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Authors

Villablanca, J Pablo
Duckwiler, Gary R
Jahan, Reza
[et al.](#)

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Natural History of Asymptomatic Unruptured Cerebral Aneurysms Evaluated at CT Angiography: Growth and Rupture Incidence and Correlation with Epidemiologic Risk Factors¹

J. Pablo Villablanca, MD
 Gary R. Duckwiler, MD
 Reza Jahan, MD
 Satoshi Tateshima, MD, PhD
 Neil A. Martin, MD
 John Frazee, MD
 Nestor R. Gonzalez, MD
 James Sayre, PhD
 Fernando V. Vinuela, MD

Purpose:

To characterize the relationship between aneurysm size and epidemiologic risk factors with growth and rupture by using computed tomographic (CT) angiography.

Materials and Methods:

In this HIPAA-compliant, institutional review board approved study, patients with known asymptomatic unruptured intracerebral aneurysms were followed up longitudinally with CT angiographic examinations. Growth was defined as an increase in one or more dimensions above the measurement error, and at least 5% volume by using the ABC/2 method. Associations of epidemiologic factors with aneurysm growth and rupture were analyzed by using logistic regression analysis. Intra- and interobserver agreement coefficients for dimension, volume, and growth were evaluated by using the Pearson correlation coefficient and difference of means with 95% confidence intervals, the agreement statistic, and the McNemar χ^2 .

Results:

Patients ($n = 165$) with aneurysms ($n = 258$) had a mean follow-up time of 2.24 years from time of diagnosis. Forty-six of 258 (18%) aneurysms in 38 patients grew larger. Spontaneous rupture occurred in four of 228 (1.8%) intradural aneurysms of average size (6.2 mm). Risk of aneurysm rupture per patient-year was 2.4% (95% CI: 0.5%, 7.12%) with growth and 0.2% (95% CI: 0.006%, 1.22%) without growth ($P = .034$). There was a 12-fold higher risk of rupture for growing aneurysms ($P < .002$), with high intra- and interobserver correlation coefficients for size, volume, and growth. Tobacco smoking (3.806, one degree of freedom; $P < .015$.) and initial size (5.895, two degrees of freedom; $P < .051$) were independent covariates, predicting 78.4% of growing aneurysms.

Conclusion:

These results support imaging follow-up of all patients with aneurysms, including those whose aneurysms are smaller than the current 7-mm treatment threshold. Aneurysm growth, size, and smoking were associated with increased rupture risk.

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¹From the Departments of Radiological Sciences (J.P.V., G.R.D., R.J., S.T., N.G., J.S., F.V.) and Neurosurgery (N.M., J.F., N.G., F.V.), University of California, Ronald Reagan UCLA Medical Center, 757 Westwood Plaza, Suite 1621A, Los Angeles, CA, 90095-1721. Received June 11, 2012; revision requested August 7; revision received February 22, 2013; accepted March 1; final version accepted March 7. Address correspondence to J.P.V. (e-mail: pvillablanca@mednet.ucla.edu).

The prevalence of intracranial cerebral aneurysms is approximately 2% of the population in the United States (1). Each year approximately 30 000 North Americans experience a rupture (2), and 15 000 die of complications of ruptured aneurysms. The estimated 30-day mortality rate after hemorrhage is approximately 45%, with substantial residual neurologic deficits in nearly half of survivors (3). Limited information is available about the natural history of unruptured intracranial aneurysms, in part because of the invasive nature of angiography (4). Identification of risk factors for rupture is critical to therapeutic decision making regarding unruptured aneurysms. The processes leading to aneurysm development and rupture are not well understood, but larger aneurysm size is believed to be an independent risk factor for rupture (5). In addition, an increase in lesion size may warrant treatment of an unruptured aneurysm (5,6). The likelihood of rupture of an intracranial aneurysm less than 10 mm in maximal diameter without a history of aneurysm rupture has been estimated to be as low as 0.05% per year (6). More recently, investigators of the International Study of Unruptured Intracranial Aneurysms reported a threshold of 7 mm as a value above which intervention may be indicated (6,7). However, there are reports that up to 37% of patients with subarachnoid hemorrhages have aneurysms smaller than 5 mm in maximal diameter (8). The relationship between aneurysm growth and rupture in patients without a

history of subarachnoid hemorrhage has not been clearly established.

