未破裂脳動脈瘤に関するご質問

問 10 あなたは今回の病気（未破裂脳動脈瘤）に際して、あなたの担当医師またはその補助者（看護師など）からの病状や病気の説明に満足しておられますか。(一番よくあてはまる番号に○をつけて下さい)

1	とても満足している	3	満足していない
2	ある程度満足している	4	極めて不満である

問 11 あなたは今回受けた治療または治療方針(経過観察など)に満足していますか。(一番よくあてはまる番号に○をつけて下さい)

1	とても満足している	3	満足していない
2	ある程度満足している	4	極めて不満である

問 12 もしもう一度さかのぼって治療(治療方針)を選択できるとしたら、同じ治療または治療方針（経過観察など）をお受けになりますか。(一番よくあてはまる番号に○をつけて下さい)

1	もちろん受ける	4	絶対受けない
2	多分受ける	5	該当しない
3	多分受けない		

問 13 あなたは今回の病気（未破裂脳動脈瘤）が発見されたことに満足していますか。(一番よくあてはまるものに○をつけてください)

1	とても満足している	3	満足していない
2	ある程度満足している	4	極めて不満である

問 14 もしもう一度、未破裂脳動脈瘤が発見される前に、検査をするか選択できるとしたら、同じ検査をお受けになり、未破裂脳動脈瘤を発見してもらいますか。(一番よくあてはまるものに○をつけてください)

1	もちろん受ける	4	絶対受けない
2	多分受ける	5	該当しない
3	多分受けない		

これですべての質問は終了です。ご協力ありがとうございました。

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Inadequate Website Disclosure of Surgical Outcome of Intracranial Aneurysms

—Survey of 1225 Sites in Japan—

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Abstract

Social demand for the disclosure of medical information is increasing, especially the treatment for unruptured intracranial aneurysms. This study investigated to what extent information on the treatment for unruptured intracranial aneurysms is disclosed on websites in Japan. We surveyed 1225 institutions authorized by The Japan Neurosurgical Society. The following factors were analyzed: percentage of institutions with websites, disclosure of number of surgeries, and disclosure of outcome of treatment for ruptured and unruptured intracranial aneurysms. Of the 1225 institutions surveyed, 1097 (89.6%) had their own websites. The total number of websites was 1262 since some institutions have several homepages in different websites. The annual number of surgeries was shown in 274 of the 1225 institutions (22.4%). The outcome of treatment for ruptured intracranial aneurysms was disclosed in 104 of the 1225 institutions (8.5%). The outcome of treatment for unruptured intracranial aneurysms was shown in only 32 of the 1225 institutions (2.6%). Disclosure of outcome of treatment for unruptured intracranial aneurysms on websites is not common. To improve disclosure of the outcome on websites, guidelines should be established.

Key words: Internet, unruptured intracranial aneurysm, outcome

Introduction

The disclosure of medical information has become one of the most significant issues for the public. This disclosure involves a wide range of information, including both basic medical science and medico-social problems such as medical liability issues and medical accidents. Information on the outcome of the treatment is the most important for the public, since it is directly related to the behavior and decision-making of the patients. In particular, individual data on specific hospitals and physicians is useful for patients to select a hospital and physician.

The World Wide Web is becoming the most convenient source of healthcare information due to the remarkable development of the Internet and information technology.[1,23,28,30,33] This medium directly provides anonymous access to the most recent information anywhere at anytime. For general information on health care such as definition of diseases and explanation of treatments, disclosure is comparatively simple and straightforward.[19,27] However, disclosure of outcome of treatment involves many complicated problems.[7,11,12,15,29]

In this study, the disclosure of outcome of treatment for intracranial aneurysms in Japan was extensively analyzed based on data on the websites of 1225 institutions authorized by The Japan Neurosurgical Society. This is the first study investigating the extent of the disclosure of outcome of treatment for intracranial aneurysms on websites.[13,18,35]

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Subjects and Methods

I. Subjects

Most intracranial aneurysms are treated in hospitals authorized by The Japan Neurosurgical Society. There are 1225 hospitals registered by The Japan Neurosurgical Society (home page, http://jns.umin.ac.jp/) in October 2003. Briefly, the requirement for this authorization is that total number of surgeries has to exceed 100 cases per year and there should be more than two neurosurgeons qualified by The Japan Neurosurgical Society.

To survey the extent of disclosure of information

Table 1 Database on Excel file

Number	Institution	District	Website	URL	Number of surgeries*	General outcome*	Aneurysm outcome*	
							Ruptured	Unruptured
1	Asahikawa Med. Univ.	Hokkaido	○	http://www.asahikawa-med.ac.jp/dept/mc/neuro/	×	△	△	△
2	Hokkaido Univ.	Hokkaido	○	http://www.med.hokudai.ac.jp/~neusur-w/	×	×	×	×
3	Sapporo Med. Univ.	Hokkaido	○	http://web.sapmed.ac.jp/nsurg/	×	×	△	×
4	Akita Univ.	Akita Pref.	○	http://www.hos.akita-u.ac.jp/	×	×	×	×
5	Iwate Medical Univ.	Iwate Pref.	○	http://www.iwate-med.ac.jp/univ/kouza/nouge.html	×	×	×	×
6	Tohoku Univ.	Miyagi Pref.	○	http://www.hosp.tohoku.ac.jp/	×	△	×	×
7	Yamagata Univ.	Yamagata Pref.	○	http://www.id.yamagata-u.ac.jp/NeuroSurge/NeuroS-j.html	×	×	×	×
8	Fukushima Univ.	Fukushima Pref.	○	http://www.fmu.ac.jp/home/ns/index-j.html	×	×	△	×

Only the first eight academic websites of 1225 institutions are shown. *×: no data, △: outline, ○: detail data. Med.: Medical, Pref.: Prefecture, Univ.: University.

by these 1225 hospitals, their websites were searched using the Internet search engines Yahoo! and Google. This survey was performed from May 2004 to June 2004.

