Rejection of WHO Grade III gliomas

TO THE EDITOR: We read with great interest the research by Fujii et al. (Fujii Y, Muragaki Y, Maruyama T, et al: Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI. J Neurosurg [epub ahead of print September 8, 2017. DOI: 10.3171/2017.3.JNS162383]) regarding extent of resection for WHO grade III gliomas. The article is well written, and the authors have demonstrated that extent of resection (EOR) of T2-weighted high–signal intensity lesions (T2-EOR) was one of the most important prognostic factors for patients with anaplastic astrocytoma (AA) and anaplastic oligoastrocytoma (AOA) and an especially significant survival advantage was seen with T2-EOR ≥ 53%. We highly commend the authors for performing this interesting study because these helpful results would be useful to make a balanced treatment decision planning to prolong patient survival. However, after a detailed analysis of this article, we would like to highlight 3 important issues that it raises.

First, 122 patients with newly diagnosed WHO grade III gliomas had undergone intraoperative MRI-guided resection during the period from March 2000 to December 2011. In the article’s Results section, however, it is unclear how many patients underwent a second reoperation for recurrent WHO Grade III gliomas after initial resection. It would be helpful to the reader to know whether reoperation for recurrent WHO grade III gliomas can improve overall survival. Unfortunately, there is no evidence to date that supports this hypothesis. However, there exists a relationship between reoperation and overall survival of patients with recurrent glioblastoma. In the report by Tully et al. of 204 patients with de novo glioblastoma, 49 patients (24%) with recurrent glioblastoma underwent reoperation, and the median overall survival in the reoperation group was 20.1 months, compared with 9.0 months in the no-reoperation group (p = 0.001), demonstrating that reoperation was associated with longer overall survival. Coburger et al. revealed similar results from their study of 170 surgeries for glioblastoma, showing that repeated surgery for recurrent disease has a beneficial effect on overall survival.

Second, the authors concluded that a significant survival advantage was associated with resection of 53% or more of the preoperative T2-weighted high–signal intensity volume in patients with AA and AOA. But if the tumor is located near an eloquent area, is it safe for resection of 53% or more of the preoperative T2-weighted high–signal intensity volume? Some studies indicate that intraoperative cortical and subcortical stimulation can be used to identify functional areas or tracts and to guide surgical removal of gliomas in eloquent areas. This approach may be able to maximize the extent of resection while minimizing the risk of permanent deficit. Furthermore, awake craniotomy as a special method can prevent motor deficits during the resection of gliomas adjacent to eloquent cortex. Ghinda et al. reported that combined awake craniotomy and intraoperative MRI was safe and efficient, allowing maximal safe resection of eloquent area gliomas with possible subsequent benefits in terms of overall survival and progression-free survival. However, what is the exact maximal safe resection for gliomas near eloquent areas? A few studies have indicated that a safe margin of 8 mm should be maintained between the limits of resection and the pyramidal tracts. So it was probably wise to tailor the resection of gliomas adjacent to eloquent cortex according to intraoperative electrophysiological investigation, manifestation of intraoperative tasks for awake surgery, and intraoperative MRI, rather than only resection of 53% or more of the T2-weighted high–signal intensity lesions.

Third, we noted that the authors did not analyze data from patients who simultaneously presented with $IDH1/2$ mutation and 1p/19q co-deletion. The authors concluded that T2-EOR was not significantly different in patients with AO at any cutoff value, which may be associated with 1p/19q co-deletions and response to chemotherapy. We wonder whether T2-EOR was also not significantly different for survival in patients with glioma with the $IDH1/2$ mutation and 1p/19q co-deletion? Kawaguchi et al. investigated the impact of gross-total resection (GTR) in their series of 124 patients with WHO grade III glioma. They found that patients with tumors with $IDH1/2$ mutation and 1p/19q co-deletion had better outcomes, and that GTR or lack of GTR had no significant effect on the survival of such patients. We expect that the authors further validated the relationship between T2-EOR and survival in patients with WHO grade III glioma with $IDH1/2$ mutation and 1p/19q co-deletion. This may influence therapeutic strategies and clinical decisions.

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eloquent region as ≥ 1 of the following areas according to previous studies: thalamus, hypothalamus, brainstem, and dentate nucleus. The authors report no conflict of interest.

## References

## Disclosures
The authors report no conflict of interest.

## Response
We thank Drs. Liu, Chen, and Chen for their interest and comments regarding our article. We would like to respond to the 3 issues they raised.

First, our further analysis demonstrated that 46 (37%) of the 122 patients with newly diagnosed WHO grade III gliomas experienced recurrence. Moreover, 16 (34.8%) of those 46 patients underwent a second reoperation for recurrence. Unexpectedly, the median survival after recurrence in those 16 patients in the reoperation group was 16.3 months, compared with 16.7 months in the 30 patients of the no-reoperation group (p = 0.97). According to these data, reoperation for recurrence was not a prognostic factor for overall survival and seemed to exert no influence on the threshold EOR for WHO grade III gliomas.

Second, with respect to tumor location, we defined the eloquent region as ≥ 1 of the following areas according to previous studies: internal capsule, basal ganglia, language cortex, sensory cortex, motor cortex, visual center, thalamus, hypothalamus, brainstem, and dentate nucleus.

This study included 59 patients (48%) who had tumors in an eloquent region, and the median T2-EOR in that group was 68.0%. Thirty-two (54%) of the 59 patients who had tumors in an eloquent region underwent awake craniotomy. The median T2-EOR in these 32 patients was 84.8%. These EOR values were higher than 53%, demonstrating that we achieved extensive resection even though the tumor was located in a radiological eloquent area. This is because, as described by Chang et al., radiological eloquent areas are not always discovered to be truly eloquent. We performed extensive resection only when the radiologically eloquent area was found to be “false-eloquent.” We agree with Dr. Liu that, regarding tumors in or near eloquent regions, surgeons should not pay excessive attention to high EOR and should resect as much tumor as possible with multiple modalities, such as awake craniotomy and functional mapping.

Third, as we mentioned in the paragraph on the limitations of our study in the Discussion section, this study lacked data from 23 patients (18.9%) concerning 1p/19q co-deletion, because that examination began in 2004 at our institution. Analyzing data from the remaining 99 patients (81.1%) for whom we had data on 1p/19q co-deletion, 41 patients had tumors showing IDH1 mutation and 1p/19q co-deletion and only 2 patients died. EOR had no significant effect on survival in this group because of the small number of events, as expected. These data are compatible with findings from previous reports regarding WHO grade II and III gliomas. We hope to report new data with molecular analyses in the future.

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## References

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