Barrow Ruptured Aneurysm Trial


BRAT was a response to the International Subarachnoid Aneurysm Trial (ISAT).2 McDougall et al1 wrote:

A major criticism of ISAT has been that a large number of patients treated at trial centers during the study were not included in the trial… Implicit in determining eligibility for ISAT was… consensus that either technique would be a suitable treatment option; and consensus that it was uncertain whether the ruptured aneurysm should be treated by neurosurgical or endovascular means. As a result of this policy, more than 9559 aneurysms were screened, but only 2143 patients were enrolled.

It is crucial to expose what was done to patients in BRAT in an attempt to address this weakness of ISAT:

… patients were assigned to a surgeon with a prestated treatment intent (coil or clip), but before embarking on that intended treatment, the assigned surgeon would naturally, as in daily practice, make a treatment decision based on what that practitioner believed would provide the best outcome for that particular patient. This decision may be to proceed with the “intended” or assigned treatment, or it may be that surgeon’s judgment that a particular patient would be better served by the other treatment modality, in which case the patient would “cross over” to the alternative treatment.

Because 205 (98%) of 209 treated patients assigned to surgical clipping underwent clip placement, but only 124 (62%) of 199 treated patients assigned to coil embolization underwent coil treatment (the other 75 were treated by means of clip placement), we can safely surmise that the real, overall treatment philosophy of the Barrow Neurological Institute was: clipping is the “standard,” default treatment; coiling may be a good option, but only in selected cases. Coil embolization was offered to 124 (30.4%) of 408 treated patients, 17% of all 725 screened patients. This is hardly better than ISAT.2

If the authors thought that imposing this process on patients served to improve the scientific credibility of their results, they were wrong. How can a group cherry-picked to include only those cases most favorable to coil embolization be fairly compared to a clip occlusion group that included everybody? (or everybody plus patients rejected from coiling?) We have in fact replaced the problem of eligibility in ISAT (what would results be had all patients been included?) with a new problem (what would have happened if patients had not been so stringently selected?). What would have happened if the surgeons had turned away a group of patients with aneurysms, and the endovascular specialists treating with coil embolization could not refuse? Finally, the burning question: how did endovascular specialists judge that coil embolization would provide the best outcome for a particular patient? It is unclear what to do with BRAT results; perhaps BRAT has taught us that a policy of “right of first refusal” for coil embolization can lead to better outcomes in a selected group of patients, as compared to a policy of clipping for all patients, but we already knew that from ISAT. What about all the other patients (with non-BRAT or non-ISAT aneurysms)?

We must remember that we cannot get answers to questions we never ask. If we want to know which of 2 options offers the best chance of the best outcome for an individual patient, both options must be available to that patient. Hence there is only 1 way to make valid comparisons that can be applied to clinical decisions in individual patients: to compare results of 2 options in patients eligible for both treatment options. There can be no ethical shortcuts; we must declare patients eligible for both options before knowing the results of treatment allocation. To do that, physicians are forced to admit the uncertainty to each patient with transparency, and to present alternatives in a truly balanced fashion prior to obtaining consent.

The BRAT was not, in fact, a randomized trial, but a registry of patients treated in 1 of 2 ways: Group A is made up of patients who happened to arrive on surgical days. They are told that surgery provides the best outcome for their particular case. Group B is made up of patients who happened to arrive on endovascular days, further selected to be the best cases for coil embolization, and patients are told that this treatment is believed to provide the best outcome for their particular case.

One purpose of BRAT was “to reflect real-world practicalities of ruptured aneurysm treatment in North America.” In that respect, the authors of the study are, unfortunately, perfectly correct, since the way medical care is delivered in almost all institutions across North America, and the way research was performed in BRAT, ensures that 1) not a single patient is really told about the uncertainty—they are told the physician always knows “the best choice;” 2) not a single patient is given a 50% chance of escaping our poorly justified beliefs; and 3) patients are not really free to participate—they are easily convinced to accept the physician’s preferred treatment. These, we claim, can be considered serious breaches in medical ethics, breaches that would be prevented with proper trials. That this way of treating patients seems “natural” to the designers of BRAT only reflects the vitiated and paradoxical nature of the notion of trust in the current physician-patient relationship: better pretend we know, even when we do not, to preserve patient trust and the illusion of physician omniscience and infallibility. But
how can we expect patients to continue to trust us, when we have admitted our uncertainty to each other, to the institution, to the ethics review board, but not to them, the ones who must bear the treatment outcome? Medicine in general and neurosurgery in particular will not progress until this conception is replaced with a more mature relationship, in research and medical care, a relationship that admits uncertainties when they exist, and squarely confronts them with properly designed trials. We are still far from this revolution.

