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. (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. 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. However, we have several concerns. First, using T2-weighted images to determine putaminal involvement, albeit the best sequence available, can introduce ambiguities. 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.

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. However, IDH1 mutated paralimbic gliomas shared many parameters with the purely insular gliomas with respect to growth patterns, survival, and microRNA profile. 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

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References

Disclosures
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 borders 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 MR imaging was well accepted in the identification of the involved regions of low-grade gliomas.2–4,6 Insular gliomas were defined as gliomas that mainly involved the insular area, which was in accordance with previous investigations on insular gliomas.17 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 oligodendrial gliomas and should be assessed only if the tumor exhibits components of oligodendroglialomas (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 oligodendrial 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.3

References

Mannitol for intraoperative brain relaxation

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