Update on the management of unruptured intracranial aneurysms

GREGORY J. ZIPFEL, M.D., AND RALPH G. DACEY, M.D.

Department of Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri

Over the past decade, several factors have led to a dramatic change in the manner in which patients with unruptured intracranial aneurysms are diagnosed and treated. These factors include the increased use of noninvasive imaging modalities for the diagnosis of intracranial aneurysms, publication of new natural history data detailing the hemorrhage risks associated with unruptured intracranial aneurysms, and the broad application of endovascular therapy for their treatment. With these new technologies and new natural history data has come considerable uncertainty about the optimal treatment strategy for patients with unruptured intracranial aneurysms. In this light, it seems prudent to review periodically and examine critically all recent data pertaining to the natural history and treatment of unruptured intracranial aneurysms, in an effort to provide a scientific update on which management recommendations can be based. This review article represents the authors' attempt at such an update, and it is their hope that members of the community of neurovascular surgeons might find this information helpful during their continuing efforts to provide optimal care for their patients with unruptured intracranial aneurysms.

KEY WORDS • unruptured intracranial aneurysm • natural history • surgical clip occlusion • endovascular therapy

OVERVIEW

A considerable debate regarding the optimal treatment of patients harboring unruptured intracranial aneurysms has developed in recent years, stemming largely from the influence of three main factors. First, increasing use of noninvasive neuroimaging modalities such as CT angiography and MR angiography in the outpatient setting has led to a marked increase in the number of truly asymptomatic, incidental unruptured intracranial aneurysms being diagnosed. Second, results from the first large-scale, randomized, multiinstitutional study directly comparing neurosurgical clip placement with endovascular coil occlusion in patients with intracranial aneurysms has been published.⁴² In this study it has been suggested that endovascular therapy may have a superior safety profile compared with surgical intervention, at least for ruptured intracranial aneurysms that are equally amenable to both treatment modalities. Third and most important, the ISUIA,²⁷ which was designed to assess the annual risk of hemorrhage associated with unruptured intracranial aneurysms, has been published recently. Results from this study indicate that unruptured intracranial aneurysms may have a more benign natural history than previously determined.

Abbreviations used in this paper: ACA = anterior cerebral artery; ADPKD = autosomal-dominant polycystic kidney disease; CT = computerized tomography; ICA = internal carotid artery; ISUIA = International Study of Unruptured Intracranial Aneurysms; MCA = middle cerebral artery; MR = magnetic resonance; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage.

In combination, these three factors have led to considerable uncertainty with regard to the optimal treatment for patients harboring unruptured intracranial aneurysms. Which particular lesions carry a hemorrhage risk significant enough to justify intervention, and when aneurysm treatment is warranted, which modality should be used? The purpose of this article is to review these issues critically and in detail, in an effort to provide a modern management strategy for unruptured intracranial aneurysms, and to provide the justification behind this paradigm.

Epidemiological Findings

A general understanding of the prevalence of unruptured intracranial aneurysms and the incidence of SAH is important when discussing management strategies for the population of patients with unruptured aneurysms. To determine the prevalence of unruptured intracranial aneurysms, three main sources of data have generally been analyzed: postmortem studies, conventional angiography, and MR angiography. Each of these data sources carries an inherent bias, which is largely the result of the manner in which patients were selected to undergo the particular evaluation. Nevertheless, meaningful inferences from such data are certainly possible.

Autopsy data have been used in multiple studies to estimate the prevalence of intracranial aneurysms, and several authors have published systematic reviews of the various autopsy studies performed during their era. In such reviews, investigators have found estimated prevalences ranging from as low as 0.2% to as high as 9%, with the majority finding prevalence rates for intracranial aneurysms in the 1 to 3% range.^{53,60}

Many researchers have also used angiographic data to estimate the prevalence of intracranial aneurysms.⁵² Prevalence estimates according to such studies range from as low as 2.3% to as high as 6%, with the majority reporting prevalences within a range of 2 to 4%. The most recent and perhaps the most exhaustive systematic review assessing the prevalence of intracranial aneurysms was performed by Rinkel, et al.,⁵² and was published in 1998. These authors reviewed both autopsy and angiographic studies and concluded that adults with no risk factors for SAH are likely to have a prevalence of approximately 2% for unruptured aneurysms.

Finally, a small number of reports have used MR angiography data to estimate aneurysm prevalence. The suggested prevalence according to such reports is approximately 3%,⁴⁰ although these studies have largely evaluated the Japanese population, which has consistently been found to have a higher prevalence rate (along with the Finnish) than the general population worldwide.^{24,55}

The incidence of SAH is also important when determining a management strategy for unruptured intracranial aneurysms, particularly when examining the reported natural history of such lesions. Many investigators have evaluated the incidence of SAH in particular patient populations, with reported estimates as low as six per 100,000 population⁴⁶ and as high as 96 per 100,000.³⁶ Certain populations have been found to have higher incidences of SAH than others, including the Finnish, in whom the incidence is approximately 25 to 33 per 100,000 population.⁵⁸ The Japanese have also been reported to have a higher incidence of SAH. For example, the Japanese town of Hisayama has the highest recorded annual incidence of SAH (96/100,000 population).³⁶ In the majority of studies involving non-Finnish and non-Japanese populations, the incidence of SAH is estimated to be approximately 10 per 100,000 population.⁶⁸

Imaging Modality and Diagnosis

For many decades cerebral angiography was the only modality available for diagnosing intracranial aneurysms. Today it continues to be the gold standard for aneurysm detection and characterization. Nevertheless, as noninvasive imaging techniques such as CT and MR angiography have improved, increasing numbers of cerebrovascular practitioners are using these modalities during their assessment of patients with aneurysms.

Most neurosurgeons use CT or MR angiography as a complementary study in addition to the standard arteriogram, because these studies often provide additional anatomical information. Others have begun using CT or MR angiography as a stand-alone preoperative examination, with many reporting satisfactory outcomes with this approach.^{2,13,23} Both CT and MR angiography avoid the small but real risks associated with cerebral angiography (for example, stroke and arterial dissection), and their accuracy in the detection of cerebral aneurysms has become very good in recent years.

