Middle cerebral artery tortuosity associated with aneurysm development

TO THE EDITOR: We read with great interest the article by Klś et al. (Kliś KM, Krzyżewski RM, Kwinta BM, et al: Computer-aided analysis of middle cerebral artery tortuosity: association with aneurysm development. J Neurosurg [epub ahead of print May 18, 2018; DOI: 10.3171/2017.12.JNS172114]). The authors conclude that “an increased deviation of the middle cerebral artery (MCA) from a straight axis (described by relative length [RL]), a decreased sum of all MCA angles (described by sum of angle metrics [SOAM]), a local increase of the MCA angle heterogeneity, and an increase in changes in an artery’s course (described by inflection count metric [ICM]) are associated with MCA aneurism formation.” They revealed that MCA tortuosity may play an important role in aneurism formation and provided important clues for exploring the pathological causes of aneurism formation. However, we still have some confusion about the article.

First, according to the calculation method for the tortuosity descriptors proposed by the authors, the size of the SOAM, ICM, and triangular index (TI) is positively related to tortuosity; that is, the larger the value, the greater the degree of tortuosity. The RL is negatively associated to the degree of tortuosity; that is, the smaller the value, the greater the degree of tortuosity. The product of the SOAM and the RL is positively associated with tortuosity since that descriptor is calculated as the product of the SOAM and the RL. The results of their study showed that patients with aneurysms had higher TI and ICM values but lower RL and PAD values. The above results clearly show that the degree of tortuosity is greater in the aneurysm group. However, in contradiction with this, the SOAM values are lower in the aneurysm group. Moreover, the authors mention in the Discussion, “In terms of a lower SOAM in arteries with an MCA aneurysm, the explanation is most probably connected with fluid dynamics. Artery tortuosity increases the resistance to blood flow.” Therefore, blood flow through an artery with larger local angles may cause a local decrease in blood pressure. This also leads to a decrease in local blood flow. Lower blood flow and blood pressure are protective factors against aneurysm formation.” Nevertheless, according to that explanation, it can be inferred that the incidence of aneurysms in patients with local tortuosity should be decreased rather than increased. Therefore, it would be better for the authors to provide an in-depth explanation about the above results and arguments.

Second, the authors stated, “There are a few rare genetic syndromes that are linked to the presence of vessel tortuosity, such as artery tortuosity syndrome or Loeys-Dietz syndrome.” The genetic syndromes they mention are systemic lesions involving multiple parts of vessels of the body and therefore often involve multiple intracranial aneurysms. However, this article did not provide detailed information on the characteristics of intracranial aneurysms, for example, the incidence of multiple aneurysms, the specific sites of the MCA aneurysms (M1, M2, M3, M4), and the size of the aneurysms, etc. We believe this information has important implications for further exploration of the factors related to the formation of an aneurysm and its relationship with arterial tortuosity.

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Disclosures
The authors report no conflict of interest.

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Response
Firstly, we would like to clarify the meaning of SOAM. The sum of angle metrics is a descriptor that shows us not the absolute value of the angle but the value additive to the angle of 180°. The hemodynamics of the tortuous blood vessel is complex and must be analyzed in three dimensions. A decrease in blood pressure on one side of the wall can mean an increase in blood pressure on the opposing side. The environment created by increased tortuosity facilitates the development of an aneurysm not only by creating decreased or increased blood pressure, but also by creating blood pressure gradients. In our current analysis, we are planning to study the relation between local wall shear stress and cerebral artery tortuosity, in a manner similar to the methodology proposed by Xie et al.² in the context of coronary arteries. It is still not clear whether aneurysm development is associated with increased or decreased wall shear stress.¹ We hypothesized that blood pressure gradient and wall shear stress gradient are more important factors in the development of an aneurysm than their absolute values. Increased SOAM may be associated with a decreased gradient in the MCA.

In response to the second query, we are adding the missing data. As a majority (75.47%) of our study group had single, one-sided MCA aneurysms, we focused mostly on the influence of tortuosity on changes in blood flow hemodynamics. Additionally, patients with connective tissue disorders were excluded from our study group. Although higher tortuosity of the MCA among patients with multiple intracranial aneurysms may naturally indicate systemic factors that promote arterial wall weakening, we found no statistically significant difference in terms of the tortuosity descriptors between these patients and those with a single aneurysm. For our next study, we plan to investigate whether increased tortuosity of the cerebral arteries is associated with the tortuosity of other arteries, e.g., coronary ones, which further addresses that issue. In terms of aneurysm characteristics, as mentioned, a total of 14 (24.53%) patients had multiple aneurysms, including 3 patients with mirror MCA aneurysms. The mean number of aneurysms was 1.33 ± 0.64, and the most common location was the M₁ bifurcation (79.63%), then M₁ (14.81%), M₂ (3.70%), and M₃ (1.85%). We also found no statistically significant relationship between tortuosity descriptors and aneurysm location. The mean size of the aneurysm dome was 4.92 ± 2.43 mm, and the mean size of the aneurysm neck was 4.14 ± 1.43 mm. Given the length limits on submitted papers, we were not able to put all necessary data into one paper and are planning to extend our research in other studies.

We are grateful for the appreciation of our paper and the insightful comments. We will supplement our future work with suggestions supplied by Dr. Yin et al. Moreover, we encourage other authors to cooperate with our team. We are planning in the next 5 years to analyze the entire intracranial arterial system in the context of arterial tortuosity.

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Imaging predictor for rebleeding after surgery in intracerebral hemorrhage

TO THE EDITOR: With great interest, we read the article by Miki et al.¹ (Miki K, Yagi K, Nonaka M, et al: Spot sign as a predictor of rebleeding after endoscopic surgery for intracerebral hemorrhage. J Neurosurg [epub ahead of print May 25, 2018; DOI: 10.3171/2017.12.JNS172335]) regarding the role of spot sign on CT angiography in predicting rebleeding after endoscopic surgery in intracerebral hemorrhage (ICH). The results of this study suggest that the spot sign is an independent predictor for rebleeding in patients with ICH receiving endoscopic surgery.

Spot sign is a reliable indicator for predicting hematoma expansion.²,³,⁹ Moreover, it has been suggested to be related to intraoperative and postoperative bleeding in patients with ICH receiving surgery.¹ In Miki et al.’s study, spot sign is shown as a predictor for rebleeding after endoscopic surgery. Thus, patients with ICH who have positive spot sign may have a higher risk of rebleeding after receiving surgery. Appropriate surgical methods should be adopted to decrease this risk in these patients.

In addition, spot sign can be used to screen eligible patients with ICH for specific surgical strategies. Recently, Li et al. have reported that ultra-early stereotactic aspiration can be adopted in patients with ICH and without positive spot sign.⁷ Ge et al. showed that only craniotomy can benefit patients with positive spot sign, whereas both craniotomy and minimally invasive craniopuncture can be used in patients with negative spot sign.⁸ Negative spot
sign represents a lower risk of rebleeding, which suggests that early minimally invasive surgery can be conducted in these patients. However, in patients with positive spot sign, surgical strategies that can effectively prevent active bleeding should be considered.

Recently, several novel predictors for hematoma expansion on noncontrast CT have been reported, such as blend sign and black hole sign.\(^6\)\(^,\)\(^7\) Moreover, in Wu et al.'s study, blend sign has been reported as a predictor for postoperative rebleeding in patients with ICH receiving stereotactic minimally invasive surgery.\(^10\) However, in Miki et al.'s study, neither blend sign nor black hole sign was related to rebleeding after endoscopic surgery in patients with ICH. This difference may be caused by the different surgical methods used in these studies. Further studies are still needed to confirm if these imaging markers can predict rebleeding after surgery in patients with ICH.

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

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Are aneurysm treatment outcomes improved by higher clipping volume or better patient selection?

TO THE EDITOR: Anderson et al.\(^1\) reviewed 6450 aneurysmal subarachnoid hemorrhage (aSAH) cases from the Neurosurgical National Audit Programme (NNAP) from 24 neurological centers in England (Anderson IA, Kailaya-Vasan A, Nelson RJ, et al: Clipping aneurysms improves outcomes for patients undergoing coiling. J Neurosurg [epub ahead of print June 8, 2018; DOI: 10.3171/2017.12.JNS172759]). The 30-day mortality rates for the 5515 (86%) endovascular cases and 935 (14%) microsurgical acute cases were 6.4% and 8.6%, respectively. A significant association was noted between centers with high volumes of microsurgical cases and improved outcomes for aSAH regardless of treatment modality. A phenomenon previously undescribed was the improved outcome associated with endovascular treatment in centers with a high volume of neurovascular microsurgery.

The authors’ insightful discussion covered factors influencing the complicated, multifactorial relationship between volume and patient outcomes. They concluded that centers where more aneurysms were clipped had better outcomes for all aneurysm patients, including those treated with coil embolization. They hypothesized that more clipping meant, in part, that neurosurgeons were closely involved in their patients’ care.

We offer another perspective, proposing that, as in many studies, methodologic flaws may have influenced these data and study conclusions. Additionally, excluding these possible flaws, we think that selection bias is more likely.

In reviewing codes at http://www.surginet.org.uk/informatics/opcs.php, we found that the OPCS4 version used to select patients has multiple uses. Additionally, code L33.9, “Unspecified operations on aneurysm of cerebral artery,”
was omitted, and codes O05.1–3 describe endovascular treatment of dural arteriovenous fistulae, not aneurysms. Also, the authors’ tables may be contradictory. Table 1’s columns “NNAP database” and “Excluding data from centers that do not contribute to the BNVG [British Neurovascular Group] database” apparently contradict Table 2’s 3330 total aSAH cases (column “Centers contributing to BNVG database”). Therefore, a potential bias that could arise is comparing emergency endovascular outcomes with emergency and elective microsurgical outcomes.

