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UNRUPTURED INTRACRANIAL ANEURYSMS — RISK OF RUPTURE AND RISKS OF SURGICAL INTERVENTION

THE INTERNATIONAL STUDY OF UNRUPTURED INTRACRANIAL ANEURYSMS INVESTIGATORS*

ABSTRACT

Background The management of unruptured intracranial aneurysms requires knowledge of the natural history of these lesions and the risks of repairing them.

Methods A total of 2621 patients at 53 participating centers in the United States, Canada, and Europe were enrolled in the study, which had retrospective and prospective components. In the retrospective component, we assessed the natural history of unruptured intracranial aneurysms in 1449 patients with 1937 such aneurysms; 727 of the patients had no history of subarachnoid hemorrhage from a different aneurysm (group 1), and 722 had a history of subarachnoid hemorrhage from a different aneurysm that had been repaired successfully (group 2). In the prospective component, we assessed treatment-related morbidity and mortality in 1172 patients with newly diagnosed unruptured intracranial aneurysms.

Results In group 1, the cumulative rate of rupture of aneurysms that were less than 10 mm in diameter at diagnosis was less than 0.05 percent per year, and in group 2, the rate was approximately 11 times as high (0.5 percent per year). The rupture rate of aneurysms that were 10 mm or more in diameter was less than 1 percent per year in both groups, but in group 1, the rate was 6 percent the first year for giant aneurysms (≥25 mm in diameter). The size and location of the aneurysm were independent predictors of rupture. The overall rate of surgery-related morbidity and mortality was 17.5 percent in group 1 and 13.6 percent in group 2 at 30 days and was 15.7 percent and 13.1 percent, respectively, at 1 year. Age independently predicted surgical outcome.

Conclusions The likelihood of rupture of unruptured intracranial aneurysms that were less than 10 mm in diameter was exceedingly low among patients in group 1 and was substantially higher among those in group 2. The risk of morbidity and mortality related to surgery greatly exceeded the 7.5-year risk of rupture among patients in group 1 with unruptured intracranial aneurysms smaller than 10 mm in diameter. (N Engl J Med 1998;339:1725-33.)

INTRACRANIAL aneurysms are common.[1-6] Autopsy studies have shown that the overall frequency in the general population ranges from 0.2 to 9.9 percent (mean frequency, approximately 5 percent),[5,6] suggesting that 10 to 15 million persons in the United States have or will have intracranial aneurysms. These data, in combination with the incidence of aneurysmal subarachnoid hemorrhage (approximately 10 cases per 100,000 persons per year),[7] suggest that most intracranial aneurysms do not rupture.

The management of unruptured intracranial aneurysms is controversial[8-12] because of a lack of understanding of the natural history of these lesions and the risks of repairing them. This report describes a large multicenter study that was conducted to determine the risk of rupture and the risks associated with the repair of unruptured intracranial aneurysms.

METHODS

Study Design and Objectives

The study consisted of a retrospective component based on data from the medical records of patients with diagnosed unruptured intracranial aneurysms and a prospective component based on data from patients with newly diagnosed unruptured intracranial aneurysms treated either conservatively or by surgical or endovascular procedures.

The specific objectives of the retrospective portion of the study were to describe the natural history of saccular unruptured intracranial aneurysms in patients without a history of subarachnoid hemorrhage from a separate aneurysm (group 1) and in those with such a history (group 2), and to determine whether there are subgroups of patients at greater risk for subsequent aneurysmal rupture, in order to determine the most appropriate treat-

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*The institutions and investigators participating in the study are listed in the Appendix. On behalf of the Steering Committee, Dr. Wiebers assumes overall responsibility for the content of the manuscript.

ment of such patients. For the prospective portion of the study, the objectives were to evaluate the risks of morbidity and mortality associated with treatment of unruptured intracranial aneurysms and to determine whether these risks are higher for some patients than for others.

Identification and Recruitment of Patients

The retrospective cohort included patients with unruptured intracranial aneurysms that had been diagnosed during the period from 1970 to 1991. At each center, retrospective cases could be included only as far back as hard-copy arteriograms and medical records were available for all patients at that center. Central medical-records systems, admission records, and records from departments of radiology, neurosurgery, and neurology were used as sources for identifying patients.

