Aneurysm growth and de novo aneurysms during aneurysm surveillance

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OBJECTIVE Many low-risk unruptured intracranial aneurysms (UIAs) are followed for growth with surveillance imaging. Growth of UIAs likely increases the risk of rupture. The incidence and risk factors of UIA growth or de novo aneurysm formation require further research. The authors retrospectively identify risk factors and annual risk for UIA growth or de novo aneurysm formation in an aneurysm surveillance protocol.

METHODS Over an 11.5-year period, the authors recommended surveillance imaging to 192 patients with 234 UIAs. The incidence of UIA growth and de novo aneurysm formation was assessed. With logistic regression, risk factors for UIA growth or de novo aneurysm formation and patient compliance with the surveillance protocol was assessed.

RESULTS During 621 patient-years of follow-up, the incidence of aneurysm growth or de novo aneurysm formation was 5.0%/patient-year. At the 6-month examination, 5.2% of patients had aneurysm growth and 4.3% of aneurysms had grown. Four de novo aneurysms formed (0.64%/patient-year). Over 793 aneurysm-years of follow-up, the annual risk of aneurysm growth was 3.7%. Only initial aneurysm size predicted aneurysm growth (UIA < 5 mm = 1.6% vs UIA ≥ 5 mm = 8.7%, $p = 0.002$). Patients with growing UIAs were more likely to also have de novo aneurysms ($p = 0.01$). Patient compliance with this protocol was 65%, with younger age predictive of better compliance ($p = 0.01$).

CONCLUSIONS Observation of low-risk UIAs with surveillance imaging can be implemented safely with good adherence. Aneurysm size is the only predictor of future growth. More frequent (semiannual) surveillance imaging for newly diagnosed UIAs and UIAs ≥ 5 mm is warranted.

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KEY WORDS aneurysm; de novo; growth; subarachnoid hemorrhage; surveillance; vascular disorders

UNRUPTURED intracranial aneurysms (UIAs) exist in 2% of the North American population.² The natural history of UIAs has been better defined recently after publication of multiple prospective series.^{14,16,21,25,28,33,34} Results from these observational studies have allowed risk stratification of UIAs to distinguish high-risk UIAs from UIAs with a relatively benign natural history.¹² With the addition of knowledge from treatment outcomes, we can better weigh the decision to observe or intervene in UIAs.

Most physicians have adopted a conservative approach toward managing small anterior circulation UIAs, which includes observation with surveillance imaging.^{2,20,36} Re-

cent series have shown that aneurysm growth increases the risk of subsequent rupture.^{13,31} This finding has led many physicians to recommend treatment for UIAs with observed growth. The rate of growth, pattern of growth (linear vs episodic), rate of de novo aneurysm formation, and risk factors for growth are inconsistent in the current literature, thus warranting further study in this area.^{4,5,7,8,13,17,19,22–24,27–30,32,33} We report our experience with an aneurysm surveillance protocol in appropriately selected patients and report the incidence and risk factors for growth of UIAs, the incidence of de novo UIA formation, and predictors of compliance to surveillance imaging.

ABBREVIATIONS CTA = CT angiography; DSA = digital subtraction angiography; MRA = MR angiography; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.

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Methods

Since July 2001, the senior author has followed with surveillance imaging UIAs felt to be at low risk for spontaneous subarachnoid hemorrhage (SAH) or UIAs whose risks of treatment outweigh the natural history. MR angiography (MRA) is the preferred imaging modality for aneurysm surveillance, which has been validated previously.^{11,26} CT angiography (CTA) or rarely digital subtraction angiography (DSA) were performed if contraindications to MRA existed. New images were compared with prior studies by the senior author and a staff radiologist. Only cases with a consensus opinion of growth or morphological change were considered positive. This surveillance protocol included MRA every 6 months for the first 2 years after diagnosis followed by annual MRA for 3 more years to complete 5 years of follow-up. After 5 years of stability, no further imaging was recommended.

Any increase in maximal diameter or a morphological change in the aneurysm was felt to indicate instability in the aneurysm wall, and this finding was usually followed with a recommendation for treatment. To account for delays in diagnosis of aneurysm growth or de novo aneurysm formation encountered with periodic imaging, a corrected time was also calculated as described by others.¹⁸ The corrected time defined the date of aneurysm growth or de novo aneurysm formation as the date halfway between the imaging with the new finding and the previous imaging study.