A systematic review investigating the accuracy of noninvasive imaging techniques for intracranial aneurysms was performed by White, et al.,⁷⁰ in 2000. In their analysis they noted an overall accuracy for CT angiography of 89%, and the accuracy of MR angiography was 90%. Sen-

sitivity was greater for detection of aneurysms larger than 3 mm (96% for CT, 94% for MR angiography) than for detection of aneurysms 3 mm or smaller (61% for CT, 38% for MR angiography). Others have noted even higher rates of accuracy, especially when advanced imaging techniques such as multislice helical CT scanning³⁴ or volume-rendering algorithms with MR angiography³⁹ were used.

Modalities like CT and MR angiography have several purported advantages compared with cerebral angiography. For example, CT angiography studies can be obtained immediately after the initial CT scan once the diagnosis of SAH or intracerebral hemorrhage has been made. This modality can also often provide more complete anatomical information, because it allows unlimited viewing angles, three-dimensional views, information regarding adjacent bone and vessel relationships, true neck/dome relationships, and it can be used to assess the presence of calcification or atheroma. Like MR angiography, CT angiography has additional benefits besides its noninvasive nature. Its primary advantage lies with its ability to obtain very thin, almost submillimeter source images that can be viewed in both 2- and 3-dimensional modes, providing an unmatched level of anatomical detail. Magnetic resonance angiography also avoids the complications associated with the use of contrast agents.

As these noninvasive imaging techniques become increasingly familiar to the cerebrovascular practitioner and as institutions continue to upgrade their imaging hardware and software, it is likely that more and more neurosurgeons will become increasingly comfortable with the notion of performing surgery without the need for cerebral angiography, at least in some patients. Moreover, it is possible that as these imaging techniques continue to evolve, CT or MR angiography may eventually even supplant conventional angiography as the gold standard for cerebral aneurysm detection and characterization.

Risk Factors

Multiple risk factors have purportedly been associated with a higher prevalence of intracranial aneurysms. Such factors include female sex, family history of aneurysms, history of cigarette smoking, excessive alcohol consumption, hypertension, ischemic heart disease, hypercholesterolemia, ADPKD, Type IV Ehlers-Danlos syndrome, pituitary tumors, aortic coarctation, Graves disease, Marfan syndrome, neurofibromatosis Type 1, cerebral arteriovenous malformation, and oral contraceptive use. Nevertheless, only a few of these risk factors have been well validated.

Female sex has been consistently cited as a risk factor for an increased prevalence of intracranial aneurysms. In most large series of patients with these lesions, the female/male ratio has been reported as approximately 1.5:1.⁶⁰

Family history has also been clearly associated with an increased prevalence of intracranial aneurysms. Several studies have evaluated the prevalence of unruptured intracranial aneurysms in individuals with a first-degree relative in whom a history of SAH or intracranial aneurysm exists. These studies document aneurysm prevalence rates as low as 4%⁴⁸ and as high as 14%, with the highest rates being reported in families from Finland⁵⁵ and Japan.⁴⁴

Moreover, the number of affected family members has been shown to influence this prevalence rate significantly. For example, individuals with only one affected first-degree relative have an aneurysm prevalence rate of approximately 4%,⁴⁸ whereas individuals with two or more affected family members have an aneurysm prevalence rate of approximately 8%.^{49,54}

Autosomal-dominant polycystic kidney disease has also been consistently associated with an increased prevalence of intracranial aneurysms.^{18,67} In a study by Huston, et al.,²⁵ 85 patients with ADPKD who had no symptoms related to intracranial aneurysms were evaluated using MR angiography. Overall, 11% of patients with ADPKD were found to harbor at least one incidental intracranial aneurysm, a prevalence rate markedly higher than that of the general population. In this patient cohort, both ADPKD and a family history of these lesions contributed to the increased aneurysm prevalence. Patients with ADPKD and a family history of intracranial aneurysms or SAH were found to harbor an incidental lesion in 22% of cases, whereas those with ADPKD but no family history of intracranial aneurysm or SAH were found to harbor an incidental lesion in 5% of cases.

A history of active cigarette smoking has also been associated with an increased risk of aneurysm formation. These data primarily come from studies in which patients underwent serial surveillance angiography during the conservative treatment of other unruptured intracranial aneurysms. In this select patient population, active cigarette smoking, as well as female sex, were the only significant independent risk factors for *de novo* aneurysm formation.³³

Finally, patients with cerebrovascular malformations are also at significant risk for harboring an associated intracranial aneurysm. Most large series examining this issue have noted that between 6.4 and 17.6% of patients with arteriovenous malformations have a coexisting cerebral aneurysm; this is most commonly associated with a high-flow feeding artery or is located within the nidus itself.^{5,11,47,62}

Although there are several factors (as listed previously) that are consistently associated with an increased prevalence, only a few have been recognized as risk factors for rupture of an existing aneurysm. Some of these factors relate directly to the characteristics of the lesion (see discussion that follows), whereas others relate to the general condition of the patient. Regarding the latter, only age (inversely), active cigarette smoking,²⁹ and hypertension³ have been identified as independent risk factors for rupture of a known cerebral aneurysm.

Natural History

The ISUIA has contributed significantly to the current debate regarding the appropriate treatment of unruptured intracranial aneurysms. This was a large-scale, multicenter, observational study designed to assess the natural history of unruptured intracranial aneurysms, and to measure the risks associated with their repair. At centers in the US, Canada, and Europe patients were enrolled who harbored at least one unruptured intracranial aneurysm, regardless of whether they had aneurysmal symptoms other than rupture (for example, cranial nerve palsy). Patients were in-

cluded even if they had undergone treatment for a ruptured aneurysm at another location, but only if they were able to care for themselves after their aneurysm treatment. Exclusion criteria for the study included the following: 1) fusiform, traumatic, or mycotic aneurysm; 2) aneurysm with a maximum diameter of less than 2 mm; 3) history of SAH from a single ruptured aneurysm or an unknown source; 4) presence of an unruptured aneurysm that had been manipulated before the patient entered the study; 5) history of intracranial hemorrhage if the cause was unknown; and 6) history of malignant brain tumor.

The initial results of this study were published in 1998 and included a retrospective analysis of 1449 patients with 1937 unruptured aneurysms that had been conservatively managed between 1970 and 1991.²⁷ The mean follow-up duration was 8.3 years. The patients were divided into those with no history of SAH and those with a history of bleeding from a separate aneurysm. The natural history of these lesions with regard to rupture was as follows: patients with aneurysms smaller than 10 mm in diameter and no history of SAH had an annual hemorrhage rate of 0.05%, whereas those with a history of SAH from a separate aneurysm had an annual hemorrhage rate of 0.5%. Annual hemorrhage rates were significantly higher for lesions larger than 10 mm in maximal diameter. This initial report from the ISUIA collaborators indicated that the 10-mm diameter may be the critical size below which an unruptured intracranial aneurysm in a patient with no history of SAH would have an extremely low risk of rupture.