Prospective patients were identified by study coordinators at the participating centers, who conducted surveillance of patients with diagnosed intracranial aneurysms between 1991 and 1995.

Patient Eligibility

Retrospective Component

Patients were eligible for enrollment in the retrospective component if they had had at least one unruptured intracranial aneurysm, whether or not they had symptoms (e.g., cranial-nerve palsy). Patients may have had a previous ruptured aneurysm at another location that was clipped, completely trapped, or isolated from the circulation by endovascular obliteration, as confirmed arteriographically. Patients had to have been able to care for themselves after the previous aneurysm had been treated (i.e., a score of 1 or 2 on the Rankin scale of neurologic disability, with scores ranging from 1 [no disability] to 5 [severe disability]).

Patients with fusiform, traumatic, or mycotic aneurysms were not eligible for the study. Also, patients with aneurysms that were found to be less than 2 mm in maximal diameter with the use of a standard measuring device were excluded. Patients with subarachnoid hemorrhage from a single ruptured aneurysm or an unknown source were excluded. In addition, patients in whom the aneurysm was manipulated within 30 days after diagnosis were not eligible. Patients with a history of intracranial hemorrhage were excluded if the cause was unknown or if an underlying structural lesion was not repaired. Patients were excluded if they did not consent to follow-up, if they had a malignant brain tumor, or if they were bedridden or unable to communicate at the time the aneurysm was identified.

Prospective Component

Eligibility criteria for patients in the prospective component were similar to those for the patients in the retrospective component, except that in the prospective component, the investigators decided whether to enroll the patients without planned surgical or endovascular treatment or with planned surgical or endovascular treatment of at least one intracranial aneurysm. All patients were required to undergo cerebral arteriography in order to confirm the presence, location, and size of intracranial aneurysms.

Radiology

Hard copies of cerebral arteriograms from all patients were reviewed at the central study office at the Mayo Clinic, Rochester, Minnesota, by two neuroradiologists. The size of the aneurysm was corrected for magnification by methods reported previously.[13] A pilot study was conducted to establish criteria for measurement, standards for evaluating the size and morphologic characteristics of the aneurysm, and interobserver reliability.[13]

Follow-up

For the retrospective cohort, follow-up information was obtained by means of an annual standardized questionnaire and a review of medical records. Neurologic symptoms, intracranial surgery, or repeated arteriographic studies undertaken since the previous assessment were recorded.

For the prospective cohort, base-line assessments were made. Prospective patients who did not undergo planned surgical treatment were followed with the use of an annual questionnaire. For patients who underwent surgical treatment, assessments were made 7 days after the procedure, at hospital discharge, at 30 days, and at yearly intervals. For both cohorts, neurologic status was measured with the use of the Rankin scale at each follow-up assessment, and cognitive status was determined with the Mini–Mental State Examination[14] or the Telephone Interview for Cognitive Status[15] at the same intervals. All complications of surgical treatment were recorded.

Determination of Events

Detailed information was obtained on all end points (definite or questionable subarachnoid or intracerebral hemorrhage and death). Comprehensive adjudication was performed centrally for all hemorrhages, strokes, and deaths on the basis of uniform criteria, with the use of available clinical, radiologic, autopsy, and other information, and hemorrhages were classified according to the location of the rupture. Subarachnoid or intracerebral hemorrhage was classified as definite (symptoms of subarachnoid or intracerebral hemorrhage and positive findings on computed tomography [CT] or magnetic resonance imaging [MRI], surgery, or autopsy), highly probable (symptoms and positive findings on cerebrospinal fluid analysis), or probable (symptoms only). All definite, highly probable, and probable aneurysmal hemorrhages were included in the primary analysis.

In the prospective component of the study, evidence of surgery-related cerebral infarction, hemorrhage, or death was confirmed centrally. Neurologic deficits 30 days or 1 year after treatment were evaluated for their relation to treatment or coexisting disorders.

Morbidity related to surgical treatment was defined as a Rankin score of 3, 4, or 5 (moderate-to-severe neurologic disability) or a score of less than 24 on the Mini–Mental State Examination or less than 27 on the Telephone Interview for Cognitive Status (both indicating a serious cognitive abnormality) at 30 days and 1 year.[14-16] Mortality was considered separately.

