Letters to the Editor

NEUROSURGICAL FORUM

Pituitary tumors and cavernous sinus extension

TO THE EDITOR: I read with interest the article by Micko et al.¹³ (Micko ASG, Wöhrer A, Wolfsberger S, et al: Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg* 122:803–811, April 2015). The authors have discussed surgery-related issues for pituitary tumors invading the cavernous sinus. The tumors are divided into groups as per the classification proposed by Knosp et al.¹² The authors reported that in Grade 2 and Grade 3 adenomas, the use of an endoscope resulted in the finding of cavernous sinus invasion significantly less frequently than when microscope was in use for tumor resection. The authors mention that when the internal carotid artery was encased by the tumor (Grade 4), all adenomas invaded into cavernous sinus and the gross-total resection rate was 0%.

The issue of pituitary adenomas invading the cavernous sinus, particularly as it relates to the possibility of radical resection of the cavernous sinus component, has been under discussion for some time. We (and others) have identified that the true radiological indicator of cavernous sinus invasion is complete and circumferential presence of tumor around the intracavernous carotid artery.^{6,7,9–11} In this respect only Grade 4 cases, using the classification system proposed by Knosp et al.,¹² will fall into the group of actual cavernous sinus invasion. When the tumor spares the lateral aspect of the carotid artery, the medial wall of the cavernous sinus is displaced and buckled into the region of the cavernous sinus, and the tumor may be both above (Grade 3A) and below (Grade 3B) the carotid artery rather than being actually present within the dural confines of the cavernous sinus.^{12,13} It is therefore not surprising that the authors identified that with the use of an endoscope they did not find cavernous sinus invasion in a number of Grade 2 and 3 cases. The authors have extensively reviewed the literature on the subject of pituitary tumors “invading” the cavernous sinus. We are surprised that they could not locate any of our articles on the subject in the literature.^{1–11} We have presented our experience of “giant” pituitary tumors in several platforms and proposed a classification of these tumors depending on their dural relationships in general and cavernous sinus invasion in particular. We identified that pituitary tumors sometimes grow to a massive size but “respect” the dura, which is

only displaced by the tumor and not transgressed. Consequently the diaphragm sellae is displaced superiorly and the medial wall of the cavernous sinus is displaced laterally by a number of tumors (Goel Grade I). It is unclear as to how some tumors invade into the cavernous sinus and transgress its medial wall and some do not. The cavernous sinus is frequently considered to be an extradural entity, and the “dural” nature of its medial wall has been under discussion for some time. We believe that the histological aggressiveness of the pituitary tumor may be a factor that determines tumor invasion into the cavernous sinus. Cavernous sinus invasion (Goel Grade II and III) is identified when the tumor circumferentially encased the internal carotid artery. Despite the cavernous sinus invasion, the tumors never transgress the lateral dural wall of the cavernous sinus. We have observed that the tumors sometimes elevate the dural roof of the cavernous sinus (Goel Grade III) but do not transgress this membranous wall. We observed that the pituitary adenomas that invade into or transgress the medial wall of the cavernous sinus (Goel Grade II) are not only anatomically, but also behaviorally aggressive when compared to Goel Grade I tumors. We have found that tumors that elevate the roof of the cavernous sinus (Goel Grade III tumors) are more prone to recurrence than tumors that invade into the cavernous sinus but do not elevate its dural roof (Goel Grade II tumors).

Surgeons using the endoscope for pituitary tumor resection claim that the lateral vision into corners in general and the cavernous sinus in particular is better with the endoscope than with the microscope. We now have an experience of surgery on over 3200 cases of pituitary tumors using the conventional microsurgical techniques. We find that if the dural relationships are appropriately understood, particularly as they relate to pituitary tumors and their potential to invade the cavernous sinus, conventional microsurgery can—if appropriately learned and practiced—provide satisfactory lateral vision to explore the tumor inside the confines of the cavernous sinus in general and also the part of the tumor that is lateral to the internal carotid artery. The radicality of resection of the part of the tumor within the cavernous sinus depends more on tumor characteristics like fragility and vascularity. We relate the issue of postoperative radiation therapy to our grading system. In general, we prefer to treat residual tumor in cases of Goel Grade III (and Grade IV) tumors with adjunctive radiation therapy.

The need and possibility of “total” resection of the intra-cavernous sinus component of the tumor and the effectiveness of the endoscope compared with conventional

microscope-based surgery will have to be evaluated in further studies of this subject. More than instrumentation, appropriate evaluation of actual need for resection of the intra-cavernous sinus component of the tumor and experience in pituitary surgery seems to be defining.

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Disclosures

The author reports no conflict of interest.

Response

We appreciate Dr. Goel's comments on our publications^{4,5} and his thoughts. Furthermore, we value his surgical experience as well as his classification of giant pituitary adenomas in general.¹

In contrast to Dr. Goel's work, the goal of our work was to revisit our previous classification of pituitary adenomas invading the cavernous sinus⁴ using the endoscopic technique and not to discuss suprasellar, supracavernous, and/or subarachnoid spreading of giant pituitary adenomas in

particular. The well-established classification of Hardy and Vezina² that already describes these growth patterns in detail was applied to all our cases.

In our experience, the endoscopic technique enabled us to remove more tumor tissue from the space of the cavernous sinus in particular and to have a better judgment whether invasion was present there than the microscopic technique. Unfortunately, histological specimens from the medial wall and from the space of the cavernous sinus are exceptionally rare, so the surgeon's judgment of tumor invasion is fundamental but subjective in some way. Despite this drawback we were able to distinguish different grades of cavernous sinus involvement in which the likelihood of invasion of the cavernous sinus space clearly increased with higher grades. We emphasize that the grade of invasiveness inversely correlates with the rate of gross-total tumor resection and endocrine remission and thus is a crucial parameter for outcome prediction.

We disagree with Dr. Goel's statement that invasion of the space of the cavernous sinus is only present in Grade 4 tumor extension, i.e., encasement of the internal carotid artery, which is absolutely not our experience. However, we agree that the structure of the medial wall as the weakest membrane of the cavernous sinus boundary³ has to be investigated further.

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Last call for clipping aneurysms?

TO THE EDITOR: With the publication of the most recent results of the Barrow Ruptured Aneurysm Trial (BRAT),³ we would like to take the opportunity to comment on the accompanying editorial¹ and the authors' response to clarify some misconceptions about other trials

such as the International Subarachnoid Aneurysm Trial II (ISAT II) (Spetzler RF, McDougall CG, Zabramski JM, et al: The Barrow Ruptured Aneurysm Trial: 6-year results. *J Neurosurg* 123:609–617, September 2015; Macdonald RL: Editorial. Clip or coil? Six years of follow-up in BRAT. *J Neurosurg* 123:605–608, September 2015). We must radically change the way we practice to enter the era of outcome-based neurovascular care.

The editorial analysis of the BRAT trial report and the authors' response raise two major concerns: 1) that open-surgery expertise is declining as practices convert from open to endovascular approaches; and 2) that the limitations of clinical trial methodology (any trial) make it unlikely that reliable answers to clinical questions can be obtained in a timely fashion.