To identify patients in aneurysm surveillance, medical records were retrospectively reviewed for patients initially evaluated from July 1, 2001, to December 31, 2012, with follow-up data reviewed through June 30, 2013. This study had approval of the institutional review board. Case collection involved searching for patients seen in clinic with the diagnosis of an untreated UIA and at least 1 follow-up clinic visit or consultation. This yielded 342 patients. Manual chart review of these cases excluded 150 patients with 1) extradural aneurysms, 2) nonsaccular aneurysms, 3) aneurysms that had been treated, and 4) patients with fewer than 2 imaging studies. We identified 192 patients in aneurysm surveillance for further analysis.

Chart review of these patients involved documentation of reason for initial imaging, aneurysm location, aneurysm size, de novo aneurysms, sex, age at diagnosis, aspirin use, hypertension, tobacco smoking status (ever used tobacco or never used tobacco), history of cerebrovascular disease, family history of SAH, personal history of SAH, ethanol use, and illicit drug use. Since patients with a history of SAH were usually offered treatment instead of surveillance, only 2 surveilled patients had a history of SAH. Thus, statistical analysis was not performed for this risk factor. The aneurysm location was classified into internal carotid artery, posterior communicating artery, anterior communicating artery/anterior cerebral artery, middle cerebral artery, or "posterior" for vertebrobasilar and posterior cerebral artery aneurysms.

Final outcomes of surveillance were recorded. This included whether a patient remained compliant with the surveillance protocol. Medical records were reviewed for evidence of spontaneous SAH. If any treatment occurred, the type of treatment, angiographic result, and clinical outcome were documented.

Statistical Analysis

Logistic regression analyses for the 192 patients and 234 aneurysms were done separately with select explanatory variables for aneurysm growth or de novo aneurysm formation. Univariate logistic regression was performed to identify variables predicting aneurysm growth or de novo aneurysm formation for the following (values in parentheses represent the number of patients with missing data): age, sex, imaging reason, aspirin use (6), hypertension (6), tobacco use (6), history of cerebrovascular disease (8), family history of SAH (7), ethanol use (6), and illicit drug use (6). To identify aneurysm-specific variables predicting growth, univariate logistic regression was performed for the following (no missing data): aneurysms size, aneurysm location, and multiplicity. To identify variables predicting patient compliance to the aneurysm surveillance protocol, univariate logistic regression was performed for the following (missing data): age, sex, family history of SAH (7), tobacco use (6), ethanol use (6), and illicit drug use (6). No model had multiple explanatory variables with p values < 0.20 in univariate analysis, so multivariate logistic regression analysis was not performed. Fisher's exact test was used to determine any association between patients with growth of UIAs and de novo aneurysm formation. Kaplan-Meier curves are presented for time to aneurysm growth as well as for time to either growth or de novo aneurysm formation (Figs. 1 and 2, respectively). Because our logistic regression analysis identified aneurysm size as a risk factor for growth, we performed a Kaplan-Meier analysis after stratifying aneurysms by size (< 5 mm and ≥ 5 mm) (Fig. 3).

Odds ratios with 95% confidence intervals were calculated and are given in Table 1 for aneurysm growth; p values < 0.05 were considered significant. IBM SPSS Statistics (version 20) and SAS (version 9.3) software were used for statistical analysis.

Literature Search and Study Eligibility

We searched the PubMed database on August 1, 2014. The following search was performed: (cerebral OR intracranial) AND aneurysm AND (growth OR "de novo").

FIG. 1. Kaplan-Meier curve showing the percentage of patients with a growing aneurysm or de novo aneurysm formation. The solid line is the uncorrected time until growth of an aneurysm or de novo aneurysm formation and the dotted line is the corrected time until growth of an aneurysm or de novo aneurysm formation.

FIG. 2. Kaplan-Meier curve showing the percentage of aneurysms with growth over time. The solid line is the uncorrected time until aneurysm growth and the dotted line is the corrected time until aneurysm growth.

For the aneurysm growth literature review, retrospective or prospective series with at least 50 patients reporting patient number, aneurysm number, duration of follow-up, and number of growing aneurysms were included. The de novo aneurysm formation literature review included all retrospective or prospective series with at least 50 patients reporting number of patients, duration of follow-up, and number of de novo aneurysms. For series from the same institutions overlapping the same time period, the largest series were chosen. Titles and abstracts were reviewed to identify relevant articles. Reference lists of relevant studies were screened for additional relevant studies.

