

Real-World Treatment Results for Ruptured Blood-blister Aneurysm of the Internal Carotid Artery: Analysis of a Japanese Nationwide Multi-Center Study

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Abstract

Objective. Ruptured blood-blister aneurysm (BBA) of the internal carotid artery (ICA) remains a challenging lesion, even in the age of modern neurosurgery and endovascular treatment. This retrospective multicenter study aimed to investigate the real-world treatment choice and treatment results.

Methods. We included 182 ruptured BBAs of the ICA treated at 51 neurosurgical centers in Japan between 2013 and 2017. The baseline patient characteristics, radiological features of the aneurysm, treatment modality, details of treatment, complications of treatment, treatment results were retrospectively collected. The treatment strategy was divided into deconstructive and reconstructive procedures. Primary clinical outcomes were evaluated using the modified Rankin Scale (mRS) at final follow-up.

Results. Direct surgery was performed in 144 (79%) cases, and the remaining 38 (21%) cases received endovascular treatment. The majority of treatment selections were deconstructive and reconstructive procedures in the direct surgery group and endovascular treatment group, respectively. Overall, favorable clinical outcomes (mRS 0 to 2) were achieved in 66% of cases, and the mortality rate was 15% at the final follow-up (mean 23 months). There was no significant difference in clinical outcome between direct and endovascular treatment groups.

Conclusion. Our large nationwide study compared the real-world treatment options for ruptured BBAs and their results. Our findings may offer beneficial information for treatment decision and for future studies investigating ruptured BBAs.

Introduction

Blood-blister aneurysms (BBAs) of the internal carotid artery (ICA) are rare subgroups of the ruptured intracranial aneurysms, that represent 0.3%–1.0% of all intracranial aneurysms and 0.9%–6.5% of ruptured ICA aneurysms.[10] Dissecting etiology may be involved in this type of aneurysm. In addition to existing several microsurgical techniques for the ruptured BBAs, such as direct clipping, wrap on clipping, parent artery occlusion, and trapping with or without extracranial-intracranial (EC-IC) bypass procedures, endovascular techniques such as endosaccular embolization, stent-assisted embolization, and flow diversion have been reported recently.[8] However, BBAs frequently cause difficulty in both direct and endovascular treatments and are associated with higher morbidity and mortality compared to saccular aneurysms because of their fragile nature.[6] Therefore, BBAs remain a challenging lesion for surgeons, even in the time of modern neurosurgery and endovascular surgery. To investigate the real-world treatment strategies and the results of treatment, a retrospective nationwide multicenter surveillance was conducted.

Methods

Study Population

This study was conducted as a nationwide survey of the Japanese Society on Surgery for Cerebral Stroke to investigate the real-world treatment selections and results for ruptured BBAs of the ICA. All study protocols were approved by the Institutional Review Board (IRB) of the Gifu University Graduate School of Medicine. Participating centers were selected from the members of the Japanese Neurosurgical Society based on a recognized reputation in the treatment of vascular disorders and an expressed interest in study participation. A total of 51 neurosurgical centers participated in this retrospective study, and the IRB of all 51 participating centers approved the study protocol. Given that the design of this study was noninvasive and retrospective, the requirement for informed written consent from included patients was waived.

A total of 193 patients with ruptured BBA initially treated at 51 participating centers between January 2013 and December 2017 were included in this study. The BBA was defined according to the following criteria: 1) aneurysms arising from the non-branching site of the supraclinoid portion of the ICA, 2) diagnosed using digital subtraction angiography (DSA) or CT angiography (CTA), and 3) exclusion of the saccular aneurysms that project posteriorly.

Data Collection

The medical information of the patient were anonymized and collected via a secured online registration system. The collected information included baseline patient characteristics (age, sex, grade of subarachnoid hemorrhage [SAH]), radiological features of the aneurysms (ruptured side, size, projection, location of distal aneurysmal neck), treatment modalities (direct or endovascular), details of treatment, complications of treatment, and treatment results. The treatment strategies were categorized as either deconstructive (treatments that interrupted the antegrade flow of the affected ICA) or reconstructive (treatments that preserved the antegrade flow of the ICA). The primary outcome of this study was clinical outcome evaluated by modified Rankin Scale (mRS) at the final follow-up visit. Favorable clinical outcomes were defined as mRS scores ranging from 0 to 2. Periprocedural complications, aneurysmal recurrence, rebleeding from treated aneurysms, and incidence of symptomatic vasospasm were investigated as secondary endpoints. The severity of symptomatic vasospasm was defined as follows: mild, transient, or permanent morbidity that did not affect final mRS; moderate, permanent morbidity caused by vasospasm that causes a one-point deterioration of the final mRS; severe, permanent morbidity caused by vasospasm that causes an at least two-point deterioration of the final mRS; and death, death caused by vasospasm.

