

# Current Perspectives on the Unruptured Cerebral Aneurysms: Origin, Natural Course, and Management

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## Abstract

**Background:** Unruptured intracranial aneurysms are common, but their rupture can cause subarachnoid hemorrhage. When managing unruptured intracranial aneurysms, we must assess the natural course and management risks of individual aneurysms. In this paper, we summarize current knowledge based on the literature about the natural course of these aneurysms and management risks and present our management strategy.

**Methods:** An extensive literature review was performed to find risk factors affecting the natural course and management outcomes of unruptured intracranial aneurysms.

**Results:** Risk factors for rupture, strongly supported by the literature, were the size, specific location, and shape of the aneurysms. Management morbidity was significantly affected by aneurysm size and location and the patient's age.

**Conclusions:** Unruptured intracranial aneurysms have various clinical characteristics, such as size, shape, and location and the patient's clinical condition, upon which management strategy should be stratified. In Japan, with national efforts to improve surgical and management standards, a national cohort study and individual case series have shown that the management morbidity of unruptured intracranial aneurysms is low. To improve care and to perform safer interventions, we must continue to seek better and less-invasive management methods and techniques.

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**Key words:** unruptured intracranial aneurysms, natural course, rupture, growth, management

## Introduction

Unruptured intracranial aneurysms are common and are found in about 3% of the adult population. A certain percentage of such aneurysms will rupture and cause subarachnoid hemorrhage<sup>1,2</sup>. Surgical intervention significantly reduces the risk of rupture, but such prophylactic treatment is associated with

significant morbidity<sup>2</sup>. To choose the most appropriate method of management, we must balance the risk of rupture, the morbidity associated with the management of individual aneurysms, and the patient's physical condition and quality of life (QOL)<sup>3</sup>.

In this review, we summarize current perspectives on the care of unruptured intracranial aneurysms.

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Table 1 Natural history of the unruptured intracranial aneurysms from retrospective series

Authors, year	Patients/ aneurysms	Mean age, years	Follow-up	Annual rupture rate (%)	Factors affecting rupture
ISUIA, 1998	727/977	56	8.3 years, 12,023 patient-years	<1 cm: 0.05; >1 cm: 0.5	size
Juvela et al., 2000	722/960 142/181	49.4 —	19.7 years, 2,575 patient-years	0.5 1.3	smoking, older age, size
Morita et al., 2005	911/—	—	3,801 patient-years	2.7	size, posterior, symptom
Wermer et al., 2007	4,705/6,556	—	26,122 patient-years	<5 years: 1.2; 5–10 years: 0.6; >10 years: 1.3	age>60, female, Japanese or Finnish, size>5 mm, posterior, symptom

## Literature Review

### The Origin, Growth, and Rupture of Cerebral Aneurysms

How cerebral aneurysms arise, grow, and rupture is unclear<sup>4</sup>. Multiple factors are likely involved in the development of cerebral aneurysms and include inborn fragility of the arterial walls and their atherosclerotic degeneration. The most common locations of unruptured aneurysms differ between young patients and older patients<sup>1</sup>. In young patients aneurysms are most frequently located around the clinoid process, whereas in older patients aneurysms are often found in the basilar and internal carotid-posterior communication locations. The pathophysiology of the development of aneurysms might differ by location and, in particular, the majority of paraclinoid aneurysms are thought to arise because of inborn fragility of the arterial wall.

