Neurosurgical Forum
LETTERS TO THE EDITOR

Detection of MRI-negative Cushing's disease by FLAIR imaging: is it reliable?

TO THE EDITOR: We read with great interest the article by Chatain et al.¹ (Chatain GP, Patronas N, Smirniotopoulos JG, et al: Potential utility of FLAIR in MRI-negative Cushing's disease. *J Neurosurg* [epub ahead of print October 13, 2017. DOI: 10.3171/2017.4.JNS17234]). In this article, the authors evaluated the diagnostic utility of FLAIR imaging in the detection of microadenomas in patients with Cushing's disease (CD). All 23 patients (24 pituitary adenomas) underwent volumetric gradient recalled echo (3D-GRE) MRI and FLAIR scanning preoperatively. Compared with intraoperative findings and postoperative histopathology, 3D-GRE sequences correctly confirmed 18 location-concordant tumors and were unable to identify 4 tumors (MRI-negative CD). In contrast, FLAIR sequences only correctly confirmed 12 tumors (noted incorrectly as 13 in the abstract) and were unable to identify 10 tumors. In the past decade, many researchers have explored the usefulness of FLAIR imaging in brain tumors, while few highlighted the significance of it in the diagnosis of pituitary adenomas.^{3,4} Exactly as the data showed in this study, compared with that of 3D-GRE MRI, the accuracy of FLAIR in detecting CD microadenomas was much lower, which means the diagnostic value of FLAIR imaging is very limited.

Chatain et al. also found all 5 patients with negative 3D-GRE MRI displayed FLAIR hyperintensity. Among them, 4 patients had location-concurrent positive histopathological findings, and in 1 patient (case 7) the concordance of imaging with histopathology was unable to be identified because the foci of FLAIR hyperintensity was not removed during surgery. The authors concluded that FLAIR helps 3D-GRE determine MRI-negative CD for surgical planning, which we think is quite debatable. The standalone specificity of 3D-GRE and FLAIR in this study was equal, but is impossible in real life. Considering the innate instability of specificity/sensitivity as well as the rather small sample size of this study, statistical errors undoubtedly existed. In addition, the positive and negative likelihood ratios (more statistically stable than specificity/sensitivity) of 3D-GRE were 1.64 and 0.36, while those of FLAIR were

1.1 and 0.9. This indicates that the possibility of confirming the foci of FLAIR hyperintensity as tumors was just 52.4%.

Even though the authors used T2-weighted sequences to screen for cysts within the pituitary gland or the adenoma, it is still difficult to differentiate.⁶ As for the localization, small Rathke cleft cysts (RCCs) usually lie within the central posterior aspect of the anterior lobe adjacent to the posterior lobe, similar to CD microadenomas. The signals of cysts on MR images are diverse due to their different compositions of cystic fluid. When protein components are in the majority, RCCs will present T2 signal hypo-/isointensity, precontrast FLAIR isointensity, and postcontrast FLAIR hyperintensity, which are similar to the radiological appearances of microadenomas. When MRI-negative microadenomas and hyperintense cysts on FLAIR coexist in the same pituitary gland, the authors may regard the cysts as tumors and then select incorrect surgical sites. In conclusion, we can use FLAIR as an auxiliary sequence in CD, but the diagnostic value of it cannot be overestimated. Further studies with a similar design are needed.

Approximately 120 patients with CD underwent surgery annually at Peking Union Medical College Hospital, which is one of the largest pituitary centers in China. Generally, T1-weighted gadolinium-enhanced MRI as well as dynamic gadolinium-enhanced MRI (routine MR sequences) are used to detect and localize about 90% of CD adenomas.² The concordance of lateralization by MRI was 80% compared with surgical findings and histopathological results. In addition, the departments of neurosurgery, endocrinology, and radiology of our medical center are cooperating to explore the diagnostic utility of the ¹⁸F-FDG and (⁶⁸Ga) DOTA-TATE dual-tracer PET/MRI in CD microadenomas.⁵ The preliminary research indicates that dual-tracer PET/MRI can detect an additional 10% of the routine MRI-negative and location-concordant microadenomas.

We sincerely hope that the investigators (neurosurgeons, endocrinologists, and radiologists) of our center can collaborate with Dr. Chatain and colleagues to explore more efficient radiological examinations of MRI-negative CD microadenomas.