More importantly, higher microsurgical volume may simply mean that the center is more selective about which patients undergo endovascular treatment. In Anderson et al., high-volume centers clipped 46% of all ruptured aneurysms and low-volume centers clipped just 2.1%. Could the low-volume microsurgical centers have pushed the envelope with too much coiling, including risky cases, because of lack of microsurgical availability? Many dual-trained neurosurgeons in the US estimate that their case volumes are 25% to 35% microsurgical. Thus, in the hands of surgeons agnostic with respect to approach but armed with Level I evidence in preference for endovascular repair, this split of microsurgical and endovascular approaches may be driven by pathology and limitations of endovascular technology. Accordingly, we advocate management of intracranial aneurysms by practitioners with expertise in both or at centers with truly collaborative microsurgical-endovascular services devoid of competition.

Anderson et al. can be applauded for their detailed, creative review of factors that influence outcomes for patients with ruptured aneurysms. Although our interpretation of the results differs, their study significantly contributes toward guiding practice patterns in favor of improving overall outcomes, and ultimately, this is our shared goal.

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Response
We thank Dr. Ringer and colleagues for their considered and insightful response to our recently published paper. In their letter, they highlighted a potential methodological flaw in the data selection process, which was based upon OPCS4 codes used.

First, it was highlighted that the code L33.9, “Unspecified operations on aneurysm of cerebral artery,” was omitted from the study. This error occurred because this procedure code has now been retired from the NNAP database, on account of its not being routinely utilized by hospitals. In order to establish the number of potentially omitted cases that this code represents, the National Health Service website was searched for national-level activity (individual hospital information is not available) data for the L33.9 OPCS4 code, and we can confirm that this represented 1 case in 2015/2016 and 0 cases in both 2014/2015 and 2013/2014. We would therefore hypothesize that the omission of this single case over the 3-year study period would likely not have significantly affected the results of our study.1

A second observation was that the OPCS4 codes O05.1, O05.2, and O05.3 that were included in the original analysis pertain to endovascular management of dural arteriovenous fistulae, rather than aneurysms. This is a valid observation. These codes were included because of the way that codes are grouped together within the NNAP database. The umbrella term that we used to perform our analysis, “Transluminal procedures for aneurysms,” incorporates these codes together with the transluminal aneurysm codes (https://www.hed.nhs.uk/SBNS/Content/Documents/20180226_OPCSS%20Procedures.xlsx). While this is a valid criticism of our paper, we would again assert that these cases would make up such a small fraction of our study population that they would not have significantly affected the results of our study.

Ringer and colleagues also remark, “Table 1’s columns ‘NNAP database’ and ‘Excluding data from centers that do not contribute to the BNVG database’ apparently contradict Table 2’s 3330 total aSAH cases (column ‘Centers contributing to BNVG database’),” but we fail to see that there is a contradiction here. We wonder whether further clarification is required beyond that which was possible within the word count restrictions of the original paper. Table 1 seeks to validate the NNAP data by searching for the equivalent information utilizing an independent database (BNVG database) of what should in theory constitute the same patient population. Not all neurological departments submit data to the BNVG database. The 3330 cases in column 1 of Table 1 represent a subset of the 6450 aSAH cases that are attributable to departments that also participate in the BNVG database. Column 2 of Table 1 should theoretically therefore be the same as column 1, but the numbers are fewer, most likely reflecting the fact that the data collection for the BNVG database is not automated and therefore is subject to human error or omissions if the staff who are due to populate the database are away from work. The fact that the proportions and median values are so similar does, however, validate the NNAP dataset as an appropriate representation of aSAH cases in the United Kingdom. The comparison presented in Table 2 was designed to investigate whether participation in the BNVG database might be a marker of microsurgical activity or outcome, and therefore the original 6450 are divided into those attributable to departments that also participate in the BNVG database and those that do not. It stands to
reason therefore that column 1 of Table 1 and column 1 of Table 2 describe the exact same cohort of patients and therefore it is quite correct that for both, n = 3330. All data in both Tables 1 and 2 are from aSAH cases, and therefore any criticism suggesting the mixing of elective and acute outcomes is unfounded.

Finally, we would agree with the observation that “Higher microsurgical volume may simply mean that the center is more selective about which patients undergo endovascular treatment.” We have implied as much within our paper. We would recommend that neurovascular patients be treated in departments that have appropriately skilled clinicians in both the microsurgical and endovascular management of cerebral aneurysms to allow for judicious treatment decisions to be made; in the United Kingdom, this would most frequently mean treatment by a collaborative microsurgical-endovascular service rather than a dual-trained neurosurgeon. In countries where the dual-trained neurosurgeon is commonplace, further work would be required to ascertain the influence of the endovascular-microsurgical ratio and patient outcome.

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Prognostic molecular panel for skull base chordoma

TO THE EDITOR: We read with great interest the recent article by Zenonos et al. (Zenonos GA, Fernandez-Miranda JC, Mukherjee D, et al: Prospective validation of a molecular prognostication panel for clival chordoma. J Neurosurg [epub ahead of print June 15, 2018. DOI: 10.3171/2018.3.JNS172321]) on a molecular prognostication panel for clival chordoma after resection. The authors performed a prospective laboratory study to validate the prognostic value of tumor Ki-67 expression and genetic aberrations on chromosomal loci 1p36 and 9p21 in clival chordoma. With univariate and multivariate Cox analyses, the authors found that percentages of cells with 1p36 and homozygous 9p21 deletions were independent predictors of clival chordoma outcome. Furthermore, a combination of these two biomarkers could effectively separate patients into different risk subgroups with significantly different survival. These findings would be useful for prognostic risk stratification and therapeutic optimization of patients with skull base chordoma (SBC).

Currently, many factors have been shown to contribute to SBC prognosis. Among them, complete or total resection and chondroid chordoma type are consistently reported to be associated with better survival of SBC patients. In this study, however, the authors only assessed the prognostic effect of the molecular panel in SBC without adjusting for other clinicopathological parameters or molecular features, which may likely introduce bias and fail to provide accurate information on prognosis. As the authors stated, although certain tumors’ molecular characteristics can be related to the subtotal resection of a tumor, whether the 1p36 and homozygous 9p21 deletions are correlated with the choice of resection type remains unknown. Previous studies have demonstrated that recurrent tumor and a large tumor size are risk factors of subtotal resection of SBC lesions. In addition, it has been shown that epigenetic dysregulation and aberrant protein expression are linked with a more aggressive chordoma phenotype, thus leading to a subtotal resection. Taken together, these results strongly indicate that resection of SBC lesions may be influenced by a complex clinical and molecular profile, which deserves further elaboration.

Published data have suggested that the tumor immune microenvironment plays a key role in cancer development and progression. Similarly, in chordoma, recent studies have revealed that the tumor-infiltrating lymphocytes within the tumor microenvironment were significant predictors of chordoma outcome, which even displayed stronger prognostic power than the traditional classification system in survival prediction. As analysis of the immune microenvironment is less affected by the intratumoral heterogeneity, researchers have recently recommended to add this microenvironmental component to prognostic analysis in order to improve outcome prediction. However, because previous studies mainly focused on spinal chordomas, data on the immune microenvironment in SBC are still lacking. Considering the different biological behavior between spinal chordoma and SBC, further studies are largely needed to disclose the prognostic role of the immune microenvironment in SBC and evaluate its correlation with the genetic abnormalities, including losses of the 1p36 and 9p21 chromosomal loci.

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References

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Disclosures
The authors report no conflict of interest.

Response
We really appreciate Dr. He’s and Dr. Dai’s interest in our study and the stimulating discussion they initiate. Congruent with the existing literature, our experience has shown the extent of resection to be a crucial prognostic factor in chordomas. The reason our analysis did not further subclassify the tumor according to the extent of resection was to avoid a type II statistical error due to the lack of power. Such an analysis is in our future plans as we accumulate more data, and could be expedited by multi-institutional efforts. Nonetheless, one has to distinguish the true oncological resections that can be achieved in spinal chordomas (either en bloc or with a rim of negative margin) from the so-called gross-total resections reported for their skull base counterparts. As such, one can view SBCs as analogous to gliomas, in which, while the extent of resection matters, the biology of the microscopic remnants is what ultimately dictates prognosis. Furthermore, it remains unclear how the biology can affect the invasiveness of a tumor and ultimately the extent of resection.1

To further support these points, we show two illustrative cases. In the first case (Fig. 1A–C), the tumor was
originally misdiagnosed as an “ectopic pituitary” at another facility, as it had been stable for several years before starting to grow. The surgical specimen was a group B tumor. Although impossible to prove retrospectively, one is led to postulate that the biology of the original lesion was different than the one that was excised. Is it possible that the original tumor belonged to group A? Perhaps chordoma, like glioma, has lower-grade precursors that evolve into more aggressive subtypes? Either way, one can see here how it would be easier to obtain a gross-total resection for the original tumor had it been correctly diagnosed from the beginning, but one can also see how the biology of the microscopic remnants of that original tumor would allow for a longer progression-free survival, which could misleadingly be attributed to the extent of resection. On the other end of the spectrum, a rapid recurrence was observed in the second illustrative case (Fig. 1D–F) of a group C tumor, despite a gross-total resection, as well as adjuvant radiation.

Undoubtedly, multiple prognostic factors are important in chordoma. Notably, the immune score cited by the authors for spinal chordomas changes the prognosis by a factor of 3.5 (HR 0.282), and incomplete resections in the cited meta-analysis changed the prognosis by a factor of 2 (HR 2.01), while none of the factors reviewed changed the prognosis by a factor of more than 12. We believe that the importance of our findings is the wide range of prognoses (up to 76-fold change) that can be predicted by simply two factors, allowing for an educated approach to their management. In the future, we are hopeful that, with the invaluable help of researchers such as Drs. He and Dai, collaborative efforts will help unlock some of the physiological underpinnings of these tumors and lead to a significant impact on the lives of our patients.

