224人のうち213人（PTAのみ5人，PTA＋ステント208人）を分析し，出血性脳卒中13人，虚血性脳卒中19人，周術期に一過性徴候を伴った脳梗塞2人を認めた．高狭窄率，低mRS，ACT延長を伴うクロピドグレルが出血性脳卒中と関連し，非喫煙，脳底動脈狭窄，糖尿病，高齢が虚血性脳卒中と関連していたとの結果であった．

一方，best medical treatmentにおいて，神経内科医などによる2週間ごとの生活指導などの監視が厳格すぎて実際の臨床と齟齬があること，また薬物治療が優位との結果ながら，1年後の脳卒中または死亡率は12%に上ることが指摘されている．

3）Wingspanステント（Striker Neurovascular）

SAMMPRIS試験で用いられた，50%以上の頭蓋内血管狭窄治療用に開発された自己拡張性のナイチノール製open-cell構造のステントで20 mm長まであるが，病変の近遠位端をそれぞれ3 mm以上カバーして留置する必要があるため，プラーク長は14 mm未満までが適応となる．しかし，SAMMPRIS試験の結果を受けて，FDAにより症候に関連する70～99%動脈硬化性狭窄であること，積極的薬物治療でも脳卒中を反復していること，最終発作が7日以上前であること，先行する脳卒中からmRS 3以下に回復していること，TIAは治療対象から除外することなど使用条件が厳しく限定された[3]．本邦では，2013年11月に経皮的血管形成術（PTA）後の血管解離，急性閉塞，切迫閉塞に対する緊急処置rescue stentingまたはほかに有効な治療法がないと判断されるPTA後再治療用として承認され，日本脳卒中学会，日本脳神経外科学会，日本脳血管内治療学会合同の適正使用指針[64]を順守することが求められている．

頭蓋内に使用可能なステントとして，ほかにNeuroform EZ（Boston Scientific）やEnterprise VRD（Codman）が薬事承認されているが，これらは動脈瘤のコイル塞栓支援用として承認されたものである[75]．

2．間接血行再建術

上述のSAMMPRISやCOSS studyの結果を受けて，もやもや病で用いられるEDAS（encephalo-duro-arterio-synangiosis）などの間接血行再建術が頭蓋内血管閉塞性疾患でも試みられている[54]．Gonzalezら[27]は，術後6カ月から1年で脳血管撮影上，側副血行形成を認め，平均54カ月の経過観察で84%でTIA，脳卒中または死亡が予防でき，出血などの合併症もなかったと報告している．

V．結　語

脳梗塞慢性期外科治療としての慢性期血行再建術について概説した．本文中に述べたように，血管内治療の発展は著しくまさに日進月歩であり，今後もopen surgery，内科的治療との関係は変容していくと思われる．ただし現状では，頭蓋内血管狭窄に対する血管内治療については慎重な対応が求められる．また，無症候性頭動脈狭窄症に対する外科治療適応への内科治療の進歩が与える影響について，現在進行中のRCTその他の試験結果が注目される．

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Neurol Med Chir (Tokyo) 54, 1–8, 2014

doi: 10.2176/nmc.oa.2013-0197
Online December 27, 2013

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

Recent Trends in Neuroendovascular Therapy in Japan: Analysis of a Nationwide Survey—Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

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Received June 8, 2013; Accepted November 1, 2013

Abstract

The present study retrospectively analyzed the database of the Japanese Registry of Neuroendovascular Therapy 1 and 2 (JR-NET1&2) to determine annual trends, including adverse events and clinical outcomes at 30 days after undergoing neuroendovascular therapy. JR-NET1&2 are surveys that targeted all patients in Japan who underwent neuroendovascular therapy delivered by physicians certified by the Japanese Society of Neuroendovascular Therapy (JSNET) between 2005 and 2009. Medical information about the patients was anonymized and retrospectively registered via a website. Data from 32,608 patients were analyzed. The number of treated patients constantly increased from 5,040 in 2005 to 7,406 in 2009 and the rate of octogenarians increased from 7.0% in 2005 to 10.4% in 2009. The proportion of procedures remained relatively constant, but ratios of angioplasty slightly increased from 32.8% in 2005 to 33.7% in 2009. Procedural complications were associated more frequently with acute stroke (9.6%), ruptured aneurysms (7.4%), intracranial artery disease (ICAD) (5.4%), and arteriovenous malformation (AVM, 5.2%). The number of patients requiring neuroendovascular treatment in Japan is increasing and the outcomes of such therapy are clinically acceptable. Details of each type of treatment will be investigated in sub-analyses of the database.