Blood stream impact forces were once thought to damage the arterial wall, particularly at the arterial bifurcation, and to thereby cause aneurysms to develop. However, a recent hemodynamic study has shown that impact forces at the origin of aneurysms do not differ significantly from those at other sites<sup>5</sup>. On the other hand, shear stress is higher adjacent to the origin of the aneurysm and is thought to initiate the damage to the artery wall. After the wall is damaged and the aneurysm begins to develop, physiological remodeling of arterial wall, stimulated by shear stress, plays an important role in the growth of the aneurysm<sup>6–8</sup>. Pathological studies of intracranial aneurysms have shown that the

degenerative processes of the arterial walls of both symptomatic unruptured aneurysms and ruptured aneurysms are similar to those in atherosclerosis and include hyalinooid necrosis and invasion of macrophages. This feature is not commonly seen in asymptomatic unruptured intracranial aneurysms<sup>9,10</sup>. Atherosclerosis is now believed to arise because of inflammation of the arterial wall. Such inflammation is also thought to be an important factor in the growth and rupture of aneurysms.

Recent studies have shown that statins and anti-inflammatory agents inhibit the growth of experimental cerebral aneurysms<sup>11–13</sup>. Furthermore, clinical evidence suggests that anti-inflammatory agents and infection are related to the rupture of cerebral aneurysms<sup>14–16</sup>. We might soon see the development of medical treatments for unruptured intracranial aneurysms.

### The Natural Course of Unruptured Intracranial Aneurysms

Numerous studies have examined the natural course of unruptured intracranial aneurysms and analyzed their risk of rupture<sup>1,2,17–26</sup>.

**Table 1** summarizes the natural course of unruptured intracranial aneurysms from retrospective series<sup>17,20,21,23</sup>. Retrospective studies suggest that the annual risk of rupture for all intracranial aneurysms is 1% to 3% (**Table 1**). In such studies, the patients included reflect an inevitable selection bias. Elderly patients, sicker patients, and patients with aneurysms carrying high management risks tend to be treated conservatively rather than surgically.

Table 2 Natural history of unruptured intracranial aneurysms from 4 prospective series

Authors, year	Patients/ aneurysms	Mean age, years	Follow-up	Annual rupture rate (%)	Factors affecting rupture
ISUIA, 2003	1,692/2,686	55.2	4.1 years, 6,544 patient-years	0.78	size, posterior location, history of subarachnoid hemorrhage
Ishibashi et al., 2009	419/529	60.8	2.5 years, 1,039 patient-years	1.4	history of subarachnoid hemorrhage, size, posterior location
SUAVE, 2010	374/448	61.9	3.5 years 1,306 patient-years	0.54	size ( $\geq 4$ mm), hypertension, multiplicity, age $< 50$ years
UCAS Japan, 2012	5,720/6,697	62.5	1.7 years, 11,660 aneurysm-years	0.95	size, location (anterior communicating artery, internal carotid posterior communicating artery), bleb

Four prospective studies of unruptured intracranial aneurysms have been published (**Table 2**)<sup>1,2,25,26</sup>. The International Study of Unruptured Intracranial Aneurysms (ISUIA), which included a prospective cohort of 1,692 cases, found that the annual rate of rupture was about 0.78% and is strongly related to aneurysm size and location (anterior or posterior)<sup>2</sup>. In this study, small aneurysms of the anterior circulation rarely ruptured (0% if the aneurysms is  $< 7$  mm and located in the anterior circulation without a history of subarachnoid hemorrhage). On the other hand, large aneurysms ruptured frequently (annual rupture rate,  $\geq 8\%$ ). Ishibashi et al. have published follow-up data on 419 untreated patients at a single institution<sup>25</sup>. They found that the annual rupture rate was 1.4% per year and was significantly affected by a history of subarachnoid hemorrhage (hazard ratio [HR]: 7.3), posterior location (HR: 2.9), and the size of the aneurysm (annual rupture risk: 0.8% if  $< 5$  mm, 1.2% if 5 to 9 mm, 7.1% if 10 to 24 mm, 43% if 25 mm or larger). The Small Unruptured Aneurysm Verification Study (SUAVE study), which included aneurysms smaller than 5 mm in diameter, followed up 448 patients with untreated, unruptured aneurysms (1,306 patient-years). This study found that the annual risk of rupture of small aneurysms was only 0.54% (95% confidence interval: 0.2% to 3%)<sup>26</sup>. Factors significantly associated with an increased risk of rupture were aneurysm multiplicity, hypertension, larger size, and patient age less than 50 years. At the same time, 30 aneurysms in 25 patients (6.7%) enlarged by 2 mm or more. Aneurysm growth was also related to

aneurysm multiplicity, size, female sex, and smoking.

The Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) Investigators published their study of the natural course of unruptured aneurysms in 2012<sup>1</sup>. This study included 5,720 patients with 6,697 aneurysms newly identified from January 2001 through April 2004 at 283 neurosurgery centers in Japan and prospectively registered through an on-line electric data capture system. After initial registration, each case was to be followed up at 3, 12, and 36 months, and e-mails were sent to the principal investigator at each institution before the scheduled follow-up of each case. This study included saccular aneurysms located in the subarachnoid spaces and aneurysms in patients with a Modified Rankin Scale score of 0 to 2. A total of 3,050 aneurysms were treated before rupture, and the period before treatment was included in the follow-up period. Treated aneurysms differed in size and shape and in patient age from aneurysms that were observed. During the 11,660-aneurysm-year follow-up, 111 aneurysms ruptured, and the overall annual rupture rate was 0.95%. Factors identified with a Cox multivariate regression hazard model to be significantly associated with rupture were the size, location, and shape of the aneurysms. Size was the most significant factor, and the HR compared with aneurysms smaller than 5 mm were 1.13 for aneurysms of 5 or 6 mm, 3.35 for those 7 to 9 mm, 9.09 in 10 to 24 mm, and 76.26 for those larger than 25 mm. Aneurysms of the anterior communicating and internal carotid-posterior communicating arteries tended to rupture more frequently than aneurysms in other locations (HR:

Table 3 Rupture risk according to the size and specific location from UCAS Japan

Location	Annual rupture rate, percent (95% confidence interval)				
	Size of aneurysm				
	3-4 mm	5-6 mm	7-9 mm	10-24 mm	≥25 mm
MCA	0.23 (0.09-0.54)	0.31 (0.10-0.96)	1.56 (0.74-3.26)	4.11 (2.22-7.66)	16.87 (2.38-119.77)
ACoM	0.90 (0.45-1.80)	0.75 (0.28-2.02)	1.97 (0.82-4.76)	5.24 (1.97-13.95)	39.77 (9.95-159.00)
ICA	0.14 (0.04-0.57)	0.00 (—)	1.19 (0.30-4.77)	1.07 (0.27-4.28)	10.61 (1.49-75.3)
PCoM	0.41 (0.15-1.10)	1.00 (0.37-2.66)	3.19 (1.66-6.12)	6.12 (1.66-6.13)	126.97 (40.95-393.68)
BA	0.23 (0.03-1.61)	0.46 (0.06-3.27)	0.97 (0.24-3.89)	6.94 (3.74-12.90)	117.82 (16.60-836.43)
VA	— (—)	— (—)	— (—)	3.49 (0.87-13.94)	— (—)
Other	0.78 (0.25-2.43)	1.37 (0.34-5.50)	— (—)	2.81 (0.40-19.99)	— (—)
Total	0.36 (0.23-0.54)	0.50 (0.29-0.84)	1.69 (1.13-5.93)	4.37 (3.22-5.93)	33.40 (16.60-66.79)

Locations classified into specific sites: MCA: middle cerebral artery; ACoM: anterior communicating artery; ICA: internal carotid artery excluding posterior communicating and cavernous portions, including internal carotid artery paraclinoid location, so-called internal carotid artery dorsal curvature location, internal carotid artery bifurcation and internal carotid-anterior choroidal artery; PCoM: internal carotid-posterior communicating artery; BA: basilar tip and basilar-superior cerebellar artery; VA: vertebral artery-posterior inferior cerebellar artery and vertebrobasilar junction; Others include aneurysms at the anterior cerebral artery A1 portion, distal anterior cerebral artery, and other supratentorial or infratentorial locations not categorized above. (From N Engl J Med 2012; 366: 2474-82. Copyright reserved)

2.02 and 1.90, respectively). Aneurysms with a daughter sac also had higher risk of rupture (HR: 1.63). On the basis of this study, the size and site-specific rupture risk could be documented (**Table 3**).

