Neurosurgical Forum

LETTERS TO THE EDITOR

Aneurysm rebleeding after subarachnoid hemorrhage

TO THE EDITOR: We read with great interest the retrospective cohort study by Horie et al.¹ (Horie N, Sato S, Kaminogo M, et al. Impact of perioperative aneurysm rebleeding after subarachnoid hemorrhage [published online September 13, 2019]. *J Neurosurg*. doi:10.3171/2019.6.JNS19704). The authors found that aneurysm rebleeding after subarachnoid hemorrhage (SAH) has specific characteristics in the preoperative, intraoperative, and postoperative periods, involving aneurysm size, heart disease, aneurysm location, family history, clipping, coiling, etc. According to Horie and colleagues, their study is the first to assess the characteristics and predictors of aneurysmal SAH rebleeding in the preoperative, intraoperative, and postoperative periods. We would like to express our respect for their achievements and to share some comments with the authors.

Firstly, and most importantly, the data were collected from 1 university hospital and 10 affiliated hospitals. The authors did not consider the role of these medical institutions in their analysis. Depending on the different medical levels of doctors in these hospitals, different degrees of surgical instruments and equipment, and different management methods after operation, these factors could affect the probability of aneurysm rupture during and after surgery. Therefore, it is difficult to control bias in data collected from 11 hospitals.

Secondly, their article does not provide inclusion criteria for the study subjects but simply describes exclusion criteria. It only rules out subjects younger than 18 years of age and nonaneurysmal SAH including dissection. However, patients with intracranial hemorrhage and on the verge of death, patients with vital organ diseases, and older patients (> 75 years of age) should also be excluded because the rate of postoperative mortality and disability is probably high in these patients, and it is difficult for surgical intervention to improve the survival rate.

Thirdly, the evaluation of aneurysm rebleeding after operation was defined as new SAH on postoperative CT scans. We think there are some flaws in this definition because postoperative hemorrhage on CT can have false-negative results and will affect the clinical outcome of different aneurysm surgeries (clipping vs endovascular coiling) in terms of postoperative rebleeding.

In addition, as for the diagnosis of postoperative rebleeding, the authors define it as new SAH on postoperative CT scans during the period from the operation to 28 days thereafter. To our knowledge, postoperative rebleeding always occurs from the operation to 7 days thereafter, so we suggest correcting the timescale for postoperative rebleeding.

Finally, the authors concluded that multiple aneurysms are protective factors for preoperative rebleeding. However, in a recent article by Suzuki et al.,² multiple aneurysms are considered as a risk factor for unruptured aneurysms, so there is somewhat of a controversy.

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online April 3, 2020; DOI: 10.3171/2019.12.JNS193444.

Response

We thank Drs. Wang and Chen for their comments. It is difficult to completely exclude technical or surgical equipment bias in all clinical studies, including ours. In this study, the surgical or endovascular procedure was performed by an experienced, certified physician. Regarding inclusion criteria, we believe it is very important to provide real-world data to assess rebleeding and clinical outcome in the aging population. In this study, most postoperative rebleeding occurred a couple of days after treatment. In terms of the association between multiple aneurysms and rebleeding, it is difficult to explain why the presence

of multiple aneurysms negatively affected preoperative rebleeding, a finding contrary to our expectations. Suzuki et al. reported that the presence of multiple aneurysms was a risk factor for the rupture of small intracranial aneurysms, and it is not possible to simply discuss the factor of multiple aneurysms because aneurysm size and aneurysm status (initial rupture or rebleeding) are different.

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INCLUDE WHEN CITING

Published online April 3, 2020; DOI: 10.3171/2020.2.JNS193536.

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Is aspirin a new silver bullet for reducing the growth of intracranial aneurysms?

TO THE EDITOR: We read with great interest the research by Zanaty et al.¹ (Zanaty M, Roa JA, Nakagawa D, et al. Aspirin associated with decreased rate of intracranial aneurysm growth [published online October 29, 2019]. *J Neurosurg*. doi:10.3171/2019.6.JNS191273) and we congratulate the authors for figuring out a solution for the management of relatively smaller unruptured intracerebral aneurysms, as literature had hypothesized earlier.² The article is well written, and the authors have demonstrated that aspirin administration is associated with decreased growth of unruptured intracranial aneurysms. We note that aspirin is a well-known drug that is widely used in clinical praxis for an extensive variety of indications including the prevention of cardiovascular events.³ Hudson et al. showed evidence of aspirin reducing the rate of growth of aneurysms. COX-2 (cyclooxygenase-2) and mPGES-1 (microsomal prostaglandin E2 synthase-1) are both inhibited by aspirin. These substances have a crucial role in aneurysm pathogenesis.⁴ However, there is a more complex interaction among aspirin, smoking, hypertension, and cerebrovascular diseases, including the increased risk of cerebral aneurysm growth. Smoking is known to exacerbate hypertension, stroke, pulmonary disease, heart diseases, and atherosclerosis.⁵ Smoking also exacerbates hypertension—with increased risk of malignant, renovascular hypertension⁶—as well as being a risk factor for intracranial aneurysm rupture.⁷

We want to highlight some important issues that this study raises. First, there is the inability to measure the smoking status of the studied cohort and the impact of

smoking on aneurysm growth. Second, there is limited analysis of the role of hypertension in the growth of the aneurysm. Also, based on recall bias, it is not clear why only the smoking risk factor was excluded and no other parameters were treated and interpreted similarly. It is necessary to distinguish recall bias from simply inaccurate information; several studies suggest that there is a greater likelihood of recall bias when recall is poor, which constitutes the majority of cases.⁸ It is important to consider that if a patient had a recall bias for smoking, then this same patient would have a recall bias for other events as well (of course this assumption may not be true, but it is possible). Another very important point is the conclusion of Zanaty et al.'s article, namely: "However, smoking is not part of the PHASES [population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, and site of aneurysm] clinical score." This finding from the PHASES clinical score needs to be interpreted with caution. Bijlenga et al.⁹ and Greving et al.¹⁰ showed that cumulative risk factors did not add value to prediction of aneurysm rupture. However, the authors also did not rule out the role of individual factors as an independent predictor of outcome. The authors further suggested that a change in smoking behavior (e.g., cessation) was probably one reason for the absence of risk effect on aneurysm rupture. The authors further suggested that the effect of continued smoking should not be interpreted as neutral for assessing the risk factors for intracranial aneurysm rupture.⁴ Zanaty et al. should be commended and thanked for this innovative treatment. However, detailed analysis of smoking behavior should be performed objectively while assessing various risk factors for growth of cerebral aneurysms. In that respect, definitely, a very well-recognized risk factor in such diseases must not be skipped.

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Disclosures

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INCLUDE WHEN CITING

Published online March 6, 2020; DOI: 10.3171/2020.1.JNS2049.

Response

We thank Martinez-Perez et al. for their interest in our research and feedback on our article. As noted in their response, smoking imposes serious cardiovascular risks and is known to exacerbate hypertension and atherosclerotic disease. Although a study that evaluates intracranial aneurysm growth or rupture cannot be complete without accounting for smoking, we had justifiable reasons to exclude it in our study. Smoking status sometimes is missing in the electronic medical chart (Epic Systems) under the appropriate section, and sometimes can be contradictory—i.e., the patient may be reported to be a smoker under the social factors section but reported as a nonsmoker in the care provider note (or vice versa). We acknowledge that recall bias can be present in other factors as well; however, in our study we relied on objective measures (such as documented hypertension along with the treatment and verification of the medication by the pharmacist). For the above reasons, and for the lack of smoking evaluation in other well-designed and accepted studies (such as the PHASES¹), we left smoking out as a factor. In addition, as highlighted by Martinez-Perez et al., there is complex interaction between smoking, hypertension, aspirin, and other risk factors. In other words, aspirin may work better—or not work at all—on smokers. This complex interaction cannot be predicted without collecting relevant information on smoking status and frequency (dose). We acknowledge that our study was limited by not evaluating the smoking status and that future prospective studies must account for it. In concordance with Martinez-Perez et al., we counsel patients with intracranial aneurysms on the risk of smoking and do take it into consideration along with other factors described in the PHASES score. We would like to thank Martinez-Perez et al. once again for

their letter, which highlighted the limitations of our study and allowed us to further clarify and avoid misguiding the readers. Smoking is a risk factor worth evaluating in intracranial aneurysms, and the finding that aspirin halted growth in small unruptured aneurysms needs to be validated in prospective well-designed studies.

