Guidelines for the Surgical Treatment of Unruptured Intracranial Aneurysms

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-Controversies in the Management of Cerebral Aneurysms-

Ricardo J. Komotar, M.D.

J Mocco, M.D.

Robert A. Solomon, M.D.

Department of Neurological Surgery
Columbia University
New York, NY

Please address all correspondence to:

Robert A. Solomon, M.D.

Byron Stookey Professor of Neurological Surgery

Chairman and Director of Service

Department of Neurological Surgery

Neurological Institute of New York

Columbia University Medical Center

710 West 168th Street, Room 439

New York, NY 10032

Telephone: (212) 305-4118

Fax: (212) 305-2026

E-mail: ras5@columbia.edu

ABSTRACT

The management of unruptured cerebral aneurysms remains one of the most controversial topics in neurosurgery. To this end, we discuss the diagnosis and estimated prevalence of these lesions, as well as review the literature regarding the rate of rupture for cerebral aneurysms and risks of operative intervention. Our interpretation of the literature concludes that aneurysms are present in about 1% of the adult population, varying between <1% in young adults to 4% in the elderly. The yearly risk of SAH for an unruptured intracranial aneurysm is approximately 1% for lesions 7 to 10 mm in diameter. Based on these assumptions, we recommend that 1) with rare exceptions, all symptomatic unruptured aneurysms should be treated; 2) small, incidental aneurysms less than 5mm should be managed conservatively in virtually all cases; 3) aneurysms greater than 5mm in patients less than 60 years of age should be seriously considered for treatment; 4) large, incidental aneurysms greater than 10mm should treated in nearly all patients less than 70 years of age; 5) microsurgical clipping rather than endovascular coiling should be the first choice in low-risk cases. Critical to our guidelines is collaboration by a highly experienced cerebrovascular team of micro-neurosurgeons and endovascular neurosurgeons, working at a tertiary medical center with high case volume, and utilizing a decision-making paradigm designed to offer only low risk treatments. In certain cases where both treatment and natural history carry a high risk, such as with giant aneurysms, non-operative management is typically elected.

INTRODUCTION

The management of unruptured cerebral aneurysms remains one of the most controversial topics in neurosurgery. The International Study of Unruptured Intracranial Aneurysms (ISUIA) investigators have published prospective evaluations regarding the morbidity and mortality (M&M) for the treatment of patients with unruptured intracranial aneurysms (UIAs) (1, 94). Their findings, however, strongly contrast with the majority of prior estimates (8, 24, 29, 38, 43, 46, 55, 69, 76, 78, 85, 88, 96). As a result, there have been a number of efforts to determine the true natural history of this condition and define the morbidity and mortality of unruptured cerebral aneurysm surgery as related to patient age, aneurysm size, and aneurysm location. Despite these concerns, no clear consensus has been reached. To this end, we discuss the diagnosis and estimated prevalence of these lesions, as well as review the literature regarding the rate of rupture for cerebral aneurysms and risks of operative intervention. Based on our interpretation of the literature and our extensive experience with managing cerebral aneurysms, we have synthesized a series of management recommendations for patients with unruptured intracranial aneurysms. These recommendations are founded in proper patient selection and the integration of microsurgical and endovascular techniques. Critical to our guidelines is collaboration by a highly experienced cerebrovascular team of micro-neurosurgeons and endovascular neurosurgeons, working at a tertiary medical center with high case volume, and utilizing a decision-making paradigm designed to offer only low risk treatments. In certain cases where both treatment and natural history carry a high risk, such as with giant aneurysms, non-operative management is typically elected.

DIAGNOSIS OF UNRUPTURED CEREBRAL ANEURYSMS

Unruptured aneurysms may be discovered incidentally or present with neurological symptoms. Raps et al. investigated the presenting symptoms in 111 patients with unruptured aneurysms (66). The authors found that while 51% were asymptomatic, 17% presented with acute symptomatology and 32% presented with chronic symptomatology. Acute neurological symptoms included ischemia (37%), headache (37%), seizures (18%), and cranial neuropathies (12%). Chronic neurological symptoms included headache (51%), visual deficits (29%), weakness (11%), and facial pain (9%). As expected, larger aneurysms tended to present with neurological symptoms, as the average aneurysm size for these three groups was 1.1, 2.1, and 2.2cm in maximum diameter, respectively. In addition, symptomatic aneurysms tended to be located along the proximal ICA with diameters never smaller than 3mm.

Initial diagnostic imaging in neurological patients includes computed tomography (CT), magnetic resonance imaging (MRI), CT angiography, and MR angiography. The vast majority of unruptured cerebral aneurysms will be identified through these techniques. The exceptions include small aneurysms less than 2-3 mm in size that may escape the resolution of CT and MR based imaging. The use of conventional head CT followed by MRA has been shown to have a sensitivity of 76-98% and specificity of 85-100% in detecting unruptured cerebral aneurysm (89, 91-93). It is worth noting that while digital subtraction angiography remains the gold-standard for aneurysm delineation, this

procedure is invasive, carries small risks, and is being gradually replaced in some situations by improved CTA and MRA technology.

PREVALENCE OF UNRUPTURED ANEURYSMS

The prevalence of unruptured cerebral aneurysms has been estimated to be between 1-6% of the population, depending on the study cited (13, 16, 18, 20, 31, 32, 49, 80). Unfortunately, many of these studies lack data regarding the age of these patients, the size and location of aneurysms, and associated pathological variables. As expected, these investigations are biased by the particular patient population included and medical center at which the study is undertaken. The following are studies that have established our currently accepted prevalence rate of unruptured cerebral aneurysms.

