Neurosurgical Forum

LETTERS TO THE EDITOR

Resection for WHO Grade III gliomas

TO THE EDITOR: We read with great interest the research by Fujii et al.⁴ (Fujii Y, Muragaki Y, Maruyama T, et al: Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI. *J Neurosurg* [epub ahead of print September 8, 2017. DOI: 10.3171/2017.3.JNS162383]) regarding extent of resection for WHO grade III gliomas. The article is well written, and the authors have demonstrated that extent of resection (EOR) of T2-weighted high-signal intensity lesions (T2-EOR) was one of the most important prognostic factors for patients with anaplastic astrocytoma (AA) and anaplastic oligoastrocytoma (AOA) and an especially significant survival advantage was seen with T2-EOR $\geq 53\%$. We highly commend the authors for performing this interesting study because these helpful results would be useful to make a balanced treatment decision planning to prolong patient survival. However, after a detailed analysis of this article, we would like to highlight 3 important issues that it raises.

First, 122 patients with newly diagnosed WHO grade III gliomas had undergone intraoperative MRI-guided resection during the period from March 2000 to December 2011. In the article's *Results* section, however, it is unclear how many patients underwent a second reoperation for recurrent WHO Grade III gliomas after initial resection. It would be helpful to the reader to know whether reoperation for recurrent WHO grade III gliomas can improve overall survival. Unfortunately, there is no evidence to date that supports this hypothesis. However, there exists a relationship between reoperation and overall survival of patients with recurrent glioblastoma.^{2,7} In the report by Tully et al. of 204 patients with de novo glioblastoma, 49 patients (24%) with recurrent glioblastoma underwent reoperation, and the median overall survival in the reoperation group was 20.1 months, compared with 9.0 months in the no-reoperation group ($p = 0.001$), demonstrating that reoperation was associated with longer overall survival.⁷ Coburger et al. revealed similar results from their study of 170 surgeries for glioblastoma, showing that repeated surgery for recurrent disease has a beneficial effect on overall survival.²

Second, the authors concluded that a significant survival advantage was associated with resection of 53% or more of the preoperative T2-weighted high-signal intensity volume in patients with AA and AOA. But if the tumor is located near an eloquent area, is it safe for resection of 53% or more

of the preoperative T2-weighted high-signal intensity volume? Some studies indicate that intraoperative cortical and subcortical stimulation can be used to identify functional areas or tracts and to guide surgical removal of gliomas in eloquent areas.^{1,3} This approach may be able to maximize the extent of resection while minimizing the risk of permanent deficit.^{1,3} Furthermore, awake craniotomy as a special method can prevent motor deficits during the resection of gliomas adjacent to eloquent cortex. Ghinda et al. reported that combined awake craniotomy and intraoperative MRI was safe and efficient, allowing maximal safe resection of eloquent area gliomas with possible subsequent benefits in terms of overall survival and progression-free survival.⁵ However, what is the exact maximal safe resection for gliomas near eloquent areas? A few studies have indicated that a safe margin of 8 mm should be maintained between the limits of resection and the pyramidal tracts.^{8,9} So it was probably wise to tailor the resection of gliomas adjacent to eloquent cortex according to intraoperative electrophysiological investigation, manifestation of intraoperative tasks for awake surgery, and intraoperative MRI, rather than only resection of 53% or more of the T2-weighted high-signal intensity lesions.

Third, we noted that the authors did not analyze data from patients who simultaneously presented with *IDH1/2* mutation and 1p/19q co-deletion. The authors concluded that T2-EOR was not significantly different in patients with AO at any cutoff value, which may be associated with 1p/19q co-deletions and response to chemotherapy.⁴ We wonder whether T2-EOR was also not significantly different for survival in patients with glioma with the *IDH1/2* mutation and 1p/19q co-deletion? Kawaguchi et al. investigated the impact of gross-total resection (GTR) in their series of 124 patients with WHO grade III glioma. They found that patients with tumors with *IDH1/2* mutation and 1p/19q co-deletion had better outcomes, and that GTR or lack of GTR had no significant effect on the survival of such patients.⁶ We expect that the authors further validated the relationship between T2-EOR and survival in patients with WHO grade III glioma with *IDH1/2* mutation and 1p/19q co-deletion. This may influence therapeutic strategies and clinical decisions.

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References

1. Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, et al: Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. **Neurosurgery** **60**:67–80, 2007
2. Coburger J, Wirtz CR, König RW: Impact of extent of resection and recurrent surgery on clinical outcome and overall survival in a consecutive series of 170 patients for glioblastoma in intraoperative high field magnetic resonance imaging. **J Neurosurg Sci** **61**:233–244, 2017
3. Duffau H: Surgery of low-grade gliomas: towards a ‘functional neurooncology’. **Curr Opin Oncol** **21**:543–549, 2009
4. Fujii Y, Muragaki Y, Maruyama T, Nitta M, Saito T, Ikuta S, et al: Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI. **J Neurosurg** [epub ahead of print September 8, 2017. DOI: 10.3171/2017.3.JNS162383]
5. Ghinda D, Zhang N, Lu J, Yao CJ, Yuan S, Wu JS: Contribution of combined intraoperative electrophysiological investigation with 3-T intraoperative MRI for awake cerebral glioma surgery: comprehensive review of the clinical implications and radiological outcomes. **Neurosurg Focus** **40**(3):E14, 2016
6. Kawaguchi T, Sonoda Y, Shibahara I, Saito R, Kanamori M, Kumabe T, et al: Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion. **J Neurooncol** **129**:505–514, 2016
7. Tully PA, Gogos AJ, Love C, Liew D, Drummond KJ, Morokoff AP: Reoperation for recurrent glioblastoma and its association with survival benefit. **Neurosurgery** **79**:678–689, 2016
8. Wu JS, Zhou LF, Tang WJ, Mao Y, Hu J, Song YY, et al: Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts. **Neurosurgery** **61**:935–949, 2007
9. Zhang J, Zhuang DX, Yao CJ, Lin CP, Wang TL, Qin ZY, et al: Metabolic approach for tumor delineation in glioma surgery: 3D MR spectroscopy image-guided resection. **J Neurosurg** **124**:1585–1593, 2016

Disclosures

The authors report no conflict of interest.

Response

We thank Drs. Liu, Chen, and Chen for their interest and comments regarding our article. We would like to respond to the 3 issues they raised.

First, our further analysis demonstrated that 46 (37%) of the 122 patients with newly diagnosed WHO grade III gliomas experienced recurrence. Moreover, 16 (34.8%) of those 46 patients underwent a second reoperation for recurrence. Unexpectedly, the median survival after recurrence in those 16 patients in the reoperation group was 16.3 months, compared with 16.7 months in the 30 patients of the no-reoperation group ($p = 0.97$). According to these data, reoperation for recurrence was not a prognostic factor for overall survival and seemed to exert no influence on the threshold EOR for WHO grade III glioma.

Second, with respect to tumor location, we defined the eloquent region as ≥ 1 of the following areas according to previous studies:^{3,5} internal capsule, basal ganglia, language cortex, sensory cortex, motor cortex, visual center, thalamus, hypothalamus, brainstem, and dentate nucleus.

This study included 59 patients (48%) who had tumors in an eloquent region, and the median T2-EOR in that group was 68.0%. Thirty-two (54%) of the 59 patients who had tumors in an eloquent region underwent awake craniotomy. The median T2-EOR in these 32 patients was 84.8%. These EOR values were higher than 53%, demonstrating that we achieved extensive resection even though the tumor was located in a radiological eloquent area. This is because, as described by Chang et al.,¹ radiological eloquent areas are not always discovered to be truly eloquent. We performed extensive resection only when the radiologically eloquent area was found to be “false-eloquent.” We agree with Dr. Liu that, regarding tumors in or near eloquent regions, surgeons should not pay excessive attention to high EOR and should resect as much tumor as possible with multiple modalities, such as awake craniotomy and functional mapping.

Third, as we mentioned in the paragraph on the limitations of our study in the *Discussion* section, this study lacked data from 23 patients (18.9%) concerning 1p/19q co-deletion, because that examination began in 2004 at our institution. Analyzing data from the remaining 99 patients (81.1%) for whom we had data on 1p/19q co-deletion, 41 patients had tumors showing *IDH1* mutation and 1p/19q co-deletion and only 2 patients died. EOR had no significant effect on survival in this group because of the small number of events, as expected. These data are compatible with findings from previous reports regarding WHO grade II and III gliomas.^{2,4} We hope to report new data with molecular analyses in the future.

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References

1. Chang EF, Clark A, Smith JS, Polley MY, Chang SM, Barbaro NM, et al: Functional mapping-guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. **J Neurosurg** **114**:566–573, 2011
2. Kawaguchi T, Sonoda Y, Shibahara I, Saito R, Kanamori M, Kumabe T, et al: Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion. **J Neurooncol** **129**:505–514, 2016
3. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. **J Neurosurg** **95**:190–198, 2001
4. Nitta M, Muragaki Y, Maruyama T, Ikuta S, Komori T, Maebayashi K, et al: Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection. **Neurosurg Focus** **38**(1):E7, 2015
5. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. **J Clin Oncol** **26**:1338–1345, 2008

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The role of preoperative MRI in predicting craniopharyngioma behavior

TO THE EDITOR: We read with great interest the article by Yue et al.¹⁰ published in the *Journal of Neurosurgery* (Yue Q, Yu Y, Shi Z, et al: Prediction of *BRAF* mutation status of craniopharyngioma using magnetic resonance imaging features. *J Neurosurg* [epub ahead of print October 6, 2017. DOI: 10.3171/2017.4.JNS163113]). The authors analyzed the correlation between preoperative MRI findings and the presence of a *BRAF* V600E mutation in a series of 52 craniopharyngiomas (CPs). First of all, we would like to congratulate the authors for calling attention to the usefulness of the detailed evaluation of conventional MRI scans in CP treatment planning. With the present Letter to the Editor, we would like to warn about the risk of recent studies focusing on the molecular profiles of CPs, which could lead to premature and confusing conclusions.

The authors classified the location of the tumors into intrasellar and suprasellar; however, this simple categorization does not provide accurate information about the relationship between the tumor and its vital adjacent neurovascular structures, a concept fundamental to avoiding any undue hypothalamic injury. In Fig. 1 we show 2 CPs that many authors would categorize as “suprasellar tumors,” yet they actually correspond to 2 different topographical categories, each associated with a different risk of hypothalamic injury.^{3,4} We have recently shown that a detailed evaluation of conventional preoperative MRI scans allows the accurate definition of the CP-hypothalamus relationship⁷ as well as the severity level of the CP attachment to the hypothalamus.⁹ Apart from mammillary body angle assessment and the type of chiasm distortion, 2 important signs that we previously described for ascertaining CP topography,^{5,6} the position of the hypothalamus relative to the tumor and the appearance of the pituitary stalk (PS) were identified as the most informative MRI variables for predicting the exact CP location. A hypothalamus positioned around the mid-third portion of the tumor strongly points to a CP with extensive and strong hypothalamic adhesions (Fig. 1).⁹ Regarding the appearance of the PS, the “amputation” of its upper infundibular portion by the tumor strongly points to the infundibulo-tuberal or not-strictly intraventricular topography, in which the tumor develops within the neural tissue of the third ventricle floor (TVF) (Fig. 1).⁷ In contrast, lack of PS visibility on MR images suggests that the tumor originated beneath the TVF, either at the sellar or suprasellar compartments. It is somewhat surprising that Yue et al. found a normal PS in about 90% of *BRAF* wild-type CPs, whereas, at the same time, they report the tumor occupation of the sellar and suprasellar compartments in 77% of these cases. Moreover, none of the patients with *BRAF* wild-type CPs whose MRI scans are displayed by Yue et al. in Fig. 2 of their paper have a normal PS.¹⁰ The PS is not visible in cases 5, 7, and 8, and it is amputated in case 6.

Finally, we wish to stress that CP molecular profile analyses from isolated tumor specimens that do not take into consideration the well-known surgical/pathological factors

FIG. 1. Example of the use of preoperative MRI findings to accurately define the topography of 2 CPs with similar appearance. **A1–A3:** Mid-sagittal (A1) and coronal (A2) contrast-enhanced T1-weighted MR images and intraoperative image (A3) obtained in a patient with a not-strictly intraventricular or infundibulo-tuberal CP that originated within the neural tissue of the TVF. The MR images show an elliptical solid-cystic tumor (t). The sella is tumor free, and the pituitary gland (PG) has a normal appearance. The chiasmatic cistern (Ch cs) is partially occupied by the tumor, and the pituitary stalk (PS) is amputated. The chiasm (Ch) is compressed forward, the mammillary body angle (MBA) has an acute measurement ($< 90^\circ$), and the hypothalamus (arrows in A2) is around the mid-third portion of the tumor. The mammillary body (MB) is the only visible structure of the TVF. The intraoperative photograph was obtained after radical removal of the tumor via a trans-lamina terminalis approach. Note the ring-like bleeding area (asterisk, *) at the lower portion of the third ventricle walls which corresponds to the plane of strong CP-hypothalamic attachment. **B1–B3:** Midsagittal T1-weighted (B1) and coronal contrast-enhanced T1-weighted (B2) MR images and intraoperative image (B3) obtained in a patient with a suprasellar-pseudointraventricular CP mimicking an intraventricular position. In the MR images, note that the sella and the suprasellar cistern are occupied by a pear-shaped tumor, whereas the upper portion of the third ventricle cavity (3V) is tumor free, and there is no hydrocephalus. The PS is not visible and the chiasm is stretched upward. The obtuse MBA value ($> 90^\circ$) and the position of the hypothalamus (arrows on B2) above the upper third of the tumor result from the upward displacement of the TVF. The intraoperative photograph, a right pterional view, shows the loose cleavage plane between the tumor and the surrounding neural structures due to the intervening arachnoid layer (arrows). ICA = internal carotid artery; rON = right optic nerve. All panels are modified with permission from Prieto R et al: *Neurosurg Focus* 41(6):E13, 2016. Figure is available in color online only.

involved in CP biological behavior^{1,2} may generate confusion about the reliability of genetic/molecular markers to predict such behavior. It is particularly important to consider the tumor topography and the pattern of tumor adherence when CP behavior is studied,⁸ factors not discussed by Yue et al.¹⁰ Further studies analyzing the molecular profiles of CPs should stratify the cases according to the tumor topography and the severity of tumor attachment.