Many investigators believe that all patients with aneurysms should receive follow-up to monitor for the possibility of growth or other signs of impending rupture, such as a bleb (9). The traditional method for follow-up of patients with cerebral aneurysms has been conventional angiography (digital subtraction angiography). However, digitally based noninvasive imaging tools facilitate quantitation and longitudinal study, and thus may be preferable. Although several studies have shown that computed tomographic (CT) angiography provides accurate lesion quantitation when compared with catheter angiography (10), the role of CT angiography in a longitudinal study design has not been formally explored.

Our purpose was to evaluate the use of CT angiography to characterize the relationship between aneurysm size and possible epidemiologic risk factors associated with growth and rupture.

Materials and Methods

Patients and Data Analysis

This retrospective study was Health Insurance Portability and Affordability Act-compliant and had institutional review approval. From May 1999 to December 2009, 178 patients with known asymptomatic intracranial aneurysms were considered for inclusion. Of these, 165 patients with 258 intracerebral aneurysms were included. Inclusion criteria included

at least one previously identified unruptured aneurysm, with no referable clinical symptoms or signs. Discovery was through prior angiography, magnetic resonance (MR) imaging, MR angiography, or CT angiography performed for reasons other than suspicion of an index aneurysm. Common patient concerns leading to discovery of the index lesion included nonspecific headaches or visual disturbance, dizziness, and suspicion of brain metastases. Patients with history of mycotic, traumatic, vasculitic, or previously treated aneurysms were excluded. Quantitative aneurysm analysis was performed prospectively; longitudinal comparisons, intra- and interoperator reliability analyses, and epidemiologic correlations were performed retrospectively.

Patients underwent follow-up CT angiographic examinations (16–64 detectors) at intervals of approximately 6 or 12 months. The scan protocol was standardized with the following parameters: kVp, 120; mA, 250–300; section thickness, 0.6–1.0 mm; reconstruction interval, 0.5 mm; matrix size, 512 × 512; field of view, 180 mm; soft-tissue kernel; injection rate, 3 mL per second of iohexol (Omnipaque 350; GE Healthcare, Milwaukee, Wis) and bolus triggering software with a carotid artery threshold of 150 HU. Axial oblique two-dimensional multiplanar reformatted grayscale images (window width = 450 HU, window level = 150 HU) were analyzed to obtain the length × width × height of the aneurysm sac relative

Advances in Knowledge

- Multidetector CT angiography is capable of showing changes in aneurysm shape and size over time, including the development of aneurysm blebs.
- Asymptomatic aneurysm growth is fairly common, and there is a 12-fold higher risk of rupture for growing aneurysms of 2.4% (95% confidence interval [CI]: 0.5, 7.12) per patient-year, versus 0.2% (95% CI: 0.006, 1.22), for aneurysms without growth ($P = .034$).

Implications for Patient Care

- Our data support the need to perform longitudinal follow-up imaging to monitor for possible growth of all incidental unruptured aneurysms, including small lesions.
- The positive association of cigarette smoking and the size and growth of aneurysms suggests that the combination of these factors is associated with an increased risk of rupture, which may influence consideration for therapeutic intervention.

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Abbreviation:

CI = confidence interval

Author contributions:

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Conflicts of interest are listed at the end of this article.

to the long and short axes of the lesion, with bidimensional neck measurements. This double axial oblique technique allowed the precise long and perpendicular short axis of each aneurysm to be measured and recorded. All measurements were made prospectively by a single trained technologist with Vitrea software (Vital Images, Minneapolis, Minn) and a previously described protocol (9). Aneurysm measurements were made by four board-certified neuroradiologists with an average of 14 years of academic practice experience, one of whom was a study author (J.P.V.) and by a clinical technologist. Remeasurements were made by J.P.V. and the technologist.

Digital caliper measurements were made by using a visual estimation of the full width at half maximum of the section sensitivity profile of aneurysm borders on the grayscale multiplanar reformatted images (10). For follow-up scans and measurements and for variability analyses, the technologist and neuroradiologist were allowed to review the orientation of the axial oblique planes of the prior study, but were blinded to prior lesion dimensions.