Greving et al. have performed a meta-analysis of data from 6 prospective studies from around the world, including ISUIA, UCAS Japan, SUAVE, and a study at Tokyo's The Jikei University, and developed a scoring system called "PHASES" to predict the risk of rupture of individual aneurysms<sup>27</sup>. According to this study, aneurysms in Japanese patients carry 2.8 times higher risk of rupture than those in patients from North American or European countries other than Finland. Other factors that influenced the risk of rupture and were selected to contribute to the PHASES score were size, site, hypertension, age more than 70 years, and earlier history of subarachnoid hemorrhage.

Several studies have compared the shapes of ruptured and unruptured intracranial aneurysms on the basis of 2-dimensional or 3-dimensional (3-D) images. Ujiie et al. initially proposed the concept of the aspect ratio (dome height/neck width)<sup>28</sup>. They found that the aspect ratio was higher for ruptured aneurysms than for unruptured aneurysms. Prestigiacomo et al. have also demonstrated a greater risk of rupture for aneurysms with a greater

height or a higher aspect ratio and aneurysms of the posterior communicating artery, the anterior communicating artery, or in the posterior circulation<sup>29</sup>. Raghnavan et al. have found that irregular shape and the presence of blebs were more common for ruptured aneurysms<sup>30</sup>. Tremmel et al. have reported that the size ratio, which is the ratio of the greatest aneurysm dimension to the parent artery diameter, is greater in aneurysms causing subarachnoid hemorrhage than in unruptured aneurysms<sup>31</sup>. They also showed that flow irregularity increases when the size ratio increases and, hence, that irregular flow inside the dome might be related to biophysiological instability of the aneurysm wall and increase the risk of rupture.

**Table 4** summarizes studies of the aneurysmal growth. In the groups with magnetic resonance angiography, 3-D computed tomography angiography follow-up, 6% to 7% of aneurysms grow within 3-4 years. Larger aneurysms often grew more than smaller aneurysms<sup>26,32-34</sup>. Aneurysms at the posterior circulation and multiple aneurysms tended to grow more frequently. In the SUAVE study, 6.7% of small aneurysms grew by more than 2 mm during average follow-up of 3.5 years. Aneurysm multiplicity, larger size, female sex, and smoking were factors associated with growth<sup>26</sup>. Inoue et al.

Table 4 Summary of reports on the growth of the unruptured intracranial aneurysms

Authors, year	Patients/ aneurysms	Follow- up	Enlargement rate (%; overall)	Factors affecting rupture
Matsubara et al., 2004	140/166	17.7 mo	10 aneurysms (6.4%) <5 mm: 2.4%; 5–10 mm: 8.8%; >10 mm: 50% <1 year: 2.5%; 2 years: 8%; 3 years: 17.6% basilar artery: 40%; middle cerebral artery: 0%	size, location (basilar artery), follow-up period
Burns et al., 2009	156/191	47 mo	10% <8 mm: 6.9%; 8–12 mm: 25%; ≥13 mm: 83%	size, location, multiplicity
SUAVE, 2010	374/448	3.5 yr	30 aneurysms, 25 patients: 6.7%	current smoking, size (≥4 mm), female, multiplicity
Inoue et al., 2012	1,002/1,325	10.1 mo	1.8% per patient-year; rupture after growth: 18.5% per patient-year	female

