Neurosurgical Forum LETTERS TO THE EDITOR

Intermediate-risk meningioma and NRG Oncology RTOG 0539

TO THE EDITOR: We read with great interest the initial results from NRG Oncology RTOG 0539 published by Rogers et al.⁹ on the treatment of intermediate-risk meningioma (Rogers L, Zhang P, Vogelbaum MA, et al: Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. *J Neurosurg* 129:35–47, July 2018). The authors provide a brief description of the trial and the division of meningioma patients into 3 risk groups according to the chance of recurrence and their treatment (low, observation; intermediate, 54 Gy in 30 fractions; and high, 60 Gy in 30 fractions). They focus on the intermediate-risk-meningioma group and their results support the use of postoperative radiotherapy in this patient cohort, stating that they achieved a progression-free survival (PFS) of 93.8% (historical cohorts: PFS 57%²–90%⁶ at 3 years following gross-total resection [GTR] alone) and overall survival (OS) of 96% at 3 years.

Nevertheless, we would like to clarify the inclusion criteria in the intermediate-risk group. In Fig. 1, it appears that patients with newly diagnosed WHO grade II meningiomas who had a subtotal resection (STR) are in both the intermediate- and high-risk groups, although our understanding from the remaining paper is that these patients were considered to be in the high-risk group.

This is particularly relevant, as immediate postoperative adjuvant radiotherapy is a matter of debate in the treatment of patients with WHO grade II meningiomas who have had STR. The studies by Masalha et al.⁷ and Champeaux et al.³ support extent of resection continuing to be the most important factor and indicate that adjuvant radiotherapy has no effect on PFS when adjusted for confounding factors.

We have reviewed the current literature describing the risk of tumor recurrence with lesion characteristics; pial invasion and peri-tumor edema (even though only Simpson grade I and II resections were compared);⁸ necrosis (both WHO grade I and II)⁵ and proliferation index.⁷ Chen and coauthors have pointed toward previous STR and radiotherapy as potential risk factors for local failure after salvage treatment for recurrent grade II meningioma.⁴ Therefore, the timing for radiotherapy administration (as the surgical resection might be defined/limited by the tu-

mor itself) may be crucial not only for PFS assessment but also for the success of further treatment and OS.

The authors have highlighted that the proportion of meningiomas that are classified as WHO grade II has also significantly increased (range 25%–35%¹—before the 2016 WHO classification revision, with the introduction of brain invasion as a criterion for the diagnosis of grade II meningioma alone). Therefore, this distinction will become even more important in the coming years, given the expected increase in the diagnosis of grade II meningioma.

We assume that STR in grade II meningioma is related to technical issues (previously planned or intraoperative events) that preclude GTR, and we therefore support the use of radiotherapy, which is proven to reduce the recurrence rate. Nevertheless, if the surgical team considers residual disease following initial debulking to be resectable, complete resection should be the goal for treatment.

Rogers and coauthors have successfully demonstrated the role of postoperative radiotherapy in a newly classified intermediate-risk meningioma group. We look forward to clarification of the inclusion criteria for this group as it will greatly help in treatment decisions and patient counseling.

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Response

We very much appreciate the careful review of our NRG/RTOG-0539 intermediate-risk meningioma article by Dr. Lavrador and colleagues and their identification of an error in Fig. 1 that requires correction. We regret this oversight. The intermediate-risk cohort (Group 2) of the NRG/RTOG-0539 trial was composed of patients with a newly diagnosed gross-totally resected (GTR; Simpson grades I–III) World Health Organization (WHO) grade II meningioma, a recurrent WHO grade I meningioma after resection of any extent, or a patient with progression of a WHO grade I meningioma identified on imaging alone. Patients with a subtotally resected (STR; Simpson grades IV and V) WHO grade II meningioma were not included in Group 2 but were instead assigned to the high-risk cohort (Group 3), which also included patients with recurrent WHO grade II with any extent of resection as well as patients with newly diagnosed or recurrent WHO grade III meningioma with any extent of resection.

Dr. Lavrador and colleagues also correctly point out that early adjuvant radiotherapy (RT) for patients with WHO grade II meningioma, irrespective of the extent of resection, remains open to debate. Many previous reports suggest that progression-free survival (PFS) is superior after GTR plus RT compared with GTR alone. Please see the applicable figure (Fig. 7) in the intermediate-risk article for graphical comparisons. However, a minority of treatment centers (7% to 30%) recommend RT after GTR.^{1,2,5,7,9,10} Thus, the appropriate approach to patients who have undergone GTR of a WHO grade II meningioma remains an important, clinically relevant, and as-yet-unanswered question.

