The publication of the retrospective arm of the ISUIA in 1998 indicated that the risk of rupture of an aneurysm smaller than 10 mm in a patient with no previous SAH was 0.05%.10 Furthermore, the morbidity and mortality rates associated with the surgical management of these lesions were 17.5% at 30 days and 15.7% at 1 year. With a risk of rupture 10 to 12 times lower than previously estimated and the risk associated with treatment approximately double that for historical controls, the recommendation was to manage patients expectantly when their aneurysms were smaller than 10 mm. This recommendation led to a maelstrom of controversy, with prominent cerebrovascular surgeons noting that the ISUIA population was heavily selected by cerebrovascular specialists to include patients with low risk for rupture because those with particularly worrisome symptoms, aneurysm morphological configuration, and family history of SAH were preferentially treated and not included in the study.3–5,13,21

In 2003, the prospective arm of the ISUIA was published (Table 1).27 The investigators who conducted this new, powerful trial reported that the 5-year cumulative rupture rates for aneurysms in the anterior circulation in patients with no previous SAH was 0% in lesions smaller than 7 mm and 2.5% in lesions of the PCoA or posterior cerebral circulation (Table 2). The risk associated with surgical treatment was 13.7% at 30 days and 12.6% at 1 year in patients with no previous SAH. Endovascular treatment resulted in overall morbidity and mortality rates of 9.3 and 9.8% at 30 days and 1 year, respectively. Aneurysm size and location were significant predictors of rupture, and patient age combined with aneurysm size and location was a significant predictor of treatment outcome. Although significantly different from the retrospective data, the ISUIA prospective data underscores the need for individual counseling with respect to lesion size, site, patient age, and comorbidities in each patient who presents with a cerebral aneurysm.

Exhaustive literature reviews on the natural history of unruptured intracranial aneurysms are available.24 In this review of the natural history of unruptured intracranial aneurysms, we will focus on the relevant practical data that a clinician should consider in the initial decision to treat or observe a patient with an unruptured aneurysm. Although previously reported risk factors for SAH include female sex, smoking, excessive alcohol consumption, hypertension, family history, ischemic heart disease, autosomal-dominant polycystic kidney disease, and use of oral contraceptive drugs, the ISUIA investigators found that aneurysm size and posterior cerebral location outweighed all other factors.17 Therefore, in this review we will focus on the risk factors of previous SAH, aneurysm size, aspect ratio (Fig. 1), aneurysm location, and symptoms other than rupture.

**Previous Hemorrhage**

In both the retrospective10 and prospective27 ISUIA reports, patients with previous aneurysmal SAH (Group 2, 615 patients) were at higher risk for rupture than those with no previous aneurysmal SAH (Group 1, 1077 patients). In the prospective data, this difference only held up for small (<7 mm) aneurysms. The 5-year cumulative

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**Abbreviations used in this paper:**
- ACoA = anterior communicating artery
- ISUIA = International Study of Unruptured Intracranial Aneurysms
- PCA = posterior cerebral artery
- PCoA = posterior communicating artery
- SAH = subarachnoid hemorrhage
rupture rate for small anterior circulation lesions was 1.5% in Group 2 compared with 0% in Group 1. For small posterior circulation aneurysms, the rates in the aforementioned groups were 3.4% compared with 2.5%. Juvela and colleagues have reported in detail a series of 142 patients with 181 aneurysms who have been followed up for more than 30 years in Finland. Although this series is often presented as a long-term, longitudinally followed group of patients with unruptured aneurysms only, the lesions in five (3.5%) of 142 patients were asymptomatic and therefore incidental, and those in six (4.2%) were symptomatic and unruptured. Nevertheless, the series does provide excellent long-term retrospective data on what are mostly Group 2 patients (those with previous SAH). The cumulative rates of bleeding were nearly continuous, with rates of 10.5, 23, and 30.3% at 10, 20, and 30 years, respectively. Nevertheless, the ISUIA data curves indicate that the incidence of hemorrhage may be highest in the first 5 years after diagnosis. With a mean follow-up duration of 4.1 years in the recent ISUIA data, it will be interesting to see how closely the ISUIA curves approximate the data acquired by Juvela and colleagues at 10 years.

Clearly, previous SAH puts patients at higher risk for rupture from an incidentally noted asymptomatic unruptured aneurysm. The potential difference between the data reported by Juvela, et al., in which they suggest a continuous hemorrhage risk, and the flattening of the curves at 5 years in the ISUIA highlights the debate regarding hemorrhage risk from aneurysms over time. Much of the debate over the original ISUIA data focused on the discrepancy noted between the 0.05% hemorrhage risk per year in small aneurysms and the previously published incidence and prevalence for both unruptured intracranial aneurysms and SAH. On the basis of these historical rates, some clinicians argued that the ISUIA data implied that almost one of six patients older than 30 years of age would harbor an incidental unruptured aneurysm.