During the study period, approximately 70 patients per year were treated by means of coiling, clipping, or combined approaches based wholly or partially on CT angiographic data. The proportion of patients with asymptomatic unruptured versus symptomatic or ruptured aneurysms undergoing CT angiography at our institution during the study period was approximately 6:1.

Aneurysm growth was defined as change in size to the nearest tenth of a millimeter greater than the measurement error per manufacturer software specifications ($<2 \text{ mm} \pm 10\%$; $2\text{--}10 \text{ mm} \pm 5\%$; $>10 \text{ mm} \pm 2\%$) for one or more aneurysm dimension and change in aneurysm volume of greater than or equal to 5%. For instance, for a 1.9-mm aneurysm dimension at baseline, measurements between 1.7 mm and 2.1 mm at follow-up imaging were considered within measurement error for that dimension and not a change in size. Aneurysm volume was determined by using the ABC/2 method, where A is the longest lesion

diameter on the section, with the largest visually estimated lesion cross-sectional area; B is the lesion diameter perpendicular to A at the same level; and C is the craniocaudal dimension (11). Percentage of change in volume from baseline was calculated by using the following formula: $[(a_2 \cdot b_2 \cdot c_2)/2 - (a_1 \cdot b_1 \cdot c_1)/2]/(a_1 \cdot b_1 \cdot c_1)/2$, where *a*, *b*, and *c* are the sac dimensions, and subscripts 1 and 2 are aneurysm dimensions at baseline and at subsequent scan times (12).

Epidemiologic data were gathered retrospectively from medical records. Examined risk factors for growth and rupture included age, sex, cigarette smoking status, aneurysm size, diabetes, family history of aneurysms, hypercholesterolemia, history of prior rupture, hypertension, mural aneurysm calcification, aneurysm location and multiplicity, and presence of vascular malformation.

Statistical Analysis

Contingency tables were generated for categorical variables, and associations were analyzed by using χ^2 statistics. Distributions of continuous variables and descriptive statistics (ie, means, standard deviations, and 95% confidence intervals [CIs]) were generated. Student *t* tests were used to compare differences. Multiple logistic regression analysis was used to assess independent predictors for growth. The population-based prevalence for growth before data analysis was assumed to be between 25% and 30% of all aneurysms, giving rise to a cut-off value of 0.29. All analyses were performed by using statistics software (SPSS 14.0, SPSS, Chicago, Ill), and a *P* value of less than .05 was considered to indicate a significant difference. Intra- and interoperator variability analysis was performed by remeasuring 100 randomly selected study aneurysms, including growing and nongrowing lesions. Pearson correlation coefficients were used for analysis of lesion measurements and differences of volumes, and the difference of the means including 95% CIs was determined by using a 2-tailed *t* test, with a *P* value less than .01 as a threshold indicating a significant difference. Intra- and interoperator

agreement coefficients for growth were determined by using the agreement statistic (13) and the McNemar χ^2 test with a no/yes dichotomization.

Results

In 165 patients (132 women, 33 men; age range, 25–90), 258 aneurysms were followed longitudinally. In 115 of 165 (70%) patients, 191 of 258 (75%) aneurysms were previously known. In 50 of 165 (30%) patients, an additional 67 aneurysms were found incidentally at baseline CT angiography. In two of 165 (1.2%) patients, an aneurysm with a measurable neck and sac arose from an aneurysmal contour deformity of the parent artery at a location where the baseline CT angiography showed no measurable lesion in two of 258 (0.8%) patients (Fig 1).

Aneurysm location frequencies generally matched naturally occurring aneurysm location frequencies. Per the convention used by investigators of the International Study of Unruptured Intracranial Aneurysms, data from posterior communicating arterial aneurysms were pooled with those of posterior circulation aneurysms (6). A total of 217 of 258 (84%) aneurysms occurred in women (ratio of 5.3:1), ($P < .001$). The mean and median follow-up intervals were 2.24 and 1.99 years, respectively (range, 0.1–8.5 years). The average age \pm standard deviation at study entry of patients with rupture was 77.2 years \pm 7.91, versus 60.7 years \pm 12.7 for the patients without rupture ($P = .01$), and 60.9 years for all study patients.