Fox and colleagues reviewed 20 autopsy series including a total of more than 160,000 cases (26). Within these, 1289 unruptured aneurysms were discovered, leading the authors to conclude an occurrence rate of 0.8%. Stehbens et al. published their personal series of 1364 autopsies conducted at one institution and discovered at least one unruptured cerebral aneurysm in 76 patients, resulting in a prevalence rate of 5.6% (80). Stehbens also published a review of the pathological literature that quoted the prevalence of unruptured cerebral aneurysm to be 2.4%, with a range from 0.2 to 9% (81). The authors noted that the number of aneurysms discovered might be influenced by both the experience of the pathologists conducting the autopsy as well as the cerebrovascular case

volume conducted at specific tertiary referral centers. McCormick's series of 7650 autopsies led to a unruptured cerebral aneurysm prevalence rate estimated at 2% (50). Of note, when compared with ruptured aneurysms, unruptured aneurysms tended to be smaller (3.9mm vs. 9.9mm) and occurred in older patients (57.9 years of age vs. 46.3). Romy and colleagues state the prevalence of these lesions to be 1.2%, based on their review of 11,696 autopsies, while Rosenorn et al. estimated this rate to be 0.6% (70, 71). Finally, studies from Japan using cerebral angiography have quoted the prevalence of unruptured cerebral aneurysms to be between 2.5-3.0% (88, 97).

The most comprehensive review regarding the prevalence of unruptured cerebral aneurysms was conducted by Rinkel et al. (69). Not surprisingly, the authors found the rates to depend on study design, as retrospective reports containing over 43,000 autopsies found lesions in 191 patients (0.4%), while prospective data including nearly 5,500 autopsies discovered aneurysms in 197 cases (3.6%). In addition, retrospective review of 2934 cerebral angiograms found lesions in 108 patients (3.7%), while prospective angiographic data including 3751 patients discovered aneurysms in 225 cases (6.0%). The authors conclude that the prevalence of unruptured cerebral aneurysms in the general population, without risk factors such as adult polycystic kidney disease or family history of aneurysmal subarachnoid hemorrhage (aSAH), is approximately 2.0%. Our interpretation of the literature asserts that aneurysms are likely present in about 1% of the adult population, varying between <1% in young adults to 4% in the elderly.

NATURAL HISTORY OF UNRUPTURED CEREBRAL ANEURYSMS

When determining whether to surgically treat an unruptured cerebral aneurysm, one must weigh the natural history of the condition against the risks of operative intervention. The annual risk of rupture of an unruptured cerebral aneurysm has been estimated by several investigations to range from 0.1 to 8% or higher, leading to much controversy regarding the appropriate management of these lesions. The publication of retrospective results from the International Study of Unruptured Intracranial Aneurysms (ISUIA), claiming that the risk of aSAH from aneurysms less than 10mm was drastically lower than previously accepted values (by a factor of 10-20), began a debate favoring observation for the vast majority of small unruptured cerebral aneurysms (1). To this end, we review critical investigations in this area, including the prospective ISUIA (94), the study by Juvela et al. with 18-year follow-up (37), and the comprehensive meta-analysis by Rinkel and colleagues (69).

ISUIA is an ongoing international collaboration of major neurosurgical centers with the goal of further delineating the natural history of unruptured intracranial aneurysms as well as interventional outcomes. Thus far, two landmark papers have been published, having a major impact on the evaluation of this condition. The first study (1), published in the *New England Journal of Medicine,* contained a retrospective component designed to assess the natural history of unruptured intracranial aneurysms. In this analysis the authors reviewed 1449 patients with 1937 aneurysms. These patients were divided into two groups: 727 who had no history of aneurysmal SAH (Group 1), and 722 who had a

history of aneurysmal SAH from a different lesion (Group 2). The mean follow-up duration was 8.3 years. For Group 1, the rate of SAH for aneurysms smaller than 10 mm was 0.05% per year, whereas for aneurysms larger than 10 mm it was approximately 1% per year. For Group 2, the SAH rate was 0.5% for aneurysms smaller than 10 mm and approximately 1% per year for aneurysms larger than 10 mm. These numbers were drastically lower than in the previous estimates. Evaluations of predictors of rupture found that increasing size and location (posterior circulation and PcomA) were significantly associated with rupture for Group 1, whereas location (basilar tip) and increasing age were predictive of rupture for Group 2. Although the large number of aneurysms and the multi-center nature of this study certainly make it an important contribution to the literature, it has a number of serious design flaws. The cohort of patients that made up the retrospective evaluation of the natural history of unruptured intracranial aneurysms was subjected to a very significant selection bias. All patients had already been evaluated for surgery and selected for observation by the participating neurosurgeon. Clearly this is a very different population from that of all patients with unruptured aneurysms. Since these patients had already been selected for conservative management of their lesions, it is likely that they harbored extremely low-risk aneurysms due to location (cavernous carotid aneurysms were identified in Groups 1 and 2 at rates of 16.9 and 9.5%, respectively) or small size (in Groups 1 and 2, 2- to 5-mm aneurysms were identified in 32.7 and 61.2% of patients, respectively). In addition, it is likely that the patients were medically ill, with increased deaths due to other causes removing them from the pool of possible patients with aneurysmal SAH. Moreover, patients whose lesions were originally selected for conservative management by their surgeons may have

later crossed over to surgical treatment because of changes in symptoms or aneurysm size. This crossover would remove patients who were imminently at risk for SAH, possibly lowering the observed rupture rate.