Regarding STR, recent reports have also suggested improvements in PFS with early RT following STR for

WHO grade II meningioma.^{3,5,9} Shakir et al.⁹ from McGill University reported a 5-year PFS of 0% in 26 patients treated with STR versus 75% in 4 patients treated with STR plus early RT. Similarly, Dohm and colleagues⁵ from Wake Forest University reported a 5-year PFS after STR alone (n = 15) of 18% compared with 73% after STR plus early RT (n = 4). Bagshaw et al.³ from the University of Utah noted that at a median follow-up of 42 months no patient with STR alone (n = 2) remained progression-free, whereas 56% were progression-free after STR plus early RT (n = 9). Although these relatively small cohorts suggest an advantage to early postoperative RT after STR, they also confirm that RT is not uniformly recommended in this setting, as its use has ranged from 13% to 74%.^{2,5,7,9,10}

Lavrador and colleagues' letter mentions 2 articles that question the value of RT after surgery for atypical meningioma.^{4,8} These articles are valuable additions to the medical literature and deserve comment. Champeaux et al.⁴ from Queen Elizabeth University in Glasgow, Scotland, reviewed outcomes from 215 patients with WHO grade II meningiomas treated surgically and reported that RT neither reduced the risk of recurrence nor improved overall survival. This report was not specifically an analysis of early RT, with a median interval of 1.1 years from surgery to RT. Moreover, the use of RT followed recurrence of the tumor in approximately 30% of cases; this situation is dramatically different from the up-front use of RT after STR. Champeaux et al.⁴ commented, "Radiotherapy indications were incomplete resection of grade II meningioma displaying a high mitotic index, tumor recurrence or tumor residual regrowth." In their series, the patients who received RT experienced poorer PFS and were more likely to need reoperation for recurrence, which the authors believed was "likely secondary to selection bias." It is indeed to be expected that patients receiving RT for considerably poorer prognostic features may have poorer outcomes.

Similar comments pertain to the publication by Masalha and colleagues⁸ from the University of Freiburg. A minority of their 161 patients received RT (n = 33, 20%), and those so treated had either recurrent disease or other poor prognostic features. For instance, 14.1% (18/128) of patients treated with surgery alone had a MIB-1 proliferation index > 10% compared with 45.5% (15/33) of those treated with surgery and RT. Masalha et al.⁸ identified 5-year and 10-year PFS rates as being numerically inferior for patients treated with RT. At 5 years, PFS was 73% (93/128) after surgery alone and 64% (21/33) with postoperative RT, whereas at 10 years, the rates were 70% (90/128) and 57% (19/33), respectively. Again, the selective use of RT only for high-risk patients is not a reasonable design for comparing outcomes with those of observed lower-risk patients.

It has become clear that meningiomas are more aggressive at recurrence, even when they retain the same WHO grade, as they often do. In a recent Revised Assessment in Neuro-Oncology publication, Kaley et al.⁶ analyzed the reported results of medical therapies for patients with multiply recurrent meningiomas. With over 500 patients from 37 reports, the weighted average PFS at 6 months was 29% for the surgery- and radiation-refractory WHO grade I meningioma group and 26% for the WHO grade II and III group, which suggests that recurrent meningiomas

behave aggressively, irrespective of grade. Safely preventing recurrence is, therefore, a clinically meaningful goal.

Although much can be learned from well-done retrospective studies, systematic reviews, guidelines, and sophisticated analyses of big data sets, difficult questions remain regarding the most appropriate postoperative management of patients with meningioma, and these questions ultimately require large, cooperative-group phase III efforts. Two such protocols presently open for enrollment will compare GTR alone versus GTR plus RT. These are the ROAM/EORTC and the NRG Oncology BN003 trials, which have similar enrollment criteria, treatment, and outcome measures inclusive of quality-of-life and neurocognitive outcomes. These trials represent years of intergroup effort, and they will help provide invaluable and clinically meaningful data as well as opportunities for many related investigations, such as studies of molecular predictors. We recommend to readers that they open these trials at their respective institutions and educate their patients about the important questions that these trials will answer.

Regarding an issue Dr. Lavrador et al. bring to bear, namely the optimal management of patients with newly diagnosed subtotal resected WHO grade II meningioma, our manuscript reporting the outcomes of such patients in the high-risk cohort of the NRG/RTOG-0539 trial is presently undergoing review, and we trust that it will be published in a timely fashion. We present the presage that these patients have considerably poorer outcomes, thus providing many opportunities for innovative ideas and motivated, well-designed investigations.

