A comparison of the prevalence and risk factors of complications in intracranial tumor embolization between the Japanese Registry of NeuroEndovascular Therapy 2 (JR-NET2) and JR-NET3

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Abstract

Background: The Japanese Registry of NeuroEndovascular Therapy 2 (JR-NET2) and 3 (JR-NET3) were nationwide surveys that evaluated clinical outcomes after neuroendovascular therapy in Japan. The aim of this study was to compare the prevalence and risk factors of complications of intracranial tumor embolization between JR-NET2 and JR-NET3.

Methods: A total of 1018 and 1545 consecutive patients with intracranial tumors treated with embolization were enrolled in JR-NET2 and JR-NET3, respectively. The prevalence of complications in intracranial tumor embolization and related risk factors were compared between JR-NET2 and JR-NET3.

Results: The prevalence of complications in JR-NET3 (3.69%) was significantly higher than that in JR-NET2 (1.48%) (p = 0.002). The multivariate analysis in JR-NET2 showed that embolization for tumors other than meningioma was the only significant risk factor for complication (odds ratio [OR], 3.88; 95% confidence interval [CI], 1.13-12.10; p = 0.032), and that in JR-NET3 revealed that embolization for feeders other than external carotid artery (ECA) (OR, 3.56; 95% CI, 2.03-6.25; p < 0.001) and use of liquid materials (OR, 2.65; 95% CI, 1.50-4.68; p < 0.001) were significant risks for complications. The frequency of embolization for feeders other than ECA in JR-NET3 (15.3%) was significantly higher than that in JR-NET2 (9.2%) (p < 0.001). Also, there was a significant difference in the frequency of use of liquid materials between JR-NET2 (21.2%) and JR-NET3 (41.2%) (p < 0.001).

Conclusions: Embolization for feeders other than ECA and use of liquid materials could increase the complication rate in intracranial tumor embolization.

Key words:

complication, embolization, intracranial tumor, risk factors

Introduction

Embolization for intracranial tumors before surgical resection, especially for extra-axial hypervascular tumors, is routine in the clinical setting in Japan. The aims of preoperative embolization are to remove devascularized tumors safely, to shorten the operation time, and to avoid blood loss and transfusion. The multicenter Japanese Registry of NeuroEndovascular Therapy (JR-NET) Study Group was formed in 2005 to determine annual trends, including adverse events and clinical outcomes 30 days after neuroendovascular therapy [17]. JR-NET1 ran from January 2005 to December 2006, JR-NET 2 from January 2007 to December 2009, and JR-NET3 from January 2010 to December 2014. JR-NET1, JR-NET2, and JR-NET3 consisted of the following kinds of treatment modalities: embolization for cerebral aneurysms, cerebral arteriovenous malformations (AVM), spinal vascular lesions, intracranial dural arteriovenous fistulas; intracranial tumor embolization; carotid artery stenting; intra/extracranial artery percutaneous transluminal angioplasty or stenting; recanalization for acute major artery occlusion and remission for cerebral vasospasm after aneurysmal subarachnoid hemorrhage [2-9,11,14,18,20,22]. The results of embolization of meningiomas and other intracranial tumors were evaluated in JR-NET2 and JR-NET3 and reported, respectively [6,21]. The aims of this study were to compare the prevalence and risk factors of complications of intracranial tumor embolization between JR-NET2 and JR-NET3 and to reveal the technological and conceptual shift between the two periods.

Patients and Methods

A total of 1018 and 1545 consecutive patients with intracranial tumors treated with embolization were enrolled in JR-NET2 and JR-NET3, respectively [6,21]. The primary end point was the proportion of patients with a modified Rankin scale (mRS) score of 0-2 at 30 days after the procedure, and the secondary end point was the occurrence of complications related to the procedures in both studies. The study protocols of JR-NET2 and JR-NET3 were approved by the institutional review board at Kobe City Medical Center General Hospital. Because this was a retrospective noninvasive study, written informed consent was not obtained from patients.

As was the case with JR-NET2 [6], age, gender, preoperative mRS, type of tumor, anesthesia, scheduled intervention, main operator, target vessels, and results of embolization were checked as baseline characteristics for 1545 patients in JR-NET3. The Japanese Society of Neuro-Endovascular Therapy has a Specialist Qualification System through which it certifies two classes of specialists: specialists and consulting specialists. A consulting specialist is a senior specialist who must already be qualified as a specialist. In JR-NET2 and JR-NET3, a specialist or consulting specialist had to participate in each patient's neuroendovascular treatment. Onyx^{TM} (Medtronic, Minneapolis, Minnesota) was newly added to the types of embolic materials as liquid materials in JR-NET3. The target vessels were categorized as the feeders from the external carotid artery (ECA) and those from other than ECA, such as internal carotid or vertebrobasilar artery. The results of embolization was graded as total, subtotal, partial and unchanged.