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Response

Although it has been suggested that preoperative visualization of microadenomas in CD may not improve surgical outcomes,¹⁰ negative preoperative imaging causes enough consternation among clinicians that it leads to adjunct imaging^{2,3,12} or extensive reviews of clinical experience.^{11,13} In MRI-negative cases, distinct adenomas are identified less commonly,⁸ leading to a more extensive exploration of the pituitary gland.^{6,9} In this setting, we attempted to improve the detection of microadenomas by applying the principle of retained contrast within microadenomas.⁴ Modern MRI techniques rely on delayed contrast wash-in to detect microadenomas as hypointense lesions. We wondered whether delayed FLAIR imaging could lead to detection of microadenomas due to retained contrast. We discovered in the current study that the standalone sensitivity of pituitary FLAIR imaging in detecting microadenomas remains poorer than best anatomical imaging (3D-GRE). However, an analysis of MRI-negative instances did reveal the potential utility of FLAIR as a complementary tool to 3D-GRE. We do not propose replacing 3D-GRE or dynamic pituitary imaging with FLAIR given the low sensitivity (55%) and fair interrater agreement ($\kappa = 0.32$). In MRI-negative cases, if a microadenoma is not immediately observed upon surgical

exposure, surgeons are forced to perform extensive surgical exploration of the sella. In light of the ineffectiveness of hemihypophysectomy guided by inferior petrosal sinus sampling lateralization,^{5,7} we hope that pituitary FLAIR provides a starting point for surgeons to initiate the surgical exploration. We agree with Drs. Wang and Xing that further studies are needed to clearly establish the role of FLAIR in the detection of microadenomas in CD. We have also been exploring other means to improve detection of microadenomas in CD including intraoperative MRI and FDG PET imaging.^{1–3} We acknowledge the gracious offer that Dr. Xing has made for a collaborative effort, and will reach out to make this a reality.

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Effect of facility costs in the treatment of neurosurgical patients using the Value Driven Outcome database

TO THE EDITOR: We read with interest the article by Florman et al.³ describing postoperative floor admissions for 200 consecutive patients (Florman JE, Cushing

D, Keller LA, et al: A protocol for postoperative admission of elective craniotomy patients to a non-ICU or step-down setting. *J Neurosurg* 127:1392–1397, December 2017). The authors described 5 situations requiring escalation of care, including 3 for agitation, 1 for seizure, and 1 for neurological status change. Inclusion criteria for patients potentially treatable in a floor setting were discussed. In summary, 98% of patients could potentially be managed in a postoperative floor setting. These findings are similar to those of other groups suggesting postoperative monitoring in step-down or hospital floor units can be a safe approach in select patients.^{1,2,4}

We have recently published^{5–7,9,10} or prepared and submitted (Abou-Al-Shaar et al., submitted; Abou-Al-Shaar et al., submitted; Guan et al., submitted) a number of studies evaluating the true cost of patient care using a proprietary database, the Value Driven Outcome database (Fig. 1). This database allows evaluation of the true costs, not price or insurance charges as in prior clinical studies, governing patient care. Our cumulative data so far suggest that facility costs account for the largest cost component of neurosurgical procedures, except for cases in

FIG. 1. Summary of cost distribution for various neurosurgical diseases and treatments using the Value Driven Outcome database. Overlapping and non-overlapping surgery included 475 cases of overlapping surgeries and 543 cases of non-overlapping surgeries involving 389 spine cases, 275 tumor cases, 35 vascular cases, 106 shunt cases, and 213 assorted cases. ACCF = anterior cervical corpectomy and fusion; ACDF = anterior cervical discectomy and fusion; TLIF = transforaminal lumbar interbody fusion. Figure is available in color online only.

which instrumentation (e.g., spine or vascular hardware) is utilized and becomes the principal cost of care. Facility costs account for the salaries of hospital workers and costs of facility maintenance and utilization, as well as ancillary hospital costs. On average in our studies, facility costs accounted for 43.5% of the total care cost, and, when excluding cases with spine or vascular hardware, facility costs amounted to 52.9% of the total. In addition, hospital length of stay correlated with increased total care cost, much more so than any specific clinician or technique.

If true cost containment of neurosurgical procedures is desired, the largest potential effect would be achieved by the reduction of hospital costs; to a lesser extent, controlling implant costs would have a similar effect. This could be achieved through improved selection of patients for various levels of care, streamlining patient care, and continuing to study the major cost drivers of various neurosurgical diseases. Much of the hospital cost of care is influenced by decisions of treating physicians and surgeons. The article by Florman et al., as well as those of other researchers, strives towards addressing the most costly aspect of neurosurgical care. As Rosenbaum and Lamas⁸ stated, “When physicians consider costs, they are serving the real interests of their patients.”