A better, more ethical way would have been to offer the new treatment to each patient, but only as a 50% chance of getting the new treatment (coil embolization), with a 50% chance of getting the conventional treatment (clip placement), and only to patients the surgeon believed had a good chance of having a better outcome with the new treatment. The important point is that the physician does not really know and must admit this to the patient. This is difficult, but possible; this is, in fact, the design of ISAT.

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References


RESPONSE: We are grateful for the opportunity to discuss our work and provide clarification where needed. Darsaut and Raymond have raised several interesting points, which are addressed below in the sequence in which they were raised.

Darsaut and Raymond “surmise” that clipping was the standard therapy and note that treating 124 patients with coil embolization in this study meant that clipping was offered to only 17% of the screened patients and that this was, therefore, “hardly better than ISAT.” The actual patient flow was clearly described in our study. To compare numerators from different parameters of the 2 studies over the common denominator of number of patients screened for their calculation is misleading. About one-fifth of patients screened for ISAT were enrolled, whereas two-thirds of patients screened for BRAT were enrolled.

As Darsaut and Raymond are well aware, no study can recruit all patients screened, and many patients screened do not meet eligibility requirements. Half of the patients in BRAT were assigned to coiling and those who did not receive coils did not receive them for the reasons stated—hematomas that required evacuation, aneurysms too small to be safely coiled, and so on. To surmise that clipping was the standard therapy is simply wrong. The standard therapy for a given patient was the therapy to which the patient was assigned during the course of the trial.

But the comparison is misplaced for a more basic reason. First, although we note that the ratio of screened to enrolled patients in ISAT was a common criticism (as referenced in our article), we did not suggest that this criticism invalidated the findings of ISAT with respect to the patient population studied or even that it was a valid criticism. It was a simple recognition that in the mind of many clinicians, the ratio of screened to enrolled patients begged the question of whether the results of ISAT were broadly generalizable to the entire population of patients with ruptured aneurysms.

We tried to address this issue with BRAT by including all patients. The study therefore predictably incorporated many patients who were not really candidates for clipping, thus creating a level of “statistical noise.” As stated, BRAT was intended as a pilot study, with a view to a more rigorous multicenter trial. Gaining insight into the level of “noise” seemed an important step in determining the viability of such a trial. We did not suggest that BRAT was a “better” trial than ISAT; the trials represent 2 ends of a spectrum.

The BRAT studied a selection process in which the standard alternated between clipping and coiling. The intention-to-treat analysis tests the decision-making process more so than the procedure and counted all patients in the assigned treatment group—not a cherry-picked group of only favorable cases. An approach to clipping that is either more or less aggressive may well produce different results. The more appropriate question is whether morbidity and mortality rates can be further lowered by more or less aggressive selection for coiling.

Likewise, this point holds as a response to Darsaut and Raymond’s question of what would have happened if the surgeons treating with clip placement “had turned away a group of patients with aneurysms, and the endovascular specialists treating with coil embolization could not refuse?” To be unable to refuse providing a particular treatment seems an unlikely hypothetical situation. Nonetheless, for the sake of argument, the answer is that a different outcome would be expected. Because of the intent-to-treat analysis, however, the result—good or bad—would have been assigned to the clipping arm. If the clipping surgeon had a patient who, for whatever reason, the surgeon believed would have a better outcome if treated with coil embolization, it would be better strategically to cross that patient over to coiling so that the presumed better outcome would be applied to the assigned (that is, clipping) group.

Their question about how decisions were made regarding particular patients is answered in the manuscript. The primary decision for coil embolization was based on the anatomical favorability of the aneurysm for endovascular treatment. In ISAT, patients with unfavorable
anatomy were excluded from the trial and no knowledge of their fate was obtained. In BRAT, such patients crossed over to surgery, but their outcomes were considered according to the coil embolization group to which they had originally been assigned.