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Pericyte-associated hemorrhage in arteriovenous malformations

TO THE EDITOR: We read with pleasure the article by Winkler et al.⁷ (Winkler EA, Birk H, Burkhardt JK, et al: Reductions in brain pericytes are associated with arteriovenous malformation vascular instability. *J Neurosurg* [epub ahead of print January 5, 2018]. DOI: 10.3171/2017.6.JNS17860) regarding the findings of reduced populations of perivascular macrophages (pericytes) in brain arteriovenous malformations (bAVMs). We commend the authors for their thorough evaluation of

the histological findings in both pathological and normal brain biopsy specimens from patients with and without bAVMs, respectively.

The authors found that pericytes are reduced in both cell quantity and capillary coverage in bAVM specimens compared to tissue of patients undergoing anterior temporal lobectomy. Ruptured bAVMs demonstrated a significant reduction in pericyte coverage compared to unruptured bAVMs. When comparing pericyte coverage to nidus blood flow on preoperative angiograms, there was a positive correlation of pericyte coverage to transit time through the bAVM nidus. The authors' findings are without a doubt interesting, particularly given our increasing appreciation of the role of pericytes in capillary blood flow (CBF) in both health and disease.^{2-4,9}

Pericytes are bone-derived macrophages implicated in neuro-inflammation and blood-brain barrier (BBB) integrity and CBF.^{1,8,10} Recent evidence suggests that pericyte coverage and activity may be significantly upregulated following hyperacute exposure to subarachnoid blood, following stroke, or even in chronic CNS injury. However, there is some controversy over the role of pericyte activation in mediating cerebral blood flow. Pericyte contractility is thought to be mediated by α -smooth muscle actin (α -SMA), but its expression is variable between pro-proliferative CD90+ cells and pro-inflammatory (and contractile) CD90- cells.⁵ Furthermore, there are different reports of the constitutive expression of α -SMA in pericytes, and so not all pericytes are capable of restricting capillary flow. It would be of significant interest if the authors could comment on the expression of α -SMA or the CD90 status of pericytes found in bAVMs. Additionally, the use of in situ hybridization techniques of mRNA would further solidify the relationship of α -SMA and contractility of pericytes to the delayed blood flow appreciated on radiography. Knowledge of the natural state of bAVM pericytes is of particular interest because they may be induced to change their expression of α -SMA through signaling cascades, which may provide a mechanism of treatment in reducing hemorrhage risk in the future.⁶

Additionally, the findings of reduced pericyte quantity and coverage are not altogether unexpected given the aberrant capillary architecture and inconsistent glial components of bAVMs. Because pericytes are bone derived and require migration and signaling to arrive at the capillary interface, the abnormal cytoarchitecture and unpredictable glial or endothelial interactions of bAVMs may prevent appropriate pericyte migration. Still, the authors should be commended for their thorough, well-designed, and topical work that further highlights the importance of pericyte activity in mediating both CBF and neuroinflammatory processes.

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Response

We thank Taylor et al. for their interest in our recent article showing reduced pericytes in bAVMs. Pericytes are versatile vascular mural cells that regulate important neurovascular functions, including BBB integrity, CBF, neuroinflammatory responses, and brain angiogenesis.^{4,5} Although the authors of this letter refer to pericytes as “perivascular macrophages” derived from bone, the literature does not support their description as macrophages. They are capable of phagocytosis in certain disease states,³ but are distinct from macrophages.

Recent work with fluorescent transgenic reporter mice has identified subpopulations of brain pericytes with variable structure and expression of specific proteins, such as the contractile protein α -SMA.¹ However, comprehensive single cell sequencing has not been performed to characterize and delineate these pericyte populations. As suggested

in their letter, pericyte contractile protein expression is also altered in a number of disease states, such as ischemic stroke or subarachnoid hemorrhage.^{2,6} We conducted the experiments suggested by Taylor et al. and observed an increase in α -SMA positivity in bAVM-associated pericytes (unpublished observations). The relationship between nidal transit time and pericyte coverage, and how this relates to pericyte contractile protein expression, remains unclear and requires further investigation, both in bAVM specimens and in bAVM rodent models.

As with other published works, our paper studied pericyte abundance globally. We agree with Taylor et al. that future studies are needed to determine whether different subpopulations of pericytes are differentially affected in bAVMs or other neurosurgical diseases in which pericytes are implicated, such as stroke, traumatic brain injury, fetal intraventricular hemorrhage, and cavernous malformations. Similarly, additional studies are needed to determine which disruptions of endothelial-pericyte signaling cascades contribute to pericyte loss in bAVMs. Pericytes may represent a novel therapeutic target for stabilizing bAVMs, and these multifaceted cells are the focus of ongoing investigation.