II. Investigated items

Percentage of institutions with websites: The percentage of institutions with websites was examined. Some institutions had two or more homepages (one homepage included in the website of the main institution and another independent homepage). In such cases, the websites were considered as one.

Disclosure of number of surgeries: Disclosure of the annual number of surgeries was examined.

Disclosure of outcome of treatment for ruptured intracranial aneurysms: Whether outcome of treatment for ruptured intracranial aneurysms was disclosed or not was examined.

Disclosure of outcome of treatment for unruptured intracranial aneurysms: Whether outcome of treatment for unruptured intracranial aneurysms was disclosed or not was examined.

The enormous amount of data obtained from these websites of more than 1000 institutions was analyzed in an Excel spreadsheet (Microsoft Co., Redmond, Wash., U.S.A.) as shown in Table 1.

III. Additional analysis

Many interesting questions can be answered based on the vast database of information on the websites of these 1225 institutions. The following three questions were investigated.

Firstly, we considered whether urban institutions located in densely populated and competitive areas may disclose their outcome more than those located in underpopulated areas. To answer this question, the Tokyo metropolitan area as a sample of a densely populated area and the Hokkaido area, exclusive of Sapporo, as a sample of an underpopulated area were selected. The second question is whether academic institutions, such as university hospitals, disclose their outcomes more than other institutions. Finally, we speculated that high-volume hospitals disclose their outcome more than low-volume hospitals. Therefore, the third question is whether institutions that disclose outcomes on their websites have a greater number of surgeries compared to those that do not.

Initially we planned to analyze the outcome data, including mortality and morbidity of unruptured aneurysm treatment in Japan, based on the data obtained from websites. However, not enough quantitative data was obtained from the websites as disclosed in this paper.

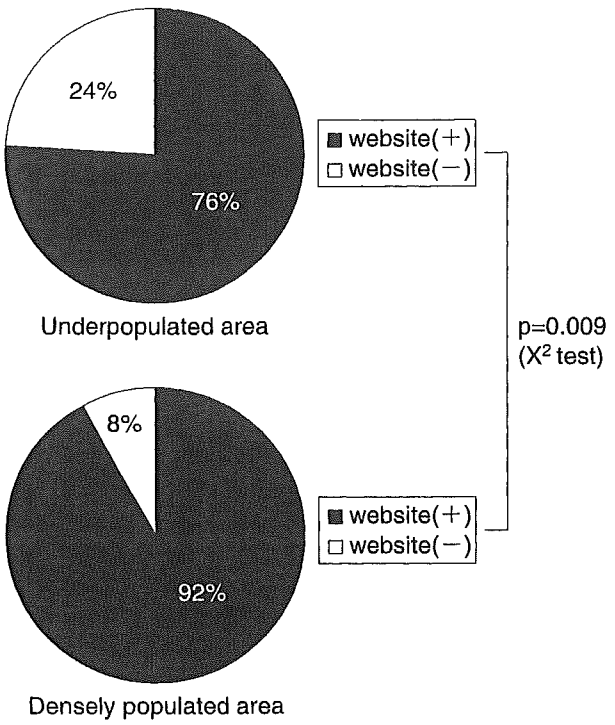

Fig. 1 More institutions have websites in the Tokyo area (densely populated and competitive area) as compared to the Hokkaido area (underpopulated area) ($p = 0.009$, chi-square test).

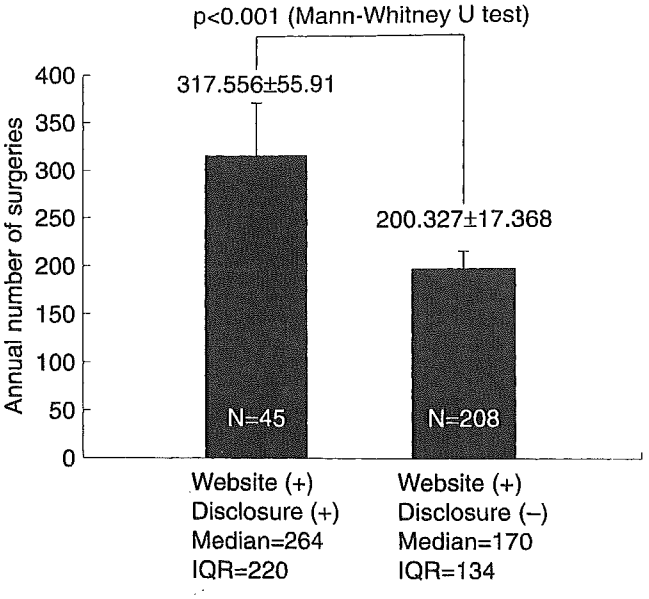

Fig. 2 Number of surgeries (annual number) was compared between the institutions that disclosed their outcome data and those that did not. Institutions that disclose their outcome had a significantly larger number of annual surgeries than those that did not. Values are given as mean ± SD ($p < 0.001$, Mann-Whitney U test). Median value was 264 and 170 and interquartile range (IQR) was 220 and 134, respectively.

Results

I. Main analysis

Percentage of institutions with websites: Out of 1225 institutions, 1097 (89.6%) had their own homepage. The total number of websites was 1262 since some institutions have several homepages in different websites.

Disclosure of number of surgeries: Among these 1225 institutions, the annual number of surgeries was disclosed in only 274 websites (22.4%).

Disclosure of outcome of treatment for ruptured intracranial aneurysms: Among the 1225 institutions, outcome of treatment for ruptured intracranial aneurysms was disclosed in 104 websites (8.5%).

Disclosure of outcome of treatment for unruptured intracranial aneurysms: The outcome of treatment for unruptured intracranial aneurysms was disclosed in only 32 websites (2.6%).

II. Additional analysis

Comparison between densely populated and underpopulated areas (Fig. 1): There were 68 institutions (27 "A ranked" and 41 "C ranked" hospitals) in the Tokyo area (23 districts) and 57 institutions (29 "A ranked" and 28 "C ranked" hospitals) in the Hokkaido area. There is no significant difference between the Tokyo and Hokkaido areas in the density of the neurosurgical institutions per unit population. However, the institutions in the Tokyo area had a greater percentage of websites (92%) compared to the Hokkaido area (76%) ($p = 0.009$, chi-square test).