The second study (94), published in *Lancet,* contains a prospective evaluation of the natural history of 2686 unruptured intracranial aneurysms in 1692 patients. In this analysis there were 1077 patients in Group 1 (those with no history of aneurysmal SAH), and 615 patients in Group 2 (those with a history of SAH). The mean follow-up duration was 4.1 years. Calculating the total risk of rupture for patients in both Groups 1 and 2, excluding those with aneurysms in the cavernous ICA, demonstrates that for aneurysms 7 to 12, 13 to 24, and greater than 25 mm in diameter the yearly rupture rates are 1.2, 3.1, and 8.6%, respectively. Unfortunately, the results for aneurysms smaller than 7 mm were presented in a stratified manner and therefore cannot be effectively combined. For patients in Group 2, aneurysms smaller than 7 mm, excluding those in the cavernous ICA, demonstrated a rupture rate of 0.4% per year, whereas for patients in Group 1, lesions smaller than 7 mm, excluding cavernous ICA aneurysms, demonstrated a 0.15% yearly rupture rate. It is important to note that, as observed in the retrospective study, the prospective ISUIA contained selection bias in the population studied. For instance, of the 1692 patients, 534 were switched to a therapeutic intervention (410 surgical, 124 endovascular) and were removed from follow-up. It is not unreasonable to conclude that in at least some significant portion of these crossover patients the management strategy was changed because of either an increase in aneurysm size or the development of new symptoms, both of which have been implicated in large increases in rupture rate.

Therefore, the population studied was not only created with an obvious selection bias, but also underwent a second selection process, by which aneurysms that may have been likely to rupture were removed from the cohort, despite the original intent to treat conservatively. Also of note, 193 patients (11%) died of causes other than aneurysmal SAH; these patients were removed from the analysis. This is a reasonable statistical technique, but it is troubling that 52 of these patients died of intracranial hemorrhage. It is unclear whether there was adequate evaluation to ensure that these intracranial hemorrhages were not due to aneurysms. In short, although the prospective ISUIA data is a useful guideline, some caution is indicated when extrapolating to the population at large.

Rinkel, et al., (69) published an invaluable analysis of the natural history of unruptured intracranial aneurysms in which they performed a thorough review of the literature published between 1955 and 1996. To estimate the prevalence of unruptured aneurysms, data were summed from 23 studies (eight autopsy, 15 angiography) to evaluate 56,304 patients. The overall prevalence of these lesions in adults with no known specific risk factors (autosomal- dominant polycystic kidney disease, family history, atherosclerosis) was 2.3%. The method of aneurysm detection strongly influenced the estimate of prevalence; retrospective autopsy, prospective autopsy, retrospective angiographic, and prospective angiographic studies demonstrated rates of 0.4, 3.6, 3.7, and 6%, respectively. For analysis of the bleeding rate of unruptured intracranial aneurysms, the authors identified nine studies in which a total of 3907 patients were evaluated. The overall risk of rupture was 1.9% per year (0.7% for unruptured aneurysms <10 mm and

4% for intact lesions > 10 mm). It is important to realize that with any meta-analysis the final conclusions are only as good as the quality of the studies that are pooled to generate the data. That being said, the sheer number of patients analyzed and the detailed analysis performed by the authors make this study an important investigation into the natural history of unruptured intracranial aneurysms. Additionally, the results reported by Rinkel and colleagues are strengthened by the fact that their estimates of the prevalence of and incidence of bleeding in unruptured intracranial aneurysms corroborate very closely with the known incidence of aneurysmal SAH.

Juvela and colleagues (37) provide a comprehensive observational cohort study that lacks the inherent bias of surgical selection found in ISUIA, as they examined all patients with unruptured intracranial aneurysms seen at their institution over a given time period. This study was achievable because it was their department policy to manage all unruptured aneurysms conservatively prior to 1979. In addition, Finland's socio-medical structure allowed 100% follow-up to record outcome over a longer period of time (mean 18.1 years) than has been achieved in any other study. A total of 142 patients with 181 unruptured intracranial aneurysms were studied. The cumulative rate of aneurysmal SAH was 10.5% at 10 years, 23% at 20 years, and 30.3% at 30 years after the diagnoses were made. Aneurysm size and patient age (inversely) were significant predictors of aneurysmal SAH, as was active cigarette smoking ($p < 0.05$ for each). Major flaws in this study are the small total number of patients, the homogeneity of the study population (it is debatable whether the Finnish population's natural history can be extrapolated to other populations), and the overwhelming proportion (92%) of patients with previous

aneurysmal SAH (it is unclear whether the natural history of incidental aneurysms is the same as that of secondarily discovered lesions after aneurysmal SAH of another etiology). Despite these major flaws, the lack of a surgical selection bias and the outstanding long-term follow-up ensure this study's equal footing with the ISUIA as far as providing imperfect but valuable data regarding the estimate of bleeding rates for unruptured intracranial aneurysms.

When interpreting the current literature regarding the natural history of unruptured cerebral aneurysms, there are several factors to be considered. For example, studies tend to break down aneurysms into size categories (ex. > or < 10mm). It is highly unlikely that such a cutoff will result in substantially different rupture rates. Rather, it must be understood that these arbitrary boundaries were set up by the investigators simply for ease of data collection, presentation, and comparison. In actuality, the risk of bleeding for unruptured intracranial aneurysms most likely reflects a non-linear continuum of exponentially increasing risk with greater aneurysm size. Additionally, it is important to realize that aneurysms may not be static, but have been demonstrated to undergo growth in a number of studies (8, 37-39, 82). For instance, Juvela, et al. (37-39) found that in 31 of 87 (36%) patients the size of conservatively managed aneurysms grew at least 3 mm over a mean follow-up period of 18.9 years. The relative effect of aneurysm growth on our ability to estimate hemorrhage risk is unknown, but it would be illogical to assume that an 8-mm aneurysm will always stay 8 mm and never become an 11-mm aneurysm, and thereby acquire an increased rupture risk.

