Surgery of Unruptured, Asymptomatic Aneurysms: a Decision Analysis

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ABSTRACT: ***Background:*** Asymptomatic cerebral aneurysms are diagnosed more frequently since the advent of computed tomography and magnetic resonance imaging. Their management is currently empirical. We have used decision analysis to place it on a more analytical basis. ***Methods:*** Decision analysis was used to determine the benefit in years of survival free of sequelae resulting from elective surgery of unruptured aneurysms over natural history. We took 2% as the annual rate of rupture (r), 73% as the risk of death or disability with rupture (M), and 6.5% for the average risk of elective surgery (S). Benefit was calculated from the equation L{[1-(1-r)L]M/2-S} [1] for life expectancy (L) corresponding to each quinquennial age group from age 15 to 100 years. Sensitivity analysis was performed to take into account increasing risk of elective surgery based on the size, and accessibility of the aneurysm, and variable risks of rupture and outcome. ***Results:*** A gain of at least one year of survival free of neurological sequelae is achieved by surgery compared to natural history for patients whose life expectancy is 19.5 years, corresponding to age 63.5 years for males and 68 years for females. The life expectancy at which a benefit accrues is longer (the patient is younger) for larger, less accessible aneurysms, for lower rates of rupture, and for lesser risks of death or disability from rupture. ***Conclusions:*** Elective surgery of unruptured asymptomatic aneurysms achieves an increased survival over the natural history of at least one year free of neurological sequelae in patients whose life expectancy is 19.5 years or more, using our baseline assumptions. Using equation [1], the corresponding life expectancy producing this benefit can be calculated to account for the increased surgical risk of large, poorly accessible aneurysms and for factors affecting natural history.

RÉSUMÉ: Chirurgie des anévrismes non rupturés, asymptomatiques: une analyse décisionnelle. ***Objectif:*** L'anévrisme cérébral asymptomatique est diagnostiqué plus fréquemment depuis l'avènement de la tomodensitométrie et de l'imagerie par résonance magnétique. Actuellement, la conduite à tenir dans ces cas est empirique. Nous avons utilisé l'analyse décisionnelle pour la placer sur une base plus analytique. ***Méthodes:*** Nous avons utilisé l'analyse décisionnelle pour déterminer le bénéfice en terme d'années de survie sans séquelle résultant d'une chirurgie élective versus l'histoire naturelle d'un anévrisme non rupturé. Nous avons utilisé 2% comme étant le taux annuel de rupture (r), 73% comme étant le risque de mortalité ou de morbidité lors de rupture (M) et 6.5% comme étant le risque moyen de la chirurgie élective (S). Le bénéfice a été calculé au moyen de l'équation L{[1-(1-r)L]M/2-S} [1] pour l'espérance de vie (L) correspondant à chaque groupe d'âge par quinquennat, de 15 à 100 ans. L'analyse de sensibilité a été réalisée en tenant compte du risque relié à la chirurgie élective selon la taille et l'accessibilité de l'anévrisme, les risques de rupture et l'issue clinique. ***Résultats:*** La chirurgie procure un gain d'au moins un an de survie sans séquelle neurologique lorsque comparée à l'histoire naturelle des patients dont l'espérance de vie est de 19.5 ans, correspondant à l'âge de 63.5 ans pour les hommes et 68 ans pour les femmes. L'espérance de vie pour laquelle il existe un bénéfice est plus longue (le patient est plus jeune) pour les anévrismes qui sont plus gros et moins accessibles, pour ceux qui ont des taux plus bas de rupture et des risques moindres de mortalité ou de morbidité reliés à la rupture. ***Conclusions:*** Compte tenu des assomptions que nous avons utilisées, la chirurgie élective des anévrismes asymptomatiques non rupturés augmente la survie sans séquelle neurologique d'au moins un an, par rapport à l'évolution naturelle de la maladie, chez les patients dont l'espérance de vie est de 19.5 ans ou plus. L'espérance de vie procurant ce bénéfice peut être calculée au moyen de l'équation [1], en tenant compte du risque chirurgical plus important des gros anévrismes qui sont peu accessibles et des facteurs modifiant l'évolution naturelle de la maladie.