Darsaut and Raymond note that “BRAT has taught us that a policy of ‘right of first refusal’ for coil embolization can lead to better outcomes in a selected group of patients.” In fact, the policy was applied to all patients. The distinction is perhaps subtle but critical. Their question, “What about all the other patients (with non-BRAT or non-ISAT aneurysms)?” is addressed by looking at the group of patients assigned to coil embolization but crossing over to clip placement. In ISAT, the patients were a systematically selected subpopulation of patients with ruptured aneurysms, and critics of the study therefore argued that the results may apply only to a proportion of aneurysm patients, possibly as few as 22% (2143 of 9559). In BRAT, better outcomes were achieved when 62.3% of all patients with subarachnoid hemorrhage were treated by coil embolization. Furthermore, the outcomes of patients assigned to coil treatment but crossed over to surgical clip placement (a group approximating the “non-BRAT or non-ISAT” coil patients in question) matched those of the patients originally assigned to clipping (poor outcomes in 33.9%).

Next, Darsaut and Raymond raise the issue of randomization. Randomization is simply a mechanism for minimizing bias by maximizing the chance that the paired treatment groups are homogeneous. Although increasingly sophisticated techniques are required as studies become more complex, tossing a coin or even alternating between treatments can produce groups of sufficient similarity for comparison. The suggestion that it is somehow inappropriate to 2 treatment strategies, both of which are in widespread clinical use, or that such an endeavor constitutes an ethical shortcoming seems puzzling. Perhaps the remark is better understood in the context of their subsequent comments.

Darsaut and Raymond express concern not only about our consent process but also state that “the way medical care is delivered in almost all institutions across North America, and the way research was performed in BRAT, ensures that 1) not a single patient is really told about the uncertainty—they are told the physician always knows “the best choice;” 2) not a single patient is given a 50% chance of escaping our poorly justified beliefs; and 3) patients are not really free to participate” and furthermore that this constitutes “serious breaches in medical ethics.”

The use of hyperbole to provoke discussion is time honored. However, we hope that at some level, Darsaut and Raymond recognize the irony of using patently false characterizations of the way our trial was conducted (apparently their omniscient expert opinion) to castigate medical care in all of North America while at the same time calling for greater purity in clinical research. Indeed in our “real-world” practice, as in the BRAT, great pains are taken to explain the uncertainty that exists. Every effort is made to ensure that patients are provided with adequate information to make the best choice possible given these uncertainties. The far most common scenario in the trial and in daily clinical practice is that patients express frustration when told by “the expert” that we do not know which treatment is best.

It is an imperfect world and much more research is needed. It is vital to get consent right, to be transparent with patients, and to protect patients in their time of vulnerability. To a point, the allegations of Darsaut and Raymond underestimate our patients’ intelligence and sophistication. In obtaining consent and relaying to our patients our lack of omniscience, they routinely demonstrate understanding by asking all the right questions—questions we can only answer through further research.

Raymond and Darsaut have previously written about the difficulties the current environment imposes on clinical research and the need for clinical care trials. We are sympathetic to their frustrations and share their hope that a stronger culture of practical clinical trials can be developed. We do not, however, believe that this goal can be accomplished through misrepresentations of sincere efforts in this direction.

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Disclosure

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To THE EDITOR: We have read with great interest the results of the Barrow Ruptured Aneurysm Trial (BRAT) (McDougall CG, Spetzler RF, Zabramski JM, et al: The Barrow Ruptured Aneurysm Trial. Clinical article. J Neurosurg 116:135–144, January 2012). This superb study overcomes some concerns of the ISAT because of its design, avoiding the unacceptable number of nonincluded patients in that study.

However, we feel obliged to emphasize the uncentered nature of the trial, because there is a danger of misinterpreting the concept of “policy of intent to treat by endovascular coil embolization” followed at the Barrow...
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Neurological Institute. In the BRAT, even with the great experience of its endovascular neurosurgeons, 75 patients were crossed from coil embolization to surgical clipping, 61 of them because of anatomical limitations to endovascular therapy. The authors explain that their policy is to avoid the intent of coiling aneurysms if they are judged to be too small, if the neck is too wide, or if there is a high chance of incomplete occlusion. Nevertheless, we should not forget that in many centers around the world, mostly in Europe, more than the 90% of the patients admitted to their institutions with ruptured aneurysms are treated with coil embolization, and obviously, the concept of “first option to treat” in those centers is far more simplistic than the case-tailored one exposed in this study.