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INCLUDE WHEN CITING

Published online March 6, 2020; DOI: 10.3171/2020.1.JNS20162.

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Vessel stenosis after Gamma Knife radiosurgery for benign lesions

TO THE EDITOR: We have read with great interest the article by Graffeo et al.¹ (Graffeo CS, Link MJ, Stafford SL, et al. Risk of internal carotid artery stenosis or occlusion after single-fraction radiosurgery for benign parasellar tumors [published online October 25, 2019]. *J Neurosurg*. doi:10.3171/2019.8.JNS191285). We would like to congratulate the authors for evaluating a complication that is otherwise limited to anecdotal case reports. However, we would also like to draw the authors' attention to a similar topic discussed by us in our earlier publication on the role of Gamma Knife radiosurgery (GKRS) for confined benign cavernous sinus tumors.²

Their article outlines several messages. Vascular complications following GKRS are uncharted territory, and the literature is very sparse and scattered in its discussion. In the authors' subgroup analysis of 283 patients with cavernous sinus meningioma (CSM) or growth hormone–secreting pituitary adenoma (GHPA), 8 (2.8%) patients showed evidence of internal carotid artery (ICA) occlusion/stenosis, of which only 2 (0.71%) cases were clinically symptomatic. No GHPA or category 1 CSM patient developed postradiosurgical ICA occlusion/stenosis. The median time to stenosis was 4.8 years (IQR 1.8–7.6 years). The 5- and 10-year actuarial risks of any new ICA stenosis/occlusion in category 2 and 3 CSM were 7.5% and 12.4%, respectively. Five- and 10-year risks of ischemic stroke in category 2 and 3 CSM patients were both 1.2%. The only variables predictive of stenosis/occlusion were the pre-stereotactic radiosurgery (SRS) carotid encasement grade and a younger patient age. Interestingly, there was no difference in outcome in terms of the dosimetry parameter.³

Post-SRS occlusive vasculopathy is a rare phenomenon. To date, the tolerance dose for a vessel has not been de-

cided.² Conventional wisdom dictates that high-flow vessels such as the carotid segment of the ICA are relatively more resistant to any radiation vasculopathy. GKRS can lead to both occlusive or proliferative vasculopathy. Our experience with post-GKRS vasculopathy is mostly driven by laboratory studies and patients with arteriovenous malformations (AVMs).^{4,5} In an unpublished analysis, we identified 19 patients who suffered from stenosis/obliteration of vessels most commonly in the zone of radiation and sometimes in the zone outside the radiation. Most of these patients were treated for AVM, CSM, or trigeminal neuralgia. Proliferative vasculopathy includes the development of additional vascular pathologies after radiation owing to the proliferation of existing vessels and neovascularization. The proliferative pathologies are cavernous malformation, angiomatic changes, capillary hemangioma, or development of moyamoya vasculature.

From the authors' study, one cannot ascertain if dosimetry does not influence vessel occlusion. Because of the inherent dose inhomogeneity of GKRS, it remains a fair possibility that zones of high radiation, also known as "hot spots," may have been on the vessel wall, causing a high dose distribution in that area. The authors themselves have mentioned this limitation in their article as the treatment plan could not be reproduced and coregistered to analyze the same. This concern has already been raised by Abe-loos et al.⁶ in their experience with a CSM patient who slowly developed occlusion of the ipsilateral cavernous ICA over 40 months but remained clinically asymptomatic. Similarly, Maher and Pollock⁷ reported occlusion of the superior cerebellar artery (SCA) along with accompanying veins in a patient with trigeminal neuralgia treated with GKRS.⁸ The patient did not respond to GKRS and underwent microvascular decompression. Intraoperatively, both the SCA and the accompanying veins had vasculopathy presumably due to radiation. Whether the exposed length of vessel or hot spot on the vessel has any significant prognostic value and in what time frame remain matters for further research. Historically, GK pallidotomy for dystonia was a contraindication, while GK thalamotomy was established as a suitable alternate technique for essential tremors. One of the reasons for the high complications with pallidotomy has been the predictability of hyperresponders in the pallidum. The popular hypothesis is radiation-induced injury to the lenticulostriate arteries in that territory whose response cannot be predicted. Contrary to this, thalamotomy results in the expected lesion size in nearly 98% of patients.

Interestingly, symptomatic occlusion is very rare and mostly manageable with observation and conservative management with aspirin. In the authors' literature review, only one patient needed emergent balloon angioplasty, and all patients but one improved significantly. The literature also stresses that most ICA stenosis/occlusion is asymptomatic thanks to sufficient flow from the contralateral side. Another possibility is the development of alternate channels (which may be a feature of compensatory proliferative vasculopathy) bypassing the occluded channel.

Over the last 3 decades, robust literature in support of GKRS for benign confined cavernous sinus tumor has documented its safety and efficacy over microsurgical resec-

tion.² However, whether one needs to change the policy in deciding the best treatment modality for future patients in light of the current article remains a question. We believe that patients with category 2–3 ICA encasement should be informed of this risk but should also be assured that the 5- and 10-year actuarial risks of symptomatic stroke are very remote (1.2%).¹ For these high-risk patients, follow-up imaging should routinely involve CT or MR angiography apart from routine follow-up radiology.

Whether we should titrate the risk as per the pathology remains elusive as, contrary to the authors' experience, other reports have shown a higher risk of occlusion in cases of pituitary adenoma (29%) than in CSM (18%).¹ It is interesting to note that no case has been reported for other cavernous sinus tumors such as cavernous sinus hemangiomas (CSHs), trigeminal schwannomas, or metastatic cavernous sinus tumors. We support the authors' hypothesis of a likely cause of vascular encroachment and contraction post-GKRS in the case of CSM, which is a less likely phenomenon with lesions such as CSHs or schwannomas, which push rather than infiltrate the vessel.

Although the authors found a statistical inverse correlation between the chance of ICA occlusion/stenosis and increased patient age, this does not seem plausible as vessels have higher chances of occlusion due to atherosclerotic changes with advancing age. Given the authors' small sample size, most likely this finding needs further evaluation and follow-up.

In the absence of conclusive evidence, vascular complications after radiosurgery for intracranial pathologies can be ignored as a freak accident. Until more robust literature becomes available, the article by Graffeo et al. may help with risk stratification in the small subgroup of CSM patients only.¹

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online January 3, 2020; DOI: 10.3171/2019.11.JNS192948.

Response

We appreciate the interest of Tripathi and colleagues in our recent article. At a center that has performed SRS for 30 years, we believe that it is important not only to report on the long-term successes of this approach for a wide variety of diseases, but also to chronicle rare complications that may not have been encountered at centers with less experience.^{1–5} We agree that patients should be fully counseled regarding the risk of infrequent complications following SRS. However, these complications should not be used as justification for choosing alternative treatment approaches over SRS for appropriate patients.

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Published online January 3, 2020; DOI: 10.3171/2019.12.JNS193018.

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The skull as a brain shape-keeper: viscoelasticity and orthostatic intracranial pressure

TO THE EDITOR: We have read the very interesting article from Lilja-Cyron and colleagues¹ (Lilja-Cyron A, Andresen M, Kelsen J, et al. Intracranial pressure before and after cranioplasty: insights into intracranial physiology [published October 18, 2019]. *J Neurosurg.* doi:10.3171/2019.7.JNS191077), and we would like to comment on some issues.