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References

- Guadagno E, de Divitiis O, Solari D, Borrelli G, Bracale UM, Di Somma A, et al: Can recurrences be predicted in craniopharyngiomas? β -catenin coexisting with stem cell markers in p-ATM in a clinicopathologic study of 45 cases. **J Exp Clin Cancer Res** 36:95, 2017
- Omay SB, Chen YN, Almeida JP, Ruiz-Treviño AS, Boockvar JA, Stieg PE, et al: Do craniopharyngioma molecular signatures correlated with clinical characteristics? **J Neurosurg** [epub ahead of print July 14, 2017. DOI: 10.3171/2017.1.JNS162232]
- Pascual JM, Carrasco R, Prieto R, Gonzalez-Llanos F, Alvarez F, Roda JM: Craniopharyngioma classification. **J Neurosurg** 109:1180–1183, 2008 (Letter)
- Pascual JM, Prieto R, Carrasco R: Infundibulo-tuberal or not strictly intraventricular craniopharyngioma: evidence for a major topographical category. **Acta Neurochir (Wien)** 153:2403–2426, 2011
- Pascual JM, Prieto R, Carrasco R, Barrios L: Displacement of mammillary bodies by craniopharyngiomas involving the third ventricle: surgical-MRI correlation and use in topographical diagnosis. **J Neurosurg** 119:381–405, 2013
- Prieto R, Pascual JM, Barrios L: Optic chiasm distortion caused by craniopharyngiomas: clinical and magnetic resonance imaging correlation and influence on visual outcome. **World Neurosurg** 83:500–529, 2015
- Prieto R, Pascual JM, Barrios L: Topographic diagnosis of craniopharyngiomas: the accuracy of MRI findings observed on conventional T1 and T2 images. **AJNR Am J Neuroradiol** 38:2073–2080, 2017
- Prieto R, Pascual JM, Subhi-Issa I, Jorquera M, Yus M, Martinez R: Predictive factors for craniopharyngioma recurrence: a systematic review and illustrative case report of a rapid recurrence. **World Neurosurg** 79:733–749, 2013
- Prieto R, Pascual JM, Rosdolsky M, Barrios L: Preoperative assessment of craniopharyngioma adherence: magnetic resonance imaging findings correlated with the severity of tumor attachment to the hypothalamus. **World Neurosurg** 110:e404–e426, 2018
- Yue Q, Yu Y, Shi Z, Wang Y, Zhu W, Du Z, et al: Prediction of *BRAF* mutation status of craniopharyngioma using magnetic resonance imaging features. **J Neurosurg** [epub ahead of print October 6, 2017. DOI: 10.3171/2017.4.JNS163113]

Disclosures

The authors report no conflict of interest.

Response

We have read the thoughtful and scholarly letter from Prieto et al., which emphasized the classification of craniopharyngioma (CP) according to tumor topography. We greatly appreciate the comments and suggestions about our article.

Thanks to the careful review by Prieto et al, we would like to clarify information in our tables. We focused on whether the pituitary stalk (PS) was thickened² and categorized the cases into 2 groups accordingly. Actually, however, the term “normal” refers to the “non-thickened” group in Table 1 and Supplemental Table 2. We apologize sincerely for our mistake if there was any misunderstanding in this subtle difference in terminology. We do not believe this change in terminology affects the results or conclusions of our paper. The 4 cases in Fig. 2 all belonged to the non-thickened PS group.

Topographic diagnosis of CP has provided important guidance in predicting the tumor involvement of vital structures such as the TVF and PS. As suggested by Prieto et al. in a series of articles and letters,^{3–5} CP topography can be defined into 5 main categories based on hypothalamic distortion: sellar-suprasellar, pseudointraventricular, secondary intraventricular, not strictly intraventricular, and strictly intraventricular. Seven parameters on conventional T1- and T2-weighted images were recently identified to predict the CP topography with a satisfactory accuracy.⁴ We admire what Prieto and colleagues have achieved in this field and fully agree that ascertaining CP topography preoperatively contributes to the optimal choice of surgical approach as well as radical removal of the tumor.

However, the main aim of our study was to predict the *BRAF* mutation status of CP based on conventional MR characteristics. Such noninvasive diagnosis of *BRAF*-mutated CP may pave the way for administration of *BRAF* mutation inhibitors, which has shown efficacy in 2 reports and might serve as first-line treatment (instead of surgery) in the future. It is obvious that the topographic classification, based on a neurosurgical approach, cannot be directly applied to predict *BRAF* mutation in daily neuroimaging practice. Toward this end, we referred to the most accepted imaging data acquisition and analysis method—2 neuroradiologists first reviewed all MR images and then resolved discrepancies in consensus. As for the term “suprasellar,” we agree with Lee and Chang that it is still widely used by most neurosurgeons and neuroradiologists, thus serving as a concise term for communication.¹

In accord with Prieto and colleagues’ comment that pathological factors involved in CP biological behavior should be taken into consideration, the relationship between molecular profiles (*BRAF/CTNNB1*) and pathological subtypes was summarized in Table 1 and Supplemental Table 2 and further illustrated in the second to fifth paragraphs of the *Discussion*. Briefly, 75% of the *BRAF*-mutated cases were squamous-papillary, while 93% of the wild-type ones were adamantinous. The mechanism underlying the contribution of *BRAF* mutation to CP tumorigenesis is still unclear and needs future investigation.

We avoid limiting our horizon to conventional interpretation of MR images and have been trying to predict molecular profiles via a quantitative radiomics approach.

We cooperated with computer scientists to obtain a huge amount of information from MR images and extract features to build a standardized gene prediction model for CP. The data have been summarized for submission and we hope the novel method can serve as a complement for current neuroimaging practice.

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References

1. Lee HJ, Chang FC: Reply. *AJNR Am J Neuroradiol* 36:E57, 2015 (Letter)
2. Lee HJ, Wu CC, Wu HM, Hung SC, Lirng JF, Luo CB, et al: Pretreatment diagnosis of suprasellar papillary craniopharyngioma and germ cell tumors of adult patients. *AJNR Am J Neuroradiol* 36:508–517, 2015
3. Prieto R, Pascual JM, Barrios L: Optic chiasm distortion caused by craniopharyngiomas: clinical and magnetic resonance imaging correlation and influence on visual outcome. *World Neurosurg* 83:500–529, 2015
4. Prieto R, Pascual JM, Barrios L: Topographic diagnosis of craniopharyngiomas: the accuracy of MRI findings observed on conventional T1 and T2 images. *AJNR Am J Neuroradiol* 38:2073–2080, 2017
5. Prieto R, Pascual JM, Subhi-Issa I, Jorquera M, Yus M, Martinez R: Predictive factors for craniopharyngioma recurrence: a systematic review and illustrative case report of a rapid recurrence. *World Neurosurg* 79:733–749, 2013

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The causative role of sinus stenosis in idiopathic intracranial hypertension

TO THE EDITOR: We read with great interest the case report by Buell et al.¹ (Buell TJ, Raper DMS, Pomeranic JJ, et al: Transient resolution of venous sinus stenosis after high-volume lumbar puncture in a patient with idiopathic intracranial hypertension. *J Neurosurg* [epub ahead of print August 25, 2017. DOI: 10.3171/2017.3.JNS163181]). The authors report on an obese woman diagnosed with idiopathic intracranial hypertension (IIH) who presented with headache and visual obscurations associated with papilledema, empty sella, and bilateral transverse sinus (TS) stenosis and who subsequently experienced significant improvement after a lumbar puncture (LP) with cerebrospinal fluid (CSF) withdrawal. Symptom remission lasted 1 month. Thereafter, the patient underwent unilateral TS stenting, with clinical improvement maintained at the 2-month follow-up.

The novelty of this report relies on the simultaneous assessment of CSF pressure, the cross-sectional area at the level of stenosis, and the trans-stenosis pressure gradi-

ent before and after the LP and at symptom recurrence. Moreover, the trans-stenosis pressure gradient was assessed after TS stenting; unfortunately, CSF pressure at this point was not assessed. The withdrawal of 32 ml of CSF during the LP determined a dramatic reduction in CSF pressure (from 520 to 230 mm H₂O) and in the trans-stenosis pressure gradient (from 38 to 6 mm Hg) with enlargement of the cross-sectional area at the stenosis level (from 12.9 to 24.5 mm²). At symptom relapse, a new LP again showed both an elevated CSF pressure of 330 mm H₂O and a trans-stenosis pressure gradient of 26 mm Hg. Ultimately, the patient underwent right TS stenting, which reduced the trans-stenosis pressure gradient to 2 mm Hg, followed by symptom improvement that was maintained at the 2-month follow-up.

In light of their findings, the authors suggest that “sinus stenosis may be a downstream effect of elevated intracranial pressure in IIH, rather than its principal mechanism,” but they acknowledge that a positive feedback loop between intracranial pressure (ICP) and sinus stenosis may significantly contribute to the disease mechanisms in selected cases.

While we congratulate the authors on this interesting and very well-documented case report, we would attempt to provide a slightly different interpretation of their findings. At symptom relapse, ICP was 330 mm H₂O, the bilateral TS stenosis recurred, and a trans-stenosis pressure gradient of 26 mm Hg was recorded. This means that, in this patient, the threshold at which the TS compression under external CSF pressure (pCSF) might start is certainly lower than 330 mm H₂O, a value close to the upper limit of the normal pCSF range (250 mm H₂O). Furthermore, after the LP (closing pCSF = 230 mm H₂O), the pressure gradient measured across the stenosis was still 6 mm Hg. Although the arbitrary cutoff of 8 mm Hg is used by many surgeons to perform the stenting procedure, successful stenting has been reported in 4 (22.2%) of 18 cases showing a trans-stenosis pressure gradient of 6 mm Hg.⁸ In a recent case series by authors of the case report under discussion,⁶ 19 IIH subjects underwent successful superior sagittal sinus stenting, and an even lower mean pressure gradient (4.2 mm Hg) was preoperatively measured across the stenosis, which reduced to 1.5 mm Hg after the procedure. Actually, after unilateral sinus stenting in the woman in the case report, the trans-stenosis pressure gradient further dropped to 2 mm Hg.

Thus, a certain degree of venous collapse was already present at a pCSF of 230 mm H₂O, sufficient to keep the pressure gradient across the stenosis at the “borderline” value of 6 mm Hg. Only after the “stiffening” of the sinus wall produced by the stenting procedure could a fully physiological value of 2 mm Hg be recorded. The above considerations and findings indicate that, in this patient, a progressive and clinically relevant sinus venous collapse by external compression actually starts at a relatively low pCSF value, close to the upper level of the normal range or perhaps even within such a range.

Now, the crucial question is, can we consider “normal” a dural sinus whose collapse, on the one hand, is a sufficient condition to promote the IIH syndrome, but on the other hand, already occurs at pCSF values close to the

normal range? In other words, which is the expected resistance to external compression of dural sinuses?

We have recently discussed this topic and its relevant pathophysiological implications in IIH syndrome with and without papilledema.² According to evidence in the animal and human experimental literature, though not recent,^{3,5,7,9} the dural sinus walls must be rigid enough not to collapse as a consequence of the large pCSF continuous variations that occur in many pathological conditions as well as during postural changes or other common daily activity implying the Valsalva effect. In a fundamental work by Johnston and co-workers,³ in 10 of 13 anesthetized baboons, the experimental increase in pCSF up to mean arterial pressure values was not associated with significant changes in dural sinus pressure (pDS). This indicates that in the majority of the studied animals, the compressibility of the dural sinus wall was negligible, even at pCSF values far beyond the physiological limits. In two similar studies on the dog,^{4,9} the pCSF increase up to 1000 mm H₂O was not associated with significant changes in pDS. These studies show that the resistance to compression of the venous sinuses in the presence of increased pCSF is optimal within a wide range of pressure variations, well beyond that physiologically expected. On the contrary, in the presence of excessively collapsible dural sinuses, it is expected that the pDS increases together with the pCSF. In the other 3 baboons in the study by Johnston et al.,³ the experimental increase in pCSF up to the arterial pressure value led to a parallel increase in pDS starting at a pCSF of 40 mm Hg (542 mm H₂O). These animals were also the only ones in the sample to show a fall in venous blood pressure between the torcular sinus confluence and the jugular gulf, a finding that may indicate the partial collapse of transverse-sigmoid sinuses in this subgroup. More recently, a CSF infusion study with simultaneous measurement of pDS and pCSF in 9 patients with IIH⁵ has shown the existence of a pressure gradient between the superior sagittal sinus and the transverse sinus (indicative of transverse sinus compression) in all cases and, importantly, has documented the strict dynamic coupling of pCSF and pDS, with the pCSF always higher than the pDS both at baseline and after CSF infusion (significant correlation, $R = 0.97$). Authors of that study concluded that in IIH patients, there is functional obstruction of the transverse sinus that induces an increase in the pDS, which in turn leads to an increase in pCSF. Of note, in a study on 12 subjects with secondary intracranial hypertension,⁴ only 3 patients (25.0%) showed direct coupling of pDS and pCSF; in the remaining 75% of the sample, the pDS remained largely unaffected by the raised pCSF.

The above considerations and data strongly suggest that clinically relevant dural sinus compression occurring at CSF pressure values close to the upper limit of the normal ICP range is to be considered the primary event leading to IIH in such a patient. In other words, we believe that in the presence of sufficiently rigid dural sinuses, an IIH syndrome would never have occurred.

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References

1. Buell TJ, Raper DMS, Pomeranec II, Ding D, Chen CJ, Taylor DG, et al: Transient resolution of venous sinus stenosis after high-volume lumbar puncture in a patient with idiopathic intracranial hypertension. *J Neurosurg* [epub ahead of print August 25, 2017. DOI: 10.3171/2017.3.JNS163181]
2. De Simone R, Ranieri A, Bonavita V: Starling resistors, autoregulation of cerebral perfusion and the pathogenesis of idiopathic intracranial hypertension. *Panminerva Med* **59**:76–89, 2017
3. Johnston IH, Rowan JO: Raised intracranial pressure and cerebral blood flow. 3. Venous outflow tract pressures and vascular resistances in experimental intracranial hypertension. *J Neurol Neurosurg Psychiatry* **37**:392–402, 1974
4. Martins AN, Kobrine AI, Larsen DF: Pressure in the sagittal sinus during intracranial hypertension in man. *J Neurosurg* **40**:603–608, 1974
5. Pickard JD, Czosnyka Z, Czosnyka M, Owler B, Higgins JN: Coupling of sagittal sinus pressure and cerebrospinal fluid pressure in idiopathic intracranial hypertension—a preliminary report. *Acta Neurochir Suppl* **102**:283–285, 2008
6. Raper DMS, Buell TJ, Ding D, Pomeranec II, Crowley RW, Liu KC: A pilot study and novel angiographic classification for superior sagittal sinus stenting in patients with non-thrombotic intracranial venous occlusive disease. *J Neurointerv Surg* [epub ahead of print], 2017
7. Shulman K, Yarnell P, Ransohoff J: Dural sinus pressure. In normal and hydrocephalic dogs. *Arch Neurol* **10**:575–80, 1964
8. Tebeb MS, Cziep ME, Issa M, Lazzaro M, Asif K, Hong SH, et al: Stenting and angioplasty for idiopathic intracranial hypertension: a case series with clinical, angiographic, ophthalmological, complication, and pressure reporting. *J Neuroimaging* **25**:72–80, 2015
9. Yada K, Nakagawa Y, Tsuru M: Circulatory disturbance of the venous system during experimental intracranial hypertension. *J Neurosurg* **39**:723–729, 1973

Disclosures

The authors report no conflict of interest.

Response

First, we thank De Simone and colleagues for their great interest in our recent article. They were concerned with our suggestion that venous sinus stenosis (VSS) may be a downstream effect of elevated ICP in IIH, rather than its principal mechanism. They provide a slightly different interpretation of our findings by suggesting that clinically relevant VSS occurring at an ICP close to the upper limit of normal should be considered the primary event leading to IIH in our patient.

De Simone states that “borderline” VSS (transverse-sigmoid sinus pressure gradient of 6 mm Hg; many surgeons use 8 mm Hg as the minimum cutoff for stenting) was present at a CSF pressure of 26 cm H₂O (close to the upper limit of the normal range: 25 cm H₂O) after CSF drainage. They conclude that “the threshold at which the TS compression under pCSF might start is certainly lower than 33 cm H₂O.” We acknowledge this interpretation but offer a possible alternate explanation. It is unclear if there is constant elasticity of the dural sinus walls. In pathological states of elevated ICP, we hypothesize that an “elastic limit” may exist. If this threshold is exceeded, permanent deformation may begin; therefore, altered dural sinus elas-

ticity under variable ICP may confound attempts to identify the inciting etiological factor of this case (VSS or elevated ICP).