Procedural complications were defined as any neurological deficit or death that occurred during or after embolization. Abnormalities after embolization, such as intracranial ischemic or hemorrhagic changes on computed tomography or magnetic resonance imaging were also classified as procedural complications even if the patients were asymptomatic.

Statistical analysis

Quantitative variables are presented as a percentage or as the median and interquartile ranges. Statistical analysis was performed using Fisher's exact probability test, the chi-square test, and the Mann-Whitney U test, as appropriate. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [10]. When variables associated with the occurrence of complications had a probability value less than 0.05 using a univariate analysis, they were selected for a multivariate analysis. Differences were considered to be significant when p values were less than 0.05.

Results

As the record for six patients in JR-NET2 and one in JR-NET3 did not have sufficient information for evaluation, 1012 (637 females, median age 60 years [interquartile range (IQR) 50-68 years]) and 1544 patients (937 females, median age 63 years [IQR 52-70 years]) were analyzed in JR-NET2 and JR-NET3, respectively.

Table 1 shows the patient characteristics in JR-NET2 and JR-NET3. Table 2 presents a comparison of patient characteristics and incidence of end points between JR-NET2 and JR-NET3. The primary end point (mRS score ≤ 2 at 30 days after the procedure) was observed in 924 patients (91.3%) and 1382 patients (89.5%), respectively. Fifteen of the 1012 patients (1.48%) suffered from procedural complications in JR-NET2, and 57 of the 1544 patients (3.69%) in JR-NET3. The prevalence of complications in JR-NET3 was significantly higher than that in JR-NET2 ($p = 0.002$).

Types and outcomes of complications

Table 3 presents the types and outcomes of complications related to the embolization procedures in both studies. The types of complications consisted of intracranial hemorrhage, ischemia, and others. There were no significant differences in the types of complications between JR-NET2 and JR-NET3 ($p = 0.33$). The outcomes of complications were classified as minor and major; minor complications included no symptoms or transient symptoms with complete remission within 30 days, and major complications included a more than 1 point decrease in mRS score. The prevalence of major complications in JR-NET3 tended to be higher than that in JR-NET2, although the p value did not reach significance ($p = 0.30$). Table

4 reveals the association between the types and outcomes of complications in JR-NET2 and JR-NET3. The hemorrhagic complication was significantly associated with major outcome in JR-NET2 ($p = 0.042$), and the ischemic complication was significantly correlated with major outcome in JR-NET3 ($p = 0.034$).

Risk factors of complications

Table 5 shows the results of univariate and multivariate analysis for risk factors related to the complications in JR-NET2 and JR-NET3. The multivariate analysis in JR-NET2 showed that embolization for tumors other than meningioma was the only significant risk factor for complication (OR, 3.88; 95% CI, 1.13-12.10; $p = 0.032$), and that in JR-NET3 revealed that embolization for feeders other than ECA (OR, 3.56; 95% CI, 2.03-6.25; $p < 0.001$) and use of liquid materials (OR, 2.65; 95% CI, 1.50-4.68; $p < 0.001$) were significant risks of complications.

Comparison of the types and outcomes of complications between with and without embolization for feeders other than ECA and use of liquid materials in JR-NET3

Table 6 demonstrates the comparison of the types and outcomes of complications between with and without embolization for feeders other than ECA and use of liquid materials in JR-NET3. The prevalence of ischemic complications with embolization for feeders other than ECA was significantly higher than that without embolization for feeders other than ECA (78.2% vs 41.2%, $p < 0.001$). The outcomes of complications with use of liquid materials were significantly poorer than those without use of liquid materials ($p = 0.03$).

Discussion

The JR-NET series were nationwide surveys and representative of large-scale studies related to the results of neuroendovascular therapies in Japan. In terms of intracranial tumor embolization, JR-NET2 and JR-NET3 were unprecedented large cohort studies, and this is the first report to compare the prevalence and risks of complications in intracranial tumor embolization between the largest cohorts in the same nation. The important findings in this investigation are as follows: first, the prevalence of complications in JR-NET3 was approximately 2.5 times higher than that in JR-NET2, and the difference was significant ($p = 0.002$); second, the significant risk factors of complications were different between JR-NET2 and JR-NET3, namely embolization for tumors other than meningioma in JR-NET2 and embolization for feeders other than ECA and use of liquid materials in JR-NET3, respectively. The increase in the prevalence of complications in JR-NET3 is likely attributable to embolization for feeders other than ECA and use of liquid materials, according to multivariate analysis for risk factors of complications.

