procedures).

II. Outcome measures

The primary endpoint was favourable outcomes as defined by a modified Rankin Scale (mRS) score from 0 to 2 at 30 days after the procedure.

The secondary endpoints were technical success of the procedure and severe complications associated with endovascular embolization within 30 days after the procedure.

Functional neurologic status was evaluated before and after endovascular embolization using mRS. Treatment-related complications with any worsening of the patient's mRS scores at 30 days after procedure were coded as "symptomatic complications," and symptomatic complications resulting in disabling deficits, defined as mRS 3–5, were classified as "disabling complications."

Demographics were recorded for each patient, including age, sex, and presenting symptoms. The angiographic features of AVM were also documented, including maximal size, presence of deep venous drainage, involvement of the eloquent cortex, nidus location, presence of deep arterial feeders, and concurrent aneurysms. AVMs were classified based on morphologic characteristics, according to the Spetzler-Martin grading system.¹¹⁾ For each embolization session, the number of embolization sessions, the number of feeding pedicles embolized, and the embolic materials used were documented.

III. Statistical analysis

Univariate logistic regression analyses were used to identify risk factors for treatment-related complications by using the following determinants: patient demographics, initial clinical presentations, morphologic characteristics of the AVM, including Spetzler-Martin grade, number of embolization sessions, and number of feeding pedicles embolized per procedure.

All variables with significant association in the univariate analyses (P < 0.05) were entered into a multivariate logistic regression model using backward elimination procedures to test their independent association with any treatment-related complications.

Results

I. Patient and AVM characteristics

Nine hundred and eighty-seven embolization procedures were registered with JR-NET 1 and 2 (424 procedures with JR-NET 1, 563 procedures with JR-NET 2). Demographic and clinical data are summarized in Table 1. There were 588 (59.6%) male and 399 (40.4%) female patients with a mean age of 40 years (range 0 to 88). Initial clinical presentations were haemorrhage in 800 (81.1%), neurologic manifestation without haemorrhage (symptomatic without haemorrhage) in 77 (7.7%), incidentally discovered (asymptomatic) AVM in 57 (5.7%), and unknown in 54 (5.5%).

Morphologic characteristics of AVMs are shown in Table 2. There were 92 (9.3%) grade I, 264 (26.7%) grade II, 293 (29.7%) grade III, 198 (20.1%) grade IV, and 40 (4.1%) grade V AVMs, according to Spetzler-Martin grade. Spetzler-Martin grades were not described in 100 AVMs (10.1%).

II. Treatments

The treatments and materials are summarized in Table 3. The treatment strategy for embolization was presurgical in 453 (45.9%), preradiosurgical in 228 (23.1%), palliative in 138 (14.0%), curative in 101 (10.2%), and others in 10 (1.0%) of the procedures. Treatment strategy was not described in 57 (5.8%) procedures. Embolization was performed with *N*-butyl cyanoacrylate (NBCA) alone or with NBCA in conjunction with other materials in 732 (74.2%), detachable coils alone in 117 (11.9%), Onyx alone or Onyx along with other materials in 54 (5.5%), other liquid materials in 15 (1.5%), particle alone in 9 (0.9%), and others in 9 (0.9%)

Table 1 Patients demographics

| Age, years, mean (range) | 40 (0-88) |
|--------------------------------|------------|
| Sex, no. (%) | |
| Male | 588 (59.6) |
| Female | 399 (40.4) |
| Clinical presentation, no. (%) | |
| Hemorrhagic | 800 (81.1) |
| Symptomatic without hemorrhage | 77 (7.7) |
| Asymptomatic | 57 (5.7) |
| Unknown | 54 (5.5) |