The answers we are given to both problems are suffused with hopelessness: "Advocates of neurosurgical clipping of ruptured aneurysms are fighting an increasingly uphill battle with fewer and fewer troops."¹ Furthermore: "It would be most unfortunate for clinical equipoise to be lost solely because open-surgery skills generally fell into decline."¹ As to trials, we learned that "Sufficient questions remain regarding the relative benefits of the 2 treatment modalities to warrant further well-designed randomized trials," but the same authors also wrote: "Nor does ISAT II seem well positioned to fill this void any time soon."¹

Let's first address the problem with trials. In both the editorial and the authors' response, as in the received view, trials are conceived as experiments performed to provide answers to research questions. Clinicians are expected to modify their practice according to the results of trials performed decades earlier or to make a treatment recommendation for their next aneurysm patient, even when no one really knows what to do. Let's see why this system cannot work, and how it could be fixed.

The BRAT and ISAT investigations involved patients recruited 8–20 years ago (ISAT recruited from 1994 to 2002; BRAT, from 2003 to 2007). Since then, what have we been doing? This question encompasses not only our research activities (still meager considering the amount of work to do) but also how we have been caring for patients. If we have allowed ourselves to make treatment recommendations despite uncertainty for 20 years, is it surprising that we are now reluctant to give up our opinions according to results of trials performed so long ago?

The gulf created by clinical research conceived as an activity separated from the very clinical practice it is supposed to inform must be corrected. The burning question, "Should I offer open or endovascular treatment for this patient?" involves serious uncertainty. It should impact practice, the way we should care for that very patient, immediately. The change in practice cannot wait for an answer. BRAT was a step in the right direction, but why was it stopped? We need outcome-driven practices, but they can only be secured *after* we have learned to rightly practice under uncertainty, using proper trials, until better outcomes are actually shown. Not all trials live up to this calling, and there is no room here to rehearse the needed methodology, which we have explained elsewhere.² In short, neurosurgical trials can be designed to offer, in real time, optimal care in the presence of uncertainty.²

Trials such as ISAT II can also address the first concern of losing open-surgical skills: open surgery is neither crowned as "best forever" nor abandoned without good reason; it is offered and performed in 50% of cases, until it is shown to be superior (in which case it is prescribed, rather than randomly allocated) or inferior (in which case the alternative treatment is prescribed).

Who should be treated within ISAT II? If you consider clipping an aneurysm in a particular patient despite Level I evidence that coiling is in general better, you should rather offer the patient a 50% chance of receiving clipping and a 50% chance of receiving endovascular treatment. If you consider endovascular treatment for the types of patients who or aneurysms that were not included in ISAT, or using devices that were not available at the time of ISAT or BRAT, this should be considered experimentation, which should be offered only as a 50% chance of getting the innovative treatment, and a 50% chance of getting surgical clipping.

As the senior generation of neurosurgeons, many of them luminaries, hands over the reins to up and coming, fully trained open-surgery neurovascular surgeons, some with dual endovascular training, the thing to abandon is not surgical clipping—it is, rather, this outdated habit of practicing unverifiable care forever. This applies not only to ruptured aneurysms (ISAT II may very well turn out to be a "last call" for practicing and eventually having a chance to demonstrate the merits of surgical clipping), but also to arteriovenous malformations, unruptured aneurysms, and almost all domains of neurovascular care. Medical care is in constant evolution, and innovative ways to care for patients are constantly challenging the notion of standard care. We must discipline ourselves to learn how to practice in such a context, reliably sorting out what practice provides the best clinical results in real time, with care trials such as ISAT II.

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Disclosures

Drs. Darsaut and Raymond report being Principal Investigators of the ISAT II study (which did not receive any funding).

Response

In their thoughtful letter to the editor, Drs. Darsaut and

Raymond define the dilemma of choosing the best treatment for our patients in a time of uncertainty. Ideally, in a perfect world, this uncertainty would be clarified by having a mechanism in place that allowed all patients to participate in clinical trials to determine the superiority of one treatment over another before establishing the standard of care. One way to accomplish this is for external funding agencies to empower it, as in the Danish study showing support for endovascular treatment for stroke, which contrasted with the negative results of previous trials.¹

In the current clinical setting, we battle our own biases, powerful industry lobbies, and a flood of newly trained physicians—many with specialized skill in an individual area of expertise. The fact is that the treatment of patients in select high-volume specialty centers yields a better outcome than treatment in low-volume hospitals.² Yet the treatment of aneurysms is being dispersed instead of concentrated; endovascular treatment is increasingly being carried out in small hospitals by practitioners lacking adequate microsurgical expertise.

We agree with the authors that uncertainty should be confronted with well-designed trials to determine the best treatment for our patients; nonetheless, how to accomplish this effectively, efficiently, and expeditiously remains a challenge.

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Response

I welcome Drs. Darsaut and Raymond's provocative and eloquent comments regarding the Barrow Ruptured Aneurysm Trial and my accompanying editorial. They raise 2 concerns, the first of which I also posed at the beginning of my editorial. First, is another randomized trial of clipping versus coiling needed to guide the treatment of patients with cerebral aneurysms? Second, can clinical trials provide reliable answers to this question in a timely fashion? To address the second concern, I agree that it would be unfortunate if clinical trials became unfeasible due to lack of clipping expertise. We cannot know the answer to whether this matters now because we do not know if clipping is going to be required in the future. Although I didn't intend to make any specific comments about how to

conduct trials or on the design of ISAT II, I also agree that clinical trials of some design are needed to guide management of patients with intracranial aneurysms, as Spetzler et al. suggest. In my editorial, I simply expressed my opinion about what I thought was going to happen, which is that another trial (maybe other than ISAT II) will be very difficult to recruit for.

When I visit one prestigious neurovascular center, they tell me they use treatment X for ruptured aneurysms because they tried other things but X was the only thing that worked. In fact, they continue, it works so well they do not feel it is ethical to randomize patients to X versus Y or versus placebo. Then I go the equally prestigious neurovascular center down the road or across the border and they tell me they tried X and it didn't work so they use treatment Z and, in fact, it works so well that.... Isn't this clinical equipoise? While there are problems with this concept, it is still a basis for Darsaut and Raymond's argument—when the treatment of patients varies among good centers based on single-center, anecdotal, nonrandomized, unblinded case series data and perceived (but only possibly true) differences, then some type of study should be done to figure out whether the outcomes are equivalent or whether one is truly better.⁶ That is how a drug gets approved and is then used according to the label in the United States. The Food and Drug Administration guidelines on drug development provide succinct and solid recommendations (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/>). There would be no argument if we were discussing a new drug. However, many of the treatments in neurovascular disease employ devices or procedures that are not regulated in the same way and for which the development pathway is different. It has already been articulated that devices' easier path to approval, which can be attained without even a single randomized, controlled trial, along with the ability to be paid to use them, influences the use of these devices.¹ For example, an early-generation clot retrieval device (mechanical embolus removal in cerebral ischemia [MERCI]) was approved for use in a limited number of patients without randomized trials having been performed. On the one hand, this was suggested to be suboptimal because evidence of clinical efficacy was absent. On the other hand, it is interesting to speculate what would have happened if this device had not been approved and clot retrieval devices were perceived as ineffective. In the setting of a negative clinical trial, would companies developing these devices see the same opportunities that led them to develop newer-generation stent retrievers that we are celebrating as efficacious now?⁷

Furthermore, randomized clinical trials haven't been the basis for some current practices. We treat almost all ruptured aneurysms within 1 or 2 days of hemorrhage, but the timing of surgery is in part based on a large observational study.⁵ Is early aneurysm repair a question that needs to be addressed in a randomized trial? If the large observational cooperative study on timing of aneurysm surgery had been a randomized study, would we have obtained an answer faster and with fewer patients? I don't know the answer, I am writing a non-peer reviewed editorial and expressing opinions, and they are not necessarily the ones I hold but are just points to consider.