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Disclosures

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Response

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Transcranial MRgFUS for movement disorder: toward a wider and affordable employment for functional neurosurgery through 1.5-T MRI?

TO THE EDITOR: We recently read with great appreciation the results of Zaaroor and colleagues' clinical series on the use of magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy for treating tremor in patients with essential tremor (ET) and/or Parkinson's disease (PD) (Zaaroor M, Sinai A, Goldsher D, et al: Magnetic resonance–guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg* 128:202–210, January 2018).⁵ In this series, 18 ET patients, 9 PD patients, and 3 patients with both ET and PD were successfully treated by VIM (ventral intermediate nucleus) thalamotomy in order to control medically refractory tremor. The excellent results obtained by the authors further support the effectiveness and safety of MRgFUS thalamotomy in the armamentarium of functional neurosurgery. In particular, only a small rate of mild and temporary adverse events was reported, and most of the patients experienced a sustained and significant improvement in their tremor.

The effectiveness of transcranial (tc) MRgFUS in the treatment of movement disorders has been demonstrated in several case series, and the spectrum of potential clinical applications and experimental involvements has already been discussed.^{1–3,5}

At the University of Palermo (Italy), we have successfully treated 18 ET and 4 PD patients suffering from refractory tremor by means of 1.5-T tcMRgFUS thalamotomy performed with the Exablate 4000 system (InSightec Ltd.). The results of our clinical series confirm the effectiveness of the technique even with the use of a weaker magnetic field.² To the best of our knowledge tcMRgFUS procedures have otherwise been performed only with 3-T MRI scanners and there was a lack of clinical evidence regarding the use of 1.5-T MRI scanners until now.³

In our experience, if patients are given the possibility of a noninvasive option to treat their movement disorders and the opportunity to select their own treatment, they tend to choose MRgFUS instead of deep brain stimulation or radiofrequency or Gamma Knife thalamotomy. Accordingly, we believe that more widespread use of tcMRgFUS, worldwide, is ethically advisable.

In comparison to 3-T MRI scanners, 1.5-T units have a wider distribution and lower purchase, installation, and maintenance costs; moreover, they have a better safety profile and lower susceptibility to dielectric artifacts.⁴ Based on our results, which demonstrate the safety and diagnostic and therapeutic effectiveness of 1.5-T tcMRgFUS for the treatment of movement disorders, we believe that there is an opportunity to establish a path for a wider application of this technology by using 1.5-T MRI units, greatly increasing the number of eligible patients who might thus be able to reclaim their lives and providing access to this treatment even in low-income countries.

In conclusion, we would like to take this opportunity to share the comments that we received from a 75-year-old man who had been suffering from severe ET. He underwent tcMRgFUS VIM thalamotomy in the early phase of our use of MRgFUS at our institution, thanks to the availability of a 1.5-T MRI unit, and at the time of his discharge from our hospital he said: "I would never undergo classical surgery with drill and probes. In this way, thanks to you, I have been able to get rid of the shame of my tremor and of the prison of my condition."

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Response

We thank Dr. Giammalva and colleagues for sharing their success in treating 22 patients, using the Exablate 4000 system on a 1.5-T MRI scanner to perform VIM thalamotomies. Their site's experience further confirms the effectiveness of this noninvasive lesioning method, even when used under a weaker magnetic field.

The fact that treatments performed under a 1.5-T MRI scanner are so successful is very encouraging, since this

significantly broadens MRgFUS accessibility to many patients who are served in areas where 3-T MRI scanners are not available or are occupied by diagnostic imaging.

It should be emphasized, however, that in addition to good anatomic imaging and accurate thermometry during treatment, patient selection is very important, as is meticulous optimization of the ablation target during treatment, based on the patient's functional feedback (i.e., maximizing tremor control while minimizing side effects by moving the target by submillimetric steps until the best response is obtained).

To date, we have successfully performed 73 MRgFUS thalamotomies under the 3-T MRI scanner in Rambam Medical Center (Haifa), and now that ET treatment is reimbursed in Israel, the availability of MRgFUS thalamotomy has broadened.

We hope that the expanding use of this promising technology will indeed result in the widespread implementation of MRgFUS for treatment of movement disorders as well as other pathological conditions.

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Injury among neurosurgeons participating in organized softball

TO THE EDITOR: We read with great interest the commemorative article by Komotar et al.² regarding the creation and history of the Annual Neurosurgery Charity Softball Tournament (The Tourney) (Komotar RJ, Goldstein HE, Bruce JN: The Annual Neurosurgery Charity Softball Tournament: 15th Anniversary Commemorative Article. The creation, development, and establishment of a neurosurgical tradition. *J Neurosurg* 128:1605–1611, June 2018). We congratulate the authors for reminding the readers of their success in developing The Tourney, and we are pleased for their good fortune in meeting celebrities and athletes alike since its inception.