Statistical Analysis

The retrospective component included two groups designated by their eligibility for enrollment. Group 1 and group 2 were analyzed as separate strata. Between-group comparisons of the distributions of demographic and clinical characteristics were made by the chi-square test for categorical variables and the t-test for continuous variables. Estimates of the risk of hemorrhage were made with the use of life-table methods, with data on death, surgical intervention, and last follow-up assessment censored. Predictors of hemorrhage were ascertained with the use of a proportional-hazards regression model.

For the prospective cohort, survival, morbidity (a Rankin score of 3, 4, or 5), and diminished mental status (a score of less than 24 on the Mini–Mental State Examination or less than 27 on the Telephone Interview for Cognitive Status), as well as overall morbidity and mortality, were analyzed. Survival estimates and 95 percent confidence intervals were calculated with life-table methods 30 days and 1 year after treatment. The risk of morbidity was estimated as the proportion of patients with impairment at the 30-day and 1-year examinations. The overall risk of morbidity or mortality was estimated as the proportion of patients who were disabled or dead at 30 days and at 1 year. Surgery-related morbidity and mortality were estimated on the basis of only those events attributed to treatment of the aneurysm. Factors related to overall morbidity and mortality were determined with the use of logistic regression. (An expanded description of the methods used in this study is available on the Internet at www.mayo.edu/ISUIA or by writing to the ISUIA Coordinating Center.)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE RETROSPECTIVE COHORT.*

CHARACTERISTIC	GROUP 1 (N=727)	GROUP 2 (N=722)	P VALUE
Age — yr			
Mean	56.0	49.4	<0.001
Range	9–87	13–80	
Female sex — no. of patients (%)	517 (71.1)	535 (74.1)	0.27
White race — no. of patients (%)	669 (92.0)	681 (94.3)	0.08
Single aneurysm — no. of patients (%)	545 (75.0)	540 (74.8)	NS†
Multiple aneurysms — no. of patients (%)	182 (25.0)	182 (25.2)	
Total no. of aneurysms	977	960	
Diameter of largest aneurysm — mm			
Mean	10.9	5.7	<0.001
Range	2–60	2–35	
Size of largest aneurysm — no. of patients (%)			
2–5 mm	238 (32.7)	442 (61.2)	0.001
6–9 mm	186 (25.6)	199 (27.6)	
10–14 mm	113 (15.5)	65 (9.0)	
15–24 mm	120 (16.5)	13 (1.8)	
≥25 mm	70 (9.6)	3 (0.4)	
Location of aneurysm — no. of aneurysms (%)			
Cavernous carotid artery	165 (16.9)	91 (9.5)	<0.001
Internal carotid artery	242 (24.8)	171 (17.8)	<0.001
Anterior communicating or anterior cerebral artery	98 (10.0)	79 (8.2)	0.22
Middle cerebral artery	222 (22.7)	363 (37.8)	<0.001
Posterior communicating artery	136 (13.9)	163 (17.0)	0.06
Vertebrobasilar or posterior cerebral artery	64 (6.6)	56 (5.8)	0.51
Tip of basilar artery	50 (5.1)	37 (3.9)	0.18

*Patients in group 1 had no history of subarachnoid hemorrhage, and those in group 2 had a history of subarachnoid hemorrhage.

†NS denotes not significant.

RESULTS

Retrospective Cohort

Demographic and Clinical Characteristics

Fifty-three centers in the United States, Canada, and Europe enrolled a total of 1449 patients with 1937 unruptured intracranial aneurysms (727 patients in group 1 and 722 patients in group 2). The aneurysms were diagnosed at the participating centers between 1970 and 1991.

Of the 1449 patients, 1085 (75 percent) had single unruptured intracranial aneurysms and 364 (25 percent) had multiple unruptured intracranial aneurysms, with similar distributions in groups 1 and 2 (Table 1). The mean age at diagnosis was higher in group 1 than in group 2 (Table 1). Almost three fourths of the patients were women. The mean duration of follow-up was 8.3 years, with a total of approximately 12,023 patient-years of follow-up.