Adequately powered, randomized trials are the best way to obtain reliable information, and they should be conducted starting with the first patient.^{3,4} So why are we doing so few and adopting treatments in the absence of them? Some of the arguments against conducting randomized clinical trials are circular or self-fulfilling. It has been argued that neurovascular diseases are too rare and trials will take too long, but, on the other hand, it has also been stated that we cannot randomize patients because we already know what to do. Another interesting and common criticism is that the trial didn't include appropriately credentialed doctors who were as good as "me." Really? There are many others.

Given the regional differences in clipping and coiling and in keeping with my comment above about differences in care between centers, anecdotally there are almost certainly other factors that also determine whether a ruptured aneurysm is repaired by clipping or coiling.^{2,8} Even though I agree with Drs. Darsaut and Raymond, I still am worried that, given the decline in neurosurgical clipping, conduct of further trials of clipping versus coiling will be difficult.

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Sensitivity and specificity levels reported in the TBI literature

TO THE EDITOR: Sensitivity and specificity are among the gold standard measures of the performance of diagnostic tests, but the definition of "what good looks like" may be subjective and dependent on the standard of care. Recent studies in this journal (Maissan IM, Dirven PJAC, Haitsma IK, et al: Ultrasonographic measured optic nerve sheath diameter as an accurate and quick monitor for changes in intracranial pressure. *J Neurosurg* 123:743–747, September 2015; and Zheng P, He B, Guo Y, et al: Decreased apparent diffusion coefficient in the pituitary and correlation with hypopituitarism in patients with traumatic brain injury. *J Neurosurg* 123:75–80, July 2015) of tests used for patients with traumatic brain injury (TBI) reported high and well-matched sensitivity and specificity, but it is important to point out that these are not the norm.

Maissan et al.¹ reported sensitivity of 94% and specificity of 98% for optic nerve sheath diameter. Zheng et al.² reported values of 90.0% and 90.1% for the apparent diffusion coefficient (ADC). It is commonly understood that there is a trade-off between sensitivity and specificity, but a search of the literature since January of 2014 suggests that these values are often much lower and less well matched.

A literature search found 72 studies published over the past year and a half in which sensitivity and specificity values were reported for tests studied in the context of TBI (Fig. 1). These included a wide variety of clinical, imaging, and molecular tests. Although approximately a quarter of the tests (30/127) used in these studies reported sensitivity or specificity values > 95%, approximately a third (47/127) reported values ≤ 75%. Assuming that some studies of low-performing tests are never published, the latter proportion is probably higher. In addition, 40% of studies reported high sensitivity but low specificity, or vice versa. Furthermore, when studies reported more than one value for either metric (e.g., for different test thresholds), ranges were often greater than 10%.

Use of sensitivity and specificity is becoming increasingly important to compare different tests (e.g., CT and MRI) or modalities (e.g., imaging and molecular tests) to demonstrate clinical utility and comparative effectiveness. However, results such as those reported by Maissan et al. and Zheng et al., while impressive, should be seen as atypical. This brief literature search suggests that tests with lower performance might still be an improvement over standard of care, and expectations should be calibrated to the use of these tests in clinical practice.

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FIG. 1. Bar graph showing performance of tests. Although many tests reported sensitivity (Sn) and specificity (Sp) levels > 95%, the most frequently reported values were $\leq 75\%$.

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Disclosures

The author is an employee of Roche.

Response

We thank Dr. Sorani for his comments on our paper. Sensitivity and specificity are indeed high due to strong correlation of our data. The optimal conditions in the ICU and the single experienced observer design might contribute to this. We strongly recommend that reproducibility be investigated in other settings and larger series.

Iscander M. Maissan, MD
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Response

In this study, we aimed to identify the role of the ADC by using a diffusion-weighted imaging technique and to evaluate the association of such changes with hypopituitarism in patients with TBI. The mean pituitary ADC in patients with TBI was significantly less than that in controls (1.83 ± 0.16 vs 4.13 ± 0.33 , $p < 0.01$). Furthermore, the mean ADC was much less in patients with TBI who had pituitary dysfunction compared to those without hypopituitarism (1.32 ± 0.09 vs 2.28 ± 0.17 , $p < 0.05$). In ad-

dition, the receiver operating characteristic (ROC) curve analysis showed that the pituitary ADC could predict the hypopituitarism with a sensitivity of 90.0% and specificity of 90.1% at the level of 1.720. Last, the ADC value was positively correlated with the neurological outcome at 6 months post-TBI ($r = 0.602$, $p < 0.05$). Based on these findings, we consider that the pituitary ADC may become a novel biomarker to predict the pituitary function in patients with TBI.

As for the ROC curve predicting the occurrence of hypopituitarism based on the pituitary ADC value, the area under the curve was 0.891, with a sensitivity of 90.0% and specificity of 90.9% at the ADC value of 1.720. There are some reasons for both high sensitivity and specificity in the study. First, the ADC values are continuous data, which are very sensitive in an ROC study. Second, the incidence rate of pituitary dysfunction is fairly high in patients with TBI. The total incidence of hypopituitarism was approximately 51.2% at 6 months post-TBI. Last, the ADC value is significantly different between patients with TBI and those without TBI, between patients with TBI who have hypopituitarism and those who do not, and between patients with TBI who have good and those who have poor neurological outcomes. Therefore, all of these factors contribute to both the high sensitivity and high specificity of the ADC value in ROC analysis in the current study.

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Failing our colleagues, are we supporting our cerebrovascular partners?

TO THE EDITOR: We read the article by Fennell et al.³ (Fennell VS, Martirosyan NL, Palejwala SK, et al: Morbidity and mortality of patients with endovascularly treated intracerebral aneurysms: does physician specialty matter? *J Neurosurg* 124:13–17, January 2016) with great enthusiasm. The authors use a large data set to address a poignant question during this area of rapid growth in the field of endovascular neurosurgery: comparing the outcome of endovascular management of unruptured and ruptured aneurysms by different specialties. They concluded that mortality and morbidity of unruptured aneurysms are greater if treated by neurologists than if treated by radiologists or neurosurgeons. They attributed this difference primarily to more robust critical care training for neurosurgeons.

However, the data seem to suggest a different mechanism that underlies this discrepancy. First, interventional radiologists have the same or lower mortality (1.3% vs 1.4%, not statistically significant) than neurosurgeons despite having no critical care training. Second, division of

the analysis into elective and urgent cases provided useful insight and suggests a potential mechanism for the differences and outcomes. A primary thrust of the discussion includes the extent of neurocritical care experience in the various training pathways. If this were to be the primary limitation of neurologists in aneurysm management, one would expect that patients presenting with subarachnoid hemorrhage and associated risk of nonischemic neurological deficits and typical extended intensive care course would have a wider discrepancy in outcome between neurosurgically and neurologically driven management. However, the data actually demonstrate the opposite: we see that mortality is effectively the same among all 3 groups (11%–13%) despite being statistically significant. Morbidity continues to have a wider range (27%–34%), but it does not have the 105% relative risk difference observed in the elective cases. In the setting of aneurysmal subarachnoid hemorrhage, the 3 specialties may be more likely to pursue the same endovascular management plan rather than an open surgical approach in an inflamed brain with a more complicated sylvian dissection, thus eliminating one confounding variable and resulting in more direct comparison of technical skills (showing no clinically significant difference).