The authors note that The Tourney may very well be responsible for improving the wellness and camaraderie of neurosurgery departments across the country, and while it is common knowledge that the University of Virginia has the most outstanding wellness and camaraderie in the nation, even we must admit the appreciable benefits of organized softball. However, the authors do not adequately detail the unanticipated risks of softball participation to resident health and thus overstate the benefits to resident well being.

From our experience in 3 years of play, there have been no less than 9 injuries during softball participation, including 3 fractured fingers, 3 pulled hamstrings, 1 torn labrum,

FIG. 1. A: Time to first major injury among neurosurgeons participating in organized softball. The actuarial injury rate was 27.7%, 36.8%, and 45.8% at 6, 12, and 24 months, respectively. B: The percentage of uninjured among trainees was 61%, 51.2%, and 40.9% at 6, 12, and 24 months, compared to 100% among attending physicians ($p = 0.086$). C–E: Representative radiographs of distal phalanges, glenoid, and metacarpal fractures (arrows), respectively.

1 bout of sepsis, and 1 severe case of veisalgia (Fig. 1). Kaplan-Meier analysis revealed an astoundingly high injury rate of 36.8% among softball participants by year 1, which is well above the injury rate of 0.56% reported for high school softball players.⁴ Upon review of injury mechanism, 5 injuries (2 broken fingers, 2 pulled hamstrings, and 1 labrum tear) occurred while at the short-stop position. Two injuries (1 pulled hamstring and 1 collision leading to infection) occurred from the runners' positions, and 1 finger fracture occurred as the catcher protected home base.

Our data identified defense as the most at-risk position for injury, which agrees with injury statistics among Major League players.¹ However, the injury rate was astoundingly higher in our cohort than the national average, which is likely representative of the 8-plus years of deconditioning experienced by most resident physicians and points to the dangers that may occur when a self-inflated belief in athletic ability is combined with an ultra-competitive mindset and an obsequious loyalty to the attending physicians. These findings support anecdotal observations from The Tourney, whereby advancing teams are largely those that have won the war of injury attrition. Interestingly, attending physicians are less likely to suffer injury, although the results were not significant ($p = 0.086$). This may represent improved decision-making that comes with increased experience but could be due to chance given the small co-

hort. Still, these findings supported existing literature suggesting a reduced morbidity in neurosurgical practice with increased experience, though the generalizability of this to softball practice has yet to be investigated.³

In conclusion, the injury rate of organized softball among neurosurgical residents is much greater than the national average. A proper consideration of the risk of injury to the benefits of improved camaraderie and wellness should be held prior to participation in organized softball. Still, we thank the authors for their work in creating The Tourney and wish them good luck in the upcoming tournament.

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Response

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Decompressive craniectomy in TBI: What is beyond static evaluations in terms of prognosis?

TO THE EDITOR: We read this interesting article by Vedantam et al.¹¹ (Vedantam A, Robertson CS, Gopinath SP: Quantitative cerebral blood flow using xenon-enhanced CT after decompressive craniectomy in traumatic brain injury. *J Neurosurg* 129:241–246, July 2018). The authors performed a study to corroborate the clinical outcomes of patients who had undergone decompressive craniectomy (DC) and xenon-enhanced computed tomography (XeCT) imaging. They assessed the earliest XeCT studies performed after DC (median 51 hours) in 27 patients, and 81.5% of the patients showed normal or hyperemic global cerebral blood flow (CBF) values despite a poor outcome (from death to severe disability) in 100% of the patients at hospital discharge and in 74% at the 6-month follow-up (among 23 patients, only 1 and 5 patients presented with good recovery and moderate disability, respectively).

Decompressive craniectomy can raise CBF and decrease intracranial pressure (ICP), as demonstrated in other studies.^{1–3} Otherwise, especially in traumatic brain injury (TBI), monitoring CBF exclusively is far from providing sufficient prognostic information because of secondary and even tertiary phenomena leading to dramatic changes in molecular and cellular environments. Prolonged hyperemia may translate into an increased lactate concentration in brain interstitium due to anaerobic metabolism established in the early phase after injury (oligemia phase) combined with hyperglycolysis to restore ion pump homeostasis in the subsequent phase (hyperemia phase).⁵ Mitochondrial dysfunction has a crucial role in secondary damages after TBI. If mitochondrial dysfunction is sustained, especially when brain contusions are present, disturbances in energy metabolism, necrosis, and apoptosis may be progressive despite a normal blood supply to the brain.⁷ When other hypermetabolic states are present, such as fever, seizures, and cortical spreading depolarization,⁸ flow-metabolism uncoupling will probably manifest despite normal or hyperemic global CBF on XeCT images.

