Natural History Simulation Models: Aneurysms Larger Than 9.5 mm and Aneurysms Growing Faster Than 0.36 mm/year Require Intense Clinical Care

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INTRODUCTION

Intracranial aneurysms affect 3-5% of the general population.[2-6] Because aneurysm rupture can be very debilitating, it is very important to understand the risks of rupture and see how unruptured aneurysms will behave over a long term.[6] However, it is difficult to follow all patients for many years, and some aneurysms are treated immediately. Thus, it is challenging to observe the natural history of these aneurysms in real life.[4] It is more practical to use a mathematical Markov chain model to simulate aneurysm behavior and examine long-term patterns of growth and rupture.[1,6,8] Multiple Markov models exist, and we aim to compare these models to see what they predict for our database in order to identify the optimal model. We can also search for risk factors for a high risk of rupture.[2,3] Our findings can determine which aneurysms have a high risk of rupture as well as at what point they should be surgically treated. This will help neurosurgeons create the appropriate treatment plan.[2,5]

OBJECTIVE

Our study used 2 Markov models to simulate the natural history of the aneurysms in our database and measure the amount of growth, growth rate, and rupture rate over 30 years. We compared the cumulative rupture probability (CRP) between different categories of initial aneurysm size, absolute amount of growth, and yearly growth rate. We then determined how high of a risk of rupture there is for certain categories (in the above variables). We then propose a treatment plan for different aneurysms and choose the best model.

METHOD

- Our database had 290 aneurysms in 206 patients (29 males and 177 females); data was collected via CTA from 2005-2008
- For both models, $Aneurysm\ Volume = \frac{(Initial\ Aneurysm\ Diameter)^3}{2}$
- For Growth Model I (GM I), the yearly growth rate is related to aneurysm volume; we varied the aneurysms' growth rates so that the mean growth rate was 10 mm^3/year, with a SD of 2.5 mm^3/year
- The rupture rate was a function of aneurysm volume: $Yearly\ Rupture\ Rate = 0.002 \times Aneurysm\ Volume$ [8]
- With Growth Model II (GM II), for each aneurysm we used the growth rate it had displayed since it was originally identified
- The rupture rate was a function of the aneurysm volume: $Yearly\ Rupture\ Rate = 1.14 \times 10^{-5} \times Aneurysm\ Diameter^3$ [1]
- The long-term simulation went 30 years into the future; the present day is Year 0, and using a cumulative probability formula, we found the CRP at 5-year intervals (Years 5, 10, 15, 20, 25, and 30)
- We used the simulation data to compare the CRP between different categories of aneurysms to see if certain variables were risk factors for rupture; we did this at each 5-year interval, using the Independent T-Test and One-Way ANOVA
- We tested the following variables: initial aneurysm diameter, absolute amount of growth, and yearly growth rate; for initial aneurysm diameter, we used two methods of categorization: Method A ("<4.6 mm", "4.6-9.4 mm", and "9.5+ mm") and Method B ("<3.5 mm", "3.5-10.5 mm", and "10.6+ mm"); for absolute amount of growth, the categories were "Significant Growth" and "Non-Significant Growth", using 3 different cutoffs for "Significant Growth" (0.8 mm, 0.9 mm, and 1.0 mm); for yearly growth rate, the categories were "Significant Growth" and "No Significant Growth", with a cutoff of 0.36 mm/year
- At each 5-year interval, we calculated the odds ratios (OR) to quantify the risk of rupture for each category within the three variables above

RESULTS

	Minimum	Maximum	Mean	Standard Deviation
Patient's Age	15 Years	87 Years	61 Years	13.22 Years
Initial Aneurysm Diameter	1.4 mm	34.3 mm	4.5 mm	3.45 mm
Initial Aneurysm Volume	1.37 mm^3	20,176.8 mm^3	205.6 mm^3	1,301.8 mm^3
Follow-Up Period	2 Months	79 Months	33 Months	20.76 Months
Absolute Amount of Growth	-1.0 mm	8.4 mm	0.5 mm	0.84 mm
Yearly Growth Rate	-1.4 mm/year	2.7 mm/year	0.27 mm/year	0.46 mm/year

Table 1: List of the demographic data for the patients and aneurysms

For GM I, the mean aneurysm volume increased from 205.6±1,301.8 mm^3 at Year 0 to 506.4±1,304.8 mm^3 at Year 30; additionally, the mean initial aneurysm size increased from 4.5±3.5 mm at Year 0 to 9.2±2.4 mm at Year 30