Table 5 Outcome of management of unruptured intracranial aneurysms

Author, year	Number of cases	Type of study	Risk	Risk factors
Wirth et al., 1983	107 patients, 119 aneurysms: open surgery	multicenter retrospective cohort: 12 centers	mortality: 0%; morbidity: 6.5%	size, location
Raaymarker et al., 1998	2,460 patients: open surgery	meta-analysis: 61 studies	mortality: 2.6% (2.0%–3.3%); morbidity: 10.9% (9.6%–12.2%)	old publication, giant aneurysm, posterior circulation
Johnston et al., 2001	2,069 patients: 1,699: open surgery; 370: endovascular	multicenter retrospective cohort	mortality: 3.5% (open); 0.5% (endovascular); morbidity: 25% (open), 11% (endovascular)	open surgery
ISUIA, 2003	1,917 patients: open surgery  451 patients: endovascular	multicenter prospective cohort: 61 centers	mortality: 1.5%; morbidity: 11.7% (1 mo)  mortality: 1.7%; morbidity: 7.3% (1 mo); complete occlusion: 51%; unsuccessful: 5%	size, age, location, ischemic disease, symptom
UCAS II, 2011	558 patients, 1,056 registered cases; 452 cases: open surgery; 106 cases: endovascular	multicenter, prospective cohort: 31 centers	mortality: 0; morbidity: 4.5%, by Modified Rankin Scale only; 5.3%, by decrease in Mini-Mental State Examination score (at discharge, 1 week.)	size, vertebrobasilar location, subarachnoid hemorrhage, endovascular

followed up 1,325 aneurysms in 1,002 patients by performing magnetic resonance angiography at least twice per year<sup>34</sup>. During the follow-up of 997 patient-years, the rate of aneurysm enlargement (to 1.5 times as great as the original diameter or the appearance of a new bleb) was 1.8% per year. The risk of rupture of enlarging aneurysms was 18.5% per year. These studies have shown that careful, periodic follow-up is required, even for small aneurysms.

### Management Outcome and Risks

Many studies have examined the management outcomes of unruptured intracranial aneurysms (Table 5)<sup>2,35–39</sup>, but published clinical outcomes differ considerably between studies of different types<sup>40</sup>. In the ISUIA<sup>2</sup>, the mortality rate during treatment was 1.6%, and significant morbidity (Modified Rankin Scale score of 3 or less or a Mini-Mental State Examination score less than 25) was found in an additional 10.9% of patients at 1 month's follow-up. A decline in cognitive function was the major type of morbidity, and the ISUIA investigators stressed the

importance of measuring high cognitive function when the assessing outcomes of the surgical treatment of aneurysms. Risks were higher for elderly patients and for patients with aneurysms of the posterior circulation. Endovascular treatments achieved better outcomes in elderly patients.

Preliminary results of management outcomes have been reported for UCAS II<sup>38</sup>. This study includes 1,059 aneurysms prospectively registered from 31 institutions in Japan. Of these aneurysms, 558 were treated surgically. Major morbidity, which was defined as either a decrease of the Modified Rankin Scale score to 2 or less or a decrease in the Mini-Mental State Examination score to less than 25, was noted in 5.3% of cases. Univariate analysis showed that factors significantly associated with a decrease in the Modified Rankin Scale score were aneurysms that were large or located in posterior circulation, that had been treated with an endovascular technique, or that were in patients with a previous history of subarachnoid hemorrhage. Hattori et al. have surveyed outcomes of surgery in 4,396 Japanese patients with unruptured intracranial aneurysms and found a mortality rate of 0.2%<sup>41</sup>. In this study, surgical outcomes were not affected by the case volume of an institution. Results of the Japanese Registry of Neuroendovascular Therapy study, which included data from 122 institutions in Japan, were also reported recently. A total of 4,767 asymptomatic unruptured cerebral aneurysms were managed with endovascular treatment<sup>39</sup>. Treatment failed in 2.1% of cases. Immediate evaluation showed that complete occlusion was obtained for 57.7% of aneurysms. The rate of major morbidity, which was defined as a decrease in the Modified Rankin Scale score, was 2.12%, and mortality rate was 0.31%.