More than two-thirds of growing aneurysms ($n = 46$) demonstrated growth by year 3 of follow-up. Six of 39 (15%) growing saccular aneurysms showed only unidimensional (bleb) growth (Fig 2), whereas 33 of 39 (85%) saccular aneurysms grew in two or three dimensions. The average percentage of growth was 61.7% (95% CI: 44.9%, 78.4%). Maximum increase in lesion volume was 201%, and minimum growth was 6%. No lesions decreased in size. Aneurysm multiplicity ($P = .258$), intraluminal thrombus ($P = .035$), and mural calcification ($P = .182$) were not

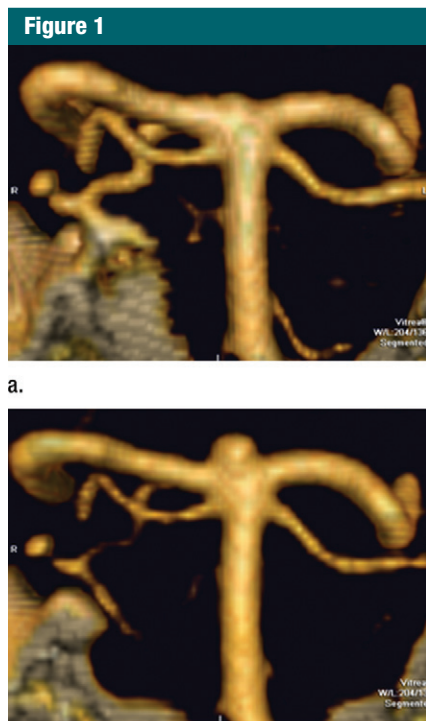
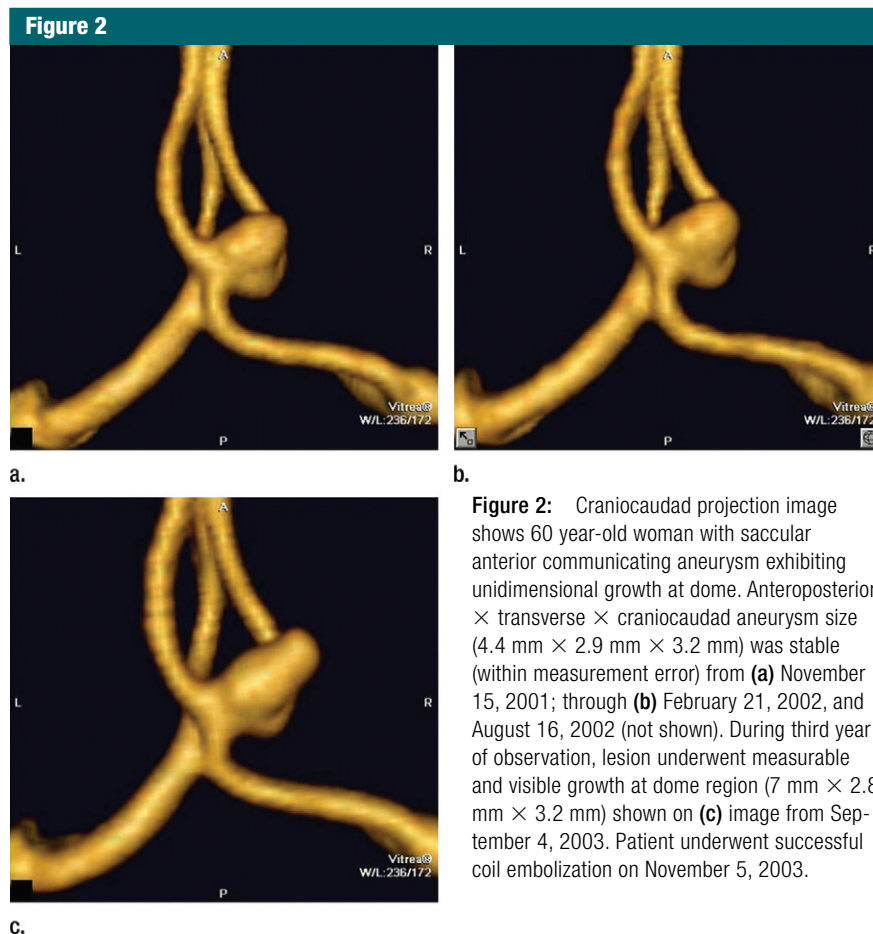