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PbtO₂ and prognosis after decompressive craniectomy

TO THE EDITOR: Decompressive craniectomy (DC)

is an effective procedure to reduce intracranial pressure (ICP) in patients with refractory intracranial hypertension, as demonstrated in our meta-analysis.^{3,5} Recently, Lubillo et al.⁹ assessed brain tissue oxygen pressure (PbtO₂) and ICP in patients with traumatic brain injury (TBI) before and after they underwent DC; in patients with an unfavorable outcome, there was a tendency towards persistently high ICP and a remarkable PbtO₂ reduction if there was a delay in DC (Lubillo ST, Parilla DM, Blacon J, et al: Prognostic value of changes in brain tissue oxygen pressure before and after decompressive craniectomy following severe traumatic brain injury. *J Neurosurg* 128:1538–1546, May 2018). Possibly, these findings alone might predict an unfavorable outcome because refractory high ICP may be associated with severe cerebral tissue hypoxia, which activates the anaerobic pathway to produce energy (with 1 glucose molecule generating 2 ATP molecules and lactate), and the energy produced by this pathway may be insufficient to maintain neuronal viability; this condition is known as hypoxic cerebral metabolic crisis (CMC).^{6,7} Some authors have asserted that a prolonged ICP > 35 mm Hg in patients with TBI is an unfavorable prognostic indicator, even in patients who have undergone DC.⁴ In a systematic review, Zeiler et al. disclosed that low PbtO₂ in patients with severe hypoxic CMC was associated with a high cerebral tissue lactate level, an elevated lactate/pyruvate ratio, an increased glutamate level, and a low glucose level due to activation of the anaerobic pathway to produce energy.¹⁰ Therefore, the increase in cerebral tissue oxygen after DC can be a key indicator of better prognosis, as demonstrated by Lubillo et al.⁹ In line with this idea, Ho et al. showed that DC can increase PbtO₂ and consequently improve hypoxic CMC.⁸ On the other hand, patients with worse outcomes had higher pre-DC PbtO₂ (3 ± 2 mm Hg vs 17 ± 4 mm Hg, respectively, in the favorable and unfavorable groups), a condition known as non-hypoxic CMC. Paradoxically, after DC, patients with worse outcomes also had higher PbtO₂ (17 ± 4 mm Hg vs 20 ± 3 mm Hg, respectively, in the favorable and unfavorable groups). This prognosis was likely linked to an inability to use O₂ to produce energy before DC and persistent non-hypoxic CMC after DC despite the additional increase in PbtO₂, which reinforces the possibility of mitochondrial dysfunction.^{1,2}

Lubillo et al. found that persistent low PbtO₂ after DC was linked with worse outcome. The reasons for postoperative low PbtO₂ might be: 1) cerebral oligemia associated with systemic arterial hypotension,^{1–3} 2) cerebral hypermetabolism, leading to O₂ consumption (seizures, cortical spreading depolarization),⁶ 3) persistent intracranial hypertension after DC, 4) partial cerebral tissue reperfusion due to microvascular thrombosis,¹ and 5) cerebral hyperglycolysis after cerebral blood flow restoration followed by increased O₂ consumption⁴ (Fig. 1). The last factor may be associated with a better prognosis.

Lubillo et al. provided an important perspective on PbtO₂ and prognosis following DC; we want to emphasize that the prognosis might depend on the relationship between PbtO₂ and cerebral metabolic status, particularly, if the patient presents with hypoxic or non-hypoxic CMC.^{2,7} The identification of hypoxic and non-hypoxic CMC allows specific clinical management and outcome prediction.

FIG. 1. The main causes of persistent reduction or increase of PbtO₂ after DC.

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Disclosures

The authors report no conflict of interest.

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Response

We have read carefully the considerations of de Lima Oliveira et al. We agree that persistent high levels of ICP

can produce a remarkable PbtO_2 decrease that could affect neuronal survival.³ All patients from our study had a high ICP for at least 6 hours and ischemic hypoxia at least 12 hours before decompressive craniectomy (DC), but not only in those whose condition evolved unfavorably. There were no significant differences in outcomes according to level and time (hours) of refractory intracranial hypertension (RICH) before DC (see Table 2 of the original study).

Although our study was retrospective, we believe that the fact that patients in our study all had the same level of RICH before DC improves the validity of the findings with respect to the prognostic utility of cerebral oxygenation. The variables that independently influenced the outcome were as follows.

- 1) Before DC: PbtO_2 values at ICU admission ($p < 0.001$); total time (hours) ($p < 0.05$) and proportion of time with $\text{PbtO}_2 < 15$ mm Hg ($p < 0.001$). All variables were significantly lower in patients with poor outcome (see Table 2 of the original study).
- 2) After DC, 40 patients (95%) had increased PbtO_2 values. Changing values were higher at all intervals of time in patients with favorable outcome ($p < 0.0001$).

