研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Morita A, Kimura T	Management of the Unruptred Intracranial Aneurysms	Kato Y, eds	**Essential Practice of Neurosurgery**	Access Publishing	Nagoya	2010	420-433
森田明夫ら	未破裂脳動脈瘤の疫学	宝金清博編	**脳神経外科エキスパート、脳動脈瘤**	中外医学社	東京	2009	258-266
森田明夫ら	くも膜下出血をきたした破裂脳動脈瘤の疫学—未破裂脳動脈瘤との対比および瘤の形成・破裂に関与する因子の検討	小林祥泰編	**脳卒中データバンク2009 くも膜下出血の実態**	中山書店	東京	2009	170-171
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雑誌

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Kimura T, Morita A, et al	Simulation of and training for Cerebral Aneurysm Clipping with 3-Dimentional Models	**Neurosurgery**	65	719-726	2009
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青木友浩、野崎和彦ら	脳卒中の先端治療研究臨床への道 NF-kappaB活性化を中心とした脳動脈瘤形成の分子機序の解明と臨床応用への展望	**脳卒中**	31	425-432	2009
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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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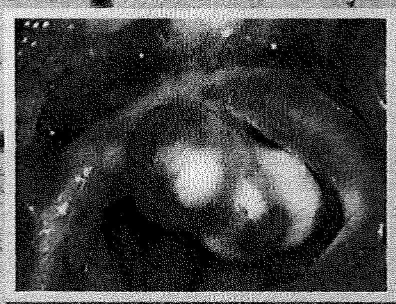
塩川芳昭、他	急性期破裂脳動脈瘤の治療選択の現状（第一報）	脳卒中の外科	37	1-6	2009
塩川芳昭、他	急性期破裂脳動脈瘤の治療選択の現状（第二報）	脳卒中の外科	37	7-11	2009

Ⅳ. 研究成果の主要刊行物・別刷

脳神経外科エキスパート

脳動脈瘤



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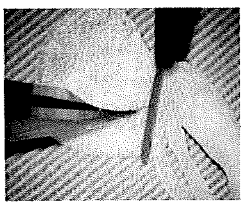

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Simulation of and Training for Cerebral Aneurysm Clipping With 3-Dimensional Models

OBJECTIVE: With improvements in endovascular techniques, fewer aneurysms are treated by surgical clipping, and those aneurysms targeted for open surgery are often complex and difficult to treat. We devised a hollow, 3-dimensional (3D) model of individual cerebral aneurysms for preoperative simulation and surgical training. The methods and initial experience with this model system are presented.

METHODS: The 3D hollow aneurysm models of 3 retrospective and 8 prospective cases were made with a prototyping technique according to data from 3D computed tomographic angiograms of each patient. Commercially available titanium clips used in our routine surgery were applied, and the internal lumen was observed with an endoscope to confirm the patency of parent vessels. The actual surgery was performed later.

RESULTS: In the 8 prospective cases, the clips were applied during surgery in the same direction and configuration as in the preoperative simulation. Fine adjustments were necessary in each case, and 2 patients needed additional clips to occlude the atherosclerotic aneurysmal wall. With these 3D models, it was easy for neurosurgical trainees to grasp the vascular configuration and the concept of neck occlusion. Practicing surgery with these models also improved their handling of the instruments used during aneurysm surgery, such as clips and appliers.

CONCLUSION: Using the hollow 3D models to simulate clipping preoperatively, we could treat the aneurysms confidently during live surgery. These models allow easy and concrete recognition of the 3D configuration of aneurysms and parent vessels.

KEY WORDS: Cerebral aneurysm, Clipping, Surgical simulation, Surgical training, 3-dimensional modeling

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Microsurgical clipping is the standard technique for cerebral aneurysm surgery. Since the International Subarachnoid Aneurysm Trial (8), and with improvements in endovascular techniques, cerebral aneurysms are increasingly treated through endovascular embolization (4). However, aneurysms that are not suited for endovascular intervention are often difficult to treat and are targeted for microsurgical treatment (1). Because the total number of aneurysms treated through clipping is decreasing, and aneurysms targeted for surgery are often of complex shape, there is a need for effective microsurgical training and a simulation system to practice clipping.

ABBREVIATIONS: CTA, computed tomographic angiography; **DICOM,** Digital Imaging and Communication in Medicine; **3D,** 3-dimensional

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With the development of information technology, virtual reality simulation has been adopted by the field of microneurosurgery (6). The technology can show 3-dimensional (3D) views of cerebral vessels and aneurysms from various angles, and even clips and clip appliers, in the virtual monitor (13). Such image simulation can improve our concepts of aneurysm configuration and approach selection. Live surgery, however, presents various difficulties in handling aneurysms, such as how to occlude aneurysms without stenosis or kinking of the parent artery, the occlusion of perforating vessels or remnants of the aneurysm, and how to apply multiple clips for satisfactory clipping. Also, actual haptic feedback during the procedure is very important in learning skills.

We have developed 3D aneurysm models that are hollow and semielastic from individual patients' images, enabling surgical simulation and actual clip application using real aneurysm surgery equipment. Herein, we describe the development of this technique and initial experience with clinical cases.

MATERIALS AND METHODS

Aneurysm Model

Our 3D elastic hollow models were created with a soft, rubber-like polymer (FullCure 930 Tango Plus; Objet Geometries, Ltd., Rehovot, Israel; http://www.2objet.com/default.aspx) by using a rapid prototyping technology. Data acquired through Digital Imaging and Communication in Medicine (DICOM) from original, enhanced computed tomographic images of 3D computed tomographic angiography (CTA) were obtained for each patient. The data were transferred to the 3D calculation software, Mimics (Materialise Japan, Inc., Kanagawa, Japan; http://www.materialise.com/materialise/view/en/65854-Homepage.html). A virtual 3D angiogram was generated, and the vascular area of interest was segmented. Data from the segmented area were transformed into a stereolithographic format and transferred to MagicsRP (Materialise Japan, Inc.), in which the data are adjusted to fit the rapid prototyping machine. In this software, the vessel wall was created with a thickness of 0.3 or 0.5 mm over the vessel image from the CTA data because the original data showed contrast media inside the wall.

The data were then transformed into thin, virtual horizontal sections, and the rapid prototyping machine sprayed raw materials to make a 0.03-mm-thick layer of polymer (FullCure 930 Tango Plus). Then, ultraviolet light was used to harden the polymer according to the image of the vessel wall. The spray nozzle of the machine rises and the thin layer piles up to make the vessel wall. After the vessels of interest were built up, the contents, which were not hardened by the ultraviolet light, were curetted away manually to make the vessel hollow.

A hard bone model (KEZLEX; Ono & Co., Ltd., Tokyo, Japan; http://ono-and.com/) was made with the same technique, except that the polymer consisted of resin and talc, which become hard when irradiated, and the thickness of 1 layer of prototyping was 0.1 mm.

We created hollow 3D models for 3 retrospective cases and 7 prospective cases. Hard models were created for 1 retrospective case and 2 prospective cases. In the retrospective models, we assessed the most appropriate conditions for creating 3D models, such as the thickness of the aneurysm and arterial wall and the extent of the parent vessels needed for simulation.

The data processing and creation of the 3D models were done at the processing laboratory of Ono & Co., Ltd after we prepared 3D DICOM images from the patient's 3D CTA and marked the area we wanted to have as the 3D model. Currently, 3 to 7 days are needed to create the 3D model. Although this process was not a commercial enterprise of this company during the study, creating the model costs 300 to 400 United States dollars per patient according to the size and complexity of the aneurysm.