Comparison between academic and other institutions: All academic institutions had websites (100%). This was significantly higher than other general neurosurgical institutions (84.0%) ($p < 0.001$, chi-square test). However, the content on the academic institution websites was not always satisfactory since disclosure of the annual number of surgeries was only 10% and disclosure of outcome of treatment for ruptured and unruptured aneurysms were 7% and 3%, respectively.

Disclosure of outcome of treatment for unruptured intracranial aneurysms as related to number of surgeries (Fig. 2): A significant difference was seen between 45 institutions that disclosed outcome of treatment for unruptured intracranial

aneurysms on their websites and 208 institutions that do not based on the annual number of surgeries (mean ± SD, 317.556 ± 55.91 and 200.327 ± 17.368, median, 264 and 170, interquartile range, 220 and 134, respectively; $p < 0.001$, Mann-Whitney U test). Larger volume hospitals tended to disclose the outcome on websites.

Discussion

The brain check-up system called "Brain Dock" is well developed in Japan. People who want to check for asymptomatic cerebral infarction and unruptured aneurysm can select hospitals that provide the "Brain Dock." The "Brain Dock" includes both imaging examinations such as brain magnetic resonance (MR) imaging, neck vascular imaging using MR angiography, and/or Doppler ultrasonography, and general medical checks such as blood examination, blood pressure, and other options. There are requirements for the quality of imaging regulated by the Japanese Society for Detection of Asymptomatic Brain Diseases (homepage, http://www.snh.or.jp/jsbd/).

The spread of this system has affected Japanese society, including the diagnosis of unruptured intracranial aneurysms in healthy people and treatment to prevent subarachnoid hemorrhage. Unruptured intracranial aneurysms have been identified in more than 6% of people who underwent the "Brain Dock" using high quality MR angiography.[26]

The Japanese Society for Detection of Asymptomatic Brain Diseases recommends that the outcome should be disclosed in the homepage of each hospital (http://www.snh.or.jp/jsbd/). The present study has shown that this advice has been not followed. Necessary information for patients who have unruptured intracranial aneurysm identified by the "Brain Dock" is not well disclosed on websites. Websites that offer information on the outcome of treatments are not common. While patients can directly ask physicians in the outpatient clinic for general information on unruptured intracranial aneurysms, it is not always easy to ask directly about the outcome of treatment. Other sources such as "Guide of Best Hospitals" and "Guide of Best Doctors" do not always provide correct information.[6,9,22] Therefore, websites are an important source of information for patients, since it is easy to access and the cost is low. On the Internet, patients can see the outcomes and strategies of other hospitals. However, our results revealed that this important source of information is not widely available.

Unruptured intracranial aneurysm is not a newly established disease, but has been one of the most important diseases for neurosurgeons for a long time. However, the swift spread of high resolution MR angiography revealed an unexpectedly high incidence of unruptured intracranial aneurysms in healthy people.[4,26] This disease has provoked controversy among medical professionals and the public. The natural history of unruptured intracranial aneurysms also remains controversial, and is still under investigation.[5,14,16,20,34] Discussion of the rupture rate of intracranial aneurysms is being debated in many journals.[3,8,10,17,24,25,32] Guidelines for the treatment of unruptured intracranial aneurysms have not been firmly established.[31] Moreover, many medical malpractice suits related to the treatment of unruptured intracranial aneurysms have been reported.[2]

Therefore, the public is interested in obtaining updated information about this disease. In particular, patients with unruptured intracranial aneurysm and their families seriously search for both general information of this disease and individual outcome data of each institution. Among the many sources of information the World Wide Web gives patients and professionals easy access to up-to-date data of individual institutions. Indeed, many papers report that the Internet is becoming the most important source of information for patients.[1,28,30,33]

On the other hand, outcome disclosure is not easy from the viewpoint of hospitals and physicians that are subject to disclose information to the public. Complicated problems arise when information about medical outcomes are disclosed. For example, if no guidelines for the disclosure of medical outcome on the Internet exist, physicians may be hesitant to do so.[11,12,29] In addition, outcome evaluation in surgery is also controversial.[21] There is no gold standard to evaluate outcome of treatment for unruptured intracranial aneurysms. In addition, some data may be involved in ongoing lawsuits or medical liability cases. Even in the absence of legal problems, institutions may hesitate to publish their data, unless the outcomes have been excellent. In addition, since each institution and any individual can set up a homepage without restriction or control, there is a risk of deliberate modification of data. It is easy to spread biased information for commercial purposes on the Internet.[30]

The present study revealed that only 2.6% of 1225 institutions in Japan disclosed outcome data of treatment for unruptured intracranial aneurysms on websites. This number is lower than we had expected when we launched this study. In other words, at present it is practically impossible for patients to obtain data on unruptured intracranial aneurysms

from individual institutions using the Internet. This problem does not seem to be specific to Japan, although there is no international comparative study on websites of medical information. Surgery for unruptured aneurysms is likely to increase in Europe, North America, and Korea. To provide the best information to patients, the creation of the websites is important. For this purpose, we need to establish minimum guidelines and ethics for the disclosure of outcome on websites.

There is no question that establishment of the appropriate guidelines is indispensable for improved treatment for unruptured intracranial aneurysms. However, at present, we do not have any reliable or scientific standards to compare the complicated outcome of such treatment. It is true that the outcome is seriously affected by the expertise of surgeons and endovascular surgeons. However, other factors such as the characteristics of the patient including the aneurysm size, location, and risk factors are strongly related to the outcomes. In other words, simple exposure of the outcome without adequate guidelines may invoke unfair interpretation of the competence of hospitals and neurosurgeons. In order to prevent this unfavorable trend, the establishment of adequate guidelines based on the peer review system is required without delay.

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See the Editorials and the Responses in this issue, pp 593–598.