We hypothesize that those cases in which patients did not show a substantial increase in cerebral oxygenation regardless of the level prior to DC can be explained by primary and structural damage in the microcirculation zone (microvascular collapse, perivascular oedema, and microthrombosis with selective neuronal loss) in areas that appeared normal on CT scan, which impedes adequate oxygen delivery. Our hypothesis was recently confirmed by Veenith et al.⁷ using PET techniques. On the other hand, we emphasize in this study that the area we suggest for monitoring (healthy area of the hemisphere most damaged) is the most representative for analyzing the pathophysiological phenomena that occur after traumatic injury.

In our study, the main cause of hypoxia was ischemia secondary to RICH before DC. Diffusion hypoxia could have contributed due to cerebral edema. Hypoxemic, anemic, high-affinity, and hypermetabolic hypoxia, all were rigorously detected and corrected following our protocol in the ICU. Other types of hypoxia (shunt, uncoupling, cytotoxic, mitochondrial dysfunction) cannot be detected without the corresponding technology.

The injured brain increases the utilization of glucose.^{2,4} Hyperglycolysis (HGL) plays an adaptive role. HGL increases lactate (L), pyruvate (P), and the L/P ratio. Lactate may be used as an additional source of energy. Therefore, in the absence of tissue hypoxia, elevated lactate is associated with good results.^{1,2,4}

The term “cerebral metabolic crisis” (CMC) represents a state of oxidative metabolism reduction. Two types of CMC can be differentiated. CMC type I is characterized by an increase in the L/P ratio and tissue hypoxia, whereas CMC type II occurs with normal tissue oxygenation.⁸ The diagnosis of HGL and CMC requires advanced multimodal monitoring (microdialysis, PET). Its presence and duration have a strong impact on the final outcome.^{1,5,6,8}

Finally, we believe that our work reveals the need to consider not only RICH for the indication of DC. We believe that cerebral oxygenation and cerebral metabolism can influence clinical management and proper selection of patients.

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Atypical pituitary adenoma

TO THE EDITOR: In the April 2018 issue, the *Journal of Neurosurgery* published a case series by Rutkowski et al.⁸ in which the authors compared nonatypical and atypical pituitary adenomas (APAs) (Rutkowski MJ, Alward RM, Chen R, et al: Atypical pituitary adenoma: a clinicopathologic case series. *J Neurosurg* **128**:1058–1065, April 2018).

In 2004, the WHO defined APAs as tumors with elevated mitotic indices, Ki-67 index levels > 3%, invasive growth, and high nuclear reactivity for p53.⁴ It was felt that these tumors demonstrated aggressive behavior and warranted closer observation; however, the clinical significance of the defining histological features was unclear.

Since that time, multiple studies have been conducted in an attempt to further our understanding of APAs.^{1–3,7,9,10}

Interpretation of the literature is challenging, as results vary, with some studies demonstrating higher recurrence rates for APAs^{9,10} and associations between recurrence and p53 immunopositivity/Ki-67 indices,^{2,3} while other studies have shown no difference in recurrence rates for APAs.¹ Additionally, the criteria utilized for diagnosing APAs vary between studies with inconsistent inclusion of tumor invasion in the diagnosis⁶ and Ki-67 cutoff values ranging from 1.5% to 4%.^{1,7}

As a result of the uncertainty surrounding APAs, the WHO removed “atypical pituitary adenoma” as a tumor category in the 2017 WHO classification of pituitary tumors.⁵ No replacement for categorizing “aggressive” tumors is suggested. Features that are thought to predict aggressive behavior are briefly discussed, including “rapid growth, radiological invasion and a high Ki-67 proliferation index,” although no Ki-67 index cutoff is provided.⁵ The WHO calls tumors with these features “high-risk” and recommends that these tumors be “investigated more intensively and followed up more closely.”⁵ No criteria for follow-up or investigation are offered.

The study by Rutkowski et al. was submitted to the *Journal of Neurosurgery* for review prior to the release of the 2017 WHO guidelines but was published long after. The study results add to our understanding of the behavior of APAs based on the 2004 WHO guidelines;⁴ however, the implications of these findings in light of the new guidelines is unclear. We feel that publishing this article in April 2018 without mention of the new guidelines was an oversight and that an addendum addressing this issue would have been appropriate and helpful.

On a global scale, it is our opinion that the abandonment of the term “atypical” by the WHO increases the risk of not appropriately managing and following patients with tumors demonstrating features that are concerning for aggressive behavior. While we agree that there is a paucity of data surrounding APAs, we feel that there is sufficient evidence to support the existence of a subset of adenomas that act aggressively, although defining immunohistological and clinical features has yet to be agreed upon.

Without formal acknowledgment of an “aggressive” adenoma subtype, treating physicians will have to rely on pathologists to alert them to aggressive features. As a result, there is a risk of this patient population being overlooked and not followed closely. Additionally, we fear that abandonment of the APA classification will result in decreased motivation for researchers.