Surgical Simulation

We fixed the aneurysm model with either flexible wires or plastic clay in the direction of the surgical view, according to the approach selected for individual aneurysms. Then, under the operative microscope, we applied various types of aneurysm clips (Vasari Titanium Aneurysm Clips; Aesculap AG & Co. KG, Tuttlingen, Germany) until we determined satisfactory positions that did not occlude or kink the parent vessels and left as small a remnant as possible. The lumen of the aneurysms was checked with a thin, flexible vascular endoscope (Fig. 1, C and D) (DAG-2218LN; Machida Endoscope Co., Ltd., Tokyo, Japan).

When deciding the surgical approach, especially in patients with complex, deep-seated vertebrobasilar aneurysms, we used a hard 3D model including the aneurysm, vessels, and cranial base bone. By creating an actual craniotomy and drilling the skull base, we simulated the access to the aneurysms. In addition, by positioning the hollow 3D model in the same direction as the surgical approach, we could confirm whether clips could be applied through the corridor.

ILLUSTRATIVE CASES

Patient 3

A 64-year-old woman had a 10-mm unruptured anterior communicating artery aneurysm (Table 1). Her 2 sisters had been diagnosed with subarachnoid hemorrhage previously, and 1 of them died. Thus, this woman came to our hospital for surgical clipping. With the DICOM data from her 3D CTA, we prepared a hard KEZLEX model, including part of the skull, and an elastic soft aneurysm model. An interhemispheric approach and a right pterional approach were tried on the KEZLEX model (Fig. 2). We achieved optimal neck clipping through the right pterional craniotomy with a Yaşargil 10-mm straight clip combined with a fenestrated clip. The actual clipping of the patient's aneurysm was done through the right pterional approach, as practiced on the model (Fig. 1). During the simulation, we confirmed that the clipping occluded the aneurysmal neck completely by observing the intraarterial lumen through the microendoscope (Fig. 1, C and D). The patient's postoperative course was uneventful, and complete neck clipping was confirmed by 3D CTA.

Patient 5

A 61-year-old woman had an 11-mm aneurysm of the left middle cerebral artery (Table 1). She also had a family history of subarachnoid hemorrhage. During simulation on a soft aneurysm model, a curved clip (10.2 mm) was applied parallel to the M1–M2 bifurcation and combined with a fenestrated clip. During the actual operation, minor bleeding occurred when a small artery attached to the wall was dissected. The application of a single curved clip could not stop the bleeding because the neck was atherosclerotic and an additional clip was needed to stop the bleeding. A fenestrated clip was applied to occlude the residual neck, as was done in the simulation (Fig. 3). The patient's postoperative course was uneventful, and neck clipping was confirmed by 3D CTA as well.

Patient 6

A 63-year-old woman presented with a 22-mm aneurysm at the union of the vertebral arteries (Fig. 4; Table 1). See Video, Supplementary Digital Content 1, http://links.lww.com/A242, which demonstrates preoperative simulation and surgery in patient 6.) Using a hard KEZLEX model, we could drill the skull base and anticipate how much bone should be removed during surgery to expose the aneurysm neck appropriately. Also, using a soft elastic hollow model, we could apply various clips and decide which clip combination would be suitable to obliterate the aneurysm without inflow vessel occlusion. Actual surgery was done as planned during hard model simulation. We performed a left suboccipital and temporal craniotomy and exposed the aneurysm dome and neck, respectively. We placed clip grafts through the anterior petrosal route as had been planned in the soft model simulation.) A hard KEZLEX model and a soft aneurysm

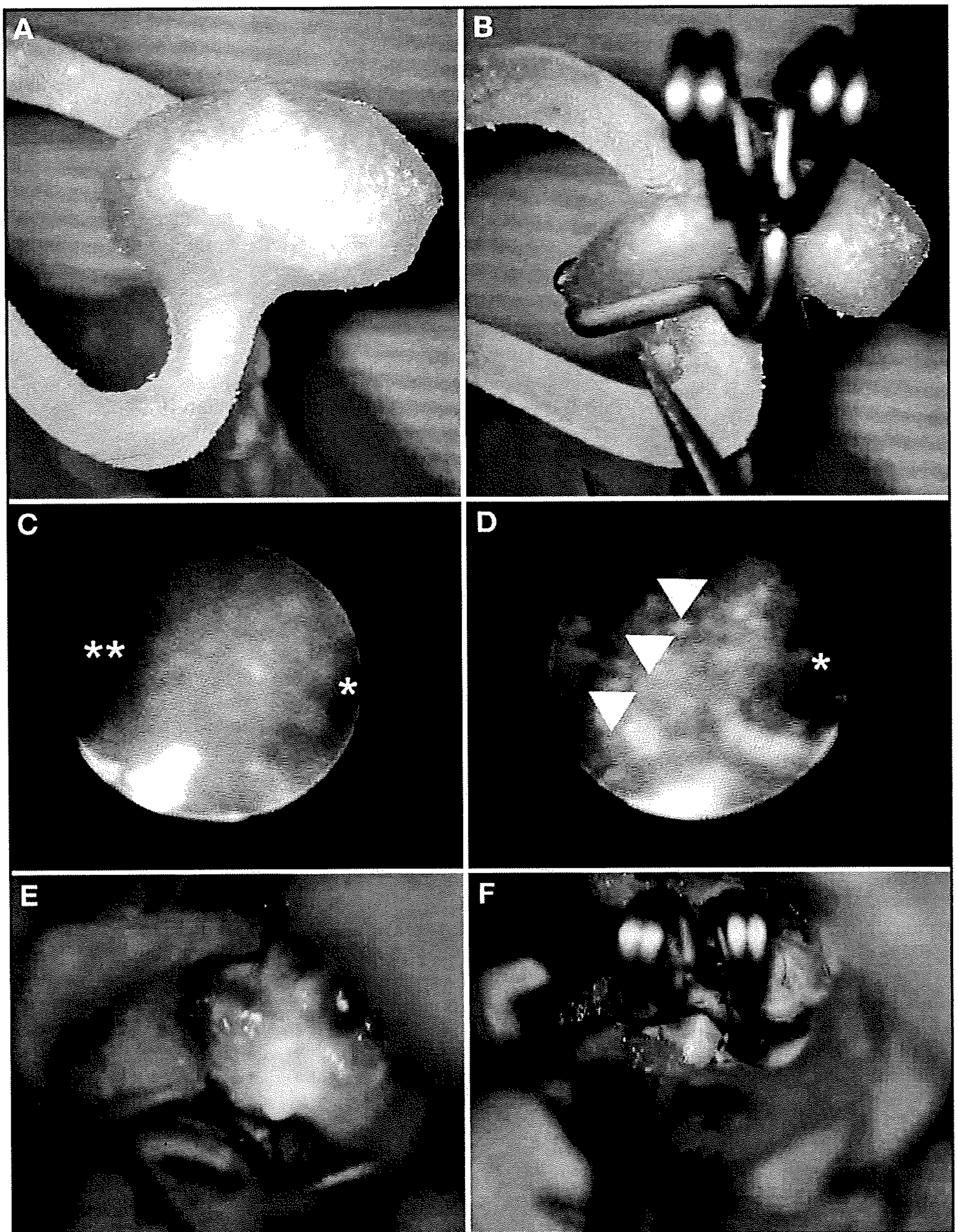

FIGURE 1. A, *simulation of surgical clipping of a left anterior communicating artery aneurysm (soft model) seen from the right pterional view.* B, *the ideal clipping—a straight clip combined with a fenestrated, bent clip.* C, *endoscopic view of the model seen from the left A2. The double asterisks show the aneurysm's orifice and the single asterisk shows the dominant left A1 orifice.* D, *after clipping simulation. The arrowheads show the closure line of the aneurysmal neck from inside the artery whereas the single asterisk shows patency and no stenosis of the parent A1.* E, *actual operative view of the aneurysm during the right pterional approach.* F, *after clipping. The aneurysm is obliterated as shown in the simulation.*

model were manufactured. Anterior petrosectomy was performed on the KEZLEX model, and the aneurysm neck was observed through this corridor. It was possible to apply clips through the window, but it seemed difficult to control the proximal vertebral artery. Therefore, in the actual surgery, a suboccipital craniotomy was added to prepare the proximal vertebral arteries. Although a 20-mm straight clip seemed appropriate to occlude the aneurysm neck of the soft model, we examined whether an additional tandem clip could be applied through the window considering the thickness of the aneurysmal wall and the pressure of the real aneurysm. In the actual surgery, a 12-mm blade fenestrated clip was added tandemly and a booster clip was applied on the anticipated 20-mm straight clip. Obliteration of the aneurysm was confirmed by digital subtraction angiography. Two months after surgery, the patient was neurologically intact, but her hearing was sacrificed.