Conditions leading to the diagnosis of unruptured intracranial aneurysms included headaches in 36 percent of patients, ischemic cerebrovascular disease in 17.6 percent, cranial-nerve deficits in 15.4 percent, aneurysmal mass effect in 5.7 percent, ill-defined spells in 4.8 percent, convulsive disorder in 4.2 percent, subdural or intracerebral hemorrhage in 2.7 percent, brain tumor in 1.7 percent, and nervous system degenerative disease in 0.5 percent. The diagnosis was suspected on the basis of CT findings in 39.8 percent and MRI findings in 5.6 percent.

Aneurysmal Characteristics

The distribution of unruptured intracranial aneurysms according to size and location (parent artery) is shown for groups 1 and 2 in Table 1. Forty-one of the patients in group 1 with small aneurysms (<10 mm in diameter) (9.7 percent) and 153 patients in the entire retrospective group (10.6 percent) had single cavernous carotid aneurysms.

Overall, 32 percent of the patients in group 1 and 11 percent of those in group 2 had unruptured aneurysms that caused symptoms other than those associated with rupture (e.g., cranial-nerve palsies).

Risk Factors

Potential risk factors for the development of an unruptured aneurysm or for subsequent rupture were documented at the time of diagnosis (Table 2). Among patients for whom data on smoking were available, 60.6 percent were current smokers and 18.6 percent were former smokers (a precise history of smoking was unavailable for 31 percent of the patients). Other potential risk factors for which there were substantial numbers of patients with missing

TABLE 2. RISK FACTORS FOR RUPTURE IN THE RETROSPECTIVE AND PROSPECTIVE COHORTS.

COHORT AND RISK FACTOR	GROUP 1	GROUP 2	TOTAL
	no./total no. (%)		
Retrospective cohort			
Hypertension	308/697 (44.2)	200/676 (29.6)	508/1373 (37.0)
Treatment for hypertension	264/698 (37.8)	124/698 (17.8)	388/1396 (27.8)
Atrial fibrillation	16/691 (2.3)	4/673 (0.6)	20/1364 (1.5)
Cardiac arrhythmias	41/688 (6.0)	16/673 (2.4)	57/1361 (4.2)
Congestive heart failure	15/695 (2.2)	2/673 (0.3)	17/1368 (1.2)
Myocardial infarction	39/689 (5.7)	21/671 (3.1)	60/1360 (4.4)
Valvular disease	11/691 (1.6)	2/673 (0.3)	13/1364 (1.0)
Alcohol use (>5 drinks in 24 hr)	38/202 (18.8)	74/155 (47.7)	112/357 (31.4)
Current smoker	284/540 (52.6)	321/459 (69.9)	605/999 (60.6)
Former smoker	120/540 (22.2)	66/459 (14.4)	186/999 (18.6)
Use of stimulants	4/129 (3.1)	6/125 (4.8)	10/254 (3.9)
Use of oral contraceptives by women	38/143 (26.6)	31/94 (33.0)	69/237 (29.1)
Prospective cohort			
Hypertension	295/798 (37.0)	70/197 (35.5)	365/995 (36.7)
Treatment for hypertension	251/798 (31.5)	54/197 (27.4)	305/995 (30.7)
Atrial fibrillation	22/798 (2.8)	0/197	22/995 (2.2)
Cardiac arrhythmias	45/798 (5.6)	5/197 (2.5)	50/995 (5.0)
Congestive heart failure	5/798 (0.6)	0/197	5/995 (0.5)
Myocardial infarction	32/798 (4.0)	7/197 (3.6)	39/995 (3.9)
Valvular disease	17/798 (2.1)	3/197 (1.5)	20/995 (2.0)
Alcohol use (>5 drinks in 24 hr)	244/798 (30.6)	71/197 (36.0)	315/995 (31.7)
Current smoker	359/798 (45.0)	106/197 (53.8)	465/995 (46.7)
Former smoker	255/798 (32.0)	61/197 (31.0)	316/995 (31.8)
Use of stimulants	63/798 (7.9)	15/197 (7.6)	78/995 (7.8)
Use of oral contraceptives by women	285/579 (49.2)	98/159 (61.6)	383/738 (51.9)

data on retrospective review included alcohol consumption and the use of oral contraceptives and stimulants.