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Small unruptured cerebral aneurysms are a common autopsy finding.[1] Above a threshold size of 5 mm, corresponding to 6-7 mm on angiography when the aneurysm is submitted to arterial pressure, the frequency of rupture increases with increasing size, according to Laplace's law which relates the tensile stresses on the wall of a sphere to its diameter.[1] The rupture of a cerebral aneurysm produces death or disability in 64-82% cases, but unruptured aneurysms can usually be treated with little morbidity and mortality.[2,3] With the advent of high resolution CT, and MRI and angiography, unruptured aneurysms are frequently discovered during the investigation of unrelated complaints. Unruptured aneurysms can also be discovered if they exert

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pressure on surrounding neural structures such as the IIIrd cranial nerve, and may be present in up to 20% of patients undergoing angiographic evaluation of subarachnoid hemorrhage produced by another aneurysm.[4,5] The management of unruptured aneurysms has largely been empirical. We have performed a decision analysis to place management on a more analytical footing.

Methods

The decision analysis was performed using the model of Levey et al. which considers age and life-expectancy, the annual and life-time risks of rupture and its complications, and surgical risk.[6] We have performed a baseline analysis using what we feel are the most likely assumptions for these parameters, as well as a sensitivity analysis incorporating a wider range of values (Table). A decision tree incorporating these baseline values is presented in Figure 1. The analysis was performed for each quinquennial age group from age 15 to 100 years using the corresponding life-expectancy obtained from current actuarial tables for North American males and females.[7] The baseline probability of rupture (r) of an asymptomatic aneurysm was taken as 2% per annum.[6] An annual risk of rupture of 1% and 4% was also analyzed. The baseline probability that the rupture of an aneurysm will produce death or disability (M) was taken as the average of the population-based studies of Pakarinen and Phillips et al., producing a value of 72.67%.[8,9] This is roughly midway between the estimated risk of death or disability of a ruptured aneurysm of 64-82% estimated by Drake and Kassel.[2,3] These two extremes were also analyzed. The baseline risk of surgery (S) was taken as 6.5% according to the multicentre study of Wirth et al.[10] As they found that the lowest risk associated with the most amenable aneurysm was 2.3% and the highest risk for more complex aneurysm was 16.8% these two values were also analyzed.

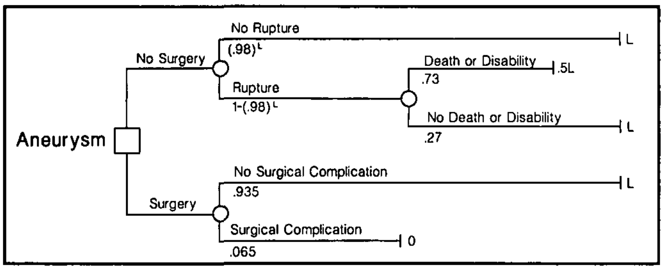


Figure 1: A decision tree and probabilities associated with natural history (no surgery) or surgery. In the upper limb if surgery is withheld the aneurysm may not rupture. The probability that the aneurysm would not rupture is 0.98^L where L is the patient's life expectancy. If the aneurysm does rupture this is expected to occur, on average, when half the life expectancy has elapsed (0.5L) and this will produce death or disability in 73% of cases. The other 27% of patients will survive to have their aneurysm treated and be discharged from hospital in good neurological condition. The bottom limb illustrates the possible outcomes when surgery is chosen. In the overwhelming majority of cases (93.5%) surgery will be uneventful. However in 6.5% surgery will result in a significant complication, usually a deficit rather than a death.

Equations

The lifetime risk of rupture (R) is given by the equation

$$1-(1-r)^L \qquad [1]$$

where "r" is the annual risk of rupture and "L" is the life expectancy. The lifetime risk of death or disability is given by the equation

$$R \bullet M \qquad [2]$$

From equation 2 the expected number of years of survival without neurological sequelae for a non-operated patient (natural history) is given by equation

$$L[1-(R \bullet M/2)] \qquad [3]$$

The denominator 2 is used because it is assumed that the annual rate of rupture is constant over the patient's life-expectancy so that rupture will occur, on the average, when half of the life-expectancy has expired if "r" is small.[6,11]