RESULTS

A summary of the cases and findings during simulation and actual surgery is provided in Table 1. For models of retrospective cases, we created small to medium aneurysms (<15 mm) with a thickness of 0.3 mm, and large aneurysms (>15 mm) with a thickness of 0.5 mm. To efficiently remove the contents of aneurysms, we needed to limit the length of the parent artery, but we also needed enough length to simulate surgery. Therefore, we chose to include at least 10 mm of the parent vessel.

With the models of prospective cases, we could repeatedly apply various types of clips and choose the most appropriate clips and approach before surgery. In patients whose aneurysm had a wide neck, we could visually assess how close to the parent vessel we could place the clip blade without occluding or kinking the vessels. In 5 of 8 patients, the same selection and config-

TABLE 1. Summary of patients with prospective clip simulation[a]

Patient no.	Age (y)/sex	Location	Size (mm)	Best configuration in simulation	Actual clipping	Reclipping	Residual neck
1	56/F	R MCA	4	Slightly curved	Same	No	No
2	81/F	R MCA	11	Straight + fenest.	Curved + fenest.	No	No
3	64/F	AComA	10	Straight + fenest.	Same	1	No
4	68/F	L IC PComA	9	Bayonet	Same	No	No
5	61/F	L MCA	10	Slightly curved + fenest.	Slightly curved ×2 + fenest.	Adjustment	No
6	63/F	VA union	22	Straight ×2	Straight + fenest.	5	+
7	39/M	M1 fusiform	12	Straight ×2 + fenest.	Fenest. ×3	6	No
8	67/F	AComA	6	Bayonet	Same	2	+

[a] R, right; MCA, middle cerebral artery; fenest., fenestrated clip; AComA, anterior communicating artery; L, left; IC, internal carotid; PComA, posterior communicating artery; VA, vertebral artery.

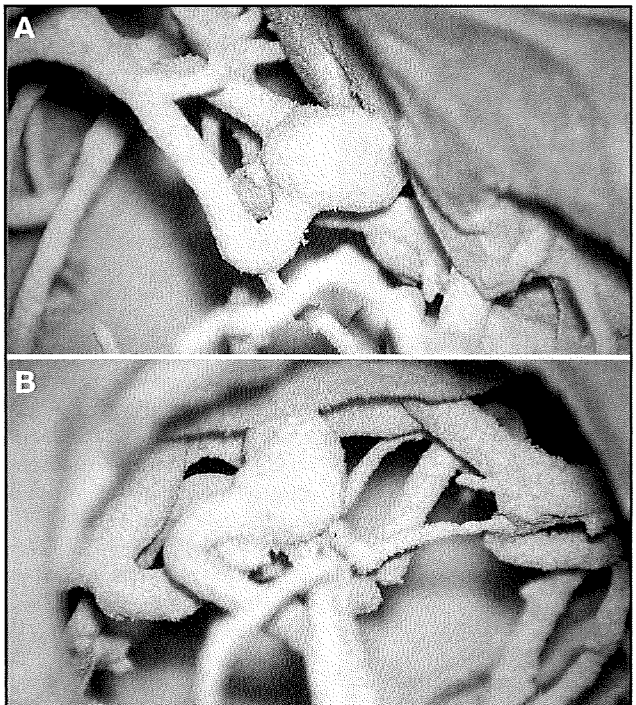

FIGURE 2. *Comparison of the surgical view of the anterior communicating artery aneurysm in case 1 using the hard KEZLEX (Ono & Co., Ltd., Tokyo, Japan) model.* **A**, *view from the right pterional craniotomy.* **B**, *during the interhemispheric approach.*

uration of clips were applied. In 1 patient with a medium-sized middle cerebral aneurysm (patient 5) and complex vertebrobasilar aneurysms (patient 6), we needed to apply additional clips to occlude the atherosclerotic aneurysmal neck. In a fusiform M1 aneurysm (patient 7), 3 ring clips were used to shape the artery, although a combination of a straight and a fenestrated clip seemed appropriate for shaping the middle cerebral artery during the preoperative simulation.

For help in selecting the surgical approach, we also created a hard artery and bone model to determine the most appropriate surgical access and bone removal. The most appropriate clip application was also assessed with the hollow model and a real clip. This concept was also used to decide the surgical approach to anterior communicating aneurysms (patient 3) and a vertebral artery union aneurysm (patient 6). In patient 3, by placing the aneurysms in the direction observed through either the interhemispheric or transsylvian approach, we could apply various clips and decide the approach or most appropriate clip combination. In patient 6, we knew whether the aneurysm neck could be dissected and the clip could be applied through the anterior petrosal corridor.

After the preoperative simulation was finished, the same models were used to train beginning neurosurgeons. With these models, they can learn how to handle clips and appliers, manipulate aneurysms, and place clips. By using the microendoscope, they can learn how the aneurysmal neck is occluded according to the direction of the clip. They can also recognize the importance of considering the intraluminal anatomy of the aneurysm and adjacent arteries during surgical repair.

DISCUSSION

With the development of embolizing materials and various techniques, endovascular treatment is becoming safer and more applicable to various types of cerebral aneurysms (8).

Now, more than 50% of aneurysms are considered manageable with endovascular treatment (4). However, some aneurysms are complex and difficult to treat through endovascular techniques that are often difficult for microsurgical clipping as well (1). The International Study of Unruptured Intracranial Aneurysms investigators showed that the rupture rate of