If, however, the risk of aneurysm hemorrhage is not constant as Juvela, et al., suggest, but is highest after the lesion’s formation and then becomes very low over time, the ISUIA data fit better with historical rates. Mitchell and Jakubowski have presented data indicating that the high-risk period after initial aneurysm formation is less than 42 weeks in Group 1 patients with aneurysms smaller than 10 mm. These authors conclude that larger aneurysms have a constant risk of hemorrhage. Further work needs to be done to test the constant compared with high-risk hypothesis. It may be that there are two phenotypes of small aneurysms: high risk and low risk. Previous SAH and time elapsed from aneurysm formation probably both play a role in calculating the true hemorrhage risk.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>SAH Rate (%)</th>
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<tr>
<td>ISUIA</td>
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<td>prospective</td>
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</tr>
<tr>
<td>retrospective</td>
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</tr>
<tr>
<td>ISAT</td>
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</tr>
</tbody>
</table>

* ISAT = International Subarachnoid Aneurysm Trial; NA = not applicable; Tx = treatment.

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### Table 2

<table>
<thead>
<tr>
<th>Size (mm) &amp; Location</th>
<th>SAH Rate (%)</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>0.05</td>
</tr>
<tr>
<td>≥10</td>
<td>1.0</td>
</tr>
<tr>
<td>prospectiev arm</td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>6.0</td>
</tr>
<tr>
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</tr>
<tr>
<td>anterior circ†</td>
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</tr>
<tr>
<td>posterior circ‡</td>
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<tr>
<td>7–12</td>
<td></td>
</tr>
<tr>
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<tr>
<td>posterior circ</td>
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<tr>
<td>13–24</td>
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<tr>
<td>posterior circ</td>
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</table>

† Includes ACoA, internal carotid artery, and middle cerebral artery.
‡ Includes PCoA, PCA, basilar artery, and vertebral artery.
Natural history of unruptured intracranial aneurysms

Aneurysm Size

Is there a critical size at which aneurysms rupture? Spontaneous SAH is most often found in aneurysms ranging from 7 to 10 mm in size, many of which are smaller than 7 mm.7,16 Do aneurysms decrease in size after the time of rupture or, as discussed earlier, is there a high-risk period for rupture after formation? There is currently not enough information to answer these questions, but the results of the prospective ISUIA indicate that data for ruptured intracerebral aneurysms should not be used to draw conclusions about their unruptured counterparts.

The investigators in the prospective ISUIA27 have reported that aneurysms smaller than 7 mm in the anterior circulation have a 0% 5-year cumulative risk of rupture in patients with no SAH and a 1.5% risk in patients with previous SAH. Aneurysms less than 7 mm in diameter that arise from the PCoA or that are located in the posterior cerebral circulation had 5-year cumulative rupture rates of 2.5% in patients with no SAH (Group 1) and 3.4% in patients with SAH (Group 2). For aneurysms larger than 7 mm, there was no difference between Group 1 and 2 patients: in both groups the risks of rupture at 5 years for aneurysms that were 7 to 12 mm, 13 to 24 mm, and 25 mm or larger in diameter were 2.6, 14.5, and 40%, respectively, in the anterior circulation, and 14.5, 18.4, and 50% in the posterior circulation. For cavernous aneurysms, the cumulative 5-year rupture risk for Groups 1 and 2 were 3% for 13- to 24-mm lesions and 6.4% for lesions 25 mm and larger.

Two major arguments have been made against the concept of a critical size threshold above which unruptured aneurysms are at high risk for bleeding. In response to the conclusions stated in the retrospective ISUIA, Dickey and Kailasnath6 reported the “diameter-cube hypothesis,” a mathematical model that described the rupture potential of any aneurysm as continuously increasing on the basis of the maximum diameter of the aneurysm cubed. The diameter-cubed model was applied to two historical pathological studies and both Groups 1 and 2 in the retrospective ISUIA. The data curves generated from the application of this model indicate that there is no critical diameter for rupture, but rather a continuous risk of hemorrhage. Assuming a continuous hemorrhage risk and not a critical threshold, these authors argued that referral bias among ISUIA investigators who work at academic medical centers and who routinely treat patients with larger aneurysms makes the smaller aneurysms in their practice artificially appear to have a lower rupture rate. Whether there is a continuous risk or a critical threshold, the true issue is this: when does the natural history of the lesion outweigh the risk associated with surgery?