Moreover, we believe that the duration of a patient's clinical symptoms prior to focused investigation with venous manometric recording must be taken into consideration. Our patient presented months after symptom onset; therefore, the exact duration of her elevated ICP was unknown. Under chronically elevated ICP, do dural venous sinus walls remain rigid initially, only to "fail" eventually and become significantly compressed after exceeding an elastic limit? In thermodynamics and fluid mechanics, compressibility of a medium and its inverse (bulk modulus) can change with high enough stresses. If this occurs in the dural sinuses of IIH patients, then our hypothesis that VSS may be a downstream effect of elevated ICP may be correct.

In conclusion, we recommend rigorous investigation of the relationship between VSS and ICP in IIH patients and propose that there is a possible elastic limit for dural sinus walls. Moreover, we hypothesize that there may be two subsets within IIH: 1) primary VSS, in which VSS is the primary inciting factor, and in which case the syndrome is not truly idiopathic; or 2) secondary VSS, in which VSS occurs as a response to elevated ICP, and in which case the syndrome is appropriately named. In our case report, although we cannot state for certain whether VSS was secondary to elevated ICP, an apparent VSS-ICP physiological coupling was present and was probably obliterated after stent deployment. Our report provides novel preliminary data, and we believe that further focused investigation of VSS-ICP physiological coupling in patients presenting with IIH (or even non-IIH headache syndromes) is warranted.

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Motor evoked potentials: details matter

TO THE EDITOR: We read with interest the article by Abdulrauf et al.¹ that appeared in the August 2017 issue

(Abdulrauf SI, Vuong P, Patel R, et al: "Awake" clipping of cerebral aneurysms: report of initial series. *J Neurosurg* 127:311–318, August 2017) in which the authors described their results using an awake craniotomy approach for surgical clipping of cerebral aneurysms. The study sought to evaluate the use of an awake procedure to allow for direct neurological testing during critical periods of the operation, such as temporary and permanent clipping maneuvers. They then compared the results of physical examination to simultaneously acquired neurophysiological data. We applaud their novel use of visual evoked potentials but have reservations about the motor evoked potential (MEP) data.

Of note in this study were the 3 patients for whom clinical assessment and the neurophysiological findings were "synchronous," i.e., in agreement, and 3 patients for whom the neurological assessment techniques were "asynchronous," i.e., discrepant. There is an unfortunate lack of technical data on the MEPs acquired in both patient groups. This is critical for evaluating and comparing the data when physical examination results are synchronous with MEP results versus when discordance arises (false-negative MEP results). How do we evaluate and explain the MEP performance? What were the magnitudes of the MEP stimulation parameters between the 2 groups of patients? How was the voltage used to generate the MEPs chosen? Of particular concern is that for cerebral aneurysm procedures, reliable MEP monitoring requires that stimulation of the motor tracts not occur distal to the tissues at risk, or false-negative responses will be obtained.² Without some MEP technical detail, the reader cannot judge the likelihood of a technical error leading to distal motor tract activation and the false-negative MEP outcomes.

In addition to establishing MEP threshold voltages, one method we recommend to evaluate the strength of the MEP stimulation is to include in the recording montage an ipsilateral hand channel. Activation of this ipsilateral hand pathway indicates that motor tract stimulation is occurring in the brainstem or pyramidal decussation.³ Either scenario would indicate that the MEP stimulus strength is too strong with activation of the motor pathway below the tissue at risk for ischemia. This technical scenario could easily explain the study results where MEPs remained unchanged while the patient experienced contralateral weakness during application of the temporary clip.

Practitioners relying on MEP data during aneurysm clipping must ensure that the stimulus applied for MEP acquisition is minimal and not activating the distal motor pathways.² The outcomes from this study emphasize the requirement for meticulous attention to neuromonitoring details that are crucial for patient safety as well as balanced performance evaluation of intraoperative neurophysiological techniques.

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References

1. Abdulrauf SI, Vuong P, Patel R, Sampath R, Ashour AM,

- Germany LM, et al: "Awake" clipping of cerebral aneurysms: report of initial series. *J Neurosurg* 127:311–318, 2017
2. Guo L, Gelb AW: The use of motor evoked potential monitoring during cerebral aneurysm surgery to predict pure motor deficits due to subcortical ischemia. *Clin Neurophysiol* 122:648–655, 2011
 3. Rothwell J, Burke D, Hicks R, Stephen J, Woodforth I, Crawford M: Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. *J Physiol* 481:243–250, 1994

Disclosures

The authors report no conflict of interest.

Response

We appreciate the observations made by Drs. Wilkin-son and Kaufmann about the technical nuances of MEPs. What their comments and our experience both reflect is that there is a clear-cut risk of false-negative results using this monitoring. Therefore, this affirms our rationale that awake testing provides the "gold standard" for motor examination.

We also would like to take the opportunity to further affirm some benefits of awake unruptured aneurysm surgery that go beyond just the motor examination.

Intraoperative Aneurysm Rupture Situation

This is the most common question I get asked since I started performing awake unruptured intracranial aneurysm (UIA) clipping procedures. In our experience so far (over 100 awake clipping procedures of UIAs), we had 2 patients with intraoperative ruptures that were handled without the need for intubation. Granted, neither case was an out-of-control rupture with accompanying brain swelling, etc. So, let's discuss this rare scenario. The specific question to be asked is, in craniotomies done under standard general anesthesia (GA), what is the overall outcome of patients who have these severe intraoperative ruptures with brain swelling, etc.? I think all of us would agree that this subset of patients has overall poor outcome (high morbidity and mortality). So, should we hinge the future of awake clipping of UIAs, for which early results are showing better outcomes, in a rare scenario that essentially universally has a poor outcome? Second, it is pure speculation, and not based on data, that patients in this scenario would fare worse under the awake protocol than the GA protocol in which they already have a very poor outcome.

Vision

Although technology exists to assess visual evoked potentials (VEPs), there is a significant issue of false positives and negatives that have been observed by colleagues who have used this monitoring technique. So, I can state, it would be very hard to make intraoperative decisions about the patient's potential vision loss in internal carotid artery aneurysm surgery based on the VEPs alone. Again, the patient "awake" visual examination is the gold standard for vision evaluation (we perform visual acuity and color

testing intraoperatively). As a result, we have documented reversal of visual loss by removing the clip and repositioning the clip reconstruction.

Level of Consciousness

Perhaps the most feared complication in neurosurgery is that the patient does not wake up. This complication is especially related to vascular procedures involving the basilar artery and P₁ perforators. There is no neurophysiological test for the level of consciousness. Some patients may tolerate long periods of basilar artery temporary clipping, and others may not tolerate seconds; however, we have no idea when the patient is under GA. We have documented this in our early experience. I have placed a temporary clip on the basilar artery for minutes and I am talking to the patient who is tolerating that just fine, and I have situations where the patient who, immediately upon placement of the temporary clip on the basilar artery, becomes sleepy and unresponsive to commands, which is immediately reversed by the removal of the temporary clip (in this latter scenario, if the clip were placed under GA, I would have kept the clip on without knowing).

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Importance of multidisciplinary morning team huddles in the neurosurgical unit

TO THE EDITOR: We congratulate Chan and Vadera¹ on their excellent report on the efficacy of short neurosurgery-led morning huddles in reducing laboratory and pharmacy costs per patient, reducing the number of ICU days, and improving patient satisfaction with the overall delivery of their neurosurgical service (Chan AY, Vadera S: Implementation of interdisciplinary neurosurgery morning huddle: cost-effectiveness and increased patient satisfaction. *J Neurosurg* 128:258–261, January 2018). The authors implemented a 30-minute multidisciplinary morning meeting on weekdays that was led by the neurosurgical team and involved pharmacists, physical/occupational therapists, ICU nurses, and case managers. Analysis of data from the 12 months prior to implementation of the huddle was compared to that of the subsequent 15 months. Of note, the average number of days spent in the ICU decreased by approximately half a day per patient (effect size 3.24, $p < 0.001$). Although both laboratory and pharmacy expenses per patient decreased, overall costs showed no change. Patient satisfaction surveys revealed that the multidisciplinary approach improved patients' understanding of their disease and how to take prescribed medication.

There was also a greater proportion of patients who stated that they would “strongly recommend” the hospital based on their experience.

We believe that the rewards of performing morning meetings such as the huddles described above are immense. At our institution we have held similar meetings for many years. First, we have a neuroradiology meeting in which we discuss new cases referred over the previous 24 hours and any pertinent scans required. We then have a preoperative morning huddle highlighting key issues surrounding the anesthetic, surgical, and postsurgical considerations for the day’s operating cases. We believe that this multidisciplinary input has multifaceted implications, including reduced medication errors, timely discharge from the ICU, more efficient bed management, greater patient satisfaction, and lower overall costs. Chen and Vadera have objectively quantified these benefits, although they rightly highlight the unexpected disparity between laboratory/pharmacy cost savings and overall savings, which clearly requires further research. Aside from these measureable effects, the multidisciplinary meetings are of great benefit in improving teamwork dynamics. Communication across specialties and between different clinicians has certainly evolved in our unit since the genesis of these meetings, and this likely improves clinicians’ overall job satisfaction. Cross-specialty consults, prioritization of investigations, and troubleshooting of issues brought up during meetings certainly facilitates more rapid joint decision-making. This is especially important in a post-reduction-of-hours era in which multiple handovers disrupt continuity of care and in which better teamwork with a more structured approach to decision-making is key.

Stapley et al. assessed the impact of huddles in the pediatric setting and demonstrated improved communication, teamwork, and efficiency.² One challenge they highlighted was the potential for more junior staff to be excluded from the meetings because of other commitments, which contributes to reinforcement of the traditional hierarchical structure ingrained in medicine. Huddles that are able to incorporate the entire team are likely to be most effective, leading to the greatest outcomes for patients and maximizing staff satisfaction.

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References

1. Chan AY, Vadera S: Implementation of interdisciplinary neurosurgery morning huddle: cost-effectiveness and increased patient satisfaction. *J Neurosurg* **128**:258–261, 2018
2. Stapley E, Sharples E, Lachman P, Lakhanpaul M, Wolpert M, Deighton J: Factors to consider in the introduction of huddles on clinical wards: perceptions of staff on the SAFE programme. *Int J Qual Health Care* **30**:44–49, 2017

Disclosures

The authors report no conflict of interest.

Response

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

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“Eloquent”

TO THE EDITOR: I read with interest the article by Kahn et al.² (Kahn E, Lane M, Sagher O: Eloquent: history of a word’s adoption into the neurosurgical lexicon. *J Neurosurg* **127**:1461–1466, December 2017). Kahn et al.² deserve to be appreciated for tracking down the first neurosurgical usage of the now ubiquitous word “eloquent” in the 1951 paper from Oxford on abscesses, authored by then registrar O. V. Jooma,¹ and the illumination of its popularization by Prof. Drake in subsequent decades. There is a link here in as much as in 1951 both Omar Jooma (born 1918) and Charles Drake (born 1920) were trainees with Hugh Cairns and Joe Pennybacker at the Radcliffe Infirmary before they began their illustrious careers in Pakistan and Canada, respectively. They were friends and kept in touch over the years. The assumption of Kahn et al. rings true, that the use of “eloquent” in the context in which we now know it was in common use in the Oxford unit in 1951, and the word would have been assimilated into the lexicon of those who worked there. Prof. O. V. Jooma on many occasions spoke of his 1951 paper but not because of any innovation of vocabulary, but rather due to its early detailing of the significant reduction of surgical mortality of brain abscess with the introduction of penicillin.

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References

1. Jooma OV, Pennybacker JB, Tutton GK: Brain abscess: aspiration, drainage, or excision? *J Neurol Neurosurg Psychiatry* **14**:308–313, 1951
2. Kahn E, Lane M, Sagher O: Eloquent: history of a word’s adoption into the neurosurgical lexicon. *J Neurosurg* **127**:1461–1466, 2017

Disclosures

The author reports no conflict of interest.

Response

We are very grateful for Prof. Rashid Jooma’s personal comments related to the early use of “eloquent” in the neurosurgical lexicon. In researching and writing our paper, we could only hope for such a supportive and insightful response. Prof. Jooma’s comments suggest that Charles Drake was likely familiar with the term well before he first used it in a published paper in 1963. Furthermore, Prof.

Jooma's comments lend credence to the notion that "eloquent" was in common use at Oxford—if not elsewhere—prior to 1951, opening the door for further investigation into earlier uses and origins of this fascinating term.

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Cyst formation after stereotactic radiosurgery for brain AVMs

TO THE EDITOR: We read with great interest the article by Ilyas et al.⁴ (Ilyas A, Chen CJ, Ding D, et al: Cyst formation after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review. *J Neurosurg* [pub ahead of print May 26, 2017. DOI: 10.3171/2016.12.JNS162478]), who pooled data from 22 studies. This pooled analysis provides helpful information about the incidence, time course, and optimal management of cyst formation after stereotactic radiosurgery (SRS) for the treatment of arteriovenous malformations (AVMs). However, there are some issues that we would like to discuss.

First, some of the included studies involved the same series of AVM cases. For instance, the study by Izawa et al. published in 2009⁵ and the study by Izawa et al. published in 2005⁶ are both based on data from patients admitted to Tokyo Women's Medical University between May 1991 and December 2002. The 2009 publication⁵ only included the 15 AVM patients who underwent embolization before SRS, whereas the 2005 publication included all the patients undergoing SRS. Thus, the patients in the later study constituted a subset of the patients in the earlier one, and the 2009 publication should therefore have been excluded. Moreover, all of the studies by Kano and colleagues^{7–10} are based on the data from AVM patients admitted to the University of Pittsburgh from 1987 to 2006 and presumably include many duplicate patients. The studies by Ding et al.^{2,3} are based on the series of AVM patients treated at the

University of Virginia between 1989 and 2009–2010, and the studies by Yen et al.¹³ and Yen and Steiner¹⁴ also included patients admitted to that same institution between 1989 and 2007. Although these studies had different inclusion criteria, it seems likely that data from many duplicate patients were pooled.

Second, because of the different inclusion criteria and duplicate patients in some of the included studies, we conducted subgroup analyses by pooling the data from studies that had the same inclusion criteria (Table 1). Eight of the studies that Ilyas et al. selected for their reviews included AVM patients undergoing SRS, and the incidence of cyst formation based on pooled data from these 8 studies was 4.335%, which is higher than the overall result of the pooled data analysis (3.0%). Moreover, our subgroup analyses showed that there was a tendency for patients with prior embolization, brainstem AVMs, or large AVMs and pediatric patients to have a lower risk of cyst formation (1.481%, 1.975%, 2.198%, and 0.187%, respectively). Eight studies that only included the patients with prior embolization, brainstem AVMs, or large AVMs and pediatric patients were included in this meta-analysis, which might affect the results.

Third, authors of some studies^{3,12} have suggested that the presence of radiation-induced changes (RICs) is associated with cyst formation after SRS in AVM patients. Thus, we conducted an analysis of the studies that provide sufficient patient data or summary statistical data about the association of cyst formation and factors. The pooled odds ratio (OR) was used to evaluate the relationship between factors and cyst formation. Five studies,^{1,3,6,11,12} involving 2330 patients, were included in our analysis. The pooled results suggested that patients undergoing prior embolization (OR 2.30, 95% CI 1.73–3.05, $p < 0.001$, Fig. 1A) and repeat radiosurgery (OR 2.74, 95% CI 1.11–6.78, $p = 0.03$, Fig. 1B) had a higher risk of cyst formation after SRS, while sex (OR 1.16, 95% CI 0.93–1.44, $p = 0.18$, Fig. 1C), incomplete obliteration of AVMs (OR 1.32, 95% CI 0.31–5.60, $p = 0.71$, Fig. 1D), RIC (OR 3.03, 95% CI 0.87–10.64, $p = 0.08$, Fig. 1E), and history of hemorrhage (OR 1.11, 95% CI 0.62–1.96, $p = 0.73$, Fig. 1F) were not associated with cyst formation after SRS. More studies are needed to provide more high-quality evidence regarding the factors involved in cyst formation.