Intracranial hypertension (ICH), often found in severe TBI, leads to cerebral vascular autoregulation (CAR) disturbance, and vice versa. Cerebral vascular autoregulation is mediated by metabolic, myogenic, and neurogenic mechanisms; therefore, the relief in ICH provided by DC is not sufficient to solve CAR impairment. Compromised CAR will lead to diminished tolerance of systemic pressure variations, increasing the risk of brain swelling or hemorrhage in the presence of arterial hypertension and increasing the risk of ischemia when arterial hypotension

is found, showing individualized ranges of arterial pressure tolerance for each patient.⁶ If cerebral dysautoregulation is occurring, we do not advise measuring cerebral perfusion pressure (CPP) exclusively with arterial pressure and ICP values. Detection of elevated CBF using XeCT, if impairment of CAR is occurring, is an indicator of arterial pressure over the normal CAR range. Therefore, dynamic CAR (dCAR) should be assessed with ICP monitoring, transcranial Doppler (TCD) ultrasonography, or laser Doppler,⁶ for example.

Vedantam et al. found CPP in an acceptable range at XeCT scanning, even among the patients who died. In terms of cellular recovery and prognosis, functional techniques¹⁰ would play a more remarkable role than static methods such as XeCT, through the assessment of CO₂ reactivity using TCD or functional MRI.⁹ Impairment of CO₂ reactivity has been proven to be a marker of disease evolution, indicating poor outcome when constantly unsettled.⁴

In conclusion, knowledge of vascular and nonvascular surrogates involved concomitantly in TBI, such as CO₂ reactivity and CAR impairment as well as biochemical derangement and mitochondrial dysfunction, require continuous real-time multimodal monitoring and expert handling. Patient transportation, multiple scanning sessions, and radiation exposure are limitations of XeCT applicability in TBI management.

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Disclosures

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Response

We thank Brasil et al. for their comments regarding our article. They point out that 74% of the TBI patients had poor neurological outcomes (based on the Glasgow Outcome Scale [GOS]) at 6 months despite normal or hyperemic CBF after DC. We agree with their statement that using CBF “exclusively is far from providing sufficient prognostic information.” The aim of our study was to describe global and regional CBF patterns after DC for TBI. Cerebral blood flow studies were used in addition to multimodal monitoring (ICP, CPP, and brain tissue oxygen tension) to guide patient management. Patients who died at discharge had significantly lower regional CBF values than the patients who survived. However, despite normal global CBF in the majority of patients (17/27 [62.9%]), favorable outcomes (GOS score 4 or 5) at 6 months were seen in only 6 (22.2%) of 27 patients. We showed that patients with low brain tissue oxygenation, despite improvement in ICP control after DC, endured poor outcomes, further emphasizing the role of continued multimodal monitoring after decompressive surgery. XeCT provides a snapshot of CBF, and a more dynamic modality with real-time CBF data may be more useful in determining outcomes. The use of invasive CBF probes² may allow for continuous CBF monitoring. Overall, there are limited data describing brain metabolism and CBF after DC, and the focus of our paper was to describe CBF patterns after DC for TBI. Although XeCT is not used clinically now, other techniques¹ can be used to measure CBF after surgery. We agree that multimodal monitoring may provide additional informa-

tion to help prognostication after DC for TBI, and further studies are needed to evaluate this.

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Simplifying the use of prognostic information in patients with traumatic brain injury

TO THE EDITOR: We read with great interest the articles recently published by Brennan et al.² and Murray et al.⁴ concerning the Glasgow Coma Scale-Pupils (GCS-P) score, and we commend the authors on the efforts undertaken to improve traumatic brain injury (TBI) prognostication (Brennan PM, Murray GD, Teasdale GM: Simplifying the use of prognostic information in traumatic brain injury. Part 1: The GCS-Pupils score: an extended index of clinical severity. *J Neurosurg* 128:1612–1620, June 2018; Murray GD, Brennan PM, Teasdale GM: Simplifying the use of prognostic information in traumatic brain injury. Part 2: Graphical presentation of probabilities. *J Neurosurg* 128:1621–1634, June 2018). In this regard, we would like to raise some issues that could contribute to the refinement of the new proposed tool.