The second argument against a critical threshold has been that most ruptured aneurysms are between 7 and 10 mm in diameter, with many being smaller than 7 mm. How do the ISUIA data compare with this fact? The prospective ISUIA, the results of which have documented a reduction in the size of aneurysms at low risk for rupture from 10 to 7 mm, answers part of this criticism.27 Unresolved questions remain regarding aneurysm formation and the possibility of continuous compared with high initial risk for rupture. Although retrospective demographic data obtained in patients harboring unruptured aneurysms who were seen at the Mayo Clinic between 1965 and 1995 are similar to data obtained in the ISUIA patient population, the latter patients are a selected group.2 Young, healthy patients with aneurysms who have worrisome symptoms other than SAH and/or patients whose aneurysms have morphological characteristics like daughter sacs or irregular borders were likely to be referred for treatment. For a clinician seeing a patient for the first time for a small, unruptured intracranial aneurysm, the decision to advise conservative treatment remains difficult because there is no absolute litmus test for continued safety. In the last 5 years, the aspect ratio has emerged as a potential tool for discerning the effects of aneurysm morphological features on rupture risk.

Aspect Ratio

In 1999, Ujiie, et al.,22 published a manuscript in which they asserted that an aspect ratio (aneurysm depth/neck width) exceeding 1.6 in an experimental artery bifurcation in rabbits recreated the extremely low-flow conditions in the dome of ruptured intracranial aneurysms. They hypothesized that these low-flow conditions lead to stasis, thrombosis, and the establishment of a fibrinolytic cascade resulting in breakdown of the intima and dome, ultimately making aneurysms with a high aspect ratio more prone to rupture. To prove the reliability of their experimental observations, the authors conducted a clinical review of angiographic images in which they determined the aspect ratios in 129 patients with ruptured aneurysms and in 72 patients with 78 unruptured aneurysms.23 They found that in 80% of ruptured aneurysms the aspect ratio was greater than 1.6 and in 90% of unruptured lesions the aspect ratio was less than 1.6.

In their follow up to the work conducted by Ujiie, et al.,24 Weir, et al.,25 examined the aspect ratio in 127 patients with unruptured aneurysms, 290 with ruptured aneurysms, and 115 with both ruptured and unruptured lesions. In their retrospective application of the aspect ratio, the odds of rupture were 20 times greater when the ratio was greater than 3.47 compared with 1.38 or less. The aspect ratio exceeded 1.38 in 7% of ruptured lesions, compared with 45% of unruptured ones. Although 1.6 no longer held up as a line of demarcation, the aspect ratio proved to be a significant indicator of rupture potential. In a recent publication, Nader-Sepahi, et al.,26 evaluated the aspect ratio in a group of 75 patients with 75 ruptured and 107 unruptured aneurysms in whom the ruptured lesions served as an internal control group for their unruptured counterparts. The mean aspect ratios in their study were 2.7 ± 1.3 for ruptured and 1.8 ± 0.8 for unruptured aneurysms. This difference reached statistical significance (p < 0.001). Independent of aspect ratio, the mean depth of the aneurysms (7.7 ± 4.9 mm compared with 5.1 ± 4.5 mm) was also statistically significant. Among the ruptured aneurysms, 75% were smaller than 10 mm, and 62% of these had aspect ratios exceeding 1.6. Although not a perfect predictor of rupture, the aspect ratio is another tool to help in choosing those smaller aneurysms at higher risk for rupture. It may be that as aneurysms form they have a higher aspect ratio and that as the parent artery remodels in an attempt to heal the aneurysm, the shape of the lesion changes, resulting in a decrease in the aspect ratio.
Aneurysm Site

Before the ISUIA results were published, previous investigators had found that ACoA aneurysms were common and frequently ruptured at a smaller size, usually just slightly larger than 7 mm.\textsuperscript{13,20,26} Additionally, in comparing major series composed of patients with ruptured and unruptured aneurysms, those in the ACoA are the least common among unruptured lesions.\textsuperscript{2} Further data predating the ISUIA indicated that aneurysms in the basilar artery had a higher rate of rupture compared with aneurysms at other locations.\textsuperscript{29} With the high rate of ACoA lesions in series dealing with ruptured aneurysms and the suggestion that a basilar location was associated with higher risk, a hypothesis developed that midline aneurysms were more prone to rupture.