Statistical Analysis

A commercially available software (JMP 11; SAS Institute Inc., Cary, NC) was used for all statistical analyses. Age, sex, grade of SAH, ruptured side, radiological features of the aneurysm, details of the intervention, complications, and clinical outcomes were summarized using descriptive statistics. Values were expressed as counts, percentages (%), or mean \pm SD. One-way ANOVA, Mann-Whitney *U* test, or Kruskal-Wallis *H* test were used to analyzed the differences between the procedures of intervention or

other clinical characteristics and either complications or clinical outcomes. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Patient and Aneurysm

Patient characteristics are shown in Table 1. We analyzed data collected from 182 patients (73 men and 109 women) with a mean age of 52.1 ± 12.0 years (range 22-88 years). Among these 182 patients, 162 (89%) had an mRS score of 0 before onset, 89 (49%) had a medical history of hypertension, 10 (5%) had diabetes, 10 (5%) had multiple aneurysms, and 14 (8%) had a familial history of SAH. The distribution of SAH severity was as follows: 56 (31%) were classified as WFNS I, 55 (30%) were WFNS II, 12 (7%) were WFNS III, 29 (16%) were WFNS IV, and 29 (16%) were WFNS V, and the remaining 1 (1%) was unknown. There were no significant differences in patient characteristics between the direct and endovascular treatment groups; while the endovascular treatment group had larger percentages of poor grade SAH (WFNS grade IV and V) than the direct surgery group (39% vs. 30%, respectively; $p=0.36$).

The characteristics of the aneurysms are shown in Table 2. Seventy-six (42%) aneurysms were located on the left side, and 106 (58%) were on the right. The maximum diameter of an aneurysm was 3.8 ± 2.5 mm, and the neck diameter was 3.5 ± 2.2 mm. One-hundred-fifteen (63%) of aneurysms were projected superiorly, 36 (20%) were projected laterally, and 31 (17%) were projected medially; no aneurysm was projected posteriorly. The location of the distal aneurysmal neck was as follows: 109 (60%) were level of the posterior communicating artery (PcoA) or proximal, 38 (21%) were between the PcoA and anterior choroidal artery (AchA), and 35 (19%) were level of Ach A or distal.

Treatment Selections and Procedure-Related Complications

Treatment selection in this study population is shown in Table 3. The duration between initial bleeding and aneurysmal treatment was 3.4 ± 6.8 days, and pre-treatment rebleeding was observed in 26 (14%) cases. Direct surgery was chosen as the initial treatment in 144 (79%) cases, and the procedures performed were as follows: 103 (57%) were trapping, 5 (3%) were proximal occlusion including carotid ligation, 16 (9%) were wrap on clipping, and 20 (11%) were clipping. In patients who underwent direct surgery, high-flow bypass was combined in 100 (55%) cases, and low-flow bypass was combined in 17 (12%) of cases. In the remaining 38 (21%) cases, endovascular treatment was performed as an initial treatment modality. Endovascular treatment included 4 (2%) internal trapping, 22 (12%) stent-assisted coiling, 1 (1%) overlapping stent, and 11 (6%) coiling. Two high-flow bypass procedures were combined with endovascular internal trapping.

Procedure-related complications are shown in Table 4. The frequency of intraoperative aneurysmal rupture was significantly higher in direct surgery than in endovascular treatment (19% vs. 3%, respectively; $p=0.04$). In total, there were no significant difference in the number of perioperative complications that occurred in both direct surgery and endovascular treatment groups (43% vs. 42%, respectively; $p=0.92$):

cerebral ischemia (31% vs. 32%, respectively), intracranial hemorrhage (2% vs. 3%, respectively), cerebral contusion (3% vs. 0%, respectively), epilepsy (3% vs. 0%, respectively), infection (4% vs. 0%, respectively), and other complications (8% vs. 10%, respectively).