Table 2Arteriovenous malformation characteristics in987 procedures

| | No. of procedures (%) |
|---|-----------------------|
| Spetzler-Martin grade | |
| Ι | 92 (9.3) |
| II | 264 (26.7) |
| III | 293 (29.7) |
| IV | 198 (20.1) |
| V | 40 (4.1) |
| Unknown | 100 (10.1) |
| AVM size | |
| < 3 cm | 364 (36.9) |
| 3 cm, < 6 cm | 449 (45.5) |
| 6 cm ≤ | 80 (8.1) |
| Unknown | 94 (9.5) |
| Eloquent location | 591 (59.9) |
| Deep venous drainage | 433 (43.9) |
| AVM location | |
| Hemispheric | 710 (71.9) |
| Cerebellum | 134 (13.6) |
| Deep* | 61 (6.2) |
| Isolated | 35 |
| With hemispheric involvement | 24 |
| With cerebellar involvement | 2 |
| Others | 28 (2.8) |
| Unknown | 54 (5.5) |
| AVMs with deep arterial feeders ** | 99 (10.0) |
| Patients with concurrent aneurysms*** | 192 (19.5) |

*: Refers to involvement of the following: basal ganglia, thalamus, brain stem, **: Defined as penetrating branches of the major intracranial arteries, or of the anterior choroidal arteries, ***: Includes aneurysms on feeding arteries, intranidal, and AVM-unrelated aneurysms. AVM: arteriovenous malformation.

Table 3 Summary of treatments in 987 procedures

| 5 | 1 |
|---------------------------------|----------------|
| | No. of $(0/)$ |
| | procedures (%) |
| Treatment strategy | |
| Presurgical | 453 (45.9) |
| Preradiosurgical | 228 (23.1) |
| Palliative | 138 (14.0) |
| Curative | 101 (10.2) |
| Others | 10 (1.0) |
| Unknown | 57 (5.8) |
| Treatment material | |
| NBCA | 732 (74.2) |
| Coil alone | 117 (11.9) |
| Onyx | 54 (5.5) |
| Other liquid emolic material | 15 (1.5) |
| Particle alone | 4 (0.4) |
| Others | 9 (0.9) |
| Unknown | 56 (5.6) |
| Number of times of embolization | |
| sessions | |
| 1 | 661 (67.0) |
| 2 | 152 (15.4) |
| 3 | 65 (6.6) |
| ≥ 4 | 54 (5.5) |
| Unknown | 55 (5.5) |
| Number of pedicles embolization | |
| 0 (trial) | 11 (1.1) |
| 1 | 306 (31.0) |
| 2 | 336 (34.0) |
| 3 | 155 (15.7) |
| ≥ 4 | 113 (11.4) |
| Unknown | 66 (6.8) |

NBCA: N-butyl cyanoacrylate.

of the procedures. Treatment materials were not described in 56 (5.6%) procedures.

III. Primary and secondary endpoints

The primary and secondary endpoints are summarized in Table 4. For the primary endpoint, a total of 790 patients (80.1%) had mRS scores ranging from 0 to 2 at 30 days after embolization. Pre- and postprocedural mRS scores are given in Table 5. In total, there were 877 patients (88.9%) with mRS scores of 0–2 at pre-embolization. Therefore, the number of patients with non-disabling deficits (mRS \leq 2) decreased by 87 after embolization.

For the secondary endpoints, technical success was documented in 975 procedures (98.8%). Complete AVM

| Table 4 | Incidences | of primary | and | secondary | endpoints |
|-----------|------------|------------|-----|-----------|-----------|
| in 987 pı | rocedures | | | | |

| | No. of procedures (%) |
|------------------------------------|-----------------------|
| Primary endpoint | |
| mRS 0–2 at 30 days after procedure | 790 (80.0) |
| Secondary endpoints | |
| Technical success | 975 (98.8) |
| Cured by embolization alone | 90 (9.1) |
| Complication | |
| Any technical complication | 91 (9.2) |
| Symptomatic complication* | 25 (2.5) |
| Disabling complication** | 15 (1.5) |
| Death | 3 (0.3) |

mRS: modified Rankin Scale. *: Complication resulting in any deterioration of mRS scores at 30 days after embolization compared with those before embolization, **: Complication resulting in disabling deficits defined as mRS 3–5 at 30 days after embolization.