The occurrence of ischemic complication in the central nervous system is of concern in patients with embolization for feeders other than ECA [15]. Our data revealed that the frequency of embolization for feeders other than ECA in JR-NET3 (15.3%) was approximately 1.5 times higher than that in JR-NET2 (9.2%) and the difference was significant (Table 2). Also, in JR-NET3, the prevalence of ischemic complications in patients with embolization for feeders other than ECA was significantly higher than that in patients with embolization for ECA feeders (Table 5). The complication rate of intracranial meningeal tumor embolization for feeders other than ECA was reported to be 9% [15]. Rosen et al. analyzed the results of embolization for 167 skull base meningiomas, in which 41% were embolized for meningohypophyseal arteries from ICA and revealed that 12.6% and 9% of all patients experienced transient and permanent neurological deficits as a result of embolization, respectively [16]. Wadron et al. put forth that the high complication rate in this study was attributable to the goal of complete occlusion of all feeders including feeders from ICA and proposed that complication avoidance should be emphasized over complete devascularization [23].

N-butyl cyanoacryllate (NBCA) is the most popular liquid material used in intracranial tumor embolization in Japan. The rapid penetration into tumor vasculature and the permanent effect of embolization are advantages of NBCA in embolization, but its use has several risks, such as penetration into the pial vessels through the intratumoral anastomosis and the reflux into normal vessels due to target vessel occlusion [12,13]. Furthermore, in contrast to particle embolizaton, technical skill and experience are required during NBCA embolization [12]. Aihara et al. demonstrated that complications occurred in 9 (16%) of 57 patients with intracranial meningiomas preoperatively embolized using NBCA, and the complications included arterio-venous fistulas, NBCA migration, and aggravation of brain edema or tumor swelling [1]. In JR-NET3, use of liquid materials was a significant risk for complication and was significantly related to the degree of complication severity (Table 5). The frequency of use of liquid materials in JR-NET3 (41.2%) was significantly higher (approximately 2 times) than that in JR-NET2 (21.2%) (Table 2) and its frequency in JR-NET3 was very high compared to other reports [15,19]. Several reasons for the high frequency of the use of liquid materials in JR-NET3 can be considered. First, some investigations have reported the efficacy of liquid materials in intracranial tumor embolization [13,24]. Second, Onyx™ was introduced to the Japanese neurosurgical field as a treatment covered by Japanese public health insurance system for cerebral AVM in 2008. Subsequently, Japanese endovascular surgeons became aware that they should be familiar with the handling of liquid materials, and this likely increased the use of liquid materials in tumor embolization. Embolization for feeders other than ECA or the use of liquid materials, so-called aggressive embolization, should be considered carefully from the risk-benefit viewpoint in intracranial tumor embolization.

There are several limitations in both JR-NET2 and JR-NET3. First, these studies are retrospective in nature with little in the way of details regarding the size and location of the tumors being embolized. The size and location of the tumors could be related to the occurrence of complications. Also, because information on operation time and volume of blood loss is not included in these studies, the benefits of intracranial tumor embolization before resection could not be clarified. Second, there is a case-selection bias in these studies. Meningiomas are more likely to be targets of preoperative embolization because of the technical ease and the indication of embolization for tumors other than meningioma is largely at the physician's discretion. Although this type of bias could prevent the accurate assessment of risk factors of complications in intracranial tumor embolization, they are thought to be unavoidable in observational studies like JR-NET2 and JR-NET3.

Conclusions

The prevalence of complications in JR-NET3 was approximately 2.5 times higher than that in JR-NET2. This increase is likely attributable to embolization for feeders other than ECA and the use of liquid materials. These aggressive embolizations should be considered carefully in order to lower the complication rate.

Compliance with Ethical Standards

Funding: JR-NET2 was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan. JR-NET3 was supported in part by a Grant-in-Aid (Junkanki-Kaihatsu H24-4-3) from the National Cerebral and Cardiovascular Center, Japan and by Hatazaki Foundation, Kobe, Japan.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: The study protocols of JR-NET2 and JR-NET3 were approved by the institutional review board at Kobe City Medical Center General Hospital.