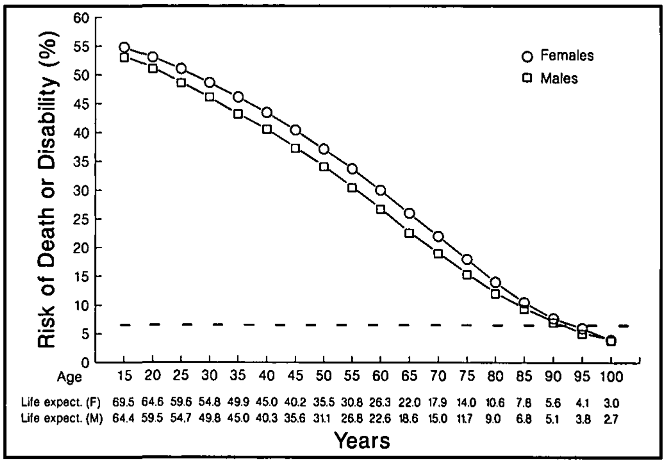
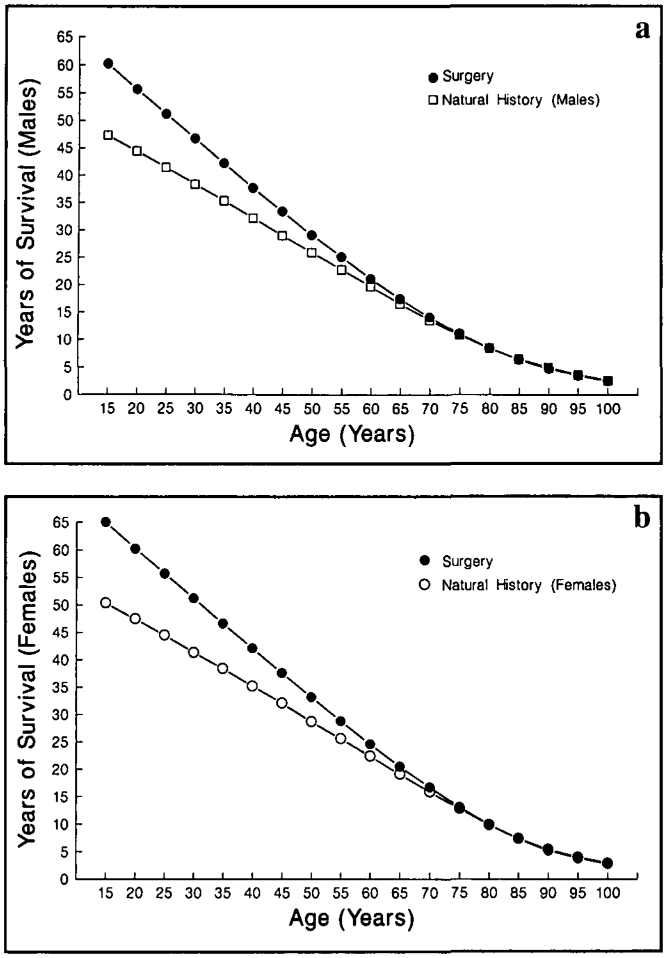


Figure 2: The percent risk of death or disability with each choice, non-intervention (natural history) and surgery, is plotted for each quinquennial age group and corresponding female and male (F & M) life expectancies (life expect). The risk of surgery (—) is constant at 6.5%. With longer life expectancy (younger age) there is a progressively greater risk with non-intervention.

Table

Variable	Symbol	Baseline Assumption	Range Studied	References
Annual probability of aneurysm rupture	r	.02	.01 - .04	1, 20, 26, 29-32
Probability of death or disability with rupture	M	.73	.62 - .82	2, 3, 8, 9
Risk of surgery	S	.065	.023 - .168	10, 17-24, 27, 29, 33, 36-38
Lifetime risk of rupture	R	$R = 1 - (1-r)^L$		
Life expectancy	L			7



Figures 3a and 3b: These tables illustrate the number of years of expected survival free of sequelae associated with non-intervention (natural history) and surgery for each quinquennial age group. Surgery equals the natural history at a life expectancy of 9 years, corresponding to age 80 in males and approximately age 82 in females. Surgery is associated with progressively greater benefit in numbers of years of survival free of neurological sequelae with longer life expectancy (younger age).