Key words: nationwide survey, endovascular treatment, cerebral aneurysm, angioplasty, clinical outcome

Introduction

Neuroendovascular therapy is a less invasive method of treating various cerebrovascular diseases such as cerebral aneurysm, supra-aortic artery stenosis/occlusion, arteriovenous shunts, and acute stroke[1–8] that has become increasingly popular. However, the current status of this therapy including numbers of procedures, clinical outcomes, and adverse events remain unknown.[9,10]

The Japanese Society of Neuroendovascular Therapy (JSNET) established a board certification system in 2000 that certified physicians with ≥200 primary operator experiences, ≥10 presentations at medical meetings, and ≥3 publications as primary author as senior trainers and specialists through a board examination. The JSNET produced an expert consensus document in 2009 when a systematic review revealed a scarcity of high-quality clinical evidence in this field, especially in Japan. Thus, the society implemented retrospective studies (Japanese Registry of Neuroendovascular Therapy 1 and 2; JR-NET1&2) to clarify the general status of neuroendovascular therapy delivered by JSNET-certified physicians. Clinical and procedural data were retrospectively collected from January 2005 through December 2007 (JR-NET1) and from January 2008 through December 2009 (JR-NET2).

These studies aimed to determine annual changes in neuroendovascular treatment modalities and in major adverse events within 30 days thereafter.

Methods

I. Study design

JR-NET1 (2005–2006): This was the first nationwide survey of neuroendovascular treatments in Japan. The registry targeted all patients treated by JSNET board-certified physicians between January 2005 and December 2006, except for those whom their physicians judged unsuitable for this registry. Medical information about the patients was anonymized and retrospectively registered via a website (https://jr-net.tri-kobe.net/jr-net/).

JR-NET2 (2007–2009): This second nationwide survey of neuroendovascular treatment in Japan targeted all patients treated by JSNET board-certified physicians between January 2007 and December 2009. Medical information of the patients was anonymized and registered as described above.

Data were collected at the Translational Research Informatics Center (TRI, http://www.tri-kobe.org/). The study protocol, which is summarized briefly here, is available on line with the full text of this article (https://jr-net.tri-kobe.net/jr-net/). All members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study with regard to the protocol.

II. Patients

All patients treated by neuroendovascular treatment at participating centers during the study period were basically enrolled in the study. The local institutional review boards at each institution approved the study protocol before the investigators proceeded with the study.

III. Primary and secondary endpoints

The primary endpoint was activities of daily life (ADL) determined according to modified Rankin scale (mRS) scores. The secondary endpoints comprised the technical success of procedures and major adverse events (MAEs) that occurred within and at 30 days after procedures.

A score of 0 on the mRS indicates no disability, whereas scores of 1 or 2 indicate slight disability (some help required with ADL but basically independent), scores of 3 to 5 indicate moderate disability (some help required with ADL) to severe disability (bedridden or constant specific care required), and a score of 6 indicates death.

Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥2 points, respectively.

IV. Statistical analysis

Data were statistically analyzed using JMP 7 software (SAS Institute, Cary, North Carolina, USA). The statistical significance of intergroup differences was assessed using the *t*-test for quantitative scales, Pearson's χ^2 test; $p < 0.05$ was considered significant.