Figure 1: Frontal projection three-dimensional volume-rendered images with anteroposterior projection in a 48-year-old woman with small saccular basilar tip aneurysm that arose from small contour deformity located at basilar tip. **(a)** Image shows minor contour deformity at basilar tip. **(b)** Image shows interval development of wide-necked 3.2-mm maximal-diameter aneurysm projecting superiorly from basilar tip. Scan interval was 9 months and 3 weeks.

associated with growth. Bleb formation was the only growth pattern in several lesions (Fig 3).

There was no relationship between aneurysm location and aneurysm growth ($P = .98$). Thirteen of 23 (57%) anterior and nine of 13 (69%) posterior circulation saccular noncavernous aneurysms with growth were less than or equal to 7 mm in maximal diameter. Four of 36 (11%) growing saccular intradural aneurysms were 2 mm or less in size. Table 1 shows the relationship between aneurysm growth, size, and shape. On average, growing saccular aneurysms were nearly 24% larger than nongrowing ones. Table 2 is an analysis of the relationship between aneurysm growth, shape, size, and location. Thirty nine of



46 (85%) growing aneurysms were saccular, while seven of 46 (15%) were fusiform ($P < .001$).

Observation was the treatment of choice for 215 of 258 (83%) of all study aneurysms. On discovery of growth at CT angiographic imaging, the plan was changed from observation to active treatment in 23 of 46 (50%) patients, while the remaining 23 patients continued to be observed. Of the 23 growing aneurysms, nine (39%) were treated by means of endovascular coiling; 12 (52%), with neurosurgical clipping; and two (9%), with neurosurgical reinforcement. Two growing lesions continued to be observed, although treatment was recommended. In comparison, 194 of 212 (92%) aneurysms without growth were observed.

Growth incidence and rupture rates and the characteristics of patients experiencing rupture are provided in Tables

Figure 2: Craniocaudad projection image shows 60 year-old woman with saccular anterior communicating aneurysm exhibiting unidimensional growth at dome. Anteroposterior \times transverse \times craniocaudad aneurysm size (4.4 mm \times 2.9 mm \times 3.2 mm) was stable (within measurement error) from **(a)** November 15, 2001; through **(b)** February 21, 2002, and August 16, 2002 (not shown). During third year of observation, lesion underwent measurable and visible growth at dome region (7 mm \times 2.8 mm \times 3.2 mm) shown on **(c)** image from September 4, 2003. Patient underwent successful coil embolization on November 5, 2003.

3 and 4. Table 5 reflects a 12-fold higher risk of rupture when aneurysm growth occurred ($P = .002$). Five of 23 (22%) fusiform aneurysms grew, with volume increases ranging from 10% to 112%. None of these lesions ruptured during the study period. Although all saccular aneurysms that ruptured grew, a single giant fusiform aneurysm without growth ruptured after more than five years of follow-up. Small sample size did not permit statistically valid subanalysis for relationship between growth and rupture for fusiform aneurysms.

Three of 39 (8%) saccular intradural aneurysms with growth ruptured, and none of the 209 (0%) aneurysms without growth ruptured ($P < .001$). The average time to rupture was 1.2 years. During the study period, these ruptured lesions had a median growth rate of 50% (range, 30%–66%).

Table 1

Aneurysm Growth versus Shape and Size

Aneurysms	No. of Aneurysms	Average Aneurysm Size at Study Entry and End by Shape							
		All		Saccular		Fusiform			
		Entry	End	Entry	End	Entry	End	No. of Aneurysms	No. of Aneurysms
Aneurysms with growth	46	7.3 (5.6, 8.9)	8.5 (5.6, 9.4)	39	5.4	6.3	7	17.9	20.8
Aneurysms without growth	212	5.4 (4.8, 6.1)	5.5 (4.8, 6.0)	196	4.8	4.8	16	14.0	14.0
Total aneurysms	258			235			23		

Note.—Unless otherwise indicated, data are millimeters, with 95% CIs in parentheses.