Aneurysmal Rupture

Of the 1449 patients, 32 had confirmed aneurysmal ruptures during follow-up, and in 28 of the 32, the rupture occurred within the first 7.5 years of follow-up. Two other patients with subarachnoid hemorrhage 2 years and 5.6 years after diagnosis had coexisting arteriovenous malformations. In neither patient was it possible to delineate whether the aneurysm or the arteriovenous malformation had ruptured. Patients with both aneurysms and arteriovenous malformations (20 in group 1 and 13 in group 2) were not included in the analysis of end points. Of the 12 patients in group 1 who had confirmed aneurysmal subarachnoid hemorrhage, only 1 had an aneurysm that was less than 10 mm in diameter, whereas 17 of the 20 patients in group 2 with ruptures had aneurysms that were less than 10 mm in diameter. Two of the 32 ruptures occurred in patients with cavernous carotid aneurysms.

Prediction of Rupture

In group 1, the only significant predictors of rupture were the size and location of the aneurysm. Aneurysms that were less than 10 mm in diameter were much less likely to rupture than those that were 10 to 24 mm in diameter (relative risk for larger aneurysms, 11.6; $P=0.03$) or 25 mm or more in diameter (relative risk, 59.0; $P<0.001$). The relative risk of rupture was 13.8 for aneurysms at the basilar tip and 13.6 for those in the vertebrobasilar or posterior cerebral distribution, as compared with other locations ($P=0.001$ and $P=0.007$, respectively). For posterior communicating aneurysms, the relative risk of rupture was 8.0 ($P=0.02$). In group 2, the relative risk of rupture was 5.1 for aneurysms at the basilar tip ($P=0.004$) and 1.31 for older age ($P=0.04$). The size of the aneurysm did not predict the risk of rupture.

Rupture Rates

Rates of confirmed subarachnoid hemorrhage 7.5 years after diagnosis are shown in Figures 1 and 2. The cumulative rate of rupture for patients in group 1 with aneurysms that were less than 10 mm in diameter at the time of discovery was 0.4 percent, or about 0.05 percent per year. In contrast, the rupture rate for patients in group 1 with aneurysms that were 10 mm or more in diameter was about 20 times that of the rate for smaller aneurysms, approaching 1 percent per year (Fig. 1). In group 2,

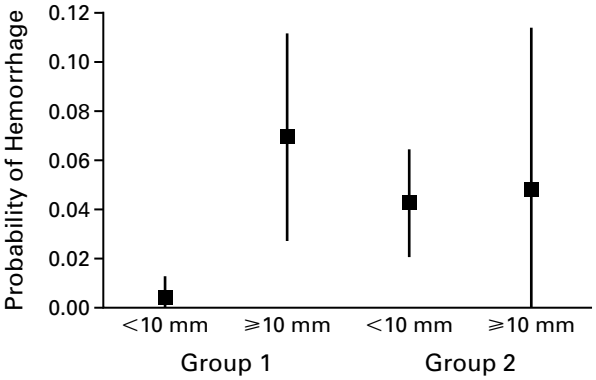

Figure 1. Probability of Subarachnoid Hemorrhage 7.5 Years after the Diagnosis of Unruptured Intracranial Aneurysm, According to the Diameter of the Aneurysm.

Patients in group 1 had no history of subarachnoid hemorrhage from a different aneurysm, and those in group 2 did have such a history. Data are from the retrospective cohort. The bars represent 95 percent confidence intervals.

the smaller aneurysms were approximately 11 times as likely to rupture as aneurysms of the same size in group 1, with a rate of approximately 0.5 percent per year. The rupture rate of larger aneurysms was similar to that in group 1, approaching 1 percent per year. Figure 2 shows rupture rates over time for groups 1 and 2 according to the size of the aneurysm. In group 1, aneurysms that were 25 mm or more in diameter had a rupture rate of 6 percent in the first year (Fig. 2A).

Mortality

Among the 32 patients with initially unruptured aneurysms and subsequent hemorrhage, the case fatality rate was 66 percent (83 percent in group 1 and 55 percent in group 2). Of the 205 patients who died during the 7.5 years of follow-up, 42 died of intracranial hemorrhage, 36 of cancer, 30 of cardiac disease, 14 of respiratory tract disease, 11 of cerebral infarction, and 72 of other, unrelated causes. On an actuarial basis, the estimated survival rate at five years for the entire retrospective cohort was 89 percent.