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References

TO THE EDITOR: We enjoyed seeing the application of the contralateral transmaxillary (CTM) approach by Pamias-Portalatin et al. (Pamias-Portalatin E, Mahato D, Rincon-Torroella J, et al: Endoscope-assisted contralateral transmaxillary approach to the clivus and the hypoglossal canal: technical case report. J Neurosurg [epub ahead of print June 22, 2018; DOI: 10.3171/2018.1.JNS171972]). In this single case report, a subtotal resection of a petroclival chondrosarcoma was performed. The article fails to adequately recognize, however, the original contribution and clinical experience of the article by Patel et al. We reported on 5 clinical cases in which patients underwent a CTM approach for chordoid neoplasms involving the petrous apex. In all cases, the CTM approach greatly enhanced our ability to remove tumor deep to the petrous internal carotid artery (ICA) with minimal risk to the artery. It is disingenuous of the authors to state, “to our knowledge, this is the first non-cadaveric presentation of this specific approach in a patient,” especially when referencing our publication.

On average, the CTM approach improved the angle of approach by 25°. In follow-up research performed in our laboratory, we have demonstrated both angle and reach advantages. Anatomical limits include the internal auditory canal and jugular foramen. In general, the hypoglossal canal is accessible with relative ease via a simple endonasal corridor, given the naturally enhanced lateral access inferior to the petrous ICA. An ipsilateral transtemporal approach with sacrifice or mobilization of the medial Eu- stachian tube provides adequate lateral exposure. The primary benefit of the CTM approach is for access to the petrous apex deep to the petrous segment of the ICA, which is well illustrated by the tumor presented in this paper.

There are nuances of the surgical technique that facilitate access to the contralateral petrous apex. Figure 4B suggests that additional bone could be removed from the lateral margin of the maxillary opening. The maxillotomy should extend to the lateral limit of the maxillary sinus in order to provide the maximal angle of approach. If preservation of the sphenopalatine artery is not a consideration for reconstruction, the CTM corridor can be enhanced by drilling the base of pterygoid on the side of the approach.

Figure 5 does not clearly indicate the use of the CTM corridor for tumor dissection. It is not clear how the authors position the endoscope and dissecting instruments. Review of the surgical video suggests that the entire procedure was performed via the CTM corridor. Exposure and visualization of skull base landmarks was limited, and, unfortunately, access to the hypoglossal canal is not well demonstrated. Use of a single corridor also constrains positioning of multiple instruments and limits options in the...
event of a vascular injury. We have found it most advantageous to position a 45° endoscope in the nasal corridor opposite the tumor with passage of dissecting instruments (drill, suction devices, etc.) through the CTM corridor. This provides excellent visualization without interference with instrumentation. The CTM corridor is longer than a transnasal corridor, however, and may exceed the length of the ultrasonic bone curette and some drills. We use an endoscopic drill with extended drill bits.

Reconstruction of the anterior maxillary wall with an osteoplastic flap is not necessary in our experience. A large window can be created without functional or cosmetic consequences for the patient. The major risks of the maxillotomy include injury to the infraorbital nerve and oral-antral fistula.

With all chondroid tumors, it is important to radically resect any involved bone or soft tissue. This is not well illustrated in the video but is also greatly facilitated by combining the endonasal and CTM corridors. The CTM is especially useful for resecting the deep margins at the petrous apex and petroclival fissure where chondrosarcomas originate.

We applaud the appropriate and effective use of this novel approach in this report and hope to see it become a standard part of the skull base armamentarium and lexicon.

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References

Disclosures
The authors report no conflict of interest.

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Response
It is with deep appreciation that we receive the comments by Dr. Snyderman and Dr. Gardner. We greatly thank the authors for taking the time to evaluate our article and share their insight and expertise on the matter.

We extend our apologies for not highlighting the importance of their thorough anatomical and clinical work on the combined endoscopic endonasal and CTM approach, which we cited in our technical note. Dr. Snyderman and Dr. Gardner presented the use of the CTM approach as an adjunct to the endoscopic endonasal approach (EEA) in order to reach the petrous apex, as well as providing excellent anatomical illustrations using cadaveric representation and neuronavigation tools. Additionally, Dr. Gardner and Dr. Snyderman presented 5 clinical cases in which patients underwent a combined CTM approach and EEA for chondroid neoplasms involving the petrous apex. As the authors identified, this combination of approaches allowed for complete resection of 3 chordomas, 1 low-grade chondrosarcoma, and subtotal resection of 1 clival chordoma. In their paper, they present how, in order to access the petrous apex, the EEA forces the surgeon to either skeletonize and lateralize the paraclival ICA or work inferior to the petrous ICA, increasing the risk for vascular injury, vidian nerve resection, or injury to the Eustachian tube and the maxillary division of the trigeminal nerve (cranial nerve V2). The CTM approach may be a good adjunct to the EEA, adding direct lateral extension and avoiding an open approach.

Our paper’s main objective was to present the surgical technique of the CTM approach as a stand-alone direct corridor via an endoscopic transfacial route to reach the clivus and the hypoglossal canal for removal of a complex chondrosarcoma. Unlike Dr. Gardner and Dr. Snyderman, who utilized the aforementioned combined approaches simultaneously to remove the tumor, we employed solely the CTM approach for tumor resection. We agree with Dr. Gardner and Dr. Snyderman that a medial maxillectomy is necessary to maximize this corridor and access the skull base, in either a combined or independent approach. We also concur with them that combining both the EEA and the CTM approach may provide the greatest flexibility and visualization in resecting select petrous apex tumors.

Our study presents a detailed step-by-step technical note that can be used for future guidance and reference. In our case, the contralateral route allowed us to better visualize the carotid artery encased by the tumor, adding complexity. Selecting the contralateral approach also allowed us to avoid mobilization of the carotid artery. We were able to access the tumor without drilling out the pterygoids or sacrificing the Eustachian tube. The feasibility of a sole CTM approach is determined based on careful review of the preoperative images aided by the views and vectors identified intraoperatively with the navigation probes. We agree with Dr. Gardner and Dr. Snyderman that the hypoglossal canal is easily accessible via EEA, and the main advantage of using a CTM approach is to be able to reach tumor at the right petroclival...
TO THE EDITOR: The recently published article by Tayebi Meybodi et al. has drawn our attention, as it described a new landmark for the lacerum segment of the ICA (Tayebi Meybodi A, Little AS, Vigo V, et al: The pterygoclvial ligament: a novel landmark for localization of the internal carotid artery during the endoscopic endonasal approach. J Neurosurg [epub ahead of print May 18, 2018. DOI: 10.3171/2017.12.JNS172435]). Their cadaveric study provided an interesting morphometric analysis of the “pterygoclvial ligament.”

Based on our experience, the most clinically relevant relationship in this study is the angle between the “pterygoclvial ligament” and the vidian nerve. The knowledge of the angle between these structures can certainly provide insights for intraoperative anatomical orientation. Nonetheless, the methodology used for the angle measurement is not clear in the article. It is also unknown whether these results can be translated to the intraoperative setting in which the angle is seen through the endoscope.

We concur that the term “pterygoclvial ligament” has not been previously described in the literature. However, the “pterygoclvial ligament” is essentially the main attachment of the pharyngobasilar fascia (PBF) superiorly until one reaches the lacerum foramen via the previously published technique. We believe that the appropriate nomenclature for what the authors call “pterygoclvial ligament” is “spheno-occipital synchondrosis” since it represents the connective tissue between the occipital and sphenoïd bones. The PBF is densely attached superiorly to these bones and more significantly to this synchondrosis.

We have been using the PBF, the eustachian tube (ET) and the vidian nerve (VN) in our endoscopic endonasal approaches to the petrous apex and infrapetrous region for multiple years. In our experience, it is always safer to have multiple landmarks for anatomical orientation, particularly when one of these landmarks is displaced or absent due to tumor invasion. We refer to our method as a triangulation technique; it consists of identifying the PBF, VN, and cartilaginous ET and understanding that they form a 3-sided pyramid with the vertex at the lacerum foramen/internal carotid artery (ICA) fibrocartilaginous tissue (Fig. 1). Hence, drilling of the bone located between the inferomedial aspect of the vidian nerve, the superior aspect of the ET, and the superolateral aspect of the PBF may be done more aggressively and safely. During the drilling process, the PBF is retracted down, the pheno-occipital synchondrosis is disrupted, and the occipital and sphenoïd bones are drilled in a ventral-dorsal direction converging to the lacerum foramen.

The triangulation technique for localizing the lacerum ICA in endoscopic endonasal skull base surgery

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References
Tayebi Meybodi et al. justified the novelty of their description by stating that Labib et al. did not describe the “pterygoclival ligament” or its relationships to surrounding anatomical structures. However, we have described the following: “the caudal surface of the paraclival segment courses above and is circumferentially surrounded by the fibrocartilaginous tissue overlying the foramen lacerum. This thick nonexpansile tissue is in continuation with the basopharyngeal fascia, which attaches the ET to the cranial base and represents the aponeurosis of these soft-tissue components with the periosteum of the petrous bone. The union of these soft-tissue components occurs at the triangulation point.”

The authors should be commended for their anatomical dissections and comprehensive morphometric analysis. Their paper certainly adds good illustration of ventral skull base anatomical relationships and calls attention to the petroclival ligament/spheno-occipital synchondrosis where the PBF adheres and leads the surgeons to safely expose the lacerum ICA.

**References**


**Disclosures**

Dr. Prevedello reports consultant relationships with Medtronic and Stryker, a patent holder relationship with KLS-Martin, and receipt of support from Storz for non–study-related clinical or research effort.

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**INCLUDE WHEN CITING**

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**Response**

We thank Dr. Beer-Furlan and colleagues for providing feedback on our work. They raised several questions regarding our recent work describing a new landmark to localize the lacerum segment of the ICA during the endoscopic endonasal approach. Beer-Furlan et al. discussed that the angle between the pterygoïd ligament and the vidian nerve has intraoperative relevance. We found this angle to be 70° on average. As mentioned in the original paper, we measured the angle between these 2 structures using a frameless stereotactic system. This angle was measured as the angle between 2 linear structures in the space defined by their anterior and posterior ends: 1) the vidian nerve and 2) the pterygoïd ligament (Fig. 3A and C in the original publication).

