Specificity and validity of putaminal involvement as a prognostic factor in Grade II insular gliomas

TO THE EDITOR: We read with great interest the article by Wang et al.6 (Wang Y, Wang Y, Fan X, et al: Putamen involvement and survival outcomes in patients with insular low-grade gliomas. J Neurosurg [epub ahead of print August 26, 2016. DOI: 10.3171/2016.5.JNS1685]). The authors classified 211 low-grade insular gliomas according to whether or not the tumors involved the putamen on MR images. They found putaminal involvement to be a significant predictor of both progression-free survival (PFS) and overall survival (OS) on multivariate analysis, in addition to extent of resection and IDH1 mutation.

We commend the authors for performing a study of a large number of Grade II insular gliomas. However, we have several concerns. First, using T2-weighted images to determine putaminal involvement, albeit the best sequence available, can introduce ambiguities.4 It is well known that tumors vary in the amount of edema that is captured by T2 hyperintensity, and that the actual tumor cells can extend far beyond the T2 hyperintense region. We believe that T1-weighted images should also be examined along with the T2-weighted images to increase the diagnostic confidence of putaminal involvement. Second, the authors did not take into account the involvement of other brain regions surrounding the tumor besides the putamen, such as the frontal and temporal lobes. We would like to know how the authors classified the Grade II gliomas as primarily insular gliomas. However, we have several concerns. First, using T2-weighted images to determine putaminal involvement, albeit the best sequence available, can introduce ambiguities.4 It is well known that tumors vary in the amount of edema that is captured by T2 hyperintensity, and that the actual tumor cells can extend far beyond the T2 hyperintense region. We believe that T1-weighted images should also be examined along with the T2-weighted images to increase the diagnostic confidence of putaminal involvement. Second, the authors did not take into account the involvement of other brain regions surrounding the tumor besides the putamen, such as the frontal and temporal lobes. We would like to know how the authors classified the Grade II gliomas as primarily insular in the first place, and how they distinguished between purely insular Grade II gliomas and paralimbic Grade II gliomas, because previous studies have demonstrated distinct IDH1/IDH2 mutation profiles between these two types of tumor.2

In a study by Tang et al. comparing 20 purely insular Grade II gliomas and 22 paralimbic Grade II gliomas that involved the frontal and/or temporal lobe, the authors showed that purely insular Grade II gliomas displayed a higher frequency of IDH1 mutations with a favorable outcome compared with IDH1 wild-type paralimbic gliomas.3 However, IDH1 mutated paralimbic gliomas shared many parameters with the purely insular gliomas with respect to growth patterns, survival, and microRNA profile.5 This suggests that the survival benefit of insular gliomas is mainly determined by molecular characteristics instead of involvement in other regions of the brain, including the putamen. Even though the current paper demonstrated the significance of putaminal involvement on the multivariate analysis, the analysis did not account for the effects of chemoradiation. Radiotherapy and chemotherapy are frequently administered in patients with Grade II gliomas and have been shown to affect survival, especially in patients after a subtotal resection or biopsy. Similarly, it is unclear if 1p19q co-deletion status was included in the multivariate analysis. Because follow-up was only available for 150 of 211 patients, loss to follow-up could have introduced patient selection bias and affected validity of the survival analysis as well.

In conclusion, putaminal involvement is likely a non-specific finding of Grade II tumors that also involve other regions of the brain. Its significance on the multivariate analysis is cast in doubt by using only T2 hyperintensity to estimate putaminal involvement, the lack of information on chemoradiation, and patient selection bias due to loss to follow-up.

Lu Deng, BS
Hao Zhou, MD
Bo Xiao, MD, PhD
The First Xiangya Hospital, Central South University, Changsha, Hunan, China

Harrison X. Bai, MD
Hospital of the University of Pennsylvania, Philadelphia, PA

Li Yang, MD, PhD
The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Acknowledgments
This work was supported by the Natural Science Foundation of China (grant no. 81301988 to Li Yang), the China Ministry of Education Doctoral Program Spot Foundation (grant no. 20130162120061 to Li Yang), and the Shenghua Yuying Project of Central South University (Li Yang).

References
Interest in the clinical classification and treatment of gliomas hinges on the accurate identification of tumor borders. T2-weighted/FLAIR MRI was well accepted in the identification of tumor borders in studies investigating gliomas, particularly insular gliomas, but may not be the region at which the tumor originated. The tumor centroid is the geometric center of the tumor lesion but may not be the region at which gliomas originated in the brain. Furthermore, the application of chemotherapy should be strictly limited and follow established guidelines. The authors report no conflict of interest.