Results

I. Backgrounds and characteristics of patients

A total of 32,068 patients (mean age, 63.5 ± 13.9

Table 1 Annual trends of JR-NET data

	2005	2006	2007	2008	2009	Total
Total number	n = 5,040	n = 6,174	n = 6,690	n = 6,758	n = 7,406	n = 32,068
Age	64.0+/–13.8	63.4+/–12.9	64.1+/–13.7	64.6+/–13.3	64.4+/–13.8	63.5+/–13.9
Female	2,341 (46.4%)	2,921 (47.3%)	3,109 (46.5%)	3,131 (46.3%)	3,495 (47.2%)	14,997 (46.8%)
mRS before treatment	0.7	0.7	0.7	0.6	0.6	0.7
Procedures	n = 4,500	n = 5,457	n = 6,466	n = 6,503	n = 7,232	n = 30,158
Aneurysm treatment	1,777 (39.5%)	2,396 (43.9%)	2,725 (42.1%)	2,668 (41.0%)	3,112 (43.0%)	12,678 (40.5%)
Dome embolization, ruptured	751 (16.7%)	963 (17.7%)	1,073 (16.6%)	1,091 (16.8%)	1,254 (17.3%)	5,132 (17.0%)
Dome embolization, unruptured	883 (19.6%)	1,105 (20.3%)	1,373 (21.2%)	1,302 (20.0%)	1,597 (22.1%)	6,260 (20.8%)
Dissection/parent artery occlusion	143 (3.2%)	328 (6.0%)	279 (4.3%)	275 (4.2%)	261 (3.6%)	1,439 (4.8%)
Angioplasty/stenting	1,476 (32.8%)	1,734 (31.2%)	2,275 (35.2%)	2,363 (36.3%)	2,438 (33.7%)	10,286 (34.1%)
Carotid artery	1,042 (23.2%)	1,281 (23.5%)	1,717 (26.6%)	1,855 (28.5%)	1,926 (26.6%)	7,821 (25.9%)
Vertebral/subclavian artery	203 (4.5%)	230 (4.2%)	281 (4.4%)	282 (4.3%)	254 (3.5%)	1,250 (4.1%)
Intracranial artery	231 (5.1%)	223 (4.1%)	277 (4.3%)	226 (3.5%)	258 (3.6%)	1,215 (4.0%)
Brain & spinal AVM embolization	217 (4.8%)	281 (5.1%)	204 (3.2%)	213 (3.3%)	259 (3.6%)	1,174 (3.9%)
DAVF embolization	317 (7.0%)	424 (7.8%)	468 (7.2%)	464 (7.1%)	525 (7.3%)	2,198 (7.3%)
Tumor embolization	347 (7.7%)	373 (6.8%)	317 (4.9%)	319 (4.9%)	382 (5.3%)	1,738 (5.8%)
Acute stroke treatment	366 (8.1%)	249 (4.6%)	277 (4.3%)	266 (4.1%)	281 (3.9%)	1,439 (4.8%)
Physicians in charge	n = 4,935	n = 5,988	n = 6,690	n = 6,758	n = 7,406	n = 31,777
Senior trainer, board certified	3,139 (63.6%)	3,573 (59.7%)	3,097 (46.3%)	3,277 (48.5%)	3,624 (48.9%)	16,710 (52.6%)
Specialist, board certified	1,355 (27.5%)	1,801 (30.1%)	3,103 (46.4%)	3,044 (45.0%)	3,358 (45.3%)	12,661 (39.8%)
Non-specialist	438 (8.9%)	617 (10.3%)	462 (6.9%)	375 (5.5%)	405 (5.5%)	2,297 (7.2%)

AVM: arteriovenous malformation, DAVF: dural arteriovenous fistula, mRS: modified Rankin Scale.

years; female, 46.8%) were registered in this study (Table 1), which involved 200 and 256 board-certified physicians at 122 and 150 centers in JR-NET[11] and in JR-NET2, respectively (Appendix). Figure 1 shows the proportions of treated patients within various age groups. Although patients aged between 40 years and 70 years were the main recipients of treatment, the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$). In contrast, the ratio of younger patients (< 40 years) remained constant ($p = 0.361$; Fig. 1).

II. Procedures

Among a total of 32,068 neuroendovascular procedures implemented between 2005 and 2009, angioplasty and treatment for aneurysms accounted for 34.1% and 40.5%, respectively. Embolization of brain and spinal arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF), tumors, and treatment for acute stroke accounted for 3.9%, 7.3%, 5.8%, and 4.8% of procedures, respectively. Carotid artery stenting (CAS) accounted for 25.9% of all procedures (Table 1). The proportions of treatments remained relatively constant, except for CAS, which slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$; Fig. 2).

Elective or emergency procedures: The total numbers of elective and emergency procedures increased annually, but the rate of emergency treatment remained relatively constant between 28% and 30% throughout the study period (Fig. 3).