Thus, reading this article on the BRAT, we can accept the conclusion that in a center like the Barrow Neurological Institute in which endovascular and open neurosurgery are applied judiciously, the policy of intent to treat by endovascular coil embolization results in better outcomes at 1-year follow-up. Extrapolating this conclusion to other institutions in which the aggressiveness of the endovascular neurosurgeons is much higher could be misleading. We greatly support the authors’ intention to test the validity of these results by a multicenter trial that should include worldwide centers.

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Disclosure

The authors report no conflict of interest.

References


RESPONSE: We appreciate the authors’ interest in the Barrow Ruptured Aneurysm Trial. We acknowledge and agree with their assessment of the limitations of our study. We likewise hope that future efforts directed toward a multicenter trial are well received.

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Transnasal surgery


I would like to thank the authors for their commendable desire to contribute to the history of neurosurgery. However, doctors tend to rely on what other doctors have written in short publications in nonhistorical journals, and misconceptions are often propagated and further distorted as the information passes from doctor to doctor. Unfortunately, this is also the case in the current publication, where the authors have been very unlucky in their selection of sources and where many statements are highly questionable or obviously incorrect. This is evident regarding the written sources, the mummification process, and the development of excerebration over time. However, due to the limited space available, I will just comment on “neurosurgery” in Egypt. Concerning medical specialties in Egypt, the authors state:

“… one of these specializations was neurosurgery.”

“Depictions of neurosurgery in ancient Egypt represent the oldest evidence of neurosurgery in the African continent.”

“… proof of brain surgery can be found in Egyptian papyrus writings.”

“Ancient Egyptians were the pioneers in many neurosurgical techniques.”

“Egyptian skulls … bear witness to trepanning….”

While different specialties did exist, there is nothing suggesting that surgery was regarded as a separate specialty. The suggestion that the Wab priests of Sachmet were specialized surgeons has been thoroughly analyzed and refuted by Jonckheere,5,6 and there is nothing to support the suggestion of neurosurgery as a specialty in ancient Egypt.

The depictions of surgical procedures in Egypt are limited to the two circumcision scenes in the tomb of Ankma hor and in the precinct of the temple of Mut in Karnak. Of a possible surgical nature, further, is the treatment of a leg in the camp of Ramses II in the temple of Abu Simbel, and the scenes in the tomb of Ipwy demonstrating a person who seems to be removing a foreign body from the eye of another person, and then another person who may possibly be performing a Koscher maneuver for a luxated shoulder.7 Depictions of neurosurgery are nonexistent. El Gindi2 presented an image from an unnamed temple dated 1500 BCE, allegedly depicting a neurosurgical procedure. This interpretation is, however, highly imaginative, and I honestly cannot see any signs of a surgical procedure being performed. He did further mention a similar painting, In the Tomb of Bany Hassan, but without providing any further
information. None of these cases have ever been mentioned in serious works concerning the history of medicine, and should not be taken too seriously.

Regarding proof of brain surgery in Egyptian papyrius writings, the authors must be referring to the Edwin Smith papyrus. Even if several of the cases described are of a neurosurgical nature, I have failed to find any examples of what might even remotely be described as brain surgery. I am further unaware of any neurosurgical techniques pioneered by the Egyptians (at least not in vivo), since trephinations had a long history before the dawn of Egyptian medicine. This brings us to the Egyptian skulls bearing witness to trepanning. Contrary to popular conceptions, there does not exist a single Egyptian skull from the pharaonic era with unmistakable signs of in vivo trephination. When one traces the references, most claims regarding trephinations originate in the two skulls described by Breasted1 and Ghalioungui,4 respectively. The skull presented by Breasted was later reinterpreted as a case of symmetrical biparietal bone resorption. This is a well-known condition often occurring in the Egyptian osteological material.8,9 Ghalioungui suggested that the skull of Princess Horsiesnest Mertamen had undergone a trephination, but wrote that it might also be a traumatic lesion (which seems more likely). Thus, even if trephinations had existed in pharaonic Egypt, they must have been extremely rare.