Clinical Outcome of Patients

Overall, the distribution of mRS at final follow-up (n=182, mean follow-up duration 23 months) was as follows: 74 (41%) were mRS 0, 27 (15%) were mRS 1, 19 (10%) were mRS 2, 9 (5%) were mRS 3, 10 (5%) were mRS 4, 15 (8%) were mRS 5, and 28 (15%) were mRS 6 (Figure 1A). Favorable clinical outcomes (mRS 0–2) were obtained in 66% of cases, and the mortality rate was 15%. There was no statistically significant difference between the patients treated by direct surgery and those treated by endovascular treatment (Figure 1B).

Comparison between Deconstructive and Reconstructive Strategies

There was no significant difference in clinical outcomes in patients treated by deconstructive methods and by reconstructive methods (Figure 1C). Table 5 shows the comparison of treatment results between deconstructive and reconstructive procedures. Aneurysmal recurrence after treatment and rebleeding from treated aneurysms were significantly less frequent in deconstructive than in reconstructive methods (3% vs. 36%; $p<0.001$, and 1% vs. 14%; $p<0.001$, respectively). In the reconstructive group, relatively higher rates of aneurysmal recurrence and rebleeding were observed in each treatment modality: 30% and 20% in clipping, 25% and 13% in wrap and clipping, 45% and 9% in endosaccular coiling, and 43% and 13% in stent-assisted coiling, respectively.

The incidence and severity of symptomatic vasospasm were not significantly different between in deconstructive and in reconstructive strategies ($p=0.62$). The severity of symptomatic vasospasm was also similar in both treatment strategies. Of note, in the deconstructive group, the incidence and severity of symptomatic vasospasm became significantly less frequent in cases combined with bypass procedures, especially in cases with high-flow procedures ($p=0.045$; Table 6).

Ischemic Complications in Patient Treated by Deconstructive Procedure

Interestingly, the occurrence of ischemic complications in patients treated by deconstructive methods was associated with the location of the aneurysmal neck, while there was no significant association between neck location and ischemic complication in patients treated by reconstructive methods. In the deconstructive treatment group, the frequency of ischemic complications in cases with distally located aneurysmal necks (the distal neck of the aneurysm was located at distal to the PcoA origin; n=42) was significantly higher than that in patients with proximally-located aneurysmal necks (the distal neck of aneurysm was located at level of PcoA or proximal; n=70) (50% vs. 17%; $p<0.01$; Figure 2A); those in patients treated by reconstructive procedures (n=31 and 39, respectively) were 35% vs. 31%, respectively ($p=0.68$; Figure 2B).

Discussion

Treatment Selection for Ruptured BBAs in Japan

Ruptured BBA is a relatively rare clinical condition, and most of previous studies involved a small number of patients. Our nationwide study displayed the following important information regarding the treatment of ruptured BBAs. First, the current treatment selection (direct or endovascular) was indicated. Classically, direct surgery was considered the gold-standard treatment for ruptured BBAs.[5] Previous studies reported several surgical techniques, such as direct clipping,[7] wrap on clipping,[3] trapping with or without EC-IC bypass.[4] In contrast, more endovascular treatments for ruptured BBA have been reported, using advances of devices and techniques.[8] In this study, approximately 80% of patients with ruptured BBA were treated by direct surgery, and the remaining 20% were treated by endovascularly. Recent systematic reviews demonstrate that higher percentage (47%–60%) of patients treated endovascularly compared to our study.[9,11] This lower percentage of endovascular treatment selection in our study might be due to the late approval of endovascular devices such as intraluminal support stents (in 2011) or flow diverters (in 2015) in Japan. In addition, these intraluminal support devices have not yet been officially approved for use in acutely ruptured aneurysms. The impact of these devices on treatment selection should be clarified in the future studies on ruptured BBAs.

The major advantages of direct surgery are a higher occlusion rate for aneurysm and durability compared with endovascular treatment. A recent meta-analysis of treatments for BBAs showed that in both immediate- and late occlusion rates in the direct surgery group (88.9 and 88.4%, respectively) were higher than those in the endovascular treatment group (63.9 and 75.9%, respectively).[11] On the other hand, the reported rate of intraoperative rupture in direct surgery was higher than that in endovascular treatment (28.8 vs. 3.2%, respectively).[11] The results of this study were quite consistent with these reported findings. The incidences of perioperative complications other than intraoperative rupture were similar in both direct surgery and endovascular treatment groups in our study.