Zengpanpan Ye, MD
Xiaolin Ai, MD

TABLE 1. Subgroup analyses for incidence of cyst formation

Groups	No. of Studies	Mean Incidence of Cyst Formation (95% CI)	Incidence of Cyst Formation
Total	21	4.268% (1.610–0.069%)	77/2604 (2.957%)
SRS*	8	7.208% (0.394–14.376%)	43/992 (4.335%)
Prior embolization	2	3.749% (–33.312 to 40.811%)	2/135 (1.481%)
Pediatrics	2	1.714% (–10.658 to 14.087%)	6/321 (0.187%)
Brainstem AVMs	2	2.081% (–9.409 to 13.571%)	3/152 (1.975%)
Large AVMs	2	2.227% (–26.605 to 31.150%)	2/91 (2.198%)
Repeat radiosurgery	2	6.190% (1.399 to 12.241%)	7/120 (5.833%)

* The studies included the patients undergoing SRS.

FIG. 1. Forest plots for relationship between cyst formation and prior embolization (A), repeat radiosurgery (B), sex (C), incomplete obliteration (D), RIC (E), and history of hemorrhage (F). df = degrees of freedom; IV = inverse variance; SE = standard error. Figure is available in color online only.

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References

1. Chang TC, Shirato H, Aoyama H, Ushikoshi S, Kato N, Kuroda S, et al: Stereotactic irradiation for intracranial arteriovenous malformation using stereotactic radiosurgery or hypofractionated stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* **60**:861–870, 2004
2. Ding D, Starke RM, Yen CP, Sheehan JP: Radiosurgery for cerebellar arteriovenous malformations: does infratentorial location affect outcome? *World Neurosurg* **82**:e209–e217, 2014
3. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP: Radiosurgery for patients with unruptured intracranial arteriovenous malformations. *J Neurosurg* **118**:958–966, 2013
4. Ilyas A, Chen CJ, Ding D, Mastorakos P, Taylor DG, Pomeraniec IJ, et al: Cyst formation after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review. *J Neurosurg* [epub ahead of print May 26, 2017; DOI: 10.3171/2016.12.JNS162478]
5. Izawa M, Chernov M, Hayashi M, Iseki H, Hori T, Takakura K: Combined management of intracranial arteriovenous malformations with embolization and gamma knife radiosurgery: comparative evaluation of the long-term results. *Surg Neurol* **71**:43–53, 2009
6. Izawa M, Hayashi M, Chernov M, Nakaya K, Ochiai T, Murata N, et al: Long-term complications after gamma knife surgery for arteriovenous malformations. *J Neurosurg* **102 Suppl**:34–37, 2005
7. Kano H, Kondziolka D, Flickinger JC, Park KJ, Iyer A, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations after embolization: a case-control study. *J Neurosurg* **117**:265–275, 2012
8. Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. *J Neurosurg* **116**:54–65, 2012
9. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 3: outcome predictors and risks after repeat radiosurgery. *J Neurosurg* **116**:21–32, 2012
10. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, part 2: management of pediatric patients. *J Neurosurg Pediatr* **9**:1–10, 2012
11. Nakajima H, Yamanaka K, Ishibashi K, Iwai Y: Delayed cyst formations and/or expanding hematomas developing after Gamma Knife surgery for cerebral arteriovenous malformations. *J Clin Neurosci* **33**:96–99, 2016
12. Pan HC, Sheehan J, Stroila M, Steiner M, Steiner L: Late cyst formation following gamma knife surgery of arteriovenous malformations. *J Neurosurg* **102 Suppl**:124–127, 2005
13. Yen CP, Monteith SJ, Nguyen JH, Rainey J, Schlesinger DJ, Sheehan JP: Gamma Knife surgery for arteriovenous malformations in children. *J Neurosurg Pediatr* **6**:426–434, 2010
14. Yen CP, Steiner L: Gamma Knife surgery for brainstem arteriovenous malformations. *World Neurosurg* **76**:87–95, 2011

Disclosures

The authors report no conflict of interest.

Response

We thank the authors, Zengpanpan Ye, Xiaolin Ai, and Chao You, for their interest in this paper and 2 others^{9,10} for which they have also written letters to the editor. We

disagree with the authors' assertion that overlap exists between the 2005¹² and 2009¹¹ studies by Izawa and colleagues. The former study included patients with previously untreated brain AVMs who underwent SRS alone, whereas the latter study reported outcomes of AVMs treated with combined neoadjuvant embolization followed by SRS. We also disagree with their assertion that substantial overlap exists among the patients included in the studies by Kano and colleagues^{13–16} due to differences in each study's inclusion criteria. For example, the embolization case-control series only included patients who underwent single-session SRS, and there is no appreciable overlap between this study and the volume-staged SRS and repeat SRS studies.^{13,15,16}

As we have noted in a prior response to the authors, some degree of overlap is sometimes unavoidable in systematic reviews, for which the availability of individual patient data are limited.^{2,9,10,17,22} Additionally, the lack of granularity within the pooled data are a critical limitation of systematic reviews and meta-analyses. These inherent limitations must be weighed against the primary advantage of systematic reviews and meta-analyses, which is the inclusion of a large number of patients. As we discuss in our paper, mean follow-up duration is an important factor that may affect the reported rates of post-SRS cyst formation. Therefore, a meta-analysis of studies with significant variability in follow-up durations, as the authors have performed, is prone to inaccuracies.^{1,8,18,19}

Notably, the authors combine potentially overlapping data from the 2005 study by Pan et al.¹⁹ and the 2013 study by Ding et al.⁸ in their own meta-analysis of the association of prior embolization and the development of post-SRS cysts, which is a major point of contention in their critique. In our single-center retrospective cohort study, we found that a greater number of isocenters ($p = 0.014$), radiological evidence of RIC ($p = 0.002$), and longer follow-up ($p = 0.034$) were independent predictors of post-SRS cyst formation in the multivariate analysis.²¹ Additionally, there was a trend toward a significant association between cyst formation and new or worsening seizures ($p = 0.054$). We agree with the authors that further studies are needed to determine predictive factors of post-SRS cyst formation in AVM patients. To this end, multicenter cohort studies and prospective registries, such as those conducted by the International Gamma Knife Research Foundation (IGKRF) and the AANS and ASTRO SRS registries, may yield more reliable findings than systematic reviews and meta-analyses.^{3–7,20,23–25}

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References

1. Chang TC, Shirato H, Aoyama H, Ushikoshi S, Kato N, Kuroda S, et al: Stereotactic irradiation for intracranial arteriovenous malformation using stereotactic radiosurgery or hypofractionated stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* **60**:861–870, 2004
2. Chen CJ, Chivukula S, Ding D, Starke RM, Lee CC, Yen CP, et al: Seizure outcomes following radiosurgery for cerebral arteriovenous malformations. *Neurosurg Focus* **37**(3):E17, 2014
3. Ding D, Starke RM, Kano H, Lee JYK, Mathieu D, Pierce J, et al: Radiosurgery for unruptured brain arteriovenous malformations: an international multicenter retrospective cohort study. *Neurosurgery* **80**:888–898, 2017
4. Ding D, Starke RM, Kano H, Lee JYK, Mathieu D, Pierce J, et al: Stereotactic radiosurgery for Spetzler-Martin grade III arteriovenous malformations: an international multicenter study. *J Neurosurg* **126**:859–871, 2017
5. Ding D, Starke RM, Kano H, Mathieu D, Huang P, Kondziolka D, et al: Radiosurgery for cerebral arteriovenous malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-eligible patients: a multicenter study. *Stroke* **47**:342–349, 2016
6. Ding D, Starke RM, Kano H, Mathieu D, Huang PP, Feliciano C, et al: International multicenter cohort study of pediatric brain arteriovenous malformations. Part 1: Predictors of hemorrhagic presentation. *J Neurosurg Pediatr* **19**:127–135, 2017
7. Ding D, Starke RM, Kano H, Mathieu D, Huang PP, Kondziolka D, et al: Stereotactic radiosurgery for ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible Spetzler-Martin grade I and II arteriovenous malformations: a multicenter study. *World Neurosurg* **102**:507–517, 2017
8. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP: Radiosurgery for patients with unruptured intracranial arteriovenous malformations. *J Neurosurg* **118**:958–966, 2013
9. Ilyas A, Chen CJ, Ding D, Buell TJ, Raper DMS, Lee CC, et al: Radiation-induced changes after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review and meta-analysis. *Neurosurgery* [epub ahead of print], 2017
10. Ilyas A, Chen CJ, Ding D, Taylor DG, Moosa S, Lee CC, et al: Volume-staged versus dose-staged stereotactic radiosurgery outcomes for large brain arteriovenous malformations: a systematic review. *J Neurosurg* **128**:154–164, 2018
11. Izawa M, Chernov M, Hayashi M, Iseki H, Hori T, Takakura K: Combined management of intracranial arteriovenous malformations with embolization and gamma knife radiosurgery: comparative evaluation of the long-term results. *Surg Neurol* **71**:43–53, 2009
12. Izawa M, Hayashi M, Chernov M, Nakaya K, Ochiai T, Murata N, et al: Long-term complications after gamma knife surgery for arteriovenous malformations. *J Neurosurg* **102** Suppl:34–37, 2005
13. Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. *J Neurosurg* **116**:54–65, 2012
14. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, part 2: management of pediatric patients. *J Neurosurg Pediatr* **9**:1–10, 2012
15. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 3: outcome predictors and risks after repeat radiosurgery. *J Neurosurg* **116**:21–32, 2012
16. Kano H, Kondziolka D, Flickinger JC, Park KJ, Iyer A, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations after embolization: a case-control study. *J Neurosurg* **117**:265–275, 2012
17. Moosa S, Chen CJ, Ding D, Lee CC, Chivukula S, Starke RM, et al: Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. *Neurosurg Focus* **37**(3):E18, 2014
18. Nakajima H, Yamanaka K, Ishibashi K, Iwai Y: Delayed cyst formations and/or expanding hematomas developing after Gamma Knife surgery for cerebral arteriovenous malformations. *J Clin Neurosci* **33**:96–99, 2016
19. Pan HC, Sheehan J, Stroila M, Steiner M, Steiner L: Late cyst formation following gamma knife surgery of arteriovenous malformations. *J Neurosurg* **102** Suppl:124–127, 2005
20. Patibandla MR, Ding D, Kano H, Xu Z, Lee JYK, Mathieu D, et al: Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study. *J Neurosurg* [epub ahead of print September 8, 2017; DOI: 10.3171/2017.3.JNS162635]
21. Pomeranec IJ, Ding D, Starke RM, Liu KC, Mrachek EK, Lopes MB, et al: Delayed cyst formation after stereotactic radiosurgery for brain arteriovenous malformations. *J Neurosurg* [epub ahead of print December 1, 2017; DOI: 10.3171/2017.6.JNS17559]
22. Russell D, Peck T, Ding D, Chen CJ, Taylor DG, Starke RM, et al: Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis. *J Neurosurg* [epub ahead of print May 12, 2017; DOI: 10.3171/2016.11.JNS162382]
23. Sheehan JP, Kavanagh BD, Asher A, Harbaugh RE: Inception of a national multidisciplinary registry for stereotactic radiosurgery. *J Neurosurg* **124**:155–162, 2016
24. Starke RM, Ding D, Kano H, Mathieu D, Huang PP, Feliciano C, et al: International multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: Outcomes after stereotactic radiosurgery. *J Neurosurg Pediatr* **19**:136–148, 2017
25. Starke RM, Kano H, Ding D, Lee JYK, Mathieu D, Whitesell J, et al: Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. *J Neurosurg* **126**:36–44, 2017

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Volume-staged vs dose-staged SRS for large brain AVMs

TO THE EDITOR: It was a great pleasure to read the article by Ilyas et al.,³ which pooled the data to compare the effects of volume-staged (VS) and dose-staged (DS) stereotactic radiosurgery (SRS) in patients with large brain arteriovenous malformations (AVMs) (Ilyas A, Chen CJ, Ding D, et al: Volume-staged versus dose-staged stereotactic radiosurgery outcomes for large brain arteriovenous malformations: a systematic review. *J Neurosurg* **128**:154–164, January 2018). The meta-analysis suggested that VS-SRS afford a higher obliteration rate and a less favorable complication profile than DS-SRS. However, there were some issues that we feel should be discussed.

First, several included studies collected the same series of patients. The study by Sirin et al.⁸ involved 37 patients who underwent VS-SRS for symptomatic large AVMs ($> 10 \text{ cm}^3$) at the University of Pittsburgh Medical Center from 1987 to 2004. Meanwhile, the study by Kano et al.⁴ included the 47 patients with large AVMs ($> 10 \text{ cm}^3$) who also received VS-SRS treatment at the University of Pittsburgh Medical Center between 1987 and 2006. Moreover, the 2015 study by Lindvall et al.⁶ included the 24 patients who received hypofractionated stereotactic radiotherapy (HSRT) treatment for large AVMs ($10\text{--}42 \text{ cm}^3$) at the University Hospital of Umeå between 1986 and 2013. The 2003 study by Lindvall et al.⁵ also included 29 patients undergoing HSRT treatment at the University Hospital of Umeå from 1986 to 2001; however, only 10 of these 29 patients had large AVMs ($> 10 \text{ cm}^3$). It appears likely that the 2006 study by Sirin et al. shared many patients with the 2012 study by Kano et al.⁴ The 2003 study by Lindvall et al.⁵ included 19 patients with moderate-sized AVMs ($2\text{--}10 \text{ cm}^3$) and shared 10 patients with the 2015 study by Lindvall et al.⁶ We believe that the 2006 study by Sirin et al.⁸ and the 2003 study by Lindvall et al.⁵ should be excluded.

Second, we performed an analysis of the results after excluding these 2 studies. The results showed complete obliteration rates of 39.8% (103/259) and 30.9% (65/210) in patients undergoing VS-SRS and DS-SRS, respectively. The partial obliteration rate was 53.6% in patients with VS-SRS, which was lower than the 75% reported in this systematic review.

Third, Seymour et al.⁷ suggested that dose and AVM volume were associated with obliteration rate in patients undergoing VS-SRS for large AVMs, so we searched for the studies that provided the statistical data for the asso-

ciation of factors and obliteration rate. The pooled results of 4 studies^{1,2,4,7} showed that lower Spetzler-Martin grade (OR 0.59, 95% CI 0.37–0.94, $p = 0.03$) and smaller AVM volume (OR 0.95, 95% CI 0.9–0.99, $p = 0.009$) were associated with a higher obliteration rate in patients undergoing VS-SRS for large AVMs, while patient sex (OR 1.02, 95% CI 0.98–1.06, $p = 0.43$), age (OR 0.99, 95% CI 0.96–1.02, $p = 0.59$), dose (OR 1.56, 95% CI 0.84–2.91, $p = 0.16$), prior hemorrhage (OR 1.07, 95% CI 0.95–1.20, $p = 0.30$), and deep location (OR 1.55, 95% CI 0.75–3.21, $p = 0.24$), including thalamus and basal ganglia, were not associated with obliteration rate (Fig. 1). However, only 1 of the included studies (the 2015 study by Lindvall et al.⁶) provided adequate data for the association of factors and obliteration rate in patients undergoing DS-SRS for large AVMs, and we found that no factor was associated with obliteration rate. Thus, more studies are needed to identify factors for predicting the outcomes of SRS treatment of large AVMs.