Similarly, the expected number of years of survival free of neurological sequelae associated with surgery is given by

$$L(1\text{-}S) \qquad [4]$$

Combining equations 3 and 4 the net benefit of surgery over natural history, in years of survival free of neurological sequelae, is given by the equation

$$L[(R \bullet M/2)-S] \qquad [5]$$

Results

Baseline Assumptions

Figure 2 expresses in percentage the risk of death or disability derived from equation 2 produced by a cerebral aneurysm. As expected the risk increases with increasing life-expectancy (younger age).

Figure 3 compares the number of years of survival expected with each choice (natural history or surgery) for both sexes. The outcome of surgery is equal to natural history at a life expectancy of 9 years, corresponding to approximately age 82 for females and age 80 for males. The benefit in terms of years gained with surgery is expressed in Figure 4, derived from equation [5], and reveals that a net benefit of one year of survival free of neurological sequelae is achieved at a life-expectancy of 19.5 years, corresponding to age 63.5 years in males and 68 years in females. With longer life-expectancy and younger age greater benefit accrues.

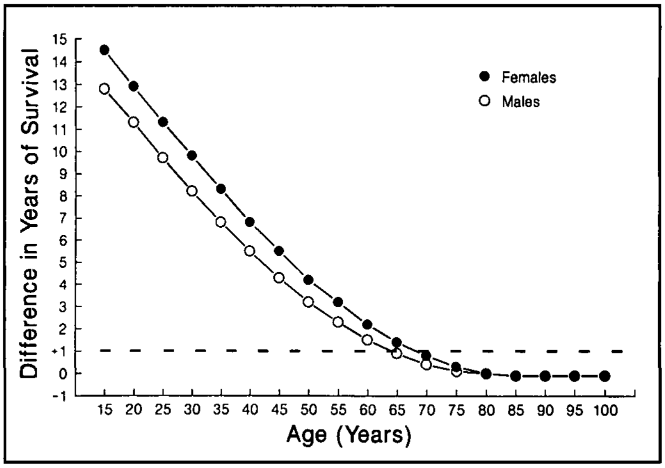


Figure 4: The difference between the survival curves for non-intervention (natural history) and surgery illustrated in Figure 3 are plotted for each age group. A net benefit of at least one year of survival free of neurological sequelae (—) results from intervention at a life expectancy of 19.5 years, corresponding to age 63.5 years in males and 68 years in females. With longer life expectancy (younger age) there is greater benefit with intervention as is seen in our illustrative case (see text) where the average 40-year-old male can expect to live 5.4 years longer if he chooses surgery than if he chooses non-intervention.

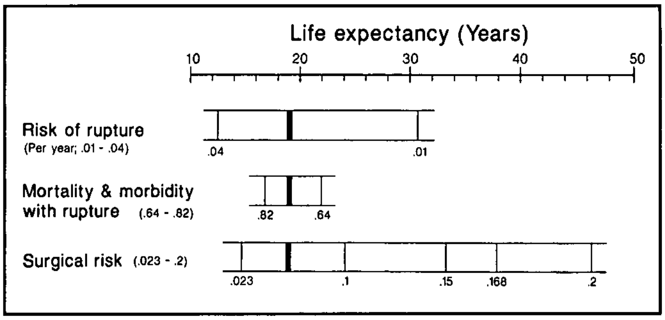


Figure 5: Sensitivity analysis relating the life expectancy at which intervention produces a net benefit of one year free of neurological sequelae over natural history for a wide variety of assumed values for risk of rupture and its associated mortality and morbidity and for the risk of surgical complication. The bold line corresponding to life expectancy of 19.5 years represents the result of our analysis using what we feel are the most likely values for each parameter.

Sensitivity analysis

Figure 5 illustrates the life-expectancy at which one year of survival free of sequelae is achieved with intervention for a variety of values for each parameter. Thus a net benefit of one year is only achieved at a life-expectancy of 31 years if the annual rate of rupture is 1% but is achieved at 12.5 years if it is 4%. Similarly, a mortality and morbidity rate of 64% associated with aneurysm rupture produces a net one year benefit at a life-expectancy of approximately 21.5 years while a rate of 82% produces a similar

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benefit for life expectancy of 17.5 years. A one year benefit is achieved at a life-expectancy of 14.7 years if the surgical complication rate is 2.3% but a life-expectancy of 38 years is necessary to obtain a similar benefit if the surgical complication risk is 16.8%.