The basic assessment of a prognostic score should comprise at least its 1) calibration (the agreement between observed outcomes and predictions); 2) discrimination (ability to distinguish between those with or without the outcome); and 3) overall performance (global accuracy). The GCS-P models were adequately calibrated, as depicted on the graphics; however, no discrimination statistics were reported. It would be interesting to report the area under the receiver operating characteristic curve (AUC-ROC) for the GCS-P model and the GCS-P plus Age & CT models. This is the most widely used discriminatory capacity measure in the medical literature and its interpretation is broadly understood, which facilitates comparisons between models.¹

The Nagelkerke R^2 (similarly to all pseudo R^2 statistics) is an overall performance measure. Although valid, it lacks intuitive understanding and its direct interpretation as “the proportion of variability in outcome that is ex-

plained by the logistic regression model” is highly vulnerable to criticism and statistical reasoning (most pseudo R^2 statistics do not have 1.0 as the maximum value, and even the adjusted Nagelkerke R^2 is not adequately scaled).³

The Nagelkerke R^2 differences between the GCS-P and GCS (for modeling death: 18.4 vs 15.5, difference 2.9; for favorable outcome: 22.2 vs 19.8, difference 2.4) are similar to those between the Corticosteroid Randomisation After Significant Head Injury (CRASH) CT model and the GCS-P/Age/CT chart (death: 41.9 vs 39.7, difference 2.2; favorable outcome: 42.1 vs 39.7, difference 2.4). Thus, some may find it difficult to understand why the GCS-P was considered superior to the GCS but the GCS-P/Age/CT chart was considered sufficiently non-inferior to the CRASH-CT model. The AUC-ROC analysis could further elucidate this question.

Considering that the incidence of pupil alteration is higher in patients with severe TBI, we could be losing valuable prognostic information for mild and moderate TBI if the GCS-P model were to be routinely recommended over the CRASH model. On the general pooled sample reported in the paper, the CRASH model was at least marginally superior to the new proposed tool. Could we hypothesize that this superiority would be higher for nonsevere TBI? It would be enlightening to see a stratified analysis by TBI severity.

Nowadays medical apps are widely used for instant prognostic score calculations, and the CRASH/International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) models can be assessed as fast as any chart.⁵ Many prognostic scores and decision rules are already routinely used in the emergency department and intensive care unit by other specialties.

In conclusion, although it may be too early to endorse the GCS-P/Age/CT model over the CRASH/IMPACT CT models for regular TBI management, it is indeed an interesting alternative approach and could be a step forward to advance prognostic reasoning and more rational decision making.

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Response

We thank Dr. Solla and colleagues for their interest in our papers. We agree that there are many different measures available to assess performance of a prognostic model, each with its own strengths and limitations. Many papers report detailed technical evaluations of prognostic models in TBI, and we have ourselves contributed to many such studies. We nonetheless very deliberately avoided the temptation of writing our two papers as statistical treatises, but instead aimed to focus on practical relevance, and we presented our results in terms of a simple overall measure of performance.

The fundamental thrust of our papers was to point out that utility and acceptability are at least as important as the “technical” performance of a prognostic model. A well-calibrated and powerfully discriminatory model is futile if its complexity deters its use in practice. In spite of the authors’ assertions to the contrary, our perception echoes previous views referred to in our papers^{1–4} and is supported by an informal survey of UK neurosurgical units, which found that statistical models are not widely used in TBI. Our suggestion is that a simple chart might make the breakthrough that leads to prognostic models for TBI becoming incorporated widely in clinical practice.

Moreover, we do not consider the performance of our charts to be “sufficiently non-inferior” to the CRASH models. What we do is present a quantification of the inevitable tradeoff in performance between complexity on the one hand and ease of use and interpretation on the other. It will be for clinicians caring for a patient to decide if the simpler, less-powerful approach is to be preferred on the grounds of utility.

We present in Table 1 the relevant data for the “area under the curve” for the receiver operating characteristic, or the c-statistic as it is also known. As might be expected, these closely mirror the results expressed in terms of Nagelkerke’s R^2 . In particular, with both the IMPACT and CRASH models, the performance of the Age/GCS-P/CT chart lies between that of the simpler and more complex models, and is generally closer to that of the more complex models than to that of the simpler models.

We have severe reservations as to the wisdom of using measures of model performance within subsets stratified by severity, for if one wished to optimize the performance of a model within a subset of patients defined by severity then one would develop a model restricted to those patients. Nevertheless, in the interests of transparency, we present in Table 2 such an analysis with the CRASH data, stratifying patients as $GCS \leq 8$ (a widely used definition of “severe” TBI) versus $GCS > 8$. This shows that the GCS-P/Age/CT chart still performs well relative to the CRASH models for the patients with a better prognosis.