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Risk of rupture associated with intact cerebral aneurysms in the Japanese population: a systematic review of the literature from Japan

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Object. Knowing the rate of rupture associated with unruptured cerebral aneurysms (UCAs) can help surgeons determine a case management strategy in patients harboring these lesions. According to large-scale cohort studies involving populations in North America and Europe, small unruptured aneurysms carry a very low risk of rupture. In Japan, however, there have been sporadic reports of higher rates of rupture. To identify the rupture risk associated with UCAs in the Japanese population, the authors systematically reviewed retrospective studies of the natural course of these lesions.

Methods. The authors searched Medline and the Japan Medical Abstract Society Index for reports of UCAs in Japan. Two of the authors verified the eligibility of the reports and extracted data independently. Additional information was directly obtained from the authors of the original reports.

Thirteen reports covering a total of 3801 patient-years fulfilled the criteria for our study. Subsequent rupture was documented in 104 patients and the annual rupture rate was 2.7% (95% confidence interval 2.2–3.3%). Large, posterior-circulation, and symptomatic aneurysms were associated with significantly higher rates of rupture (relative risks 6.4, 2.3, and 2.1, respectively). The risk of rupture determined by the authors' review was significantly higher than that reported by investigators from international cohort studies.

Conclusions. Although a selection bias of patients may be the cause of the higher rupture risk, untreated UCAs that have been followed in Japanese institutions have a considerably high rate of rupture. The natural course of UCAs should be carefully estimated in countries not included in the international studies.

KEY WORDS • **unruptured aneurysm** • **natural history** • **aneurysm rupture** • **population study**

RECENT reports from large-scale retrospective and prospective cohort studies have concluded that the risk of rupture associated with small UCAs is extremely low. These studies included data primarily from Caucasian populations (> 90% of patients) in North America and Europe.[11,12] The clinical behavior of UCAs is known to vary according to characteristics such as patient sex and age, size and location of the aneurysm, and other factors.[11,13,22] We believe that the genetic background of race should also be incorporated into an analysis of the rupture risk associated with UCAs. Although some investigators have considered variations in the rate of SAH according to race or nation,[1,4,9] few have addressed racial differences in the rupture risk associated with UCAs. Several retrospective series documented a high risk of rupture among UCAs in Japan and Finland;[13,26,27] however, because these studies included only limited numbers of patients, they cannot be compared with large-scale cohort studies. To clarify the rupture risk among untreated UCAs in Japan and to determine whether this risk differs from that shown in international studies, we systematically reviewed the literature on the natural history of UCAs published exclusively by Japanese institutions.

Abbreviations used in this paper: CI = confidence interval; ISUIA = International Study of Unruptured Intracranial Aneurysms; OR = odds ratio; RR = relative risk; SAH = subarachnoid hemorrhage; UCA = unruptured cerebral aneurysm.

Clinical Material and Methods

Inclusion Criteria

To locate studies of the natural course of UCAs published by Japanese institutions from 1980 to 2003, we searched Medline from 1981 onward and the Index of the Japan Medical Abstract Society from 1983 onward. We also searched reference lists of all relevant publications for additional studies. Two authors (A.M. and S.F.) independently evaluated each study to assess its eligibility for this review. The following inclusion criteria were used. 1) The study was performed in a Japanese institution and reported in a peer-reviewed journal in either English or Japanese. 2) Each study included at least 10 patients with unruptured aneurysms, and the exact number of cases and mean follow-up periods were documented. 3) The number of patients presenting with SAH or aneurysm-related symptoms was available. 4) In cases presenting with SAH in which additional aneurysms were present, the ruptured aneurysm had

TABLE 1

*Risk of rupture associated with UCAs in Japan**

Category	No. of Included Studies	No. of Cases	Patient-Years	No. of Ruptures	% Risk of Rupture per 100 Patient-Years (95% CI)	RR (95% CI)	OR of Rupture (95% CI)
overall	13	922	3801	104	2.7 (2.2–3.3)		
patient sex	10						
male†		294	1370	30	2.2 (1.5–3.1)		
female		435	1803	55	3.0 (2.3–4.0)	1.4 (0.9–2.2)	1.3 (0.85–2.22)
patient age (yrs)	11						
<60†		297	1543	35	2.3 (1.6–3.2)		
≥60		520	2077	62	3.0 (2.3–3.8)	1.2 (0.8–1.9)	1.17 (0.74–4.96)
history of SAH	13						
no†		709	2786	62	2.7 (2.1–3.4)		
yes		209	1010	28	2.8 (1.8–4.0)	1.3 (0.85–2.0)	1.06 (0.64–1.74)
symptoms present	13						
no†		876	3657	94	2.6 (2.1–3.1)		
yes		42	137	10	7.3 (3.5–13.4)	2.1 (1.1–3.9)‡	2.20 (0.97–4.96)
aneurysm site	10						
ant†		770	3370	59	1.8 (1.3–2.3)		
pst		127	618	20	3.2 (2.0–5.0)	2.3 (1.4–3.7)‡	2.18 (1.23–3.86)‡
aneurysm size (mm)	11						
<10†		585	2045	31	1.5 (1.0–2.2)		
≥10		100	344	32	9.3 (6.4–13.1)	6.4 (4.0–10.4)‡	8.68 (4.59–16.41)‡

* Ant = aneurysm located in the anterior circle of Willis; pst = aneurysm located in the posterior circle of Willis.
† Referenced category.
‡ Statistically significant RR or rupture rate and OR of rupture were obtained according to the method described by Breslow and Day. In the table the OR represents (odds of rupture in the group)/(OR of rupture of the referenced group).

been obliterated or no other known source of hemorrhage was detected. 5) The UCA was diagnosed using either conventional or digital subtraction angiography, magnetic resonance angiography, three-dimensional computerized tomographic angiography, or a combination of these methods. 6) Documentation of the rupture of the aneurysm (that is, the SAH) could be confirmed with the aid of computerized tomography scanning, lumbar puncture, surgery, or a postmortem examination.

If several publications originated at the same institution, the most recent series or the series including the largest number of cases was selected for review. In studies missing some inclusion criteria,[17,19,20,27,28] we sent requests to the authors and included the study if they could provide the missing data.