Physicians in charge: Senior trainers certified by JSNET were in charge of 63.6% and 48.9% of procedures during 2005 and in 2009 (Table 1), respectively. The total number of treatment procedures with JSNET senior trainers and specialists in charge increased annually, but the rate of procedures supervised by JSNET senior trainers gradually decreased, although the difference did not reach significance. However, treatment delivered with JSNET non-specialist in charge decreased from 8.9% in 2005 to 5.5% in 2009 ($p = 0.029$).

mRS scores before and after treatment: Figure 4A and 4B shows the overall proportions of mRS scores before and after treatment. Before treatment, ≥90% of patients were in relatively good condition, with mRS scores of 0–2 (Fig. 4A). At 30 days after undergoing procedures, >80% of patients maintained mRS scores of 0–2 (Fig. 4B).

mRS scores after each type of procedure: Figure 5 shows the outcomes of each type of treatment

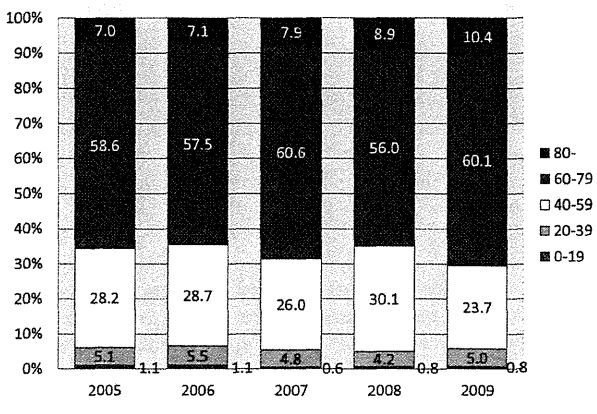

Fig. 1 Annual changes in patients' age during JR-NET1&2. Rates of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$), whereas the ratio of younger patients (< 40 years) remained constant ($p = 0.361$). JR-NET1&2: Japanese Registry of Neuroendovascular Therapy 1 and 2.

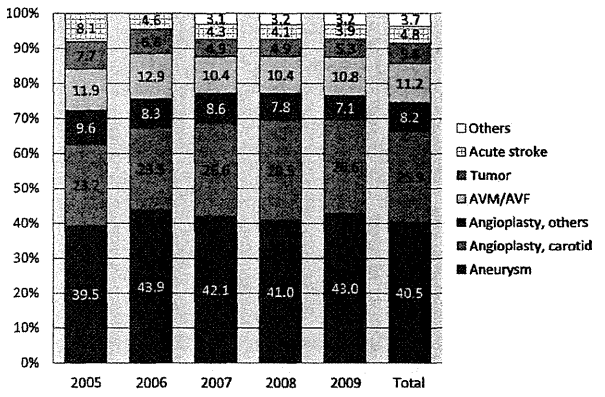

Fig. 2 Annual changes in the types of procedures. The proportion of treatments remained relatively constant, but carotid artery stenting (CAS) slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$).

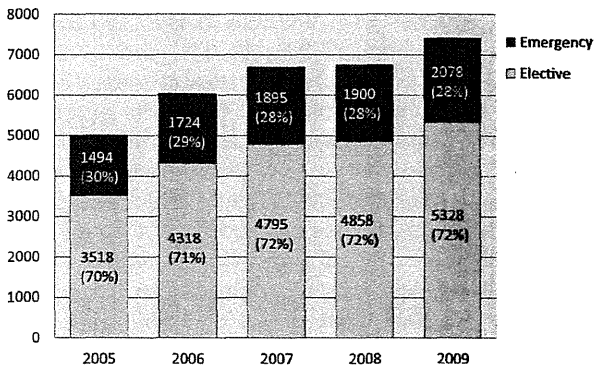

Fig. 3 Number of elective and emergency procedures. The total numbers of elective and emergency procedures increased annually, although the overall rate of emergency treatment remained between 28% and 30% throughout the period.