Second, any estimation of rupture risk must take into account the aneurysm location. For instance, the results of the ISUIA demonstrate that aneurysms of the PcomA and posterior circulation display a much higher risk of rupture (~2–7 times higher) than those of the middle cerebral artery and ICA. A survey of the literature indicates that posterior circulation, PcomA, and anterior communicating artery aneurysms carry the highest risk of SAH, whereas aneurysms of the cavernous ICA carry an extremely low rupture risk (1, 4, 8, 94).

Last, it has been our experience that there is a very real phenomenon of excessive psychological stress in patients harboring an unruptured intracranial aneurysm. Even when patients fall into a subgroup of minimal or unknown treatment benefit and are appropriately counseled, they often insist on treatment. Although rigorous studies of this issue have yet to be performed, it appears that the psychological stress associated with harboring an unruptured intracranial aneurysm is great enough to cause a patient to forgo the conservative management recommended in the literature for the perceived peace of mind in knowing that a treatment has been exercised (62). Our universal policy is to recommend management based on our experience with thousands of aneurysm patients and according to our best interpretation of the literature. However, there is a subset of patients who insist on an intervention regardless of our recommendation. These patients may be borderline candidates to begin with, and such strong feelings on the patients' part indicating quality of life issues may tilt the risk/benefit analysis toward performing an intervention.

Despite conflicting data in the current literature, we have the following recommendations. The natural history of a given unruptured intracranial aneurysm should be individually assessed for each case, since there are a number of factors that alter predicted rupture rates. For instance, family history, smoking, excessive alcohol consumption, female sex, previous aneurysmal SAH, presence of symptoms attributable to the lesion, aneurysm location, and lesion size have all been demonstrated to predict a worse natural history (12, 20, 38-40, 44, 54, 59, 73, 74, 77). Therefore, all of these factors must be taken into account when evaluating an unruptured intracranial aneurysm. In addition, any risk/benefit analysis of proceeding with intervention must take into account the patient's life expectancy and medical comorbidities. Despite these important concerns, it is helpful to have a general, nonspecific algorithm for predicting rupture risk that may then be adjusted appropriately depending on the aforementioned risk factors.

Of the two ISUIAs, the prospective portion most likely provides the best estimate of the natural history of unruptured intracranial aneurysms. However, the reported selection bias and questionable study design make it highly likely that this paper underestimates the risk of bleeding in some groups of unruptured intracranial aneurysms. The paper by Juvela, et al., is the best designed and executed investigation, but due to its observational nature, it is also subject to significant selection bias, because it has been suggested that the Finnish population has a higher incidence of aneurysmal SAH than the international community. The meta-analysis published by Rinkel et al. minimizes the biases of individual studies through aggregate analysis and evaluates the largest number of

patients. As a result, it provides a very reasonable estimate of rupture risk. Further support for their results is afforded by their close agreement with those of Juvela, et al.

Taking the results of these studies together, our general estimate for the yearly risk of SAH for an unruptured intracranial aneurysm is approximately 1% for lesions 7 to 10 mm in diameter. The risk of rupture grows logarithmically as aneurysm size increases, and likewise diminishes as aneurysm size decreases. Although 7mm is the average size of ruptured aneurysms, and smaller aneurysms have a very small risk of rupture, we generally advocate treatment for aneurysms ≥ 5mm in diameter. These size criteria ensure that 99% of all aneurysms that should be treated will have treatment offered.

SURGICAL TREATMENT OF UNRUPTURED ANEURYSMS

Indications for Surgery

Microsurgical clipping excludes an aneurysm from the parent circulation and offers definitive treatment. In 2004, Britz and colleagues quantified the impact of surgical intervention on survival in unruptured and ruptured cerebral aneurysms (11). By reviewing the clinical course of 4619 patients hospitalized with cerebral aneurysms, the authors found that surgical clipping of unruptured aneurysms was associated with both significantly higher survival estimates (hazard rate of death 30% ($P<0.001$)) and significantly less neurologically related causes of death (5.6% vs. 2.3%, $P<0.001$). While there are no strict guidelines, certain factors may represent indications to undergo

surgical treatment of unruptured cerebral aneurysms. Regardless of aneurysm size, any neurological symptoms attributable to the lesion are generally considered a strong indication for surgery. Moreover, depending on the exact symptoms, many would favor urgent rather than elective treatment. Samejima and collegues questioned 92 aSAH patients regarding their pre-ictal events (75). The authors found that 74% experienced head, eye, or neck pain in the hours leading up to the recognized aneurysmal rupture. Interestingly, many of these patients report these pains as being present for weeks to months prior. A minority of patients also complained of visual, motor, and sensory disturbances during this time period. Radiographic evidence of aneurysm growth should also influence clinicians to consider definitive treatment. Juvela et al. followed 111 unruptured aneurysms for nearly 19 years and found lesion growth to be significantly associated with subsequent rupture ($P<0.001$) (37-39). Compared with aneurysms that did not rupture, those that did had larger mean overall growth (6.3mm vs. 0.8mm) and mean growth rate (0.95mm/year vs. 0.04mm/year). At the time of rupture, aneurysms averaged 11.2mm in diameter, compared with 6.0mm for ones that did not rupture.