Data Extraction and Analysis

Once a study was deemed eligible for review, two of us independently extracted the following data: the total number of cases, the period of follow up, and the number of aneurysm ruptures. We also sent out requests to authors of the studies for additional detailed data not described in the papers. When data were available for stratification, we extracted information concerning patient age (11 studies) and sex (10 studies), the size of the aneurysm (11 studies), the site of the aneurysm (10 studies), any history of SAH (all 13 studies), symptoms caused by the aneurysm (all 13 studies), and incidences of death from SAH (11 studies). If data were available, we also extracted the number of surgeries performed on UCAs during the same period of study at the same institution, and the timing of lesion rupture. The influences of high blood pressure or smoking and their association with the rupture were discussed in very limited series[2,7,17] and were not assessed in this review.

To calculate the risk of aneurysm rupture, we multiplied the total number of patients by the average period of follow up in each study to obtain the total number of patient-years of follow up. The number of patients with subsequent SAH was then divided by the number of patient-years to yield the risk of rupture per 100 patient-years.[22] We used this method to calculate the risk of rupture in all patients and in the various subgroups. We asked the authors of all 13 studies to provide follow-up periods for each subgroup, but only four authors could do so.[17,26–28] Therefore, the other subgroups were analyzed using the average follow-up period of the total number of cases in each study.[3,22]

Analysis of the Review

To identify any variations among the studies in this review, we compared data between factors in the following subgroups: 1) studies including more than and fewer than 50 patients; 2) studies published in English and those in Japanese; and 3) studies from four districts: Touhoku, Kanto, Kinki-Hokuriku, and Chyuugoku-Shikoku.

Comparison With Large-Scale Cohorts and Other Retrospective Reviews

We compared the findings of our review with those of two large-scale international cohort studies (the ISUIA retrospective and prospective cohorts)[11,12] and a systematic review by Rinkel, et al.[22] The review of Rinkel and colleagues incorporated three Japanese series, and we analyzed the data both to include and exclude Japanese cases. We also compared patient characteristics and the overall rupture rate obtained by calculating total patient-years and total cases of rupture.

Statistical Analysis

The chi-square and Fisher exact tests were used to com-

TABLE 2

*Summary of included studies**

Authors & Year	No. of Cases	Patient-Years	No. of Ruptures	% Rupture Rate (95% CI)	No. of Deaths	Location of Institution
Inagawa, et al., 1992	47	240	1	4.0 (0–1.5)	NA	CS
Asari & Ohmoto, 1993	54	197	11	5.6 (2.8–10.0)	10	CS
Mizoi, et al., 1995	49	211	4	1.9 (0.5–4.9)	3	TH
Yasui, et al., 1997	234	1463	34	2.3 (1.6–3.2)	18	TH
Ikawa, et al., 1998†	36	155	7	4.5 (1.8–9.3)	7	CS
Yasui, et al., 1998†	10	25	1	4.0 (0–14.8)	0	KH
Ikeda, et al., 2000†	33	158	11	6.9 (3.5–12.4)	NA	KH
Tsutsumi, et al., 2000	62	267	7	2.6 (1.1–5.4)	6	TH
Murata, et al., 2001†	48	121	4	3.3 (0.9–8.4)	1	KH
Suga, et al., 2002†	100	317	5	1.6 (0.5–3.7)	3	CS
Tsukahara, et al., 2002	110	217	7	3.2 (1.3–6.6)	2	NA
Matsumoto E, et al., 2003	48	158	7	4.4 (1.8–9.1)	7	KT
Matsumoto K, et al., 2003	91	273	5	1.8 (0.6–4.3)	4	KH

* CS = Chyuugoku-Shikoku district; KH = Kinki-Hokuriku district; KT = Kanto district; NA = not available; TH = Touhoku district.
† Published in Japanese.

pare differences between risk factors and the studies. The Mantel–Haenzel method was also used to compare differences in the included series and to obtain RRs and ORs between subgroups.[3] A probability value less than 0.05 was considered significant. Statistical analyses were performed with the aid of a commercially available software program (SAS, version 8; SAS Institute, Inc., Cary, NC).

Results

Rupture Rate of Untreated UCAs in Japanese Institutions

Thirteen studies fulfilled our inclusion criteria.[2,6–8,16,17,19,20,24–28] Of these, eight were reported in English and the other five in Japanese. Twelve authors responded to our requests and nine provided additional information regarding subgroups.[6,8,17,19,20,24,26–28] Five studies included only asymptomatic cases,[7,20,24,26,28] and two studies included only cases without SAH.[24,26] One study included only aneurysms located in the anterior circulation,[17] and one included only patients older than 70 years.[28] We were able to incorporate these studies because the numbers of patients and ruptures were provided. A summary of the studies is shown in Table 1.

The 13 studies included 922 patients with UCAs who were followed up for a total of 3801 patient-years. There were 104 subsequent ruptures among the entire patient population (11%), constituting an annual rupture rate of 2.7% (95% CI 2.2–3.3%). The risk of rupture was significantly higher for large aneurysms (RR 6.4, 95% CI 4.0–10.4), aneurysms located in the posterior circulation (RR 2.3, 95% CI 1.4–3.7), and symptomatic aneurysms (RR 2.1, 95% CI 1.1–3.9) compared with each referenced category. Unruptured cerebral aneurysms tended to burst more often in patients presenting with SAH, in women, and in patients older than 60 years, but the differences between these groups were not significant. Because our rupture risks were calculated on the basis of an estimated average follow-up period in some series, we also obtained the OR for the net number of all cases of ruptured aneurysms/all cases of unruptured aneurysms in each subgroup, which would not be affected by the follow-up period. The OR of ruptured lesions in the subgroups also showed a similar tendency for a high rupture risk in large aneurysms, posterior-circulation lesions, and aneurysms with symptomatic presentation (ORs 8.68, 2.18, and 2.20, respectively).