TABLE 1. Predictive yield for a range of models including GCS

Model	c-Statistic	
	Modeling Death	Modeling Favorable Outcome
GCS score as linear variable	0.717	0.731
GCS-P as linear variable	0.731	0.741
GCS-P as linear variable & age as linear variable	0.778	0.787
GCS-P as linear variable & age as linear variable & CT findings in 3 groups	0.806	0.803
IMPACT patient group		
IMPACT core model	0.734	0.749
IMPACT extended model	0.775	0.788
Age/GCS-P/CT chart	0.765	0.774
CRASH patient group		
CRASH basic model	0.820	0.817
CRASH CT model	0.849	0.834
Age/GCS-P/CT chart	0.840	0.825

TABLE 2. Predictive yield for a range of models based on a stratified analysis of the CRASH data set

Model	c-Statistic	
	Modeling Death	Modeling Favorable Outcome
CRASH patient group w/ GCS score ≤ 8		
CRASH basic model	0.742	0.746
CRASH CT model	0.790	0.780
Age/GCS-P/CT chart	0.772	0.767
CRASH patient group w/ GCS score > 8		
CRASH basic model	0.778	0.759
CRASH CT model	0.824	0.783
Age/GCS-P/CT chart	0.815	0.767

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Brain invasion and the risk for postoperative hemorrhage and neurological deterioration after meningioma surgery

TO THE EDITOR: In his interesting letter, Chernov showed an increased rate of seizures in patients with macroscopically brain-invasive meningiomas as compared to patients with noninvasive tumors (Chernov M: Seizures and invasive meningiomas. *J Neurosurg* 125:1615–1616, December 2016 [Letter]). However, correlations of brain invasion with other clinical variables and perioperative symptoms in meningiomas are sparsely investigated.¹ Hypothesizing that invasion of the cortex as well as adhesions of the tumor to the adjacent brain⁸ lead to an increased risk of postoperative hemorrhage and neurological deterioration, we compared the frequencies of both complications in 817 primary microscopically diagnosed brain-invasive and noninvasive meningiomas. Data recovery, patient characteristics, and tumor characteristics have been described previously (Table 1).^{2,4,6,7} All tumors were neuropathologically diagnosed according to the 2016 WHO classification⁵ and microscopically reviewed for brain invasion. Postoperative hemorrhage was registered when subsequent surgery was indicated. Any new or increased motor, sensory, speech, or cranial nerve deficit, or reduced level of consciousness or orientation was classified as postoperative neurological deterioration and registered 1) at the time of discharge (“early”—after a median of 9 days after surgery), and 2) at the date of initial outpatient examination (“median-term”—after a median of 3 months after surgery).

Early (60%, 24 of 40 vs 19%, 145 of 756) and median-term (48%, 15 of 31 vs 88%, 563 of 643) neurological deterioration was more frequent in patients with than in individuals without postoperative hemorrhage ($p < 0.001$ for both early and median-term groups). Postoperative hemorrhage was found in 7 of 47 brain-invasive but in 35 of the 766 noninvasive tumors for which data were available (15% vs 5%, $p = 0.008$). However, rates of neurological deterioration at the time of discharge ($p = 1.00$) and during median-term follow-up ($p = 0.145$) were similar in invasive and noninvasive meningiomas. Correspondingly, in multi-

TABLE 1. Summary of clinical and histopathological variables in 817 patients with meningioma

Variable	No. (%)
Median age in yrs	58, range 7–88
Males	238 (29)
Females	579 (71)
Mean Karnofsky Performance Scale score	80, range 10–100
Tumor location	
Convexity	297 (36)
Falx/parasagittal	108 (13)
Skull base	356 (44)
Posterior fossa	46 (6)
Intraventricular	10 (1)
Extent of resection	
Simpson grade I	237 (31)
Simpson grade II	341 (45)
Simpson grade III	97 (13)
Simpson grade IV	79 (10)
Simpson grade V	2 (<0.5)
WHO grade	
I	708 (87)
II	102 (13)
III	7 (1)
Brain invasion	
Absent	770 (94)
Present	47 (6)
Postop hemorrhage	42 (5)
Early postop neurological deterioration	169 (21)
Median-term postop neurological deterioration	95 (14)

Data about age, sex, tumor location, WHO grade, and brain invasion were available in all 817 patients, whereas data about Karnofsky Performance Scale score, extent of resection, postoperative hemorrhage, and early and median-term neurological deterioration could be detected in 794 (97%), 756 (93%), 796 (97%), and 674 (83%) patients.

variate analyses adjusted for patients' age, sex, and tumor location, brain invasion was associated with a distinctly increased risk of postoperative hemorrhage (OR 3.31, 95% CI 1.36–8.07; $p = 0.009$) but not with neurological deterioration during short- (OR 0.95, 95% CI 0.44–2.06; $p = 0.896$) and median-term (OR 0.50, 95% CI 0.21–1.18; $p = 0.113$) follow-up.