Regarding the naming of the structure, we favor the use of the term “pterygoïdligament” over other nomenclature for several reasons. According to *Gray’s Anatomy*, a synchondrosis is an articulation “where the connecting medium is cartilage ... This is a temporary form of joint, for the cartilage is converted into bone before adult life.” The sphen-occipital synchondrosis completely ossifies by the age of 25 years, although ossification may even happen earlier. We examined adult cadavers (all aged > 40 years), and discovered this “ligamentous structure” between 2 clearly osseous regions (i.e., the pterygoid process and the clivus). Therefore, the pterygoïdligament does not correspond to the sphen-occipital synchondrosis, because it is actually located on the exocranial surface of the synchondrosis. We also prefer the term “pterygoïd” to “spheno-occipital” because as mentioned above, “spheno-occipital” denotes a location different from that of the “pterygoïdligament.” In addition, “spheno-occipital” is more general and may have some forensic implications. The term “pterygoïd,” on the other hand, is more specific, referring to the exact parts of the occipital and sphenoid bones between which the ligament is found.

We believe that our description of the pterygoïdligament is novel. We referenced the study by Labib et al. in our paper and discussed the differences between the “carotid sock” (described by Labib et al.) and the pterygoïdligament. Labib et al. state “the caudal surface of the paraclival segment courses above and is circumferentially surrounded by the fibrocartilaginous tissue overlying the foramen lacerum. This thick non-expansile tissue is in continuation with the basopharyngeal fascia, which...
attaches the Eustachian tube to the cranial base and represents the aponeurosis of these soft-tissue components with the periosteum of the petrous bone. The union of these soft-tissue components occurs at the triangulation point. The “thick non-expansile tissue” covering the genu of the lacerum segment of the ICA artery is not the pterygocleival ligament but what the pterygocleival ligament eventually leads to when followed posteriorly. On the other hand, the PBF covers a wide area on the exocranial surface of the occipital and sphenoid bones. The pterygocleival ligament and the “carotid sock” are different parts of this fascia which are attached to each other. During the initial stages of drilling the floor of the sphenoid sinus, only the pterygocleival ligament is exposed. On the other hand, the PBF and the “carotid sock” are exposed after complete drilling of the medial part of the pterygoid process, sphenoid floor, and part of the clivus.

We agree with Beer-Furlan et al. on the use of multiple landmarks to increase safety. In our original paper, we have discussed that the pterygocleival ligament may also be used as an ancillary landmark during the localization of the internal carotid artery along with the vidian nerve. Overall, we believe that the pterygocleival ligament, or whatever name the neurosurgical community finally settles on for this structure, is a valuable landmark best utilized in conjunction with other landmarks to maximize safety during endoscopic endonasal skull base surgery. However, when other landmarks (such as the vidian nerve) are already distorted or unavailable because of the pathology, the pterygocleival ligament may still be present as a fibrous structure to facilitate carotid artery localization.

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References

INCLUDE WHEN CITING
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3D-printed polymethylmethacrylate implant for cranioplasty

TO THE EDITOR: We read with great interest the article by Morales-Gómez et al. (Morales-Gómez JA, Gar-
widespread use of PMMA customized cranial implants. Thus, with the encouraging developments described by Morales-Gómez et al., and many others, neurosurgical patients will have increasing access to customized PMMA cranial implants, which we agree are the superior choice compared to autologous bone.9

References

Disclosures
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Response
We thank Santiago et al. very much for their encouraging response; we are grateful to receive their kind feedback.

The number of trials available for review is scarce. There are only two small randomized controlled trials, and study results of low quality and high heterogeneity make it difficult to arrive at a definitive conclusion.5

The best evidence, published in the systematic reviews of Malcolm et al. and van de Vijfeijken et al., shows a higher failure risk in autologous bone than allografts, which brings to light synthetic implants and favors the decision to use them.6,7

In this analysis, the significantly higher rates of reoperation in patients with autologous implants are primarily due to bone resorption. The factors that result in clinically relevant bone resorption remain unclear. One significant variable could be the bone-handling protocols, which can lead to maintaining the cells in the flap, or not. Without a standard method to handle the explanted bone reported in the published data, a definitive conclusion cannot be drawn.

At our institution, we decided to use PMMA as our preferred material because of its superior outcome. We tried to store autologous bone in the abdominal pocket and to perform cryopreservation, but there were higher infection rates or reabsorption. Also, in bone cryopreservation storage, significant aggregate upfront costs to the patients prevent its widespread use.

Indeed, integrating neurotechnology or using a modified implant to correct the persistent temporal hollowing2 can be anticipated when designing the implants and is a cutting-edge development, as Gordon et al. have already masterfully described.3,4

Adding these variables to our method is feasible and encouraging. Like Gordon and colleagues’ and Santiago et al.’s research groups, and many others, we are looking forward to the new frontier of not only reconstructive but regenerative neurosurgery.

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References
Microsurgical rhizotomy as treatment for trigeminal neuralgia in patients with multiple sclerosis: turnpike or dirt road?

TO THE EDITOR: We have read with great interest the article by Bigder and colleagues1 (Bigder MG, Krishnan S, Cook EF, et al: Microsurgical rhizotomy for trigeminal neuralgia in MS patients: technique, patient satisfaction, and clinical outcomes. J Neurosurg [epub ahead of print July 13, 2018; DOI: 10.3171/2017.12.JNS171647]).

The authors should be congratulated for their remarkable record of patient population and long-term follow-up. Such results differentiate the plebeian from the patrician neurosurgical centers and is of great value for having valuable data in a rare subset of patient population. The disease is not so common in India, but the severity and frustrations in management are the same. The authors have explained their definition of “refractory MS [multiple sclerosis]-associated TN [trigeminal neuralgia]” and medical management protocol. They have also reported the prevalence of TN in MS patients at a rate of 3%–7%, while the prevalence of the disease in their province is 261 per 100,000 population. However, the proportion of patients undergoing microsurgical rhizotomy (MSR) for MS-associated TN seems to be quite low.

Although time to treatment failure (TTF) was used as the primary outcome measure, the decision for further intervention was still based on the Barrow Neurological Institute (BNI) pain score. The authors aptly described the BNI score and the difficulty in its usage for this particular cohort. It remains unclear if the literature review for different treatment options was based on BNI score or TTF. However, the authors’ point is well taken for choosing TTF as an independent outcome assessment feature in this patient population compared with a patient population with typical TN, as MS is a multifactorial disease. There might be other variables affecting the patient satisfaction score. Similar to typical TN, the results of rescue MSR are inferior to primary MSR (in terms of TTF).

It can be assumed that selective resection of nerve roots is well tolerated, as the authors did not face any adverse events in patients after performing MSR as a primary treatment modality. The authors have a reputable experience with this technique; any comment on intraoperative monitoring and its difference from a routine microvascular decompression (MVD) might have been valuable.

A few questions remain unanswered, such as the pathophysiology behind the pain recurrence. The authors offered re-treatment in cases of early severe pain recurrence (within 1–2 weeks) with good outcome (patient 11). It would be interesting to know the surgical steps and pitfalls in this particular patient population (How was it different from the primary MSR?). Again, the surgical pitfalls and intraoperative findings in patients who undergo a second MSR after a long interval would have been an added finding.

The mean number of procedures in the MS TN cohort before MSR was 4.5 (range 0–10), which testifies to either the unawareness or prevailing nihilism of the caregivers, as aptly stated by the authors as a “last-ditch” procedure. It is interesting to note that the second cohort of patients (non-MSR) underwent only 2.1 (range 0–10) procedures prior to the last treatment, when the remaining patient parameters (age, duration of illness) were exactly comparable. It might suggest that even within the spectrum of MS, there are some different patient subgroups that may or may not respond to non-MSR procedures, and those factors demand prospective long-term follow-up studies. The patients’ mean age was 59.4 years. The chances of a visible vascular compression increases with advancing age because of the age-related cerebellar atrophy. In some patients, the authors found potential neurovascular conflict, but this subset is not further detailed in the article.

Different series of TN for MS have reported a 5-year pain control rate of up to 54% (Table 1).1–7,8–11 For Gamma Knife surgery (GKS) in MS, the target point needs to be definitely determined. As the pathophysiology in MS lies inside the brainstem, targeting the conventional points along the cisternal component of the trigeminal nerve (Marseille point) might not always help in the pain control. In cases of MS, the plaque of demyelination encompasses the root entry zone of the trigeminal nerve while some studies have also shown the association of neurovascular conflict.3 Results of GKS as a primary or secondary treatment modality for MS TN as reported by Tuleasca et al. is impressive, albeit only for the short term. Although the initial rate of pain cessation is high (up to 91%), GKS for TN in MS has a high recurrence rate (up to 61.5%).5 Being noninvasive and offering satisfactory pain control, GKS may be considered as an initial treatment modality before advising any invasive surgical treatment, considering the existing pathological status.8

Although the sample size is small and the study is retro-
### TABLE 1. Review of various surgical interventions and their outcomes for trigeminal neuralgia for multiple sclerosis