Response

We are very pleased that neurologists expressed great interest in the clinical classification and treatment of glioma cases that were routinely admitted to hospital neurosurgery departments in China. The participation of clinicians not focused on gliomas, in multidisciplinary teams for glioma, should be greatly encouraged.

In T1-weighted imaging sequences, a majority of low-grade gliomas present with signal intensity lower than or equal to that of surrounding normal tissues; this is why T1-weighted imaging is not suggested for the identification of the border of tumor involvement, or for clinical diagnosis or radiological investigations. Moreover, compared to using T2-weighted/FLAIR images alone, a larger bias may exist with the identification of tumor regions using additional T1-weighted images, as the signal intensity of tumor tissue is equal to that of brain tissue; this may result in misidentification of tumor borders. In the majority of studies investigating gliomas, particularly insular gliomas, T2-weighted/FLAIR MRI was well accepted in the identification of the involved regions of low-grade gliomas.

Insular gliomas were defined as gliomas that mainly involved the insular area, which was in accordance with previous investigations on insular gliomas. Because the exact location at which gliomas originated in the brain could not be identified, the centroid of the lesion was used in our study to describe the tumor location. Please note that the tumor centroid is the geometric center of the tumor lesion but may not be the region at which the tumor originated.

Furthermore, the application of chemotherapy should be strictly limited and follow established guidelines (National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines of Central Nervous System Cancers [version 1.2016]) in the treatment of Grade II gliomas to avoid unnecessary drug resistance and side effects. Chemotherapy is not suggested as the first-line treatment in low-risk patients (those < 40 years old and with gross-total resection) with Grade II gliomas.

In addition, 1p/19q co-deletions only occurred in oligodendri- nal gliomas and should be assessed only if the tumor exhibits components of oligodendrogliomas (NCCN Clinical Practice Guidelines of Central Nervous System Cancers [version 1.2016]). Therefore, strictly speaking, the 1p/19q co-deletion was considered a classifying factor for oligodendri- nal gliomas, and was not included in the multivariate regression analysis of the entire patient cohort to avoid statistical bias.

In this study, the newly proposed putamen classification may allow for preoperative prediction of survival in patients with insular gliomas. The genetic variation between the two types of insular gliomas based on the putamen classification requires further study.

For further information regarding the management of adult diffuse gliomas in China, please check the newly updated Chinese Glioma Cooperative Group Clinical Practice Guidelines.

References


Mannitol for intraoperative brain relaxation

TO THE EDITOR: We read with great interest the ar-
ticle by Seo et al.1 (Seo H, Kim E, Jung H, et al: A prospective randomized trial of the optimal dose of mannitol for intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection. J Neurosurg [epub ahead of print August 19, 2016. DOI: 10.3171/2016.6.JNS16537]). Tumor volume itself and edema in the surrounding brain can cause a significant rise in intracranial pressure, which can hinder the successful surgical removal of brain tumors. Particularly for tumors involving skull base, where brain retraction may be required to even visualize the tumor, relaxation of the brain can facilitate tumor removal and prevent retraction-related injury, which can occur in about 10% of skull base procedures.1

In this study, Seo and colleagues randomized 124 adult patients to 4 groups according to the dose of mannitol to be administered. Patients in Group A received 0.25 g/kg; Group B, 0.5 g/kg; Group C, 1.0 g/kg; and Group D, 1.5 g/kg. We believe that another group of patients treated with a dose of 0.7 g/kg or 0.75 g/kg would have made the randomized trial more effective in establishing the adequate dose of mannitol, as a study carried out by Quentin et al. showed that the use of mannitol at a dose of 1.4 g/kg or 0.7 g/kg resulted in equivalent brain relaxation scores.2

The age of the patients in the study by Seo et al. ranged from 20 to 80 years, and the age distribution appears similar across all 4 groups. Brain atrophy is normally observed with advancing age (after the age of 40 years, at the rate of 5% per decade).4 Hence, a similar volume of tumor in both young and elderly patients would be expected to produce a dissimilar perception of brain fullness to the operating surgeon. So, conclusions regarding the safe dose of mannitol for producing “adequate” brain relaxation with a similar volume of tumor are likely to differ in young and old patients. This potential confounding factor should have been taken into account while designing such a randomized controlled trial.

In this study, 3 neurosurgeons assessed brain relaxation using a 4-point scale, and only one of them rated each case. The 4-point scale assessment is a subjective method and can be a source of bias. To eliminate such potential bias, consideration should have been given to evaluate interobserver agreement with assessment of brain relaxation by all 3 neurosurgeons or the use of objective methods to measure the decline in intracranial pressure after mannitol administration. Inadvertent durotomies while fashioning the craniotomy in elderly patients can lead to slow seepage of CSF, which can interfere with the assessment of brain relaxation attributable to osmotic agents.