In atypical meningiomas, grading was solely based on brain invasion in 31 patients (30%), on other histopathological criteria in 59 patients (58%), and on a combination of both in 12 individuals (12%). No correlation was found between the grading criteria and postoperative hemorrhage ($p = 0.208$), and the frequency of both early ($p = 0.768$) and median-term ($p = 0.053$) postoperative neurological deterioration was not correlated with histopathological grading criteria.

Notably, the risk of postoperative hemorrhage was more than 3-fold increased in brain-invasive compared to noninvasive meningiomas. Although the rates of neurolog-

ical deterioration were similar in both groups, postoperative hemorrhage was shown to significantly correlate with patients' outcome. Hence, this finding is in accordance with previous studies, which reported higher rates of preoperative behavior changes⁸ and seizures^{3,4} as well as distinct edema formation in individuals with brain-invasive meningiomas. In contrast and with some limitations due to the small sample size, the risk of hemorrhage did not significantly differ between the grading criteria in atypical meningiomas.

In conclusion, our results further delineate an increased risk of perioperative complications in patients harboring brain-invasive meningiomas.

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Response

I am thankful to our colleagues from Münster for their interest in the study, the results of which were reflected in part in the referenced letter to the editor, and were presented in greater detail a couple of years ago.^{1–3} Our group evaluated the role of single-voxel proton magnetic resonance spectroscopy (¹H-MRS) in preoperative assessment of 100 intracranial meningiomas and adjacent peritumoral brain. The protocol presumed prospective collection of the multiple clinical, radiological, surgical, and histopathological factors (19 in total). Their associations with 5 variables of interest, namely WHO grade of meningioma, its histopathological subtype, MIB-1 index, the presence of macroscopically invasive growth, and consistency of the neoplasm, were evaluated using both univariate and multivariate statistical analyses. Among a variety of results, that study revealed a statistically significant association between preoperative seizures (along with male sex, large size and irregular shape of the tumor, and prominent peritumoral edema) and invasive growth of the neoplasm,² a predictive sign not reported before. This finding has been confirmed recently by the Münster group,⁴ although, regrettably, without sufficient reference to our work. Evaluation of the postoperative course after resection of meningioma was beyond the objectives of our analysis.

It is well recognized that invasive growth of meningioma may increase the risk of neurological complications after surgery, especially if the tumor is located in the vicinity of eloquent cortex or critically important basal brain structures, and may result in less aggressive resection and greater possibility of recurrence. The data presented herein demonstrate that in comparison with their benign counterparts, invasive meningiomas may be also more prone to postoperative hemorrhage. Hemorrhagic complications after brain tumor surgery may be caused by a variety of factors, but in particular they may be related to local fibrinolysis due to increased activity of plasminogen activators, for which increased content in meningiomas has been reported.^{6,8} On the other hand, both plasminogen activators and their inhibitors are playing an important role in tumor cell proliferation, migration, invasion, and metastases.^{5,7} Thus, pathophysiological processes leading to perioperative hemorrhage and aggressive growth of meningioma may be interlinked.

My only concern regarding the presented data is related to pure microscopic evaluation of meningioma invasion. The problem is that in cases of such tumors surgery is usually directed at maximum preservation of the adjacent neuronal tissue—thus the interface between the lesion and surrounding brain may be not available for histopathological assessment. It is especially true in cases of invasive growth, in which a more or less large piece of the neoplasm inherently attached to eloquent cortex or brainstem may be intentionally left in situ for prevention of neurological complications. Of note, in the presented series 24% of tumors underwent incomplete resection (i.e., Simpson grades III–V). Finally, invasive growth may be present not at the entire interface between the lesion and adjacent tissue, but at some part of it, which may be occasionally overlooked. These pitfalls may result in a false-negative identification of brain invasion in the histopathological

samples. Therefore, combined evaluation of both macroscopic and microscopic features of invasive meningioma growth seems more suitable for clinical studies.

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