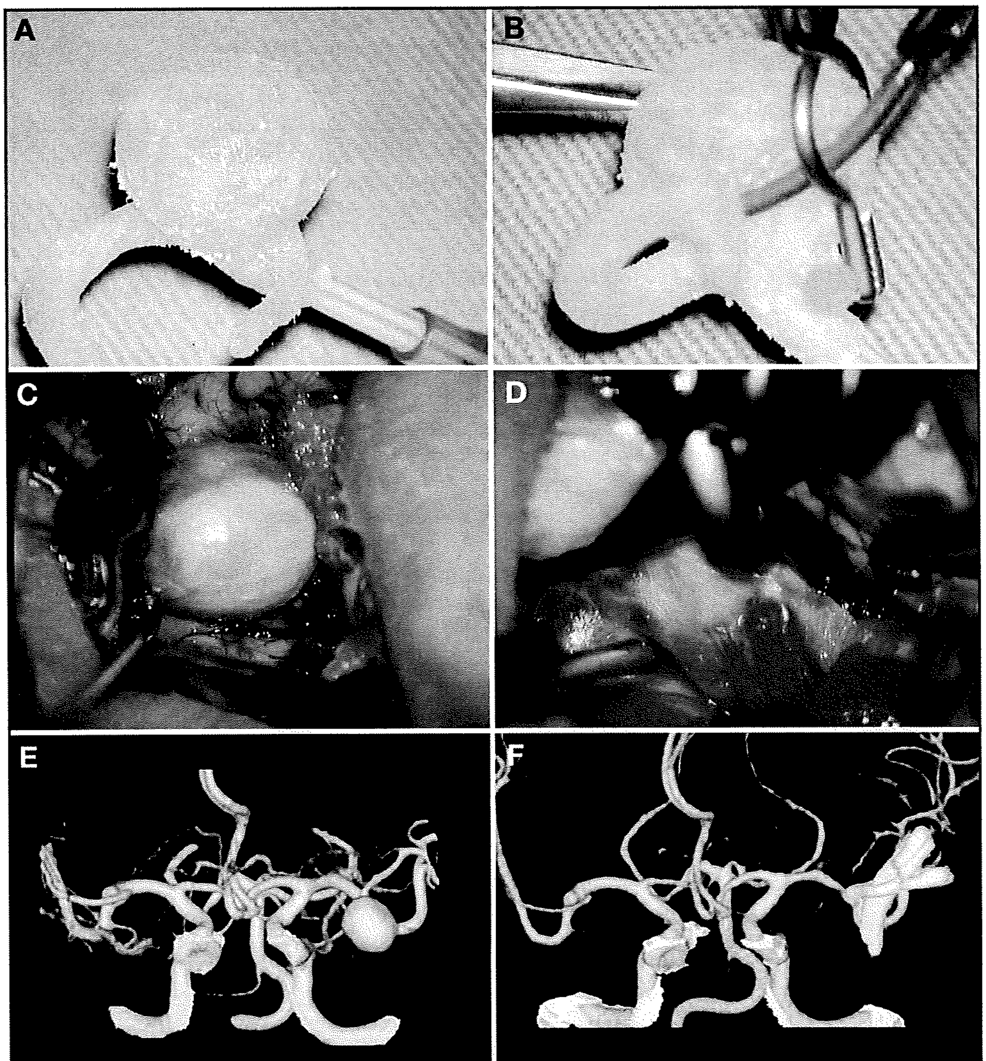

FIGURE 3. A, *left middle cerebral bifurcation aneurysm in a supposed surgical view.* B, *ideal clipping with a slightly curved clip combined with a fenestrated clip.* C, *actual operative view after sylvian dissection and elevation from the left frontal lobe.* D, *magnified view of the bifurcation after clipping. The configuration is the same as in the preoperative simulation, but 2 parallel clips were needed for sufficient closing pressure.* E, *preoperative 3-dimensional (3D) computed tomographic angiogram showing a large left middle cerebral artery aneurysm.* F, *postoperative 3D computed tomographic angiogram confirming satisfactory obliteration of the aneurysm.*

unruptured cerebral aneurysms depends on the size of the aneurysm. Small aneurysms are less often indicated for treatment, but larger aneurysms, with high surgical risks, are often indicated for surgery (12). With this scenario, the case load each neurosurgeon experiences is limited, and there are fewer chances to develop surgical skills in managing simple cerebral aneurysms (9). At the same time, neurosurgeons are faced with very difficult aneurysms needing surgical treatment. Therefore, there is a definite need for practical surgical simulation and an effective training system for aneurysm clipping procedures.

With the advancement of radiological modalities and information technology, 3D virtual reality models can be constructed on a personal computer (3, 7). More intricate images can be created on a workstation. As is prevalent in other fields of surgery, virtual reality training is being done on such applications as the Dextroscope (BRACCO AMT, Inc., Princeton, NJ) (11, 13). These 3D models help neurosurgeons grasp the 3D configuration of vascular anatomy both before and during surgery and make it easier to plan the operative procedure. However, in practical surgery, some difficulties are associated with vascular texture and distinct devices, specifically clips and clip appliers. The aneurysm and its parent artery change morphologically according to the application of the clip, but the virtual reality systems available today cannot yet provide sufficient images for each scenario and each aneurysm. Futami et al. (3) described simulating the positioning of a single straight clip on a workstation and assessed the aneurysmal remnant. This technique is very promising with further advancements in software, but it is not adequate for actual patients who require other or multiple types of clips.

Although an aneurysm clip and its applier are well designed for occlusion, a certain level of experience is necessary to handle these devices properly near the aneurysm, especially when reclipping or multiple clipping is needed. Although temporary clip systems are available, multiple reclipping in patients should be avoided because of the risk of premature rupture and inadvertent vessel injury.

Wurm et al. (14) reported on the utility of solid plastic models to grasp 3D anatomy of aneurysms. Because our 3D model is hollow and made of soft elastic silicone, the aneurysmal neck can be occluded with an actual aneurysm clip as is done during the actual operation, and we can assess the endoluminal

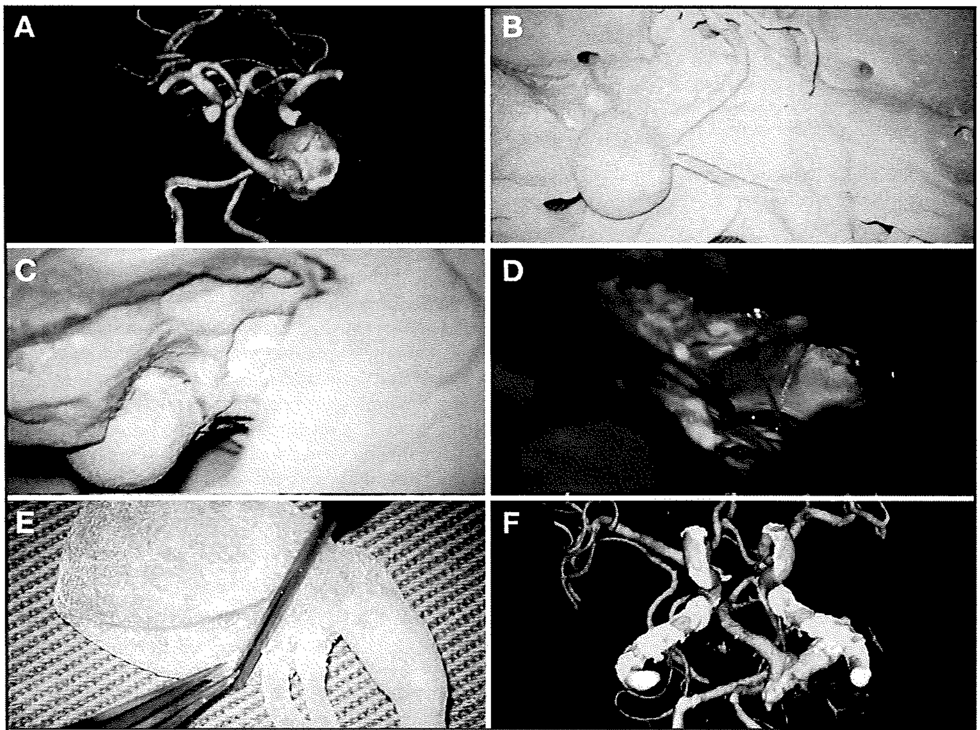

FIGURE 4. A, *vertebral artery union aneurysm projecting to the left.* B, *posterior view of the KEZLEX model after anterior petrosectomy and lateral suboccipital craniotomy. Anterior petrosal view of the KEZLEX model* (C), *and the actual aneurysm* (D). E, *clipping simulation on the soft model.* F, *postoperative computed tomographic angiogram.*

patency in addition to the ease of preoperative stereognostic understanding. Especially in complex cases, in which the aneurysm was large or had a wide neck, this model allowed us to estimate how close to the neck we could place the clip without occluding parent vessels. It also helped us to choose the best clip placement and combination to obliterate aneurysms. Our models were very similar to the actual aneurysms and, in all 8 prospective cases, we could manage the real aneurysms with the same configuration of clips.