Several outcome studies have analyzed QOL<sup>42-44</sup>. Some studies have found significant declines in QOL long after aneurysm repair. However, Yamashiro et al.<sup>44</sup> have reported that preoperative anxiety was relieved by the repair of the aneurysm and that QOL also improved in a year. Otawara et al. have also reported that with meticulous surgical repair cognitive function decreases in only a small percentage of cases<sup>45</sup>. Our recent study (UCAS II) also examined patients' QOL<sup>38</sup>. Among patients who

underwent treatment, QOL scores measured with the Short-Form 8 Health Survey and EuroQol 5D health questionnaire immediately after treatment did not show any decrease compared with scores before surgery. Depression scores measured with the Mental Health and Vitality domains of the 36-Item Short-Form Health Survey were lower than in a healthy Japanese population and did not show change immediately after treatment. We are following up these scores for a longer term.

## Discussion

According to the registry of the Japan Neurosurgical Society, more than 10,000 unruptured cerebral aneurysms are treated in Japan in a year, but the incidence of subarachnoid hemorrhage has decreased only slightly. To improve the efficacy of preventive surgery, we need to further define rupture-prone aneurysms.

On the basis of current knowledge about the origin and growth of cerebral aneurysms, 3 types of origin and natural course of unruptured intracranial aneurysms have been proposed (**Fig. 1**: modified from Yonekura et al.<sup>24</sup>). In type 1 an aneurysm that ruptures immediately after its formation. In type 2 an aneurysm stops enlarging sometime after its formation but then grows with some inflammatory process and ruptures. In type 3 a stable aneurysm shows no growth for a long time after its formation. Even after aneurysms stop growing, some may start to grow again owing to some unknown biological cues. Because aneurysms with a type 1 course present as subarachnoid hemorrhage and are discovered only after rupture, we should discriminate between unruptured intracranial aneurysms with courses of types 2 and 3 when encountered incidentally.

The risks factors affecting the growth and rupture of intracranial aneurysms are summarized as follows. 1) Group 1 risk factors (evidenced by high-level prospective studies) are size ( $\geq 7$  mm); location (posterior circulation > anterior circulation); and specific locations, such as anterior communicating and posterior communicating aneurysms and aneurysms with blebs<sup>1,2</sup>. Aneurysms