A typically little-mentioned function of the skull, beyond protecting the brain and allowing intracranial pulsatility, is to preserve the shape of the organ. Acting as a suction cup, its rigidity allows the existence of negative pressures within and prevents brain distortion. We can conjecture that the sunken skin flap that occurs in the “syndrome of the trephined” adds to neurological dysfunction by distorting not only the vasculature and its perivascular spaces but also the axonal framework itself.

Little is known about intracranial pressure (ICP) in the upright position. Regarding this intriguing point, the authors found progressively negative parenchymal pressures in orthostatism in the 3-week period following cranioplasty. Assuming that the zero level for cerebrospinal fluid (CSF) pressure in the upright position is at, or a few centimeters below, the foramen magnum,² more negative pressures would be expected than those found by the authors (–4 to –6 mm Hg in Fig. 4 of the article by Lilja-Cyron et al.) considering that the position of the transducer was at least 10 cm above the CSF zero-pressure level (see Fig. 1 of the article by Lilja-Cyron et al.).¹ Beyond the differences attributable to hydrostatic factors, it is usually assumed that the ICP (parenchymal and CSF pressures) is homogeneous throughout the craniospinal space, implying that the discrepancies in readings are mainly as inaccuracies in the methodologies or local pressure gradients.^{3,4} Viscoelastic properties of brain tissue call into question whether CSF and parenchymal pressures could be considered indistinct and freely interchangeable, with researchers finding varying degrees of correlation between simultaneous ventricular and parenchymal pressures.^{3,5} It would be interesting, then, to know if the difference between the measured parenchymal pressure in orthostatism discussed by the authors and the theoretically expected CSF pressure is only due to the fact that the intracranial physiology had still not recovered by the 3rd week after cranioplasty, or because in orthostatism the parenchyma handles different pressures than the liquid column that surrounds it; or perhaps both factors.

Finally, it is important to remember that everyday activities involve many efforts besides lying down and standing up, such as talking, coughing, sneezing, and other Valsalva-like maneuvers. In patients with large bone defects, these efforts impose sudden and sometimes significant volumetric flows inside the craniospinal system, with immediate protrusion of the flap and distortion of the underlying brain, mainly in the region of the tentorial notch.⁶ In orthostatism, this instantaneous protrusion is mainly due to the brisk rise of spinal CSF squeezed by the sudden engulfed epidural venous plexus. However, this phenomenon is still difficult to assess by MRI and so is frequently overlooked, but from our point of view, it likely contributes to the neurological deterioration of these patients and should be added to those factors discussed by the authors.¹

We congratulate the authors for the elegance of their research.

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online March 20, 2020; DOI: 10.3171/2019.12.JNS193367.

Response

We thank the *Journal of Neurosurgery* for the opportunity to respond to the letter by Drs. Picard and Zanardi, and we thank these colleagues for their interest in our recent paper regarding ICP in patients with large skull defects following decompressive craniectomy (DC). In this study, we implanted telemetric ICP sensors in patients undergoing DC for trauma (primary or secondary DC) or

malignant infarction of the middle cerebral artery territory¹ and performed weekly ICP measurements after patients were discharged from the neurointensive care unit² and until 3 weeks after the cranioplasty. Our data show that the normal decrease in ICP occurring from postural change (supine to the upright position) is lost in patients with large skull defects and restored following cranioplasty. The same applies for intracranial pulsatility, which is absent after DC and (probably) normal after cranioplasty.

We found ICP in the upright position (45° elevated head rest) to be -3.9 ± 2.7 mm Hg 3 weeks after cranioplasty. Our data are in line with results from previous studies by Petersen et al.³ and Qvarlander et al.⁴ (in different patient groups), where ICP in the standing position was reported to be -2.4 ± 4.2 mm Hg and -1.8 ± 3.2 mm Hg, respectively. In both of these articles, the largest decrease in ICP for head-up-tilt of 20°–40°, indicating the presence of a defense mechanism against low ICP in the upright position, counteracting the ICP decrease otherwise caused by hydrostatic forces when elevating the head even further. This defense mechanism might involve passive jugular vein collapse.⁵ Regarding the relationship between parenchymal ICP and CSF pressure, we generally assume that these are identical, although focal intracranial space-occupying lesions may cause ICP gradients even within the supratentorial compartment.⁶ However, we will not exclude the possibility of minor differences in (or at least a delay in pressure transmission between) these pressures due to the viscoelastic properties of brain tissue.

Indeed, everyday activities involve other ICP-changing events, as Drs. Picard and Zanardi state, “such as talking, coughing, sneezing, and other Valsalva-like maneuvers.” We did not systematically assess the effect of these events on ICP in our patients but expect the ICP change to be less pronounced in patients with large skull defects. This is exemplified by the diminished intracranial pulse wave amplitude we see after DC.^{1,2} In conclusion, our findings of decreased “circadian” ICP changes and absent intracranial pulsatility might explain the known CSF-related complications to DC, such as hydrocephalus and hygroma formation.⁷ These changes in intracranial physiology following DC (in combination with changes to the cerebral vasculature, perivascular spaces, and probably axonal strain⁸) might also be involved in the pathogenesis of syndrome of the trephined.⁹

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Published online March 20, 2020; DOI: 10.3171/2020.2.JNS193535.

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Structural retinotopic analysis at 7-Tesla MRI in pituitary macroadenomas

TO THE EDITOR: We read the article by Rutland et al.¹ with great interest (Rutland JW, Delman BN, Huang K-H, et al. Primary visual cortical thickness in correlation with visual field defects in patients with pituitary macroadenomas: a structural 7-Tesla retinotopic analysis [published online October 18, 2019]. *J Neurosurg*. doi:10.3171/2019.7.JNS191712).

First, we would like to congratulate the authors for using 7-Tesla (7T) MRI to investigate the secondary damage of the visual cortex that may be attributed to the remote effect of chiasmatic compression in patients with pituitary macroadenomas (PMAs). They found that the global thickness of V1 in patients with PMA was greater than that in controls, although the differences were not statistically significant. Interestingly, the cortical thickness was significantly decreased at the median bottom 10th percentile of V1 thickness in PMA patients. Moreover, positive correlations between V1 thickness ratios and pattern deviation metrics were demonstrated in all patients. We appreciate the significance of these findings and the application of 7T MRI in the clinical setting for the quantitative assessment of the posterior visual pathway. However, we would like to highlight some methodological issues that should be addressed in future studies.

It still remains controversial whether 7T MRI is superior to 3T MRI in cortical thickness estimation. The 7T MRI scanners can generally acquire images with a higher signal-to-noise ratio, and the magnetization-prepared 2 rapid acquisition gradient echo (MP2RAGE) sequence has been widely used in imaging the brain microstructure

at a submillimeter scale.² However, it is known that T1-weighted images acquired on 7T scanners suffer the transmit and receive B₁-related imaging inhomogeneities, and T1-weighted image quality can heavily affect cortical construction.² Seiger et al.³ performed a systematic comparison between conventional 3T MPRAGE scans and 7T MP2RAGE scans in the estimations of gray matter volume (GMV). They found a higher GMV in several visual regions (including fusiform gyrus, middle, and inferior occipital gyrus) and a higher test-retest reliability at 3T.³ Moreover, the residual B₁ transmit imaging inhomogeneities, even after the self-correction of MP2RAGE, may still lead to biased classification among gray matter, white matter, and CSF, resulting in misestimation of cortical thickness.⁴ Haast et al. have found that additional B₁ transmit imaging inhomogeneity corrections on MP2RAGE images significantly improve the accuracy of cortical thickness measurements compared with uncorrected ones.⁴ These results raise a crucial question: are 7T scanners necessary for detecting atypical anatomical structures in patients with PMA?⁵ Given the lower accessibility and higher cost of 7T compared to 3T scanners,⁵ the necessity of using 7T MRI in the structural retinotopic analysis in PMAs still needs to be further explored.