The most recent results from the ISUIA investigators, which included a prospective analysis of the natural history of unruptured intracranial aneurysms, documented rupture rates significantly higher than those in the first study.²⁶ In addition, the critical aneurysm size associated with significant hemorrhage risk was reduced from 10 to 7 mm. In this report the patients examined met the same inclusion and exclusion criteria as in the first ISUIA,²⁷ but these patients were prospectively entered and evaluated between the years 1991 and 1998. In this report 4060 patients from 61 centers (US, Canada, and Europe) were enrolled, with 2686 aneurysms treated conservatively and followed prospectively. The mean follow-up duration was 4.1 years. Again, the aneurysms were divided into those identified in patients with no history of SAH and those found in patients with a history of bleeding from a separate aneurysm (Table 1).

Regarding cavernous ICA aneurysms, no ruptures were noted in lesions measuring 12 mm in diameter or less, whereas larger lesions did carry some risk of rupture: 0.6% per year for large and 1.3% per year for giant aneurysms. In this location, a history of SAH did not affect the risk of hemorrhage.

Anterior circulation aneurysms were defined as those lesions located along the ACA, ICA, and MCA. Notably, PCoA lesions were not included in this aneurysm category. Results showed that no aneurysm ruptures occurred in patients with lesions smaller than 7 mm in diameter and no history of SAH. In patients with a history of SAH, lesions less than 7 mm in diameter had an annual hemorrhage risk of 0.3%. Lesions 7 mm or larger, regardless of the patient's history of SAH, had a more significant risk of rupture, a risk that escalated greatly as the aneurysm diameter reached 13 mm or larger.

TABLE 1
Annual risk of hemorrhage
in unruptured intracranial aneurysms*

Aneurysm Location	No. of Lesions	Size (mm), % Ruptured				
		<7		7–12	13–24	≥25
		Group 1	Group 2			
cavernous CA	210	0	0	0	0.6	1.3
ACA, MCA, ICA	1037	0	0.3	0.5	2.9	8.0
post circ, PCoA	445	0.5	0.7	2.9	3.7	10.0

* According to the ISUIA Group 1, patients with no history of SAH, Group 2, patients with SAH from a separate aneurysm. Abbreviations: CA = carotid artery; post circ = posterior circulation.

Regarding posterior circulation aneurysms, including those in the region of the PCoA, the risk of hemorrhage was significant even in the smallest aneurysm category. In patients harboring aneurysms less than 7 mm in diameter, the annual hemorrhage rate was 0.5% for those with no history of SAH and 0.7% for those with such a history. Lesions that were 7 mm or larger carried very high annual hemorrhage rates, ranging from 2.9 to 10% depending on aneurysm size.

The initial results from the ISUIA collaborators were met with considerable skepticism, and multiple reports critically analyzing the study have been published.^{4,6–10,15,35,51,61,71} Common issues raised included problems with patient recruitment and selection bias (for example, an excess number of small and cavernous ICA aneurysms). The most recent report from the ISUIA investigators has been met with considerably less criticism, largely because of its prospective nature and its robust power. Nevertheless, several weaknesses of the study have been described.⁶⁹

One predominant criticism of the study involved the manner in which patients were recruited into conservative treatment groups. Because all patients in the study were selected for observation only after consultation with a neurosurgeon, it is certainly plausible that those patients with aneurysm characteristics considered high risk (for example, irregular aneurysm shape, suggestive clinical history, and aneurysm location, among others) were more likely to have been advised to undergo aneurysm treatment. Selection bias of this sort would have led to a general underestimation of the hemorrhage risk. Because the majority of patients initially enrolled in this study (58%) were ultimately advised to undergo treatment, it seems likely that surgeon bias of some kind may have affected the ultimate results. Other study criticisms include the relatively broad exclusion criteria, an underrepresentation of certain aneurysm subtypes (for example, ACA and anterior communicating artery lesions), and the significant numbers of patients with aneurysms who were likely to have been evaluated at participating centers but not enrolled in the study (that is, additional selection bias).

In the majority of studies other than the ISUIA reports, bleeding risks for unruptured intracranial aneurysms have been documented as considerably higher than detailed earlier. Several prominent studies have been based on a series of patients with unruptured intracranial aneurysms who were originally diagnosed between 1956 and 1978 at

the Helsinki University Central Hospital in Finland.^{19,21,31,32} The original series was a single-institution, retrospective review consisting of 142 patients who harbored 181 aneurysms and who were treated conservatively. A great advantage of a study conducted in this particular patient population was the absence of surgical bias; all unruptured intracranial aneurysms during this era were treated conservatively. The extended duration of follow up (median 13.9 years in the most recent series update)³⁰ is also a major advantage, because it represents the longest follow-up duration for any reported natural history series. Weaknesses include the smaller number of patients, the retrospective nature of the study, and the fact that the majority of patients had suffered a previous SAH from a separate aneurysm. The annual hemorrhage risk reported in this series is 1.3%, equally distributed over the three decades of follow up. This aneurysm rupture rate is in accordance with that found in many other previous natural history studies.^{3,16}

A metaanalysis performed by Rinkel, et al.,⁵² in 1998 included all natural history studies of unruptured intracranial aneurysms that met prespecified inclusion criteria and that were published between 1955 and 1996 (neither arm of the ISUIA was included). Nine studies with 3907 patients harboring unruptured intracranial aneurysms were included in this analysis. The overall annual hemorrhage risk in this analysis was 1.9%, and the annual risk of hemorrhage for lesions smaller than 10 mm in diameter was 0.7%. No specific aneurysm size below which rupture was highly unlikely was noted in this analysis. The strengths of this study were its large size, multicenter design, and robust statistical power, whereas the weaknesses consisted of the retrospective nature of all included studies and the inherent limitations associated with the metaanalysis format. Overall, this study again presented findings of a significantly higher annual hemorrhage rate compared with either arm of the ISUIA.

Although considerable differences clearly exist between the hemorrhage risks reported by the ISUIA investigators and the majority of other available data, it remains true that the prospective ISUIA report represents the most robust prospective data available regarding the natural history of unruptured intracranial aneurysms. Despite the aforementioned weaknesses, these prospective ISUIA data have provided neurosurgeons and endovascular therapists with an improved scientific foundation on which they can better stratify the risk of rupture in their patients who harbor incidental aneurysms. Treatment recommendations and ultimately patient care have certainly benefited.