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Response

The loss of atypical pituitary adenoma (APA) as a distinct clinical and pathologic tumor entity within the 2017 WHO classification omits an important subset of pituitary tumors that clearly demonstrate more aggressive clinical characteristics. While our analysis found clear differences in the behavior of APAs versus non-APAs and argues for their inclusion in the latest guidelines, a lack of uniform agreement in the pituitary literature on defining characteristics contributed to their disappearance from the classification. As our paper was submitted before the 2017 classification was released but published soon thereafter, we appreciate the response of Rotman and colleagues for highlighting the ongoing need to identify and triage patients who possess more “aggressive” adenomas.

We believe that the former criteria for atypicality still provide the greatest diagnostic accuracy in identifying aggressive tumors and find the new features suggestive of aggressive behavior more difficult to quantify. In fact, the former criteria for atypicality (mitotic activity, p53 reactivity, and Ki-67 index ≥ 3) are invaluable precisely because they offer objective means for assessment rather than relying on more subjective clinical criteria such as the presence of tumor invasion or growth. Reversion to these more

nebulous features complicates attempts to standardize definitions of pituitary adenomas, properly identify and research aggressive phenotypes, and effectively counsel patients with higher-risk tumors. For example, should sellar expansion with sphenoidal and/or clival extension be considered tumor invasion or simply cavernous sinus invasion? What growth rate should trigger suspicion of a more aggressive phenotype? What threshold for cellular proliferation should be considered worrisome?

Reintroducing strict cutoffs and thresholds for diagnosis are critical components of any future discussion on aggressive pituitary adenomas. We hope that our paper provides enough evidence that tumors should still be regularly screened for atypical features by neuropathologists. The presence of mitoses, p53, and elevated markers of cellular proliferation remain worrisome, objective features of aggressive behavior that can help neurosurgeons, neuroendocrinologists, and their patients make the most informed decisions about follow-up care and surveillance.

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Hydrocephalus following decompressive hemicraniectomy: a foe or a silent bystander?

TO THE EDITOR: I read with interest a recent article by Vedantam et al.⁴ (Vedantam A, Yamal JM, Hwang H, et al: Factors associated with shunt-dependent hydrocephalus after decompressive craniectomy for traumatic brain injury. *J Neurosurg* 128:1547–1552, May 2018), who concluded that the presence of interhemispheric hygroma and young age are high risk factors for need for CSF shunting for the treatment of hydrocephalus following decompressive hemicraniectomy in patients with traumatic brain injury (TBI). There are few pivotal factors that are cornerstones in the development of hydrocephalus following decompressive hemicraniectomy. First, if the superior aspect of the craniectomy is extended too close to the midline (< 2.5 cm), it leads to loss of the bone bar that acts as a “Starling resistor,” creating a pressure gradient between the draining vein and the sagittal sinus that is crucial for CSF absorption.^{1,3} Second, loss of bone shell coverage with the resultant direct exposure of the brain to the atmospheric pressure leads to loss of dicrotic CSF pulse waveform, thereby altering CSF dynamics and predisposing the patient to hydrocephalus.⁵ Furthermore, the presence of hygroma can be a benign counterpart resulting from the extracalvarial herniation due to axonal stretch following malignant brain edema, the resolution of which takes

time, depending on the compliance and the elastance of the brain. Sometimes, there is also secondary compensatory dilatation of the ventricles following gliotic changes to the traumatic brain without any clinical features of raised intracranial pressure.

This study had some patients who required shunt revision procedures due to overdrainage, which points to the same phenomenon of altered CSF flow dynamics following closure of the cranial vault. It would therefore be a more rational approach to perform early cranioplasty, and if clinical features of hydrocephalus still persist, then place a ventriculoperitoneal shunt with a valve of optimal pressure following validation of the correct CSF pressure via external ventricular drain placement. This step would help avoid lifelong risks associated with CSF shunting in some subsets of patients and also minimize the risk of multiple shunting owing to the gradual reversal in the CSF dynamics following cranioplasty in others.² Due to cost considerations, a programmable shunt is not a feasible solution for many patients from developing nations where the impact of TBI is still at its peak. So, early but safe cranioplasty followed by close clinical as well as radiological observation for progression of hydrocephalus and then CSF shunting, if required, after monitoring CSF pressure would be a more realistic approach in managing this paradox. This study has certainly benefitted us in encouraging us to be more vigilant in monitoring for progressive hydrocephalus following decompressive hemicraniectomy when caring for young patients and those with interhemispheric hygroma.