We note that this study has been classified as a prospective study; however, the neuroophthalmological data was collected retrospectively, and therefore it would be useful to conduct this part of the study prospectively. The study includes a small sample size, and therefore strict inclusion criteria must be used. The patient and control groups were indeed matched by age and sex; however, we would like to highlight that the visual field may also be affected in people with high myopia, glaucoma,^{6,7} and macular disease,⁸ and therefore additional steps to reduce confounding factors should be taken into account. We suggest that detailed eye examination results from participants such as intraocular pressure and diopter inspection be recorded. To visualize the anatomy and rule out other diseases, we recommend that fundus photography and optical coherence tomography scans should be conducted on all patients with PMA. We hope our discussions and suggestions can foster greater research interests in the mechanisms of PMAs.

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Dr. Yao gratefully acknowledges funding from the China Postdoctoral Science Foundation (grant no. 2019M663271)

and the scholarship from the State Scholarship Fund, China Scholarship Council (no. 201808440461).

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online February 14, 2020; DOI: 10.3171/2019.11.JNS193149.

Response

We thank Yao et al. for their interest in our recent publication. In this study we sought to take advantage of available high-resolution 7T scans to perform cortical thickness assessments. Although ultrahigh-field MRI may not be necessary for detecting changes in cortical thickness, 7T is a useful tool for studying structural retinotopic changes in the context of pituitary adenoma due to the resolution and contrast advantage imparted by high-field scanners. These results may eventually be translated to performing similar studies at 3T with lower permitted resolutions and larger sample sizes. Furthermore, 7T scanners are increasingly available since recent FDA and Conformité Européenne approval, with at least 87 whole-body MRI systems of 7T or greater field strength installed worldwide as of December 2019. These 7T scanners offer exquisite sensitivity and resolution for imaging modalities required to detect subtle alterations in structure, metabolism, and connectivity in various neurological diseases.^{1–3}

While we acknowledge that signal-to-noise ratio and contrast in certain brain regions suffer from increased B₁

inhomogeneity at ultrahigh field, in our experience, this is less of a problem in the primary visual cortex than in portions of the brain in closer proximity with the skull base. Careful placement of dielectric pads and adjustment of the transmit B₁ to provide the most uniform B₁ profiles in the regions of interest were employed in this study to minimize transmit B₁ inhomogeneity. We used the MP2RAGE sequence in which flip angles are optimized to create image contrast that was independent of the reception B₁ field [B₁⁻] and largely independent of the transmission B₁ field [B₁⁺].⁴ This more homogenous T1-weighted image, called the UNIDEN image, is created by combining two different gradient echo images with two different inversion times produced by MP2RAGE.^{4,5}

Reducing the effect of inhomogeneous transmit B₁ field at 7T is an active area of research. Solutions include the use of parallel transmit coils and universal radiofrequency pulses to achieve a more uniform B₁ profile.^{6,7} This could provide whole-brain uniform MP2RAGE images at the higher resolution achievable by 7T MRI.

Lusebrink et al. systemically compared thicknesses of the human cerebral cortex using 3T and 7T and found consistent results across field strengths, confirming the validity of cortical thickness measurement at ultrahigh field.⁸ However, the average cortical thickness was shown to be greater at 3T and Lusebrink et al. concluded that 3T overestimates cortical thickness as a result of partial volume effects, which are greater at lower field strength. This potential overestimation could contribute to the higher gray matter volumes reported by Seiger et al. using 3T, suggesting that 7T MRI may be useful in mitigating volume averaging effects.⁹ Due to a small number of studies comparing 3T and 7T, there is currently not a final consensus on the optimal magnetic field strength for high-resolution precision volumetric quantification of cortical thickness. More research in this area is warranted to determine preferred field strengths for specific applications such as retinotopic imaging of pituitary adenoma.

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INCLUDE WHEN CITING

Published online February 14, 2020; DOI: 10.3171/2020.1.JNS193265.

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ClearPoint versus frame-based MRI-guided and MRI-verified deep brain stimulation

TO THE EDITOR: We read with interest the article by Sharma et al.¹ (Sharma VD, Bezchlibnyk YB, Isbaine F, et al. Clinical outcomes of pallidal deep brain stimulation for dystonia implanted using intraoperative MRI [published online October 11, 2019]. *J Neurosurg*. doi:10.3171/2019.6.JNS19548).

“First do no harm” is a central tenet of medical practice that is especially relevant in functional neurosurgery, where the procedure is supposed to improve quality of life.

The pioneers of stereotactic functional neurosurgery had to rely on ventriculography and stereotactic atlases to guide the initial trajectory, and often performed multiple brain passes while collecting physiological and clinical observations in awake patients under local anesthesia to guide and verify the surgical procedure. The availability of high-quality MRI and commercially available deep brain stimulation (DBS) hardware provides contemporary functional neurosurgeons with an alternative approach. Dedicated stereotactic MRI sequences can be used as follows: 1) to visualize the anatomical target in the specific patient undergoing surgery; 2) to confirm that the DBS lead has reached the intended target; and 3) to refine lead location with one additional brain pass if initial lead placement is suboptimal.

A stereotactic, frame-based approach to MRI-guided and MRI-verified DBS has several benefits. 1) It dispenses with clinical and physiological observations under local anesthesia, reducing patient discomfort as well as the cost involved in terms of equipment and personnel. 2) It allows surgery under general anesthesia, which is especially useful in young children or patients whose symptom severity precludes surgery under local anesthesia. 3) It focuses on lead location within the visible radiological anatomy, which has been increasingly recognized as the best predictor of long-term clinical outcome.^{2,3} 4) It avoids the use of sharp probes within the brain. 5) It minimizes the number of surgical trajectories through the brain. These last 2 factors reduce the risk of damaging vessels, leading to hemor-

rhage that can result in neurological deficit or death.⁴ This approach has been shown to deliver clinical results that are equivalent to traditional approaches but with less risk of serious complications.^{5–8}

We are therefore concerned when an MRI-based approach reports high complication rates, especially when 4 of 30 patients suffer an intracerebral hemorrhage, as reported by Sharma et al.¹ The discrepancy from other MRI-based approaches might be explained by the surgical technique used in the study.

Instead of using a stereotactic frame to obtain images before and after DBS lead introduction, the ClearPoint system uses “real-time” tracking during introduction of a ceramic stylet and peel-away sheath prior to introduction of the DBS lead. Whereas a frame-based approach requires access to an MRI machine for approximately 20 minutes before and 20 minutes after lead implantation, the ClearPoint system adds considerable cost to an already expensive procedure because it requires high-priced consumables and access to an MRI machine throughout surgery.

The authors argue in favor of a real-time approach by suggesting that “postoperative verification risks delayed recognition of procedural complications.” However, this is a moot point because the options of dealing with a deep-seated hematoma are limited once it has been visualized on MRI. Moreover, it is counterproductive if the new method actually increases the risk of procedural complications. Indeed, bleeds that caused neurological deficit in 2 patients (and ultimately death in 1 patient) “resulted from technical failures related to the introducer peel-away sheath being inserted too deep.”

It is for this reason that we have adopted the modified “KISS” principle in our surgical practice: “Keep It Simple and Safe.” Rather than introducing novel and complex practices to stereotactic functional neurosurgery, we have streamlined the process, removing unnecessary or redundant steps that increase the risk of errors and complications.⁹ Why fuse a nonstereotactic MR image to a stereotactic CT image to plan the initial trajectory, risking the introduction of co-registration errors, when a stereotactic MR image avoids this? Why use a cannula when the DBS lead will follow the exact path of a rigid probe after it has been removed from the brain? Why perform microelectrode recording when lead location on MRI is a good predictor of long-term outcome? Why perform an MRI study several days after surgery when performing the same investigation while the frame is still on allows the surgeon to relocate a suboptimally placed lead immediately?

The authors are to be congratulated for their in-depth reporting of adverse events and feedback of potential pitfalls to the company when using their equipment. They have emphasized that most of the complications occurred early in their series and are related to adoption of a novel surgical strategy into a busy surgical practice. However, if moving away from frame-based surgery to adopt this more expensive and complex technique was a challenge for such experienced and distinguished functional neurosurgeons, it will certainly test others.