Illustrative Case

The application of this model of decision analysis can be illustrated with the following case recently seen at our institution. The patient was a 40-year-old male with a 1 cm, unruptured aneurysm of the left internal carotid artery at the origin of the left ophthalmic artery discovered during investigation of a ruptured, giant, right ophthalmic artery aneurysm which was clipped acutely at the time of rupture. The annual risk of rupture of the left ophthalmic artery aneurysm (r) is taken as 0.02 while his life expectancy (L) is taken, from the ordinate of Figure 2, as 40 years.

The lifetime risk of rupture (R), from equation [1], is calculated as follows:

$$R = 1-(1-r)^L$$

$$= 1-(0.98)^{40}$$

$$= .55$$

The lifetime risk that rupture would produce death or disability (M, taken as 0.73) is given by equation [2]:

$$R \bullet M = 0.55 \times 0.73 = 0.4$$

The expected number of years of survival free of sequelae if surgery is not performed (natural history) is given by equation [3]:

$$L[1-(R \bullet M/2)]$$

$$40[1-0.2] = 32 \text{ years}$$

Thus, from equation [3] the average 40-year-old male with an unruptured aneurysm, using our baseline assumptions, sees his life expectancy free of sequelae drop from 40 to 32 years.

From equation [4] the number of years of survival free of sequelae if the patient undergoes surgery, with the risk of surgery (S) taken as 0.065 is:

$$L\ (1-S)$$

$$40\ (1-0.065) = 37.4 \text{ years}$$

Subtracting the results of equation [4] from equation [3] the net benefit of surgery is:

$$\text{Net benefit (years)} = 37.4 \text{ years} - 32 \text{ years} = 5.4 \text{ years}$$

This result can be achieved directly from equation [5]:

$$\text{Net benefit (years)} = L[(R \bullet M/2-S]$$

$$= 40[0.2 - 0.065] = 5.4 \text{ years.}$$

Discussion

Decision analysis

Decision analysis has been applied to the management of unruptured familial and sporadic aneurysms, to the management of cerebral aneurysms in the setting of myocardial infarction and in the post-partum state, and to cerebral angiographic screening of patients with adult polycystic kidney disease.[6,11-16] Various models with different assumptions have been used. We prefer the model of Levey et al. for its simplicity and for its concrete end point expressed as a net gain (or loss) in years of survival free of neurological sequelae.[6] We did not assign a different weight to death or significant neurological disability, considering either as equally undesirable for the purposes of our analysis. Such a weighing would bias our analysis in favour of surgery, as the most common outcome of aneurysmal rupture is death while the most frequent complication of elective surgery of unruptured aneurysms is neurological disability: King et al. in a Meta-analysis of 733 patients reported in 28 studies of elective surgery of unruptured aneurysms identified 7 deaths (1%) and 30 neurological deficits (4%).[17] Thus the overwhelming benefit of elective surgery of unruptured aneurysms is to prevent premature death.

We feel that our baseline values are representative of the usual case in that the population-based estimation of the mortality and morbidity produced by aneurysmal rupture that we used is also at the mid-point of two estimates based on a review of the literature.[2,3,8,9] The surgical complication rate that we used is the one observed in a large multicentre study on the treatment of unruptured aneurysms of all sizes and is probably more representative than the very low complication rate reported by highly specialized centres.[10,18-24] However, whatever values are assigned to individual parameters in equation [5], this equation allows an individual physician to determine the net benefit of surgery for a specific patient based on his or her own understanding of the rate of rupture and its attendant mortality and morbidity, and of the risk of surgery in his or her hands, using only the simplest of hand-held calculators. Other decision analysis models addressing this question are computationally quite complex, require specialized computer software, and singular computer literacy.