Table 2

Average Size of Growing Aneurysms: Anterior versus Posterior Circulation

Aneurysm Circulation	Aneurysm Shape			
	Saccular		Fusiform	
	Size (mm)	No.	Size (mm)	No.
Anterior	6.8	23	19.5	1
Posterior	6.1	13	18.9	4
Total	6.5	36	19.0	5

Note.—These data are for aneurysms after the exclusion of cavernous aneurysms with growth.

All patients with saccular ruptures underwent subsequent endovascular coiling. All patients with growing aneurysms remained asymptomatic during the study period, except for those who presented with rupture and subarachnoid hemorrhage (Table 4 and Figure 4).

CT angiography showed growth in nearly 18% of intracranial aneurysms of all sizes that was associated with a 12-fold higher rupture risk ($P < .002$), thus supporting imaging follow-up of all aneurysms, including those currently smaller than the recommended 7-mm treatment threshold.

For the study population as a whole, the risk of aneurysm rupture in the no-growth group was one in 451 (0.2%) per patient-year of follow-up versus three of 123 (2.4%) per patient-year in the group with aneurysm growth ($P = .034$). Table 5 shows the relationship between aneurysm size, growth, and rupture based on the criteria of the International Study of Unruptured Intracranial Aneurysms.

Figure 3

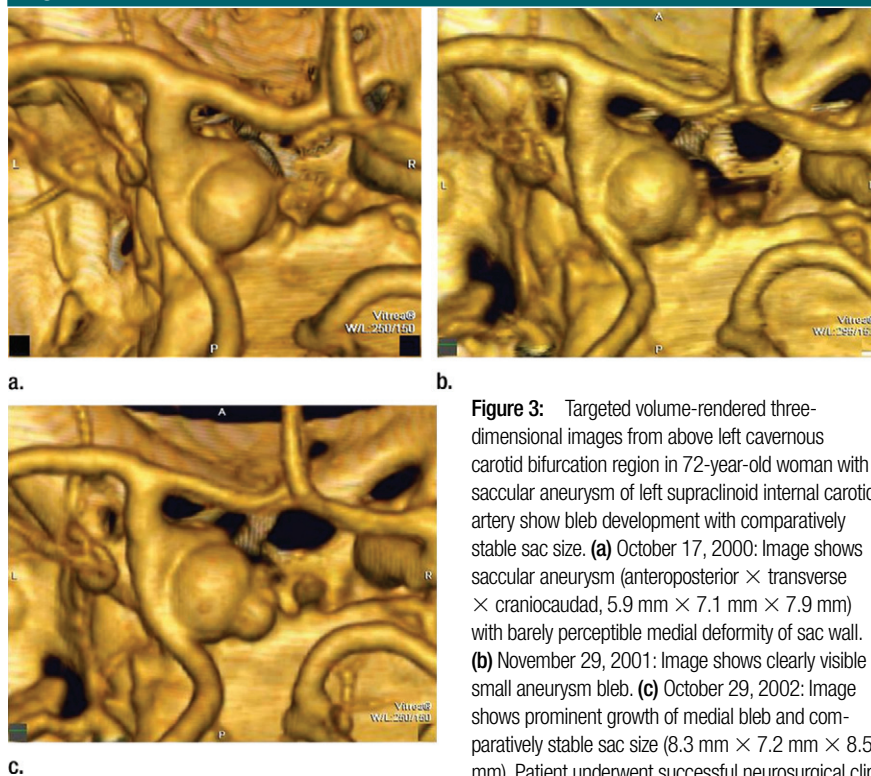


Figure 3: Targeted volume-rendered three-dimensional images from above left cavernous carotid bifurcation region in 72-year-old woman with saccular aneurysm of left supraclinoid internal carotid artery show bleb development with comparatively stable sac size. (a) October 17, 2000: Image shows saccular aneurysm (anteroposterior \times transverse \times craniocaudad, 5.9 mm \times 7.1 mm \times 7.9 mm) with barely perceptible medial deformity of sac wall. (b) November 29, 2001: Image shows clearly visible small aneurysm bleb. (c) October 29, 2002: Image shows prominent growth of medial bleb and comparatively stable sac size (8.3 mm \times 7.2 mm \times 8.5 mm). Patient underwent successful neurosurgical clip placement before rupture on December 30, 2002.