Table 5mRS scores pre- and postembolization

| mPS score - | Preembo | olization | Postemb | olization |
|-------------|---------|-----------|---------|-----------|
| | No. | % | No. | % |
| 0 | 664 | 67.3 | 462 | 46.8 |
| 1 | 130 | 13.2 | 200 | 20.3 |
| 2 | 83 | 8.4 | 128 | 13.0 |
| 3 | 27 | 2.7 | 72 | 7.3 |
| 4 | 41 | 4.2 | 60 | 6.1 |
| 5 | 29 | 2.9 | 33 | 3.3 |
| 6 | 0 | 0.0 | 14 | 1.4 |
| Unknown | 13 | 1.3 | 18 | 1.8 |

mRS: modified Rankin Scale.

obliteration by embolization alone was achieved in 90 procedures (9.1%). A total of 91 complications (9.2%) with or without worsening of mRS occurred after embolization: 38 were ischemic, 37 were haemorrhagic, 2 were arterial dissections, 1 was catheter gluing, and 13 were others or unknown. Complications included 25 (2.5%) symptomatic (any worsening of mRS) and 15 (1.5%) disabling (mRS 3-5) complications. Symptomatic complications included 16 intracranial haemorrhages, 7 cerebral ischemia, 1 cholesterol crystal embolization, and 1 other complication. Another 3 patients (0.3%) died from intracranial haemorrhage within 30 days after embolization. Therefore, procedural morbidity and mortality rates were 2.5% and 0.3% per procedure, respectively.

Table 6 Factors predictive for embolization relatedcomplications by univariate analysis

| Parameter | OR | (95%CI) | Р |
|------------------------------------|-------|---------------|--------|
| Patient demographics | | | |
| Male gender | 0.60 | (0.40-0.92) | 0.03 |
| Presenting symptoms | | | |
| Hemorrhagic | 1.50 | (0.92 - 2.44) | 0.13 |
| Symptomatic without hemorrhage | 0.91 | (0.52–1.58) | 0.83 |
| Asymptomatic | 0.48 | (0.22 - 1.06) | 0.09 |
| AVM characteristics | | | |
| Spetzler-Martin grade | | | |
| I and II | 1.05 | (0.67 - 1.63) | 0.93 |
| III and IV | 1.07 | (0.69 - 1.66) | 0.85 |
| V | 0.45 | (0.11–1.91) | 0.40 |
| AVM size | | | |
| < 3 cm | 1.51 | (0.98 - 2.35) | 0.08 |
| $3 \text{ cm} \le, < 6 \text{ cm}$ | 0.89 | (0.58 - 1.38) | 0.69 |
| 6 cm ≤ | 0.21 | (0.05–0.88) | 0.03 |
| Eloquent cortex involved | 1.22 | (0.77–1.94) | 0.46 |
| Deep venous drainage | 1.59 | (1.03 - 2.46) | 0.047 |
| Deep arterial feeders | 1.57 | (0.85 - 2.90) | 0.20 |
| Concurrent aneurysms | 1.67 | (1.03 - 2.71) | 0.048 |
| Deep seated location | 1.65 | (0.75 - 3.60) | 0.31 |
| Treatment | | | |
| Number of embolization sessions | | | |
| 1 | 0.93 | (0.58 - 1.49) | 0.86 |
| 2 | 0.91 | (0.50 - 1.66) | 0.88 |
| 3 | 1.74 | (0.85 - 3.54) | 0.18 |
| ≥ 4 | 0.72 | (0.25 - 2.04) | 0.70 |
| Number of pedicles embo | lized | | |
| 0 (trial) | 0.92 | (0.12–7.23) | 0.67 |
| 1 | 1.12 | (0.70–1.75) | 0.74 |
| 2 | 0.64 | (0.39–1.03) | 0.08 |
| 3 | 0.66 | (0.34–1.27) | 0.27 |
| ≥ 4 | 2.60 | (1.54-4.41) | 0.0005 |

AVM: arteriovenous malformation, CI: confidence interval, OR: odds ratio.