For GM II, the mean aneurysm volume increased from 205.6±1,301.8 mm^3 at Year 0 to 1,209.1±6,488.4 mm^3 at Year 30. Additionally, the initial aneurysm size increased from 4.5± 3.5 mm at Year 0 to 7.8± 6.4 mm at Year 30

Markov Model I				
	Aneurysm Volume		Aneurysm Diameter	
	Range (mm^3)	Mean (mm^3)	Range (mm)	Mean (mm)
Year 0	1.4-20,176.8	205.6±1,301.8	1.4-34.3	4.5±3.5
Year 5	29.9-20,205.1	255.8±1,302.0	3.9-34.3	6.1±2.9
Year 10	50.4-20,233.4	305.9±1,302.3	4.7-34.3	7.0±2.7
Year 15	66.7-20,261.7	356.0±1,302.8	5.1-34.4	7.7±2.6
Year 20	82.9-20,290.1	406.2±1,303.3	5.5-34.4	8.3±2.5
Year 25	99.1-20,318.4	456.3±1,304.0	5.8-34.4	8.8±2.4
Year 30	115.3-20,346.7	506.4±1,304.8	6.1-34.4	9.2±2.4
Markov Model II				
	Aneurysm Volume		Aneurysm Diameter	
	Range (mm^3)	Mean (mm^3)	Range (mm)	Mean (mm)
Year 0	1.4-20,176.8	205.6±1,301.8	1.4-34.3	4.5±3.5
Year 5	1.4-20,176.8	372.9±1,882.9	1.4-34.3	5.5±4.2
Year 10	1.4-26,061.4	540.1±2,711.0	1.4-37.4	6.2±4.8
Year 15	1.4-36,874.6	707.4±3,620.4	1.4-41.9	6.7±5.3
Year 20	1.4-47,687.9	874.6±4,562.6	1.4-45.7	7.1±5.8
Year 25	1.4-58,501.2	1,041.8±5,521.0	1.4-48.9	7.5±6.1
Year 30	1.4-69,314.4	1,209.1±6,488.4	1.4-51.8	7.8±6.4

Table 2: Data for the aneurysm volumes and diameters at each 5-year interval

For GM I, the mean YRR at Year 30 was 1.0±2.6%, and the mean CRP at Year 30 was 13.9±12.9%; for GM II, the mean YRR at Year 30 was 2.3±10.8%, and the mean CRP at Year 30 was 14.2±22.0%

Markov Model I				
	Yearly Rupture Rate (YRR)		Cumulative Rupture Probability (CRP)	
	Range	Mean	Range	Mean
Year 5	0.1-40.4%	0.5±2.6%	0.2-92.5%	1.9±7.1%
Year 10	0.1-40.5%	0.6±2.6%	0.7-99.4%	3.7±9.4%
Year 15	0.1-40.5%	0.7±2.6%	1.3-100.0%	5.8±10.9%
Year 20	0.2-40.6%	0.8±2.6%	2.1-100.0%	8.2±11.9%
Year 25	0.2-40.6%	0.9±2.6%	3.0-100.0%	10.9±12.5%
Year 30	0.2-40.7%	1.0±2.6%	4.0-100.0%	13.9±12.9%
Markov Model II				
	Yearly Rupture Rate (YRR)		Cumulative Rupture Probability (CRP)	
	Range	Mean	Range	Mean
Year 5	0.0-46.0%	0.9±4.3%	0.0-95.4%	2.5±9.9%
Year 10	0.0-59.4%	1.2±6.2%	0.0-99.8%	4.7±13.4%
Year 15	0.0-84.1%	1.6±8.3%	0.1-100.0%	6.9±15.4%
Year 20	0.0-100.0%	2.0±10.1%	0.1-100.0%	9.2±17.6%
Year 25	0.0-100.0%	2.2±10.7%	0.1-100.0%	11.7±19.8%
Year 30	0.0-100.0%	2.3±10.8%	0.1-100.0%	14.2±22.0%

Table 3: Data for the yearly rupture rate and cumulative rupture probability for the aneurysms at each 5-year interval

RESULTS (CONTINUED)

Under GM I, the T-Tests and One-Way ANOVAs yielded statistically significant differences in CRP using both Method A and B for initial aneurysm diameter (p<0.001 for all 5-year intervals)

For absolute amount of growth, we found a statistically significant difference in the CRP at every 5-year interval except Year 5 when using the 0.8 mm cutoff; when using the 0.9 mm and 1.0 mm cutoffs, there was a statistically significant difference in the CRP at all 5-year intervals

For yearly growth rate, there was a statistically significant difference in the CRP for all 5-year intervals except Year 5