An analysis of epidemiologic risk factors and their relationship to aneurysm growth revealed that both tobacco smoking (3.806, one degree of freedom; $P < .015$) and initial aneurysm size (5.895, two degrees of freedom; $P < .051$) were independent covariates associated with aneurysm growth. Other epidemiologic risk factors were not significant ($P = .186-.655$). The odds ratio estimate for aneurysm size was 1.065 (95% CI: 1.006, 1.127) and for tobacco smoking was 1.805 (95% CI: 1.193,

2.725). When both were used together, these risk factors were associated with 78.4% of all aneurysm growth events.

Interoperator reliability analysis for aneurysm dimensions yielded Pearson correlation coefficients for the x, y, and z axes of 0.994, 0.997, and 0.996, respectively, with a difference of means and 95% CIs of -0.41 (95% CI: $-0.086, -0.004$), 0.003 (95% CI: $-0.003, -0.038$), and -0.027

Table 3
Characteristics of Patients and Ruptured Aneurysms

Patient	Patient Characteristic				Aneurysm Characteristic					
	Age (y)*	Sex	No. of Scans	Result	Location	Shape	Size at Entry (mm)	Size at Rupture (mm)	Time to Rupture (y)	Growth
1	90	F	4	Died	ACOM	Saccular	6.0	6.2	1.06	Yes
2	79	F	4	Survived	PCOM	Saccular	6.7	11.0	2.22	Yes
3	78	F	3	Survived	BT	Saccular	5.8	6.6	0.36	Yes
4	73	M	3	Survived	VA	Giant fusiform	22.0	21.0	5.22	No

Note.—ACOM = anterior communicating artery, PCOM = posterior communicating artery, BT = basilar tip, VA = vertebral artery.
* Patient age at time of rupture.

(95% CI: -0.066, -0.012), respectively. Intraoperator reliability analysis for aneurysm dimensions yielded Pearson correlation coefficients for the x, y, and z axes of 0.984, 0.987, and 0.985, with a difference of means and 95% CIs of -0.009 (95% CI: -0.087, -0.069), -0.039 (95% CI: -0.108, -0.030), and 0.043 (95% CI: 0.029, -0.115), respectively. Intra- and interoperator Pearson correlation values for aneurysm volumes were 0.996 and 0.99, respectively ($P < .001$). The agreement statistic for aneurysm growth yielded intra- and interater statistics \pm standard error of 0.5174 ± 0.2093 , and 0.8144 ± 0.1315 , respectively. The McNemar χ^2 test for growth versus no growth between readers and in multiple readings by the same reader was not statistically significant ($P = .99$).

Discussion

We found that growth of asymptomatic unruptured intracranial aneurysms of all sizes was not uncommon and was associated with a higher rupture risk, thus supporting follow-up imaging of all aneurysms, including those smaller than the current 7-mm treatment threshold (7).

Burns et al (14) also reported that unruptured intracranial aneurysm growth is not uncommon, noting a 6.9% frequency of enlargement for aneurysms smaller than 8 mm in diameter, a frequency lower than our value of 14% for lesions smaller than 7 mm. This difference may have been due to the exclusion of aneurysms smaller than

Table 4
Growth and Rupture Rates versus Shape Including and Excluding Cavernous Aneurysms

Variable	All Aneurysms			Cavernous Aneurysms Excluded		
	Saccular (n = 235)	Fusiform (n = 23)	Saccular and Fusiform (n = 258)	Saccular (n = 209)	Fusiform (n = 19)	Saccular and Fusiform (n = 228)
Growth incidence	39 (16)	7 (30)	46 (18)	36 (17)	5 (26)	41 (18)
Rupture rate	3 (1)	1 (4)	4 (2)	3 (1)	1 (5)	4 (2)

Note.—Data are numbers, with percentage in parentheses.