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Disclosures

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Response

We thank the author for his interest in our article on posttraumatic hydrocephalus (PTH) after decompressive craniectomy. The author highlights several characteristics of PTH after decompressive craniectomy that make this a challenging entity to diagnose and treat. At present, there is an incomplete understanding of the pathophysiology of hydrocephalus after decompressive craniectomy. Several theories have been proposed, many of which were cited in our paper, including the effect of atmospheric pressure acting directly on the sagittal sinus and cortical veins,³ potentially impairing venous drainage and CSF reabsorption. The limits of the craniectomy may also play a role in the development of hydrocephalus. There appears to be an increased risk of PTH if the hemicraniectomy is less than 2.5 cm from the midline¹ or if it extends behind the coronal suture for a bifrontal craniectomy.

The second point that is raised relates to the need for and timing of CSF shunting in patients with PTH after decompressive craniectomy. We agree with the author that early cranioplasty may result in spontaneous resolution of hydrocephalus and some of these patients may not require a shunt. However, these patients need to be followed up with serial imaging, since clinical signs of hydrocephalus may not be apparent in patients with considerable neurological injury after TBI. In our study, 10 of the 15 patients requiring a shunt underwent early cranioplasty (median duration 33.5 days), and of these 10 patients, 8 underwent a cranioplasty first, followed by shunt placement later, due to either clinical or radiological evidence of hydrocephalus. Only 2 patients with early cranioplasty underwent simultaneous cranioplasty and shunt placement. The use of temporary external ventricular drainage may reduce the number of patients requiring a ventriculoperitoneal shunt. However, patients who do not undergo shunt placement require close clinical and radiological follow-up since delayed hydrocephalus is still a potential risk.² It can be difficult to choose a shunt valve for TBI patients since the change in CSF dynamics after cranioplasty is not always predictable. While a programmable valve is particularly useful in such cases, we understand that it may be prohibitively expensive in some regions of the world. Our experience is that although patients with PTH often have low intracranial pressure, there is a risk of overdrainage over time if a fixed low-pressure shunt valve is implanted. If a fixed pressure valve is used, the patient and family must be counseled on the need for close clinical and radiological follow-up and the possibility of shunt revision. We thank the author for his remarks on our paper and for further emphasizing the challenge of treating PTH after decompressive craniectomy for TBI.

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Dose-fractionated Gamma Knife radiosurgery for large-volume arteriovenous malformations

TO THE EDITOR: I read with great interest the article by Ilyas et al.¹ (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) and the commentary by Ye et al.⁴ (Ye Z, Ai X, You C: Volume-staged vs dose-staged SRS for large brain AVMs. *J Neurosurg* 129:262–265, July 2018).

Management of a large-volume symptomatic arteriovenous malformation (AVM) is a daunting task, not only for the treatment team but also for the patient. The competitive and adjunctive roles of surgeons, radiosurgeons, radiotherapists, and neurointerventional colleagues are ill-defined, and the boundaries are overlapping. I frequently wonder, if I had a similar pathology, what would I choose, and no evidence in the literature helps me to provide a definite answer to this dilemma. In a recent publication, Meybodi and Lawton² have beautifully described the various classification schemes of AVMs from radiosurgical and endovascular perspectives. Classification schemes are drafted to help in the category-based management of the disease. The presence of so many classification schemes testifies to the prevailing confusion among the experts. Both the published article of Ilyas et al. and the commentary by Ye et al. succinctly enrich the literature with the comparative evaluation of both the techniques of stereotactic radiosurgery (SRS).

I would like to draw the attention of the authors to our published experience on dose-fractionated Gamma Knife radiosurgery (DF-GKRS) for large-volume AVMs (> 10.00 cm³) published in 2017.³ We evaluated 14 patients with large-volume AVMs (median volume 26.5 cm³) managed with primary DF-GKRS in 2–3 fractions on a daily/alternate day schedule, keeping at least a 24-hour interval between two treatment fractions, with the Leksell G frame (Elekta AB) in situ and a median of 35.6 months (range 8–57 months) of follow-up. The marginal dose was fractionated into two or three fractions of the ideal prescription dose of 23–25 Gy of a single fraction. Among patients with more than 3 years of follow-up, 43% achieved complete nidus obliteration. Overall, there was a 67.8% reduction in AVM volume on imaging at 3 years follow-up. Nidus obliteration at 3 years had a direct correlation ($r =$

0.95, $p = 0.01$) with the cumulative prescription dose, with attainment of near-total obliteration rates beyond 29 Gy of the cumulative prescription dose. Only the cumulative prescription dose had a significant correlation with common terminology criteria for adverse events (CTCAE; version 4.03) severity ($p = 0.04$), independent of age, AVM volume, number of fractions, and volume of brain receiving at least 8 Gy of radiation. No patient receiving the cumulative prescription dose of 31 Gy or less suffered from any severe adverse event.