The purpose of this model is to simulate the surgical repair of aneurysms for training. Information regarding surrounding tissue, such as adjacent structures or the Sylvian fissure, is not provided. Such information should be well recognized on each patient's preoperative imaging, such as magnetic resonance imaging. In addition, the models are supplied only with short segments of the vessels around the aneurysms. Placing such models in the appropriate direction under the microscope during simulation is a critical step in understanding the aneurysm's configuration and selecting the appropriate surgical approach. Also, the use of instruments needs to be confined during the simulation according to anticipated limitations caused by the surrounding brain tissue.

With this model, surgeons who do not have sufficient experience with clipping can practice as many times as necessary to be confident to perform clipping on actual patients. In addition, they can practice on and examine difficult past cases and improve their skills. This model has also been used to explain surgery and surgical risks before obtaining informed consent from patients. With such a model, patients and their families can easily understand the surgery and its risks (5). In the future, this system will be used to simulate endovascular procedures for individual complex aneurysms requiring various devices.

There are, however, several aspects of the model that need improvement. Because our model takes several days to be prepared, it cannot be used to simulate emergent cases such as ruptured aneurysms. The model creation process should be simplified and quickened. Furthermore, as D'Urso et al. (2) and Wurm et al. (14) have noted previously, because this model is created with data from the aneurysmal cavity, the thickness or consistency of the wall is not reflected. In part because of this insufficiency, we needed to add an extra clip in our patient with middle cerebral and vertebral artery union aneurysm. In addition, the perforators in the model are too small to be made hollow, and surgeons still need to make conceptual images so that those perforators are not occluded during actual clipping. They must also confirm the patency through multiple methods, such as micro-Dopplers, intraoperative fluorescent angiography using indocyanine green, and electrophysiological monitoring (10).

Disclosure

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COMMENTS

Kimura et al. used individual patients' images to develop 3-dimensional (3D) aneurysm models that are hollow and semielastic. The models can be used to simulate surgery and clip application. This article describes their use of this technique with clinical cases. Surgeons were able to plan preoperatively which clip to use and how to apply it. Their 3D model also includes a cranial base bone to evaluate the optimal surgical corridor. Placement of a clip also depends on the surrounding brain, nerves, and pliability of the vessels.

This model is unique in that the vessels and aneurysm are hollow, and an endoscope can be used to confirm patency of the parent vessel after clipping. We agree with the authors' belief that this is a useful tool for preoperative planning and for training and practice, especially in the current environment, in which aneurysms are being treated increasingly by endovascular methods.

Francisco Ponce
Robert F. Spetzler
Phoenix, Arizona

3D models and surgical simulation are important topics for resident training. Whether or not this type of simulation really is helpful for an experienced aneurysm surgeon is hard to quantify. The preliminary attempts at modeling explained in this study are intriguing, but there are very significant limitations, as the authors outline. The models are very time consuming and cumbersome to construct, and they are unlikely to be used on a routine basis in the present form. In these models, the aneurysm and vessel wall thickness is not accounted for; however, wall thickness may be a critical factor in choosing and positioning clips. More importantly, in this model, the presence of perforators is not accounted for. Sparing perforators and understanding perforator anatomy may be the most important aspect of safe aneurysm clipping.

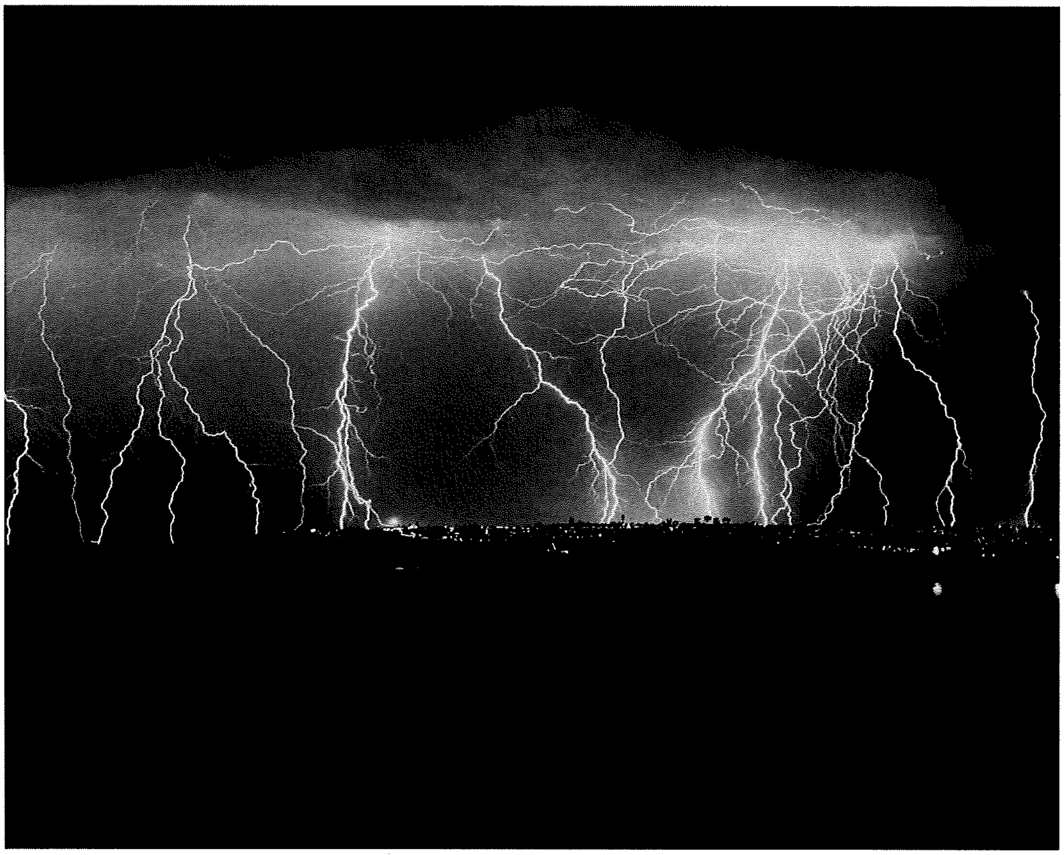
Robert A. Solomon
New York, New York

The authors have presented a clever and innovative method of creating models of intracranial aneurysms based on preoperative 3D imaging studies. These models were used for both simulation of the actual operative procedure and for training residents and young surgeons. Although the technique of developing these models appears to be somewhat cumbersome and possibly expensive, the concept of generating 3D models for surgical training and practice is a sound one. As stated by the authors, the number of intracranial aneurysms undergoing surgical treatment has declined with the advent of endovascular therapy. Simultaneously, the complexity of those aneurysms coming to surgery is increasing. This challenges the skills of the cerebrovascular surgeon and creates difficulties in training the next generation of cerebrovascular surgeons. Additionally, restrictions on resident work hours make it even more challenging to expose neurosurgical residents to an adequate volume of complicated cases to prepare them for practice. The discipline of surgery is far behind other professions, such as the airline industry, in creating simulators for the purpose of training. This is a step in the right direction.

Daniel L. Barrow
Atlanta, Georgia

Endovascular case volume is increasing with better technology and new techniques. This evolution is decreasing open microsurgical case volume and increasing case complexity. Residents are exposed to fewer training cases, and their involvement in complex cases may be limited. Young aneurysm surgeons are struggling to advance their proficiency in this environment. This article describes a technique to manufacture soft rubber aneurysm models for surgical simulation that replicate a patient's individual anatomy. These models enable the neurosurgeon to decide on the optimal surgical approach, select the best clip configurations, practice the clip application, and examine the reconstructed aneurysm neck from outside and inside the arteries. This tool would undoubtedly be helpful with surgical preparation and with retrospective re-examination of complicated cases that were associated with morbidity or poor results. Good aneurysm surgeons spend time before surgery studying their patient's aneurysm anatomy, usually on the computer screen with 3D computed tomographic angiography or catheter angiography. A thorough appreciation of specific anatomy facilitates the dissection and minimizes surprises intraoperatively. The busy neurosurgeon does not have time to wait for models to be built for simulation but creates these models in his head, with his mind's eye. These models can help residents to develop these spatial perspectives and preoperative habits. In the current environment of aneurysm scarcity, these models should become an integral teaching tool for residents to develop their surgical and analytical skills.