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References

- Hanakita S, Shin M, Koga T, Igaki H, Saito N: Outcomes of volume-staged radiosurgery for cerebral arteriovenous malformations larger than 20 cm^3 with more than 3 years of follow-up. *World Neurosurg* 87:242–249, 2016
- Huang PP, Rush SC, Donahue B, Narayana A, Bekske T, Nelson PK, et al: Long-term outcomes after staged-volume stereotactic radiosurgery for large arteriovenous malformations. *Neurosurgery* 71:632–634, 2012

FIG. 1. Forest plots for relationship between obliteration rates and Spetzler-Martin grade (A), AVM volume (B), sex (C), age (D), dose (E), prior hemorrhage (F), and deep location (G) in patients undergoing VS-SRS for large AVMs. IV = inverse variance. Figure is available in color online only.

3. Ilyas A, Chen CJ, Ding D, Taylor DG, Moosa S, Lee CC, et al: Volume-staged versus dose-staged stereotactic radiosurgery outcomes for large brain arteriovenous malformations: a systematic review. **J Neurosurg** **128**:154–164, 2018
4. Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. **J Neurosurg** **116**:54–65, 2012
5. Lindvall P, Bergstrom P, Lofroth PO, Hariz MI, Henriksson R, Jonasson P, et al: Hypofractionated conformal stereotactic radiotherapy for arteriovenous malformations. **Neurosurgery** **53**:1036–1033, 2003
6. Lindvall P, Grayson D, Bergstrom P, Bergenheim AT: Hypofractionated stereotactic radiotherapy in medium-sized to large arteriovenous malformations. **J Clin Neurosci** **22**:955–958, 2015
7. Seymour ZA, Sneed PK, Gupta N, Lawton MT, Molinaro AM, Young W, et al: Volume-staged radiosurgery for large arteriovenous malformations: an evolving paradigm. **J Neurosurg** **124**:163–174, 2016
8. Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz AH, Lunsford LD: Prospective staged volume radiosurgery for large arteriovenous malformations: indications and outcomes in otherwise untreatable patients. **Neurosurgery** **58**:17–27, 2006

Disclosures

The authors report no conflict of interest.

Response

We thank the authors, Drs. Ye, Ai, and You, for their interest in our paper and two other published studies of ours for which they have written letters to the editor.^{16,17} Indeed, the authors have composed a number of letters commenting on recent articles.^{2,30–32} We agree with the authors that there is likely some degree of overlap among the 28 patients included for analysis in the Sirin et al. 2006 study of outcomes following VS-SRS for brain AVM and the 47 patients reported in the Kano et al. 2012 series.^{19,27} There is also likely some degree of overlap among the 10 patients with large AVMs treated with DS-SRS in the Lindvall et al. 2003 study and the 24 patients reported in the Lindvall et al. 2015 study.^{20,21} Regarding VS-SRS, the previously reported rates of obliteration, radiation-induced changes (RIC), post-SRS hemorrhage, and death were 40%, 14%, 20%, and 7%, respectively; excluding the Sirin et al. 2006 study, the updated rates are 40% (103/259), 13% (37/294), 20% (46/228), and 8% (22/295), respectively. Regarding DS-SRS, the previously reported rates were 33%, 12%, 11%, and 5%, respectively; excluding the Lindvall et al. 2003 study, the updated rates are 31% (65/210), 12% (27/225), 11% (28/253), and 5% (13/252), respectively. Therefore, the minor aforementioned changes to the selection methodology do not substantially impact the original findings of our study.

Unfortunately, some degree of overlap is typically unavoidable in systematic reviews, where access to individual patient data is limited.^{1,16,17,22,25} Furthermore, the degree of overlap cannot be fully quantified. Thus, the effects of including potentially overlapping articles on the results are difficult to predict. Additionally, including patients from se-

ries with longer follow-up durations has merit, particularly given the rarity of the patient population and need for long-term follow-up to determine the success and complications associated with SRS for large AVMs.^{8,18} These inherent limitations to systematic reviews must be weighed against the primary advantage of this type of study, which is the inclusion of a large number of patients. However, some of these limitations can be overcome by multicenter cohort studies and prospective registries, such as those put forth by the International Gamma Knife Research Foundation (IGKRF) and NeuroPoint Alliance's SRS registry.^{3–7,23,26,28}

The authors have conducted a meta-analysis of 4 VS-SRS studies and found that lower Spetzler-Martin grade and smaller AVM volume are associated with higher obliteration rates. These results have been consistently reported in the literature, and, therefore, they do not represent novel findings.^{9–15,24,29} Further studies are needed to better elucidate the role of VS- and DS-SRS in the treatment of large AVMs.

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References

1. Chen CJ, Chivukula S, Ding D, Starke RM, Lee CC, Yen CP, et al: Seizure outcomes following radiosurgery for cerebral arteriovenous malformations. **Neurosurg Focus** **37**(3):E17, 2014
2. Chen R, Xing L, You C: Letter to the editor regarding "Do serially recorded prognostic scores predict outcome better than one-time recorded score on admission? A prospective study in adult intensive care patients." **J Intensive Care Med** **32**:239, 2017 (Letter)
3. Ding D, Starke RM, Kano H, Lee JYK, Mathieu D, Pierce J, et al: Radiosurgery for unruptured brain arteriovenous malformations: an international multicenter retrospective cohort study. **Neurosurgery** **80**:888–898, 2017
4. Ding D, Starke RM, Kano H, Lee JYK, Mathieu D, Pierce J, et al: Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations: an international multicenter study. **J Neurosurg** **126**:859–871, 2017
5. Ding D, Starke RM, Kano H, Mathieu D, Huang P, Kondziolka D, et al: Radiosurgery for cerebral arteriovenous malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-eligible patients: a multicenter study. **Stroke** **47**:342–349, 2016
6. Ding D, Starke RM, Kano H, Mathieu D, Huang PP, Feliciano C, et al: International multicenter cohort study of pediatric brain arteriovenous malformations. Part 1: Predictors of hemorrhagic presentation. **J Neurosurg Pediatr** **19**:127–135, 2017

7. Ding D, Starke RM, Kano H, Mathieu D, Huang PP, Kondziolka D, et al: Stereotactic radiosurgery for ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible Spetzler-Martin Grade I and II arteriovenous malformations: a multicenter study. **World Neurosurg** 102:507–517, 2017
8. Ding D, Starke RM, Sheehan JP: Radiosurgery for the management of cerebral arteriovenous malformations. **Handb Clin Neurol** 143:69–83, 2017
9. Ding D, Yen CP, Starke RM, Xu Z, Sheehan JP: Radiosurgery for ruptured intracranial arteriovenous malformations. **J Neurosurg** 121:470–481, 2014
10. Ding D, Yen CP, Starke RM, Xu Z, Sun X, Sheehan JP: Outcomes following single-session radiosurgery for high-grade intracranial arteriovenous malformations. **Br J Neurosurg** 28:666–674, 2014
11. Ding D, Yen CP, Starke RM, Xu Z, Sun X, Sheehan JP: Radiosurgery for Spetzler-Martin Grade III arteriovenous malformations. **J Neurosurg** 120:959–969, 2014
12. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP: Radiosurgery for low-grade intracranial arteriovenous malformations. **J Neurosurg** 121:457–467, 2014
13. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP: Radiosurgery for patients with unruptured intracranial arteriovenous malformations. **J Neurosurg** 118:958–966, 2013
14. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP: Radiosurgery for primary motor and sensory cortex arteriovenous malformations: outcomes and the effect of eloquent location. **Neurosurgery** 73:816–824, 2013
15. Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD: A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. **Int J Radiat Oncol Biol Phys** 36:873–879, 1996
16. Ilyas A, Chen CJ, Ding D, Buell TJ, Raper DMS, Lee CC, et al: Radiation-induced changes after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review and meta-analysis. **Neurosurgery** [epub ahead of print], 2017
17. Ilyas A, Chen CJ, Ding D, Mastorakos P, Taylor DG, Pomerniac IJ, et al: Cyst formation after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review. **J Neurosurg** [epub ahead of print May 26, 2017; DOI: 10.3171/2016.12.JNS162478]
18. Ilyas A, Chen CJ, Raper DM, Ding D, Buell T, Mastorakos P, et al: Endovascular mechanical thrombectomy for cerebral venous sinus thrombosis: a systematic review. **J Neurointerv Surg** 9:1086–1092, 2017
19. Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. **J Neurosurg** 116:54–65, 2012
20. Lindvall P, Bergström P, Löfroth POO, Hariz MI, Henriksson R, Jonasson P, et al: Hypofractionated conformal stereotactic radiotherapy for arteriovenous malformations. **Neurosurgery** 53:1036–1043, 2003
21. Lindvall P, Grayson D, Bergström P, Bergenheim AT: Hypofractionated stereotactic radiotherapy in medium-sized to large arteriovenous malformations. **J Clin Neurosci** 22:955–958, 2015
22. Moosa S, Chen CJ, Ding D, Lee CC, Chivukula S, Starke RM, et al: Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. **Neurosurg Focus** 37(3):E18, 2014
23. Patibandla MR, Ding D, Kano H, Xu Z, Lee JYK, Mathieu D, et al: Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study. **J Neurosurg** [epub ahead of print September 8, 2017; DOI: 10.3171/2017.3.JNS162635]
24. Pollock BE, Flickinger JC, Lunsford LD, Maitz A, Kondziolka D: Factors associated with successful arteriovenous malformation radiosurgery. **Neurosurgery** 42:1239–1247, 1998
25. Russell D, Peck T, Ding D, Chen CJ, Taylor DG, Starke RM, et al: Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis. **J Neurosurg** [epub ahead of print May 12, 2017; DOI: 10.3171/2016.11.JNS162382]
26. Sheehan JP, Kavanagh BD, Asher A, Harbaugh RE: Inception of a national multidisciplinary registry for stereotactic radiosurgery. **J Neurosurg** 124:155–162, 2016
27. Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz AH, Lunsford LD: Prospective staged volume radiosurgery for large arteriovenous malformations: indications and outcomes in otherwise untreatable patients. **Neurosurgery** 58:17–27, 2006
28. Starke RM, Kano H, Ding D, Lee JYK, Mathieu D, Whitesell J, et al: Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. **J Neurosurg** 126:36–44, 2017
29. Starke RM, Yen CP, Ding D, Sheehan JP: A practical grading scale for predicting outcome after radiosurgery for arteriovenous malformations: analysis of 1012 treated patients. **J Neurosurg** 119:981–987, 2013
30. Xie Z, Hu X, Li H, Lin S, You C: Risk factors for shunt dependency after aneurysmal subarachnoid hemorrhage. **J Neurosurg** 126:652–654, 2017 (Letter)
31. Yao Z, You C: Letter to the editor regarding “Safety and efficacy of noncompliant balloon angioplasty for the treatment of subarachnoid hemorrhage-induced vasospasm: a multicenter study.” **World Neurosurg** 105:1022, 2017 (Letter)
32. Yao Z, You C: A reliable grading system for prediction of chronic subdural hematoma recurrence requiring reoperation after initial burr-hole surgery. **Neurosurgery** 81:E77, 2017 (Letter)

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Computed tomography angiography for the diagnosis of blunt cerebrovascular injury

TO THE EDITOR: We would like to commend Grandhi et al.² for their study assessing the limitations of CT angiography (CTA) for diagnosis of blunt cerebrovascular injury (BCVI) (Grandhi R, Weiner GM, Agarwal N, et al: Limitations of multidetector computed tomography angiography for the diagnosis of blunt cerebrovascular injury. *J Neurosurg* [epub ahead of print August 11, 2017. DOI: 10.3171/2017.2.JNS163264]). However, we have a few questions and concerns about the study.

There has been significant controversy regarding the use of CTA for BCVI screening. Low sensitivity for BCVI has been ascribed to CTA in multiple studies. Some groups have justified CTA use despite showing only a 68% sensitivity (and 92% specificity) for 64-channel multidetector CTA, thereby recommending digital subtraction angiography (DSA) for patients with CTA-negative results and persistent neurological symptoms.⁷ However, most published literature has shown a high specificity for CTA. In a

previous meta-analysis, Roberts et al. found that CTA had a 97% specificity for BCVI.⁸

In the current study, the authors are reporting a very high false-positive rate (> 47%). The only possible explanation provided for the high false-positive CTA studies is that “a number” of indeterminate readings were considered CTA-positive findings. Since the paper is justifying the use of DSA based on false-positive CT angiograms, we believe that the authors should detail how many such CT angiograms were “indeterminate.”

Amongst the false-positive CT angiograms (Table 3 of the article), the majority were internal carotid artery or vertebral artery dissections. DSA was used in this study as the reference standard to determine the utility of CTA for identifying dissections. However, DSA cannot detect mural hematomas or vessel wall abnormalities and might miss the diagnosis if the lumen is only minimally affected.^{9,12} Conventional angiography is no longer recommended for diagnosing cervical arterial dissection.¹ Assuming DSA to be perfect for diagnosing BCVI might be a flaw. Retrospective review of both DSA and CTA studies would be helpful with blinding and would be helpful before drawing strong conclusions.

The authors' claim that CTA followed by DSA for definitive diagnosis is proved to be safe and effective also has to be seen in context. The justification for DSA is to prevent anticoagulation in patients with false-positive CTA findings. Recent literature has shown the relative safety of antithrombotic therapy, even in patients with traumatic brain injury and solid organ injury.^{6,10} However, we agree that starting a regimen of antithrombotic treatment after a false-positive CT angiogram in almost 50% cases (if indeed true) would not be acceptable.