Another data trend may merit further investigation. The authors noted an increase in the endovascular treatment of unruptured aneurysm by neurologists (14% to 21% over the 6-year time course), which may be due to increasing aggressive endovascular treatment plans and which can account for increasing mortality and morbidity. Case selection is not discussed as a potential concern for differences in outcomes. Although the study is based on a data set from the University HealthSystem Consortium, there is still a discrepancy in the availability of open cerebral vascular surgery across the 117 academic medical centers and 333 affiliated hospitals. Several studies have demonstrated that differences in access to aneurysm treatment are dependent on socioeconomic factors and hospital volume.^{1,2} Discrepant access to high-volume open cerebrovascular surgeons may lead to more aggressive endovascular techniques. While a hybrid neurosurgeon might feel comfortable taking an equivocal elective case to the operating room, a neurology-trained interventionalist might not consistently have this option and may routinely adapt his or her tools to pursue more difficult elective aneurysms with an associated higher risk.

This paper comments on differences in morbidity across specialties and infers a training discrepancy. Is there further information on what the morbidities are? Are there further data on whether neurologists, interventional radiologists, and neurosurgeons are treating the same pathology or, for example, are neurologists treating more middle cerebral aneurysms with endovascular techniques than others? Although training standardization and transparency in outcomes continue to be an important topic, further investigation into local referral patterns may reveal that we may improve outcomes by facilitating relationships, access, and collaboration among the 3 specialties.

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Disclosures

Dr. Aziz-Sultan is a proctor for Covidien.

Response

No response was received from the authors of the original article.

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A paradigm shift toward MRI-guided and MRI-verified DBS surgery

TO THE EDITOR: We read with interest the editorial by Elias⁵ (Elias WJ: Editorial. Deep brain stimulation and intraoperative MRI. *J Neurosurg* 124:59–61, January 2016) and the accompanying article by Cui et al.⁴ (Cui Z, Pan L, Song H, et al: Intraoperative MRI for optimizing electrode placement for deep brain stimulation of the subthalamic nucleus in Parkinson disease. *J Neurosurg* 124:62–69, January 2016). The use of electrophysiology, clinical testing, and intraoperative MRI in deep brain stimulation (DBS) surgery on patients under local anesthesia is described as a “paradigm shift.”^{7,5} However, many European centers and, more recently, a few US centers have long moved past this particular milestone. The paradigm shift in functional neurosurgery is not simply the use of MRI to guide the surgical procedure. It is the use of stereotactic imaging to both guide and verify the DBS procedure.

Appropriate stereotactic MRI sequences can localize intracranial structures directly in patients under general anesthesia (GA), without the need for intraoperative clinical testing or neurophysiological recording.¹⁸ The radiological anatomy enables direct targeting, confirms lead position, and guides relocation if required. Moreover, systematic analysis of targeting errors permits development of

strategies to improve surgical accuracy and precision during subsequent procedures, thus tending to minimize the number of brain penetrations.⁷ Audit of lead location and its correlation with long-term clinical outcome can also inform targeting strategies to improve clinical outcome and minimize adverse effects secondary to stimulation.^{16,17}

The editorial rightly points out a major limitation of its accompanying study: the lack of clinical information and outcome data.⁴ However, other studies using a purely image-guided and image-verified approach do provide clinical outcome data and are not cited by either article. The Montpellier group has published excellent long-term results after MRI-verified pallidal DBS for dystonia in patients under GA.^{3,8} The Bristol group presented clinical hemibody results 6 months after MRI-verified DBS for Parkinson's disease.¹³ UPDRS (Unified Parkinson's Disease Rating Scale) data 9 months following MRI-verified subthalamic nucleus (STN) DBS in patients under GA have also been published by the San Francisco group.¹⁵ The Phoenix group is currently collecting clinical outcomes data after employing an image-verified approach to DBS in patients under GA.¹⁰ Yet another US center advertises the benefits of the MRI-verified technique under GA to patients via their website (http://my.clevelandclinic.org/health/diseases/conditions/hic_parkinsons_disease_an_overview).

Our group at Queen Square, London, has performed MRI-guided and MRI-verified DBS without microelectrode recording (MER) since 2002. Clinical results after surgery performed with patients in a state of GA and comprehensive clinical results 1, 5, and 8 years after STN DBS surgery have been published, including UPDRS data, quality of life scores, and neuropsychological evaluations.^{1,6,11}

As DBS aims to improve quality of life, safety is an absolute priority. An MRI-guided and MRI-verified approach is associated with a significantly lower incidence of all types of intracranial hemorrhage, including those leading to death or disability—an observation readily explainable by the fewer brain penetrations required by this technique.¹⁹

Additional benefits of the MRI-guided and MRI-verified approach include increased patient comfort and reduced anxiety as well as avoidance of complete levodopa withdrawal and consequently less confusion experienced by the patient in the perioperative period. Moreover, significantly shorter operative times and reduced cost ultimately allow more patients to access DBS therapy.⁹ During DBS surgery under GA, positive-pressure ventilation increases intracranial pressure that, combined with meticulous entry planning on a gyrus and short “dura open” time, prevents brain slump. Consequently, CSF egress, pneumocephalus, and brain shift are minimized.¹² Conversely, and somewhat perversely, huge targeting errors of greater than 5–10 mm have been reported in patients undergoing MER during awake stereotactic surgery, presumably as a result of large amounts of pneumocephalus and brain shift.^{2,14}

The editorial suggestion that “a hybrid technique that emphasizes electrophysiology and intraoperative imaging may become the standard for stereotactic surgery” may instead negate many of the advantages of a purely MRI-guided and MRI-verified approach. Ultimately, individual neurosurgeons should decide which techniques to

use when performing a procedure. However, many of the benefits of a paradigm shift toward MRI-guided and MRI-verified DBS surgery may never materialize if combined with traditional techniques.

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Disclosures

Dr. Hariz has received fees and travel expenses for speaking at meetings from Medtronic Inc. and St. Jude Medical. Dr. Hyam has received honoraria for attendance at scientific congresses from Medtronic Inc. and St. Jude Medical.

Response

The degree of clinical improvement achieved by DBS is largely dependent on the accuracy of lead placement.^{2,5,8} Various methods have been used to localize the STN, including MRI, image fusion, and a brain atlas preoperatively; intraoperative microelectrodes, intraoperative MRI, and temporary efficacy during the operation; and postoperative MRI and long efficacy postoperatively. In most functional neurosurgery centers, a combination of anatomical and physiological methods is usually used for STN localization.