Table 5
Relationship among Aneurysm Size, Growth, and Rupture

Aneurysm Size Category (mm)	No. of Aneurysms	Growth	Rupture with Growth	No. of Ruptures	Rupture without Growth
< 7	193 (75)	27/193 (14)	3/27 (11)	3	0/166 (0)
8–12	46 (18)	12/46 (26)	0/12 (0)	0	0/34 (0)
13–24	16 (6)	6/16 (38)	1/6 (17)	1	1/10 (10)
≥ 25	3 (1)	1/3 (33)	0/1 (0)	0	0/2 (0)
Total	258 (100)	46/258 (18)	3/46 (7)	4	1/212 (0.05)

Note.—Data are numbers or proportion of aneurysms, with percentage in parentheses.

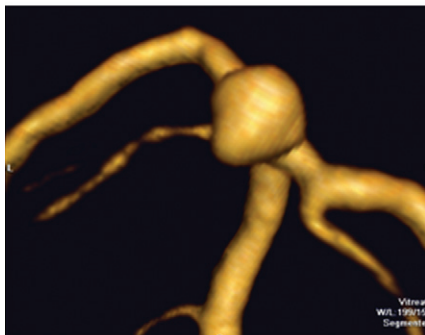
2 mm in the Burns et al study, a size category in which we identified growing aneurysms and performed statistical analysis on the averaged sac measurements obtained by two readers. The average size of saccular aneurysms with growth and with growth ending in rupture both at study entry and at study terminus was below the threshold value for lesions with a higher risk of rupture based only on size identified by the investigators of the International Study of Unruptured Intracranial Aneurysms.

To our knowledge, there are no previously published outcome studies comparing observation of asymptomatic growing aneurysms until rupture with treatment of asymptomatic aneurysms before rupture. Without this comparison, it is not possible to define the true risk-to-benefit ratio of treating asymptomatic aneurysms. A long-term outcome study of 156 patients showed that the annual rupture rate of cerebral aneurysms was 1.3 per 100 person-years, with a higher survival rate

Figure 4



a.



b.

Figure 4: Volume-rendered three-dimensional CT angiographic image with superior to inferior projection and posterolateral perspective in a 77-year-old woman with asymptomatic 5.8-mm saccular basilar tip aneurysm shows rapid and eccentric growth at dome before rupture. **(a)** Patient was scheduled for 6-month follow-up scan, but presented at 4 months with subarachnoid hemorrhage due to rupture of lesion. **(b)** At time of rupture, lesion had grown to maximal diameter of 6.6 mm with substantial posteriorly directed eccentric growth at dome region and 50% increase in sac volume.

natural growth and rupture rates because some patients with both stable and growing aneurysms underwent intervention. Our patient population was likely older than the general population of patients treated at symptomatic diagnosis, adding a possible age selection bias. Some patients declined study participation, possibly introducing a selection bias. A strength of our study was inclusion of aneurysms smaller than 2 mm in diameter, which were excluded in the International Study of Unruptured Intracranial Aneurysms. Our analysis represents experience at a single institution, possibly introducing a demographic bias. In addition, it is possible that a lack of significance for other variables may have been a reflection of a lack of statistical power. Finally, although we defined growth as 5% or more increase in volume, all three saccular aneurysms that ruptured showed at least a 30% increase in volume. Because of the small numbers of ruptured aneurysms in our series, it was not possible to determine statistically valid values for minimal growth, growth rate, or time to growth that increase risk for rupture. This will require further studies with larger numbers of aneurysms.

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for treated patients (15). Emphasizing the importance of imaging follow-up for small aneurysms, other authors have also documented rupture of small (4.5–8 mm) asymptomatic aneurysms (16,17). Our findings support these findings, as well as the observation of other researchers of a higher rupture risk for posterior circulation aneurysms (18).

Our data showed that aneurysm size and patient smoking status were both significant independent growth predictors. Juvela (8) also identified cigarette smoking as an independent risk factor for aneurysm growth and rupture. In our CT angiographic series, all ruptured saccular aneurysms demonstrated growth before rupture, including bleb formation (Fig 2). Bleb formation has also been associated with a higher risk of rupture in other studies (19,20). Recently, bleb formation was also included in the definition of growth in a study evaluating annual rupture risk (21).

One of the limitations of our study was that we could not determine true

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