Aneurysm Screening

Because of the relatively high prevalence rate associated with intracranial aneurysms (~2% in the general population), many researchers have investigated whether aneurysm screening may be of benefit. This has been most extensively evaluated in the setting of familial aneurysms. For example, a study designed to examine the utility of screening for incidental aneurysms in individuals with one first-degree relative affected by aneurysmal SAH was recently published.³⁸ In this multiinstitutional, observational study, 626 first-degree relatives of 160 patients with SAH

were screened with MR angiography, yielding an aneurysm prevalence of 4% in this select patient population. Although this rate was higher than that in the general population, the authors calculated that 149 relatives would need to be screened to prevent one SAH on a lifetime basis. From this they concluded that screening in this particular patient population did not seem warranted. In contrast, others have screened individuals with two or more affected first-degree relatives, documenting aneurysm prevalence rates of approximately 8%.^{49,54} High rates such as these have led many to recommend noninvasive screening for those with two or more affected first-degree relatives. This may be particularly important if other risk factors such as active cigarette smoking, hypertension, or ADPKD are also present.

TREATMENT

Surgical Intervention

Direct surgical approaches for the obliteration of intracranial aneurysms have been the mainstay of treatment since results from the cooperative aneurysm study became available in the late 1960s and mid-1970s.^{16,17,37,56} The results of these studies placed surgical clip occlusion of ruptured intracranial aneurysms on firm scientific ground. Soon afterward, surgical intervention for the treatment of unruptured intracranial aneurysms steadily gained favor, particularly after many surgeons began reporting favorable patient outcomes after clip occlusion of incidental aneurysms.^{14,20,28,41,50,57,59,72} By the early 1990s a general consensus in the neurological community had been achieved: unruptured intracranial aneurysms were believed to be quite dangerous and it was thought that these lesions should be repaired by surgical means.

Since the early 1990s, however, new data regarding the natural history of unruptured intracranial aneurysms^{27,42} and the widespread application of endovascular therapy has led to a reconsideration of the indications and optimal treatment strategy for patients harboring unruptured intracranial aneurysms. This debate, although sometimes contentious, has been positive in many ways. One benefit has been a more exhaustive assessment of the risks associated with the treatment of unruptured intracranial aneurysms.

In both reports from the ISUIA investigators, prospective assessments of the morbidity and mortality rates associated with surgical intervention were obtained. In the initial report published in 1998,²⁷ the overall surgical morbidity and mortality rate for patients with a history of SAH from a separate aneurysm was 13.1%, whereas the surgical morbidity and mortality rate for those with no history of SAH was 15.7%. In this initial study, patient age was found to have the greatest influence on surgical risk. For example, the combined morbidity and mortality rate at 1 year for patients with no history of SAH was 6.5% for patients younger than 45 years of age, 14.4% for those between the ages of 45 and 64 years, and 32% for those older than 64 years of age.

The follow-up ISUIA results published in 2003²⁶ revealed an overall surgical morbidity and mortality rate of 10.1% for patients with a history of SAH from a separate aneurysm, whereas the surgical morbidity and mortality rate was 12.6% for those with no history of SAH. In the

follow-up study, independent risk factors for surgical outcome included age (substantial increase in risk for those older than 50 years, and even greater risk for patients older than 60 to 70 years), large aneurysm size, aneurysm location in the posterior circulation, history of ischemic cerebrovascular disease, and presence of aneurysm symptoms other than rupture. On the whole, the ISUIA results demonstrate a surgical morbidity and mortality rate that was higher than that seen in previous retrospective analyses. The majority of this increased surgical risk was related to cognitive impairment, as demonstrated on the Mini-Mental State Examination. In addition, the effect of older age on surgical outcome was well delineated in both arms of the ISUIA.

In addition to the risks associated with aneurysm surgery, it is important also to assess its efficacy. Fortunately, during the endovascular era, several reports addressing the efficacy of aneurysm surgery have been published. The most common and most easily determined measure by which to investigate surgical efficacy has been the rate of complete aneurysm occlusion after surgical clip placement. Ultimately, however, the best measure of efficacy is arrived at by assessing the rate of SAH in the years following aneurysm treatment, a measure that is superior but more difficult because of the extended duration of follow up required, particularly in the case of unruptured lesions.

With regard to the rate of complete aneurysm occlusion after surgery, many authors have addressed this issue. Several large series featuring immediate angiographic assessment to evaluate the completeness of aneurysm obliteration have reported high rates (90–95%) of total aneurysm obliteration.^{1,12,63,64} Unfortunately, the ISUIA did not provide information regarding the completeness of surgical occlusion of aneurysms. Regarding the risk of SAH after surgical repair of unruptured intracranial aneurysms, very few investigators have specifically addressed this issue, but Tsutsumi, et al.,⁶⁵ have recently provided some insight. They performed a single-institution, retrospective study examining 115 consecutive patients who underwent surgical repair of their unruptured intracranial aneurysms. The median follow-up duration was 8.8 years. These authors' analysis documented four late aneurysm ruptures (two from de novo aneurysms, one from a wrapped lesion, and one from a completely clip-occluded aneurysm). Overall, the annual risk of SAH after surgical repair of an unruptured intracranial aneurysm was calculated to be 0.14% during the first decade and 0.62% for the second decade postsurgery. Most delayed hemorrhages originated from either de novo aneurysms or lesions deemed unsuitable for clip occlusion (the latter were wrapped). When examining those aneurysms (105 lesions) that were treated with surgical clip placement, only one SAH (from aneurysm regrowth 11 years after complete surgical clip occlusion) was noted. The annual risk of hemorrhage from a surgically obliterated unruptured intracranial aneurysm therefore appears to be exceedingly small (~0.04–0.16%/year).

Overall, the surgical treatment of intracranial aneurysms has proven to be highly effective, with reported rates of complete aneurysm occlusion of approximately 90 to 95% and the risk of subsequent SAH from a surgically obliterated aneurysm being exceedingly low. Although highly effective, direct surgical obliteration of un-

ruptured intracranial aneurysms does carry a significant risk of surgical morbidity and death, as is delineated in the ISUIA reports. Of the several purported factors that influence surgery-related risk, the most significant appear to be patient age and aneurysm characteristics such as size, location, and the presence of aneurysm symptoms.