Prospective Cohort

Surgical Intervention

In the prospective cohort, 1172 patients were enrolled in the treatment group (961 patients in group 1 and 211 in group 2). Intracranial surgery was performed in 798 patients (83 percent) in group 1 and in 198 (94 percent) in group 2. The rest of the patients were treated with various endovascular procedures.

Demographic and Clinical Characteristics

The mean age at diagnosis was 52 years (range, 19 to 91), with a higher mean age in group 1 than in

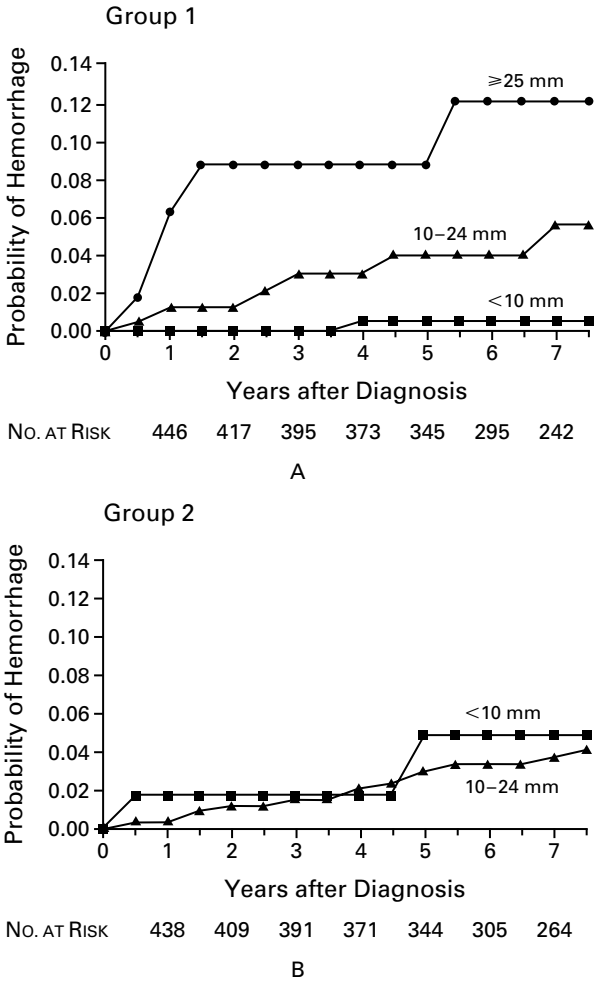

Figure 2. Probability of Subarachnoid Hemorrhage over Time in Group 1 (Panel A) and Group 2 (Panel B), According to the Size of the Aneurysm.

In Panel B, no rates are shown for aneurysms in the largest category (≥25 mm) because there were only three patients with aneurysms in this category. The numbers at the bottom of each panel are the numbers of patients not operated on who were at risk for a first hemorrhage. Data are from the retrospective cohort.

group 2 (53 vs. 47 years) (Table 3). Approximately three fourths of the patients were women.

Conditions leading to the diagnosis of an unruptured intracranial aneurysm and enrollment in the treatment group included headache in 34 percent of patients, cranial-nerve deficits in 14 percent, ischemic cerebrovascular disease in 11 percent, ill-defined spells in 10 percent, aneurysmal mass effect in 6 percent, convulsive disorder in 5 percent, subdural or intracerebral hemorrhage in 0.4 percent, brain tumor in 0.4 percent, and nervous system degenerative disease in 0.3 percent. The diagnosis was suspected on the basis of CT findings in 40 percent of patients and MRI findings in 37 percent.

TABLE 3. BASE-LINE CHARACTERISTICS OF THE PROSPECTIVE COHORT.