Michael T. Lawton
San Francisco, California



No Shinkei Geka, 37(4): 399-411, 2009

連載 脳神経外科疾患治療のスタンダード

5. 未破裂脳動脈瘤の治療 —脳ドックのガイドライン2008を中心に*

森田 明夫**, 木村 俊運**, 楚良 繁雄**

Key words : unruptured intracranial aneurysms, guideline, management strategy, natural course, risk communication
No Shinkei Geka 37(4): 399-411, 2009

I. はじめに

未破裂脳動脈瘤の治療方針の決定は難しい．その理由は第1に未破裂脳動脈瘤の自然歴が個々の瘤に関しては不明なこと[54]，第2に治療リスクが報告によってかなり異なり，動脈瘤の部位や大きさ，患者の状況によっても施設ごとで治療成績に差があること[56,63]，また3つ目には，治療は予防治療の色合いが濃く，その意義について患者と医療側の考えに大きな差がありうること[3,27]，もし何らかの合併症を併発すると訴訟を含めた問題となりうることなどである．また破裂率の高い瘤ほど治療のリスクも高いという大きな問題がある．

現在日本では，年間1万例超の未破裂脳動脈瘤患者が開頭クリッピングまたは血管内コイル治療のいずれかを受けている．社団法人日本脳神経外科学会調べでは2006年には日本全国で8,839件の開頭クリッピング術，3,053件のコイル塞栓術が施行されている（http://ucas-j.umin.ac.jp/UCAS2007/index.html）．このような治療の根拠を明らかとし，医療者としてしっかりとした基準をつくる努力をしなければならない．

このたび筆者が中心となって，脳ドックのガイドライン2008，無症候性未破裂脳動脈瘤への対応を改定した（http://www.snh.or.jp/jsbd/pdf/guideline2008.pdf）．本稿ではその内容を中心に，未破裂脳動脈瘤の治療方針について現時点で得られている情報から考えうることを解説したい．また現在筆者の施設において気をつけている未破裂脳動脈瘤の治療のポイントについて示したい．

II. 未破裂脳動脈瘤治療方針を検討するにあたっての問題点とその対応

脳ドックのガイドラインが策定された2003年より2008年までに，未破裂脳動脈瘤の診療に関する大きなエビデンスは少ない．しかし，最も重大なのが，医師と患者間のリスクコミュニケーションの構築であることが少しずつ明らかとなってきた．そこで今回のガイドライン改訂では下記の項目を検討しつつ作業を進めた．

①未破裂脳動脈瘤と不安症状，発見・治療による生活の質（QOL）の変化，およびインフォームド・コンセント・リスクコミュニケーショ

*Clinical Standard of Neurosurgical Disorder (5) Management of the Unruptured Intracranial Aneurysms

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Table 1 Natural history of unruptured intracranial aneurysms

Authors, year	No. of cases	Mean age	Follow-up	Annual rupture rate(%)	Factors affecting rupture
Yasui, et al. (1997)[60]	234 pt, 303 an	59.6	75.1mo	2.3	multiplicity
Rinkel, et al. (1998)[43]	3,907 pt·yr	-		1.9(1.5～2.4) <1 cm: 0.7 >1 cm: 4.0	symptomatic, sex size, location
ISUIA, (1998)	727 pt, 977 an	56	8.3 yr, 12,023 pt·yr	<1 cm: 0.05 >1 cm: 0.5	size
	722 pt, 960 an	49.4		0.5	
Juvela, et al. (2000)[22]	142 pt, 181 an	41.9	19.7 yr 2,575 pt·yr	1.3	smoking older age, size
Tsutsumi, et al. (2000)[49]	62 pt,	70.8	4.8 yr	2.3	size
Morita, et al. (2005)[32]	911 pt		3,801 pt · yr	2.7	size, posterior, symptom
Wermer,et al. (2007)[54]	4,705 pt, 6,556 an		26,122 pt · yr	1.2: ～5 y 0.6 5～10 y 1.3: 10 y～	age>60, female, Japanese or Finish, size>5 mm, posterior, symptom

〔Abbreviations〕 pt: patients, an: aneurysms, pt·yr: patient·year, mo: month

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②未破裂脳動脈瘤の治療適応

③治療成績とその公表方法

④経過観察の方法

⑤治療後の経過観察

以下にそれぞれについての検討内容と，推奨項目を記載する．

1. 未破裂脳動脈瘤と不安症状，発見・治療による生活の質（QOL：quality of life）の変化，およびインフォームド・コンセント・リスクコミュニケーションについて

未破裂脳動脈瘤が発見されると不安症状，うつ症状が惹起され，QOL が低下するという報告がある．

Yamashiro らは 64 例の未破裂脳動脈瘤の治療前，治療後の QOL について SF36 およびうつスケールを用いて解析した[59]．未破裂脳動脈瘤を有する患者では，SF36 値が 8 つのすべてのドメインにおいて一般人に比較して低かった．これは，治療直後に 20％の患者に認められた何らかの合併症によって，一時的に低下したものである．しかし 3 年の経過を経て，すべての患者で QOL は一般人のものと同等となっていた．Raaymakers らは，MARS（Magnetic Resonance Angiography in Ralatives of Patients with Subarachnoid Hemorrhage）Study の一環で発見された未破裂脳動脈瘤 18 例 25 個の治療前，3 カ月後，1 年後の QOL を検討し，未破裂脳動脈瘤の治療に際して手術はかなりの危険性があり短期的な障害を来すか，1 年間に相当な回復が見込まれる．しかしその時点でも QOL の低下を訴えるものも多いと結論した[39]．Brilstra らはコイル症例 19 例，クリッピング症例 32 例において SF-36 およびうつスケールを用いて術前後の変化を検討した[7]．未破裂脳動脈瘤術前において，うつスケールで一般人よりも値が低かった．またクリッピング術後 3 名で合併症を生じ，1 年で QOL は改善するが，元の水準には戻っていなかった．一方コイル症例では 1 例がコイル後破裂にて死亡しているが，それ以外の症例では術前後で変化がなかった．これらより手術は未破裂脳動脈瘤患者の QOL に大きなインパクトがあり回復には時間がかかることが示された．現在日本では，UCAS Ⅱ（日本未破裂脳動脈瘤前向き QOL 調査）で 1,000 例の経過観察，手術例に関して定期的に QOL を含めた経過観察を行っ

ている．その結果により，未破裂脳動脈瘤が発見されることによる患者のQOL変化，時間を経た変化，さらに治療の効果が明らかとなることが期待される．

リスクコミュニケーションに関しての報告は少ない．Kingらは患者と脳神経外科医の44ペア双方に質問票を送り，診察説明後，手術適応，内容，最良の治療，そのリスクについてどの程度見解が一致しているかを検討した[27]．治療の方法・内容については80～90%の合致率でよく理解しているが，最良の治療方針については50%程度の合致率であり，また各治療のリスクについては2～3倍以上の不一致があることを報告した．例えば脳神経外科医が手術のリスクが10%程度と説明すると，患者は30%程度と理解していた．現在厚生労働省研究班u-Care，u-Shareでは，未破裂脳動脈瘤に関するリスクコミュニケーションの研究を進めており[3]，DVDによる患者説明補充が患者の疾患理解や治療選択に役立つことを実証した[36]．