I think that doctors should definitely read and write on the history of medicine. However, doctors writing on medicine are sometimes characterized more by enthusiasm than by a critical evaluation of the historical sources, and perhaps we doctors should read more before writing on this subject.

Disclosure

The author reports no conflict of interest.

References


Response: We would like to thank Dr. Blomstedt for his comments on our recently published paper. We note, however, that the author has largely overlooked the central theme of our paper. While we indeed commented on the history of medicine and neurosurgery in ancient Egypt, the two main points of the paper dealt with the development of the Egyptian technique of transnasal excerebration and the laterality of that technique.

As noted in the acknowledgments, the historical components of our paper were evaluated and verified by academic scholars at the American University in Cairo. The historical documents used and referenced in our paper, such as Herodotus’s Persian Wars and the Edwin Smith papyrus, are widely accepted historical accounts. These and other historical sources referenced in our paper support the presence of specialized ancient Egyptian physicians who surgically handled diseases of neurological basis.1,4

Furthermore, contrary to Dr. Blomstedt’s suggestion that the evidence of surgery is limited in ancient Egypt, the entire Edwin Smith surgical papyrus is dedicated to surgery and detailed anatomical observations.2 While there is currently no substantial evidence that ancient Egyptians practiced surgery on the brain itself, the papyrus includes 13 cases dealing with neurosurgical trauma to the skull and spinal cord,3 which are akin to procedures performed today by neurosurgeons. Case 3, for instance, describes stitching and bandaging of a penetrating cranial trauma reaching the brain in a patient with nuchal rigidity. The papyrus also comprises the first accounts of various types of dressings used in surgical procedures. Another papyrus, namely the Ebers papyrus, which dates back to approximately 1500 BCE, shows further evidence of surgery in ancient Egypt, including the surgical excision of tumors and abscesses.1 By use of the term “depictions,” we intended to refer to these descriptions rather than any illustrative representations of neurosurgery.

We thank the author once again for taking the time to comment on our work.

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References

Tumor model


The orthotopic brain tumor model has been widely used for investigating new molecular targets, chemotherapy, and radiation therapy. Iwami et al. conducted a study to create a simple and accurate method for percutaneous intracranial injection of cells into the brain through the mouse postglenoid foramen. This study demonstrated that the murine postglenoid foramen is “a well-conserved anatomical structure that allows percutaneous injection into the cerebrum, cerebellum, brainstem, and basal cistern in mice.” Importantly, the mean time for conduction of this injection technique through the postglenoid foramen was less than 2 minutes. A high rate of in-target brain tumor formation in the xenograft model beyond 80% was reported.

We agreed that intracranial injection through the postglenoid foramen is easy and less time consuming. However, since postglenoid foramen injection is performed through a manual percutaneous puncture procedure, it is difficult to assess the exact angle or depth of needle puncture into brain parenchyma without an external fixation device to repeat the same accurate neuroanatomical location as is possible with a stereotactic injection device in each mouse. This point is very important for the assessment of survival studies in an orthotopic brain tumor model. A minor deviation of angle or depth would lead to great variation in studies in such small animals. The incidental injection of glioma cells into cerebral ventricles would lead to hydrocephalus and contribute to the early death of mice. This phenomenon was not uncommon in MRI-based studies of an orthotopic murine glioma model (unpublished data).

Despite the aforementioned limitations, the authors’ study provided an easy intracranial brain tumor model through a percutaneous route. To achieve an ideal animal model, they should perform survival analyses corresponding with histological or imaging studies to confirm reliability in the aspect of survival data regarding postglenoid foramen injection in a mouse brain tumor model.

Disclosure

The authors report no conflict of interest.

Responses


Response: We thank Hueng et al. for their interest in our recent study. Brain tumor mouse models are important tools for developing new therapies, and stereotactic injection with an external fixation device is the standard method so far. But the stereotactic method is a complicated and time-consuming way resulting in excessive stress on mice. Therefore, we developed an easy and rapid manual procedure of percutaneous puncture into the mouse brain.

We agree that our novel method of postglenoid foramen injection is relatively difficult for assessing the exact angle or depth of needle puncture. In fact, the method requires a little ingenuity and skill to achieve good reproducibility with the freehand technique. However, a disposable pipette tip fit over the glass syringe provides consistent insertion depth. The insertion angles can be estimated visually with relative ease, because they consist of the standard angles—30°, 45°, and 90°. The 1-mm grid sheet laid under the mouse also helps to enhance the accuracy of these insertion angles.