Results

We evaluated 192 patients with 234 UIAs in our surveillance protocol. Baseline characteristics are presented in Table 1. Excluding the initial imaging, there were 746 surveillance imaging studies with a mean of 3.9 studies per patient. The initial imaging modality was MRA in 73%, CTA in 20%, and DSA in 7%. Subsequent studies were MRA in 87%, CTA in 9%, and DSA in 4%. There was an average follow-up duration of 3.2 years per patient and 3.3 years per aneurysm, yielding 621 patient-years of follow-up and 793 aneurysm-years of follow-up. Seventy-one percent of patients had at least 2 years of imaging follow-up.

Overall Surveillance Results

During the surveillance period, growth was identified in 28 of 234 UIAs followed in 192 patients. Additionally, 4 de novo aneurysms formed over the same period. In 31 of 746 surveillance imaging studies, a growing aneurysm and/or de novo aneurysm was discovered (27 studies with growing aneurysms, 3 studies with de novo aneurysms, and 1 study with a growing aneurysm and a de novo aneurysm). These 31 events occurring during 621 patient-years of follow-up led to a 5.0% incidence of aneurysm growth or de novo aneurysm formation per patient-year of follow-up. Growth or de novo aneurysm formation at the 6-month examination was found in 10 patients (5.2%). The Kaplan-Meier curve in Fig. 1 illustrates the percentage of patients with a growing aneurysm or de novo aneurysm over time. The mean uncorrected time until growth or de novo aneu-

FIG. 3. Kaplan-Meier curve showing the percentage of aneurysms with growth over time dichotomized by size. Both lines are the corrected time until growth.

rysm formation was 2.2 years (range 0.4–5.8 years) with a corrected time of 1.4 years (range 0.2–5.5 years).

Aneurysm Growth

The incidence of aneurysm growth per aneurysm-year of follow-up was 3.7%. No growth was seen in 206 aneurysms (88%), 10 aneurysms (4.3%) had early growth at the initial 6-month examination, 17 aneurysms (7.3%) had late growth, and 1 aneurysm grew at a late examination but did not have early imaging to rule out early growth. Figure 2 illustrates the percentage of aneurysms with growth over time through Kaplan-Meier curves. The mean uncorrected time until aneurysm growth was 2.4 years (range 0.4–8.3 years) and the corrected time was 1.5 years (range 0.25–5.5 years) (Fig. 2). An enlargement in the maximum aneurysm diameter was seen in 25 aneurysms and a morphological change was seen in 3 aneurysms. The mean growth was 1.9 mm (range 0.7–6 mm).

Initial aneurysm size was the only predictor of aneurysm growth ($p = 0.002$) (Table 1). The OR for continuous aneurysm size predicting aneurysm growth was 1.15 (95% CI 1.05–1.27) so that every 1-mm increase of initial aneurysm diameter increased the risk of growth during the protocol by 15%. The incidence of growth for UIAs < 5 mm versus UIA ≥ 5 mm was 1.6% and 8.7% per aneurysm-year, respectively ($p = 0.002$) (Fig. 3).

De Novo Aneurysm Formation

Four of 192 patients developed de novo aneurysms during follow-up at an average uncorrected time until formation of 1.4 years (range 0.7–2.1 years) with a corrected time of 1.0 years (range 0.3–1.8 years). The incidence of de novo aneurysm formation per patient-year of follow-up was 0.64%. No patient-specific factor predicted de novo aneurysm formation. However, 3 of 4 patients with de novo aneurysms also had a growing aneurysm, and this was statistically significant (Fisher's exact, $p = 0.01$).