Age and aneurysmal rupture

The probability that an aneurysm will rupture is a function of time. The Cooperative Study found that 1.5% of ruptured aneurysms had ruptured by age 19, 5.8% by age 29, and 17.7% by age 39.[5] Similar findings were reported by McCormick and Acosta-Rua who observed that only 7.4% of aneurysms destined to rupture had done so by age 29, but 22% had ruptured by age 39.[1] Thus, the risk of aneurysm rupture before age 30 is small (5.8-7.4%) but by age 40 approximately 20% of aneurysms destined to rupture will have done so. As the risk of rupture before the age of 30 (5.8-7.4%) approaches the risk of surgery (6.5%) it would seem advisable to operate in males aged 30 to 63 years and in females aged 30 to 68 years to achieve the benefit identified in our study. Familial aneurysms appear to rupture at a younger age than sporadic ones.[25] Few familial aneurysms rupture before the age of 20 years but by the age of 30 years fully one-quarter of familial aneurysms that are destined to rupture will have done so.[25] Thus, patients with an unruptured familial aneurysm should be considered for surgery even if they are only in their third decade.[11] It is to be noted, however, that familial aneurysms may carry a higher surgical risk than sporadic ones.[10]

Risk of rupture

This value is a very sensitive determinant in our study. The risk of rupture of an intact aneurysm approximates 2% per year. Mount and Brisman, in a review of 4 studies, found a 10% rupture rate with 40% fatality over 5 years.[20] Moyes found a 27.6% rupture rate over a period of 1-10 years, and Winn estimated a bleeding rate of 1% to 2.2% per annum.[21,26] Heiskanen initially found a rupture rate of 11.5% with 57% fatality over 10 years.[27] However, continued observation of his patients over the subsequent 10 years indicated an increasing risk of rupture with the passage of time.[28] The persistent risk of aneurysmal rupture has been stressed by Mount who observed that a patient is never free of this risk; one of his patients died of a subarachnoid hemorrhage (SAH) 23 years after discovery of his aneurysms.[20] The risk of rupture is proportional, according to Laplace's law, to the size of the aneurysm. Thus McCormick and Acosta-Rua, in a study of 136 aneurysm cases from 1673 consecutive autopsies found that only 3% of aneurysms 5 mm or smaller had ruptured, but 41%, 87% and 94% of aneurysms 6-10 mm, 11-15 mm and 16 mm or larger had done so.[1] A review of 130 patients with initially unruptured aneurysms followed for an average of 8.3 years found that rupture occurred only in patients whose aneurysm was 10 mm or more.[28] However, Kassell et al. observed that the median diameter of ruptured aneurysms is 7 mm, that 71% are smaller than 10 mm, and that 13% are smaller than 5 mm.[29] In interpreting these data it must be remembered that aneurysms may appear larger on angiography prior to rupture than they do once rupture has occurred.[30] Further, it has been observed that initially unruptured aneurysms as small as 3 mm on angiography have subsequently ruptured.[32] Finally, as familial aneurysms seem to rupture at a smaller size, especially in females, than do sporadic ones,[25] a familial history may militate in favour of treating unruptured aneurysms even if they are 5 mm or smaller. A history of arterial hypertension was present in up to half of patients dying from a ruptured aneurysm studied by Sacco et al., and cardiac hypertrophy was present in 69% of these.[33] Further, a history of pre-existing arterial hypertension is associated with a more severe SAH, poorer grade at admission, and higher mortality. Weibers et al. found that half of untreated, initially unruptured aneurysms that eventually ruptured were in patients with arterial hypertension.[28] Thus the presence of hypertension may unfavourably affect natural history as reflected in equation [2] by increasing the risk of rupture (R) or of its effect (M). There may, therefore, be a further incentive to treat unruptured aneurysms in hypertensive patients. However, the presence of arterial hypertension and of other risk factors for SAH, such as the use of anovulants, the chronic use of alcohol, and cigarette smoking[34] is difficult to incorporate in our model because there are no quantitated data on how these factors might affect risk of rupture, outcome of rupture or life expectancy.

Outcome of aneurysmal rupture

Drake and Kassel have estimated that a ruptured aneurysm produces death or neurological disability in 64-82% of cases.[2,3] Phillips et al. and Pakarinen in population-based studies observed values roughly midway between these two extremes.[8,9] A recent study by Edner et al. of the overall outcome of aneurysmal SAH in a defined population admitted to the single, designated regional neurosurgical unit found a good outcome, based on the Glasgow Outcome Scale, in 46% of patients 12 months after hemorrhage.[35] Using their value of 54% for the risk of death or poor outcome a 1 year benefit of surgery is achieved for patients with life-expectancy of 25 years, as opposed to 19.5 using our baseline estimate. It is important to note, however, that the good outcome group in Edner et al. included patients with moderate disability and that 63% hospital admissions occurred within the first 24 hours after hemorrhage. Thus, the outcomes reported by Edner et al. may not reflect the situation in most communities where transfer to an expert centre may not occur or may be delayed longer than 24 hours, more patients dying or suffering neurological disability in the interval.