We agree with Dr. Zrinzo regarding the advances in neuroimaging for DBS surgery. In recent years, studies using a purely image-guided and image-verified approach have shown good or excellent results for STN localization. For example, Aviles-Olmos et al.¹ reported on a cohort of 41 patients who underwent STN DBS in which an MRI-guided/MRI-verified approach was used without MER. The patients were followed up for a minimum of 5 years, with a subgroup of 12 patients followed up for 8–11 years. In that study, the long-term outcomes of patients evaluated using Part III of the UPDRS was satisfactory. Foltynie et al.⁶ reported on a study of 79 consecutive patients who received bilateral STN DBS in which an MRI-guided surgical technique was performed without MER. This procedure led to substantial improvements in motor disability of well-selected Parkinson's disease patients with accompanying improvements in quality of life and, most importantly, with a very low morbidity rate. Furthermore,

Starr et al.¹² reported that the use of high-field interventional MRI and a skull-mounted aiming device without physiological recording provided good control of Parkinson's disease symptoms. MRI-guided and MRI-verified approaches without MER and intraoperative neurostimulation testing have other benefits including lower risk of hemorrhagic complication, shorter operative times, lower cost, less CSF loss and pneumocephalus, mild brain slump, and increased comfort owing to general anesthesia and no levodopa withdrawal.^{8–10,12}

Despite such recent advances in neuroimaging for DBS surgery, the most commonly accepted method for DBS device placement requires conscious clinical and/or electrophysiological assessment.^{4,12} Both MER and intraoperative MRI can be used to pinpoint the STN from distinct electrophysiological and anatomical points of view. However, there are no comparative studies of the long-term postoperative outcomes between only MER-guided and only MRI-guided approaches.

MER can record electrical activity from different brain areas, especially in the STN. However, not every patient provides a typical STN signal. The traditional view of STN organization localizes the motor territory to the dorsolateral region of the nucleus.¹² We can clearly observe the STN and red nucleus on T2-weighted sequences from a 1.5-T MRI system. However, on axial T2-weighted MR images, the STN displays an irregular shape, and it is difficult to distinguish the dorsolateral region. Some of STN showed a left-right asymmetry and only a part of the STN structure. Thus, other locating measures should be used for these patients. In particular, MER can be used to guide electrode implantation. Intraoperative neurostimulation testing also allows early estimation of the efficacy of DBS. This allows us to reposition the electrodes if there is poor efficacy or obvious side effects—such as numbness, limb and facial twitching, eye deviation, or mood changes—during the low-voltage intraoperative neurostimulation testing. In our opinion, use of MRI guidance alone or the absence of intraoperative neurostimulation testing is insufficient, and rather should be combined with electrophysiology for the treatment of functional disorders.

We advocate the use of a simple and safe operative process in implanting the electrodes, although more attention should be paid to postoperative effects. Comprehensive analysis of various positioning measures with intraoperative MER, intraoperative MRI, and combined preoperative and intraoperative MRI data is key for accurate electrode targeting, relief of patient's symptoms (e.g., rigidity and tremor), and reduction of side effects of intraoperative stimulation.

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Response

No response was received from the author of the editorial.

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The endoscopic endonasal approach in the treatment of olfactory groove meningiomas

TO THE EDITOR: We read with interest the article by Banu et al.¹ (Banu MA, Mehta A, Ottenhausen M, et al: Endoscope-assisted endonasal versus supraorbital keyhole

resection of olfactory groove meningiomas: comparison and combination of 2 minimally invasive approaches. *J Neurosurg* **124**:605–620, March 2016).

The role of the endoscopic endonasal approach (EEA) in the treatment of olfactory groove meningiomas is controversial and has been a matter of discussion in the current literature. Various surgical approaches have been advocated to resect these tumors, among which the subfrontal (unilateral or bilateral) and pterional approaches are the most popular.

Supporters of transcranial approaches highlight the advantages of the faster surgical route, better vascular control, potential to preserve olfactory function, and lower rates of postoperative CSF leakage. Conversely, defenders of the EEA emphasize the lack of retraction and less manipulation of the brain, early tumor devascularization, and maximal resection of the base of the skull that may be infiltrated by the meningioma. Both approaches have caveats to achieve a complete tumor resection.

In the midst of this debate, Banu et al.¹ compared the EEA with the supraorbital keyhole approach (microsurgical with endoscope assistance) and a combined approach applying both techniques (i.e., “above-and-below” approach) for resection of olfactory groove meningiomas. They reviewed a prospectively acquired database of minimal access surgeries performed between 2004 and 2014 where 19 patients were classified according to operative technique. Tumors were assessed based on the Mohr radiological classification and the presence of the lion's mane sign. Adequacy of the resection was ascertained using volumetric analysis of postoperative MR images.

The authors reported that their selection criteria evolved over time. Initially, an EEA was attempted in all patients with olfactory groove meningiomas that did not extend laterally more than 1 cm beyond the lamina papyracea. A supraorbital keyhole approach was adopted after obtaining suboptimal results with respect to the extent of resection (EOR), closure of the skull base defect, and olfactory function. In their latter experience, patients with tumors extending through the cribriform plate, which required skull base repairs that could not be performed through a transcranial approach, the EEA was used in combination with a transcranial approach, concurrently or as a staged surgery. Therefore, as a result of their change in selection criteria, the authors rarely perform an independent EEA for olfactory groove meningiomas. They conclude that the limitations of an EEA might outweigh the benefits in the treatment of olfactory meningiomas, and they advocate the use of the supraorbital eyebrow mini-craniotomy with endoscopic assistance due to the greater EOR with fewer associated complications.

This is an interesting report that deserves the consideration of all skull base surgeons interested in this subject. However, we believe that there are factors that may have influenced the approach selection and analysis of the outcomes that were not highlighted by the authors. First, from a statistical viewpoint, the data are insufficient to draw dogmatic statements regarding the role of the EEA in the treatment of olfactory groove meningiomas.

Furthermore, early in their experience the authors attempted an EEA in all patients with olfactory groove meningioma extending no more than 1 cm lateral to the

lamina papyracea. Their series extends back to 2004, when EEA was available at very few centers worldwide. Surgical technology and customized instrumentation, as well as approach, resection, and reconstruction techniques, have undergone significant progress. Endoscopic surgical groups have achieved experience with increased improvement and refinement of patient selection. Therefore, one could attribute the reported suboptimal outcomes on their lack of experience or the so-called learning curve. We have to ask ourselves if the authors' extent of tumor resection and complications rates would be different under current circumstances and after 10 years of additional experience.

It is a well-known fact, and reinforced in the paper, that the risk of residual tumor laterally over the orbits is a limitation of the EEA, and, therefore, its presence could compromise EOR. Nevertheless, we are puzzled by the fact that most of the residual tumors, following an EEA, were located at median areas (i.e., cribriform plate, ethmoid sinuses, planum sphenoidale, and crista galli). Similarly, residual tumors for the "above-and-below" group were located at the planum sphenoidale and lamina papyracea. These locations are readily accessed as part of the endonasal approach. This indicates that the outcomes regarding the EOR are not necessarily related to limitations of the EEA.

Additionally, in these cases of tumors extending through the cribriform plate, in which the authors opted for the "above-and-below" approach, the EEA was performed either concomitantly or after a transcranial approach in 5 of 6 cases. We wonder if any of these tumors could have been completely removed through an exclusively EEA.

Likewise, the aforementioned small number of patients is an important limitation of the study. Aside from the lack of statistical power, there are other weaknesses in the analysis. Case 1 in the EEA group, for example, could be considered an outlier, as its extremely low EOR of 40.2%, significantly decreases the EOR average for this group (6 cases).