Protocol Compliance, Treatment Outcomes, and Occurrence of SAH

Compliance with surveillance imaging was seen in 65% of patients. Older patients were less likely to be compliant with each additional year of age, decreasing compli-

TABLE 1. Baseline characteristics and risk factors for aneurysm growth and de novo aneurysm formation in 192 patients with 234 aneurysms*

Baseline Characteristic/ Risk Factor	Number	Growing or De Novo Aneurysm (%)	No Growing or De Novo Aneurysm (%)	OR	95% CI	p Value
Patient-based data						
Number of patients	192	29 (14.6)	163 (85.4)			
Sex				1.03	0.35–3.02	0.81
Male	40	6 (12.5)	34 (87.5)			
Female	152	22 (14.5)	130 (85.5)			
Mean age in yrs $\pm$ SD	61.1 $\pm$ 12.5	62.1 $\pm$ 12.3	60.9 $\pm$ 12.6	1.008	0.98–1.04	0.53
Imaging reason						
Stroke/TIA	39	4 (10.6)	35 (89.4)	Reference	Reference	Reference†
Screening	11	2 (18.1)	9 (81.9)	1.51	0.25–9.11	0.79
Headache	62	9 (14.5)	53 (85.5)	1.16	0.36–3.74	0.84
Dizziness	24	3 (12.5)	21 (87.5)	0.97	0.21–4.49	0.67
Memory loss	9	2 (22.2)	7 (78.8)	1.94	0.31–12.12	0.54
Vision loss	8	1 (12.5)	7 (87.5)	0.97	0.098–9.65	0.79
Other/unknown	39	7 (17.9)	32 (82.1)	1.49	0.43–5.17	0.69
Aspirin				0.72	0.29–1.81	0.17
Yes	75	8 (10.7)	67 (90.3)			
No	111	20 (18.0)	91 (82.0)			
HTN				0.77	0.33–1.82	0.80
Yes	107	16 (15.0)	91 (85.0)			
No	79	11 (13.9)	68 (86.1)			
Tobacco				2.02	0.81–5.00	0.26
Ever used	115	20 (17.4)	95 (82.6)			
Never used	71	7 (9.8)	64 (90.2)			
CVD				0.43	0.13–1.45	0.57
Yes	38	3 (7.9)	35 (92.1)			
No	146	24 (16.4)	122 (83.6)			
Family Hx of SAH				1.06	0.29–3.85	0.96
Yes	20	3 (15)	17 (85)			
No	165	24 (14.5)	141 (85.5)			
EtOH use				0.54	0.21–1.38	0.52
Yes	58	7 (12.1)	51 (87.9)			
No	128	20 (15.6)	108 (84.4)			
Illicit drug use				0.16	0.01–2.58	0.24
Yes	15	0 (0)	15 (100)			
No	171	27 (15.8)	144 (84.2)			
Aneurysm-based data						
Number of aneurysms	234	28 (12.0)	206 (88.0)			
Location						
ACoA/ACA	44 (18.9)	3 (6.8)	41 (93.2)	Reference	Reference	Reference‡
ICA	80 (34.2)	11 (13.8)	69 (86.2)	2.47	0.60–10.1	0.21
PCoA	21 (9.0)	3 (14.3)	18 (85.7)	2.67	0.46–15.4	0.27
MCA	67 (28.6)	7 (10.4)	60 (89.6)	1.38	0.30–6.30	0.68
Posterior§	22 (9.4)	4 (18.1)	18 (81.9)	2.73	0.50–14.8	0.25
Aneurysm size				1.15	1.05–1.27	0.0024¶
<3 mm	48 (20.5)	1 (2.1)	37 (97.9)			
3–6 mm	146 (62.4)	18 (12.3)	128 (87.7)			
7–11 mm	32 (13.7)	8 (25.0)	24 (75.0)			
12–24 mm	8 (3.4)	1 (12.5)	7 (87.5)			
>25 mm	0					

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TABLE 1. Baseline characteristics and risk factors for aneurysm growth and de novo aneurysm formation in 192 patients with 234 aneurysms*

Baseline Characteristic/ Risk Factor	Number	Growing or De Novo Aneurysm (%)	No Growing or De Novo Aneurysm (%)	OR	95% CI	p Value
Aneurysm-based data (<i>continued</i>)						
Multiplicity				0.87	0.35–2.20	0.77
Yes	73 (31.2)	8 (11.0)	65 (89.0)			
No	161 (68.8)	20 (12.4)	141 (87.6)			

ACA = anterior cerebral artery; ACoA = anterior communicating artery; CVD = cerebrovascular disease; EtOH = ethanol; HTN = hypertension; Hx = history; ICA = internal carotid artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; TIA = transient ischemic attack.

* Results of univariate logistic regression analysis are presented. Given that neither the patient-based data nor aneurysm-based data had 2 variables with a p value < 0.20, multivariate analysis was not performed for these models.