The reported clinical outcome of patients did not differ between direct and endovascular treatment; the rates of poor clinical outcome were 27.8% in the direct surgery group and 26.2% in the endovascular treatment group.[11] In our study, although there was the difference was not statistically significance, favorable clinical outcomes (mRS 0 to 2) were less frequent in the endovascularly treated group than in the direct surgery group (61% vs. 67%, respectively). Poorer grade patients (WFNS grade IV and V) were more represented in the endovascular group than in the direct surgery group (39% vs. 30%, respectively), and this might have affected poorer clinical outcomes in the endovascular treatment group. Taken together, it is still unclear which treatment strategy is safer and more feasible for the ruptured BBAs. Further investigations focusing on appropriate patient recruitment for each treatment modality are desirable.

Comparison Between Deconstructive and Reconstructive Strategies

This study demonstrated that the majority of treatment selections in the direct surgery group were deconstructive procedures (108/144, 75%), and those in the endovascular treatment group were reconstructive procedures (34/38, 89%). Of note, the clinical outcomes in patients treated by deconstructive methods and by reconstructive methods were similar, while aneurysmal recurrence and rebleeding from treated aneurysms were significantly less frequent in deconstructive than in reconstructive methods (3% vs. 36% and 1% vs. 15%, respectively). Wrap and clipping is reported one of the most common and reliable reconstructive procedure for ruptured BBAs.[1] However, the rates of recurrence and rebleeding of aneurysms demonstrated in our study were high even in patients treated by wrap and clipping procedure (25% and 13%, respectively). The efficacy and durability of this surgical method should be discussed in future studies.

The major potential concern of deconstructive treatment is delayed cerebral ischemia due to vasospasm following SAH. The incidence of severe vasospasm in patients with BBA treated by direct surgery without bypass can be as high as 50%.[2] A recent review indicated that a combination of EC-IC bypass and deconstructive strategy might improve surgical results for BBA.[4] The majority of bypass procedures were high-flow ECA-MCA bypasses (81%), and low-flow STA-MCA bypass was selected in less frequent cases (19%).[4] A similar selection tendency for bypass procedures was observed in our study. Our study also indicated that the lower incidence and severity of symptomatic vasospasm, which were equivalent to reconstructive procedures. Thus, high-flow bypass was suggested to contribute in reducing the severity of vasospasm-induced neurological deficits in patients treated by a deconstructive procedure.

Possible Causative Mechanisms of Ischemic Complications in Deconstructive Procedures

While the precise causative mechanisms were unknown, our study showed that the symptomatic ischemic complications were more frequently observed in cases with distally-located aneurysmal necks than in those with proximally-located aneurysmal necks when the deconstructive procedure was selected. One possible explanation of ischemic complications might be associated with the AchA. In cases with distally-located aneurysms, the risk of obstruction of AchA by the trapping procedure might be higher. When the ICA is surgically obstructed, the distal portion of the ICA is supplied by the retrograde flow via the bypass or Willis ring, and the distal ICA becomes blind alley fashion. The perfusion pressure in the distal ICA with AchA at the blind end might be significantly reduced because the caliber of AchA, which works as a flow outlet, is usually small. This condition easily causes thrombus at the blind end, which leads to occlusion of the AchA.[12] To overcome this kind of potential concern, the oblique clipping technique that makes tapering shape outlet to AchA, or the intraoperative use of antiplatelet agents were advocated for.[12] Future large-scale studies focusing on ischemic complications, especially in deconstructive procedures, will be required.

Study Limitations

This study has three major limitations. First, this was a retrospective study. Second, the treatment strategy was not uniform, and treatment selection was left up to each surgeon's or institution's decision. Third, our current study included a small number of patients treated by reconstructive endovascular

procedures, although the endovascular technique has been rapidly evolving, and more BBA patients are treated with the latest reconstructive endovascular techniques, including the use of a flow diverter.[13]

Conclusion

Our nationwide large-scale study displayed the real-world treatment selections and results of ruptured BBAs. The results of this study may offer valuable information for treatment selection and in future studies investigating ruptured BBAs.

Declarations

Previous Presentations: There have been no presentations regarding this data.

Funding: No funding was provided for this study.

Conflict of interest: The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethics approval: All study protocols were approved by the Institutional Review Board of the Gifu University Graduate School of Medicine.