Risk of surgery

The risk of surgery is a major determinant in our study. Surgery of unruptured, non-giant aneurysms can be accomplished with little mortality and infrequent morbidity while withholding surgery can result in death or disability in a significant proportion of patients. The treatment of intact aneurysms is safer than ruptured aneurysms because the sac is usually resilient and, in the absence of subarachnoid clot or inflammatory response, its dissection is easy.[18] Wirth et al. observed a 6.5% risk of elective surgery of unruptured aneurysms smaller than 25 mm.[10] They found that certain characteristics of the aneurysms or of the patients who harbour them may alter the risk of surgery. Thus surgery of aneurysms smaller than 5 mm was associated with a 2.3% complication rate, while the complication rate for aneurysms 6-15 mm and 16-24 mm was 6.8% and 14% respectively. Similarly different surgical risks were associated with aneurysms at different sites so that aneurysms arising at the posterior communicating artery had a 4.8% surgical risk while aneurysms arising at the carotid bifurcation, the most dangerous site in their series, had a 16.8% risk of surgery. The patients older than 40 years had a (contra-intuitive) lower surgical risk, at 4.8%, than patients younger than 40 years who had a surgical risk of 13.6%; and the risk of complications for females (3%) was lower than that of males (16%). These different risks of surgery are not, to our analysis, statistically significant. Thus we have used the average value of 6.5% as reflecting the risk of operating on the average aneurysm in the usual patient. Similarly King et al., in the meta analysis of 28 studies including 733 patients were unable to find a statistically significant difference in outcome of elective surgery according to size or location of aneurysm or age or sex of the patient.[17] In their meta analysis the risk of death or disability was 5.1%. Recently Nakagawa and Hashi had no neurological complication during the course of surgery of 20 aneurysms 3-20 mm in largest diameter.[36] Solomon et al. had no neurological deficits with aneurysms 10 mm or smaller, a 5% incidence of morbidity with aneurysms 11-25 mm, and a 21% risk of surgery with aneurysms larger than 25 mm.[37] A recent Canadian series, reported by Dix et al., observed 2 neurological complications in 57 patients operated on for unruptured aneurysms that were asymptomatic or discovered because of their mass effect.[38] Individual surgeons can use equation [5] using a figure that may more accurately reflect the estimated risk of surgery in their hands. We have not considered the risk of angiography in our analysis as we have assumed that angiography will have been performed as part of the investigation that identified the aneurysm or that it will be performed if the aneurysm is initially suspected on CT, MRI or MRA, whether or not the aneurysm is to be operated. In any event, the risk of angiography has not been identified as an important parameter in previous decision analysis as it is too small to be of consequence.[6,11]

Non-hemorrhagic, symptomatic aneurysms

Unruptured aneurysms can present with symptoms other than SAH resulting from compression of neighbouring structures and from turbulent flow within their fundi producing distal emboli.[4,39] Such a symptomatic albeit non-hemorrhagic presentation may represent a dynamic change in the aneurysm associated with a much higher risk of imminent rupture. These patients, in our opinion, should not be considered for decision analysis but should be treated promptly by surgical clipping or by other means if this is impossible.

We provide an equation whereby the benefit of elective surgery over the natural history of unruptured aneurysms can be calculated for an individual patient using only a hand-held calculator. Our decision analysis has identified that, using our baseline assumptions, elective surgery produces at least a one year net benefit of survival free of neurological sequelae in patients whose life expectancy is 19.5 years or more, corresponding to age 63.5 years in males and 68 years in females. Thus, based on an analysis of the cumulative decennial risk of rupture, males aged 30-63.5 years and females aged 30-68 years should be considered for elective surgery especially if other risk factors, such as a familial history of cerebral aneurysms, arterial hypertension, the current or previous use of oral anovulants, and the use of alcohol or tobacco are present. Our analysis assumes a normal life-expectancy once the aneurysm is treated and is only valid in this circumstance. Thus, patients with diminished life-expectancy because of an underlying disease may not benefit from treatment of an unruptured aneurysm.

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