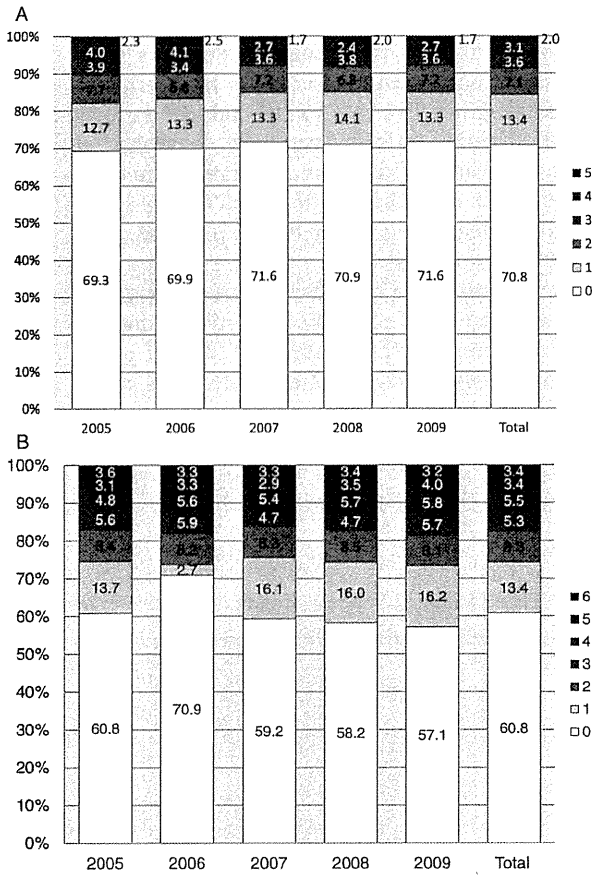

Fig. 4 Proportions of modified Rankin scale (mRS) scores before and after procedures. Ratio of patients with mRS 0–2 was ≥90% before therapeutic procedures (A), decreased at 30 days thereafter (B), but remained >80%.

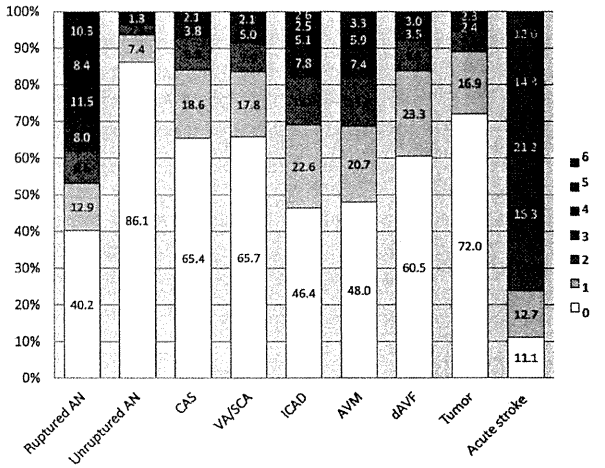

Fig. 5 Proportions of modified Rankin scale (mRS) scores at 30 days after various procedures. Outcomes were favorable (mRS 0–2) for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms respectively. Ratios of favorable outcomes of carotid artery stenting (CAS), vertebral artery (VA)/SCA (subclavian artery), dural arteriovenous fistula (dAVF), and tumor embolization were >90%. On the other hand, the ratios of favorable outcomes were 82.0%, 81.9%, and only 37.2% in intracranial artery disease (ICAD), arteriovenous malformation (AVM) and acute stroke, respectively.

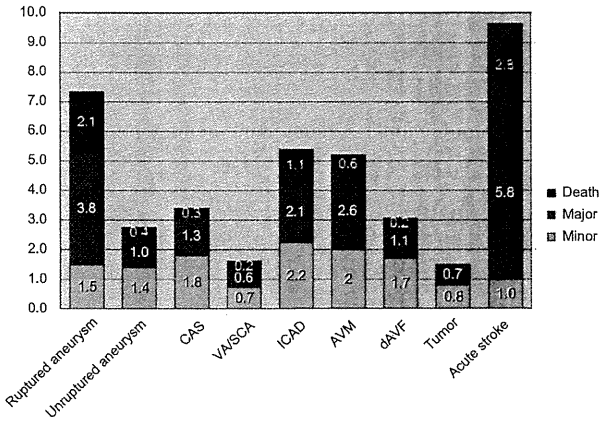

Fig. 6 Complications associated with each procedure. Complication rates were higher after procedures for ruptured aneurysm (7.4%) and acute stroke (9.5%), but less frequent for those that treated unruptured aneurysms (2.8%), VA/SCA (1.5%), and tumor embolization (1.5%).

according to mRS scores. Outcomes were favorable for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms, respectively, (mRS 0–2) and for ≥90% those after CAS, VA/SCA, dAVF, and tumors. On the other hand, 82.0%, 81.9%, and 37.2% of those treated for intracranial artery disease (ICAD), in AVM, and acute stroke had favorable outcomes.

Procedural complications of each treatment: Figure 6 shows the frequency of procedural complications after each type of treatment. Death, major and minor procedural complications occurred in 7.4% and 2.8% of patients treated for ruptured and unruptured aneurysms, respectively. Among angioplasties, procedural complications occurred in 3.4%, 1.5%, and 5.4% in the carotid artery, the VA/SCA and in ICAD, respectively. Among arteriovenous shunt diseases, complications developed in 5.2% and 3.0% of those treated for AVM and dAVF, respectively. The rate of complications of tumor embolization was 1.5%, and none of the patients died of procedure-related complications. On the other hand, complications developed at a rate of 9.6% in patients treated for acute stroke, including 2.8% who died.