IV. Predictors of complication after embolization The results of univariate analyses are shown in Table 6. Deep venous drainage, concurrent aneurysm, and embolization of 4 or more feeding pedicles per session were significantly associated with treatment-related complications (P = 0.047, P = 0.048, and P = 0.0005, respectively). Male sex and ≥ 6 cm in maximum nidus diameter had a negative correlation with complications (P = 0.03for both). In multivariate logistic regression models (Table 7), deep venous drainage and embolization

Table 7Predictors for embolization related complicationsby multivariate logistic regression model test

| Parameter | OR | (95%CI) | Р |
|-------------------------------------|------|--------------|-------|
| Male gender | 0.55 | (0.30–1.02) | 0.06 |
| AVM size $6 \text{ cm} \leq$ | 0.09 | (0.02–0.43) | 0.003 |
| Deep venous drainage | 2.02 | (1.09–3.72) | 0.02 |
| Concurrent aneurysms | 2.06 | (0.99–4.30) | 0.053 |
| Number of pedicles embolized ≥ 4 | 4.14 | (1.65–10.40) | 0.003 |

AVM: arteriovenous malformation, CI: confidence interval, OR: odds ratio.

of 4 or more feeding pedicles per session were independently associated with treatment-related complications (P = 0.02 and P = 0.003, respectively). A maximum nidus diameter of ≥ 6 cm had an independent negative correlation with complications (P = 0.003).

Discussion

This study is a retrospective registry investigating the endovascular embolization of cerebral AVMs performed between January 2005 and December 2009. Although it is a non-randomized, retrospective study, it may reflect the current state of embolization for cerebral AVMs in Japan, because the data were gathered from a wide range of institutions employing board certified instructors and neurointervention specialists of JSNET.

I. Treatment strategy

In the treatment of cerebral AVMs, the goals of embolization are classified into four types as follows: presurgical, preradiosurgical, curative, and palliative embolization. The goal of presurgical embolization is to minimize the risk of intraoperative complications. The reported predictors of intraoperative complications are diffuse nidus,12) deep-seated nidus,¹³⁻¹⁵⁾ perforating artery supply,¹²⁾ fistulous feeder,¹⁶⁾ and ruptured intranidal or flow-related aneurysms.¹⁷⁾ Presurgical embolizations should be planned not only for reduction of nidus volume but also for the obliteration of the aforementioned harmful angioarchitecture. Regarding preradiosurgical embolization, although its efficacy has been controversial, a recent study found that preradiosurgical embolization targeting ruptured intranidal or flow-related aneurysms can decrease the rate of rebleeding after stereotactic radiosurgery.¹⁷⁾ Curative

embolization aims to completely occlude the AVM by embolization alone.

In the present study, presurgical and preradiosurgical embolization accounted for 69.0% of all procedures, while curative embolization was undertaken in only 10.2% of procedures (Table 3). This trend is attributable to the predominance of NBCA (74.2%) over Onyx (5.5%) as embolic material during the study period (Table 3). According to previous reports, the success rate of curative embolization is higher in embolizations using Onyx compared with that using NBCA.^{4,7,8,10,18–23)} However, in Japan, Onyx was only approved for use in a limited number of institutions on September 26, 2009, and it is covered by public insurance only for presurgical embolization. This could be the chief reason why curative embolization was used as a treatment strategy only in the minority of cases in this study.

II. Primary endpoint (mRS after Embolization)

Thirty days after embolization, 790 of 987 patients (80.0%) were nondisabled (mRS \leq 2), compared with 877 of 987 patients (88.6%) at baseline. In other words, in 87 procedures, patents' mRS scores deteriorated from nondisabled (mRS \leq 2) to disabled or dead (mRS \geq 3) after treatments.