Morbidity and Mortality of Surgery

In addition to understanding the natural history of unruptured cerebral aneurysms, implementing a therapeutic paradigm with highly experienced cerebrovascular surgeons designed to offer low-risk treatments is essential to the management of this patient population. While the morbidity and mortality of aneurysm surgery clearly depends on the particular neurosurgeon and medical center being evaluated, several studies have attempted to formulate currently acceptable values. Unfortunately, no consensus has

been reached. As Benderson et al. pointed out in their 2000 review, these values range from 0-7% for death and from 4-15% for complications (7). By comparison, endovascular coiling has been shown to carry complication rates of 0.9-30.0% (6, 15, 17, 21, 25, 27, 33-36, 45, 47, 53, 57, 63, 65, 72, 90, 94)

With the advent of improved technology and operative techniques, the risks associated with unruptured aneurysm surgery have trended down over time (76). In 1983, Wirth et al. retrospectively reviewed the outcomes following unruptured aneurysm treatment at 12 medical centers (95). Excluding those lesions associated with an intracerebral hematoma, arteriovenous malformations, or tumor, the authors compiled 107 incidentally discovered aneurysms and reported 7% permanent morbidity rate and 8% transient morbidity rate following surgery. Further analysis revealed risk of operative morbidity was associated with lesion size and location, with lesions <5mm, 2%; 6-15mm, 7%; 16-24mm, 14%; posterior communicating artery (PcomA), 5%; middle cerebral artery (MCA), 8%; internal carotid artery (ICA), 12%; and anterior communicating artery (AcomA), 16%. Poor outcome occurred more often in patients presenting with ischemic symptoms (11%), as compared to those presenting with headache (6%).

In 1990, Rice et al. reported their series of microsurgery for 179 posterior circulation unruptured aneurysms over a 17-year period (68). The majority of these lesions were asymptomatic (89%), located at the basilar apex (84%), smaller than 12mm (72%), and part of a multiple constellation syndrome (68%). Giant aneurysms were excluded from

the study. The authors report encouraging postoperative morbidity and mortality rates of 3.6 and 0.5%, respectively.

In 1991, Hadeishi and colleagues cited that 18 of 72 (25%) of their patients undergoing unruptured aneurysm surgery experienced neurological deficits (28). The authors note, however, the transient nature of these deficits, as the overwhelming majority of patients (17 of 18), had resolution of their symptoms within two weeks, with only one patient demonstrating persistent dysarthria. In another study by Matsumoto and associates, initial outcomes after treatment of 84 unruptured cerebral aneurysms revealed a relatively high morbidity rate of 13.1% (48). Fortunately, over half of these deficits resolved upon follow-up, dropping the final morbidity rate to 5.9%. Not unexpectedly, the occurrence of postoperative neurological deficits was correlated with the patient's medical comorbidities, increasing aneurysm size, posterior circulation aneurysms, and the presence of multiple lesions.

A 1994 paper from Columbia University documented outcomes after 202 consecutive surgeries for microsurgical clipping of unruptured cerebral aneurysms (78). Overall, minor complications, major complications, and death occurred in 5%, 7%, and 3.5% of patients, respectively. Further cohort analysis, however, showed 100% of patients with lesions smaller than 10mm experienced excellent or good outcomes. In contrast, patients with lesions 11-25mm and >25mm in diameter had similar outcomes in 95% and 79% of cases, respectively, further supporting the notion that aneurysm size is an essential predictor of operative related morbidity and mortality. Of note, 56% of lesions were

symptomatic, and the majority (50%) were located on the ICA. In patients with incidental aneurysms (17%), the mortality rate was 2.9%. During the follow-up period (mean 33 months) there were no documented cases of aSAH, supporting definitive aneurysm obliteration. The same year Dickey et al. published their results treating 44 patients with unruptured aneurysms and relayed a 4.6% procedure-related morbidity rate with no associated deaths (23), while Asari et al. treated 76 unruptured aneurysms and reported 0.0% operative mortality, 7.2% operative morbidity, 15.9% long-term morbidity (3, 4).

Deruty and colleagues published their outcomes in 1996, consisting of elective treatment for 83 unruptured cerebral aneurysms in 62 patients (22). The authors report 1.5% severe morbidity and 3.0% mortality rates, all which were admittedly secondary to either surgical technique or underlying atherosclerotic disease. With this cohort, MCA was the most common aneurysm location (35%), followed by PcomA (22%), ophthalmic artery (12%), ICA (11%), AcomA (11%), and vertebrobasilar (5%). The majority of these aneurysms (58%) were incidental.

In 2003, Ogilvy and colleagues at the Massachusetts General Hospital retrospectively reviewed their series of 604 unruptured aneurysms in an attempt to identify risk factors (58). Mean age of this cohort was 53 years old with an average lesion size of 8.8mm. Aneurysms were located on the ICA (43%), MCA (28%), ACA (17%), and posterior circulation (11%). As expected, the authors found patient age (OR 1.03), aneurysm size (OR 1.13), and location within the posterior circulation (OR 2.90) to be independently

associated with poor outcome or death ($p<0.05$). Overall, the rates of morbidity and mortality for the entire group were 15.9 and 0.8%. Outcome stratification reveals that treatment risk for young patients with small aneurysms (<10mm) is 1-2%, compared to 5 and 15% in elderly patients with large aneurysms of the anterior and posterior circulation, respectively.

Clearly study design may influence results obtained. In 2003, Yashimoto investigated the bias present when estimating the operative risk for unruptured cerebral aneurysms (98). The authors identified 10 type I studies (retrospective studies from a single institution) and 4 type II studies (multicenter or community-based studies). In general, type I studies reported excellent surgical outcome, with mean combined mortality and morbidity of 7.8%, as opposed to a mean combined mortality and morbidity of 20.3% in type II studies. This translated into a relative risk of 2.6 for patients enrolled in type II studies compared with those in type I studies. This paper emphasizes the presence of publication bias in neurosurgery literature, as studies with an excellent surgical outcome are more likely to be published than those with an average outcome. As a result, conclusions based on reviews or meta-analyses may be misleading. The authors suggest generating a community-based prospective registration for all such patients, thereby providing a sampling frame free from publication bias.