インフォームド・コンセントを得る上では，各施設の治療アウトカムを提示することが望ましい．しかし日本の脳神経外科診療施設においてwebページに脳動脈瘤の治療数や治療成績を開示しているものは非常に少ない[16]．日本脳神経外科学会認定1,225施設のうち治療数は22.4%，破裂脳動脈瘤の治療成績は8.5%，未破裂脳動脈瘤の治療成績は2.6%の施設が公表しているにすぎなかった．

上記を踏まえてガイドラインでは下記のように推奨した．

- ● 未破裂脳動脈瘤が発見された場合，年齢・健康状態などの患者の背景因子，個々の動脈瘤のサイズや部位・形状など病変の特徴から推測される自然歴，および施設や術者の治療成績を勘案して，治療の適応を検討することが推奨される．なお，治療の適否や方針は十分なインフォームド・コンセントを経て決定されることを推奨する．
- ● 未破裂脳動脈瘤診断により患者がうつ症状・不安を来すことがあるため，インフォームド・コンセントに際してはこの点への配慮が重要である．うつ症状や不安が強度の場合はカウンセリングを推奨する．
- ● 患者および医師のリスクコミュニケーションがうまく構築できない場合，他医師または他施設によるセカンドオピニオンが推奨される．

2. 未破裂脳動脈瘤の治療適応

未破裂脳動脈瘤の年間破裂率や治療に伴う合併症の発生率，患者の年齢などの諸条件を入力することにより，治療に関する費用効果について複数の分析がなされている．しかしこれらの検討は入力条件によりその分析結果が異なり，動脈瘤全体として一括した検討が多く，個々の動脈瘤に対してどうするかという明確な推奨を与える根拠とはなっていない[1,2,10,19,53,62]．

未破裂脳動脈瘤の自然歴に関してエビデンスレベルの高い報告は少ない．未破裂脳動脈瘤の破裂率は大きさ，部位によって異なり，サイズが大きいものや，症候性の未破裂脳動脈瘤は破裂しやすいとされている．その他，高齢，女性，多発性，くも膜下出血の既往，喫煙，不規則な瘤の形状・ブレブの存在，dome-neck aspect 比の高いものなどが破裂しやすい因子として報告されている（Table 1）[5,22,32,41,43,49,52,54,56,60]．

欧米の61施設で行われた国際未破裂脳動脈瘤研究（ISUIA：International Study of Unruptured Intracranial Aneurysms）では2003年に前向き（prospective）データの報告がなされている[56]．くも膜下出血の既往のない7 mm以下の未破裂脳動脈瘤のうち，内頚動脈－後交通動脈瘤を除くWillis輪前方の動脈瘤はほとんど破裂しないことが示された．後方の動脈瘤では破裂率は年間0.5%であった．サイズがより大きな脳動脈瘤：7～12 mmでは前方の動脈瘤は破裂率は年間0.5%，後方は年間2.9%，13～24 mmでは前方年間2.9%，後方は年間3.7%，24 mm以上では前方年間8%，後方年間10%であった．5年間死亡率は12.7%で，破裂を認めた51例中33例（65%）が死亡した（Table 2）．

Table 2　Natural history of prospective cohort of ISUIA

ISUIA 2003	Size				
	<7 mm		7～12 mm	13～24 mm	24 mm<
	Group I	Group II			
Cavernous IC (n=210)	0	0	0	3.0%	6.4%
ACA/MCA/IC (n=1037)	0	0.3%	0.5%	2.9%	8%
Post-P com (n=445)	0.5%	0.7%	2.9%	3.7%	10%

〔Abbreviations〕 ISUIA: International Study of Unruptured Intracranial Aneurysms. IC: internal carotid artery, ACA: anterior cerebral artery, MCA: middle cerebral artery, Post: posterior circulation, P com: posterior communicating artery
Group I: not associated with subarachnoid hemorrhage, Group II: aneurysm found in patients with previous subarachnoid hemorrhage

Table 3　Outcome one month after intervention in the treatment cohort of ISUIA

	Surgery (n=1,917)	Endovascular (n=451)
Mortality	29 (1.5%)	8 (1.8%)
mRankin>2	55 (2.9%)	10 (2.2%)
MMSE<25	89 (4.6%)	15 (3.3%)
Both	81 (4.2%)	8 (1.8%)
Mortality & morbidity	254 (13.2%)	41 (9.1%)

〔Abbreviations〕 mRankin: modified Rankin scale, MMSE: mini-mental state examination

未破裂脳動脈瘤の頻度に関して人種別の差は未だ明らかではない[43]．しかし，くも膜下出血発症率はフィンランドと日本において他の地域よりも高いとされているため[17]，未破裂脳動脈瘤の破裂率が人種別で異なる可能性もある．最新のオランダグループのメタ解析（19論文より4,795患者，26,122人・年）では，未破裂脳動脈瘤の年間破裂率は5年以下の観察で1.2%，5～10年で0.6%，10年以上で1.3%と経過観察年数で破裂率がやや異なっていた．また，サイズによっても破裂率は異なり，5 mm以下でも0.5%，5～10 mmで1.2%，10 mm以上で1.5%であった．有意差をもつ因子は，5 mm以上の大きさ，後方循環，症候性，また日本およびフィンランドの研究であった[54]．

日本では未破裂脳動脈瘤に関して以下のように報告されている．瘤全体の年間破裂率については1.9～2.7%となっており，サイズが大きいもの，後方循環，症候性，多発性および多房性の形状などが破裂のリスクが高い因子であるという報告がある一方で，合併疾患や瘤の部位による破裂率の差は認めないとする報告もある[5,32,49,60]．

UCAS Japan（日本未破裂脳動脈瘤悉皆調査）はまだ中間段階であり，正確な破裂率は公開されていないが，破裂率は全体で年間約1%前後，破裂に関与する因子として，脳動脈瘤の大きさと部位が重要であり，現段階では有意差はないが高血圧，高齢者などもリスクファクターとして挙げられている[31]．

Yonekuraらは5 mm未満の小型未破裂脳動脈瘤を全例（329例，380病変），前向きに観察するSUAVe（Small Unruptured Aneurysm Verification）研究を行っており，375人・年の経過観察で3人に破裂（0.8%／年 95% CI：0.2～3%），18病変（4.7%）に2 mm以上の拡大が認められたと報告している．拡大や破裂に関与する因子として多発性・女性・70歳以上の高齢，部位として前交通動脈瘤および脳底動脈瘤を挙げている[61]．

治療に伴う合併症率も，未破裂脳動脈瘤の治療適応を決定する上で大きな因子である．治療による合併症の発生率は1.9～12%と報告されている[40,56]．

2003年に報告されたISUIAの前向き研究[56]では，開頭術後1カ月の時点における重篤合併症［modified Rankin scale 3以上，MMSE（mini-mental state examination）24未満となったもの］の発生率は12%，死亡率は1.5%，血管内治療ではそれぞれ7.3%，1.8%であった[56]．治療成績を悪化させる因子として開頭手術例では動脈瘤の大きさ（12 mm以上），部位（後方循環），症候性脳虚血の既往，症候性動脈瘤の関与が，血管内治療でも動脈瘤の大きさ（12 mm以上），部位（後方循環）の関与が報告されている（Table 3）．

この他，開頭クリッピング手術のリスクに関する因子として前交通動脈瘤や内頸動脈部分岐部動脈瘤という部位を挙げている報告，巨大ではない

前方循環の脳動脈瘤に限定すると死亡率は0.8%，合併症発生率は1.9%と治療に関するリスクは低いとする報告[57]，症例数や調査報告年度，年齢，性別，動脈瘤サイズ，部位に関して有意差は検出できなかったとする報告もある[26]．UCAS Japanの中間解析においても，2,600例超の治療成績では，modified Rankin scaleが2ポイント以上悪化する例は5%以下であった[31]．