Endovascular Therapy

As in aneurysm surgery, a critical assessment of endovascular treatment of unruptured intracranial aneurysms must include an evaluation of both procedural risk and long-term efficacy. The follow-up ISUIA²⁶ published in 2003 has provided some of the best prospective data on the morbidity and mortality rates associated with endovascular aneurysm therapy. Of the 4060 patients enrolled in this study, 451 underwent endovascular treatment for unruptured intracranial aneurysms and were prospectively followed. The combined morbidity and mortality rate for patients with a history of SAH from a separate aneurysm was 7.1%, whereas the morbidity and mortality rate for those with no history of SAH was 9.8%. Multivariate analysis of factors portending poor outcome after endovascular therapy showed two factors to be independently significant: aneurysm size larger than 12 mm and posterior circulation location. Of note, patient age had little effect on the morbidity and mortality rates associated with this procedure, in contradistinction to the effect of surgical treatment.

Similar to differences noted between prospective and retrospective surgical data, the combined morbidity and mortality rate in the ISUIA after endovascular therapy was higher than that reported in most retrospective analyses. One of the most rigorous of these retrospective studies was that of Murayama, et al.,⁴³ who performed a single-institution, nonrandomized, retrospective review of the 916 aneurysms treated with endovascular therapy at their institution between 1990 and 2002. The overall surgical morbidity and mortality rate for patients harboring aneurysms that had not recently ruptured was 5.3%. In another large-scale, retrospective review, Henkes, et al.,²² examined 1811 aneurysms that had been treated with endovascular therapy at their institution between 1992 and 2003. A combined morbidity and mortality rate of 6.8% was observed for the entire series, a rate that was not affected by the aneurysm status (ruptured or unruptured). Correlative statistical analysis revealed that aneurysms that were larger in diameter or that had a wider neck had higher complication rates, as did those undergoing modified treatment techniques such as aneurysm remodeling and stent placement.

Measures of efficacy for endovascular aneurysm therapy are essentially the same as for surgery; these consist of the rate of complete aneurysm occlusion and the rate of aneurysm rupture after treatment. The follow-up ISUIA, as well as several single-institution retrospective case series, have provided detailed information regarding the initial rate of aneurysm occlusion after endovascular therapy. Aneurysm obliteration for the ISUIA²⁶ was complete in 51%, partial in 21%, not achieved in 23%, and the obliteration status was unknown in 5% of patients. Unfortunately, no further analysis regarding factors potentially affecting the degree of aneurysm occlusion (for example,

lesion size, neck width, aneurysm location) was included in this report, nor were long-term angiographic results.

More extensive analyses of aneurysm occlusion rates after endovascular therapy have been provided by several nonrandomized, retrospective studies; however, such studies have not in general reported results for unruptured intracranial aneurysms alone. Murayama, et al.,⁴³ as noted earlier, examined 916 patients with aneurysms treated with endovascular therapy at their institution. Aneurysms were subdivided by size and neck width as follows: small size/small neck, small size/large neck, large size, and giant size. Immediate angiographic results were reported as follows: complete occlusion in 55%, significant neck remnants in 35%, incomplete occlusion in 3.5%, and no occlusion in 5%. The rate of complete aneurysm occlusion was significantly higher in lesions that were in the small size/small neck category (75%), whereas complete occlusion rates for other aneurysm categories were significantly lower (26–43%). In addition, long-term angiographic data were reported, albeit in only 53% of patients, providing an assessment of the durability of aneurysm coil embolization. The overall recanalization rate in this series was 20.9%. The rate for smaller aneurysms in the small size/small neck category was considerably lower (5.1%), whereas the rate for aneurysms that were large or giant lesions was considerably greater (35.3 and 59.1%, respectively). Although many lesions were incompletely occluded by coils and the rate of recanalization was relatively high, the rate of delayed aneurysm rupture after initial treatment was only 4.1% over 5 years. In the context of ruptured intracranial aneurysms, these data support the notion that endovascular therapy markedly reduces the rate of early rebleeding, but it may not eliminate the risk of late aneurysmal hemorrhages. In the context of unruptured intracranial aneurysms, whether endovascular therapy significantly changes the natural history of these lesions has not been well documented.

In the analysis by Henkes, et al.,²² in which as noted earlier 1811 aneurysms treated with endovascular therapy at their institution were examined, very similar occlusion rates were documented (65.8% complete, 20.7% neck remnant, 10.7% partial occlusion, 2.9% no occlusion) as were reported by Murayama, et al.⁴³ In addition, this study provided a detailed correlative statistical analysis in an effort to identify which factors were associated with higher complication rates. The following factors were found to be associated with higher risk: 1) larger aneurysm size; 2) larger aneurysm neck; and 3) use of modified treatment techniques such as aneurysm remodeling and stent placement. Unfortunately, data regarding late angiographic results and rates of delayed aneurysmal hemorrhage were not included in this analysis.

Surgery Compared With Endovascular Therapy

No prospective, randomized, multicenter trial directly comparing surgical clip occlusion and endovascular coil therapy for the treatment of unruptured intracranial aneurysms has been initiated. The only large-scale, randomized, multicenter trial in which surgery was directly compared with endovascular therapy was conducted in patients harboring ruptured intracranial aneurysms. Therefore, no direct evidence indicating superiority of one

Update on the management of unruptured intracranial aneurysms

treatment modality over the other exists at present in the case of unruptured intracranial aneurysms.

Management Recommendations

Because randomized trials comparing conservative management with surgical clip occlusion and with endovascular therapy have not been performed to date for unruptured intracranial aneurysms, the individual cerebrovascular practitioner must use his or her best judgment based on the available clinical data as outlined earlier to determine which treatment modality, if any, should be advocated for a particular patient with an unruptured intracranial aneurysm. Our analysis of the literature, including data pertaining to natural history, surgical risk and efficacy, and endovascular risk and efficacy, has led us to the following general conclusions.

It is very likely that all unruptured intracranial aneurysms residing within the subarachnoid space carry at least some risk of rupture. Although the overall annual hemorrhage risk likely remains in the 0.5 to 1% range, new natural history data have allowed better subcategorization of the hemorrhage risk by aneurysm size and location. The vast majority of studies indicate that the annual hemorrhage risk for all unruptured intracranial aneurysms 10 mm or more in diameter (excluding truly cavernous lesions) is substantial. There is also general agreement that aneurysms located in the posterior circulation are at particular risk for hemorrhage over time, even those lesions smaller than 10 mm in diameter. For example, the prospective ISUIA report documented a 0.7% annual hemorrhage risk for posterior circulation aneurysms 2 to 6 mm in diameter. The majority of studies also support the notion that patients who have suffered a previous SAH from a separate intracranial aneurysm have an increased risk of rupture in any remaining intracranial lesions, compared with those in whom there is no history of SAH.