For GM II, there was a statistically significant difference in the CRP using both Methods A and B for initial aneurysm size (p<0.001 for all 5-year intervals)

For both absolute amount of growth (for all 3 cutoffs) and yearly growth rate, we found a statistically significant difference in the CRP for all 5-year intervals

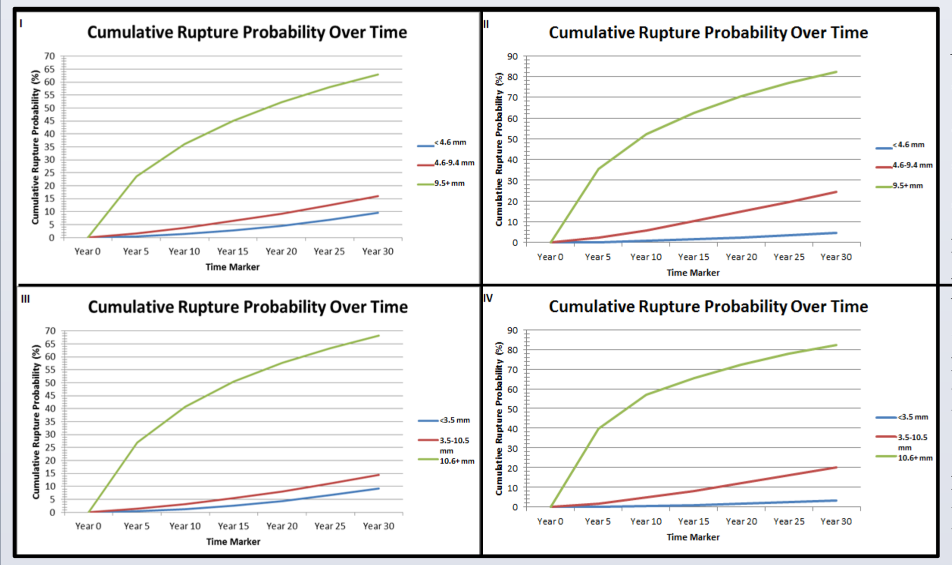

Figure 1: Graph of initial aneurysm diameter vs. cumulative rupture probability; graphs I and III represent Growth Model I while graphs II and IV represent Growth Model II

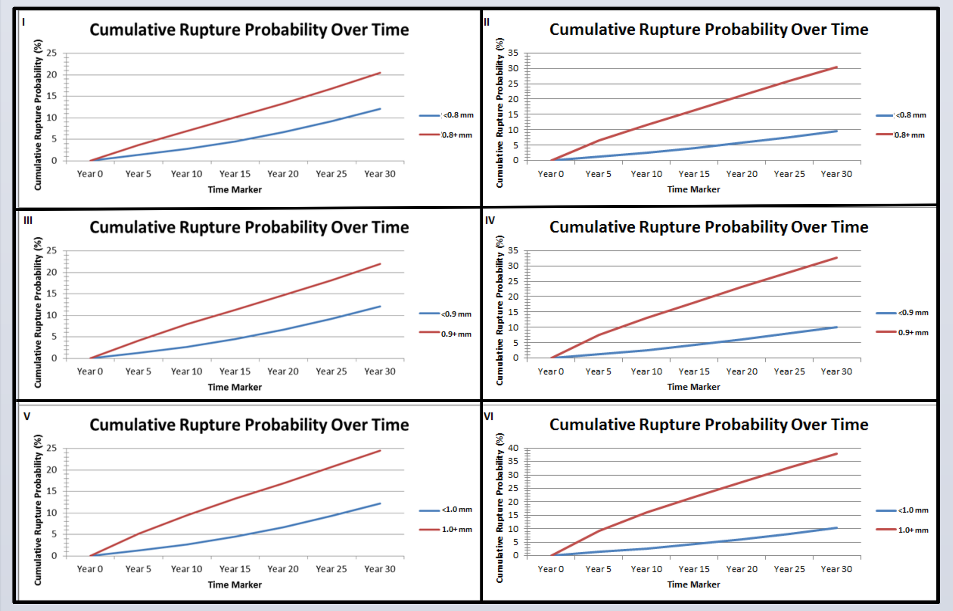

Figure 2: Graph of absolute amount of growth vs. cumulative rupture probability; graphs I, III, and V represent Growth Model I while graphs II, IV, and VI represent Growth Model II