In eight reports the authors discussed the risk of rupture of small aneurysms (< 5 mm); seven of 40 ruptured aneurysms in these studies were smaller than 5 mm.[6,8,17,19,20,24–26] Among patients with aneurysms measuring 5 or 6 mm, an additional four of 40 lesions ruptured; hence, 27.5% (11 aneurysms) of the ruptured aneurysms were smaller than 7 mm. Because of the low number of small aneurysms and the lack of details about the follow-up period, we could not calculate the rupture rate for this group.

Data on this incidence of death caused by SAH from 11 studies showed that 61 (66%) of 92 patients died of SAH.

Eleven reports provided data about surgery during the same period as the studies.[2,7,8,16,17,19,20,25–28] In these 11 studies, surgery was performed in 1601 patients, compared with 787 who were only observed.

The timing of rupture was documented in 11 series, but the total number of ruptures in each year could be obtained from only eight series.[2,6–8,20,24,26,28] Among 47 cases of subsequent rupture, 19 lesions ruptured within 1 year, nine ruptured within the 2nd year, and the remaining 19 aneurysms ruptured after the 2nd year. When we included three additional series that provided Kaplan–Meier life tables showing the timing of rupture,[16,17,27] we noted no acute increase in the rupture rate in any specific year.

Variations Among the Included Studies

A summary of the included studies appears in Table 2 and Fig. 1. The series reported by Ikeda and colleagues[7] and Inagawa, et al.,[8] demonstrated statistically significant differences when they were compared with other studies regarding the rupture rate ($p = 0.0068$). Excluding these two studies from the analysis did not alter the results of our review. Although the overall rupture rate was higher in studies written in Japanese and in those studies including fewer than 50 patients, no significant difference was noted between groups. Geographic location, which can influence the patient's living environment, did not influence the risk of rupture.

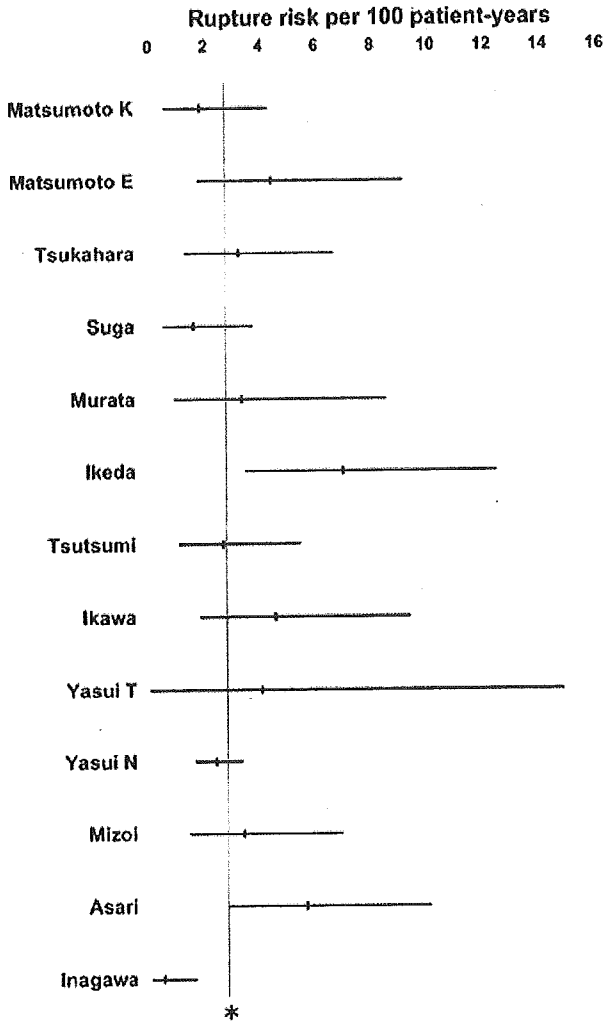

FIG. 1. Chart showing the risk of rupture associated with UCAs in the included studies. The *asterisked line* indicates the average rupture rate of all cases.

Comparison With International Studies

Table 3 offers a comparison of our findings and those of the ISUIA[11,12] and the systematic review from Europe by Rinkel and colleagues.[22] The ISUIA retrospective and prospective cohorts included significantly more female patients, symptomatic aneurysms, and lesions presenting with SAH than our review did. The retrospective cohort included significantly more cases of large aneurysms but fewer cases in which the lesion was located in the posterior circulation. Compared with our study, the prospective group did not show any differences in these subgroups. The ages of patients who were included could not be compared. The overall rupture rate in the 13 studies we reviewed was significantly higher compared with the rates of both the prospective and retrospective ISUIA cohorts. Our review also showed a higher risk of rupture compared with the review by Rinkel, et al.,[22] whereas the significance was less ($p = 0.02$). Excluding Japanese series from the European study did not change our findings. The European review included more cases of anteriorly located lesions, symptomatic aneurysms, and lesions with SAH.

Discussion

Rupture Rate Associated With UCAs

This systematic review shows that the rupture risk of UCAs observed over time in Japanese institutions is relatively high. Eleven percent of all patients who were included in the articles we reviewed experienced rupture of the aneurysm and the average annual rupture rate was 2.7% (95% CI 2.2–3.3%). An analysis of subgroups by RRs of rupture per 100 patient-years and the OR of cases of rupture versus those of nonrupture showed that significant factors influencing the rupture risk include the size, location, and symptomatic presentation of the aneurysm. Patient sex and age and a history of SAH also affected the risk, but these factors did not reach statistical significance. Papers published in Japanese and papers including fewer cases documented a slightly higher risk of rupture, but no significant difference was recognized. Multiple trials have failed to identify any influence of climate, physical stress, or emotional stress on the rate of SAH.[23] To determine whether there was any influence of climate or environmental stress on the rupture risk of UCAs among Japanese patients, in addition to the geographical location of the institution, we compared studies according to average yearly temperature, the largest difference in the average temperature within a year in the territory of each institution (data extracted from the database of the Japan Meteorological Society, http://www.jma.go.jp/JMA_HP/jma/indexe.html), and the population data (data obtained from the database of the Japan Statistics Bureau, http://www.stat.go.jp/english/index.htm). Japanese people usually seek medical care close to their homes, and thus we assumed that the statistics and climate information of a particular institute reflect the patient's living environment. Our comparison of 12 studies (the 13th was a multicenter study that could not be confined to a single area) revealed no apparent differences in climate or population subgroups. In this review, we could not assess other previously documented risk factors associated with the rupture rate, such as hypertension or smoking. Of note, the prevalence of hypertension or smoking in Japanese adults is not higher than that of the US population.[5,18,21]