As we have also considered that additional information about the survival of mice would be valuable to understanding the utility of this procedure, we here demonstrate disease-free survival times (that is, the time until the symptom appeared and the mouse was euthanized) for each target site (Fig. 1). In all groups, we observed...
consistent survival curves for mice with an even duration of 6 days. In this series, no mice were lost to early death, and hydrocephalus did not develop in any of them as determined by histopathological analysis.

We therefore consider that this novel method of post-glenoid foramen injection is useful and feasible for many other researchers in the field of neuroscience, although a case-by-case application should be made. We are now developing a method of increasing the accuracy of postglenoid foramen injection with a simple device of external fixation. We believe that these efforts will contribute to a more accurate and simpler way of intracranial injection in preclinical studies.

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Brain biopsy


Tissue confirmation is the most important step of stereotactic brain biopsy. Traditionally, the tissue diagnosis is determined by the final pathological confirmation. However, sampling bias may occur when there is lack of adequate support. 5-Aminolevulinic acid is helpful for intraoperative confirmation of the brain tumor in vivo in fluorescence-assisted procedures.1,2,5 Moriuchi et al.2 reported their pioneering experiences using 5-ALA during stereotactic biopsy for confirmation of target tumor samples. The biopsy specimens were assessed as tumor when irradiated with a 440-nm ultraviolet light source, which produces charcoal-red fluorescence in malignant tumor tissue. Therefore, one can easily and objectively discern the differences between tumor and control tissues.

The sensitivity of this method depends on the malignancy of the tumor.3–5 Valdés et al.6 reported that the high-grade gliomas demonstrated visible levels of fluorescence while the low-grade gliomas, metastatic tumors, and meningiomas revealed no visible fluorescence. We found it interesting that Valdés et al. reported that low-grade glioma exhibits no visible level of fluorescence, and Moriuchi et al.2 showed that pontine glioma only displayed slight charcoal-red fluorescence. However, we did not find Fig. 2D entirely convincing.2 This has prompted us to ask what kind of limitations would exist in the clinical application of 5-ALA. Discussion of this aspect of 5-ALA use could clarify this issue for curious readers and open other fields of clinical oncology applications.

The 2 cases reported by Moriuchi et al. have given neurosurgeons valuable information to consider regarding the application of 5-ALA in the diagnosis and treatment of deep brain tumors. Large-scale studies are necessary to confirm the statistical significance of the reduction of bleeding complications in stereotactic deep brain biopsy.

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Disclosure
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References

RESPONSE: We appreciate the kind words of Dr. Hueng and colleagues regarding our recent article demonstrating the efficacy of 5-ALA in stereotactic biopsy.

The intensity of the fluorescence depends on the grade of the glioma as reported.1 In malignant glioma, the fluorescence depends on certain conditions, such as the malignancy grade (MIB-1 index), cell density, and the density of the microvessels.3 In Case 2, involving a patient with a pontine glioma with an MIB-1 index of 12%, the tumor was thought to have a high degree of malignancy for a low-grade glioma. We could discriminate the areas of weak charcoal-red fluorescence from the other areas, in which there was no fluorescence. If this tumor were a low-grade glioma with a low MIB-1 index, the fluorescence would be too faint to discriminate it from healthy brain tissue. However, 5-ALA fluorescence still has limitations in other types of tumors. In some cases of metastatic brain tumors the tumor itself did not show any fluorescence (false-negative fluorescence), and fluorescent areas were observed in surrounding brain (false-positive fluorescence).4 Some malignant lymphomas did not show any fluorescence (false-negative fluorescence), especially after administration of steroid. Even in meningiomas, 83% of tumors fluoresced with 5-ALA under violet-blue light.2

We agree that further large-scale studies are necessary to confirm the statistical significance of the reduction of bleeding complications in stereotactic deep brain biopsy. To secure a histological diagnosis, intraoperative consultation with a pathologist is highly recommended for every biopsy that shows negative fluorescence, such as lymphoma, metastatic brain tumor, or other nontumorous lesions. The presence of positive fluorescence indicates that tumor cells are present in the samples, unless the samples are from tissue surrounding metastatic brain tumors.

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