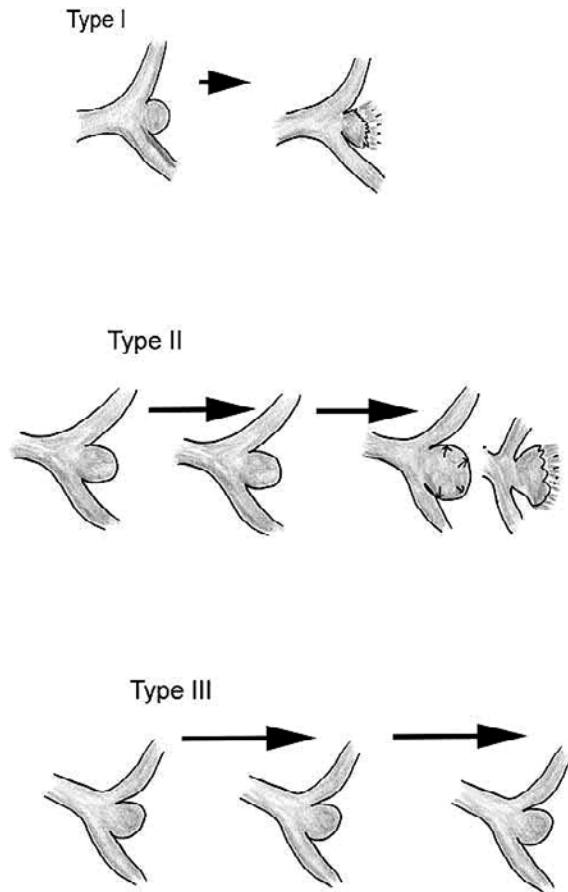


Fig. 1 The 3 types of natural course of intracranial aneurysms. We can propose 3 types of natural course of intracranial aneurysms after their formation<sup>24</sup>. In type I, the aneurysm continues to enlarge until rupture. Most subarachnoid hemorrhages are caused by such aneurysms, whereas small aneurysms rarely rupture. In type II, the aneurysm stops growing, but with some physiological or other external stimulus, it starts grow again and eventually ruptures. Growth might repeatedly start and stop. In type III, the aneurysm stops growing and becomes stable.

[Reproduced with permission from Fig. 1 in "Yonekura M. Small unruptured aneurysm verification (SUAVE Study, Japan) —interim report. *Neurol Med Chir (Tokyo)* 2004; 44: 214."]

in Japanese and Finnish patients tend to rupture more frequently than do aneurysms in other populations<sup>27</sup>. While their effects are small, multiplicity of aneurysms, female sex, age greater than 70 years, previous history of subarachnoid hemorrhage, and history of hypertension increase the risk of rupture<sup>25,26</sup>. 2) Group 2 risk factors

(evidenced by retrospective case series and studies) are a history of smoking, symptomatic aneurysm, and shape of aneurysms (high aspect ratio or size ratio)<sup>20,21,31,46</sup>. Unruptured aneurysms should be stratified according to their specific features, such as location, size, and shape, and various patient factors.

Risk factors that affect management outcomes are summarized as follows. 1) Group 1 management risk factors (evidenced by high-level prospective studies) are size, location (vertebrobasilar > anterior circulation), history of subarachnoid hemorrhage, and age<sup>2</sup>. 2) Group 2 management risk factors (evidenced by retrospective case series, studies) are history of ischemia and type of management<sup>35,37</sup>.

The management of unruptured intracranial aneurysms is not without risk, and published outcomes vary according to study design and how outcomes are measured. Each institution should evaluate its own management risks according to scientifically proven criteria. We can then carefully decide on indications for management by assessing the natural course, institutional outcome, and the patient's condition and QOL. Etminan et al. have recently published a multidisciplinary consensus opinion regarding decision-making factors for the management of unruptured intracranial aneurysms<sup>3</sup>. Key factors included 1) patient age, life expectancy, and comorbid disease; 2) previous subarachnoid hemorrhage, family history of subarachnoid hemorrhage, or nicotine use; 3) aneurysm size, location, and lobulation; 4) growth or de novo aneurysm formation on serial imaging; 5) symptoms of aneurysms, including cranial neuropathy, mass effect, or embolic events; and 6) risk factors of treatment, including age, life expectancy, aneurysm size, and estimated treatment risks.

In Japan, even carefully designed prospective studies have shown low overall rates of morbidity and mortality in the management of unruptured intracranial aneurysms<sup>38,39</sup>. Low-risk intervention requires meticulous care in preoperative assessments and involvement of advanced surgical and interventional techniques. These involve high-resolution magnetic resonance imaging, preoperative 3-D simulation, meticulous surgical technique, skull-base techniques, and bypass surgery, as well as



advanced neurophysiological, neuroimaging monitoring and strategic cooperative management by open and endovascular neurovascular team<sup>47</sup>.

### Conclusions

Unruptured intracranial aneurysms show various clinical characteristics, upon which risk analysis should be done. Indications for and decisions on management should be determined carefully on the basis of features and updated institutional management risks. All possible measures, including advanced endovascular techniques, should be considered so that surgery can be performed in the safest manner possible. To improve the future care of unruptured intracranial aneurysms, we must continue to obtain more precise natural course data through well-designed prospective studies and to develop less-invasive methods of management, including medical treatment, with minimal morbidity.

**Conflict of Interest:** There is no conflict of interest to disclose.

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