By systematically collecting data from case series, we determined the number of patient-years and used that number in our analysis of the data. Although our review showed that there were fewer female patients and fewer patients with SAH or symptomatic aneurysms, overall these characteristics did not significantly differ from those of large cohort studies. The rupture rate documented in our review, however, was significantly higher.[11,12] A comparison with the systemic review by Rinkel, et al.,[22] also showed a difference, but this difference was smaller ($p = 0.02$). Even in the patient group with the least risk (patients with aneurysms < 10 cm), the calculated rupture rate was 1.5% per year in our review (95% CI 1.0–2.15%). In addition, rupture was reported in 11 cases in which the aneurysm was smaller than 7 mm (27.5% of all ruptured cases in the pertinent series).

Race or Bias

To explain the high rupture rate documented in our re-

TABLE 3
Comparison of the current review with international studies

Authors & Year	Total No. of Cases	Patient-Years	No. of Ruptures	% Rupture Rate (95% CI)	p Value*
ISUIA, 1998	1449	12023	32	0.3 (0.2–0.4)	<0.0001
Rinkel, et al., 1998	NA	3907	75	1.9 (1.5–2.4)	0.02
ISUIA, 2003	1692	6544	51	0.8 (0.6–1.0)	<0.0001
present study	922	3801	104	2.7 (2.2–3.3)	

* Fisher exact test.

view, we considered at least two factors. First, UCAs in Japanese patients may have a higher risk of rupture due to a genetic or habitual background. The rate of SAH in the Japanese population is reported to be very high, as high as 96 per 100,000 annually[15]—almost nine times higher than the incidence observed in Rochester, MN (11 per 100,000 annually[10]). Nevertheless, the prevalence of UCAs is not significantly different among the populations studied,[22] which might indicate that UCAs in Japanese patients may rupture more frequently than they do in the Caucasian population. An SAH, however, is not necessarily a consequence of the rupture of a UCA that has already formed. Kataoka, et al.,[14] noted that the pathological analysis of ruptured aneurysms showed evidence of acute formation of the lesion's wall, and some SAHs may be caused by acutely formed aneurysms, which would not be detected as UCAs during routine physical or imaging examinations. Furthermore, the prevalence of SAH may differ according to the study design and how the rate was determined. Nevertheless, the high rupture risk of documented UCAs may explain the high rate of SAH in Japan, and this high risk may relate to the genetic or habitual backgrounds of the Japanese patients.

Secondly, we considered that our review might simply incorporate series that included highly biased cases. Two possible steps could create such a bias in patient selection. Large aneurysms and those located in the posterior circulation are known to be associated with a high risk of rupture.[11] Elderly people are also known to have a higher rate of SAH.[15] These factors elevate surgical risks,[11] which may make surgeons reluctant to perform surgery in patients with these factors. Hence, these patients may be left untreated. Except for the inclusion of more cases with aneurysms of the posterior circulation, however, the characteristics of patients in this review included more patients with lower risk than those found in either the ISUIA cohorts[11,12] or the review written in Europe.[22] Therefore, this bias does not appear to be the main reason for the difference in rupture risk.

As a second bias, we may need to consider intrinsic variations in the design of the studies. Large-scale cohorts, especially in prospective studies, may include all patients who have been encountered, even those seen only in outpatient clinics. On the other hand, retrospective series tend to include patients who were admitted to the hospital for some reason and then evaluated for intervention. These nuances in the selection criteria for patients might produce a bias in the studies. In part of this study (11 series), the number of patients who underwent surgery for UCAs was twice that of patients who were merely observed. Hence, our study does not represent all UCAs that we encountered in our daily practice and should always take into account the selection bias.

Based on these findings, patients with UCAs that were not treated but observed in Japanese institutions may indeed carry a relatively high risk of lesion rupture. These patients, however, might also have high medical risks, surgical risks, or both, and treatment should be chosen according to a detailed risk–benefit analysis for each scenario. Although we cannot currently define the genetic factors influencing rupture, we would like to warn physicians that UCAs might have a different natural course in different races, and the data reported by the ISUIA[11] may not apply to all cases.

To understand the real risks of rupture in all patients with UCAs encountered in daily practice, we should rely on prospective cohort studies conducted in individual countries or on those with an international basis. In Japan, there are two ongoing prospective studies. When these studies are completed, we should be better equipped to determine the natural history of UCAs, whether that history differs among countries or races, and what treatment should be used for patients with UCAs in Japan.

Conclusions

A systemic review of untreated UCAs in Japan showed that the risk of rupture is significantly higher than that reported by international large-scale cohort studies. This difference in the rupture risk might be induced by differences in racial or genetic backgrounds or by differences in study designs or patient backgrounds. Based on these findings, we can state that untreated UCAs in Japan, once excluded from surgical indications, have a significantly high rate of rupture, but this rate may not apply to all patients treated in outpatient clinics.

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Editorial

The risk of rupture of unruptured cerebral aneurysms in the Japanese population: a systematic review of the literature from Japan by Morita, et al.