The morbidity and mortality of surgery for unruptured cerebral aneurysms was one of the main outcomes assessed in the ISUIA studies (1, 94). The initial cohort studied consisted of 1172 patients, of which 211 had a prior history of SAH from another lesion (1). Many

of these unruptured aneurysms were symptomatic, with 34% having headaches, 14% with cranial nerve deficits, 11% with cerebrovascular ischemic events, 6% with lesion-induced mass effect, and 5% with epilepsy. The authors found age dependent outcomes, as the morbidity and mortality at one-year follow-up for patients younger than 45 to be 6.5%; for those 45-64, 14.4%, and for those older than 64, 32% ($p<0.001$). Surprisingly, 3.1% of the treated patients without prior aSAH died from operative-related complications compared with only 0.9% of those with a history of aSAH. Close inspection, however, reveals that the latter group was on average younger (47 vs. 53-years-old) and harbored smaller aneurysms (27 vs. 51% of lesions >10mm) located more often in the anterior circulation (83.4 vs. 73.6%). It is unclear whether these cohort differences are enough to account for this discrepancy in postsurgical outcomes, particularly since the presence of medical co-morbidities, a known risk factor, was not recorded in ISUIA. The follow-up ISUIA study in 2003 assessed 1591 patients at 7days, discharge, 30 days, and yearly (94). Findings included 1.8% and 12.0% mortality and morbidity at 30 days, and 2.7% and 10.1% mortality and morbidity at 1 year. In this cohort, asymptomatic patients younger than 50 years of age with unruptured aneurysms less than 24mm in diameter located in the anterior circulation had the lowest rates of surgical risk, quoted at 5-6% at 1 year. When interpreting these results against those of other studies, it is important to recognize that both ISUIA studies included major cognitive impairment in their analysis, which was not considered in the vast majority of prior papers.

In 2005, Moroi released their results after treating 549 unruptured aneurysms at the Research Institute for Brain and Blood Vessels (51). Their reported success is

remarkable, with 0.3% mortality and 2.2% morbidity overall. More specifically, for aneurysms less than 10mm their mortality and morbidity was only 0.0 and 0.6%, and for aneurysms greater than 10mm these rates were 1.2 and 6.1%. The authors also divided their outcome by lesion location, with essentially 0% risk for all ACA and MCA aneurysms. ICA aneurysms carried anywhere from a 0% mortality and 1.0% morbidity rate for those less than 5mm, to 12.5% mortality and 25.0% morbidity rate for those greater than 20mm. Vertebrobasilar aneurysms were associated with a 0% mortality and morbidity rate for those lesions less than 5mm and 11.1% morbidity rate for those greater than 5mm.

A meta-analysis of outcomes following unruptured aneurysm surgery was published by Raaymakers and colleagues in 1998, and represents the most comprehensive review to date (64). The authors of this paper reported 2.6% mortality and 10.9% morbidity rates in 2460 patients, substantially higher than those quoted in a prior meta-analysis by King et al (42). In general, complications tended to be serious, with half of affected individuals becoming dependent on others for their activities of daily living. Mortality rates varied substantially, with 62% of studies reporting no deaths, while other studies demonstrated death rates as high as 29%. As a general trend, mortality rates were lower in more recent studies and those with a greater proportion of anterior circulation lesions. Giant aneurysm surgery carried a poor prognosis regardless of publication year. Specifically, the authors found the following mortality and morbidity rates: giant posterior circulation aneurysms (9.6 and 37.9%); giant anterior circulation aneurysms (7.4 and 26.9%); non-giant posterior circulation aneurysms (3.0 and 12.9%); and non-

giant anterior circulation aneurysms (0.8 and 1.9%). When comparing the findings of these studies it is important to note that the earlier report by King et al. excluded symptomatic lesions, which tend to carry a worse prognosis. Moreover, the cohort of lesions reviewed by King et al. contained a higher proportion of small aneurysms located in the anterior circulation, which are technically less demanding to obliterate.

Underlying atherosclerotic disease may have adverse effects on outcome following clipping of unruptured aneurysms, particularly in patients with ischemic lesions and calcified vessel walls. In one study, Ohno and colleagues found a 50% complication rate after treating such patients (60), while Asari et al experienced a morbidity rate of 25% (3). These papers argue against operative intervention in those individuals with ipsilateral CT-demonstrated ischemic lesions, as vessel manipulation and clip application in this patient population may be prone to generate emboli.

Neurocognitive Decline

Neurocognitive decline likely represents a subclinical form of procedure-related morbidity of aneurysm surgery. Hillis et al. performed detailed cognitive evaluation in 12 patients with unruptured cerebral aneurysms, both before and after surgery (30). Fortunately, the authors noted differences in only a few test items that were of questionable significance. In 2003, Ohue et al. demonstrated the importance of neuropsychological evaluation after surgery in patients with unruptured cerebral aneurysms (61). The authors reviewed 43 patients who underwent neurospych testing before and after craniotomy for UIA treatment. Although all patients had "good"

outcome according to the GOS, 17/43 (40%) had significant deterioration in cognitive function one month after surgery. Upon follow-up six months later, six had completely recovered, five partially recovered, and three did not recover. Risk factors for cognitive deterioration were age greater than 65, AcomA aneurysm, an interhemispheric approach, and the presence of systemic comorbidities.