As mentioned above, 25 symptomatic complications and 3 deaths (28 in total) were recorded in this study. Among the 28 symptomatic or fatal complications, 17 complications exacerbated patients' mRS scores from nondisabled (mRS \leq 2) to disabled or dead (mRS \geq 3). In the remaining 70 procedures that resulted in a deterioration of mRS scores, the causes of deterioration were not clarified within the parameters of this study. There are few articles focusing on the change in mRS following treatment, and the results are controversial. Hartmann et al.²⁴⁾ and Weber et al.²⁵⁾ reported changes in mRS scores in patients receiving endovascular embolization subsequent to surgical treatment. According to the former, the population of nondisabled (mRS ≤ 2) patients decreased for each treatment stage (99% at baseline, 97% after embolization, and 91% after surgery).²⁴⁾ Weber et al. reported that the population of nondisabled patients was equal before and after embolization (91%), decreased after surgery (82%), and increased after a mean follow-up of 13 months (93%).²⁵⁾ Javaraman et al. also described the rate of nondisabled patients before and after embolization as being equal (89% and 90%, respectively).³⁾ Previous reports revealed that surgery affected mRS scores more than embolization. It is likely that surgery subsequent to embolization was associated with a decrease in nondisabled patients in the present study. However, this is only a speculation,

| Table 8 Literat | ure repo | rting on e | mbolizatio | n of cerebra | al AVMs | | | | | | | | | |
|--|----------|----------------------|---------------------|---------------|---------------|----------|---------|---------|------------|-----------|--------------|-------------|-------------|-----------|
| | | | Dominant | Ŋ | Ŋ | Subs | sequent | treatme | nt (%) | Cured# | Per proce | dure (%) | Per pati | int (%) |
| Author | Year | Design | embolic material | patients | procedures | \$ * | R** | S + R | None*** | (%) | Morbidity | Mortality | Morbidity | Mortality |
| Haw et al. ¹⁸⁾ | 2006 | Retro | NBCA | 306 | 513 | 23.6 | 55.9 | 0.0 | 20.5 | 9.2 | 3.5 | 1.4 | 5.9 | 2.3 |
| Kim et al. ¹⁹⁾ | 2006 | Retro | NBCA | 153 | 203 | 70.6 | 13.1 | 3.9 | 12.4 | 1.3 | 8.4 | 0.5 | 11.1 | 0.7 |
| Ledezma et al. ²⁰⁾ | 2006 | Retro | NBCA | 168 | 295 | 73.8 | 16.7 | 0.0 | 9.5 | 2.4 | 3.7 | 0.7 | 6.5 | 1.2 |
| Mounayer et al. ^{2:} | 2007 | Retro | Onyx | 94 | 210 | 7.4 | 21.3 | 0.0 | 71.3 | 27.7 | 3.8 | 1.4 | 8.5 | 3.2 |
| van Rooij et al. ²⁶ | 2007 | Retro | 0nyx | 44 | 52 | 22.7 | 45.5 | 0.0 | 31.8 | 15.9 | 3.8 | 1.9 | 4.6 | 2.3 |
| Weber et al. ²⁵⁾ | 2007 | Retro | 0nyx | 47 | 112 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.6 | 0.0 | 8.6 | 0.0 |
| Jayaraman et al.³ | 2008 | Retro | NBCA / Onyx | 192 | 489 | 36.5 | 35.9 | 17.7 | 9.9 | NA | 1.2 | 0.4 | 3.1 | 1.0 |
| Katsaridis et al. ⁷⁾ | 2008 | Retro | Onyx | 101 | 219 | 1.0 | 0.0 | 0.0 | 99.0 | 27.7 | 3.7 | 1.4 | 7.9 | 3.0 |
| Hauck et al. ²⁷⁾ | 2009 | Retro | 0nyx | 41 | 82 | 70.7 | 14.6 | 0.0 | 14.6 | 10.0 | 6.1 | 0.0 | 12.2 | 0.0 |
| Panagiotopoulos et al. ²²⁾ | 2009 | Retro | Onyx | 82 | 119 | 59.8 | 3.7 | 0.0 | 24.4 | 24.4 | 13.4 | 1.7 | 19.5 | 2.4 |
| Pierot et al. ⁹⁾ | 2009 | Pro | Onyx | 50 | 149 | 0.0 | 74.0 | 0.0 | 26.0 | 8.3 | 2.7 | 0.7 | 8.0 | 2.0 |
| Loh et al. ²⁸⁾ | 2010 | RCT | NBCA / Onyx | 117 | 216 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 2.3 | 0.0 | 4.3 | 0.0 |
| Maimon et al. ⁸⁾ | 2010 | Retro | Onyx | 43 | 76 | 7.0 | 0.0 | 0.0 | 93.0 | 37.2 | 3.9 | 0.0 | 7.0 | 0.0 |
| Saatci et al. ¹⁰⁾ | 2011 | Retro | Onyx | 350 | 607 | 6.3 | 38.9 | 0.0 | 54.9 | 51.1 | 4.1 | 0.7 | 7.1 | 1.1 |
| Sahlein et al. ⁴⁾ | 2012 | Retro | NBCA | 130 | 168 | 71.5 | 15.4 | 0.0 | 12.3 | 8.5 | 0.6 | 0.6 | 0.8 | 0.8 |
| Present study | 2013 | Retro | NBCA | NA | 987 | 45.9 | 23.1 | NA | 24.2 | 9.1 | 2.5 | 0.3 | NA | NA |
| *: surgery, **: rac cyanoacrylate. | iosurger | y, ***: em | bolization a | llone. #: coi | mplete occlus | ion of A | VM by | emboliz | ation alon | e. AVM: a | urteriovenou | ıs malforma | ation, NBCA | : N-butyl |