Some disagreement still exists, largely revolving around the risk attributed to smaller anterior circulation aneurysms. The ISUIA has provided prospective data that indicate a very low hemorrhage risk for anterior circulation aneurysms (apart from the PCoA region) that are less than 7 mm in diameter. The rupture risk in patients with and without a history of SAH from a separate aneurysm was 0.0 and 0.3%, respectively. Anterior circulation aneurysms (apart from the PCoA region) that measured 7 to 12 mm in diameter carried a higher annual hemorrhage risk (0.5%), although this was still somewhat lower than previous estimates.

These latter data have led us to be somewhat more conservative with our recommendations for intervention when counseling a patient harboring an anterior circulation aneurysm (apart from a lesion located in the PCoA region). This is particularly so for lesions that are smaller than 7 mm. We remain relatively aggressive when treating patients harboring unruptured intracranial aneurysms in the posterior circulation, even when the lesions are smaller in diameter. Regarding the PCoA region, it is somewhat surprising that the hemorrhage risk associated with these lesions appears to be more similar to the higher-risk posterior circulation aneurysms than to the lower-risk anterior circulation lesions. Because this finding has not been substantiated in other studies, it is not clear that these le-

sions should be treated much differently from other anterior circulation aneurysms at this time.

Finally, other factors besides hemorrhage risk can also affect treatment recommendations. For example, aneurysms associated with cranial nerve palsies often require intervention to stabilize or improve the patient's neurological deficit. In addition, the well-documented psychological burden associated with harboring an unruptured intracranial aneurysm^{45,66} can become debilitating for some patients. In such circumstances, which are relatively uncommon, aneurysm treatment might be recommended primarily to address the patient's psychological condition.

When it is believed that aneurysm treatment is required, uncertainties regarding the choice of modality clearly exist. One important factor contributing to the choice of treatment is patient age. The ISUIA has provided compelling evidence that older age has a significant impact on the risks associated with aneurysm surgery, whereas age did not prove to be a significant risk factor in endovascular therapy. Therefore, we are much more likely to recommend endovascular therapy for patients with aneurysms who are older than 60 years of age. On the other hand, we more commonly advocate surgery for patients who are younger than 50 years of age, because concerns regarding long-term durability of the occlusion after endovascular therapy still exist.

Besides patient age and comorbid medical conditions, decision-making often focuses on a critical assessment of various aneurysm characteristics (Table 2). Important aneurysm factors include lesion size, neck width, location, and complexity (for example, atheroma, calcification, or intraluminal thrombus). In general, aneurysms that are located along the basilar artery or basilar apex are more commonly treated with endovascular therapy, whereas lesions along the MCA and distal ACA are typically treated with surgery. Regarding other aneurysm locations, no general consensus has been reached regarding superiority of one modality to the other in their treatment, and often other aneurysm characteristics are considered during the decision making process. For example, larger lesions are more likely to be treated with surgery because of the rather poor initial and long-term angiographic results following platinum coil therapy. Similarly, wide-necked aneurysms are more commonly treated with surgery, because endovascular therapy for such lesions often mandates the use of higher-risk techniques such as balloon remodeling or stent placement. Finally, aneurysm complexity must be carefully assessed, because the presence of calcification and/or atheroma would make endovascular therapy more attractive, whereas the presence of intraluminal thrombus would make surgical treatment more likely.

The availability of endovascular therapy, in addition to influencing the pretreatment decision-making process, has also changed the manner in which many surgeons approach aneurysm surgery today. These surgeons now continue their risk assessment for a particular patient in the operating room itself. If at any point during the surgical procedure additional risk factors are encountered, the surgeon can pause to reassess the overall risk to the patient. For example, if unexpected atheroma or calcification is noted during exposure of an intracranial aneurysm, the

TABLE 2
Aneurysm characteristics
related to choice of surgery or endovascular therapy*

Characteristic	Treatment	
	Endo (coil)	Op (clip)
size		
small (<10 mm)		
w/ small neck	++	++
w/ large neck	++	+++
large (10–24 mm)	++	+++
giant (≥25 mm)	+	+++
location		
ACoA	++	++
distal ACA	+	+++
MCA	+	+++
PCoA	++	+++
paraclinoid ICA	+++	++
basilar apex	+++	+
SCA/PCA	++	++
PICA	++	++
complexity		
atheroma/calcification	+++	+
intraluminal thrombus	+	+++

* The pluses are arbitrary units used to compare the desirability of one treatment modality with another for a particular aneurysm. One plus means less desirable and multiple pluses mean more desirable. If surgery is designated + and endovascular therapy is +++, then endovascular therapy would more likely be the appropriate choice, and vice versa. If each treatment modality is designated ++, then either would be appropriate. Abbreviations: ACoA = anterior communicating artery; endo = endovascular; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery.

surgeon may elect to abort the procedure rather than continuing with what has clearly become a higher-risk surgical endeavor. With the availability of endovascular therapy as a viable alternative, the surgeon of today has a choice not available a decade ago; to back off and send the patient for endovascular treatment.

CONCLUSIONS

The landscape for the treatment of unruptured intracranial aneurysms has changed dramatically in recent years. More truly asymptomatic, incidental intracranial aneurysms are being diagnosed today than ever before, largely due to the ease and sensitivity of noninvasive imaging studies like MR and CT angiography. In addition, new natural history data have surfaced, indicating that the hemorrhage risk associated with incidental intracranial aneurysms may be lower than previously thought. Finally, a viable treatment alternative to surgical clip occlusion, endovascular therapy with platinum coils, has gained widespread acceptance within the cerebrovascular community. These changes and more have led to an ongoing debate about the optimal management strategy for patients harboring unruptured intracranial aneurysms. Because no randomized clinical trials addressing incidental aneurysm treatment have been conducted, the individual practitioner is left with the responsibility of attempting to assimilate all available data him- or herself, in an effort to provide the most appropriate therapy.