Discussion

The present study investigated recent trends in neuroendovascular therapy through analyses of 32,608 patients registered in the nationwide JR-NET1&2 surveys. The number of procedures constantly increased from 5,040 in 2005 to 7,406 in 2009, and the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009. The proportion of treatments remained relatively constant, but angioplasty/stenting for carotid diseases slightly increased from 23.2% in 2005 to 26.6% in 2009. More procedural complications were associated with acute stroke (9.5%), ruptured aneurysm (7.4%), ICAD (5.4%), and AVM (5.2%).

The number of annual neuroendovascular procedures increased by 46.9% (from 5,040 to 7,406). The annual numbers of procedures required to treat intracranial aneurysms and angioplasty/stenting for atherosclerotic disease between 2005 and 2009 increased by 75.1% (from 1,777 to 3,112) and 65.2% (1,476 to 2,438), respectively. The mRS scores after procedures remained favorable in >80% of the patients each year. Clinical outcomes and complication rates significantly differed among procedures. Rates of favorable outcomes of procedures to treat ruptured aneurysms and acute stroke were around 60% and < 40%, respectively, and more procedural complications were also associated with these conditions. However, whether complications were major or minor was sometimes difficult to judge in emergency patients under general anesthesia or sedation, and in patients with poor neurological status. Thus, procedural complications in these two groups might have been over- or underestimated.

Several reports have described nationwide trends in neuroendovascular therapies.[12–19] Some of them are analyses of a national healthcare database in the United States.[12–15,17,20] For example, Huang et al. reported trends in the management of unruptured cerebral aneurysms in the United States.[15] They analyzed the length of hospital stay, in-hospital mortality rates, the number of hospitalizations, and total national charges related to inpatient treatment. Their findings provide valuable information regarding trends, but obtaining clinical data about neurological status, neuroendovascular procedures, and follow-up results might be difficult. Detailed evaluations and analyses could be achieved if areas or centers were selected. Higashida et al. described endovascular treatment for unruptured intracranial aneurysms in 18 of 47 states in the United Staes during 2007.[21] Qureshi et al. described how class I evidence (ISAT) from a nationwide impact survey impacted clinical practice. Their database was derived from stratified sampling at 20% of US hospitals.[20] In that regard, data from the nationwide JR-NET1&2 surveys are valuable because the study collected precise information regarding not only patient's characteristics, but also neurological status, types of treatment, devices, complications, and follow-up at 30 days after procedures.

This study has some limitations. Although JR-NET 1&2 provided a robust amount of patient information including clinical details, particularly information related to neuroendovascular therapies, it covered only about 35% of all procedures performed in Japan, which was calculated according to annual reports of training facilities of the Japan neurosurgical society (unpublished). This was a significant drawback in terms of avoiding selection bias. This shortcoming might be improved in a new nationwide survey (JR-NET 3), which is collecting information between 2010 and 2013 in a similar setting to that of JR-NET 1&2.

Conclusion

Data from this study suggest an increasing trend towards neuroendovascular treatment in Japan. The rate of neuroendovascular intervention is increasing annually and clinical outcomes seem acceptable. Details about each treatment or disease will be assessed in sub-analyses of this database.

Acknowledgments

The authors express their special thanks to the study group members: The JR-NET Study Group: Principle investigator, N. Sakai; Investigators: A. Hyodo, S. Miyachi, Y. Nagai, C. Sakai, T. Satow, W. Taki, T. Terada, M. Ezura, T. Hyogo, S. Matsubara, K. Hayashi; Co-investigators; T. Fujinaka, Y. Ito, S. Kobayashi, M. Komiyama, N. Kuwayama, Y. Matsumaru, Y. Matsumoto, Y. Murayama, I. Nakahara, S. Nemoto, K. Satoh, K. Sugiu S. Yoshimura and the specialists certified by the Japanese Society for Neuroendovascular Therapy listed in the Appendix. This study was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan.

Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS members.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal.