because the timing and the results of surgery were not included in the present survey items.

III. Secondary endpoints (morbidity and mortality after embolization)

To compare the results of the present study with those of previous reports, the published studies of endovascular embolization of cerebral AVMs are summarized in Table 8. Studies in which sufficient data were not provided to analyse complications were not included in this table. Morbidity and mortality in the previous studies ranged from 1.2% to 13.4% and 0.0 to 1.9% per procedure, respectively. A recent meta-analysis of treatments of cerebral AVMs reported a 6.6% (range, 0-28%) morbi-mortality after embolization.²⁹⁾ In the present study, morbidity and mortality were 2.5% and 0.3% per procedure, respectively, which are within the range of morbidity and mortality rates reported in the previous articles. We should note that the present study included data not only from experienced, high-volume centres, but also from relatively inexperienced institutions in Japan, while most of the previous studies were based on data from a single experienced, high-volume centre. Although the results of these different studies are not directly comparable to each other, it appears that the safety of embolization in Japan as a whole is not inferior to that of foreign high-volume centres.

IV. Predictors of embolization-related complications

In multivariate logistic regression models, deep venous drainage and embolization of 4 or more feeding pedicles per session were independent predictors of treatment-related complications, while a maximum nidus diameter of ≥ 6 cm had a negative correlation with treatment-complications.

The reported predictors of complications during surgery are diffuse nidus,¹²⁾ deep-seated nidus,^{11,14,15)} perforating artery supply,¹²⁾ fistulous feeder,¹⁶⁾ and ruptured intranidal or flow-related aneurysms.¹⁷⁾ Regarding embolization, three previous reports investigated the predictors of complications using univariate and multivariate analyses.^{3,20,24)} Among these studies, only the one conducted by Ledezma et al. could identify a Spetzler-Martin grade of III to V and periprocedural haemorrhage as significantly positive predictors of unfavourable embolization outcomes.²⁰⁾ They suggested that the morphologic character of grade III-V AVMs, including large size, deep and eloquent location, deep arterial supply, and deep drainage, makes it difficult to embolize AVMs sufficiently.²⁰⁾ The other two studies failed to detect any significant predictors.^{3,24)}

The results of our analysis regarding the morpho-

logic character of AVMs were as follows: Spetzler-Martin grade was not a predictor of complications, the presence of deep venous drainage, which is a component of the Spetzler-Martin grading system was independently associated with complications (odds ratio 2.02, P = 0.02), and large size of nidus (≥ 6 cm) was a negative predictor of complications (odds ratio 0.09, P = 0.003). Other morphologic characters of AVMs, including location, deep arterial feeders, and concurrent aneurysms, did not have independent associations with complications.