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Morita and colleagues present a very interesting paper about an important topic that may be particularly pertinent in Japan given that some of the highest incidence rates for subarachnoid hemorrhage (SAH) have been cited in reports from that country. There are obviously many challenges inherent in the approach of collating and combining data from several relatively small retrospective reports, as illustrated by this study and substantially acknowledged by the authors. We faced similar challenges in North America and Europe in an attempt to evaluate small retrospective studies, and our inability to provide uniform, robust results while using this approach led to the development of the International Study of Unruptured Intracranial Aneurysms (ISUIA). It is nevertheless interesting that the results of the current study indicating increased rupture risk for large, posterior circulation, and symptomatic unruptured cerebral aneurysms were very similar to the pattern observed in the ISUIA[1,2] (a multivariate analysis performed in the ISUIA indicated that the increased risk associated with symptomatic unruptured aneurysms was related to the increased size of these lesions). Moreover, the overall rupture rate of 2.7% per year reported in the current study would not differ statistically from the overall rupture rates we reported from early small retrospective series from a single institution.[3,4] It is difficult to evaluate the apparent cases of rupture of small aneurysms in the absence of information about which patients had prior SAH and without sufficient follow-up information to allow calculation of rupture rates. Given the substantial differences in patient populations, study design, and follow-up analyses, it is not statistically possible to compare the results of the current metaanalysis with the results of the ISUIA by using traditional probability values.

Notwithstanding the aforementioned points, the results of the study by Morita, et al., are intriguing and provide food for thought as we anticipate the results of the two ongoing prospective studies in Japan that the authors mention in their paper. A difference in risk factors and the behavior of unruptured intracranial aneurysms in substantially different genetic populations cannot be excluded.

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Response: We appreciate Dr. Wiebers' thoughtful comments about our systematic review. As he has emphasized, reviewing and summarizing small series is difficult because the case material, classification, follow-up methods, and study periods differ among series. Because of these difficulties, we asked the authors of each study included in our review to provide their own data reclassified according to our criteria. Most of the authors kindly fulfilled our request, and we particularly appreciate their cooperation. The strength of our study relies on their efforts, which we could request because our report is based on single-nation studies and we know each other very well. Without such a relationship with each author, we might not have been able to obtain uniformly classified data. Nonetheless, as Dr. Wiebers notes, it was still a difficult task to collect such information because some of the authors' data were already lost—some from a change in recording style occurring during software upgrades and some because of computer breakdowns. Furthermore, some of the older raw data had not been obtained with informed consent from patients and we did not collect raw data. To carry out a multivariate analysis regarding risk factors (such as a comparison of the influence of symptomatic and larger aneurysms), we need patients' raw data. Problems such as publication biases be-

come more serious when assessing management results collected from surgical series.[4] With these problems in mind, we strongly recommend that authors who wish to publish their own series of specific diseases obtain informed consent from each patient for a generalized data analysis. Authors should also keep raw data obtained in each patient with their report in a format that will not be lost. Such efforts can contribute tremendously to future scientific study. Furthermore, the method of classification, measures used to evaluate outcomes or events, and other pertinent information should be uniform. We hope that guidelines developed to direct the management of specific diseases also contain recommendations about methods of follow up and other pertinent issues.[1] The two on-going prospective studies in Japan have been constructed to overcome the innate problems of retrospective data collection. The first study is a prospective on-line collection of data from patients with unruptured cerebral aneurysms treated in the involved institutions (Unruptured Cerebral Aneurysm Study in Japan, UCAS Japan).[2] Each patient chose a treatment plan based on the recommendations of the attending physician, and prospective follow-up and management data are being assessed. No results about rupture risk or management outcome have yet been published. The second study is being conducted by a group of neurosurgeons at national hospitals who agreed to observe all patients harboring unruptured aneurysms with a diameter less than 5 mm (Small Unruptured Aneurysm Verification; SUAVe study). The latest publication from this group[3] shows that, even among these small lesions, four aneurysms ruptured and the calculated rupture risk was 0.8% per year (95 confidence interval 0.2–3%). Eighteen aneurysms enlarged, seven of which were surgically treated. A location on the anterior communicating artery and the occurrence of multiple aneurysms in older women were factors affecting the rupture risk. Because the study is limited to a select group and the follow-up period is short, the confidence interval is wide and longer follow-up periods and further case involvement are required to establish acceptable data. Nonetheless, a close follow-up review with reasonable sensitivity to enlargement of the lesion has proved to be a valid method for managing small aneurysms. We hope such efforts to build valid prospective data obtained via uniform measures from multiple institutions will solve some of the mystery surrounding unruptured aneurysms and provide useful information for their appropriate treatment. This cannot be accomplished using the current retrospective analysis of data. These efforts might also be used to identify the reason for the difference in incidence of SAH between patients in Japan and those in Western countries. Nevertheless, there will still be some patients in whom detailed prospective data analysis may not clarify the optimal management strategy and a randomized controlled trial is required. The aforementioned prospective studies may help us define the group of patients best served by randomized controlled trials.

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3. 未破裂脳動脈瘤―治療適応と到達目標．何がゴールか？

①日本未破裂脳動脈瘤悉皆調査：UCAS Japan の最新知見

日本未破裂脳動脈瘤悉皆調査事務局（東京大学脳神経外科内）
森田　明夫

【目的】UCAS Japan（日本未破裂脳動脈瘤悉皆調査）は未破裂脳動脈瘤の自然歴・治療に関するリスクの検証，データバンクの構築を目的とした前向きコホート研究である．本発表では UCAS Japan 登録例の最新データを報告する．【方法】参加施設において 2001 年 1 月から 2004 年 4 月までの間に発見された治療例・経過観察例すべての未破裂脳動脈瘤の診断時状況，3 カ月・12 カ月・36 カ月における経過観察をインフォームド・コンセント取得後オンライン登録する．【結果】開始 39 カ月（2004 年 6 月）の段階で参加施設は 404 施設，登録症例数は 6,646 例，動脈瘤数は 8,161 個である．男女比は 1：2，中間年齢は 63 歳である．瘤のサイズは 3～45 mm（中間 5 mm），部位は中大脳動脈（33％），内頸動脈（34％）の順に多く，多発性は 17％であった．瘤発見のきっかけは頭痛やめまいなどの精査で発見されたものが最も多かった．治療は 2,431 例に適応された．【結論】今後さらに症例の追跡を徹底し，未破裂脳動脈瘤の治療方針決定に資するデータ構築を目指す．

Stroke

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Impaired Progression of Cerebral Aneurysms in Interleukin- 1β-deficient Mice

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