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Disclosures

Boston Scientific has provided honoraria and travel expenses to Prof. Hariz for speaking at meetings and to Prof. Zrinzo for attending and presenting at educational activities.

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INCLUDE WHEN CITING

Published online January 17, 2020; DOI: 10.3171/2019.10.JNS192845.

Response

We appreciate the interest shown by Drs. Zrinzo, Akram, and Hariz in our paper and for taking time to express their concerns. We wholeheartedly agree with the authors that the tenet “first do no harm” is the central principle in medical practice, and an aspiration that guides our surgical practice. Yet, all surgical treatments present risks in the pursuit of benefits; the drive to advance surgical practice, as Zrinzo et al. exemplify, is motivated by the goal to minimize risks in pursuit of greater benefits, and secondarily to decrease resource utilization and expense. Innovation and the use of new technology plays a role in advancing these goals, and indeed that was our impetus to adopt an MRI-guided implantation technique in which

a recently developed MRI-based stereotactic platform (which is, in fact, conceptually a stereotactic “frame”) was used.¹ Unfortunately, it is all but unavoidable that any new approach or surgical innovation has an associated learning curve to understand and optimize it, by mitigating risks and maximizing efficacy. We reported our efforts in so doing.

Zrinzo et al. do not argue against the acquisition of new technologies; rather, they present an alternative strategy that they have successfully used to improve the effectiveness, safety, and cost of surgical treatment of movement (and other) disorders, for which they are to be congratulated. In contrast to their previously published approach,² they (personal communication), like us, perform the entire procedure in an intraoperative MRI (iMRI) scanner: the advantage is that the lead can be readily repositioned (if needed) immediately following its insertion—to attain the greatest accuracy without having to return to the operating room (OR) from a nonsterile environment and reopen the incision, etc. Our use of the MRI targeting platform was motivated by the hope that this advantage might decrease if not eliminate the need to reoperate on patients with misplaced leads.

The other motivations for the use of MRI-based procedures are in common between us and Zrinzo et al., as they nicely listed, and they appropriately reference the literature to support both of our approaches. We found similar clinical outcomes in the study group using iMRI and the MRI platform as compared to the conventional stereotactic frame approach (using microelectrode mapping), supporting our view that the pursuit of greater patient comfort does not sacrifice effectiveness. But the authors raised valid concerns about the higher complication rate in the dystonia group who underwent iMRI DBS placement. We acknowledged this concern in our paper and addressed it by several means. First, we assessed all our serious adverse effects to determine how and why they occurred. As mentioned in the *Discussion* section of our paper, several technical issues became apparent, which were discussed with the manufacturer (ClearPoint System; MRI Interventions, Inc.) and rectified, including the addition of product inserts, revision of protocols, and modifications to physician training. Notably, none of these technical errors and complications occurred in cases treated later in the cohort. Second, because our dystonia group was small, we assessed the incidence of serious adverse events in a larger group by including patients with Parkinson disease (PD) who underwent iMRI-guided globus pallidus internus–DBS placement over the same time interval. In the overall group, the incidence of all serious adverse events (including those due to technical issues as discussed above) was similar to previously reported rates, and none of the patients with PD sustained an intracerebral hemorrhage. This has been discussed briefly in our results and we are in the process of publishing complete data on this cohort of patients with PD. Therefore, based on the present study per se it is too early to say that this method, in its current practice, has a greater complication rate than other techniques.

Zrinzo et al. emphasize that they use a “Keep It Simple and Safe” approach, and suggest avoiding the introduction of “novel and complex practices to stereotactic functional neurosurgery” and “removing unnecessary or redundant

steps that increase the risk of errors and complications.”² We agree with the general premise that reducing unnecessary steps can potentially reduce complications. However, novel technology has been the basis of the advancement of stereotactic and functional neurosurgery practice for more than 75 years. This includes the introduction of the Leksell stereotactic frame and advancing from ventriculography (via CT imaging) to MRI, both of which Zrinzo et al. use and for which they advocate.

Similar to the iMRI platform used in our study, the Leksell frame is a highly specialized piece of equipment that requires specialized training and constant vigilance on the part of the neurosurgeon. However, the ability to reposition a wayward lead at the time of implantation allows neurosurgeons to make sure they get it right prior to the end of the procedure without the need to go back and forth from the MR or CT scanner to the OR (what would be done differently the second time round?), which some surgeons may be more or less inclined to do, given the time, effort, and presumed increased risk of so doing. The other approach that allows this is the use of the intraoperative CT scanner,^{3,4} which Zrinzo et al. refer to: the negligible registration error between intraoperative CT and preoperative MRI—which is not actually necessary to determine the stereotactic accuracy of the implant—is more than counterbalanced by the ability to reposition the lead if needed without having to break the sterile field, transport the patient to the MRI scanner and then back to the OR for repositioning, etc., to reposition a misplaced or displaced lead. In our workflow, despite the opportunity cost of doing procedures in the diagnostic scanner, the use of MRI time is justified for this reason.

We believe that surgical innovation or inclusion of novel techniques geared toward optimizing patient outcomes is crucial to expand the field of surgery, and to eventually improve patient outcomes. Our objective in this study was to present, in an open and honest way, the sum total of our experience with iMRI-guided DBS placement, and to assess whether the iMRI approach is comparable to other conventional techniques. As with all innovations we did encounter challenges during successfully transitioning to this technique. However, we hope that our experience can guide other centers in adopting this technique. We agree that the long-term cost-effectiveness of this technique has yet to be determined and that future studies comparing different techniques are needed.

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INCLUDE WHEN CITING

Published online January 17, 2020; DOI: 10.3171/2019.12.JNS192928.

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Cost-effectiveness of sodium fluorescein in high-grade gliomas

TO THE EDITOR: We read with great interest the article by Hansen et al.³ (Hansen RW, Pedersen CB, Halle B, et al: Comparison of 5-aminolevulinic acid and sodium fluorescein for intraoperative tumor visualization in patients with high-grade gliomas: a single-center retrospective study. *J Neurosurg* [epub ahead of print October 4, 2019. DOI: 10.3171/2019.6.JNS191531]). Their retrospective study compares 5-aminolevulinic acid (5-ALA) with sodium fluorescein in the resection of high-grade gliomas (HGGs), showing a comparable extent of resection with the two agents. The authors concluded that fluorescein is a viable alternative to 5-ALA, a conclusion that harbors an important economic impact since fluorescein is inexpensive compared to 5-ALA. The authors admit that the patients were not randomly assigned; instead, there was a departmental shift from 5-ALA to fluorescein because of the cost-effectiveness of the latter. For the same reason, we have shifted from 5-ALA to fluorescein over the years in our department. We were glad to read the results of this study given our aim of always improving the quality of care of our patients; however, caution must be exercised in the data interpretation. One randomized controlled trial showed that 5-ALA in HGG increases the extent of resection and overall survival by optimizing visualization and thus the completeness of tumor resection through the agent's accumulation in the tumor cells.⁴ The use of 5-ALA may be synergistic with other strategies.¹ Several studies, but none with level I evidence, have indicated the utility of sodium fluorescein in HGG surgery. Fluorescein extravagates in the absence of the blood-brain barrier and accumulates in the tumor via a mechanism similar to gadolinium contrast on MRI. 5-ALA detects tumor cells outside the contrast-enhancing layer on MRI.² In our experience, fluorescein is also present outside the contrast-enhancing lesion on MRI, but because of the edema, and thus is not entirely reliable.

The cost-effectiveness message about fluorescein is important; however, as the authors suggest, studies with level I evidence are needed.

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online December 13, 2019; DOI: 10.3171/2019.10.JNS192817.

Response

We thank the authors for their interest in our work.

The overall goal in HGG surgery is maximal safe resection. Substances that visualize tumor tissue, such as 5-ALA and fluorescein, play an important role in achieving this goal by increasing resection rates without compromising the safety of the procedure.^{1,5} Other modalities such as pre- and intraoperative MRI, neuronavigation, and awake surgical procedures² are also tools that can be used to increase precision and the degree of resection, and as long as the modality used results in maximal safe tumor resection, the choice of modality is probably less important.