A considerable proportion of the tumors in this study were meningiomas, which are extra-axial tumors. The pathology, mechanism of peritumoral edema, and surgical approach are substantially different in intra-axial and extra-axial tumors. Even among meningiomas, “brain fullness” is less bothersome for the surgeon in a case of a convexity meningioma as compared to one of a skull base meningioma. These 2 groups of tumors should probably have been assessed separately from other tumors in evaluating the adequate dose of mannitol for brain relaxation. In the present study, although the distribution of tumors is proportionate in each group, extra-axial and intra-axial tumors are grouped together and skull base lesions were not considered separately.

In this study, there was no significant difference in brain relaxation between Group B and Groups C and D. This means that the authors found no significant difference in brain relaxation whether a dose of 0.5, 1, or 1.5 g/kg was used. Furthermore, with increasing dose of mannitol the authors found imbalances in osmolality gap and serum electrolyte levels, particularly in Groups C and D. Hence, it is difficult to agree with their conclusion that in patients undergoing craniotomy for supratentorial brain tumors, 1 g/kg is the optimal dose of mannitol for satisfactory brain relaxation and is the dose associated with the fewest complications.

Raman A. Mahalangikar, MS
Pankaj Kumar Singh, MCh
Shashwat Mishra, MCh
Bhawani Shanker Sharma, MCh
All India Institute of Medical Sciences, New Delhi, India

References

Disclosures
The authors report no conflict of interest.

Response
First of all, we appreciate the great enthusiasm that Dr. Mahalangikar and his colleagues have shown for our recent paper. We agree with their opinion that brain relaxation induced by mannitol administration can facilitate tumor removal and prevent retraction-related injury in patients undergoing surgical removal of a brain tumor. They suggest that an additional group treated with a mannitol dose of 0.7 or 0.75 g/kg would have been helpful in establishing the linear relationship between mannitol dose and brain relaxation. In clinical practice, mannitol has been used for brain relaxation with various dose ranges between 0.2 g/kg and 1.5 g/kg. Quentin et al.1 reported that the incidence of satisfactory brain relaxation was 55% after administration of a 0.7-g/kg dose of mannitol. In our study, the incidence of satisfactory brain relaxation was 52% after administration of a 0.5-g/kg dose of mannitol and 68% after a 1.0-g/kg dose of mannitol. Therefore, we
believe that administration of 1.0-g/kgmannitol may be preferable to 0.7 g/kg in terms of the incidence of satisfactory brain relaxation. However, increased mannitol dose was associated with increased adverse effects. Therefore, when using mannitol in clinical practice, the balance between benefits and risks should be considered.

With respect to the effect of age on mannitol dose, we agree that the safe dose of mannitol for producing satisfactory brain relaxation is likely to be different in young and old patients with a similar volume of tumor. In our study, the factor of age was initially not considered because of randomization for group assignment. However, in a subgroup analysis, there was a positive linear relationship between the mannitol dose and the proportion of patients with satisfactory brain relaxation (p = 0.008) in 106 patients 40 years of age or older (but not in 18 patients younger than 40 years). In addition, there were no significant differences in the tumor volume and midline shift distance among 4 different mannitol dose groups. As Dr. Mahalangikar and colleagues indicated, brain atrophy is normally observed with aging, especially after the age of 40 years. Therefore, the extent of brain fullness in the cranium may differ between young and elderly patients. The effect of age on mannitol dose would be an interesting topic for further studies.

With regard to the method for assessing brain relaxation, we totally agree with the authors’ opinion that the 4-point scale assessment for brain relaxation is a subjective method and can be a source of bias. We clearly described this pitfall in the limitations section of our article. Inadvertent durotomy during craniotomy can cause cerebrospinal fluid leak, leading to a disturbance in assessing mannitol-induced brain relaxation, but there were no instances of inadvertent durotomy in our study.

On the issue of tumor pathology and location on mannitol dose, unfortunately, these factors were not discussed in our study because the type and location of tumors were similar in each group. However, the pathology, mechanism of peritumoral edema, and surgical approach are substantially different in intra-axial and extra-axial tumors. Therefore, the suggestion that the adequate dose of mannitol for brain relaxation may be dependent on the pathology and location of brain tumor seems reasonable. In our subgroup analysis, only 66 patients with extra-axial brain tumor showed a positive linear relationship between the mannitol dose and the proportion of patients with satisfactory brain relaxation (p = 0.012), suggesting that further research may be needed to investigate the relationship between tumor pathology and location and mannitol dose.