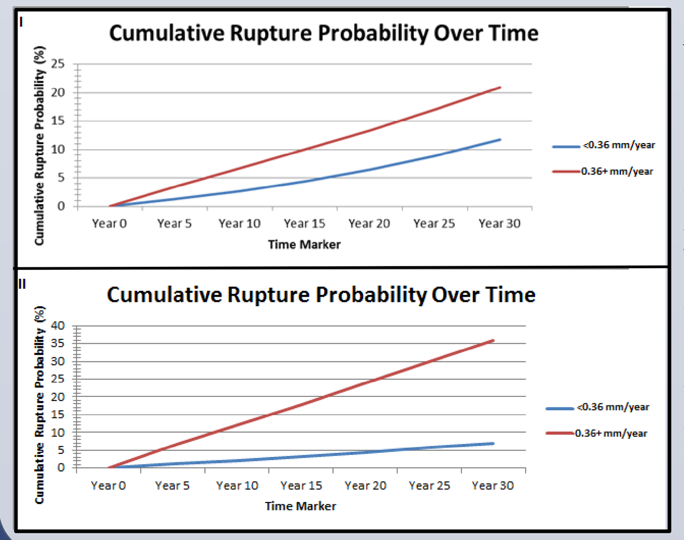

Figure 3: Graph of yearly growth rate vs. cumulative rupture probability; graph I represents Growth Model I while graph II represents Growth Model II

RESULTS (CONTINUED)

Odds Ratio for GM I: with Method A for initial aneurysm diameter, we saw a significant OR at every 5-year interval for the "9.5+ mm" category; with Method B, there was a significant OR at each 5-year interval for the "10.6+ mm" category.

For absolute amount of growth, there was a significant OR for every 5-year interval when 1.0 mm was used as a cutoff

Initial Aneurysm Diameter						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
Method A- "4.6-9.4 mm"	3.9 (0.26-58.47)	2.9 (0.56-14.82)	2.4 (0.70-8.10)	2.1 (0.78-5.68)	1.9 (0.83-4.50)	1.8 (0.85-3.81)
Method A- "9.5+ mm"	70.8 (5.77-867.83)	40.8 (7.71-216.12)	28.9 (7.17-116.60)	22.5 (6.25-81.09)	18.6 (5.40-63.96)	16.0 (4.71-54.62)
Method B- "3.5-10.5 mm"	3.6 (0.18-71.39)	2.6 (0.45-14.84)	2.1 (0.61-7.59)	1.9 (0.70-5.20)	1.8 (0.75-4.07)	1.6 (0.78-3.44)
Method B- "10.6+ mm"	94.7 (5.00-1,796.64)	53.7 (8.08-356.48)	37.7 (7.91-180.17)	29.4 (6.99-123.30)	24.3 (6.04-97.44)	20.9 (5.21-83.51)
Absolute Amount of Growth						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
0.8 mm Cutoff	2.8 (0.49-15.67)	2.6 (0.75-9.24)	2.4 (0.84-6.63)	2.2 (0.88-5.24)	2.0 (0.90-4.42)	1.9 (0.90-3.89)
0.9 mm Cutoff	3.3 (0.58-18.74)	3.0 (0.85-10.83)	2.7 (0.94-7.67)	2.4 (0.96-5.99)	2.2 (0.96-4.99)	2.0 (0.96-4.36)
1.0 mm Cutoff	4.1 (0.71-23.94)	3.7 (1.02-13.68)	3.2 (1.09-9.54)	2.8 (1.09-7.37)	2.6 (1.07-6.08)	2.3 (1.05-5.25)
Yearly Growth Rate						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
0.36 mm/year Cutoff	2.7 (0.48-15.01)	2.6 (0.76-9.07)	2.4 (0.88-6.65)	2.2 (0.94-5.33)	2.1 (0.97-4.55)	2.0 (0.99-4.06)

Table 4: Results for the odds ratio tests using Growth Model I (GM I); the 95% confidence intervals are in parentheses

Odds Ratio for GM II: when we used Method A for initial aneurysm diameter, there were significant ORs at each 5-year interval for the "9.5+ mm" category as well as at every 5-year interval (except Year 5) for the "4.6-9.4 mm" category; for Method B, there were significant ORs at every 5-year interval for the "10.6+ mm" category, and for the "3.5-10.5 mm" category, there were significant ORs for Years 15, 20, 25, and 30

For both absolute amount of growth (using all three cutoffs) and yearly growth rate, there were significant ORs for all 5-year intervals