Several studies have indicated that fluorescein is effective for HGG surgery, but none with level I evidence, as is the case for 5-ALA.⁵ Even dual labeling has been investigated.⁴ Obviously, the results of a prospective randomized controlled trial directly comparing 5-ALA and fluorescein would be of interest, and we would be happy to participate in such a trial. As mentioned in our study, 5-ALA is believed to detect HGG cells outside the gadolinium contrast-enhancing region on MRI and thus perhaps better represents the diffuse transition from HGG to healthy tissue (comparable to FLAIR MRI sequences). When using fluorescein, the enhancement is comparable to that of gadolinium contrast on MRI; therefore, the surgeon should always keep the preoperative MRI and tumor location in mind so that tumor cells in non-eloquent brain areas adjacent to the contrast enhancement can also be removed.

Intraoperative fluorescence will likely continue to be a

key part of the surgical treatment of HGG in the future. As fluorescein (as opposed to 5-ALA) extravagates passively through a leaky blood-brain barrier (BBB),³ this opens up its potential use in cerebral metastases, as the neovascularization of these tissues also lacks BBB. Future research on fluorescein-guided resection of metastases will, we hope, shed light on whether or not this group of patients benefits from intraoperative fluorophores.

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INCLUDE WHEN CITING

Published online December 13, 2019; DOI: 10.3171/2019.11.JNS192963.

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Sodium fluorescein versus 5-aminolevulinic acid to visualize high-grade gliomas

TO THE EDITOR: With great interest we have read the article by Hansen and coauthors¹ (Hansen RW, Pedersen CB, Halle B, et al. Comparison of 5-aminolevulinic acid and sodium fluorescein for intraoperative tumor visualiza-

tion in patients with high-grade gliomas: a single-center retrospective study [published online October 4, 2019]. *J Neurosurg*. doi:10.3171/2019.6.JNS191531. After carefully reading this report, we believe that several points merit mention given our own extensive experience with fluorescein.²⁻⁴

The authors present a retrospective evaluation of two cohorts of patients harboring high-grade gliomas who received either 5-aminolevulinic acid (5-ALA; n = 158) at a dose of 20 mg/kg body weight (BW) or fluorescein (n = 48) at 200 mg (regardless of BW) prior to fluorescence-guided resection (FGR). During the study period, the department changed from 5-ALA to fluorescein, and the authors now retrospectively compare resection rates, progression-free survival (PFS), and overall survival (OS) in the two cohorts.

The authors report that they achieved similar resection rates regardless of the fluorochrome. Remarkably, however, the two cohorts present with different outcomes. Patients operated on with fluorescein demonstrated a longer PFS and a minimally longer OS with a hazard ratio of 0.66 for the fluorescein group (p = 0.06), which suggests superior survival in an underpowered study. Extent of resection (EOR) has repetitively been acknowledged as one of the strongest predictors of prognosis.^{5,6} Thus, if the authors' results were accepted to be valid, the only explanation for differing outcomes would be an intrinsic anti-glioma activity of fluorescein. This would be a very surprising finding indeed, seeing that so many rational approaches and medical trials in malignant gliomas have failed. Furthermore, no possible intrinsic anti-tumor mechanism of fluorescein can be envisioned.

The answer to this unexpected observation may be simpler. The authors describe complete resection of contrast-enhancing tumor (CRET) of only 30% in the 5-ALA group and 36.2% in the fluorescein group. These values are remarkably low and cannot be considered standard in modern neurosurgery. Resection rates were not even this low in the white-light control arm in the old randomized 5-ALA phase III trial published in 2006.⁷ In that study, which was among the first experiences with the use of 5-ALA, surgeons achieved a 65% rate of complete resection in the 5-ALA group, compared to 35% in the white-light microscopy group.⁷ Modern reports document CRET in more than 89% of patients when using 5-ALA.⁸ Even Neira et al.,⁹ in their earlier assessment of fluorescein, achieved CRET in 84% of cases, without finding any significantly increased resection rates compared to those with conventional microsurgery.

While the low resection rates may provide one good explanation, other factors, such as changes in nonsurgical therapy at the authors' center over time, the distinctly shorter follow-up period in the 5-ALA group, or the different sizes of the compared cohorts, may have also contributed to the authors' results.

The authors also state that "fluorescein shows only the area of MRI-depicted contrast enhancement."¹ This statement is worrisome and questions the scientific assumptions of this work. Fluorescein is merely a marker of blood-brain barrier disruption and has been proven to be non-tumor specific.¹⁰ Immediately after injection, fluo-

rescein will be present in all perfused tissues, including normal brain. After several hours (2–3 hours in our experience), extravasation in regions of blood-brain barrier disruption will be observed, i.e., the contrast-enhancing tissue, something we have termed "pseudoselectivity."¹⁴ With time, however, fluorescein will propagate into the peritumoral edema zone, outside the resection target.²⁻⁴ This "edema marker" quality was already demonstrated in 1993¹¹ and was further mentioned as problematic the first time fluorescein was documented in the context of tumor surgery in 1948.¹² Hence, fluorescein-induced fluorescence must not be blindly pursued, and, in fact, the figure provided in their article clearly demonstrates the unspecific fluorescence of the dye (e.g., yellow staining of the cortex far outside the resection zone; see their Fig. 1).

On the other hand, 5-ALA is specifically metabolized by tumor cells and is a proxy for tumor cellularity. We know that around 10%–20% of tumor cell density is needed to create fluorescence that can be detected visually.¹³ This resection margin extends beyond the region of contrast enhancement and has been associated with a better outcome.¹⁴

It must be remembered that fluorescent dyes and FGR are merely surgical techniques or tools and are not alone responsible for resection outcomes. The information acquired from these tools is only as good as the surgeon using said tools, and in any assessment of intraoperative tools, the principles of case selection as well as mapping and monitoring of neurological functions have to be respected.¹⁵ 5-ALA does not go "deeper" into the brain, as stated by the authors—it depicts the metabolic active tumor tissue. It is not about "tempting" the surgeon, it is about understanding the disease and actively deciding which tumor regions to resect.

Hansen and coworkers conclude that fluorescein can be used as a viable alternative to 5-ALA, a conclusion that may not be supported by the data presented. However, we agree with the authors in their beliefs that the efficacy of fluorescein in glioma surgery has not been well documented, nor well compared to 5-ALA, and that the patient numbers in the published fluorescein studies are lower than those in the studies investigating 5-ALA, with the fluorescein studies lacking both randomization and control groups.¹ We believe that only multicenter randomized controlled trials will give answers to this question, but there is little here to support such an effort.

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online January 24, 2020; DOI: 10.3171/2019.12.JNS193180.

Response

We thank the authors for their interest in our work and comments on our study. Although most of the points mentioned are already discussed in the *Discussion* section of our article, their comments deserve a reply.

They posit that the relatively low resection rates may

explain the differences in PFS within the population. This topic is already included in the *Discussion* section: “Compared to existing literature, EOR in this study was relatively low. As delineation was performed manually, bias regarding determination between contrast enhancement in the diffuse tumor border, and thereby potential overestimation of tumor residue, is considered the best explanation of this concern.” As they correctly mention, “EOR has repetitively been acknowledged as one of the strongest predictors of prognosis.” The prognosis in our cohort (PFS: 8.7 months for 5-ALA, 9.2 months for fluorescein; OS: 14.75 months for 5-ALA and 19.75 months for fluorescein) is fully comparable to that in the existing literature on patients with high-grade glioma.^{1,2} Using the authors’ own deduction, it would seem unlikely that an estimated low EOR is not underestimating the actual EOR given the prognosis in terms of OS and PFS in our study. In addition, comparing EOR in our retrospective study, which includes all malignant gliomas, with those in prospective randomized studies is misleading.

