Reoperation for Recurrent High-Grade Glioma: Does Tumor Genetics Play a Role?

To the Editor:

We read with interest the systematic review published by Hervey-Jumper et al. The authors examined the role of reoperation in patients with World Health Organization grade III or IV recurrent gliomas. Of the 31 studies included in their analysis, 29 demonstrated survival benefit with reoperation for recurrence. Therefore, the authors concluded that, despite the selection bias, mounting evidence suggests a survival benefit in patients receiving a reoperation at the time of high-grade glioma recurrence.

We commend the authors for their comprehensive review of the available literature on a topic where large prospective studies do not exist and randomized controlled trials are impractical. However, we would like to point out that, among the 29 studies that showed survival benefit to reoperation for recurrent high-grade gliomas, only 5 directly compared the median survival of patients with recurrent high-grade glioma who underwent reoperation with the median survival of those who did not undergo reoperation. The lack of a proper control group makes it impossible for the other studies to conclude any survival benefit in patients who underwent reoperation for recurrent high-grade gliomas over those who did not.

In their review, the authors reported that age is not a contraindication to reoperation. A time interval of at least 6 months between operations and favorable performance status (Karnofsky Performance Scale score $>70$) are predictors of improved survival after reoperation. However, the authors were unable to comment on the role of reoperation in high-grade recurrent gliomas and its relationship to patient survival in the context of the recent advances in molecular genetics and metabolic imaging. Basic tumor biology may dictate which patients will benefit the most from reoperation when their high-grade gliomas recur.

Although no study in the literature has directly looked at the role of genetic alterations on patient survival after reoperation, numerous studies have compared the molecular genetics of primary malignant gliomas with their recurrences. Some studies have shown that $O^6$-methylguanine-DNA methyltransferase promoter methylation status in high-grade gliomas (particularly glioblastomas) changed when the tumor relapsed and this change was associated with survival after recurrence. Other studies demonstrated that methylation profiles were remarkably stable across glioma evolution, even in tumor recurrence. In oligodendrogliomas, both IDH1 mutation and 1p19q codeletion were associated with longer patient survival after recurrence. In other types of tumors, IDH1 was associated with patient survival but not malignant transformation.

In a study of 3 pairs of pediatric high-grade gliomas, the authors found a substantial rescue of ADAR2 editing activity in the relapsed tumor of the only patient showing prolonged survival. Similarly, parameters on positron emission tomography-computed tomography and proton nuclear magnetic resonance spectroscopy have been shown to either correlate with tumor progression or were strong predictors of survival in patients with recurrent malignant gliomas, sometimes even more predictive than traditional measures such as tumor volume on magnetic resonance imaging or Karnofsky Performance Scale scores.

Therefore, we suggest that the decision to reoperate and its effect on patient survival will become increasingly dependent on our understanding of tumor genetics. In the future, genome-wide studies on the transcriptional, translational, and epigenetic level will provide guidance for treatment choices of recurrent high-grade gliomas as we embark on the path to personalized cancer medicine.

Disclosure

This work was supported by the Natural Science Foundation of China (grant 81301988) to Dr Yang, and China Ministry of Education Doctoral Program Spot Foundation (grant 20130162120061) to Dr Yang. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1227/NEU.0000000000000666