Critical assessment of both the patient and the natural

history of the incidental lesion (taking into account such factors such as patient age, history of cigarette smoking or hypertension, history of SAH from a separate lesion, aneurysm size, and aneurysm location) must be weighed against the procedural risks and the long-term efficacy associated with each treatment modality. We hope that topic reviews such as this will provide some help to practitioners as they encounter patients in their practice who harbor unruptured intracranial aneurysms.

References

1. Akyuz M, Tuncer R, Yilmaz S, et al: Angiographic follow-up after surgical treatment of intracranial aneurysms. *Acta Neurochir* **146**:245–250, 2004
2. Anderson GB, Steinke DE, Petruk KC, et al: Computed tomographic angiography versus digital subtraction angiography for the diagnosis and early treatment of ruptured intracranial aneurysms. *Neurosurgery* **45**:1315–1322, 1999
3. Asari S, Ohmoto T: Natural history and risk factors of unruptured cerebral aneurysms. *Clin Neurol Neurosurg* **95**:205–214, 1993
4. Ausman JI: The New England Journal of Medicine report on unruptured intracranial aneurysms: a critique. *Surg Neurol* **51**:227–229, 1999
5. Batjer H, Suss RA, Samson D: Intracranial arteriovenous malformations associated with aneurysms. *Neurosurgery* **18**:29–35, 1986
6. Berenstein A, Flamm ES, Kupersmith MJ: Unruptured intracranial aneurysms. *N Engl J Med* **340**:1439–1442, 1999
7. Brennan JW, Schwartz ML: Unruptured intracranial aneurysms: appraisal of the literature and suggested recommendations for surgery, using evidence-based medicine criteria. *Neurosurgery* **47**:1359–1372, 2000
8. Brett A: Unruptured intracranial aneurysms. *N Engl J Med* **340**:1441–1442, 1999
9. Caplan LR: Should intracranial aneurysms be treated before they rupture? *N Engl J Med* **339**:1774–1775, 1998
10. Connolly ES Jr, Mohr JP, Solomon RA: Unruptured intracranial aneurysms. *N Engl J Med* **340**:1440–1442, 1999
11. Cronqvist S, Troupp H: Intracranial arteriovenous malformation and arterial aneurysm in the same patient. *Acta Neurol Scand* **42**:307–316, 1966
12. David CA, Vishteh AG, Spetzler RF, et al: Late angiographic follow-up review of surgically treated aneurysms. *J Neurosurg* **91**:396–401, 1999
13. Dehdashti AR, Rufenacht DA, Delaville J, et al: Therapeutic decision and management of aneurysmal subarachnoid haemorrhage based on computed tomographic angiography. *Br J Neurosurg* **17**:46–53, 2003
14. Deruty R, Pelissou-Guyotat I, Mottotese C, et al: Management of unruptured cerebral aneurysms. *Neurol Res* **18**:39–44, 1996
15. Dumont AS, Lanzino G, Kassell NF: Unruptured aneurysms. *J Neurosurg* **96**:52–60, 2002
16. Graf CJ: Prognosis for patients with nonsurgically-treated aneurysms. Analysis of the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. *J Neurosurg* **35**:438–443, 1971
17. Graf CJ, Nibbelink DW: Cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Report on a randomized treatment study. 3. Intracranial surgery. *Stroke* **5**:557–601, 1974
18. Graf S, Schischma A, Eberhardt KE, et al: Intracranial aneurysms and dolichoectasia in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* **17**:819–823, 2002
19. Heiskanen O: Risk of bleeding from unruptured aneurysm in cases with multiple intracranial aneurysms. *J Neurosurg* **55**:524–526, 1981