† All statistical comparisons were made to stroke/transient ischemic attack, which had the lowest incidence of growth.

‡ All statistical comparisons were made to anterior communicating artery/anterior cerebral artery, which had the lowest incidence of growth.

§ Indicates vertebrobasilar and posterior cerebral artery aneurysms.

¶ p value calculated from continuous data from aneurysm size.

ance by 3% (OR 0.97 [95% CI 0.94–0.99], $p = 0.01$). Treatment was undertaken in 22 of 32 growing or de novo aneurysms over 621 patient-years of follow-up (3.5% chance of treatment per patient-year of follow-up). Ten growing or de novo aneurysms were not treated because 4 patients declined treatment, 3 patients were of advanced age, 1 patient was too medically ill, 1 de novo aneurysm was deemed too small for treatment, and 1 de novo aneurysm was observed because the initial surveillance aneurysm was a stable basilar terminus aneurysm of higher risk.

Of 22 patients receiving treatment, 7 underwent clip ligation and 15 received endovascular treatment. Twenty patients had a good neurological outcome with complete or near-complete aneurysm occlusion. One patient had partial monocular vision loss after embolization of an ophthalmic segment ICA aneurysm, and another patient died of a retroperitoneal hematoma after placement of a stent for staged treatment of a growing basilar terminus aneurysm.

Aneurysmal SAH occurred during follow-up in 1 patient and after completion of follow-up in another patient. The first patient was an 85-year-old man with a 14-mm basilar terminus aneurysm that was stable for 1.2 years into surveillance. He became noncompliant with imaging surveillance and presented 2.3 years after initial diagnosis with aneurysmal SAH. The other patient was a 66-year-old woman with a 10-mm basilar aneurysm that was stable on imaging for 4.7 years. She presented with SAH 3.5 years after completion of follow-up. Of note, both aneurysms were larger on their treatment DSA studies than on prior images.

Discussion

This report demonstrates a high rate of early growth in surveilled UIAs and much higher rate of growth in UIAs ≥ 5 mm. The study also demonstrates the feasibility of implementing an aneurysm surveillance protocol into practice for appropriately selected UIAs. The high rate of early growth in surveilled UIAs implicates that these lesions should be imaged more frequently during the initial

surveillance period. Second, due to an increased incidence of growth for aneurysms ≥ 5 mm in diameter, these UIAs may warrant more frequent surveillance imaging, longer duration surveillance, or immediate occlusion. With these considerations, any recommendation regarding imaging frequency must balance costs and patient inconvenience with the risk of SAH due to an undetected growing UIA.

The concept of a growing aneurysm being unstable and posing a risk of imminent SAH has support from recent publications. These so-called “Yonekura type 2” aneurysms, are defined by growth immediately prior to rupture.³⁵ Inoue et al. found growing aneurysms that subsequently underwent surgical clipping to have walls that were “reddish, thin, and fragile” intraoperatively.¹³ Frösen et al. have noticed similar thin hypocellular aneurysm walls (Type D) to be most common in ruptured aneurysms.¹⁰ These same investigators suggest that loss of smooth muscle cells in the aneurysm wall underlies growth and subsequent rupture.⁹

The incidence of rupture from an acutely growing untreated UIA has been evaluated in 2 series in the literature. Inoue et al. cited an annual incidence of rupture in growing UIAs at 18.5%. Because some growing aneurysms were treated in their study (i.e., interrupting the natural history), the true risk of hemorrhage could be as high as 45%. Due to their use of low-resolution MRA, these investigators subselected very significantly enlarging UIAs. This accounted for the lower overall annual risk of growth (1.8%) with a very high annual incidence of rupture among growing UIAs (18.5%).¹³

Villablanca et al. followed UIAs with CTA, a more sensitive methodology to detect growth. This highly sensitive method underlies their very high reported annual growth rate of 18%. Because they selected very subtly growing aneurysms, they found a lower annual risk of rupture of growing UIAs (2.4%). However, Villablanca et al. similarly found growing UIAs to be at higher risk of SAH. In their series, the risk of rupture in growing UIAs was 12-fold higher than the risk of rupture in nongrowing UIAs (2.4% vs 0.2%, $p = 0.034$).³¹ These 2 studies highlight how the incidence of UIA growth or the incidence of rupture in