CHARACTERISTIC	GROUP 1 (N=798)	GROUP 2 (N=197)	P VALUE
Age — yr			
Mean	53.0	47.2	<0.001
Range	19–91	24–78	
Female sex — no. of patients (%)	598 (74.9)	163 (82.7)	
White race — no. of patients (%)	735 (92.1)	175 (88.8)	
Total no. of aneurysms	1039	262	
Diameter of largest aneurysm — mm			
Mean	11.6	8.3	
Range	2–50	2–60	
Size of largest aneurysm — no. of patients (%)			
2–5 mm	128 (16.0)	65 (33.0)	<0.001
6–9 mm	262 (32.8)	79 (40.1)	
10–14 mm	203 (25.4)	39 (19.8)	
15–24 mm	148 (18.5)	11 (5.6)	
≥25 mm	57 (7.1)	3 (1.5)	
Location of aneurysm — no. of aneurysms (%)			
Cavernous carotid artery	24 (2.3)	3 (1.1)	0.24
Internal carotid artery	393 (37.8)	82 (31.3)	0.05
Anterior communicating or anterior cerebral artery	167 (16.1)	23 (8.8)	0.003
Middle cerebral artery	305 (29.4)	116 (44.3)	<0.001
Posterior communicating artery	43 (4.1)	15 (5.7)	0.27
Vertebrobasilar or posterior cerebral artery	50 (4.8)	15 (5.7)	0.54
Tip of basilar artery	57 (5.5)	8 (3.1)	0.11

Aneurysmal Characteristics

The distribution of unruptured intracranial aneurysms according to size and location (parent artery) is shown for groups 1 and 2 in Table 3. The distributions of aneurysms were very similar to those in the retrospective cohort.

Overall, 21 percent of the patients had specific symptoms, including 23 percent of the patients in group 1 and 10 percent of those in group 2.

Risk Factors

Various potential risk factors for the development of an intracranial aneurysm as well as treatment-related morbidity and mortality were documented at the time of diagnosis (Table 2). Overall, 47 percent of the patients were current smokers, and 32 percent were former smokers.

With regard to base-line neurologic status, 94 percent of the patients had a Rankin score of 1 (96 percent in group 1 and 89 percent in group 2). The Barthel score was 100 (indicating normal ability to perform the activities of daily living) for 98 percent of patients, and the score on the Mini–Mental State Examination was higher than 23 (indicating no serious cognitive abnormality) for 98 percent of the patients.

Surgical Outcome

The morbidity and mortality rates at 30 days and 1 year are shown in Table 4. Thirty days after surgery, 18 of 996 patients (all in group 1) had died. Ten deaths were due to cerebral infarction, five to intracranial hemorrhage, and two to pulmonary embolism; one death was related to respiratory complications. One year after surgery, 34 deaths had occurred in group 1 (30 related to surgery) and 2 in group 2 (both related to surgery).

Seventy-eight patients in group 1 and eight in group 2 had a Rankin score of 3, 4, or 5 at 30 days. Ninety-three patients in group 1 and 21 in group 2 had impaired cognitive status.

Age was the only independent predictor of a poor surgical outcome. In group 1, surgery-related morbidity and mortality at one year among patients younger than 45 years was 6.5 percent, as compared with 14.4 percent for those between 45 and 64 years old and 32 percent for those over 64 ($P<0.001$).

DISCUSSION

Among patients without a history of subarachnoid hemorrhage (group 1), those with unruptured intracranial aneurysms that were less than 10 mm in diameter had an exceedingly low risk of rupture (approximately 0.05 percent per year). Unruptured aneurysms of the same size in patients with a history of subarachnoid hemorrhage (group 2) were approximately 11 times as likely to rupture (a risk of approximately 0.5 percent per year). The size and location of the aneurysm were significant independent predictors of rupture in patients in group 1 (larger