In 2005, Kim et al. investigated the utility of various outcomes measures by comparing six instruments (Rankin, GOS, Barthel Index, NIHSS, SF-36, and MMSE) at 3 and 12 months in 520 patients who underwent craniotomy for ruptured and unruptured aneurysms (41). Results revealed that correlation between scores were poor (0.15 when the GOS was compared with the MMSE and 0.27 when compared with the SF-36) and many patients given the highest GOS or Rankin scores showed significant cognitive deficits. These findings emphasize the importance of incorporating cognitive outcome measures when accurately estimating the morbidity and mortality of aneurysm surgery.

Regionalization of Aneurysm Management

Several studies have investigated the role of regionalization in aneurysm management. In 1996, Solomon et al. found an inverse relationship between the volume of craniotomies for aneurysm clipping performed and in-hospital mortality rates (79). The authors reviewed 47,408 patients reported in the New York State database during an eight-year period. The data demonstrated a 43% decrease in mortality rate in hospitals performing at least 30 craniotomies for aneurysm clipping per year versus lower volume hospitals (4.6% versus 8.1% mortality, respectively). Divided by case volume, there was 12%

mortality in hospitals performing <6 craniotomies/year, 11% mortality in hospitals performing 6-10 craniotomies/year, 7% mortality in hospitals performing 11-20 craniotomies/year, 5% mortality in hospitals performing 21-30 craniotomies/year, 6% mortality in hospitals performing 31-100 craniotomies/year, and only 3% mortality in hospitals performing >100 craniotomies/year. Overall, there appears to be an inflection point at 30 aneurysm operations per year where the morbidity and mortality rates change substantially between hospitals. In addition, one must consider that complex and technically challenging aneurysms are usually referred to tertiary, high-volume medical centers, while straightforward cases are treated at low-volume hospitals.

Although the majority of high volume hospitals are academic medical centers, concern exists regarding the impact of resident education on outcome during technically difficult cases. In 1997, however, Taylor showed that surgery-related mortality was significantly lower (16.3%) in teaching hospitals than in non-teaching ones (23.1%) with equal operative volume (83). In 2001, Johnston and colleagues utilized the California state database to review the outcomes following surgery for unruptured cerebral aneurysms in 1321 patients (36). The data revealed that adverse events, including death or discharge to a nursing home or rehabilitation hospitals, occurred significantly more often at low-volume hospitals. More specifically, in-hospital death was 2.5 times more likely at non-tertiary care medical centers. The same year, Chyatte et al. at the Cleveland Clinic demonstrated that the number aneurysms treated by a specific surgeon is a strong predictor of better functional outcome ($r=0.99$, $P=0.05$) by reviewing the clinical course of 449 aneurysms treated by 10 different surgeons (14). In support of other studies, the

authors also found increasing patient age (r=0.16, P=0.003) and aneurysm size (r=0.15, P=0.004) to be associated with worse functional outcome. Barker and colleagues also investigated the in-hospital mortality and morbidity of 3498 patients with unruptured intracranial aneurysms treated at 463 hospitals by 585 surgeons (5). The authors found that compared to high-volume hospitals (>20cases/yr), low-volume hospitals (<4cases/yr) discharged less patients to home, 76.2% vs. 84.4%, and had higher mortality rates, 2.2% vs. 1.6%. In 2003, Berman and colleagues (9) reviewed the treatment of 2200 unruptured cerebral aneurysms with an overall mortality and morbidity rate of 2.5 and 21.3%, respectively, and found hospital volume to be associated with less operative risk (OR morbidity 0.89, P<0.0001 and OR mortality 0.94, P<0.002 for each 10 additional cases/year). In contrast, Naso and partners demonstrated the highest level of care may also be available at low-volume cerebral aneurysm practices (56). Their group achieved results comparable with the best published data, citing a morbidity rate of 7.7% and mortality rate of 3.8%, despite only treating approximately eight unruptured cerebral aneurysms per year.

Rates of Recurrence

Microsurgical aneurysm clipping has been demonstrated to provide definitive long-term treatment of cerebral aneurysms. Spetzler and colleagues reviewed 160 surgically managed aneurysm that underwent late angiographic follow-up (mean 4.4 years postoperatively) and found only 1.5% of initially obliterated lesions exhibited recurrence (19). In aneurysms with known residua, 25% enlarged on follow-up imaging. Eight new lesions developed in six patients. This translates into a 0.52% annual regrowth rate for

completely clipped aneurysms and a 1.8% annual rate of de novo aneurysm formation. Not unexpectedly, patients with multiple lesions were found to be at higher risk for de novo aneurysms. Tsutsumi et al. have also investigated this topic. In 1999 they published their data after following 115 patients with surgically treated unruptured aneurysm for an average of 8.8 years (87). Although four patients suffered aSAH, only one patient bled from regrowth of a successfully clipped aneurysm, leading to a 0.10% annual regrowth rate for completely clipped aneurysms and a 0.20% annual rate of de novo aneurysm formation. In 2001 the same authors published their data after following 140 patients with surgically treated aneurysms (88 ruptured, 52 unruptured) for an average of 9.3 years and found a 0.26% annual regrowth rate for completely clipped aneurysms and a 0.89% annual rate of de novo aneurysm formation (86). In 2004 Akyuz and colleagues (2) demonstrated a 99.4% aneurysm cure rate after open surgery, as they reviewed 166 cases with late angiography (mean 47 months post-operative). Of the 159 aneurysms confirmed to be totally occluded on immediate postoperative angiogram, 158 remained obliterated on follow-up imaging. Boet et al. further supported the efficacy of clipping in 2005 by reporting a 0% recurrence rate of paraclinoid/ophthalmic aneurysms after open surgery versus 53% following endovascular treatment (10).