Finally, Dr. Mahalangikar and colleagues seem doubtful that 1 g/kg is the optimal dose of mannitol for satisfactory brain relaxation in patients undergoing craniotomy for supratentorial brain tumors and is associated with the fewest complications. Mannitol relaxes the brain in a dose-dependent manner. 1-4 Similarly, our study showed an increasing trend in the brain relaxation score with the incremental dose of mannitol, but there was no significant difference in the proportions of patients with satisfactory brain relaxation among the 0.5-g/kg, 1.0-g/kg, and 1.5-g/kg mannitol groups. These findings may be due to the small sample size, because the sample size was calculated to observe a linear trend in proportions of patients with satisfactory brain relaxation among 4 different mannitol dose groups. A large-scale prospective study is required to verify a significant difference in the proportion of patients with satisfactory brain relaxation among 4 groups. In our study, the incidences of serum osmolality gap and electrolyte imbalances were increased with increasing dose of mannitol, particularly in the 1.0-g/kg and 1.5-g/kg mannitol groups. Moreover, the osmolality gap was still higher in the 1.5-g/kg mannitol group than in other groups at 180 minutes after the end of mannitol administration, which might increase the risk of nephrotoxicity with mannitol. The incidences of moderate hyponatremia (a serum sodium level of at least 125 mmol/L but less then 130 mmol/L) and the serum potassium levels were significantly higher in the 1.5-g/kg mannitol group than in the 1.0-g/kg mannitol group. Therefore, we suggest that 1.0 g/kg of mannitol may be the optimal dose for satisfactory brain relaxation with the fewest complications.

Hyungseok Seo, MD, PhD
Dankook University Hospital, Cheonan, Korea
Ho-Geol Ryu, MD, PhD
Hye-Pyoung Park, MD, PhD
Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

References

Unilateral or bilateral drainage for chronic subdural hematoma

TO THE EDITOR: We read with keen interest the article by Andersen-Ranberg et al.1 (Andersen-Ranberg NC, Poulsen FR, Bergholt B, et al: Bilateral chronic subdural hematoma: unilateral or bilateral drainage? J Neurosurg [pub ahead of print July 8, 2016. DOI: 10.3171/2016.4.JNS152642]). In their study of 291 patients with bilateral chronic subdural hematoma (bCSDH), the authors identified 264 patients who underwent unilateral or bilateral surgery for chronic subdural hematoma (CSDH). They concluded that patients treated with unilateral...
eral surgery had twice the risk of retreatment as compared to patients who underwent bilateral surgery. The authors have added a valuable contribution to the management of bCSDH, the management protocol of which is not clearly defined.

The authors have rightly pointed out that in cases of bCSDH, surgical intervention may be difficult and risky on the side with thin CSDH because the distance from the dural surface to the cortex may be small. Under such circumstances, we suggest surgical intervention for the side with the larger volume of hematoma for which the patient is symptomatic and a trial of steroids for the side with the lesser volume of hematoma, especially in patients with thin hematomas that may not be amenable to simultaneous surgical intervention. In their study of 26 patients, Thotakura and Marabathina were able to manage 11 cases successfully with steroids. Steroids act by decreasing or inhibiting the inflammatory pathway, which is believed to play a role in enlargement of CSDHs. A 2012 systemic review of the role of steroids in the management of CSDH found 5 observational studies that provided Class III evidence regarding the beneficial effects of steroids in the management of CSDH. In reporting on their randomized controlled trial (RCT) on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation, Chan et al. concluded that steroid therapy with surgical drainage was associated with a lower rate of recurrence requiring reoperation, although the difference was not statistically significant. A study is warranted in order to explore this option, which can be of immense use in caring for patients with bCSDH.

Chinmaya Dash, MCh
Raghav Singla, MBBS
All India Institute of Medical Sciences, New Delhi, India

References

Disclosures
The authors report no conflict of interest.

Response
We thank Drs. Dash and Singla for their interest in our paper. We understand that the proposed approach is to treat the larger hematoma with surgery and the smaller hematoma not suitable for surgery with corticosteroids.

In theory, the effect of steroids on CSDH is probably the same, whether the hematoma is uni- or bilateral. A small number of studies have shown that corticosteroids might be beneficial in the treatment of CSDH, but there is no strong evidence to support this treatment yet. Therefore, treatment of CSDH with corticosteroids is an exception in our department. There is a recent suggestion that the side effects of corticosteroid treatment may be unacceptable even if there is a possible small advantage in terms of a lower recurrence rate.