In adequately selected patients, the EEA yields superior surgical results in the management of other ventral median skull base tumors and has become a safe and reliable option in the armamentarium of skull base approaches. Improvement and development of surgical tools have reduced some of the limitations of the approach; for example, angled instrumentation has circumvented the limitation to resect tumors at the most anterior aspect of the skull base. Similarly, progressive refinements of the surgical techniques have improved the access and resection of tumors in this area; removal of the lamina papyracea allows the displacement of the orbital soft tissues, thus allowing the resection of tumors that extend beyond 1 cm lateral to the lamina. In our experience, as long as the meningioma does not have a dural attachment that extends superiorly at the level of the posterior table of the frontal sinus, or laterally over the orbital apex (where displacement of the orbital soft tissues is limited), it may be safely dissected and removed via an endoscopic endonasal route.

Similarly, the reconstruction of the most anterior region of the skull base defect has also improved through the use of a variety of multilayer techniques, including the development of pedicled endonasal flaps (first reported in 2006) and further refinements in the temporary bolster to support the reconstruction.

As for any other skull base approach, patient selection is critical for the success of an EEA. Nonetheless, one should recognize that patient selection is not only influenced by the histology and extent of the lesion, but also by the surgical team's experience, skills, and resources, as well as by the patient's comorbidities and preferences. Use of an EEA for olfactory groove meningiomas does have important limitations. Those of greater significance include the risk of anosmia in patients with adequate preoperative function, risk of hemorrhage or cerebrovascular accidents in patients with tumors that show vascular encasement, and the risk of residual tumor in patients with lateral or anterior dural attachments. Albeit important, these caveats do not eliminate the EEA as an alternative in adequately selected patients. In our opinion, in the presence of an experienced team with adequate institutional resources, the EEA remains as one of the main surgical approaches to manage olfactory groove meningiomas. One can maximize the advantages of the EEA with an unbiased and appropriate patient selection.

Furthermore, we believe that the EEA is suitable for a broader range of olfactory groove meningiomas than Banu et al.¹ suggested. The ideal patient would be one with impaired olfaction and with a tumor that is not attached to the posterior wall of the frontal sinus and that does not extend beyond the meridian of the orbit or to the superolateral aspect of the optic canal (anterior clinoid). The size of the tumor does not seem to be a significant factor. Presence of sinonasal invasion is not mandatory in order to indicate an EEA. Conversely, vascular encasement is not an absolute contraindication, although it definitely compounds the difficulty and risks of the surgery.

In addition, the EEA offers supplementary value in the surgical management of giant olfactory groove meningiomas with significant bi-frontal lobe edema. In our experience, patients with these tumors are the ones who benefit from staged or combined procedures. Different from most "above-and-below" cases presented in the paper by Banu et al.,¹ our strategy consists of an initial EEA procedure with the goal of debulking and devascularizing the tumor. This creates the possibility for tumor collapse and improvement of brain edema, thus facilitating a less traumatic dissection at a second stage, which can be through another EEA or an alternative transcranial approach.

In conclusion, each skull base approach and technique has advantages and limitations that must be weighted and considered when selecting the best treatment management for a particular patient. Endoscopic endonasal approaches represent an excellent alternative for the surgical management of the majority of olfactory groove meningiomas independently or in combination with open approaches. The use of EEAs for olfactory groove meningiomas must not be excluded based on the initial poor outcomes of a single surgical team.

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Disclosures

Dr. Carrau reports that he has received travel expenses to participate as faculty in a hands-on course from Medtronic.

Response

Dr. Beer-Furlan and colleagues present a thoughtful assessment of our paper and we thank them for taking the time to read and analyze our paper and provide their valuable opinions. We also thank the *Journal of Neurosurgery* for the opportunity to respond. We will first address each of the authors' comments and then provide some analysis of the published literature to support our perspective.

The first claim made is that, given the limited number of patients reported, there is not enough statistical power to make any dogmatic statements. We could not agree more. Our observations were meant to be food for thought to encourage further investigation and discussion in this area and to provide some data, rather than anecdotes, regarding outcomes of surgery for olfactory groove meningiomas using different approaches. The reviewers also correctly point out that the initial cases were done in 2004, at the beginning of our learning curve. There is no doubt that the technical abilities and decision making of our center have improved over time.¹ However, during this same time period, we were also learning how to remove planum and tuberculum meningiomas, and, while our results continued to improve with respect to meningiomas in other locations, the results for olfactory groove meningiomas remained suboptimal.¹⁰ Moreover, we also embarked on a learning curve for the supraorbital craniotomy with endoscopic assistance and a learning curve was in effect for these cases as well, which we performed less frequently than endonasal cases.

The authors' main point to support their use of the EEA for olfactory groove meningiomas is that it has been shown to be superior to transcranial approaches for other pathologies. This seems like a weak argument, since an approach cannot be evaluated without the context of a specific pathology. While we agree that the endonasal approach has been shown to be better for other pathologies and have even published several articles supporting this claim,^{2–8} the same cannot be said for olfactory groove meningiomas, where the data from the literature show inferior results using the endonasal approach.⁷ The authors go on to recommend the endonasal approach based on their anecdotal unpublished experience. There is no question that the surgeons in Ohio are outstanding endonasal surgeons and that their results are likely as good as they can be for the endonasal approach. Nevertheless, until results are published and evaluated objectively, it is difficult to draw any conclusions. We have only the existing published results in the literature to go on and, absent any prospec-

tive randomized data, must rely on retrospective data with all its inherent biases.

The largest series of endonasal endoscopic resections of olfactory groove meningiomas published to date is a series of 50 patients operated on at the University of Pittsburgh Medical Center (UPMC), which was published in 2014.⁹ One could hardly argue that this group does not have adequate experience or technical expertise to perform this surgery in a highly skilled manner. In these patients, gross-total resection (GTR) was achieved in 30 of 50 patients (60%), the average length of surgery was 9 hours, and the average length of stay was 11 days; 36% of patients required more than 1 endonasal surgery to achieve their results, which further increases the amount of time in the operating room and hospital stays for each patient. Although Beer-Furlan et al. claim that size is not a significant factor in EOR, the group at UPMC clearly stated that size significantly limited EOR ($p = 0.002$). Moreover, complication rates were fairly high. Although a total complication rate is never reported, there were 44 complications, so the overall rate may have been 88%, including CSF leak (30%), deep venous thrombosis/pulmonary embolism (20%), sinusitis (10%), respiratory failure requiring tracheotomy (8%), ventriculoperitoneal shunt (6%), abscess formation (6%), seizure (4%), and stroke (2%). Moreover, while only 8 patients complained of anosmia before surgery, all 50 patients were clearly anosmic after surgery given the approach. As for the learning curve, the rate of GTR improved to 80% at the end of their series, but the introduction of the nasoseptal flap had no influence on CSF leaks, which remained at 30%.