Before the introduction of the Leksell Icon model (Elekta AB), DF-GKRS was considered a less preferred option to volume-fractionated (VF)-GKRS. There are many reasons for this, such as ill-defined radiobiology of AVMs, dosing schedules, the time interval between two treatment fractions, and logistic issues. In its comparison, volume fractionation began with inherent confidence in the treating team as it fits into the traditional definition of single-fraction treatment to the targeted volume, and delivery of the ideal dose at once. A few issues with volume fractionation are the interval between two treatment schedules and the dynamic nature of an AVM. The preferred use of VF-GKRS is evident from the significantly greater number of publications on VF-GKRS in comparison to DF-GKRS. However, with the frameless technique of the Leksell Icon model, I am hopeful to see more publications on DF-GKRS with different dosing regimens.

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Disclosures

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Response

We thank the author for his interest in our systematic review.⁵ As highlighted by the authors, the pilot study of 14 patients demonstrates promising results, and they are to be commended for their work. However, a larger sample

size would seem necessary to evaluate the effectiveness of dose-staged SRS (DS-SRS) for the treatment of large AVMs.⁶ DS- and volume-staged (VS-) SRS have been utilized for quite some time, and each has been performed using Gamma Knife- and linear accelerator (LINAC)-based systems for the treatment of large AVMs.³ Regarding the methodology in the Mukherjee et al. study,⁶ patients appear to have been arbitrarily treated at 24- or 48-hour intervals. Furthermore, it is unclear why the total margin dose varied by 10% depending upon the treatment era.⁸ The margin dose and fractionation schemes should be standardized, as variations in the methodology limit the reproducibility and significance of the outcomes.⁷

Based on digital subtraction angiography, the complete obliteration rate was 21%, which is consistent with the findings of our review.^{5,6} Notably, an AVM located near the internal capsule with a volume < 10 cm³ was treated with DS-SRS and included in the study cohort. At our institution, this AVM would likely have been treated with single-session SRS.^{2,4} Generally, multisession frame-based SRS approaches are not appealing to patients, especially in the modern era of masked-based systems (i.e., Gamma Knife Icon and LINAC systems), which offer an alternative form of cranial immobilization. We agree with the author that outcomes of DS-SRS are underreported in the literature. Additionally, neoadjuvant embolization can be used to reduce the volume of large AVMs prior to targeting of the residual nidus with single-session SRS. However, the relationship between AVM embolization and SRS is complex and multifactorial.^{1,9} Further studies, including data from prospective registries, are necessary to determine the natural history of large AVMs, as well as the comparative effectiveness among DS-SRS, VS-SRS, and combined embolization and SRS for the management of these challenging lesions.

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Temporary occlusion during clipping of ruptured intracranial aneurysms

TO THE EDITOR: I read with interest the article by Malinova et al.,⁴ who have reconfirmed the benefits of temporary clipping during microvascular clipping of ruptured intracranial aneurysms without the added risk of inducing postoperative vasospasm (Malinova V, Schatlo B, Voit M, et al: The impact of temporary clipping during aneurysm surgery on the incidence of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 129:84–90, July 2018).

Cerebral vasospasm has overtaken rebleeding as the main factor leading to death or major disabilities among patients with ruptured intracranial aneurysms.⁶ Angiographic vasospasm has been seen in up to 70% of cases, with 40% of them having clinical symptoms attributable to it.¹ Temporary arterial occlusion (TAO) is a novel method by which to minimize the load of subarachnoid hemorrhage from premature rupture, thereby minimizing the risks of clinical or radiological vasospasm.

However, studies have shown that TAO can itself be attributed to radiological and clinical evidence of vasospasm in up to 30% and 16% of cases, respectively.² In this regard, the addition of a FLOW 800 vascular map study, which is reproduced from the routinely performed indocyanine green (ICG)–based angiography, can help us quantitatively

determine patterns of flow velocities (in terms of average absorption intensities) and time lag for the appearance of the dye between the parent and the branching vessels.³ ICG angiography is a safe, simple, accurate, and easily performed study requiring minimal time, with provisions for repeat sessions whenever deemed necessary.⁵ The information we garner helps us in predetermining those patients who are at high risk for developing vasospasm (higher discrepancies in average intensities or time lags for dye visualization between parent and branching vessels) and thereby implementing better plans such as intermittent temporary occlusion to ensure better outcomes. Furthermore, this study also confirms complete occlusion of the aneurysm and patency of the parent vessels, the branches, and the perforators, thereby safeguarding patients from the risk of rebleeding or inadvertent vasospasm.

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Disclosures

The author reports no conflict of interest.

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Response

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