Initial Aneurysm Diameter						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
Method A- "4.6-9.4 mm"	7.8 (0.44-139.17)	7.3 (1.22-44.13)	7.3 (1.88-28.09)	6.9 (2.31-20.41)	6.6 (2.60-16.71)	6.3 (2.78-14.43)
Method A- "9.5+ mm"	172.9 (10.75-2,779.91)	129.2 (19.34-862.53)	106.7 (21.24-535.44)	95.5 (21.18-430.15)	89.8 (20.03-402.55)	91.4 (19.00-439.90)
Method B- "3.5-10.5 mm"	9.4 (0.21-414.89)	8.9 (0.86-92.15)	8.6 (1.54-48.05)	7.8 (2.02-30.28)	7.5 (2.40-23.54)	7.1 (2.64-19.27)
Method B- "10.6+ mm"	319.3 (7.29-13,989.74)	239.9 (19.67-2,926.51)	180.0 (23.57-1,374.46)	144.2 (23.52-884.58)	132.6 (22.91-767.55)	127.7 (21.60-755.57)
Absolute Amount of Growth						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
0.8 mm Cutoff	4.9 (1.10-21.60)	4.8 (1.59-14.65)	4.4 (1.75-11.21)	4.2 (1.87-9.59)	4.2 (1.97-8.74)	4.1 (2.06-8.27)
0.9 mm Cutoff	5.8 (1.30-25.64)	5.4 (1.77-16.43)	4.9 (1.91-12.43)	4.6 (2.02-10.64)	4.4 (2.07-9.46)	4.3 (2.13-8.86)
1.0 mm Cutoff	7.4 (1.64-33.18)	6.8 (2.21-21.13)	6.1 (2.32-15.80)	5.7 (2.40-13.35)	5.4 (2.45-11.97)	5.3 (2.50-11.25)
Yearly Growth Rate						
	Year 5	Year 10	Year 15	Year 20	Year 25	Year 30
0.36 mm/year Cutoff	5.2 (1.15-23.82)	6.0 (1.92-18.92)	6.3 (2.40-16.29)	6.7 (2.87-15.48)	7.0 (3.28-15.05)	7.3 (3.60-14.82)

Table 5: Results for the odds ratio tests using Growth Model I (GM I); the 95% confidence intervals are in parentheses

DISCUSSION

- The CRP is significantly different for each category of initial aneurysm diameter; large aneurysms ("9.5+ mm" and "10.6+ mm") have the highest CRP; medium-sized aneurysms ("4.6-9.4 mm" and "3.5-10.5 mm") have a higher CRP than the smallest aneurysms after 10 years; the risks of surgery (10-20%) may outweigh the benefits of preventing an unlikely case of rupture in smaller aneurysms[1,4,6-8]
- The CRP is significantly higher for "Significant Growth" aneurysms
- The OR tests suggest that we need immediate aggressive treatment for large aneurysms
- However, not all medium-sized aneurysms need aggressive treatment; we should use invasive treatment if there is significant growth (due to the high OR for "Significant Growth" aneurysms); if the growth rate >0.36 mm/year for medium-sized aneurysms (3.5-9.5 mm), surgical intervention is recommended
- Comparing models: GM I has a smaller range of aneurysm sizes; the largest diameter at Year 30 is 34.4 mm, which is realistic; with GM II, the largest diameter is 51.8 mm, which seems unrealistic; this weighs against GM II
- However, the smallest aneurysm after 30 years is 6.1 mm under GM I, compared to 1.4 mm under GM II; it is more realistic to expect some aneurysms to remain small; this weighs in favor of GM II
- GM I did not produce a significant p-value for absolute amount of growth (0.8 mm cutoff) and yearly growth rate at Year 5, while GM II produced significant p-values for all tests; GM II also produced lower p-values, and this weighs in favor of GM II
- There were no significant ORs (under GM I) for medium-sized aneurysms, and with aneurysm growth, the only significant OR occurred with the 1.0 mm cutoff for absolute amount of growth; under GM II, we found significant ORs at most 5-year intervals for medium-sized aneurysms as well as for all tests for aneurysm growth; this weighs in favor of GM II
- We conclude that GM I is better; the biggest factor was the aneurysm sizes, where GM II produces many very large aneurysms; although GM II had more statistically significant results, they can be attributed to the unrealistically large aneurysm sizes, making those results less meaningful when comparing between models

SUMMARY

Untreated aneurysms can grow significantly in the long run, and the aneurysms in our database could potentially double in size over 30 years. Larger aneurysms and "Significant Growth" aneurysms had a significantly higher CRP. The large aneurysms (initial diameter >9.5 mm) have a high-risk of rupture and should be treated immediately. Medium-sized aneurysms (initial diameter between 3.5-9.5 mm) have a moderate risk of rupture and should be monitored for significant growth. If the growth rate for any of these aneurysms exceeds 0.36 mm/year, surgical intervention may be necessary. When comparing the two models, GM I was the optimal model due to the more realistic aneurysm sizes.

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