TABLE 4. SURGICAL OUTCOME IN GROUP 1 AND GROUP 2.*

OUTCOME	GROUP 1 (N=798)		GROUP 2 (N=197)	
	NO. OF PATIENTS	% (95% CI)	NO. OF PATIENTS	% (95% CI)
At 1 mo				
Surgery-related death	18	2.3 (1.3–3.3)	0	0 (0–1.4)
Disability	122	15.3	27	13.7
Rankin score of 3–5 only	29	3.6	6	3.0
Impaired cognitive status only	44	5.5	19	9.6
Both	49	6.1	2	1.0
Overall morbidity and mortality				
All patients	140	17.5 (15.5–20.5)	27	13.6 (8.0–17.2)
Patients with normal neurologic status at base line†	130	17.0	24	12.8
At 1 yr				
Surgery-related death	30	3.8 (2.4–5.4)	2	1.0 (0–2.6)
Disability	95	12.0	24	12.1
Rankin score of 3–5 only	26	3.3	3	1.5
Impaired cognitive status only	43	5.4	18	9.1
Both	26	3.3	3	1.5
Overall morbidity and mortality				
All patients	125	15.7 (13.2–18.2)	26	13.1 (8.0–17.2)
Patients with normal neurologic status at base line†	119	15.6	21	11.2

*CI denotes confidence interval.

†Normal neurologic status was defined as a Rankin score of 1 and no cognitive impairment as measured by the Mini–Mental State Examination. There were 764 patients in group 1 and 188 in group 2 who had normal neurologic status at base line.

aneurysms and those in the tip of the basilar artery, vertebrobasilar or posterior cerebral artery, or posterior communicating artery were more likely to rupture). In group 2, only the basilar-tip location was predictive of rupture. In view of these findings, it is pertinent to begin considering patients with previous subarachnoid hemorrhage and those without previous hemorrhage differently when making decisions about the management of unruptured intracranial aneurysms.

The overall rupture rate for the 1449 patients in the retrospective component of our study (0.5 percent per year) was lower than the rates reported in previous natural-history studies,[8,17] and the rate in group 1 was significantly lower than that in group 2. The aneurysms were considerably larger in group 1 (mean diameter, 10.9 mm) than in group 2 (mean diameter, 5.7 mm), and the number of giant aneurysms was markedly lower in group 2. These differences are most likely the result of the rupture or repair (or both) of larger aneurysms in the patients in group 2 before enrollment in the study. The exceedingly low rupture rate in the patients in group 1 with aneurysms that were less than 10 mm in diameter is consistent with the findings of previous studies.[8,9]

Although the retrospective component of our study provides indispensable long-term follow-up data as a basis for determining future rupture rates, it is possible that a systematic bias we cannot identify has been introduced because of the nature of this cohort.

The overall morbidity and mortality rates associated with surgical repair of unruptured intracranial aneurysms were higher than those reported previously. The 30-day rates of mortality and morbidity (a score of 3, 4, or 5 on the Rankin scale) were only slightly higher than those predicted on the basis of a systematic review of previous reports on repair of unruptured aneurysms.[18-23] In our study, however, impaired mental status added substantially to morbidity at 30 days and 1 year, and this variable was not assessed in the previous studies.

The lower rates of treatment-related mortality and neurologic morbidity (as measured by the Rankin score) in group 2 are probably the result of the selection of survivors of a first subarachnoid hemorrhage and a craniotomy performed to repair a ruptured aneurysm. However, patients in group 2 were more likely to have a deterioration in mental status, which may have resulted from three consecutive cerebral events (one subarachnoid hemorrhage and two craniotomies) as compared with only one event (craniotomy) in most patients in group 1.

In the surgically treated cohort, age was the only significant independent predictor of surgical outcome. The rates of surgery-related morbidity and

mortality were substantially lower for younger patients than for older patients. Other potential predictors of surgery-related morbidity and mortality (including the location and size of the aneurysm) and endovascular results could not be assessed adequately with the number of patients in the prospective cohort.

With aneurysmal size and location included in the multivariate model, the presence of aneurysmal symptoms other than those related to rupture was not a predictor of rupture. Similarly, the presence of symptoms did not independently predict the outcome of surgery.

The management of unruptured intracranial aneurysms depends on the natural history of these lesions and on morbidity and mortality rates associated with repair. On the basis of the rupture rates and treatment risks in our study, it appears unlikely that surgery will reduce the rates of disability and death in patients with unruptured intracranial aneurysms smaller than 10 mm in diameter and no history of subarachnoid hemorrhage. Data on treatment-related morbidity and mortality rates according to aneurysmal size and location and specific symptoms are required to determine whether surgical or endovascular intervention may be warranted in various subgroups of patients with unruptured intracranial aneurysms, including those with acutely symptomatic unruptured aneurysms.

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APPENDIX

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