Consent to participate: Given that the design of this study was noninvasive and retrospective, the requirement for informed written consent from included patients was waived.

Consent to publication: Given that the design of this study was noninvasive and retrospective, the requirement for informed written consent from included patients was waived.

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Author contribution:

Study conception and design: Iwama, Egashira, Enomoto, Nakayama. Drafting the article: Egashira. Revising the manuscript critically for important intellectual content: All authors. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Study supervision: Iwama. Final approval of the version to be submission: All authors.

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Tables

Table 1. Baseline characteristics of patient

	Total	Direct surgery	Endovascular treatment	P value
Number of patients, n	182	144	38	
Mean age, years \pm SD	52.1 \pm 12.0	52.1 \pm 12.1	52.3 \pm 11.8	0.93
Female, n (%)	109 (60%)	90 (63%)	19 (50%)	0.16
mRS 0 before onset, n (%)	162 (89%)	126 (88%)	36 (95%)	0.49
Hypertension, n (%)	89 (49%)	73 (51%)	16 (42%)	0.50
Diabetes mellitus, n (%)	10 (5%)	7 (5%)	3 (8%)	0.66
Multiple aneurysms, n (%)	10 (5%)	8 (6%)	2 (5%)	0.58
Familial history of SAH, n (%)	14 (8%)	12 (8%)	2 (5%)	0.53
WFNS SAH grade, n (%)				0.36
I, n (%)	56 (31%)	46 (32%)	10 (26%)	
II, n (%)	55 (30%)	45 (31%)	10 (26%)	
III, n (%)	12 (7%)	10 (7%)	2 (5%)	
IV, n (%)	29 (16%)	21 (15%)	8 (21%)	
V, n (%)	29 (16%)	22 (15%)	7 (18%)	
Unknown, n (%)	1 (16%)	0 (0%)	1 (3%)	

SD, standard deviation; mRS, modified Rankin Score; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies

Table 2. Characteristics of aneurysm

Left / Right, n (%)	76 (42%) / 106 (58%)
Maximum diameter, mm, mean \pm SD	3.8 \pm 2.5
Neck diameter, mm, mean \pm SD	3.5 \pm 2.2
Aneurysmal projection	
Superior projection, n (%)	115 (63%)
lateral projection, n (%)	36 (20%)
Medial Projection, n (%)	31 (17%)
Location of aneurysmal distal neck	
Level of PcoA or proximal, n (%)	109 (60%)
between PcoA and Ach, n (%)	38 (21%)
Level of AchA or distal, n (%)	35 (19%)

SD, standard deviation; PcoA, posterior communicating artery; AchA, anterior choroidal artery

Table 3. Details of treatment selection

Onset to treatment, days, mean \pm SD	3.4 \pm 6.8
Pre-treatment rebleeding, n (%)	26 (14%)
Treatment modality	
Direct surgery, n (%)	144 (79%)
Trapping, n (%)	103 (57%)
Proximal clipping*, n (%)	5 (3%)
Wrap on clipping, n (%)	16 (9%)
with high-flow bypass, n (%)	100 (55%)
with low-flow bypass, n (%)	17 (12%)
Endovascular surgery, n (%)	38 (21%)
Internal trapping, n (%)	4 (2%)
Stent-assisted coiling, n (%)	22 (12%)
Overlapping stent, n (%)	1 (1%)
Endosaccular coiling, n (%)	11 (6%)
with high-flow bypass, n (%)	2 (1%)

*including proximal carotid ligation

Table 4. Complications of treatment

	Direct surgery (n=144)	Endovascular Treatment (n=38)	P value
Intraoperative rupture, n (%)	28 (19%)	1 (3%)	0.04
Any complications, n (%)	62 (43%)	16 (42%)	0.92
Cerebral ischemia, n (%)	44 (31%)	12 (32%)	
Intracranial hemorrhage, n (%)	3 (2%)	1 (3%)	
Cerebral contusion, n (%)	5 (3%)	0 (0%)	
Epilepsy, n (%)	4 (3%)	0 (0%)	
Infection, n (%)	6 (4%)	0 (0%)	
Others, n (%)	12 (8%)	4 (10%)	

Table 5. Comparison of treatment results between reconstructive and deconstructive procedures