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Diagnostic Criteria</th>
<th>Affected Cases w/ Only 1 Division Affected</th>
<th>No. of Cases w/ Only 1 Division Affected</th>
<th>Outcome Measurement</th>
<th>Technique Used</th>
<th>Duration (yrs)</th>
<th>Mean Age (yrs)</th>
<th>Pain Relief (%)</th>
<th>Recurrence Rate (%)</th>
<th>Median Time to Recurrence (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broggi et al., 2004</td>
<td>NR</td>
<td>Lt, 12; rt, 20; bilat, 3</td>
<td>19</td>
<td>Excellent, pain relief w/o meds; good, pain relief w/ intermittent low-dose meds; fair, pain relief w/ high-dose meds; poor, drug-resistant recurrence or intolerance to antineuralgic therapy</td>
<td>MVD</td>
<td>8</td>
<td>52</td>
<td>100</td>
<td>39</td>
<td>13.5</td>
</tr>
<tr>
<td>Sandell &amp; Eide, 2010</td>
<td>Burchiel classification</td>
<td>Lt, 11; rt, 8; bilat, 0</td>
<td>4</td>
<td>VAS; pain relief, no pain &amp; no medication w/ significant improvement when pain score 0–3</td>
<td>MVD</td>
<td>8</td>
<td>53</td>
<td>47</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Abhinav et al., 2012</td>
<td>Typical and atypical without definition</td>
<td>Lt, 9; rt, 14; bilat, 0</td>
<td>NR</td>
<td>No or mild pain, moderate, no relief</td>
<td>Partial sensory rhizotomy; 5 pts had compression</td>
<td>12</td>
<td>50</td>
<td>87</td>
<td>21.7</td>
<td>NR</td>
</tr>
<tr>
<td>Zorro et al., 2009</td>
<td>NR</td>
<td>Bilat, 11</td>
<td>13</td>
<td>BNI</td>
<td>Majority: 14-mm isocenter, 80-Gy GKS</td>
<td>12</td>
<td>59</td>
<td>97</td>
<td>37.8</td>
<td>74.5</td>
</tr>
<tr>
<td>Mathieu et al., 2012</td>
<td>Typical episodic, atypical background pain, constant pain</td>
<td>Lt, 12; rt, 15</td>
<td>13</td>
<td>BNI</td>
<td>GKS, 80 Gy 1 isocenter</td>
<td>5</td>
<td>59</td>
<td>81.4</td>
<td>51.9</td>
<td>26.5</td>
</tr>
<tr>
<td>Weller et al., 2014</td>
<td>NR</td>
<td>Lt, 22; rt, 21; bilat, 2</td>
<td>22</td>
<td>BNI, Burchiel, Regis</td>
<td>4-mm 1 isocenter, median dose 85 Gy</td>
<td>18</td>
<td>NR</td>
<td>90.7</td>
<td>61.5</td>
<td>16</td>
</tr>
<tr>
<td>Mohammad-Mohammadi et al., 2013</td>
<td>Typical episodic, atypical background pain, constant pain</td>
<td>Bilat, 4</td>
<td>54</td>
<td>NR</td>
<td>75–86 Gy, 1 isocenter</td>
<td>16</td>
<td>NR</td>
<td>50</td>
<td>67</td>
<td>23</td>
</tr>
<tr>
<td>Tuleasca et al., 2014</td>
<td>Types I &amp; II as per Burchiel classification</td>
<td>Lt, 22; rt, 21; bilat, 2</td>
<td>22</td>
<td>BNI, Burchiel, Regis</td>
<td>4-mm 1 isocenter, median dose 85 Gy</td>
<td>18</td>
<td>NR</td>
<td>90.7</td>
<td>61.5</td>
<td>16</td>
</tr>
<tr>
<td>Taich et al., 2016</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>BNI</td>
<td>4-mm isocenter dose 85–90 Gy</td>
<td>12</td>
<td>NR</td>
<td>92</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bigder et al., 2018</td>
<td>NR</td>
<td>Bilat, 1</td>
<td>NR</td>
<td>BNI, BNI, BNI facial numbness scale</td>
<td>Partial sensory rhizotomy</td>
<td>3</td>
<td>59.4</td>
<td>85.7</td>
<td>23.1</td>
<td>79</td>
</tr>
</tbody>
</table>

BNI = Barrow Neurological Institute; meds = medications; MVD = microvascular decompression; NR = not recorded; pts = patients.
spective in nature, it definitely enriches the existing literature especially for a nearly forbidden surgical procedure. It is surprising to find that such an effective technique is not very popular or commonly practiced.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Response

We appreciate the comments and observations presented by Dr. Tripathi and colleagues. We agree that MSR, as originally developed by Walter Dandy, has a valuable role in the neurosurgical treatment of trigeminal neuralgia (TN). Our long-term results for both MS-related TN and recurrent classic TN have been satisfying. It remains an individualized decision, however, when to perform this operation, and nearly always it is performed after the failure of less invasive destructive procedures or microvascular decompression (MVD) surgery.

The question regarding intraoperative monitoring includes a special caveat. We advise routine use of brainstem auditory evoked potentials and strive to maintain a latency shift of less than 0.5 millisecond compared with early operative baseline potentials. This is achieved by approaching the trigeminal nerve root over the anterosuperior cerebellum, minimizing retraction, and freeing any arachnoid tethered between the cerebellum and vestibulocochlear nerve. Continuous electromyography of the masseter muscle is utilized, and direct stimulation confirms identification of the motor fibers. Special consideration is given to the potential cardiovascular response to trigeminal nerve root manipulation and selective sectioning. Unlike the atraumatic techniques of MVD, MSR occasionally induces dramatic hypertension and/or bradycardia. We distinctly maintain communication about these concerns with the anesthesiology team and pay attention to the audible heart rate monitor that may demonstrate slowing, even with the preliminary dissection of the trigeminal nerve.

We have experience with recurrent TN in MS patients after MSR, manifesting with new involvement of an untreated trigeminal distribution. In these cases, a second MSR was performed to selectively section an additional extent of the nerve root. The uppermost portion of the portia major is retained to preserve corneal sensation (if present), as well as the portia intermedius (accessory fibers) to minimize complete deafferentation risks. In patient 11 in our series, for example, we initially performed a 50% section of the caudal portion of the trigeminal nerve root for V2/3 distribution pain, which provided the patient with complete resolution of her TN symptoms. She experienced new pain onset predominantly in the V1 distribution at 11 months, which was well controlled with medications. At 22 months after MSR, she developed refractory pain involving predominantly the V1 distribution, at which point we elected to perform a second MSR, in which the caudal 90% of the nerve root was sectioned; this provided her complete pain relief, which persisted through her last follow-up at 23 months.
The occurrence of culprit neurovascular compression in patients with MS and TN is very rare and can be quite well delineated with high-resolution MRI sequences. A finding of clear cerebellar artery compression may justify MVD, although patients with brainstem MS plaques will have a high likelihood of treatment failure prior to MSR.

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Academic neurosurgeon development

TO THE EDITOR: We read with much interest the paper by Dr. Dacey1 on the developmental stages of an academic neurosurgeon (Dacey RG Jr: Developmental stages in the career of an academic neurosurgeon. J Neurosurg 129:1364–1369, November 2018). The manuscript echoes several sentiments we articulated in a publication last year that conceptualized the development of a neurosurgeon as moving along discrete stages, replete with conflicts to overcome and virtues to obtain.2 Dr. Dacey’s paper extends this work beyond residency, and it proposes that the academic neurosurgeon develops along three domains: clinical, research, and leadership. The roots of these domains are sown in residency, and provided the right factors and environment, they are shaped throughout training and well into practice. We appreciate, and wholly agree with, Dr. Dacey’s view that “development has no end” and that academic neurosurgeon, in his view, and the “actualized neurosurgeon” in ours, is one who is constantly learning, evolving, and changing, influenced by and an influence of his/her surroundings.

It is more important now than ever to think about surgical development in new ways. Work-hour restrictions, competing demands for time, and a reorientation away from time-based residencies to competence-based curricula, among many other factors, contribute to an evolving surgical education landscape. As we’ve written, events during residency and the success, or lack thereof, of navigating through its many challenges and conflicts have profound and long-lasting influences on one’s career. This is the reason why most human developmental theories focus on the first few years of life, when critical periods and experiences are embedded. We would argue that to avoid the development of a “useless” neurosurgeon, in Dr. Dacey’s parlance, one need not look further than residency, where early experiences can shape one’s trajectory well after training.

Recognizing that residents progress through training in identifiable developmental stages is important, but not enough. This is a narrative description, but what is needed is a prescription for healthy development—in other words, an empirical and operationalized definition for each stage that permits measurement of residents’ progress and, more importantly, the recognition of failing ones. The earlier the issues are identified, the better the opportunity to course correct—and to provide struggling residents with resources and support and superlative residents with the challenges they need to excel.

Once more, we thank Dr. Dacey for his thoughtful article and approach, and we share his view that the development of a neurosurgeon, whether in residency or beyond, is as dynamic and unique a process as the surgeons themselves.

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1. Dacey RG Jr: Developmental stages in the career of an academic neurosurgeon. J Neurosurg 129:1364–1369, 2018

Disclosures
The authors report no conflict of interest.

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Response
I was not aware of the publication of Lipsman et al.1 when I wrote my paper. I appreciate their bringing it to my attention. I think it is remarkable that we both came to the same general conclusions with regard to the developmental stages in career development and the challenges that neurosurgeons face.

I believe that the authors are absolutely correct in recognizing the developmental evolutions of a neurological career and the importance of effectively dealing with the challenges that occur at various career stages. Their paper is excellent in that it concentrates on the evolution of neurological resident training. I was impressed especially with their careful description of the important roles of autonomy, confidence, initiative, and an authoritative leadership style.

The authors did a great job in describing this process a couple of years ago, and I am sorry that I was not aware of their excellent analysis before now. I appreciate their gracious assessment of my paper.

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References
1. Lipsman N, Khan O, Kulkarni AV: “The Actualized Neuro-
Conscious sedation with dexmedetomidine compared with asleep-awake-asleep craniotomies

TO THE EDITOR: I read with great interest the article by Suero Molina and colleagues regarding their study on the use of dexmedetomidine in awake craniotomy for glioma (Suero Molina E, Schipmann S, Mueller I, et al: Conscious sedation with dexmedetomidine compared with asleep-awake-asleep craniotomies in glioma surgery: an analysis of 180 patients. J Neurosurg 129:1223–1230, November 2018). The authors showed that the use of dexmedetomidine creates excellent conditions for awake craniotomy, and I think that the evidence from 180 cases will affect the future of awake craniotomy anesthesia.