Although the authors found DSA to be safe in the current study, it is an invasive procedure with a known risk of complications. Also, the authors reported no bump in serum creatinine to state the safety of extra contrast used. However, creatinine levels typically peak at 3 to 5 days after contrast administration, and earlier levels might not be reflective of extent of renal injury.⁵

Ultimately, it is the incidence and, hopefully, the prevention of subsequent stroke that would determine the utility of imaging. It would be interesting to know if the patients with DSA-negative, CTA-positive findings had any subsequent strokes. The authors cited Shahan et al., who also reported a high false-positive rate on CTA.¹¹ Their group had previously reported low sensitivity of CTA, raising the possibility that the radiologists were reporting high false positives, bringing into question the need for the radiology review process. Previous studies have also shown a learning curve with intervention that resulted in improved sensitivity of CTA without an increase in false positives.⁴ Greater awareness of BCVI, the grading of injury, and imaging pitfalls would help improve noninvasive imaging diagnosis.¹³ Optimized, selective CTA in high-risk populations may be the most cost-effective strategy for BCVI detection.³

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References

1. Dobbie S, Leys D: Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurol* 8:668–678, 2009
2. Grandhi R, Weiner GM, Agarwal N, Panczykowski DM, Ares WJ, Rodriguez JS, et al: Limitations of multidetector computed tomography angiography for the diagnosis of blunt cerebrovascular injury. *J Neurosurg* [epub ahead of print August 11, 2017; DOI: 10.3171/2017.2.JNS163264]
3. Malhotra A, Wu X, Kalra VB, Schindler J, Matouk CC, Forman HP: Evaluation for blunt cerebrovascular injury: review of the literature and a cost-effectiveness analysis. *AJNR Am J Neuroradiol* 37:330–335, 2016
4. Malhotra AK, Camacho M, Ivatury RR, Davis IC, Komorowski DJ, Leung DA, et al: Computed tomographic angiography for the diagnosis of blunt carotid/vertebral artery injury: a note of caution. *Ann Surg* 246:632–634, 2007
5. McCullough PA, Sandberg KR: Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 4 (Suppl 5):S3–S9, 2003
6. McNutt MK, Kale AC, Kitagawa RS, Turkmani AH, Fields DW, Baraniuk S, et al: Management of blunt cerebrovascular injury (BCVI) in the multisystem injury patient with contraindications to immediate anti-thrombotic therapy. *Injury* 49:67–74, 2018
7. Paulus EM, Fabian TC, Savage SA, Zarza BL, Botta V, Dutton W, et al: Blunt cerebrovascular injury screening with 64-channel multidetector computed tomography: more slices finally cut it. *J Trauma Acute Care Surg* 76:279–285, 2014
8. Roberts DJ, Chaubey VP, Zygun DA, Lorenzetti D, Faris PD, Ball CG, et al: Diagnostic accuracy of computed tomographic angiography for blunt cerebrovascular injury detection in trauma patients: a systematic review and meta-analysis. *Ann Surg* 257:621–632, 2013
9. Rodallec MH, Marteau V, Gerber S, Desmottes L, Zins M: Craniocervical arterial dissection: spectrum of imaging findings and differential diagnosis. *Radiographics* 28:1711–1728, 2008
10. Shahan CP, Magnotti LJ, McBeth PB, Weinberg JA, Croce MA, Fabian TC: Early antithrombotic therapy is safe and effective in patients with blunt cerebrovascular injury and solid organ injury or traumatic brain injury. *J Trauma Acute Care Surg* 81:173–177, 2016
11. Shahan CP, Magnotti LJ, Stickley SM, Weinberg JA, Hendrick LE, Uhlmann RA, et al: A safe and effective management strategy for blunt cerebrovascular injury: avoiding unnecessary anticoagulation and eliminating stroke. *J Trauma Acute Care Surg* 80:915–922, 2016
12. Teasdale E, Zampakis P, Santosh C, Razvi S: Multidetector computed tomography angiography: application in vertebral artery dissection. *Ann Indian Acad Neurol* 14:35–41, 2011
13. Wu X, Malhotra A, Forman HP, Nunez D, Sanelli P: The use of high-risk criteria in screening patients for blunt cerebrovascular injury: a survey. *Acad Radiol* 24:456–461, 2017

Disclosures

The authors report no conflict of interest.

Response

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

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Chronic subdural hematoma management and outcomes

TO THE EDITOR: I read with great interest the article published by Brennan and colleagues¹ (Brennan PM, Kolias AG, Joannides AJ, et al: The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg* 127:732–739, October 2017). The authors prospectively reviewed the data from 1205 adult patients in 26 neurosurgical units in the United Kingdom and Ireland, the largest study of primary chronic subdural hematoma (CSDH) management in the current literature, providing Level I evidence with which they confirmed the effectiveness of subdural drain placement following intraoperative irrigation in the surgical treatment of CSDH. There is no doubt that this publication has the potential to draw enormous attention from neurosurgeons working in other countries because CSDH is the most common clinical condition in neurosurgery and points of controversy remain. Based on my personal experience, as well as on data in the literature, I would like to point out a few limitations of the study that I noticed.

First, the authors prefer to use the modified Rankin Scale (mRS) and Glasgow Coma Scale (GCS) for the evaluation of their patients upon admission to the hospital and at discharge, whereas most studies in the literature have used the clinical grades described by Markwalder for classifying patients with CSDH.^{2–4} Accordingly, I also think that the GCS is not useful for CSDH because the relevant score assigned for almost 88% of the patients in their series is 13–15 on the GCS scale and the median mRS score was 3.¹

Second, I noticed that the authors neglected an interesting and exceptional issue in the management of patients with CSDHs: the presence of calcification/ossification.^{7,8} Unfortunately, its exact pathogenesis and its optimal management have not been described in detail, while CSDH is a frequently encountered disorder in clinical practice in neurosurgery.

Third, it has been recently suggested that the existence of niveau formation and acute subdural bleeding over the CSDH demonstrated on CT scans should be seen, on arrival to the hospital, as signs implying brain herniation and as a poor prognostic finding in these cases;⁵ Brennan and colleagues,¹ however, reported that the preoperative appearance of a mixed-density subdural collection on CT scans did not predict recurrence. Furthermore, it would be interesting to know the rate of associated “insular infarct” in their series, as a marker of greater disease severity suggested by Sacchetti and colleagues,⁶ since cognitive impairment was the most common presenting symptom in the patients reported on by Brennan and colleagues.¹

Last, the authors reported that duration of burr-hole

drainage after insertion of a subdural drain was 24–48 hours.¹ However, I think that this duration is not sufficient to prevent a recurrence of CSDH after the surgery in some exceptional cases in which the amount of daily drainage from the subdural space may aid the neurosurgeon in making a final decision in clinical practice.

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References

1. Brennan PM, Kolias AG, Joannides AJ, Shapely J, Marcus HJ, Gregson BA, et al: The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg* 127:732–739, 2017
2. Gelabert-González M, Iglesias-Pais M, García-Allut A, Martínez-Rumbo R: Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. *Clin Neurol Neurosurg* 107:223–229, 2005
3. Markwalder TM: Chronic subdural hematomas: a review. *J Neurosurg* 54:637–645, 1981
4. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H: The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. *J Neurosurg* 55:390–396, 1981
5. Matsumoto H, Hanayama H, Okada T, Sakurai Y, Minami H, Masuda A, et al: Clinical investigation of chronic subdural hematoma with impending brain herniation on arrival. *Neurosurg Rev* [epub ahead of print], 2017
6. Sacchetti DC, Yan SC, Thompson BB, Fehnel CR: Insular infarction in subdural hematoma: a case series and pathophysiologic review. *J Clin Neurosci* 39:4–8, 2017
7. Turgut M, Palaoğlu S, Sağlam S: Huge ossified crust-like subdural hematoma covering the hemisphere and causing acute signs of increased intracranial pressure. *Childs Nerv Syst* 13:415–417, 1997
8. Turgut M, Samancıoğlu H, Özsunar Y, Erkuş M: Ossified chronic subdural hematoma. *Cent Eur Neurosurg* 71:146–148, 2010

Disclosures

The authors report no conflict of interest.

Response

We are grateful to Dr. Turgut for his comments on our research.

It is not the case that the majority of patients in the CSDH literature are classified by the Markwalder grading scale. We have previously reviewed the CSDH literature and found that the GCS score and the Markwalder score are equally used for classifying the neurological status of patients on admission.¹ Also, this scale is not in routine clinical use in the United Kingdom, and we therefore utilized the GCS and mRS, which are validated across a range of neurological conditions and are in regular clinical use. The 5-point Markwalder scale uses descriptive terms about the level of consciousness (e.g., drowsy, stuporous, etc.) in combination with the presence of focal signs.² Our approach was to accurately document the level of consciousness with the use of the GCS (rather than descriptive terms) and also to document the presence of focal signs.

We believe that this approach is more useful, but we would also like to state that standardization of data collected by future CSDH studies would help advance the field.

Imaging characteristics that may predict clinical progression or the likelihood of recovery might be important adjuncts to clinical decision-making, provided they can be validated in a large cohort or in prospective studies. Clinical assessment is nevertheless crucial. We are unclear as to whether Dr. Turgut is suggesting that some radiological features predicting poor prognosis should result in a decision not to operate. We would not advocate this. In a subsidiary analysis of our data awaiting publication, we have examined the role of age, GCS score, and radiological findings on outcome. Elderly patients and those in a coma can still have good outcomes. However, we acknowledge that more work needs to be done with regard to whether radiological findings (CT or MRI), including calcification/ossification of CSDH, may predict recurrence or outcome. With respect to the paper by Sacchetti and colleagues,³ it would certainly be of interest to examine the proportion of patients in whom improvement fails to occur after CSDH drainage because of an associated ischemia event. We do not have the data to examine this in our population, but we note that if ischemic events are responsible for a failure to improve after CSDH drainage, this suggests a greater urgency to drain the CSDH in the first place, because drainage may reduce the ischemic risk.

Through the evidence from our study and that of the Cambridge Chronic Subdural Haematoma Trial, a time window of up to 48 hours is emerging as adequate for keeping the drain in place after burr-hole drainage. Longer periods of drainage may potentially be associated with increased morbidity, but we acknowledge that in rare cases with significant ongoing drain output, a longer period of drainage may be necessary.

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References

1. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, et al: Core outcomes and common data elements in chronic subdural hematoma: a systematic review of

the literature focusing on reported outcomes. *J Neurotrauma* **33**:1212–1219, 2016

2. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H: The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. *J Neurosurg* **55**:390–396, 1981
3. Sacchetti DC, Yan SC, Thompson BB, Fehnel CR: Insular infarction in subdural hematoma: a case series and pathophysiology review. *J Clin Neurosci* **39**:4–8, 2017

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Burr-hole drainage of chronic subdural hematoma under local anesthesia

TO THE EDITOR: We are responding to the article by Brennan et al.¹ (Brennan PM, Kolias AG, Joannides AJ, et al: The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg* **127**:732–739, October 2017). First, we wish to congratulate the authors on this interesting paper. Chronic subdural hematoma is a highly common disorder, which is why this study, the largest prospective, observational, multicenter study on management of chronic subdural hematoma to be published to date, is an important way of gaining more insight in the most optimal choice of therapy. However, the authors have neglected a major aspect of surgical treatment: the type of anesthesia.

As expected in chronic subdural hematomas, the patients were mainly elderly. The median age of the population was 77 years.¹ Also, the most frequent presenting complaint of patients transferred to a neurosurgical unit was cognitive impairment (see Table 2 in the article).¹ Nevertheless, to our surprise, nearly all surgical procedures (93%) were performed under general anesthesia (GA).¹ Particularly in elderly patients, GA poses a risk for postoperative cognitive impairment and postoperative delirium, hindering recovery.² Furthermore, GA can be challenging in the elderly due to concomitant diseases. In this light, it would be interesting to make a comparison with hip surgery, which also primarily concerns an aging population. It has been demonstrated that locoregional anesthesia, instead of GA, reduces both the in-hospital mortality rate and length of hospitalization.³

In our neurosurgical practice, the default treatment for chronic subdural hematoma is burr-hole craniostomy (BHC) under local anesthesia, except in the few patients who are unable to cooperate. In our considerable collective experience, when performed with the patient under local anesthesia, the procedure is well tolerated, has no cognitive complications, and has the great advantage that patients can immediately mobilize after surgery. The only drawback to mention is that the BHC creates a lot of noise for patients, which can be largely reduced by having them open their mouths.

The authors conclude that they have defined the preferred strategy for treatment of chronic subdural hematoma. We would like to add to this conclusion that BHC under local anesthesia should be the preferred treatment in the predominantly elderly population of patients.

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References

1. Brennan PM, Kolias AG, Joannides AJ, Shapely J, Marcus HJ, Gregson BA, et al: The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg* 127:732–739, 2017
2. Strøm C, Rasmussen LS, Sieber FE: Should general anaesthesia be avoided in the elderly? *Anaesthesia* 69 (Suppl 1):35–44, 2014
3. Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M: General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiology* 17:87, 2017

Disclosures

The authors report no conflict of interest.

Response

We are grateful to Potgieser and colleagues for their comments on our paper. It certainly sounds plausible, as they suggest, that there might be an advantage to the elderly and frail population to have surgery under local anaesthesia (LA). Our United Kingdom (UK)–wide study demonstrated that 93% of the operations were performed under general anaesthesia (GA), so rather than necessarily neglecting the issue, we restricted our recommendations to the evidence we obtained. In our study, patients treated under LA were, in fact, significantly older than those treated under GA ($p < 0.0001$). More work needs to be done to understand whether or not this is beneficial for patients.

The predominance of GA in CSDH management in the UK begs the question as to why? Does this reflect a patient preference, surgeon preference, surgeon perception of patient preference, anesthetist preference, or a combination thereof?

We briefly reviewed the impact of anaesthesia type on CSDH management in the elderly in a 2016 review.⁶ Few studies had compared the influence of LA and GA on surgical CSDH evacuation, and the results were contradictory. Recently, we also demonstrated that approximately one-third of the studies in the field did not even report whether the operations were performed under GA or LA.¹ Improved reporting is a prerequisite for meaningful cross-study comparisons. It is also worth considering that comparisons of GA and regional/LA have been made in nonneurosurgical practice. For example, a review of 18,715 geriatric patients undergoing hip fracture surgery concluded that spinal anaesthesia was associated with sig-

nificantly reduced early mortality and a decreased risk of venous thromboembolism, delirium, myocardial infarction, pneumonia, and postoperative hypoxia.⁴ In contrast, the GALA trial (general anaesthesia versus local anaesthesia for carotid surgery) failed to demonstrate a difference in outcomes (stroke, myocardial infarction, or death at 30 days) between GA and LA in 3523 patients undergoing carotid artery surgery.³ A study in the *Cochrane Database of Systematic Reviews* in 2004 of 13,500 patients also found no difference between LA and GA in carotid endarterectomy. Interestingly, data from patients in the UK national audit of CSDH suggest that many have similar baseline characteristics as those included in the GALA trial.⁵

The emergence of bedside minimally invasive drainage techniques (e.g., with the use of hollow screws) may obviate the need for GA, if these techniques are proven to be as effective as burr-hole craniostomy.² However, for now, we would recommend that the anaesthetist and surgeon, in consultation with patients and/or their next-of-kin, decide which anaesthesia technique to use on an individual basis. An assessment of the impact of LA versus GA on CSDH outcomes might best be tested in a prospective randomized controlled trial and should include a qualitative component to understand the acceptability of the anaesthesia mode to the patients.

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References

1. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, et al: Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes. *J Neurotrauma* 33:1212–1219, 2016
2. Chari A, Kolias A, Santarius T, Bond S, Hutchinson PJ: Twist-drill craniostomy with hollow screws for evacuation of chronic subdural hematoma. A systematic review. *J Neurosurg* 121:176–183, 2014
3. Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D, et al: General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. *Lancet* 372:2132–2142, 2008
4. Luger TJ, Kammerlander C, Gosch M, Luger MF, Kammer-

- lander-Knauer U, Roth T, et al: Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? *Osteoporos Int* 21 (Suppl 4):S555–S572, 2010
5. Rerkasem K, Bond R, Rothwell PM: Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database Syst Rev*:CD000126.pub2, 2004
6. Shapey J, Glancz LJ, Brennan PM: Chronic subdural haematoma in the elderly: is it time for a new paradigm in management? *Curr Geriatr Reports* 5:71–77, 2016

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The surgical outcomes of symptomatic moyamoya disease in adults

TO THE EDITOR: We read with great interest the meta-analysis by Jeon et al.⁵ (Jeon JP, Kim JE, Cho WS, et al: Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults. *J Neurosurg* 128:793–799,

March 2018) evaluating the clinical outcomes in patients with moyamoya disease (MMD) after different treatments and surgical techniques. In this study, the authors demonstrated that bypass surgery reduced the risk of future stroke in patients with MMD, and the direct bypass had a better angiographic outcome and lower incidence of future stroke than indirect bypass. However, there were some issues that should be discussed.

First, several of the included studies were based on the same series of patients. The studies by Lee et al. (2012),⁸ Kim et al. (2012),⁶ and Choi et al. (2013)² were based on the patients who were diagnosed with MMD in Mary's Hospital (the Catholic University of Korea School of Medicine) during 1998 and 2010. The studies by Bang (2012)¹ and Kim et al. (2016),⁷ had many of the same subjects who were admitted to Seoul National University Bundang Hospital. Lee et al.⁸ collected 142 patients (> 18 years old) with MMD, including 124 patients who underwent bypass surgery and 44 treated hemispheres with hemorrhagic MMD. Kim et al.⁶ only included the 96 patients with MMD who underwent the bypass surgery in the same period. Choi et al.² retrospectively included 44 patients with hemorrhagic MMD to evaluate the efficacy of different treatments. Thus, the data of these studies should not be pooled be-

FIG. 1. Comparison of recurrent stroke between surgically and conservatively treated groups in patients with MMD (A), patients with hemorrhagic MMD (B), and patients with ischemic MMD (C). M-H = Mantel-Haenszel.

cause of the duplicate data. However, this meta-analysis pooled the data of studies by Lee and Choi to compare the outcomes of surgery and conservative treatment (Fig. 2A and B in their article).