In contrast, the recurrence rate of coiled aneurysms has been reported to be much higher. In 2002, Ng et al. quoted a 23% recanalization rate in 30 coiled aneurysms with one-year angiographic follow-up (57). That same year, Thorton et al. obtained angiographic one-year follow-up on 143 coiled aneurysms and documented a 1.8% recanalization rate for completely occluded aneurysms and a 28% recanalization rate for incompletely occluded

ones (84). In 2003, Raymond et al. cited a 33.6% recanalization rate in 383 coiled aneurysms with 12.3 month mean angiographic follow-up (67).

Most recently, Vinuela et al. reported their 11 years' experience with embolization of cerebral aneurysms using GDC technology (52). After analyzing 6 and 12-month angiographic follow-up images for 916 coiled aneurysms, the authors demonstrated a 20.9% overall recanalization rate. The patients were divided into two groups: Group A included their initial 5 years' experience with 230 patients harboring 251 aneurysms and Group B included the later 6 years' experience with 588 patients harboring 665 aneurysms. Complete occlusion was obtained in only 55% of aneurysms, with neck remnants present in 35.4% of lesions. Complications occurred in 9.4% of cases. The results reveal both a higher complete embolization rate and lower recanalization rate in Group B patients as compared to those in Group A (56.8 and 17.2% vs. 50.2% and 26.1%, respectively), likely a reflection of improved technique, greater experience, and advanced GDC technology. Of note, recanalization was related to the size of the dome and neck of the aneurysm. In small aneurysms (4-10mm) with small necks (< 4mm) the overall recanalization rate was only 5.1%. In contrast, for small aneurysms with wide necks (>4mm) the overall recanalization rate was 20%. Moreover, among large aneurysms (11-25mm) and giant aneurysms (>25mm) the overall recanalization rate was 35% and 59.1%, respectively. These data strongly suggest that while clinical and post-embolization outcomes in patients treated with the GDC system have improved over time, larger lesions with wider necks continue to carry a high risk for recanalization.

CONCLUSIONS AND RECOMMENDATIONS

In 2000, the Stroke Council of the American Heart Association issued a scientific statement with the following recommendations for the management of unruptured intracranial aneurysms (7): "In consideration of the apparent low risk of hemorrhage from incidental small (<10 mm) aneurysms in patients without previous SAH, treatment rather than observation cannot be generally advocated." This statement is now clearly antiquated, and it is time for a new consensus committee to issue updated recommendations. The most conclusive data regarding the natural history of unruptured intracranial aneurysms is from ISUIA (1, 94) and Juvela's Helsinki experience (37). Vinuela's experience with aneurysm regrowth after coil embolization gives important insight for comparison to the relative permanence of surgical clipping (39). Raaymaker's meta-analysis of the literature on surgical morbidity for clipping of unruptured aneurysms (64) compares almost exactly with our own published data (56) and ongoing experience. These published data sets and our own experience, provide an invaluable although imperfect framework for the following structured guidelines:

1) With rare exceptions, all symptomatic unruptured aneurysms should be treated. Extensive medical comorbidity, advanced age, and anatomic configuration of the aneurysm may contraindicate intervention when treatment risks approach 25%.

2) Small, incidental aneurysms less than 5mm should be managed conservatively in virtually all cases. An important exception to this rule involves those young patients with severe psychological disturbances secondary to harboring an unruptured aneurysm. In such patients, particularly those psychologically crippled by their condition, definitive treatment can be justified and is often pursued.

3) Aneurysms greater than 5mm in patients less than 60 years of age should be offered treatment unless there is a significant contraindication. Although 7mm was the cut-off in the ISUIA data, there are limitations to using such an exact measurement, particularly since this study was limited by selection bias. Certainly aneurysms less than 7mm in diameter are known to infrequently rupture. The accuracy of measurement, even with angiographic data, is at least ± 2mm. Therefore, if 7mm is used as a cutoff, some aneurysms will not be treated that should be treated. Rather, we suggest using a standard error of measurement below this cut-off, so that the 99% of patients at risk for rupture are offered treatment. When managing older patients (>60 years of age) the decision to treat becomes less clear. In these situations, lesion location plays a critical role, as AcomA, PcomA, and basilar apex aneurysms carry higher rupture risk than aneurysms in other locations. Thus, we strongly advocate treatment of such lesions, even in older healthy individuals, since there is low associated treatment morbidity.

4) Large, incidental aneurysms greater than 10mm should treated in all healthy patients less than 70 years of age. The indications are less compelling in older individuals.

5) Microsurgical clipping rather than endovascular coiling should be the first choice in low-risk cases (young patients with small, anterior circulation aneurysms). In these cases, the risk of open microsurgery and endovascular surgery is about the same in terms of stroke and death, although endovascular coiling is definitely less invasive. On the other hand, surgical clipping provides a repair that is at least an order of magnitude more durable than coiling. In cases where the invasion of clipping and the 6 weeks of recuperation do not pose an undo risk or hardship, clipping is a better option.

Very large and giant aneurysms, and aneurysms with high neck to dome ratios, will generally benefit more from surgical approaches than from endovascular treatment. In the most complex aneurysms, combined approaches such as arterial bypass techniques followed by proximal endovascular occlusion, have proved invaluable.

Endovascular coiling represents a reasonable alternative that should be instituted whenever open surgical intervention carries high risk such as with elderly or medically ill patients and in anatomically unfavorable situations (ex. posterior projecting basilar apex aneurysm). The improvement in stent and coil technology offers an excellent alternative in this group of poor surgical candidates, even in those aneurysms with wide necks and unfavorable neck/dome ratios.

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