Until other groups start to publish their results in large numbers, the series out of UPMC represents the best assessment of the results following endonasal endoscopic resection of olfactory groove meningiomas. A recent review of the literature showed that traditional craniotomy resulted in GTR rates of 92.8%.⁷ At some point we have to look closely at our results and decide whether an EEA truly offers the best possible outcome for our patients in this situation. As we clearly discussed in our paper, the endonasal approach will always have an important role to play in the management of olfactory groove meningiomas in selected cases. The real issue is whether it should be offered to all patients as the initial surgery of choice. We eagerly await the publication of additional large series of consecutive endonasal operations for olfactory groove meningiomas so that this discussion can continue.

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Cadaveric CSF reconstitution model for neuroendoscopic intraventricular procedures

TO THE EDITOR: We read with avid interest the article by Winer et al.⁸ (Winer JL, Kramer DR, Robison RA, et al: Cerebrospinal fluid reconstitution via a perfusion-based cadaveric model: feasibility study demonstrating surgical simulation of neuroendoscopic procedures. *J Neurosurg* 123:1316–1321, November 2015). We commend the authors for promoting the concept of “lifelike” cadaveric laboratory training. They describe a cadaveric surgical simulation for intraventricular neuroendoscopic approaches and techniques by reconstituting natural CSF flow in fresh human cadavers. An arterial catheter was inserted through a simple cervical laminectomy and dural opening, and saline as a CSF substitute was continuously perfused at physiological pressures to reconstitute the subarachnoid space and ventricles. Endoscopic third ventricu-

lostomy, navigation of ventricular cavities, and a variety of endoscopic procedures were practiced.

Having described this technique more than 13 years ago in an article we published in the *Journal of Neurosurgery*,¹ we believe our model provides more benefits and succeeds in dealing with the shortcomings of their procedure. We described a more sophisticated model for neurosurgical training in which we reconstructed life-like circulation in the cerebral vessels and CSF flow in the subarachnoid space. We cannulated the carotid arteries, vertebral arteries, and internal jugular veins on both sides of the neck section in cadaveric heads. Two tubes were introduced into the spinal canal, and each one was advanced into one of the cerebellopontine angle cisterns (Fig. 1). One of the tubes inside the spinal canal was then connected to a serum bag filled with clear fluid, which was located at a higher level than the specimen. The fluid advanced through the tubes to the subarachnoid space under gravity, and the flow rate of the fluid was adjusted as desired. The other tube was connected to another fluid container near the specimen. This tube was designed to receive fluid running through

FIG. 1. View of the neck section showing cannulation of a head specimen in our “live cadaver” model. C = tube in the carotid; J = tube in the jugular vein; V = tube in the vertebral artery; S = tube in the subarachnoid space. Reproduced from Aboud E, Al-Mefty O, Yaşargil MG. *J Neurosurg* 97:1367–1372, 2002.

the subarachnoid space or was kept closed when suction was used during the training procedures.

After a frontal bur hole had been made, the sheath of the endoscope was introduced toward the lateral ventricle. The optic apparatus was introduced after the introducer had been pulled out, and the choroid plexus and the septal and thalamic veins led the way to the foramen of Monro. The endoscope passed the foramen into the third ventricle, and the mammillary bodies and the infundibular recess were identified. The floor of the third ventricle was perforated in front of the basilar artery (BA) bifurcation in the area of the tuber cinereum. The BA trunk and branches, which were filled and pulsating, were identified in the interpeduncular cistern. One can practice irrigation and clearing of liquid inside the ventricles and can observe pulsation of the BA and identify the liquid flow through the fenestra (Video 1).

VIDEO 1. Endoscopic access to the ventricles using the "Live Cadaver." Copyright Emad Aboud. Published with permission. Click here to view.

Other issues in their article⁸ are the way that the authors reconstituted the CSF and their use of fresh cadavers, which led to limitations regarding the integrity of cerebral tissue and the reliability of accessing and completing the intended neurosurgical procedure. The Medtronic Bio-Pump that they used built a pressure of 15–30 mm Hg in a closed system. Intracranial pressure (ICP) values of 20–30 mm Hg represent mild intracranial hypertension; however, in certain cases, herniation can occur with ICP values less than 20 mm Hg.³ According to the Monro-Kellie doctrine, the total volume of intracranial compartments (blood, CSF, brain) is constant; therefore, any change in the volume of one must be accompanied by an equal and opposite change in the other.^{6,7} This would be more prominent in the case of a fresh cadaver, in which the brain is so soft and most of the arteries and veins are blocked with noncompressible clots and blood debris. Therefore, as the pressure builds up in the subarachnoid space, the volume changes will occur largely at the level of the brain parenchyma, which will be compressed against the ventricles, and the anatomy will be shifted and herniation can happen. We noticed such events in our model when we used fresh cadavers even when the blood flow to the vessels was turned off. Another factor that adds more congestion in the brain is the outflow of the CSF through the arachnoid granulations to what was left patent of the cerebral venous system. Postmortem flow via arachnoid granulations in both ways has been proved and observed in our model and by other authors as well.^{2,5}

To overcome some of the shortcomings in using fresh cadavers, we advise the authors to use cadavers preserved with light embalming techniques such as the one described by Benet et al.⁴ These techniques have benefits from both cryopreservation and formaldehyde embalming. We have been using similar embalming techniques for many years and with satisfactory results.

In our model, to achieve adequate filling of the ventricles, after reconstituting the subarachnoid space, we tend to fill the ventricles through the trocar itself. Having liquid under higher pressure in the ventricles will provide a more

realistic ventriculostomy in which the flow through the fenestra into the interpeduncular cistern can be appreciated.

We have been using this model successfully for many years in neurosurgical training workshops and courses in different training facilities and institutions in the US and abroad.

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Disclosures

The authors report no conflict of interest.

Supplemental Information

Videos

Video 1. <https://vimeo.com/148138126>.

Response

We thank Aboud et al. for their important comments pertaining to our paper and for drawing attention to their report on the model they previously developed, which was regrettably absent from our literature review.¹ There are clearly certain advantages in tissue integrity when using chemically preserved specimens (as described by Aboud et al.) over the cryopreservation techniques used at our institution, although the techniques advocated by the authors require significantly more preparation time, the use of toxic chemicals, and potentially higher costs. Furthermore, we agree that direct, concurrent cannulation of the cerebral vasculature can add to the lifelike reproducibility of cerebral blood flow in neurosurgical simulations, but in

our experience it can also compromise visualization because of the poor integrity of the microvasculature in some cadavers. In our model we have found that by perfusing the ventricular space indirectly in a fresh-frozen cadaveric specimen, we can perform several novel procedures not described by Aboud et al. For example, with our simplified CSF perfusion model we could successfully perform septum pellucidotomy, aqueductoplasty, and exploration of the fourth ventricle using standard neuroendoscopic instruments, techniques not described in the model developed by Aboud and colleagues. In addition, we described the benefits of reliably reproducing the haptic sensation and visual response of CSF flow when inserting an external ventriculostomy catheter into a previously uncanalated ventricular space, an educational experience that is nearly equivalent to practicing this technique in a live patient. Finally, by perfusing the CSF spaces via a cervical laminectomy, our trainees can gain experience with that procedure as well, although a rudimentary version can be easily achieved by a technician, and thus allowing for either additional surgical training or a simple setup prior to trainee arrival. We are honored to have the opportunity to describe the feasibility of our novel variations on this important model championed by Aboud et al. over the past decade.