The predictors of complications were inconsistent not only between embolization and surgery, but also among the studies investigating embolization. Another important result of our study, which may help interpret this inconsistency is that the embolization of more than adequate number of feeding pedicles (\geq 4) in one session is the strongest predictor of complications (odds ratio 4.14, P = 0.003). This result suggests that the risk of complications can depend on the aggressiveness of the embolization procedure, in addition to the morphologic character of AVMs. Similarly, Hauck et al. concluded, on the basis of previous articles, that too much reduction of nidus volume was associated with high morbidity.27) Furthermore, it should be taken into consideration that the present study predominantly reflects the results of presurgical or preradiosurgical embolization procedures using NBCA. Therefore, it is likely that the AVMs with risky morphologic characters were embolized by safer, more conservative procedures, such as staged embolization, in the present study.

However, the situation will probably change with the spread of Onyx. The behaviour of the embolic material widely differs between Onyx and NBCA. Because Onyx is not adhesive and can penetrate the drainers and other feeding arteries through the nidus, this material can enable a more aggressive and curative embolization of cerebral AVMs compared to NBCA.^{10,23)} However, further studies are needed to investigate the predictors of complications in AVM embolization procedures using Onyx.

V. Limitations

One of the limitations of the present study is that the efficacy of presurgical and preradiosurgical embolization could not be evaluated, because the final outcomes for patients after surgery or radiosurgery were not available. Additionally, long-term outcomes, including recanalization rate and bleeding rate after "cured" embolization, are also unknown due to a lack of long-term follow-up.

Conclusion

Embolization of cerebral AVMs was performed with a high degree of safety and a low rate of symptomatic complications in Japan.

Acknowledgements

The authors would like to thank the doctors listed below, who participated in this investigation.

The JR-NET Study Group: Principle Investigator; Nobuyuki Sakai, Kobe City Medical Center General Hospital, Kobe, Japan: Investigators; Akio Hyodo, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan (17C-1, 20C-2), Shigeru Miyachi, Nagoya University, Nagoya, Japan (17C-1, 20C-2), Yoji Nagai, Translational Research Informatics Center, Kobe, Japan (17C-1, 20C-2), Chiaki Sakai, Institute of Biomedical Research and Innovation, Kobe, Japan (17C-1, 20C-2), Tetsu Satow, National Cerebral and Cardiovascular Center, Suita, Japan (17C-1, 20C-2) Waro Taki, Mie University, Tsu, Japan (17C-1, 20C-2), Tomoaki Terada, Wakayama Rosai Hospital, Wakayama, Japan (17C-1, 20C-2), Masayuki Ezura, Sendai Medical Center, Sendai, Japan (17C-1). Toshio Hyogo, Nakamura Memorial Hospital, Sapporo, Japan (17C-1), Shunji Matsubara, Tokushima University, Tokushima, Japan (17C-1), Kentaro Hayashi, Nagasaki University, Nagasaki Japan (20C-2); Co-Investigators; Toshiyuki Fujinaka, Osaka University, Suita, Japan, Yasushi Ito, Niigata University, Niigata, Japan, Shigeki Kobayashi, Chiba Emergency Medical Center, Chiba, Japan, Masaki Komiyama, Osaka City General Hospital, Osaka, Japan, Naoya Kuwayama, Toyama University, Toyama, Japan, Yuji Matsumaru, Toranomon Hospital, Japan, Yasushi Matsumoto, Konan Hospital, Sendai, Japan, Yuichi Murayama, Jikei Medical University, Tokyo, Japan, Ichiro Nokahara, Kokura Memorial Hospital, Kokura, Japan, Shigeru Nemoto, Jichi Medical University, Shimotsuke, Japan, Koichi Sato, Tokushima Red Cross Hospital, Tokushima, Japan, Kenji Sugiu, Okayama University, Okayama, Japan, Shinichi Yoshimura, Gifu University, Gifu, Japan, and certified specialist of Japanese Society of Neuroendovascular Therapy.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices discussed in the articles. The first author who is member of The Japanese Society for Neuroendovascular Therapy (JSNET) and other authors who are members of The Japan Neurosurgical Society [JNS] have registered online Self-reported COI Disclosure Statement Forms through the website for members of each Society.

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