Dexmedetomidine, a selective α2 adrenergic receptor agonist, is used clinically for perioperative high-quality sedation, anesthesia, and analgesia. However, there are some caveats regarding the use of dexmedetomidine. Suero Molina and colleagues sedated the patients with 0.5–1.6 μg/kg/hr of dexmedetomidine outside of the assessment phase. I think that this dose of dexmedetomidine is larger than what is recommended. When using dexmedetomidine for perioperative sedation, a dose of 0.2–0.7 μg/kg/hr is recommended, and a larger dose can cause adverse events (i.e., hypotension, severe bradycardia, and excessive sedation).

According to the study reported by Chen et al., infusion of dexmedetomidine at 0.8 μg/kg/hr in patients undergoing spine surgery did not affect somatosensory evoked potentials, but inhibited motor evoked potentials (MEPs). These authors also reported that the median time taken for the MEP waveform to recover was 47 minutes. If MEP monitoring is needed during craniotomy, disappearance of MEPs might hinder the progress of surgery. In awake craniotomy, surgeons often precede awake craniotomy by measuring MEPs, and anesthesiologists need to take great care about the dose of dexmedetomidine.

Unlike propofol, the blood concentration of dexmedetomidine is not decreased steeply even if administration is canceled. This characteristic is shown by pharmacokinetic analysis of intravenous dexmedetomidine—the Dyck model. In the dexmedetomidine group in this study, I doubt whether the neurophysiologist can communicate with the patient precisely and evaluate brain functions in the awake phase. Indeed, my colleagues and I have used an asleep-awake-asleep method in our clinical settings, and we use dexmedetomidine only for cases requiring prevention of agitation leading into the awake phase or cases in which it is predicted that the quality of awakening will not be clear. In our 30 recent cases, the mean time until awakening was 11.97 minutes (range 3–27 minutes) with propofol and remifentanil anesthesia (the mean age of those patients was 48.17 years [range 22–79 years]). Therefore, I contend that the authors’ protocol and dose in dexmedetomidine sedation is controversial. I believe that dexmedetomidine is not required for all patients from young patients to elderly patients.

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References

Disclosures
The author reports no conflict of interest.

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INCLUSIVE WHEN CITING
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Response
We thank Dr. Tachibana for this interesting comment regarding our published article about patients undergoing awake craniotomies under different anesthetic regimens. In this article, we retrospectively analyzed 180 patients who were sedated only with dexmedetomidine (conscious sedation, spontaneously breathing without intubation) or propofol/remifentanil (asleep-awake-sleep, intubation for opening and closure). The data represent a single-center historical comparison of a large neurosurgical collective (mean patient age 48 years, range 16–78 years). We started using dexmedetomidine in 2013, at an early phase when guidelines and recommendations regarding its application in neurosurgical awake procedures were scarce in the literature. Based on the available data and our own clinical experience, we created our algorithm for awake surgeries.

In detail, we applied dexmedetomidine as the sole anesthetic drug at a rate of 0.5–1.6 μg/kg/hr (mean 0.6 μg/kg/hr), apart from a small number of cases in which low-dose remifentanil (0.05 μg/kg/min) was additionally used. We did not administer an initial bolus of dexmedetomidine, even though a bolus infusion is generally recommended according to pharmaceutical instructions. We started infusion at a rate of 0.5–0.7 μg/kg/hr. We recommend a slow upward titration tailored to the patient’s level of sedation.

Dr. Tachibana states that a perioperative dose of 0.2–0.7 μg/kg/hr is recommended, and that “higher doses” can...
cause adverse events. It is not clear, however, on what this recommendation for neurosurgical procedures is based. In our evaluated cases, only a few patients (n = 4, 5.3%) required an infusion rate higher than 1.2 μg/kg/hr (mostly during the craniotomy phase of surgery or in cases of discomfort, back pain, or hip pain). Please note that the vast majority of published articles combine dexmedetomidine with other anesthetic compounds.1–3 Thus, dose recommendations from published articles need to be critically questioned when solely administering dexmedetomidine.

In our experience, a maximum of 0.7 μg/kg/hr dexmedetomidine will not provide sufficient sedation in a large number of patients in every phase of surgery. We can report that neither serious hypotension nor severe bradycardia was encountered in our cohort with the described dosage. Only 2 patients (2.7%) required termination of monitoring due to lack of compliance.

Based on our published results, we have now almost completely abandoned the asleep-awake-asleep procedure. Patients in the conscious sedation group required significantly less vasoactive and antihypertensive drugs as well as opioids in comparison to the awake-asleep-awake group (p < 0.001). Furthermore, postoperative length of stay and time of surgery were shorter (p < 0.001).

Regarding the author’s concerns about neurophysiological monitoring and MEPs, the cited study by Chen et al.2 is not representative for our patients, since these authors only analyzed elderly patients (65–80 years old) during spine surgery, and all patients in their cohort received propofol and remifentanil in addition to dexmedetomidine. Pharmacological interactions are thus hard to predict. Even though we never use MEPs in awake patients, it is further known that the depth of anesthesia influences the MEP response.3 Moreover, prior sedation with total intravenous anesthesia has been shown to compromise cognitive and motor performance,4 which is the case in the asleep-awake-asleep setting.

Early termination of monitoring due to lack of compliance as a consequence of excessive sedation has become a rarity in our department, whereas this was encountered more frequently when using propofol/remifentanil. Even if the asleep-awake-asleep setting is performed worldwide and remains a feasible setting in awake glioma surgery, from our experience this regimen provides a less favorable setting for awake surgeries in glioma patients.

In our study, we included patients who underwent surgery between 2009 and 2015. By now, we have performed more than 250 awake surgeries with dexmedetomidine as the main anesthetic drug. We strongly recommend dexmedetomidine as an excellent compound in awake neurosurgery when intraoperative mapping and monitoring is required. There is no question that the interdisciplinary setting as well as the know-how and timing with respect to drug pharmacodynamics is essential.

We have come a long way since 1991 when the senior author performed his first awake craniotomy using fentanyl and midazolam. Too much sedation led to hypercapnia and swollen brains, too little sedation led to confused patients trying to rise. Drapes were sewn to the patients’ heads in an attempt to maintain antisepsis. The senior author changed to larynx masks together with remifentanil and propofol in 2003, clamping all patients’ heads in the Mayfield head holder—a regimen still favored by most surgeons. Finally, we have now switched to the current regimen, and with our study we are happy to have helped clarify the safety and usefulness of our approach with our large cohort. Anesthesiologists and their expertise play an essential part in awake craniotomies, and our published experience, which constitutes the largest cohort so far, clearly demonstrates our regimen to be safe and effective, provided that the necessary neurosurgical and anesthesiological expertise and experience are available.

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References

Confucius updated: on reinventing the wheel

TO THE EDITOR: In his well-thought-out article on reinventing the wheel1 (Mattei TA: “Reinventing the wheel”: reflections on a recurrent phenomenon in the history of neurosurgery. J Neurosurg 129:1641–1648, December 2018), Mattei quotes Confucius (“Study the past if you would define the future”). I am reminded of the sage advice given by Dr. Peter Jannetta when reviewing my presentation on the prescient concept of trigeminal nerve decompression contained in the early surgical treatments by Nicolas André, who coined the term “tic douloureux.” André wrote of this in 1756, 2 centuries before Jannetta “rediscovered” the concept of removing compressive elements from the surface of the trigeminal nerve that had been “first discovered” by Walter Dandy as the means to
treat the “suicide” disease. Dr. Jannetta’s modernization of Confucius’ philosophical musing was that “Young doctors should read old books and old ones should read new books.” Or before them all, there was Ecclesiastes: “not all new beneath the sun,” but better said as “there is nothing new under the sun.”

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References

Disclosures
The author reports no conflict of interest.

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TO THE EDITOR: We have read with great respect the article by Di Somma and colleagues1 (Di Somma A, Andaluz N, Cavallo LM, et al: Endoscopic transorbital superior eyelid approach: anatomical study from a neurosurgical perspective. J Neurosurg 129:1203–1216, November 2018). The authors were able to define 3 modular routes that could be combined to unveil the temporal pole region, lateral wall of the cavernous sinus, middle cranial fossa floor, and frontobasal area. Moreover, an excellent qualitative stepwise endoscopic transorbital superior eyelid approach was analyzed.2

As our lead author (A.N.) is involved in transorbital neuroendoscopic surgery (TONES), we would like to discuss 2 identified limitations: the restricted surgical exposure via the middle corridor to the opticocarotid region, and how to minimize the risk of postoperative cerebrospinal fluid (CSF) leakage.

First, given our lead author’s experience with cadaveric transpalpebral transorbital study (Fig. 1), we know such techniques are not without disadvantages. The presence of medial and lateral malleable retractors to manipulate the orbit and the temporal lobe (as documented in the authors’ study), respectively, means that we are facing an exceptionally deep and narrow surgical corridor. Additionally, the crowding of surgical instruments forces the surgeon to become accustomed to uncomfortable maneuverability and places the orbit at great risk. Therefore, our lead author now opts for adding endoscopic endonasal medial orbital apex decompression (EEMOAD) before starting the transorbital approaches to regions beyond the orbital cone to avoid several drawbacks (Fig. 1). This nuance allows early release of the optic nerve, which may permit safer manipulation around the orbital apex before dealing with tumors in this area. Moreover, it creates an extra surgical window that accommodates the medially retracted orbit with reasonable accessibility and better maneuverability.3–4

We wonder, do the authors think that such EEMOAD can overcome the restricted surgical exposure via the middle corridor to the opticocarotid region? During extradural inferior dissection, do the authors face any restricted maneuverability attributed to the ligamentous attachment to Whitnall’s tubercle (Fig. 1)?