Informed consent: Because this was a retrospective noninvasive study, written informed consent was not obtained from patients.

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Table 1 Patient characteristics in JR-NET2 and JR-NET3

	JR-NET2 (n=1012)	JR-NET3 (n=1544)
Age, yr (median, IQR)	60 (50-68)	63 (52-70)
Female sex	637 (62.9)	937 (60.7)
Preoperative mRS		
0	696 (68.8)	1034 (67.0)
1	173 (17.1)	271 (17.5)
2	77 (7.6)	137 (8.9)
3	26 (2.6)	58 (3.7)
4	25 (2.4)	34 (2.2)
5	3 (0.3)	6 (0.4)
Data not acquired	12 (1.2)	4 (0.3)
Type of tumors		
Meningioma	898 (88.7)	1337 (86.6)
Hemangioblastoma	25 (2.5)	72 (4.7)
Glioma	6 (0.6)	10 (0.6)
Others	78 (7.7)	121 (7.8)
Data not acquired	5 (0.5)	4 (0.3)
Anesthesia		
General	42 (4.2)	203 (13.1)
Local	968 (94.4)	1338 (86.7)
Data not acquired	2 (0.2)	3 (0.2)
Scheduled intervention		
Yes	966 (98.4)	1520 (98.4)
No	16 (1.6)	21 (1.4)
Data not acquired	0	3 (0.2)
Main operator		
Consulting specialist	427 (42.2)	648 (42.0)
Specialist	460 (45.4)	772 (50.0)
Non-specialist	125 (12.3)	122 (7.9)
Data not acquired	0	2 (0.1)
Target vessels		
ECA only	908 (89.7)	1294 (83.8)
Other than ECA	92 (9.1)	233 (15.1)
Data not acquired	12 (1.2)	17 (1.1)
Embolic materials		

Coil	607 (60.0)	827 (53.6)
Particle	596 (58.9)	632 (40.9)
Liquid	214 (21.1)	627 (40.6)
Data not acquired	2 (0.2)	23 (1.5)
Results of embolization		
Total	344 (34.0)	385 (24.9)
Subtotal	414 (40.9)	627 (40.6)
Partial	238 (23.5)	492 (31.9)
Unchanged	7 (0.7)	16 (1.0)
Data not acquired	9 (0.9)	24 (1.6)

Age is presented as the median and interquartile range (IQR); other values are presented as the raw numbers with percentages in parentheses.

ECA, external carotid artery; mRS, modified Rankin scale.

Table 2 Comparison of patient characteristics and incidence of end points between JR-NET2 and JR-NET3

	JR-NET2	JR-NET3	*p* value
Age, yr (median, IQR)	60 (50-68)	63 (52-70)	<0.001
Female sex	637 (62.9)	937 (60.7)	0.27
Preoperative mRS			0.36
0-2	946 (94.6)	1442 (93.6)	
3-5	54 (5.4)	98 (6.4)	
Type of tumors			
Meningioma	898 (89.2)	1337 (86.8)	0.09
Other than meningioma	109 (10.8)	203 (13.2)	
Anesthesia			<0.001
General	42 (4.2)	203 (13.2)	
Local	968 (95.8)	1338 (86.8)	
Scheduled intervention			0.71
Yes	966 (98.4)	1520 (98.6)	
No	16 (1.6)	21 (1.4)	
Main operator			
Non-specialist	125 (12.4)	122 (7.9)	<0.001
Other than non-specialist	887 (87.6)	1420 (92.1)	
Target vessels			<0.001
ECA only	908 (90.8)	1294 (84.7)	
Other than ECA	92 (9.2)	233 (15.3)	
Embolic materials			
Coil	607 (60.1)	827 (54.4)	0.005
Other than coil	403 (39.9)	694 (45.6)	
Particle	596 (59.0)	632 (41.6)	<0.001
Other than particle	414 (41.0)	889 (58.4)	
Liquid	214 (21.2)	627 (41.2)	<0.001
Other than liquid	796 (78.8)	894 (58.8)	
Results of embolization			
Total	344 (34.3)	385 (25.3)	<0.001
Other than total	659 (65.7)	1135 (74.7)	
End points			
mRS score ≤ 2 at 30 days after procedure (primary end point)	924 (91.3)	1382 (89.5)	<0.001

Procedural complications (secondary end point)	15 (1.48)	57 (3.69)	0.002

Age is presented as the median and interquartile range (IQR); other values are presented as the raw numbers with percentages in parentheses.
ECA, external carotid artery; mRS, modified Rankin scale.