As our study was conducted on pre-existing data, one cannot expect an even distribution of participants. Suero Molina and Brokinkel mention that “the distinctly shorter follow-up period in the 5-ALA group . . . may have also contributed to the authors’ results” (i.e., a significant difference in PFS). Median PFS and OS are some of the most frequently reported measures of survival, and as they are both within the median follow-up time, this explanation does not seem compelling. If, however, one assumes that this line of thinking is appropriate, the authors’ reference to the follow-up time is incorrect, as we did not report a shorter follow-up time for 5-ALA (46.7 months for 5-ALA and 21.2 months for fluorescein).

The authors criticize our statement that “fluorescein shows only the area of MRI-depicted contrast enhancement.” We agree that with time, and as a consequence of resection, fluorescein visualizes, among other structures, the peritumoral edema zone. However, in contrast to their statement, the study they cite concludes that “our intraoperative observations and histopathological analysis demonstrate a good correlation between intraoperative fluorescein fluorescence and gadolinium enhancement on MR imaging.”³

We agree that FGR, neuronavigation, and other modalities themselves are not responsible for the resection outcomes. As they play a key part in guiding the surgeon performing the resection, and as the variety of techniques, tools, and modalities to choose from are significant, comparison of the different tools is important from both a patient-oriented and an economic point of view. As mentioned in our study, “prospective randomized controlled trials are needed to further investigate these findings,” but performing such a study would be unethical; thus, retrospective evaluation of pre-existing data on this exact topic, as was done in our study, is necessary.

Finally, the authors state that “Hansen and coworkers conclude that fluorescein can be used as a viable alternative to 5-ALA, a conclusion that may not be supported by the data presented.” Unfortunately, this represents a considerable misunderstanding of an otherwise quite specific conclusion. Our study was performed to investigate retro-

spectively an already widely adopted approach of preoperative fluorescein visualization of high-grade glioma (and to compare it to 5-ALA), and within the comprehensively described limits of our study, we concluded from the collected data that “fluorescein was found to produce EOR and postoperative residual tumor volume comparable to 5-ALA. In addition, the use of fluorescein resulted in longer PFS compared to 5-ALA.” We agree that the definite answer to this can only be given by randomized controlled trials, but as mentioned previously, we believe that calculations based on retrospective data play an important role in motivating such studies, and our study contributes just that.

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Published online January 24, 2020; DOI: 10.3171/2019.12.JNS193279.

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The value and limitations of SSEP/MEP monitoring in intracranial aneurysm surgery

TO THE EDITOR: I have read with interest the analysis performed by Greve et al.¹ of a retrospective cohort of elective aneurysm surgery patients who underwent intraoperative neuromonitoring (IONM) and historical controls (Greve T, Stoecklein VM, Dorn F, et al. Introduction of intraoperative neuromonitoring does not necessarily improve overall long-term outcome in elective aneurysm clipping. *J Neurosurg*. 2020;132[4]:1188–1196).

Though evidence is lacking from randomized controlled trials, there are many systematic reviews^{2–5} detailing the value of somatosensory-evoked potential (SSEP) and motor-evoked potential (MEP) monitoring in intracranial aneurysm surgery. Zhu et al.⁴ reported that the pooled sensitivities and specificities of combined SSEP and MEP monitoring for predicting postoperative neurological deficits were 92% (95% CI 62%–100%) and 88% (95% CI 83%–93%), respectively. SSEP monitoring has been used for more than 40 years to prevent cortical and subcortical ischemia. Posterior tibial and medial nerve SSEPs are used for identifying cerebral hypoperfusion of the anterior cerebral artery and middle cerebral artery vascular territory, respectively. MEP monitoring has been introduced as a supplementary technique for improving the detection of pure motor deficits caused by perforating artery occlusion and subcortical ischemia.⁶

In the study reported by Greve et al.,¹ 8 of 11 patients suffered from SSEP/MEP changes that were transient, yet the authors designated these changes without new neurological deficits as “false positive” (FP) results, a decision which might not have been appropriate according to the IONM literature, in which reversible signal changes are commonly reported as “true positive” (TP). Skinner and Holdefer⁷ discussed this issue in detail and defined transient SSEP/MEP changes as “true negative” (TN). Regarding 4 patients reported by Greve et al. who had permanent MEP changes but who were without new neurological deficits and whose results were considered FP, 1 patient was diagnosed with radiological stroke, which should have been revised to TP. The MEP declines in another 2 patients might have been due to inhalation anesthetics, a finding that should not be considered an FP result. And, using high or increasing stimulus intensity for transcranial stimulation MEP (tcs-MEP) can cause FN results, since the ischemia level could have been bypassed by the activated brain on a deeper level,⁸ as happened in one of the “FN” patients reported in the study by Greve et al. In this patient, MEP reduction was transient, and the amplitude was almost back to the baseline after the stimulus power was increased from the threshold level. For the other 5 of 12 patients, who suffered from hemiparesis or upper-extremity paresis with a correlated ischemic area, tcs-MEP would not have detected the relatively superficial area of ischemia if high stimulus intensity had been used on these patients.

Speaking of the limitations of SSEP/MEP monitoring, first, it cannot monitor cranial nerves. As to the “FN” patients described by Greve et al. who exhibited new cranial nerve deficits, electromyography of corresponding muscles might have been performed. Second, SSEP/MEP monitoring cannot monitor visual function. For “FN” patients with vision deficits, intraoperative visual evoked potentials should be used to assess these deficits. Last but not least, SSEP has been used to predict the outcome in comatose patients, and the absence of N20 responses is a finding that is very specific for poor outcome; conversely, preserved N20 responses are not definite predictive factors for good outcome.⁹ Mende et al.¹⁰ also confirmed that early SSEP measurements in patients with high-grade aneurysmal subarachnoid hemorrhage did not correlate with clinical outcomes.

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Disclosures

The author reports no conflict of interest.

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INCLUDE WHEN CITING

Published online August 21, 2020; DOI: 10.3171/2020.5.JNS201729.

Response

We thank Dr. Fang for this interesting letter to the editor in response to our study.

We share Dr. Fang's opinion that the diagnostic accuracy of IONM in intracranial aneurysm surgery has been substantially studied in the past. However, there is a fundamental difference between studies on the diagnostic accuracy of a given test and studies on whether the use of a test actually improves patient outcome by providing a way to prevent postoperative deficits. This difference is frequently overlooked, and the favorable sensitivity and specificity of IONM is falsely equated to improved clinical outcome.

This concern is well illustrated in the literature cited by Dr. Fang, thereby corroborating our presumption about missing outcome studies in the field.^{1–3}

Holdefer et al.⁴ discussed the problem of lacking randomized controlled trials and attributed this finding to nonneutrality of neurophysiologists who believe in the usefulness of IONM. Holdefer et al. formulate an essential question, which will likely remain controversial without randomized controlled trials: Would new postoperative deficits have occurred if the surgeon withheld intervention in response to an MEP alert? Moreover, our study sheds light on the possibility that false-positive alerts might even misguide the surgeon to unnecessary and risky manipulations. Because of the challenges of performing randomized controlled trials in the field of IONM, cohort studies using historical control groups like ours could, in part, fill that gap.

Dr. Fang draws attention to the attribution of test results in our study, suggesting that transient IONM changes that are not followed by a neurological deficit might have been registered inappropriately as “false positive” instead of “true negative.” However, Zhu et al.³ follow our approach in their study, naming it a “conservative” or “worst-case scenario” approach. They correctly state that by attributing a false-positive finding to transient changes that are not following a deficit, we “assumed no beneficial treatment effect produced by intraoperative rescue interventions,” thereby generating a lower range of plausible estimates of diagnostic value of warning criteria. As there is apparent discord about the definition of positive and negative events when signal changes are transient and followed by rescue interventions,⁵ we provided data on a historical control group and showed that outcome was not necessarily improved when using IONM in elective aneurysm clipping. As laid out above, this finding is interesting since it adds real-world evidence to the question about the beneficial treatment effect produced by surgical interventions.