Appendix

Participants, their hospitals, and the number of registered patients in JR-NET2 are listed when >100 patients were registered; names of investigators are listed when < 100 patients were registered. This information has already been reported for JR-NET1.[11]

Y Matsumoto, R Kondo, E Kondo, Y Matsumori, Kohnan Hp., 913; N Sakai, H Adachi, Y Ueno, H Imamura, H Yamagami, Y Kuramoto, Kobe City Med. Ctr General Hp., 809; I Nakahara, Y Watanabe, Kokura Memorial Hp., 586; T Abe, M Hirohata, Kurume Univ., 535; K Sugiu, K Tokunaga, Okayama Univ., 485; M Ezura, S Nishimura, N Kimura, I Suzuki, Sendai Med. Ctr, 471; M Nakamura, Hyogo Brain and Heart Ctr at Himeji, 448; T Suyama, M Nagashima, Tominaga Hp., 427; K Goto, S Ota, Brain Attack Ctr Ota Memorial Hp., 409; S Yamazaki, Tsuchiura Kyodo Hp., 348; T Nakazawa, Shiga Med. Univ., 347; Y Matsumaru, W Tsuruta, M Hayakawa, Toranomon Hp., 344; K Kazekawa, M Tsutsumi, H Aikawa, T Kodama, Fukuoka Univ. Chikushi Hp., 334; W Taki, H Sakaida, N Toma, F Asakura, Mie Univ. 324; E Kobayashi, N Hayasaka, Chiba Univ., 322; S Yoshimura, Y Enomoto, Gifu Univ., 290; K Iihara, T Satow, N Nakajima, Y Takenobu, National Cardiovascular Ctr, 289; M Kawanishi, A Shindo, K Kawakita, T Yano, Kagawa Univ., 276; H Shibuya, Sagamihara Kyodo Hp., 262; C Sakai, N Sakai, Institute of BioMed. Research and Innovation, 258; N Fukui, Kochi Med. Ctr, 258; T Hyogo, T Kataoka, Nakamura Memorial Hp., 230; I Naito, T Iwai, M Takatama, N Miyamoto, Geriatrics Research Institute and Hp., 228; T Ueda, T Takada, Y Otsuka, St. Marianna Univ. Toyoko Hp., 222; N Kuwayama, N Eiraku, N Akioka, Toyama Univ., 217; H Ishihara, Yamaguchi Univ., 214; T Nonaka, A Takahashi, Shiroishi Neurosurgical Hp., 213; T Hatano, M Murakami, Kyoto Med. Ctr, 205; T Hashimoto, Tokyo Med. Univ., 201; D Sato, Aizawa Hp, 200; A Nakahara, R Ogami, M Hp., 200; T Ichihashi, Fukuroi Municipal Hp., 196; T Fujinaka, M Hirata, M Sakaguchi, T Nishida, Osaka Univ., 196; M Komiyama, T Ishiguro, Osaka City General Hp., 193; Y Kiura, T Okazaki, S Sakamoto, Hiroshima Univ., 193; Y Akiyama, Tenri Hp., 186; H Sato, Tokyo Police Hp.,185; A Ishii, A Morizane, Kyoto Univ., 182; K Takayama, Ishinkai Yao Hp., 181; M Imaoka, Aso General Hp., 177; J Hamada, N Uchiyama, M Mori, Kanazawa Univ., 173; H Abe, Tachikawa General Hp., 170; A Nishio, Y Mitsuhashi, T Kawakami, Osaka City Univ., 170; S Iwabuchi, M Hayashi, Toho Med. Univ. Ohashi Hp., 162; M Nagahata, N Shimamura, Hirosaki Univ., 159; T Kubota, Hakodate Neurosurgical Hp., 158; K Imai, T Takeshita, Kyoto First Red Cross Hp., 153; H Sakai, Toyohashi Med. Ctr, 150; K Fujimoto, Osaka General Med. Ctr, 150; T Higa, Tokyo Women's Med. Univ., 147; K Harada, Fukuoka Wajiro Hp., 145; S Kobayashi, N Koguchi, T Yamauchi, Chiba Emergency Med. Center, 144; N Ikeda, Ube Kosan Central Hp.; H Hiramatsu, Hamamatsu Med. Univ., 142; J Satomi, Tokushima Univ.,139; H Ota, I Ikushima, Miyakonojo Med. Association Hp., 138; H Tenjin, Y Kosaka, Kyoto Second Red Cross Hp.,134; K Akaji, Mihara Memorial Hp., 128; S Aketa, Osaka Police Hp., 124; K Hayashi, M Morikawa, N Horie, K Hiu, Nagasaki Univ., 121; H Morishima, St. Marianna Univ. School of Medicine, 111; F Oya, Nagano Municipal Hp., 111; A Hyodo, K Suzuki, Dokkyo Med. Univ. Koshigaya Hp., 109; Y Arai, Fukui Univ., 106; M Sakamoto, Tottori Univ., 103; J-H Son, Shinmatsudo Chuo General Hp., 101; K Hayasaki, Saiseikai Ibaraki Hp., 101; S Tamatani, S Yamamoto, Dokkyo Med. Univ., 100; M Yasuda, Y Fumoto, Kano Hp., 100.