TABLE 2. Previous published series on aneurysm growth*

Authors & Year	Number of Patients	Number of Aneurysms	Mean Aneurysm Follow-Up (yrs)	Aneurysm- Years Follow-Up	Number of Growing Aneurysms	Growing Aneurysm/ Year	Risk Factors for Aneurysm Growth										Family Hx of SAH
							Age	Sex	Size	Location	Multiple	HTN	CVD	Tob	EtOH	Illicit Drug	
Juvela et al., 2001	87	111	18.9	2098	39	1.86%	—	↑	—	—	—	—	—	↑	—	—	—
Matsubara et al., 2004	140	166	1.5	245	10	4.08%	—	—	↑	—	—	—	—	—	—	—	—
Miyazawa et al., 2006	130	159	2.4	388	16	4.12%	—	—	↑	↑↑	↑	—	—	—	—	↑	—
Werner et al., 2006	93	125	1.3	163	3	1.85%	—	—	—	—	—	—	—	—	—	↑	↑
Burns et al., 2009	165	191	3.9	748	20	2.67%	—	—	↑	—	—	—	—	—	—	—	—
So et al., 2010	208	285	1.8	518	95	18.35%	—	—	—	—	—	—	—	—	↑	—	—
Sonobe et al., 2010	374	448	3.4	1531	30	1.96%	↓	—	—	—	—	—	—	—	—	—	—
Ferns et al., 2011	55	63	4.8	302	5	1.65%	—	—	—	—	—	—	—	—	—	—	—
Inoue et al., 2012	1002	1325	0.8	1115	18	1.61%	—	↑	—	—	—	—	—	—	—	—	—
Chien et al., 2013	235	319	2.4	776	42	5.41%	—	—	—	—	—	—	↑	—	—	—	—
Matsumoto et al., 2013	111	136	2.5	333	13	3.90%	—	—	—	—	↑	—	—	—	—	—	—
Present study	192	234	3.3	793	28	3.74%	—	—	↑	—	—	—	—	—	—	—	—
Total or average	2792	3562	2.7	9010	319	3.54%	—	—	—	—	—	—	—	—	—	—	—

Tob = tobacco; ↑ = increased risk of growth; ↓ = decreased risk of growth; — = not a risk factor.

* The literature search included all retrospective or prospective series with at least 50 patients reporting patient number, aneurysm number, duration of follow-up, and number of growing aneurysms. For series from the same institutions overlapping the same time period, the largest series were chosen.

† MCA location had increased risk of growth.

growing UIAs can depend on the sensitivity of the imaging modality. More importantly, they strongly suggest that growing UIAs are unstable and are at higher risk for SAH than nongrowing UIAs.

Based on the premise that growing UIAs are at higher risk of rupture, assessment of risk factors for aneurysm growth, especially modifiable risk factors, is clinically pertinent. The annual incidence of UIA growth is about 3.5% and the annual incidence of de novo aneurysm formation approaches 1% (Tables 2 and 3). As is evident from Table 2, aneurysm size is the most consistent risk factor for aneurysm growth from the literature. We found larger aneurysm size to be the only predictor of aneurysm growth. Of 9 previous studies evaluating aneurysm size as a risk factor for aneurysm growth, 3 found that larger aneurysms grow more than smaller aneurysms (Table 2). These studies reported that UIAs larger than 5 mm, 8 mm, and 10 mm were more likely to grow.^{4,22,24} We noted an increased risk of growth for aneurysms that are ≥ 5 mm (Fig. 3). Since the risk of aneurysm rupture begins to increase at 7 mm, 5 mm may serve as a reasonable size to increase surveillance intensity or offer immediate treatment for aneurysm occlusion.

The ideal frequency of surveillance imaging for UIAs is not currently well defined.³ Long-term frequent surveillance imaging is costly and burdensome to patients. However, the growth of aneurysms is likely nonlinear with episodic phases of growth being associated with high risks of SAH.^{1,6,15,19} We found the rate of growth at the 6-month examination to be much higher than expected. Using the multiplicative law of probability with an annual growth rate of 3.74%, and the occurrence of 6-month examination at 0.56 years, we find the expected incidence of aneurysm growth for a linear model would be 2.11%:

$$\text{Annual Risk of Growth} = 3.74\% = 0.0374$$

$$\text{Annual Risk of No Growth} = 1 - 0.0374 = 0.9626$$

$$\text{Risk of Growth} = 1 - (\text{Annual Risk of No Growth})^{\text{follow-up period in years}}$$