Discussing the method of MEP elicitation in our study and potential lesion bypassing by deep structure activation, we can safely claim that IONM was conducted according to international guidelines and similarly to the methods used in other important studies on MEP monitoring in aneurysm surgery.^{6,7}

In summary, the historical control group of our study provides additional evidence about the impact of IONM on outcome in aneurysm surgery. Our study, therefore, advocates and justifies prospective cohort trials with sample size estimation and a randomized protocol to obtain definitive evidence on the benefits of IONM and further understanding of the relationship between warning criteria, surgical intervention, and clinical outcome during intracranial aneurysm clipping.

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INCLUDE WHEN CITING

Published online August 21, 2020; DOI: 10.3171/2020.6.JNS201793.

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Feasibility and safety of supratotal resection for low-grade gliomas

TO THE EDITOR: We read with great interest the article by Rossi et al.¹ on the feasibility and safety of supratotal resection (STR) for low-grade gliomas (LGGs) (Rossi M, Ambrogi F, Gay L, et al. Is supratotal resection achievable in low-grade gliomas? Feasibility, putative factors, safety, and functional outcome. *J Neurosurg.* 2020;132[6]:1692–1705). At the outset, we congratulate the authors for reporting a large series of LGGs. They also deserve to be praised for their conclusion that STR is feasible and safe in routine surgery for LGGs. According to Rossi and colleagues, their study is the first to describe the feasibility and safety of STR for LGGs in routine clinical practice. In the meantime, we would like to express our respect for their achievements and share some comments with them.

First, the authors defined STR as the complete removal of any signal abnormalities, with the volume of the postoperative cavity being larger than the preoperative tumor volume. However, there are different definitions of STR in anatomy and radiology. Moreover, conventional MRI underestimates the spatial extent of LGG since tumor cells have been found up to 20 mm around MRI abnormalities. Because of the frequent location of LGGs within “eloquent” brain areas, it is often difficult to achieve STR.² We believe that this definition has some defects because the microstructure of the tumor cannot be fully recognized under the microscope and because the bleeding site can also show abnormal signals on MRI, which interferes with clinicians’ judgment of the outcome of STR. Therefore, we think that postoperative pathological examination is very necessary. Whether LGGs are supratotally resected depends on the pathological results.

Second, in their paper, the authors mentioned that the possible influencing factors for STR include 1) factors related to the patient; 2) tumor-related factors that could be deduced by evaluating preoperative conventional MRI; 3) intraoperative factors such as the location of subcortical functional borders or previous biopsy or recurrence; and 4) integrated molecular/histological diagnosis, histological grade, and *IDH1* mutation. Yet, we believe that another more significant factor may be the important blood vessels around or inside the tumor. If blood vessels in the tumor site are important arteries or large veins, intracranial hemorrhage can occur in patients during and after the operation, thus affecting the surgical outcome.

Third, total and supratotal resections were significantly higher in tumors with a frontal or temporal location, and subtotal/partial resections were significantly higher in tumors with an insular location (respectively, $p < 0.001$). Then the authors concluded that the incidence of permanent neurological deficits was low in all resection groups but was significantly higher in patients in the subtotal/partial resection group in comparison to the total or supratotal groups. However, because of the significant difference in tumor location among the three groups, there are contradictory statistics with regard to the conclusion that the incidence of a permanent neurological deficit in the subtotal/partial resection group was significantly higher than that in the total resection group or STR group.

In their *Discussion*, the authors considered that “the rate of deficits or complications registered in partial or subtotal resection was higher, suggesting that persistence of tumors in the surgical cavity may expose the patient to immediate or delayed complications.” However, this aggressive approach (STR) is not without a significant risk of neurological loss due to potential damage to important cortical or subcortical tissues.³ However, there is short-term protection from immediate or delayed complications with partial or subtotal resection, suggesting that there is short-term protection of the patient’s neurological function, which may be impaired in the long term.

These limitations are enlightening in and of themselves. The concept of STR is still an interesting hypothesis, but more rigorous randomized controlled trials are needed to verify the safety and effectiveness of STR in LGG. Therefore, we propose that supramaximal tumor resection based on neurological function should be considered as the treatment concept for LGGs.

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Disclosures

The authors report no conflict of interest.

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INCLUDE WHEN CITING

Published online August 28, 2020; DOI: 10.3171/2020.7.JNS202601.

Response

We really appreciated Mr. Wang and Dr. Chen's Letter to the Editor about our paper, and we would like to thank them for their interest. We agree with the authors that the definition of STR may be controversial. At the moment, there is no consensus on the definition of STR in LGGs. The initial and largely accepted definition of STR is that proposed by Professor Duffau,¹ which we adopted in our work: complete resection of the MRI (FLAIR)-visible tumor, with the resection cavity larger than the preoperative tumor volume. This is a "radiological" definition based on an evaluation of the extent of resection (EOR) on postoperative MRI. As a matter of fact, according to European Association of Neuro-Oncology (EANO) guidelines, an "oncological" complete resection of an LLG is defined as complete resection of a FLAIR-visible tumor mass, as evaluated on postoperative MRI.^{2,3} Consequently, in current neurooncological practice, the evaluation of EOR is radiological, and according to current practice, the definition of STR should be based on imaging evaluation as well. We absolutely agree that the radiological definition does not reflect the highly infiltrative nature of gliomas and of LLGs in particular. Unlike in other types of cancer, gastrointestinal, for instance, the evaluation of the cancer cell-free border to establish the limits of resection during the procedure is not a practice in neurooncological surgery. We agree with the authors that this may be the way to go in future neurooncological surgery, to reduce the gap between the current radiological definition of EOR and the "biological" one. Given these considerations, the aim of our paper was to show that pursuing a radiological STR for LGG in current practice is feasible and safe. Starting from the radiological definition, a complete resection is defined as the "absence of any signal abnormalities on postoperative MRI." Such measurement is generally recommended on the 2-month postoperative MRI, on which most of the signal abnormalities due to small bleeding or tissue or hemostatic debris have usually disappeared.

We agree with the authors that bleeding or ischemia is the most relevant factor influencing functional outcome in glioma patients who have undergone surgery with the aid of brain mapping techniques. It is generally recommended to adopt a strict subpial resection technique, to dissect the tumor from minor or major vessels, and to limit as much as possible the use of coagulation. These surgical tips may reduce the incidence of ischemic insult and ischemia-related deficits.

Mr. Wang and Dr. Chen may be right regarding the slightly higher percentage of insular locations (34.7%) in the subtotal/partial resection group in comparison to the other resection groups (18.6% in total resection group and 16.6% in the STR group), partially explaining the higher

incidence of postoperative neurological deficit recorded in this group. Interestingly, in the subtotal/partial group we also documented a higher (although not significant) incidence of perioperative complications (1.6% vs <1%). The interaction of these two variables may explain the higher postoperative morbidity in the partial resection group. Interestingly, when all variables were analyzed together in the multivariate analysis, partial/subtotal resection was associated with a higher incidence of complications.

Regarding the association between postoperative permanent deficits and EOR, when a functional neurooncological approach is used to pursue the resection, the incidence of deficits does not correlate with the location of functional boundaries, but instead with the appearance of ischemic insult. Therefore, the assumption of the larger the resection, the higher the incidence of deficits is misleading. Perhaps patients in whom a partial or subtotal resection is achieved are those harboring more complicated tumors, exposing the patients to a higher rate of complications.

Nevertheless, we agree with the authors that the currently available armamentarium to evaluate the functional impact of surgery (independent of any EOR) is still limited and that more sophisticated neuropsychological testing should be implemented.

We agree with the authors that STR in LLGs is a very interesting hypothesis. Our paper shows that when a functional neurooncological approach is applied in each patient, without any patient or tumor "a priori" selection, a radiological STR can be achieved in at least one-third of cases in a highly safe manner. The proposal for a randomized trial to assess the oncological impact is of interest, but unlike with *IDH* wild-type tumors, such a study should cover the long natural history of the disease and the issue of the very long accrual needed for this rare type of tumor, which, in addition to relevant ethical issues, limits the study's feasibility.

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Published online August 28, 2020; DOI: 10.3171/2020.7.JNS202668.

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