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Low-flow bypass and wrap-clipping for ruptured blister aneurysms of the ICA

TO THE EDITOR: We read with great interest the article by Bojanowski et al.¹ (Bojanowski MW, Weil AG, McLaughlin N, et al: Morphological aspects of blister aneurysms and nuances for surgical treatment. *J Neurosurg* 123:1156–1165, November 2015).

Blister aneurysms are extremely difficult to treat by surgical or endovascular means because of their small size, very fragile walls, lack of an aneurysm neck, and tendency to avulse with minimal manipulation. Surgical strategies

have included clipping, wrapping, wrap-clipping, and trapping with bypass. Direct clipping is considered too hazardous; it often results in aneurysm avulsion and internal carotid artery (ICA) laceration,⁵ as well as ischemic complications secondary to hemodynamic hypoperfusion or occlusion of the perforating artery or vasospasm. Therefore, it is important to consider both the repair of the ruptured blister aneurysm and the potential for cerebral ischemia intraoperatively. If reconstruction of the cerebral circulation with bypass is performed, tolerance for ischemia could be carefully anticipated.

This paper by Bojanowski et al. gave us new insight to think about the morphology of the blister aneurysms according to the stages of morphological changes. For different types of blister aneurysms, different clip strategies were applied. However, there are a few issues about which we felt uncertain.

First, blister aneurysms occur most frequently on the superior or anteromedial wall of the ICA, but may also be found on the anterior, anterolateral, lateral, and postero-medial wall of the supraclinoid ICA.^{6,10} It is not easy to expose an overall perspective to distinguish the aneurysmal configuration, especially in laterally projected aneurysms. Some aneurysms may have a normal wall (like Type I and II) and can be clipped at the neck. However, just accessing the aneurysm for observation can result in massive hemorrhage. Once massive bleeding has occurred, rescue of normal blood flow through the ICA is not always possible.⁵

Second, to assess the necessity of bypass by using only balloon test occlusion may be troublesome because analysis of results may be difficult in patients with a decreased level of consciousness, neurological deficits, or both. There may also be a bleeding risk due to the use of constant irrigation while systemic heparin administration is being performed in patients with ruptured cerebral aneurysms. The risk of immediate ischemic complications after permanent ICA occlusion has been reported to be between 2% and 22% in patients with good ischemic tolerance to carotid artery occlusion tests, based on findings from SPECT cerebral blood flow studies.^{2,7,9} The so-called “collateral blood flow compensation” can be insufficient if the patients participate in sports or any exercise that increases the hemodynamic stress, and it can lead them to delayed cerebral ischemia or infarction.

It is speculated that permanent ICA closure is riskier not only in the acute phase of subarachnoid hemorrhage but also in the subsequent phase. A previous investigation revealed poor outcomes in patients who were not treated with combined revascularization surgery.⁵ As described by Bojanowski et al., these authors prefer to purposely include a portion of the healthy wall while clipping the blister aneurysm (Types I–III), producing a small stenosis of the parent artery. Ogawa et al. reported ischemic complications in a patient with ICA stenosis after blister aneurysm clipping.⁶ Therefore, reconstruction of hemodynamic circulation is essential intraoperatively, especially in cases with stenosis of the affected artery or insufficient collateral blood flow compensation. This is true because ischemic complications are prone to occur secondary to hemodynamic hypoperfusion or vasospasm.

Third, simple clipping may be a dangerous and inap-

appropriate treatment for most blister aneurysms, and forced trapping after intraoperative bleeding when approaching a blister aneurysm is associated with high morbidity and mortality.⁵ Wrap-clipping combined with bypass surgery may be a useful surgical strategy.^{3,4} Although superficial temporal artery–middle cerebral artery (STA-MCA) bypass is not always sufficient as a substitute for the ICA, low-flow bypass surgery is minimally invasive, does not take as much time as would be needed in high-flow bypass, and has a short learning curve. The aforementioned low-flow bypass could increase cerebral ischemic tolerance when intraoperative aneurysm rupture makes parent arterial sacrifice unavoidable and high-flow bypass is indicated. If the aneurysm can be clipped, the STA-MCA bypass does not disturb the clipping procedure at all.

Even though there are no randomized clinical trials evaluating the outcome of extracranial-intracranial bypass surgery in intracranial aneurysms, there is a long list of case series that support our practices and show that these revascularization procedures can reduce the risk of late ischemic stroke.⁸ We believe that it is important to perform routine STA-MCA bypass before trapping of the ICA in patients with a ruptured blister aneurysm, and to perform wrap-clipping rather than only trapping or clipping, although the present strategy seems to require more time and some effort to establish the bypass.

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Disclosures

The authors report no conflict of interest.

Response

We thank Dr. Han et al. for their interest in our paper. Their comments give us the opportunity to point out certain fundamental elements regarding the structure of a blister aneurysmal wall.

By definition, blister aneurysms have no “normal” wall; the entire wall of a blister aneurysm is diseased. This understanding is critical when considering direct clipping. Types I and II blister aneurysms may resemble saccular aneurysms, but are not.¹ Contrary to Dr. Han et al.’s statement that “Some aneurysms may have a normal wall (like Type I and II) and can be clipped at the neck,” blister aneurysms, even Types I and II, must not be clipped at the neck without including a portion of the healthy wall of the parent artery. Otherwise, indeed massive bleeding may occur. This is why it is so critical to recognize when we are dealing with a blister aneurysm as opposed to a typical saccular aneurysm. We suspect that such nonrecognition as well as insufficient knowledge about the diseased wall of all blister aneurysms may be the reason for the reportedly high risk of intraoperative rupture.

Despite Dr. Han et al.’s concern regarding the difficulty “to expose an overall perspective to distinguish the aneurysmal configuration,” in all cases in our series we were able to easily identify the extent of the diseased wall. Also, in reviewing the literature, most aneurysms were Type I or II, involving a limited portion of the carotid wall, thus making them easy to identify. In addition, although we agree that there is a possibility of cerebral ischemia when the clipping includes a small portion of the wall of the normal parent artery, if adapted surgical strategies are used, blister aneurysms can be successfully clipped while maintaining normal blood flow, which may be assessed during surgery by using transsonic Doppler studies, indocyanine green angiography, or intraoperative neurophysiological monitoring. We do not recommend routine wrap-clipping because wrapping may obstruct proper viewing when clipping and may jeopardize perforators. We use wrap-clipping for Type IV aneurysms, although it may also be appropriate for some Type III aneurysms.

Only as a last resort, when the parent artery has to be occluded or when blood flow after clipping is insufficient, would we perform an extracranial-intracranial bypass. We believe that indiscriminate, routine use of the bypass may be potentially harmful.¹ Once the skull is open, the change

in transmural pressure may cause an aneurysm to rupture. Therefore, our main goal is to achieve proximal control first. Performing a bypass in advance prolongs the time during which uncontrolled bleeding may occur. In addition, although the literature reports that in an elective setting the risk associated with a bypass is low, in cases in which we are dealing with a subarachnoid hemorrhage a bypass is more difficult, with the possible risk of occlusion of the recipient artery.¹⁻³ In none of the cases in our series was a bypass necessary.

Nonetheless, having said this, a neurosurgeon must be prepared to perform a bypass if needed; cerebrovascular neurosurgeons must bring to bear a complete surgical armamentarium when managing blister aneurysms. Being ready by dissecting the donor artery prior to the craniotomy is certainly a good strategy.

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