Table 3 Comparison of types and outcomes of complications between JR-NET2 and JR-NET3

	JR-NET2 (n=15)	JR-NET3 (n=57)	*p* value
Types of complications			0.33
Hemorrhage	4 (26.7)	7 (12.3)	
Ischemia	6 (40.0)	32 (56.1)	
Others	5 (33.3)	18 (31.6)	
Outcomes of complications			0.30
Minor	13 (86.7)	38 (66.7)	
Major	2 (13.3)	17 (29.8)	
Data not acquired	0	2 (3.5)	

Values are presented as the raw numbers with percentages in parentheses.

Table 4 Association between the types and outcomes of complications in JR-NET2 and JR-NET3.

	JR-NET2 (n=15)		*p* value	JR-NET3 (n=57)		*p* value
	Outcomes of complications			Outcomes of complications		
	Minor	Major		Minor	Major	
Types of complications						
Hemorrhage	2 (15.4)	2 (100)		6 (15.8)	1 (5.9)	
Ischemia	6 (46.1)	0 (0)	0.042	17 (44.7)	14 (82.3)	0.034
Others	5 (38.5)	0 (0)		15 (39.5)	2 (11.8)	

Values are presented as the raw numbers with percentages in parentheses.

Table 5 Univariate and multivariate analysis: Risk factors related to the development of complication in JR-NET2 and JR-NET3

	JR-NET2					JR-NET3				
	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
Risk factors	Occurrence of complications		*p* value	Hazard ratio (95% CI)	*p* value	Occurrence of complications		*p* value	Hazard ratio (95% CI)	*p* value
	Yes	No				Yes	No			
No of patients	15	996				57	1487			
Age (median, IQR)	65 (52-76.5)	60 (50-68)	0.26			62 (50-68)	63 (52-70)	0.27		
Female sex	13 (87)	623 (63)	0.062			26 (46)	911 (61)	0.025	0.64 (0.37-1.09)	0.1
mRS 3-5	3 (20)	51 (5)	0.043	4.54 (0.96-16.01)	0.055	7 (12)	91 (6)	0.11		
Other than meningioma	6 (40)	103 (10)	0.0003	3.88 (1.13-12.10)	0.032	12 (21)	191 (13)	0.097		
General anesthesia	2 (13)	40 (4)	0.13			11 (19)	192 (13)	0.23		
Scheduled procedure	14 (93)	981 (98)	0.21			55 (98)	1465 (99)	1		
Non-specialist	2 (15)	123 (12)	0.71			4 (7)	118 (8)	1		
Other than ECA	4 (27)	93 (9)	0.049	1.98 (0.46-6.97)	0.34	23 (40)	210 (14)	<0.001	3.56 (2.03-6.25)	<0.001
Coil	9 (60)	598 (60)	0.99			22 (39)	805 (55)	0.021		
Liquid materials	7 (47)	206 (21)	0.015	2.70 (0.87-8.03)	0.083	38 (67)	589 (40)	<0.001	2.65 (1.50-4.68)	<0.001
Particle materials	5 (33)	591 (59)	0.061			13 (23)	619 (42)	0.005		
Total embolization	3 (20)	341 (34)	0.29			9 (16)	376 (26)	0.13		

Age is presented as the median and interquartile range (IQR); other values are presented as the raw numbers with percentages in parentheses.
CI, confidence interval; ECA, external carotid artery; mRS, modified Rankin scale.

Table 6 Comparison of the types and outcomes of complications between with and without embolization for feeders other than ECA and the use of liquid materials in JR-NET3

	Embolization for feeders other than ECA		*p* value	Use of liquid materials		*p* value
	Yes	No		Yes	No	
Types of complications			<0.001			0.29
Hemorrhage	4 (17.4)	3 (8.8)		4 (10.5)	3 (15.8)	
Ischemia	18 (78.2)	14 (41.2)		24 (60.2)	8 (42.1)	
Others	1 (4.4)	17 (50.0)		10 (29.3)	8 (42.1)	
Outcomes of complications			1			0.03
Minor	16 (69.6)	22 (68.8)		22 (57.9)	15 (88.2)	
Major	7 (30.4)	10 (31.2)		16 (42.1)	2 (11.8)	

Values are presented as the raw numbers with percentages in parentheses.

Appendix

JR-NET2: The authors would like to express heartfelt thanks to doctors who devoted their time to 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 Satoh, 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

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