未破裂脳動脈瘤に対する開頭手術が大脳高次機能へ与える影響について，ISUIAでは特に高齢者で高次機能低下が高率に発生していることを報告しているが[56]，未破裂脳動脈瘤開頭手術の術後に高次機能はむしろ向上し，ほかの数値の変化には差が認められなかったことを，術前後の知能・記憶検査，血流等の詳細な検討により示した研究もあり[37]，丁寧な手術手技により大脳高次機能面での合併症の発生は極力低く抑えることができることが示されている．

未破裂脳動脈瘤の血管内治療に関しては1999年にMurayamaらが報告しているが，115例（120瘤）の偶然発見された未破裂脳動脈瘤にGuglielmi detachable coil（GDC）を用いて血管内治療を行い，91%の瘤を完全あるいは準完全に閉塞することができ，4%が不完全閉塞，5%は閉塞不可能であった．治療後合併症は4.3%にみられたが，すべて初期の50例に発生し，後期の65例に合併症はなかった．不完全閉塞例のうち1例が治療後3年目に破裂した[35]．Brilstraらは未破裂脳動脈瘤・破裂脳動脈瘤の血管内治療のリスクに関して46報告の集計を行い[8]，総症例1,256例（うち未破裂脳動脈瘤276個）のうち合併症を3.7%に認め，744動脈瘤の完全閉塞率は54%と報告した．治療結果に明らかに関与する因子（未破裂と破裂，部位など）は認められなかった．

血管内治療と開頭手術の治療成績の相違についてはJohnstonらが報告している[18,20,21]．彼らは1施設，大学病院およびカリフォルニア州の病院における未破裂脳動脈瘤の開頭手術および血管内手術の成績の相違，入院日数，費用などの比較を行い，どの比較においても血管内治療は開頭手術に勝っていたという結果を報告している．血管内治療の治療成績は観察期間中年々改善しているが，手術においてはこの傾向は認められなかった．また施設間の治療成績格差については，手術症例数が多いほど，また血管内治療の割合が多いほど合併症が少ないというデータが示されている．Higashidaらは米国18州の429病院から集計されたデータバンクから，1998～2000年の間に治療された2,535例の未破裂脳動脈瘤の治療後1年間の有効性をクリッピング術と血管内コイル術で比較検討した[14]．血管内手術が開頭手術と比較し有意に合併症率（4.7%：7.4%），死亡率（0.9%：2.5%），費用（$42,044：$47,567）が低かった．上記報告はいずれも血管内治療の臨床的優位性を示唆している．しかし実際には，これらは無作為臨床試験ではないため単純に症例のアウトカム比較は困難である．また未破裂脳動脈瘤の破裂率は低いため，治療の有効性は1年間や短期間の観察で判断することは困難である．

治療適応は一般化することは困難であるが，10年以上の生命予後を有する患者では，一生涯の破裂危険性が治療リスクよりも十分高ければ治療を適応すべきであると考えられた．治療合併症発症率が3%未満であり，年間破裂率が0.5%以上の瘤は治療適応があると考えられる．上記の検討および日本でまとめられた動脈瘤の破裂危険性や治療合併症を検討すると，脳ドックのガイドライン2003でまとめられた推奨はほぼそのまま適用すると考えられた．しかし，大型～巨大動脈瘤では治療のリスクも高く，また新たな治療法も模索されている．そのような症例において治療をどのように推奨すべきかは未解決な問題も多い．

以下に治療適応に関する推奨をまとめる．

- 破裂率や合併症のリスクに基づいた治療の有用性の分析ないし費用効果分析は総合的評価であり，個々の動脈瘤に関する評価ができない．単純化された費用効果分析に基づいて治療方針を決定すべきではない．
- 未破裂脳動脈瘤の自然歴（破裂リスク）から考察すれば，原則として患者の余命が10～15年以上ある場合に，下記の病変について治療を検討することが推奨される．
  ①大きさ5～7 mm以上の未破裂脳動脈瘤

②上記未満であっても，
A．症候性の脳動脈瘤
B．後方循環，前交通動脈，および内頚動脈－後交通動脈部などの部位に存在する脳動脈瘤
C．Dome/neck aspect 比が大きい・不整形・ブレブを有するなどの形態的特徴をもつ脳動脈瘤

3．治療成績とその公表方法

前項でまとめたように治療成績に関してはさまざまな報告があるが，治療結果の判定が一定の基準で行われてはおらず，それぞれの結果を比較することは困難である．また publication バイアスも問題となりうる．Yoshimoto は 50 例以上の未破裂脳動脈瘤報告をまとめ，報告の種類により合併症率が大きく異なることを指摘した[63]．単一施設の後ろ向き報告では，1,457 例のうち合併症＋死亡率 7.8％と比較的合併症率が低い傾向があり，一方で 4 つの多施設研究またはコミュニティー研究（5,401 例）ではこの値は 20.3％，メタアナリシスは合併症＋死亡率はそれぞれ 5.0％，12.7％であり，単一施設報告の結果を反映していた．成績のよい報告が出版されやすく，その出版されたデータをもとにしたメタアナリシスはよい成績になりやすい．

今後は modified Rankin scale など単純なスケールによる調査のみではなく，患者の実際の活動レベルを測定すべく生活の質（HRQOL）や高次脳機能検査を含め詳細な術前・術後の検討を加え，その上で独自の施設の治療成績を公開していくべきと考えられる．

以上を踏まえ下記のように推奨した．

- 治療成績の評価にあたっては，単純なアウトカムスケールのみではなく，脳高次機能や生活の質評価などを併用して術前・術後の評価を行うことが推奨される．
- 治療にあたっては，治療施設の成績を提示しインフォームド・コンセントを得ることが推奨される．

4．経過観察の方法

動脈瘤を治療せず経過観察すると決定された場合，まず破裂に関与する後天的因子（喫煙，高血圧，大量飲酒）を避け[48]，さらに以後の瘤の拡大や変化，破裂に注意して慎重な観察を行わねばならない．

未破裂脳動脈瘤の拡大や新生に関しての報告は少ない．MRA や 3DCTA を用いた観察研究では，7％前後で瘤の拡大が認められたとの報告があり，Kaplan-Meier 法でみた拡大率推移は 1 年目 2.5％，2 年目 8％，3 年目 17.6％と年月を経過するごとに拡大するリスクが高まることが示されている[23,29]．拡大に関与する因子として大きさと多形性，病変部位としては脳底動脈瘤や前交通動脈瘤などが挙げられている[23,29,61]．

一方，動脈瘤の新生についてはいくつかの検討があるが，既に動脈瘤が発見された症例における新たな瘤の発生率を検討したものが多い．瘤の新生は年齢に比例し，女性，喫煙者，高血圧患者，多発動脈瘤のある患者に多いと報告されている．年間 0.2 ～ 1.6％程度の率で新生すると報告されている[9,11,15,23,50,55]．

近年実験的脳動脈瘤ではスタチンの服用により動脈瘤の拡大が抑制されるという報告もあり，今後未破裂脳動脈瘤に対する拡大・破裂防止のための内服治療が開発される可能性がある[4]．

以上より経過観察の方法として次のように推奨した．

- 開頭手術や血管内治療などの外科的治療を行わず経過観察する場合は，喫煙・大量の飲酒を避け，高血圧を治療する．経過観察する場合は半年から 1 年ごとの画像による経過観察を行うことが推奨される．
- 経過観察にて瘤の拡大や変形，症状の変化が明らかとなった場合，治療に関して再度評価を行うことが推奨される．

5．治療後の経過観察

未破裂脳動脈瘤治療後の長期成績に関しての報告は少ない．未破裂脳動脈瘤に対する血管内治療の根治性については，GDC を用いて 91％の病変