Second, skull base reconstruction following TONES remains challenging.2 Herein, we would like to discuss the endoscopically harvested vascularized pedicle pericranial flap (eVPPF; 80 × 55 mm), which is based on the supraorbital neurovascular pedicle, and whether it can overcome this

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References
daunting challenge as an alternative durable reconstructive option. In one of our TONES-based cadaveric studies, after extended intradural maneuvers, our lead author was able to cover the skull base and dural defects, which are located in a deep narrow corridor, by using an easily fashioned eVPPF (Fig. 1). The 80 × 55–mm size seems to be an indispensable prerequisite to adequately cover the large dural defect, particularly when the frontobasal area, infra- and supratentorial compartments, and Sylvian fissure are exposed via the transorbital route. Do the authors think that eVPPF application for transorbital skull base reconstruction may be useful?

Before clinical application, we would like to consider several relevant issues for better outcomes and to contribute to decreasing the expected high-flow CSF leakage (Fig. 1) following such new approaches. Thus, we are looking forward to receiving the authors’ valuable remarks.

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References

FIG. 1. Additional medial surgical corridor for reasonable accessibility and better maneuverability. A: Macrophotograph of the left orbit showing major bony landmarks including the greater wing of the sphenoid bone (GWS), lamina papyracea, anterior cranial base, frontozygomatic suture, Whitnall’s tubercle (WT), optic strut (white asterisk), maxillary strut (black asterisk), and anterior clinoid process (green arrow). The optic canal, foramen rotundum, lacrimal fossa (blue arrow), cranio-orbital foramen (black circle), superior orbital fissure (SOF), and inferior orbital fissure (IOF) can also be appreciated. B: Macrophotograph of the left orbit showing the surgical windows via the endoscopic endonasal route (red area), which is significantly larger than the medial corridor in the authors’ study, the endoscopic transpalpebral route (yellow area), and the corridor to the anterior cranial base (green area). Inset: Transnasal video-captured endoscopic view showing the benefits from an early decompressed left optic nerve. The surrounding pertinent neurovascular structures can be appreciated. Note that 1) the WT is kept intact to preserve the important ligamentous attachment, and that 2) the blue mark inside the carotid cave indicates reasonable release of the optic nerve. C: Macrophotograph of the left orbit showing the merits of the additional endoscopic endonasal surgical window. Once those 3 surgical windows (red, yellow, and green areas in B) are combined (turquoise outline), reasonable accessibility and better maneuverability (to regions beyond the orbital cone) can be achieved. Note that the clival recess can be seen via the transorbital route. Transorbital skull base reconstruction following modified TONES (D–G). Endoscopically harvested vascularized pericranial flap to reconstruct the left-sided combined extended transorbital anterior petrosectomy (ETOAP) with minimally invasive endoscopic endonasal medial orbital decompression (EEMOD). D: Transorbital video-captured endoscopic view of the left orbit showing the pertinent anatomical landmarks following EEMOD and ETOAP. E: Following transorbital anterior petrosectomy the supra- and infratentorial compartments were exposed. Red asterisk indicates the facial and vestibulocochlear nerve complex at the internal auditory canal, and orange asterisk indicates the brainstem. F: Macrophotographs of the eVPPF (red dotted line), which is reflected via the transpalpebral incision (yellow dashed line) based on the supraorbital neurovascular pedicle and its surface area (insets). Notice that when the eVPPF can cover the area between the tip of the nose (yellow arrows) and the zygomatic bone (black arrows), it indicates that the eVPPF can adequately reconstruct the deeply seated dural defect when reflected intraorbitally. G: Transnasal video-captured endoscopic view obtained following reflection of the eVPPF intraorbitally, showing that the eVPPF can adequately cover the entire challenging defects. Anatomical dissection by the lead author (A.N.). CN II = optic nerve; GSPN = greater superficial petrosal nerve; ICA = internal carotid artery; ITC = infratentorial compartment; MMA = middle meningeal artery; OC = orbital contents; PA = petrous apex; SHA = superior hypophyseal artery; SPS = superior petrosal sinus; STC = supratentorial compartment; T = tentorium; V2 = maxillary nerve; V3 = mandibular nerve. Figure is available in color online only.
FIG. 2. A: The skin incision was made through an eyelid wrinkle and extended laterally beyond the lateral canthal angle in order to expose the anterior and superior portions of the temporalis muscle (left orbit is represented). Accordingly, the lateral orbital rim is identified and completely skeletonized. Medial endo-orbital (light blue area featured in inset) and lateral extra-orbital (light green area featured in inset) corridors are recognized and prepared for further dissection. B: Three-dimensional computer-based illustrations showing endo-orbital (light blue) and extra-orbital (light green) corridors to the middle fossa. Surgical freedoms have been calculated near the superior orbital fissure, slightly lateral to the opticocarotid region. A coronal/oblique view (left), similar to the surgical orientation, and an axial perspective (right) are provided. The axial perspective has been rendered at the level of the lamina papyracea. The reconstructions were obtained using Amira Visage Imaging (Amira Visage Imaging Inc.). FZS = frontozygomatic suture; GSW = greater sphenoid wing; PO = periorbital; SOF = superior orbital fissure; TM = temporal muscle. Figure is available in color online only.


Disclosures
The authors report no conflict of interest.

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Response
We are grateful to Nagm et al. for sharing their interest in our paper, their valuable experience, and their comments. They questioned the potential restricted exposure to the opticocarotid region when performing an endoscopic superior eyelid transorbital (ESETO) approach. They propose an EEMOAD preceding the ESETO approach for access beyond the orbital cone to avoid approach-related limitations.4 We think that this technical gesture is a good point for limiting compression of intraorbital structures and that it could potentially improve exposure of the opticocarotid region, particularly at its deepest aspect. Accordingly, we are currently evaluating a corridor expansion through the addition of an extra-orbital path-
way underneath the temporalis muscle to obtain additional space (unpublished data; Fig. 2A). The extra-orbital corridor can be accessed by laterally extending the superior eyelid incision to expose the anterosuperior temporalis muscle. Subperiosteal dissection of the temporalis muscle uncovers the extracranial surface of the greater sphenoid wing and the pterion. Subsequently, instruments can be inserted between the temporalis muscle (laterally) and the zygomatic bone/greater sphenoid wing (medially). Hence, the orbit (and the optico-carotid region, if necessary) can be entered via its lateral wall, after proper drilling has been performed. Figure 2B elucidates the concept through a three-dimensional computer-based illustration depicting endo-orbital and extra-orbital corridors to the optico-carotid region. Using the methodology described in our paper,1 we calculated surgical freedoms in an example specimen near the most lateral and superior portion of the superor orbital fissure, slightly lateral to the optic canal. Reconstructions were created using Amira Visage Imaging (Amira Visage Imaging Inc.).

The authors also expressed concerns about working comfortably when reaching the optico-carotid region via the transorbital route. Discomfort may apply in the event of a single surgeon. However, when using our four-handed technique, the assistant holds the endoscope in the upper portion of the surgical field while the surgeon works in a lower position with both hands. The value of angled endoscopes is proven here, especially when aiming the endoscope medially, that is, toward the optico-carotid region. As emphasized by the authors, Whitnall’s tubercle is kept intact to preserve its ligamentous attachments. This generally does not restrict maneuverability when aiming toward the anteromedial skull base.

Nagm et al. expressed concern about the risk of CSF leakage during this approach and proposed endoscopically harvesting a vascularized pedicle pericranial flap to accomplish reconstruction. We agree that vascularized pedicle flaps represent the gold standard for skull base reconstruction.2,3 However, we would like to stress that anatomical laboratories are not satisfactory milieus from which to derive all information about the possible clinical complications of a novel surgical approach. Thus, cadaveric models cannot be used to validate the benefits of reconstruction techniques. For that, live animal models and clinical studies may prove better arenas to validate and assess this concept. The establishment of a safe anatomical basis and a feasibility study, such as the one we presented, serve as required preliminary steps in that direction.

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INCLUSIVE When citing
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Factors predicting reoperation for chronic subdural hematoma

TO THE EDITOR: We read with great interest the recently published article by Motiei-Langroudi et al.6 (Motiei-Langroudi R, Stippler M, Shi S, et al: Factors predicting reoperation of chronic subdural hematoma following primary surgical evacuation. J Neurosurg 129:1143–1150, November 2018). The authors studied various clinical and radiological variables for any possible association with need for reoperation and found that the presence of loculations, clopidogrel use, warfarin use, increased amount of residual hematoma/fluid, and decreased percent of hematoma change after surgery significantly predicted the need for reoperation. However, we have some concerns that we would like to share, as well as some questions for the authors.

The authors identified use of warfarin or clopidogrel as a significant factor for recurrence, but they did not mention whether patients underwent surgery 5 or 7 days after stopping these agents or immediately after pharmacological reversal. They also did not mention their protocol time for re-starting antiplatelet agents and anticoagulants after surgery. Also, they did not take into consideration the roles of agents such as steroids, tranexamic acid, atorvastatin, etc., in prevention of recurrence, for which many trials (DECSA,5 SUCRE,2 TRACS,3 ATOCH,4 etc.) are being conducted.
A significant proportion of the patients underwent craniotomy (performed in 255 of 466 operations), but the authors did not mention the type of craniotomy: mini-craniotomy or large craniotomy. They also did not mention their technique of dealing with membranes: partial membranectomy or subtotal membranectomy. Unterhofer et al. found no change in the recurrence rate of chronic subdural hematoma (CSDH) with opening of the internal membrane. Balevi concluded in his study that large cranio- tiomies and extended membrane excision carry a high risk of morbidity and mortality in elderly patients. Post-operative management strategies such as keeping patients on a flat bed (without elevation of the head), administration of 100% O2, and use of an incentive spirometer for re-expansion of brain were not defined in Motiei-Langroudi and colleagues’ study protocol. Moreover, we would like to know how the cases of repeated recurrence were managed and what clinical and radiological characteristics were seen in the patients with refractory CSDH.

Finally, we would like to express our appreciation for the authors’ effort in this study. Further prospective studies are warranted to identify the factors associated with recurrences and to study the role of pharmacological agents in the management of CSDH.

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Disclosures
The authors report no conflict of interest.