	Deconstructive procedures (n=112)	Reconstructive procedures (n=70)	P value
Recurrence of aneurysm, n (%)	3 (3%)	25 (36%)	<0.001
Rebleeding after treatment, n (%)	1 (1%)	10 (14%)	<0.001
Symptomatic vasospasm, n (%)	34 (30%)	20 (29%)	0.62
Mild, n (%)	13 (12%)	8 (11%)	
Moderate, n (%)	6 (5%)	4 (6%)	
Severe, n (%)	9 (8%)	2 (3%)	
Death, n (%)	6 (5%)	6 (9%)	

Table 6. Incidence and severity of vasospasm in patients treated by deconstructive procedures

Deconstructive procedure (n=112)				
	High-flow bypass (n=93)	Low-flow bypass (n=14)	Without bypass (n=5)	P value
Symptomatic vasospasm, n (%)	25 (27%)	5 (36%)	4 (80%)	0.045
Mild, n (%)	10 (11%)	2 (14%)	1 (20%)	
Moderate, n (%)	5 (5%)	1 (7%)	0 (0%)	
Severe, n (%)	7 (8%)	1 (7%)	1 (20%)	
Death, n (%)	3 (3%)	1 (7%)	2 (40%)	

Figures

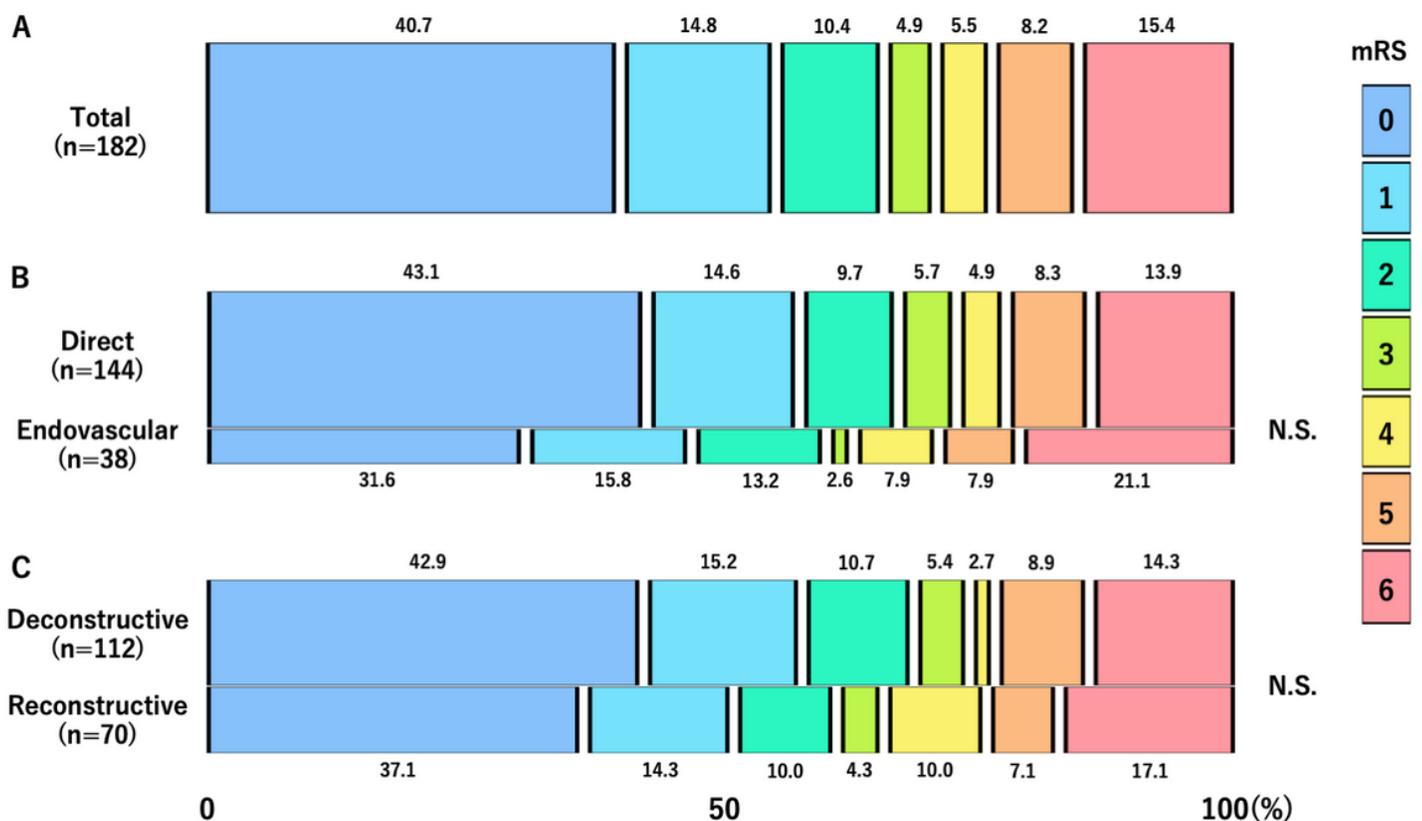


Figure 1

A: Distribution of clinical outcomes at final follow-up (mean: 23 months) evaluated by the modified Rankin Scale (mRS) in overall patients (n=182). B: Comparison of clinical outcomes between the direct surgery