Update on the management of unruptured intracranial aneurysms

20. Heiskanen O: Risks of surgery for unruptured intracranial aneurysms. **J Neurosurg** 65:451–453, 1986
21. Heiskanen O, Marttila I: Risk of rupture of a second aneurysm in patients with multiple aneurysms. **J Neurosurg** 32:295–299, 1970
22. Henkes H, Fischer S, Weber W, et al: Endovascular coil occlusion of 1811 intracranial aneurysms: early angiographic and clinical results. **Neurosurgery** 54:268–285, 2004
23. Hoh BL, Cheung AC, Rabinov JD, et al: Results of a prospective protocol of computed tomographic angiography in place of catheter angiography as the only diagnostic and pretreatment planning study for cerebral aneurysms by a combined neurovascular team. **Neurosurgery** 54:1329–1342, 2004
24. Horikoshi T, Akiyama I, Yamagata Z, et al: Retrospective analysis of the prevalence of asymptomatic cerebral aneurysm in 4518 patients undergoing magnetic resonance angiography—when does cerebral aneurysm develop? **Neurol Med Chir** 42:105–113, 2002
25. Huston J III, Torres VE, Sullivan PP, et al: Value of magnetic resonance angiography for the detection of intracranial aneurysms in autosomal dominant polycystic kidney disease. **J Am Soc Nephrol** 3:1871–1877, 1993
26. The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet** 362:103–110, 2003
27. The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. **N Engl J Med** 339:1725–1733, 1998
28. Jomin M, Lesoin F, Lozes G, et al: Surgical prognosis of unruptured intracranial arterial aneurysms. Report of 50 cases. **Acta Neurochir** 84:85–88, 1987
29. Juvela S: Natural history of unruptured intracranial aneurysms: risks for aneurysm formation, growth, and rupture. **Acta Neurochir Suppl** 82:27–30, 2002
30. Juvela S: Risk factors for multiple intracranial aneurysms. **Stroke** 31:392–397, 2000
31. Juvela S, Porras M, Heiskanen O: Natural history of unruptured intracranial aneurysms: a long-term follow-up study. **J Neurosurg** 79:174–182, 1993
32. Juvela S, Porras M, Poussa K: Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. **J Neurosurg** 93:379–387, 2000
33. Juvela S, Poussa K, Porras M: Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. **Stroke** 32:485–491, 2001
34. Kangasniemi M, Makela T, Koskinen S, et al: Detection of intracranial aneurysms with two-dimensional and three-dimensional multislice helical computed tomographic angiography. **Neurosurgery** 54:336–341, 2004
35. Kassell NF, Lanzino G: Editorial comment on Johnston SC, Zhao S, Dudley RA, et al: Treatment of unruptured cerebral aneurysms in California. **Stroke** 32:597–605, 2001
36. Kiyohara Y, Ueda K, Hasuo Y, et al: Incidence and prognosis of subarachnoid hemorrhage in a Japanese rural community. **Stroke** 20:1150–1155, 1989
37. Locksley HB: Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Based on 6368 cases in the cooperative study. **J Neurosurg** 25:219–239, 1966
38. The Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group: Risks and benefits of screening for intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. **N Engl J Med** 341:1344–1350, 1999
39. Mallouhi A, Rieger M, Czermak B, et al: Volume-rendered multidetector CT angiography: noninvasive follow-up of patients treated with renal artery stents. **AJR** 180:233–239, 2003
40. Matsumoto E, Shinoda S, Masuzawa T, et al: [Observation of statistics of screening for unruptured cerebral aneurysms in Tochigi prefecture.] **No Shinkei Geka** 30:829–836, 2002 (Jpn)
41. Mizoi K, Yoshimoto T, Nagamine Y, et al: How to treat incidental cerebral aneurysms: a review of 139 consecutive cases. **Surg Neurol** 44:114–121, 1995
42. Molyneux A, Kerr R, Stratton I, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. **Lancet** 360:1267–1274, 2002
43. Murayama Y, Nien YL, Duckwiler G, et al: Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. **J Neurosurg** 98:959–966, 2003
44. Nakagawa T, Hashi K, Kurokawa Y, et al: Family history of subarachnoid hemorrhage and the incidence of asymptomatic, unruptured cerebral aneurysms. **J Neurosurg** 91:391–395, 1999
45. Otawara Y, Ogasawara K, Kubo Y, et al: Anxiety before and after surgical repair in patients with asymptomatic unruptured intracranial aneurysm. **Surg Neurol** 62:28–31, 2004
46. Pakarinen S: Incidence, aetiology, and prognosis of primary subarachnoid haemorrhage. A study based on 589 cases diagnosed in a defined urban population during a defined period. **Acta Neurol Scand** 43 (Suppl 29):21–28, 1967
47. Perret G, Nishioka H: Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI. Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the cooperative study. **J Neurosurg** 25:467–490, 1966
48. Raaymakers TW: Aneurysms in relatives of patients with subarachnoid hemorrhage: frequency and risk factors. MARS Study Group. Magnetic Resonance Angiography in Relatives of patients with Subarachnoid hemorrhage. **Neurology** 53:982–988, 1999
49. Raaymakers TW, Rinkel GJ, Ramos LM: Initial and follow-up screening for aneurysms in families with familial subarachnoid hemorrhage. **Neurology** 51:1125–1130, 1998
50. Rice BJ, Peerless SJ, Drake CG: Surgical treatment of unruptured aneurysms of the posterior circulation. **J Neurosurg** 73:165–173, 1990
51. Riina HA, Spetzler RF: Unruptured aneurysms. **J Neurosurg** 96:61–62, 2002
52. Rinkel GJ, Djibuti M, Algra A, et al: Prevalence and risk of rupture of intracranial aneurysms: a systematic review. **Stroke** 29:251–256, 1998
53. Romy M, Werner A, Wildi E: [Occurrence of intracranial arterial aneurysms and their rupture, from a series of routine autopsies.] **Neurochirurgie** 19:611–626, 1973 (Fre)
54. Ronkainen A, Hernesniemi J, Puranen M, et al: Familial intracranial aneurysms. **Lancet** 349:380–384, 1997
55. Ronkainen A, Miettinen H, Karkola K, et al: Risk of harboring an unruptured intracranial aneurysm. **Stroke** 29:359–362, 1998
56. Sahs AL: Cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Report on a randomized treatment study. I. Introduction. **Stroke** 5:550–551, 1974
57. Samsom DS, Hodosh RM, Clark WK: Surgical management of unruptured asymptomatic aneurysms. **J Neurosurg** 46:731–734, 1977
58. Sarti C, Tuomilehto J, Salomaa V, et al: Epidemiology of subarachnoid hemorrhage in Finland from 1983 to 1985. **Stroke** 22:848–853, 1991
59. Solomon RA, Fink ME, Pile-Spellman J: Surgical management of unruptured intracranial aneurysms. **J Neurosurg** 80:440–446, 1994
60. Stehbens WE: **Pathology of the Cerebral Blood Vessels**. St. Louis: Mosby, 1972
61. Stieg PE, Friedlander R: Unruptured intracranial aneurysms. **N Engl J Med** 340:1441–1442, 1999

62. Suzuki J, Onuma T: Intracranial aneurysms associated with arteriovenous malformations. **J Neurosurg** **50**:742–746, 1979
63. Thornton J, Bashir Q, Aletich VA, et al: What percentage of surgically clipped intracranial aneurysms have residual necks? **Neurosurgery** **46**:1294–1300, 2000
64. Tsutsumi K, Ueki K, Morita A, et al: Risk of aneurysm recurrence in patients with clipped cerebral aneurysms: results of long-term follow-up angiography. **Stroke** **32**:1191–1194, 2001
65. Tsutsumi K, Ueki K, Usui M, et al: Risk of subarachnoid hemorrhage after surgical treatment of unruptured cerebral aneurysms. **Stroke** **30**:1181–1184, 1999
66. van der Schaaf IC, Brilstra EH, Rinkel GJ, et al: Quality of life, anxiety, and depression in patients with an untreated intracranial aneurysm or arteriovenous malformation. **Stroke** **33**:440–443, 2002
67. van Dijk MA, Chang PC, Peters DJ, et al: Intracranial aneurysms in polycystic kidney disease linked to chromosome 4. **J Am Soc Nephrol** **6**:1670–1673, 1995
68. Weir B: Unruptured intracranial aneurysms: a review. **J Neurosurg** **96**:3–42, 2002
69. White PM, Wardlaw J: Unruptured intracranial aneurysms: prospective data have arrived. **Lancet** **362**:90–91, 2003
70. White PM, Wardlaw JM, Easton V: Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. **Radiology** **217**:361–370, 2000
71. Winn HR: Section overview: unruptured aneurysms. **J Neurosurg** **96**:1–2, 2002
72. Wirth FP, Laws ER Jr, Piepgras D, et al: Surgical treatment of incidental intracranial aneurysms. **Neurosurgery** **12**:507–511, 1983

Manuscript received October 12, 2004.

Accepted in final form October 20, 2004.

Address reprint requests to: Gregory J. Zipfel, M.D., Washington University School of Medicine, Department of Neurological Surgery, 660 South Euclid Avenue, Campus Box 8057, St. Louis, Missouri 63110. email: zipfelg@nsurg.wustl.edu.