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INCLUDE WHEN CITING
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Response
Drs. Kumar and Yadav raise pertinent questions about our published article.

In the retrospective study, we assessed clinical and imaging factors associated with need for reoperation after CSDH evacuation. We would like to briefly answer the questions posed by Kumar and Yadav.

Our results showed that use of warfarin or clopidogrel (but not aspirin, ticagrelor, or heparin) was a significant cause of recurrence. In our study, the patients received pharmacological reversal of their anticoagulation or platelet transfusion and were taken to the operating room upon normalization of coagulation tests (INR, for instance), rather than wait 5–7 days for the effects of the medication to wash out. Although this protocol may have resulted in higher rates of recurrence, many CSDH patients present with precarious neurologic status (loss of consciousness, severe neurologic deficits, etc.), and may require timely decompression.

The decision to resume anticoagulation or antiplatelet therapy was made on a case by case basis. Generally such agents were started after CT scan showed adequate resolution of the CSDH. In some situations, such as if patients had prosthetic mechanical heart valves, earlier anticoagulant therapy was reinstated. Most often this decision was made in conjunction with the cardiologist or primary care physician. Over the last 6 months, we have used middle meningeal artery (MMA) embolization in situations in which early anticoagulant therapy or dual antiplatelet therapy was indicated.

As patients on antiplatelet or anticoagulant agents presenting with some type of intracranial hematoma have always represented a challenge for neurosurgeons, we certainly agree with Kumar and Yadav that there is an ultimate need for well-designed dedicated studies to investigate the effect of medications such as tranexamic acid on CSDH recurrence. The role of MMA embolization is evolving rapidly and may prove to be a very efficacious way of treating this pathology.

As discussed in the original article, we failed to show a role for evacuation technique (craniotomy vs burr hole drainage), number and location of burr holes in burr hole drainage, or membranectomy in recurrence. Of note, in patients undergoing craniotomy and membranectomy, the procedure was mostly done through minicraniotomy (a craniotomy flap with a diameter of approximately 2–3 inches), and a partial membranectomy was performed. We believe that extending the craniotomy size and membranectomy extent not only is ineffective in decreasing recurrence but also increases the morbidity, as confirmed by our and other authors’ results.

As mentioned by Kumar and Yadav, postoperative management strategies (patient and bed position, administration of 100% O2, etc.) were not evaluated in our study, because of its retrospective nature. Steroids, tranexamic acid, and atorvastatin are not routinely used in our institution and thus were not studied. Another challenge is management of suboptimal hematoma evacuation. Although recurrence is better defined in the literature (re-accumulation of new CSDH within 3 months after index surgery), the definition and hence treatment protocol for residual
hematoma is less clear. As such, most surgeons base their decision upon neurologic status and residual hematoma size on postoperative imaging. This is very subjective and the threshold varies from surgeon to surgeon. Reoperation most often involves accessing the subdural space through the same craniotomy and evacuating the hematoma/subdural fluid and leaving a drain. Rarely was the craniotomy enlarged.

We have proposed a simple formula—that a 50% decrease in maximal hematoma thickness on the first postoperative CT scan (done within 24 hours after surgery) is associated with < 10% reoperation risk (for either residual hematoma or recurrence).

Again, we should emphasize that this is not a magic formula, and eventually each case will have to be evaluated on an individual basis.

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The authors mention preparation of the cervical carotid artery with or without retrograde suction decompression, although we saw no data as to how often this technique was used or its relationship to visual outcome. Since its description in 1990, the Dallas technique has allowed clipping of truly massive aneurysms with remarkably good visual outcomes as documented by our group and others. The decompression afforded by the Dallas technique often makes drilling of the clinoid unnecessary, particularly for the classic superiorly pointing carotid-ophthalmic aneurysms, eliminating the only factor the authors found associated with new postoperative visual deficits.

In terms of overall visual outcome, the authors’ paper would have been enhanced by more detailed quantification of these deficits. Did these mild changes in visual field or acuity allow driving according to medical standards for driving, or were they more severe, leading to loss of driving privileges?

While the authors’ series of ophthalmic artery aneurysms is large enough to perform statistical analysis, the loss of granularity in neuroophthalmological outcomes unfortunately limits the applicability of their conclusions.

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References

Disclosure
The authors report no conflict of interest concerning the material or methods used in this study or the findings specified in this paper.

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Response
We appreciate the comments of Drs. Mattingly and Lownie in their letter to the editor regarding our published article. We recognize the importance of objective visual outcome measures in comparing results from different studies and different treatment modalities, such as endovascular occlusion and microsurgical clipping. Rigorous neuro-ophthalmological examination before and after surgery is the gold standard but was difficult to achieve in our cohort. Bedside visual field and visual acuity examinations...
were performed before and after the procedure by an independent neurologist and a neurosurgeon, reflecting the real-world conduct of a busy vascular service. Patients with impairment were referred to a neuro-ophthalmologist for further evaluation to ensure the detection and quantification of surgical deficits.

With regards to retrograde suction decompression,\(^1\) we applaud the authors for their 2013 report demonstrating excellent outcomes with the technique in selected cases, especially giant aneurysms.\(^2\) We rarely used the Dallas technique and instead just softened the aneurysm with temporary trapping, using either the cervical carotid artery or clinoidal segment for proximal control. With such infrequent use, no specific analysis of the technique was possible. We contend that anterior clinoidectomy is a critical step to fully expose and prepare OphA aneurysms for clip application. We disagree that anterior clinoidectomy is unnecessary with these aneurysms, and would not endorse a surgical strategy that does not include this step. We have found instead that inadequate anterior clinoidectomy can complicate or compromise the permanent clipping. Although not statistically proven, our experience suggests that increasing familiarity with this complex anatomy and greater expertise at anterior clinoidectomy tend to increase the technical success rate of clipping and lower the risk of visual deficits.

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References

Neurosurgical forum

New biomarkers for the management of aneurysmal subarachnoid hemorrhage

TO THE EDITOR: We read with great interest the clinical article by Fujiki and colleagues\(^1\) (Fujiki Y, Matano F, Mizunari T, et al: Serum glucose/potassium ratio as a clinical risk factor for aneurysmal subarachnoid hemorrhage. J Neurosurg 129:870–875, October 2018) describing the use of the glucose/potassium ratio as a biomarker for outcomes following aneurysmal subarachnoid hemorrhage (aSAH). We commend the authors for their efforts in identifying new biomarkers that may better inform the management of aSAH. However, we found the title of the paper to be somewhat misleading, as the study centered on the association between the glucose/potassium ratio and post-aSAH outcome rather than the glucose/potassium ratio as a risk factor for aSAH, the latter of which would require an observational study comparing patients with versus those without aSAH. In addition, the time point of the glucose and potassium laboratory values reported in this study was not specified. Although one can assume that these laboratory values were obtained at the time of admission, the serum glucose and potassium levels at subsequent time points during the hospitalization (e.g., following aneurysm treatment, during the vasospasm window, at discharge) may also serve as biomarkers.

It should also be noted that no distinction was made between patients with versus those without diabetes mellitus, which could confound the results. In order to isolate hyperglycemia or a high glucose/potassium ratio as a biomarker for a poor outcome after aSAH, the study should distinguish between stress-induced hyperglycemia and diabetes mellitus. The authors listed Glasgow Outcome Scale (GOS) both at discharge and at 3 months in their outcome assessment. However, only predictors of poor outcome at discharge were analyzed and presented. We are interested to know whether these predictors at discharge remain significant at 3 months’ follow-up.

With regard to the multivariable logistic regression model (their Table 4) that was developed to identify independent predictors of poor outcome, it is unclear to the reader how the covariates were selected. Additionally, there appear to be variables unaccounted for in their Table 4, compared with those that were listed as included covariates in the Statistical Analysis section. Thus, it is unclear to the reader whether these variables were dropped due to multicollinearity or removed in a stepwise regression. Furthermore, there was no indication of how missing data were treated. In their Table 4, the odds ratios for glucose/potassium ratio, glucose, and potassium are missing, and the \(p\) values in boldface type were noted to be significant \((p < 0.05)\) in the “univariate analysis,” while the table presents the results of the multivariable model.

Lastly, it is also unclear to the reader whether the patient’s clinical grade (i.e., Hunt and Kosnik grade) or glucose/potassium ratio serves as a better predictor of outcome after aSAH, as the study did not compare the predictive capability of the two variables.\(^3\) Although the authors argued, as the premise of their study, that biomarkers such as the glucose/potassium ratio can be used in aSAH patients without a reliable neurological exam (e.g., due to sedation or poor neurological presentation), no subgroup analysis for these patients was performed. Therefore, the utility of the glucose/potassium ratio in aSAH management remains unproven. We hope that our comments will sharpen the present analysis and serve as points of consideration for future studies.

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Response

Thank you for your insightful comments regarding our article. We appreciate the opportunity to respond.

We agree that the title we selected for our paper may not have been the best choice, and we apologize for that. In the paper we do discuss the serum glucose/potassium ratio as a clinical risk factor for aneurysmal subarachnoid hemorrhage. \textit{J Neurosurg} 129:870–875, 2018

Regarding the multivariable logistic regression model to assess independent risk factors associated with poor prognosis at the time of admission, multivariate analysis was performed using the stepwise logistic regression method, including all initial variables. Factors with p < 0.2 from the bivariate analysis were included in this model.

Regarding the last suggestion, we have not provided information on that paper.

In the severe group (H-K grade IV and V), 9 (4.9%) cases with good outcomes had a glucose/potassium ratio over 60, whereas 19 (17.4%) cases with good outcomes had a glucose/potassium ratio under 60. That showed a better predictor of outcomes after severe SAH. As you mentioned, the glucose/potassium ratio cannot be used in a manner equivalent to H-K grade. However, using the glucose/potassium ratio as a prognostic factor, for example, in patients with severe aSAH, is required to determine the treatment policy in those patients with a high possibility of a good outcome.

Thank you for your helpful review of our article.

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