$$2.11\% = 1 - (0.9626)^{0.56}$$

However, 4.3% of aneurysms in our series grew as noted on the 6-month examination, suggesting more frequent early imaging is necessary to identify acutely growing UIAs for intervention to prevent SAH. Inoue et al. predicted that the likelihood of finding a growing aneurysm before rupture was 81.5% if evaluated every 12 months and 90.3% if evaluated every 6 months.¹³ Given this much improved sensitivity with semiannual examinations and the higher than expected incidence of aneurysm growth seen at the 6-month examination in our protocol, it is our contention that future guidelines should recommend more frequent early surveillance imaging.

Modern treatment algorithms are beginning to define the natural history of specific aneurysms by the aneurysm location, aneurysm size, patient history of SAH, hypertension, and genetic risk factors.¹² New guidelines should also include documented growth during surveillance as a risk factor for aneurysm rupture. As more data are gained about the growth and formation of aneurysms, guidelines may begin to recommend treatment in younger patients if predictive modeling suggests an aneurysm is likely to grow and require treatment within a patient's lifetime. This model of treatment may save costs by foregoing years of unnecessary surveillance imaging for aneurysms that will be treated anyway, reduce morbidity by offering treatment to patients while they are younger with smaller aneurysms (both predictive of better treatment outcomes), and, most importantly, reduce the incidence of SAH.³⁴

Our study has several limitations. One limitation of this study is its retrospective design. Although the surveillance protocol was initiated in a prospective manner by the senior author, case selection and data collection were performed retrospectively. The imaging modalities and protocols used were nonuniform as was the interpretation of the new imaging studies by multiple radiologists. Long-term follow-up after completion of surveillance was not performed, meaning that some patients could have had delayed SAH undetected in this study. Lastly, almost the entire study population has no history of SAH and this should be acknowledged with comparison with other patient populations.

TABLE 3. Previously published series on de novo aneurysm formation*

Authors & Year	Number of Patients	Mean Patient Follow-Up (yrs)	Number of Patients w/ De Novo Aneurysms	Patient-Years Follow-Up	De Novo Aneurysm/ Patient-Year
David et al., 1999	102	4.3	6	443	1.35%
Juvela et al., 2001	87	18.9	15	1644	0.91%
Tsutsumi et al., 2001	112	9.3	9	1042	0.86%
Wermer et al., 2005	610	8.3	61	5078	1.20%
Miyazawa et al., 2006	130	2.4	3	317	0.95%
Sprengers et al., 2009	65	5.1	1	332	0.30%
Ferns et al., 2011	276	4.8	2	1325	0.15%
Matsumoto et al., 2013	111	2.5	2	272	0.74%
Present study	192	3.2	4	621	0.64%
Total or average	1685	6.6	103	11074	0.93%

* The literature search included all retrospective or prospective series with at least 50 patients reporting patient number, duration of follow-up, and number of de novo aneurysms.

Conclusions

The annual risk of growth for UIAs is approximately 3.5% and the risk of de novo aneurysm formation during surveillance of UIAs approaches 1%. The risk of aneurysm growth is highest in the early period of surveillance and is increased for larger aneurysms (≥ 5 mm). Future guidelines on the management of UIAs should recommend an increased frequency of early surveillance imaging. More frequent imaging or immediate treatment for aneurysms ≥ 5 mm should be considered.

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Disclosures

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

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Conception and design: Serrone, Tackla, Grossman, Ringer. Acquisition of data: Serrone, Tackla, Gozal, Gogela, Vuong, Kosty, Steiner, Krueger. Analysis and interpretation of data: Serrone, Gozal, Gogela, Grossman. Drafting the article: Serrone, Gozal, Hanseman, Grossman, Ringer. Critically revising the article: Serrone, Tackla, Gozal, Gogela, Grossman, Ringer. Reviewed submitted version of manuscript: Serrone, Tackla, Gozal, Hanseman, Vuong, Kosty, Steiner, Krueger, Grossman, Ringer. Approved the final version of the manuscript on behalf of all authors: Serrone. Statistical analysis: Serrone, Gozal, Hanseman. Administrative/technical/material support: Ringer. Study supervision: Serrone, Ringer.

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