group (n=144) and the endovascular treatment group (n=38). There was no significant difference between the groups. N.S. = not significant. C: Comparison of clinical outcomes between the

deconstructive (n=112) and reconstructive treatment (n=70) groups. There was no significant difference between the groups. N.S. = not significant.

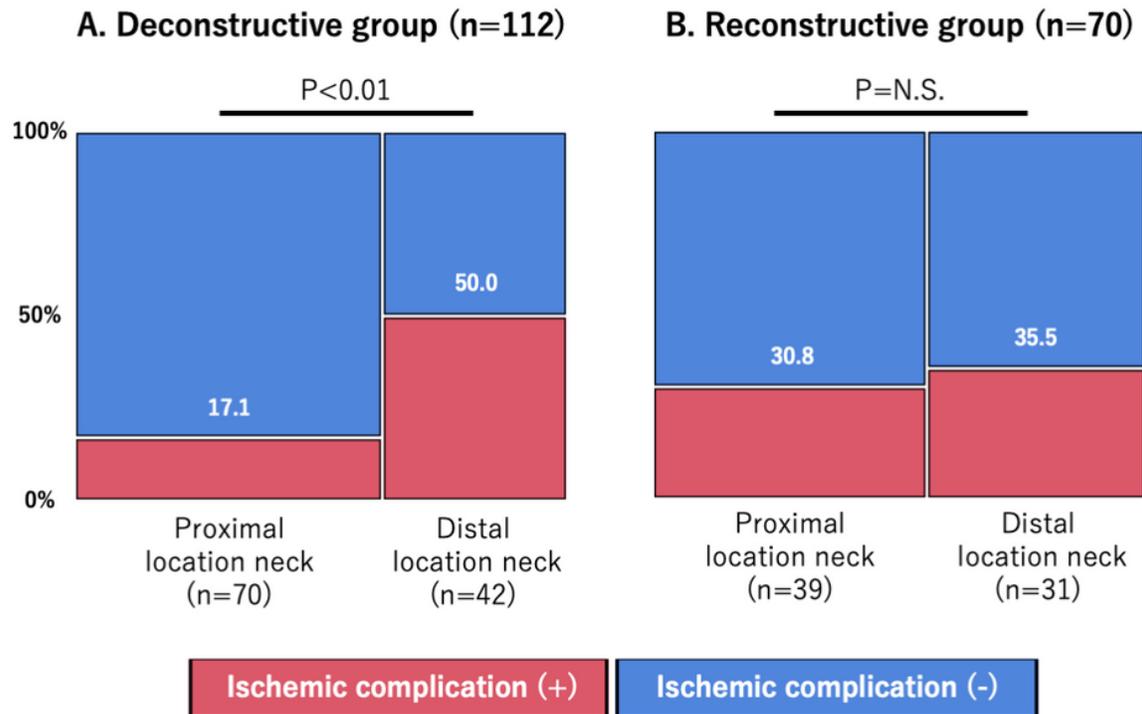


Figure 2

Relationship between the location of aneurysmal distal neck and postoperative ischemic complication. (A) In the deconstructive treatment group, patients with distally located necks (level of distal neck of aneurysm located at distal to posterior communicating artery [PcoA] origin) more frequently developed postoperative ischemic complications than patients with proximally located necks (distal neck of aneurysm located at the level of PcoA or proximal). (B) In the reconstructive treatment group, there was no significant relationship between the location of the aneurysmal distal neck and postoperative ischemic complications. N.S. = not significant.