In the retrospective ISUIA analysis,\textsuperscript{10} aneurysms of the basilar tip, PCoA, vertebrobasilar artery, and PCA had a higher risk of rupture in Group 1 patients. In Group 2, only basilar tip location was predictive of rupture. In the prospective analysis,\textsuperscript{2} aneurysms smaller than 7 mm located in the basilar tip, PCoA, vertebrobasilar artery, and PCA had a 5-year hemorrhage risk of 2.5% in Group 1 and 3.4% in Group 2. Rupture risks for aneurysms in anterior cerebral, middle cerebral, and internal carotid artery locations were 0 and 1.5% in Groups 1 and 2, respectively, at 5 years. Cavernous aneurysms had a 0% risk of rupture until they reached 13 to 24 mm in size, when the risk rose to 3%. The increased risk of rupture in the posterior circulation continued for the larger aneurysm sizes. Nevertheless, unlike the findings in the series of ruptured aneurysms mentioned earlier, the ACoA location showed no greater tendency to rupture. The conclusion to be drawn from the prospective data is clearly that aneurysms in the PCoA present a higher risk of rupture and cavernous aneurysms present a low risk of rupture until they are larger than 13 mm.

Symptoms Other Than Rupture

Traditionally, patients presenting with cranial nerve palsy, ischemia, or vision loss due to an intracranial aneurysm are treated both to ameliorate their symptoms and because unruptured aneurysms causing symptoms other than bleeding have been considered to present a higher risk of rupture. The data supporting the latter conjecture is scant and retrospective. Three patients with unruptured aneurysms smaller than 1 cm and symptoms other than rupture were included in the original Cooperative Study on Intracranial Aneurysms.\textsuperscript{16} All three aneurysms bled between 1 and 7 weeks from the day of diagnosis. Other small retrospective series demonstrate rupture rates ranging from 33 to 50%, but all include fewer than 10 patients, aneurysms larger than 1 cm, and no clear standard for the measurement of aneurysm size.\textsuperscript{19,12}

In response to the retrospective data in the original ISUIA, Friedman, et al.\textsuperscript{8} reported their series of 15 (15.5%) of 97 patients with unruptured aneurysms smaller than 1 cm who presented with symptoms other than rupture at the Mayo Clinic between 1980 and 1991. Based on a comparison with the ISUIA data, these authors surmise that 7% of all small aneurysms present with symptoms other than rupture. Importantly, none of these symptomatic patients at the Mayo Clinic were enrolled in the ISUIA; all were surgically treated. In the prospective ISUIA report,\textsuperscript{27} aneurysm signs other than rupture were manifested by 11% of untreated, 16% of surgically treated, and 34% of endovascularly treated patients. There is no breakdown of these symptomatic aneurysms by size, site, or future hemorrhage; size and location outweighed all other risk factors. In future spinoff projects from the ISUIA, it will be interesting to see how symptomatic small aneurysms compare with their asymptomatic counterparts. This subgroup likely will and should, in our opinion, continue to be preferentially referred for consideration of treatment.

CONCLUSIONS

The initial decision to treat or manage an unruptured intracranial aneurysm conservatively cannot be rigidly based on maximal aneurysm diameter. In addition to the specific topics already reviewed, the risk associated with treatment for a particular aneurysm in an individual patient will be based on both aneurysm and patient-specific comorbidities. The findings in the retrospective ISUIA reinforced the belief that the surgical treatment of intracranial aneurysms is not low risk. The overall morbidity and mortality rates at 1 year in patients in Groups 1 and 2 was 15.7 and 13.1%, respectively.\textsuperscript{10} The prospective study reported a lower risk associated with surgical treatment, at 12.6 and 10.1% for Groups 1 and 2, respectively.\textsuperscript{19,27} Although their findings are not directly comparable with the ISUIA data, investigators in the International Subarachnoid Aneurysm Trial\textsuperscript{19} reported that 24% of the endovascularly treated patients were dependent or dead at 1 year, compared with 31% of surgically treated patients. In the ISUIA, the endovascular treatment risk was 9.8 and 7.1% for death and morbidity at 1 year in Groups 1 and 2, respectively. Patient age, posterior circulation location, and increasing aneurysm size added significantly to the risk associated with aneurysm treatment. Older patients fared better with endovascular management.

Previous rupture, aneurysm size, anatomical location, aneurysm morphology, patient symptoms, and patient-specific factors including age and comorbidities are all relevant when counseling for aneurysm treatment. Additionally, it is important for clinicians to recognize the treatment risks specific to their institution for patients with unruptured intracranial aneurysms. An institution’s experience rating will become increasingly important as endovascular techniques mature and the risks associated with endovascular treatment are lowered. In the future, the threshold for aneurysm treatment may change, even based on the low rupture risk for small aneurysms in the prospective ISUIA data. If an intracranial aneurysm can be treated with a 1% or lower risk of rupture, which size should be observed?

Acknowledgment

We thank Paul H. Dressel for preparation of the illustration.

References

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Manuscript received September 23, 2004. Accepted in final form October 5, 2004.

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