We look forward to a full-scale RCT to investigate the role of corticosteroids further, and it may be that the results of such a trial can support the authors’ suggestion regarding the corticosteroid treatment of a thin hematoma in bCSDHs.

Nina Christine Andersen-Ranberg, MD
Kåre Fugleholm, MD, PhD
Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
Frantz Rom Poulsen, MD, PhD
Odense University Hospital, Odense, Denmark
Bo Bergholt, MD
Aarhus University Hospital, Aarhus, Denmark
Torben Hundsholt, MD
Aalborg University Hospital, Aalborg, Denmark

References

Is gender a factor in long-term outcomes after radiosurgery for vestibular schwannoma?

TO THE EDITOR: We read with great interest the article by Mousavi et al. in which the authors reported that hearing subclassification may predict long-term auditory outcomes after stereotactic radiosurgery (SRS) for vestibular schwannoma patients with good hearing (Mousavi SH, Niranjan A, Akpinar B, et al: Hearing subclassification may predict long-term auditory outcomes after radiosurgery for vestibular schwannoma patients with good hearing. J Neurosurg 125:845–852, October 2016). We appreciate the potential benefit of the hearing subclassi-
fication. However, we noticed that, although overall the percentages of female and male patients were similar (51% and 49%, respectively), the percentage of female and male patients in the subclasses showed a significant difference and ordered in the opposite direction. In female patients the percentages were 64%, 52%, and 39%, for Gardner-Robertson Classes I-A, I-B1, and I-B2, whereas in male patients the percentages were 36%, 48%, and 61%, respectively. We wonder whether the authors considered the gender influences on the subclassifications and the outcomes.

Gender difference in hearing loss has been well recognized. For example, recently Park et al. showed gender differences at hearing thresholds of 3 kHz, 4 kHz, and 6 kHz in a highly screened population. Most importantly, early study has observed significant sex differences in the presentation and size of unilateral vestibular schwannomas. Harun et al. reported that in their study male patients continued to have a borderline significant positive association with tumor size \( p = 0.066 \) and were 2-fold more likely to have hearing loss \( \text{OR} 2.082, 95\% \text{CI} 1.300–3.336 \) but were half as likely to have dizziness \( \text{OR} 0.501, 95\% \text{CI} 0.387–0.649 \) as were female subjects.

Although the question of whether there is a gender difference with regard to the use of SRS for vestibular schwannoma patients has not been studied, a gender difference has been reported for male versus female patients' perception of other procedures and their consequent usage. For example, Meira et al. reported that the use of hearing protection devices among women is positively influenced by their perception of a safe workplace. In a study performed in cochlear implant users to investigate their perception of a target voice in the presence of a competing talker of the same or different sex as the target, in implant-alone and bimodal conditions, Visram et al. reported that in both listening conditions the participants showed a benefit from target and competing talker gender difference.

The gender difference is always a complicated issue, but should not be ignored. We look forward to examining future solid data including subgroup analyses for the differences.

References

Acknowledgments
We thank all colleagues for scientific discussion and support from the University of Tennessee Health Science Center.

Disclosure
The authors report no conflict of interest.

Response
We thank Wang et al. for their interest in our study and for pointing out the significance of gender differences in hearing loss. They have correctly noted that Class I-A had a higher percentage of female patients compared to Classes I-B1 and I-B2. To account for this we had performed multivariate analysis with propensity score adjustment.

We have mentioned in the Results section that we performed patient matching to balance the covariates and to reduce potentially confounding effects. We performed multivariate proportional hazards regression analysis to correlate serviceable hearing preservation with several factors, including age and sex. Serviceable hearing preservation was significantly associated with the pre-SRS hearing class, younger age, and female gender. Through multivariate stepwise logistic regression analysis of Class I-A hearing status, we noted that female gender and young age were significantly more likely to be found in Class I-A. Sixty-four percent of patients in Class I-A were female, compared to 45% female \( p = 0.027 \) in the group with Class I-B hearing. Similarly, the mean age of patients in Group I-A was 44.4 years, compared to 50.8 years in Group I-B \( p = 0.001 \). To further study the role of gender and age, we constructed propensity scores accounting for the higher propensity of female and younger patients to have Class I-A hearing and then added it to the Cox proportional hazards model for serviceable hearing preservation. Our analysis showed that better pre-SRS hearing class (I-A) remained as the only significant factor associated with higher rates of serviceable hearing preservation following SRS \( p < 0.0001 \).