K Haraguchi, H Manabe, M Hayashi, O Kikuchi, S Iihoshi, K Miyata, J Sakurai, S Yamauchi, A Takahashi, N Tamagawa, J Moroi, A Shimada, K Asakura, H Shimaguchi, O Miyagi, M Matsumoto, A Kojima, T Takahashi, S Ishihara, S Kohyama, F Yamane, T Dembo, R Kanazawa, K Nakai, M Katayama, S Kittipong, M Tanaka, Y Numaguchi, M Fujimoto, A Uemura, T Saguchi, O Tone, Y Sato, K Shigeta, Y Yoshida, T Ohashi, K Amari, Y Sakata, S Tateshima, Y Ito, T Sorimachi, S Inagawa, K Morita, K Kitazawa, M Arai, N Minamide, Y Hirota, Y Takabatake, K Kanemaru, J Yamada, H Kitajima, S Fukazawa, T Okamoto, T Nakano, A Tsurumi, T Kojima, M Negoro, A Sadato, M Hayakawa, T Watanabe, K Irie, T Tanaka, T Hattori, N Kobayashi, A Tsuji, M Kawanishi, M Yamada, M Hirai, K Owada, M Ohashi, T Ota, K Maeno, S Sakamoto, T Kuroiwa, K Murao, K Nakazawa, J Kobayashi, N Nakagawa, T Fukawa, A Fujita, K Matsumoto, Y Yoshida, I Yamaura, A Masuda, H Minami, K Uchida, M Shirakawa, H Nakagawa, I Nakagawa, H Takeuchi, S Kawada, A Handa, M Koyanagi, K Yoshida, S Matsubara, T Mizogami, K Migita, H Yasuda, S Kato, K Satoh, M Hanaoka, N Hayashi, K Yoshino, A Nishida, T Shiraishi, O Nishizaki, M Iwanaga, T Higashi, M Iwaasa, M Okawa, K Nakahara, T Yoshioka, M Kaji, Y Hori, T Asano, M Okahara, A Kashiwagi, H Kiyosue, S Tanoue, T Kubo, and H Yonaha.

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Neurol Med Chir (Tokyo) 54, 54–62, 2014

doi: 10.2176/nmc.oa2013-0183
Online November 29, 2013

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 2 Arteriovenous malformation characteristics in 987 procedures

	No. of procedures (%)
Spetzler-Martin grade	
I	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

	No. of 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 ≤ 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 procedures

	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 5 mRS scores pre- and postembolization

mRS score	Preembolization		Postembolization	
	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 related complications by univariate analysis

Parameter	OR	(95%CI)	P
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 cm ≤, < 6 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 embolized			
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 = 0.03 for both). In multivariate logistic regression models (Table 7), deep venous drainage and embolization

Table 7 Predictors for embolization related complications by multivariate logistic regression model test

Parameter	OR	(95%CI)	P
Male gender	0.55	(0.30–1.02)	0.06
AVM size 6 cm ≤	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 ≤ 2), compared with 877 of 987 patients (88.6%) at baseline. In other words, in 87 procedures, patents' mRS scores deteriorated from nondisabled (mRS ≤ 2) to disabled or dead (mRS ≥ 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 ≤ 2) to disabled or dead (mRS ≥ 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] Jayaraman 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 Literature reporting on embolization of cerebral AVMs

Author	Year	Design	Dominant embolic material	No. patients	No. procedures	Subsequent treatment (%)				Cured# (%)	Per procedure (%)		Per patient (%)	
						S*	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.[21]	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	Onyx	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	Onyx	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	Onyx	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, **: radiosurgery, ***: embolization alone. #: complete occlusion of AVM by embolization alone. AVM: arteriovenous malformation, NBCA: *N*-butyl cyanoacrylate.

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 morphologic 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 (≥ 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.