Second, the method of data collection was not unified. In Fig. 2, they collected the outcomes of some studies^{2,4,8,10} according to the number of brain hemispheres, whereas the data in the rest of the studies^{7,9} were collected according to the number of patients. This may affect the pooled results. For instance, in Fig. 2A, Choi et al.² included 35 patients (53 of 70 hemispheres underwent surgery and 17 hemispheres underwent conservative treatment) in the bypass group, and 9 patients (18 hemispheres underwent conservative treatment) in the conservative group. However, the authors only included the 18 hemispheres of 9 patients in the conservative group without consideration of the 17 hemispheres undergoing conservative treatment in the bypass group. Most of the included studies evaluated the outcomes according to the number of patients rather than hemispheres. Thus, we excluded the study by Choi et al. and conducted a meta-analysis according to the number of patients. We found that the patients in the conservative group had a higher risk of future stroke than those in the surgical group (OR 3.07, 95% CI 1.95–4.84, $p < 0.00001$; Fig. 1A), which was consistent with the results of this meta-analysis. However, no heterogeneity ($I^2 = 0\%$) was found in our analysis, and the heterogeneity of the meta-analysis ($I^2 = 26\%$, Fig. 2A in Choi et al.) might be attributable to the non-unified collection methods.

Third, one recent study,³ which evaluated the long-term outcomes of 82 patients with MMD, demonstrated the bypass surgery could not reduce future stroke. After pooling the results with this study, we found that bypass surgery could decrease future stroke in patients with hemorrhagic MMD (OR 2.47, 95% CI 1.18–5.15, $p = 0.02$; Fig. 1B), but not in patients with ischemic MMD (OR 2.31, 95% CI 0.65–8.16, $p = 0.19$; Fig. 1C), which was inconsistent with this meta-analysis. For the limited number of studies, more studies are encouraged to elucidate the efficacy of bypass surgery in patients with ischemic MMD.

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References

1. Bang JS, Kwon OK, Kim JE, Kang HS, Park H, Cho SY, et al: Quantitative angiographic comparison with the OSIRIS program between the direct and indirect revascularization modalities in adult moyamoya disease. *Neurosurgery* **70**:625–633, 2012
2. Choi WS, Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, et al: Thirteen-year experience of 44 patients with adult hemorrhagic moyamoya disease from a single institution: clinical analysis by management modality. *J Cerebrovasc Endovasc Neurosurg* **15**:191–199, 2013
3. Ge P, Zhang Q, Ye X, Liu X, Deng X, Li H, et al: Long-term outcome after conservative treatment and direct bypass surgery of moyamoya disease at late Suzuki stage. *World Neurosurg* **103**:283–290, 2017
4. Hallemeier CL, Rich KM, Grubb RL Jr, Chicoine MR, Moran CJ, Cross DT III, et al: Clinical features and outcome in North American adults with moyamoya phenomenon. *Stroke* **37**:1490–1496, 2006
5. Jeon JP, Kim JE, Cho WS, Bang JS, Son YJ, Oh CW: Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults. *J Neurosurg* **128**:793–799, 2018
6. Kim DS, Huh PW, Kim HS, Kim IS, Choi S, Mok JH, et al: Surgical treatment of moyamoya disease in adults: combined direct and indirect vs. indirect bypass surgery. *Neurol Med Chir (Tokyo)* **52**:333–338, 2012
7. Kim T, Oh CW, Kwon OK, Hwang G, Kim JE, Kang HS, et al: Stroke prevention by direct revascularization for patients with adult-onset moyamoya disease presenting with ischemia. *J Neurosurg* **124**:1788–1793, 2016
8. Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, Cho KS: Long-term follow-up results in 142 adult patients with moyamoya disease according to management modality. *Acta Neurochir (Wien)* **154**:1179–1187, 2012
9. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, et al: Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. *Stroke* **45**:1415–1421, 2014
10. Oyama H, Kito A, Maki H, Hattori K, Noda T, Wada K: Cerebral hemorrhage and cerebral infarction in 30 cases of adult moyamoya disease: comparison between conservative therapy and superficial temporal artery-middle cerebral artery anastomosis. *Nagoya J Med Sci* **75**:37–40, 2013

Disclosures

The authors have no conflicts of interest.

Response

We appreciate Dr. Ye and colleagues and the *Journal of Neurosurgery* for this opportunity to respond to the letter and review a recent article.³ We have explained further regarding the concerns. First, we have included studies such as Lee et al. (2012),⁹ Kim et al. (2012),⁶ and Choi et al. (2013).² Surely, those are retrospective studies conducted by several affiliated hospitals at Catholic University in Korea. We admit that partially overlapped data could exist, because they did not provide clear information on data for each study. However, previous systematic review and meta-analyses evaluated treatment outcomes including those studies collectively.^{12,13} Accordingly, we have included those studies in this meta-analysis after discussion. For the studies conducted by Bang et al. (2012)¹ and Kim et al. (2016),⁸ Bang et al.¹ compared treatment outcomes according to surgical techniques (direct vs indirect revascularization). In contrast, Kim et al.⁸ demonstrated better surgical efficacy of direct revascularization in preventing further strokes in patients with MMD presenting with ischemia than in those treated conservatively. Therefore, we have included the Bang study for comparative studies between direct and indirect revascularization, and the Kim study for comparative studies between surgical and conservative treatment.

Second, per Dr. Ye's comment, the method of data collection could be biased toward results. Some studies calculated future stroke events according to the number of patients, whereas others did it according to the number of brain hemispheres. Mostly, symptomatic MMD with hemodynamic impairment is an indication for surgical revascularization.^{3,5,7} Accordingly, a more accurate as-

assessment of surgical efficacy for MMD can be conducted by comparison with conservatively treated symptomatic hemispheres, not nonsymptomatic hemispheres. Most studies did not clearly provide information about treated symptomatic hemispheres. Additionally, differences in future stroke event site (ipsilateral vs contralateral side to the surgical treatment) and definition of control group (other MMD patients or the side contralateral to the surgery in the same patients) could also be biased toward results when assessing stroke events by the number of patients. Accordingly, there may be controversy over the fact that the meta-analysis included the study by Choi et al.² When calculating the future stroke event, only 35 patients with 53 hemispheres were the main concern in their study. Recent meta-analysis conducted by Qian et al.¹² compared the future stroke events by the number of hemispheres (53 in the surgical treatment group and 18 in the medical treatment group). In our meta-analysis, subsequent subgroup analysis of treatment outcomes according to the method of data collection was conducted. We observed that adult patients with MMD who received conservative treatment experienced a higher risk of future stroke than those who received surgical revascularization (OR 2.539, 95% CI 1.422–4.532, $p = 0.002$), without heterogeneity ($I^2 = 0\%$).^{2,8,10,11} When calculating stroke events by the number of hemispheres,^{4,9} future stroke events were significantly increased in medically treated hemispheres compared to surgically treated hemispheres (OR 4.652, 95% CI 2.420–8.946, $p < 0.001$), with moderate heterogeneity ($I^2 = 26.697\%$). A small number of cases are a concern regarding interpretation when assessing future stroke events according to the data collection method. Ye et al. compared recurrent stroke events between surgical and conservative groups irrespective of the data collection method in their Fig. 1B and C. Comparison of treatment outcome of the study by Ge et al. (2017)³ is revealed as recurrent stroke events by the number of hemispheres, whereas other comparisons done by Lee et al. (2012)⁹ and Kim et al. (2016)⁸ are revealed as recurrent stroke events by the number of patients. After discussion, with reference to previous meta-analysis,¹² data were provided without considering the data collection method. Additionally, we pointed out that the results of our meta-analysis should be interpreted with caution because of heterogeneity in the articles.

Third, you recommend a recent article authored by Ge et al.³ in which they retrospectively evaluated surgical efficacy of direct revascularization for 82 patients with MMD (164 hemispheres) at late Suzuki stage 4–6. Surgery was indicated for ischemic or hemorrhagic symptoms related to hemodynamic impairment. During a mean follow-up of 55.1 ± 16.2 months, the recurrent stroke rate was 9.3% (7 of 75) in conservatively treated hemispheres and 10.1% (9 of 89) in surgically treated hemispheres. However, all hemispheres that received conservative treatment were contralateral to the surgically treated hemispheres in patients with bilateral MMD. In contrast, the remaining studies (shown in Fig. 1B and C) defined control subjects who were conservatively treated patients with MMD.^{8–10} Additionally, the rate of late Suzuki stage 4–6 was 50% (71 of 142) in Lee et al.'s study⁹ and 60.3% (266 of 441) in Kim et al.'s study.⁸ Accordingly, such a difference in baseline

characteristics could be attributed to heterogeneity across studies and appears to be different from previous meta-analysis.

There are limitations for meta-analysis of surgical efficacy in patients with MMD. First, most studies were retrospective investigations including a relatively small number of the patients. Second, differences in MMD diagnosis, surgical techniques, and definitions of control groups among studies are limitations in reaching conclusions. Therefore, further meta-analysis based on an individual patient-level database is needed to confirm surgical efficacy for adult patients with MMD.

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References

1. Bang JS, Kwon OK, Kim JE, Kang HS, Park H, Cho SY, et al: Quantitative angiographic comparison with the OSIRIS program between the direct and indirect revascularization modalities in adult moyamoya disease. **Neurosurgery** **70**:625–633, 2012
2. Choi WS, Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, et al: Thirteen-year experience of 44 patients with adult hemorrhagic moyamoya disease from a single institution: clinical analysis by management modality. **J Cerebrovasc Endovasc Neurosurg** **15**:191–199, 2013
3. Ge P, Zhang Q, Ye X, Liu X, Deng X, Li H, et al: Long-term outcome after conservative treatment and direct bypass surgery of moyamoya disease at late Suzuki stage. **World Neurosurg** **103**:283–290, 2017
4. Hallemeier CL, Rich KM, Grubb RL Jr, Chicoine MR, Moran CJ, Cross DT III, et al: Clinical features and outcome in North American adults with moyamoya phenomenon. **Stroke** **37**:1490–1496, 2006
5. Jeon JP, Kim JE: A recent update of clinical and research topics concerning adult moyamoya disease. **J Korean Neurosurg Soc** **59**:537–543, 2016
6. Kim DS, Huh PW, Kim HS, Kim IS, Choi S, Mok JH, et al: Surgical treatment of moyamoya disease in adults: combined direct and indirect vs. indirect bypass surgery. **Neurol Med Chir (Tokyo)** **52**:333–338, 2012
7. Kim JE, Jeon JS: An update on the diagnosis and treatment of adult moyamoya disease taking into consideration controversial issues. **Neurol Res** **36**:407–416, 2014
8. Kim T, Oh CW, Kwon OK, Hwang G, Kim JE, Kang HS, et al: Stroke prevention by direct revascularization for patients with adult-onset moyamoya disease presenting with ischemia. **J Neurosurg** **124**:1788–1793, 2016
9. Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, Cho KS: Long-term follow-up results in 142 adult patients with moyamoya disease according to management modality. **Acta Neurochir (Wien)** **154**:1179–1187, 2012
10. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, et al: Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. **Stroke** **45**:1415–1421, 2014
11. Oyama H, Kito A, Maki H, Hattori K, Noda T, Wada K: Cerebral hemorrhage and cerebral infarction in 30 cases of adult moyamoya disease: comparison between conservative therapy and superficial temporal artery-middle cerebral artery anastomosis. **Nagoya J Med Sci** **75**:37–40, 2013

12. Qian C, Yu X, Li J, Chen J, Wang L, Chen G: The efficacy of surgical treatment for the secondary prevention of stroke in symptomatic moyamoya disease: a meta-analysis. **Medicine (Baltimore)** 94:e2218, 2015
13. Sun H, Wilson C, Ozpinar A, Safavi-Abbasi S, Zhao Y, Nakaji P, et al: Perioperative complications and long-term outcomes after bypasses in adults with moyamoya disease: a systematic review and meta-analysis. **World Neurosurg** 92:179–188, 2016

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Brachyury as prognostic biomarker in chordoma

TO THE EDITOR: We read with great interest the article by Otani et al.⁷ (Otani R, Mukasa A, Shin M, et al: *Brachyury* gene copy number gain and activation of the PI3K/Akt pathway: association with upregulation of oncogenic Brachyury expression in skull base chordoma. *J Neurosurg* [epub ahead of print July 28, 2017. DOI: 10.3171/2016.12.JNS161444]). The authors performed a clinical and experimental study with regard to the role of *Brachyury* in skull base chordoma (SBC). They found that *Brachyury* mRNA expression was negatively associated with progression-free survival (PFS) of patients, and overexpression of Brachyury was partially due to the PI3K/Akt pathway activation and *Brachyury* copy number gain in SBC. We commend the authors for performing this interesting study as these helpful results would be useful for the development of novel molecular targets to treat this challenging tumor entity.

Brachyury (also called T gene) is an important transcriptional factor that regulates the mesoderm development in the early human embryo. While Brachyury is reported to be expressed in the majority of chordoma tissues, recent studies have also shown Brachyury expression in several other types of human cancers and its significant association with prognosis.^{4,8,10,14} To date, although the prognostic role of Brachyury expression in chordoma has been discussed in the literature, the results are still inconclusive.^{23,24} For example, similar to the current findings by Otani et al.,⁷ researchers also found that positive Brachyury expression as assessed by an immunohistochemical method was correlated with shorter PFS of patients with SBC.⁵ In contrast, most studies exploring Brachyury status in chordoma showed no prognostic implication.^{16–18,21,22} Although the difference in categorization and the choice of experimental technique may be responsible for the conflicting results, we cannot obtain definitive conclusions regarding the prognostic relevance of Brachyury expression in chordoma according to the limited evidence available. More large-sample studies with more uniform data reporting and study design are needed to further determine the role of Brachyury expression in chordoma prognosis.

Mechanically, how Brachyury expression is upregu-

lated in chordoma remains unclear. Besides the potential molecular basis described by Otani et al.,⁷ recent studies also reported several other molecular mechanisms underlying Brachyury regulation in chordoma. Using in-silico analysis and dual luciferase report assay, Wei et al.²⁰ found that downregulation of miR-219-5p in SBC could exert its oncogenic effects by directly targeting Brachyury, and then promote the proliferation and clonogenicity of chordoma cells, leading to an aggressive phenotype. Feng et al.² investigated the expression profile of the BMP4/SMAD signaling pathway in SBC and found that overexpression of the pathway was significantly correlated with a poor clinical outcome. As BMP4 signaling acts upstream of Brachyury, these results collectively suggest a potential regulatory role for the BMP4/SMAD signaling pathway in Brachyury overexpression. Similarly, published data also provided evidence of the FGF/FGFR signaling pathway modulating the expression of Brachyury in chordoma.^{3,13} Furthermore, it has been demonstrated that the brachyury single nucleotide polymorphism (SNP) rs2305089 is linked to chordoma susceptibility.⁹ However, the impact of rs2305089 SNP on Brachyury expression remains unknown. Previous studies showed that the rs2305089 SNP could change the binding capacity of Brachyury, thereby altering its expression level.⁹ A recent large multicenter cohort study found that the rs2305089 SNP could independently predict overall survival in patients with spinal chordoma.¹ Taken together, these data indicate that the *Brachyury* gene SNP may influence the chordoma outcomes at least in part through regulating Brachyury expression. Finally, in several other human cancers, TGF- β and Wnt/ β -catenin pathways have been shown to be implicated in the regulation of Brachyury;¹⁵ it is worth investigating whether Brachyury expression can be driven by similar molecular mechanisms in chordoma.

In their study, the authors failed to further define how Brachyury expression affected the survival outcomes in patients with SBC. Prior data have demonstrated that Brachyury expression can influence patient outcomes by driving epithelial-to-mesenchymal transition, inducing acquisition of cancer stem cell characteristics, or modulating androgen receptor activity in human cancers.^{11,12,15} In view of this, whether Brachyury impacts chordoma outcomes through similar mechanisms or other pathways deserves further investigation. In addition, recent studies reported that Brachyury was positively correlated with PDGFR- β and Ki-67 expression in SBC.^{7,21} We consider that Brachyury may function as an oncogene in association with upregulation of PDGFR- β and Ki-67 as they are shown to be closely associated with tumor growth, proliferation, and patient survival in human cancers, including chordoma.^{6,19}

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References

- Bettegowda C, Yip S, Lo SL, Fisher CG, Boriani S, Rhines LD, et al: Spinal column chordoma: prognostic significance of clinical variables and T (brachyury) gene SNP rs2305089 for local recurrence and overall survival. **Neuro Oncol** **19**:405–413, 2017
- Feng Y, Zhang Q, Wang Z, Yan B, Wei W, Li P: Overexpression of the BMP4/SMAD signaling pathway in skull base chordomas is associated with poor prognosis. **Int J Clin Exp Pathol** **8**:8268–8275, 2015
- Hu Y, Mintz A, Shah SR, Quinones-Hinojosa A, Hsu W: The FGFR/MEK/ERK/brachyury pathway is critical for chordoma cell growth and survival. **Carcinogenesis** **35**:1491–1499, 2014
- Kilic N, Feldhaus S, Kilic E, Tennstedt P, Wicklein D, Wasielewski Rv, et al: Brachyury expression predicts poor prognosis at early stages of colorectal cancer. **Eur J Cancer** **47**:1080–1085, 2011
- Kitamura Y, Sasaki H, Kimura T, Miwa T, Takahashi S, Kawase T, et al: Molecular and clinical risk factors for recurrence of skull base chordomas: gain on chromosome 2p, expression of brachyury, and lack of irradiation negatively correlate with patient prognosis. **J Neuropathol Exp Neurol** **72**:816–823, 2013
- Morgan TM, Koreckij TD, Corey E: Targeted therapy for advanced prostate cancer: inhibition of the PI3K/Akt/mTOR pathway. **Curr Cancer Drug Targets** **9**:237–249, 2009
- Otani R, Mukasa A, Shin M, Omata M, Takayanagi S, Tanaka S, et al: *Brachyury* gene copy number gain and activation of the PI3K/Akt pathway: association with upregulation of oncogenic *Brachyury* expression in skull base chordoma. **J Neurosurg** [epub ahead of print July 28, 2017. DOI: 10.3171/2016.12.JNS161444]
- Palena C, Roselli M, Litzinger MT, Ferroni P, Costarelli L, Spila A, et al: Overexpression of the EMT driver *brachyury* in breast carcinomas: association with poor prognosis. **J Natl Cancer Inst** **106**:dju054, 2014
- Pillay N, Plagnol V, Tarpey PS, Lobo SB, Presneau N, Szuhai K, et al: A common single-nucleotide variant in T is strongly associated with chordoma. **Nat Genet** **44**:1185–1187, 2012
- Pinto F, Pértiga-Gomes N, Pereira MS, Vizcaíno JR, Monteiro P, Henrique RM, et al: T-box transcription factor *brachyury* is associated with prostate cancer progression and aggressiveness. **Clin Cancer Res** **20**:4949–4961, 2014
- Pinto F, Pértiga-Gomes N, Vizcaíno JR, Andrade RP, Cárcano FM, Reis RM: *Brachyury* as a potential modulator of androgen receptor activity and a key player in therapy resistance in prostate cancer. **Oncotarget** **7**:28891–28902, 2016
- Sarkar D, Shields B, Davies ML, Müller J, Wakeman JA: *BRACHYURY* confers cancer stem cell characteristics on colorectal cancer cells. **Int J Cancer** **130**:328–337, 2012
- Shalaby AA, Presneau N, Idowu BD, Thompson L, Briggs TR, Tirabosco R, et al: Analysis of the fibroblastic growth factor receptor-RAS/RAF/MEK/ERK-ETS2/*brachyury* signalling pathway in chordomas. **Mod Pathol** **22**:996–1005, 2009
- Shimamatsu S, Okamoto T, Haro A, Kitahara H, Kohno M, Morodomi Y, et al: Prognostic significance of expression of the epithelial-mesenchymal transition-related factor *brachyury* in intrathoracic lymphatic spread of non-small cell lung cancer. **Ann Surg Oncol** **23** (5 Suppl 5):1012–1020, 2016
- Song W, Gobe GC: Understanding molecular pathways and targets of *brachyury* in epithelial-mesenchymal transition (EMT) in human cancers. **Curr Cancer Drug Targets** **16**:586–593, 2016
- Stacchiotti S, Casali PG, Lo Vullo S, Mariani L, Palassini E, Mercuri M, et al: Chordoma of the mobile spine and sacrum: a retrospective analysis of a series of patients surgically treated at two referral centers. **Ann Surg Oncol** **17**:211–219, 2010
- Sun I, Güdük M, Güçyetmez B, Yapıcıer Ö, Pamir MN: Chordoma: immunohistochemical analysis of *brachyury*. **Turk Neurosurg** [epub ahead of print], 2016
- Wang K, Tian K, Wang L, Wu Z, Ren C, Hao S, et al: *Brachyury*: a sensitive marker, but not a prognostic factor, for skull base chordomas. **Mol Med Rep** **12**:4298–4304, 2015
- Wang XB, Lv GH, Li J, Zou MX: Ki-67 index as a prognostic marker in chordomas: a systematic review of the literature. **World Neurosurg** **101**:782–784, 2017
- Wei W, Zhang Q, Wang Z, Yan B, Feng Y, Li P: miR-219-5p inhibits proliferation and clonogenicity in chordoma cells and is associated with tumor recurrence. **Oncol Lett** **12**:4568–4576, 2016
- Zhai Y, Bai J, Gao H, Wang S, Li M, Gui S, et al: Clinical features and prognostic factors of children and adolescents with clival chordomas. **World Neurosurg** **98**:323–328, 2017
- Zhang L, Guo S, Schwab JH, Nielsen GP, Choy E, Ye S, et al: Tissue microarray immunohistochemical detection of *brachyury* is not a prognostic indicator in chordoma. **PLoS One** **8**:e75851, 2013
- Zou MX, Lv GH, Wang XB, Li J: Prognostic biomarkers in spinal chordoma: a systematic review. **J Neuropathol Exp Neurol** **75**:1184–1187, 2016
- Zou MX, Lv GH, Wang XB, Li J: Factors predicting recurrence after resection of clival chordoma using variable surgical approaches and radiation modalities. **Neurosurgery** **81**:E28–E31, 2017 (Letter)

Disclosures

The authors report no conflict of interest.

Response

We sincerely appreciate Dr. Zhong et al.'s interest in and comments about our study. We agree with their point that the correlation between *Brachyury* expression and prognosis shown in our study is not in accordance with some other studies, partly because of the small sample size and methodological inconsistencies among the previous studies. To address these issues, larger-scale studies involving collaboration among multiple hospitals will be necessary in the future.

We also thank Dr. Zhong and colleagues for mentioning several interesting studies in the literature that showed the mechanisms of how *Brachyury* expression is regulated in chordoma. Such candidate molecules or pathways associated with *Brachyury* expression include miR-219-5p, BMP4/SMAD signaling, FGF/FGFR signaling, TGF- β pathway, and Wnt/ β -catenin pathways. In our study, activation of PI3K/Akt signaling, which had also been demonstrated in studies from other groups as we discussed in our paper, was the most significantly associated gene network, whereas we observed no obvious activation of BMP4/SMAD, FGF/FGFR, TGF- β , or Wnt/ β -catenin signaling pathway. Again, larger-scale studies may further clarify the role of those different pathways in the *Brachyury* expression status in chordomas.

We also investigated the SNP rs2305089 in germline DNA; rs2305089 is located in the region that encodes the DNA-binding domain of *Brachyury*. The previous report demonstrated that the A allele at this SNP site was frequently observed in patients with chordoma compared with controls, and that A allele cases showed higher *Brachyury* expression than G allele cases.² However, in our 19 patients with SBC, the SNP genotypes determined with Sanger se-

quencing were G/G in 10, G/A in 8, and A/A in 1 case, and the frequency of the A allele was not significantly different from the frequency in the Japanese controls obtained from the HapMap Project ($n = 172$, 26% vs 31%, $p = 0.18$, Fisher's exact test). Furthermore, we found no relationship between the germline SNP genotype and the *Brachyury* expression level in our cases (G/G, 1241 ± 719 ; G/A, 1124 ± 785 ; A/A, 1068). According to previous reports, the odds ratios between the SNP genotype and chordoma development were 5.3, 2.8, and 1.1 in European,² American/Canadian,¹ and Chinese populations,³ respectively. In contrast, the odds ratio from our data for the Japanese population was 0.78. Therefore, ethnic differences may account for the different results in association data.

We could not determine how *Brachyury* drives chordoma cell proliferation. Our microarray data did not indicate an association between *Brachyury* expression and epithelial-mesenchymal transition or *PDGFR-β* expression, unlike the positive correlation that was observed in previous reports of chordoma and other cancers. Further investigation is needed to elucidate the role of *Brachyury* in chordoma cell proliferation.

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References

1. Kelley MJ, Shi J, Ballew B, Hyland PL, Li WQ, Rotunno M, et al: Characterization of T gene sequence variants and germline duplications in familial and sporadic chordoma. *Hum Genet* 133:1289–1297, 2014
2. Pillay N, Plagnol V, Tarpey PS, Lobo SB, Presneau N, Szuhai K, et al: A common single-nucleotide variant in T is strongly associated with chordoma. *Nat Genet* 44:1185–1187, 2012
3. Wu Z, Wang K, Wang L, Feng J, Hao S, Tian K, et al: The brachyury Gly177Asp SNP is not associated with a risk of skull base chordoma in the Chinese population. *Int J Mol Sci* 14:21258–21265, 2013

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Collecting data about the transorbital endoscopic eyelid approach

TO THE EDITOR: We have read with interest the article by Almeida and colleagues¹ (Almeida JP, Omay

SB, Shetty SR, et al: Transorbital endoscopic eyelid approach for resection of sphenoorbital meningiomas with predominant hyperostosis: report of 2 cases. *J Neurosurg* [pub ahead of print September 1, 2017. DOI: 10.3171/2017.3.JNS163110]). The authors presented a novel, minimally invasive option for the treatment of the anterior and middle cranial fossae lesions. Based on this initial experience, the same group has introduced an interesting anatomical study, and they described the limitations of their technique.² Additionally, they recommended more reports for a better understanding of the benefits of this new surgical approach, particularly for sphenoorbital meningiomas (SOMs) with predominant hyperostosis.¹ Accordingly, because we have the same kind of patient group, we would like to discuss with the authors the specific surgical nuances that might allow surgeons to create an ideal new space (predominantly at the orbital apex) that can lead to a significant reduction of the proptosis. Detailed supplementary radiographic data might also be required. Subsequently, we can apply this unique technique based on the authors' highly accurate records.

Almeida et al. stated the following: “The transorbital endoscopic approach provides access to the superolateral orbital region, which makes this an interesting option for the treatment of select SOMs in which hyperostosis and proptosis are the primary issues...,” “Debulking of the hyperostosis and orbital decompression were the primary goals...,” “Transorbital endoscopic drilling may not be sufficient for all cases...,” and “The presence of significant soft-tissue enlargement may be a limitation for successful reduction of the proptosis via an endoscopic transorbital approach.”¹

By carefully studying the exposure and maneuverability of this anatomical study¹ in correlation with the presented preoperative and postoperative neuroimaging (Figs. 1,6,7,9 and 10) of the reported cases (case 1 and 2),¹ our lead author (A.N.) tried to extract detailed radiographic-based surgical nuances and he found some interesting points that raised several questions.

First, regarding case 1; we can appreciate the reduction of hyperostosis, particularly along the lateral wall and orbital roof, but it is difficult to know how far posteriorly and/or laterally we can drill to create a significant space to accommodate the proptosis. Is it mandatory to remove the lateral portion of the lesser wing of sphenoid² in such cases? Is it possible to add anterior clinoidectomy to better deal with the orbital apex?

Is the approach you describe a selective posterior ethmoidectomy? If so, do you think an extensive transnasal decompression can facilitate a more medial orbital retraction that might result in a wider transorbital operative corridor, with better access to the orbital apex via both approaches?

Second, regarding case 2, we cannot confirm significant debulking of the hyperostotic part and adequate orbital decompression, as the authors kindly concluded from the presented figures. Perhaps additional radiographic detail would help here. Is it possible to assess the extent of bone removal with additional 3D reconstructed CT via different angles to make the view of the greater sphenoid wing fall in a direct line?

Third, we could not find satisfactory answers to our questions on the supplemental videos. Is it possible to have more descriptive data?

Finally, we appreciate the authors' contributions to neurosurgery, and we consider the abovementioned study¹ as a fundamental reference in treating our patients. Thus we are looking forward to receiving the valuable comments and additional data from these authors.

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References

1. Almeida JP, Omay SB, Shetty SR, Chen YN, Ruiz-Treviño AS, Liang B, et al: Transorbital endoscopic eyelid approach for resection of sphenoorbital meningiomas with predominant hyperostosis: report of 2 cases. **J Neurosurg** [epub ahead of print September 1, 2017. DOI: 10.3171/2017.3.JNS163110]
2. Almeida JP, Ruiz-Treviño AS, Shetty SR, Omay SB, Anand VK, Schwartz TH: Transorbital endoscopic approach for exposure of the sylvian fissure, middle cerebral artery and crural cistern: an anatomical study. **Acta Neurochir (Wien)** **159**:1893–1907, 2017

Disclosures

The authors report no conflict of interest.

Response

Thank you for your interest in our article. The authors

have specific questions regarding the technique, which we will try to address. The first question is how can the orbit be drilled to create a significant space, and is it mandatory to remove the lateral portion of the lesser wing of the sphenoid and can anterior clinoidectomy be added. In response, there must of course be a graded removal of bone depending on the patient's individual anatomy and the location of the hyperostosis. The lateral and superior walls of the orbit can be drilled all the way to the superior orbital fissure, with removal of the greater wing of the sphenoid. Following the superior wall, portions of the lesser wing of the sphenoid can also be removed, but reaching the clinoid and optic nerve may be challenging. Ethmoidectomy may facilitate medial mobilization of the orbit once the lamina papyracea is removed, but this is often not necessary. Lateral orbitotomy can be performed to help with the lateral to medial exposure to avoid excessive retraction on the globe. With regard to the second case, this patient had soft tissue in the globe, namely meningioma invading the lateral rectus and intraconal area. Hence, the bone decompression alone was not adequate to reduce proptosis. We will send 3D CT scans to the authors so they can further appreciate the details of the surgery.

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Disclosures

Dr. Schwartz is a consultant for Elliquence, and he has direct stock ownership in Visionsense.

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