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Editorial

Low-grade glioma

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The controversies surrounding the management of low-grade gliomas (LGGs) remain unresolved, particularly when it comes to the role of resection. Still, the results of the majority of careful retrospective reviews support radical resection and suggest that increased extent of resection is associated with longer-term survival. In addition, resection seems reasonable to reduce symptoms from seizures or mass effect, to provide a complete survey of the pathological content of the tumor, and to reduce the number of tumor cells available for progressive genetic change or therapeutic resistance. However, none of these rationales for resection is supported by indisputable evidence.

Despite this, the last few decades have produced an explosion of technological advances designed to enhance the neurosurgeon's ability to remove these tumors. Advances such as preoperative functional MR imaging, real-time stereotactic navigation, and intraoperative imaging all purport to provide the neurosurgeon useful tools in this regard. In this issue of the *Journal of Neurosurgery*, Chang and his colleagues from the University of California, San Francisco, report their experience using one of the oldest tools in the neurosurgeon's armamentarium—intraoperative electrophysiologic functional brain mapping—to better resect these tumors.[1] In contrast to the newest tools available today, this technique was developed and popularized by Foerster, Penfield and Jasper, and others starting more than half a century ago.[3] In this manuscript the authors retrospectively review the results in 281 consecutive adult patients with hemispheric infiltrative WHO Grade II gliomas who were surgically treated at their institution over more than 15 years. Patients with pilocytic or gemistocytic astrocytomas were excluded. Preoperative MR images were reviewed independently by 2 investigators who were blinded to patient outcome. Based on this review the patients' tumors were classified according to whether or not they infiltrated eloquent brain areas (precentral and postcentral gyri, the dominant hemisphere perisylvian language areas, and the basal ganglia, internal capsule, thalamus, and calcarine visual cortex, as shown in Fig. 2 of the article). Functional MR imaging was not considered.

The take-home messages in this manuscript are 4-fold. First, patients with tumors thought to be in eloquent cortex based on preoperative MR imaging had significantly shorter estimated overall survival ($p < 0.0001$) and progression-free survival ($p < 0.0001$). These conclusions survive the adjustment for other prognostic factors such as age, performance status, tumor histological type, and tumor size when subjected to multivariate analysis by Cox proportional hazards modeling. Second, in the subset of 127 patients who underwent intraoperative mapping, those found to have tumor that actually infiltrated eloquent cortex had a shorter overall survival ($p < 0.001$) but not a shorter progression-free survival ($p = 0.18$) than those whose tumors did not involve eloquent cortex. Third, it is clear from this manuscript, that we cannot rely on preoperative standard anatomical MR imaging to be certain that LGGs actually involve eloquent cortex. The authors advance a strong claim that intraoperative functional brain mapping can distinguish many patients in whom intraoperative brain mapping does not confirm eloquent cortex involvement despite the appearance on anatomical MR imaging. Finally, the authors report that the extent of resection was greatest in patients with tumors in noneloquent cortex and that in patients with tumors in eloquent cortex the extent of resection was greater when functional mapping was used than when it was not used. The authors conclude that the location of an LGG in eloquent cortex at the time of surgery is an important prognostic indicator. They further conclude that the delineation of eloquent cortex by intraoperative mapping maximizes tumor resection and can dramatically improve long-term survival. Given the authors' conclusions, we may wish to reconsider any decision not to operate on a patient simply because their tumor appears to involve eloquent cortex based on traditional anatomical criteria.

In the absence of a randomized controlled trial (RCT), which is unlikely to ever be performed in this context, the data provided by these authors are some of the best data so far supporting aggressive resection of LGGs and strongly suggest that intraoperative identification of eloquent brain areas may maximize resection. If we are convinced on the basis of previous reports in the literature that radical resection has a significant impact on the survival of patients with LGGs despite the lack of Class I

evidence, then the conclusions put forth by these authors are in line with our emerging thinking in this field. It is important to note, however, that inasmuch as each of the patients in the cases reviewed in this article underwent resection, the variable of resection was not directly evaluated. In fact, the variable being evaluated is the existence of tumor in eloquent cortex as defined by MR imaging and intraoperative mapping. Isn't the most defendable conclusion from this study then actually that patients with LGGs in eloquent cortex have a poorer prognosis? Still, in the absence of an RCT, this article is important in that it provides additional evidence that resection may benefit patients with LGG. Within that context, these authors use tried-and-true technology to provide us with an elegant means to optimize these patients' treatment.

While not an RCT, the study reported here is statistically sound, and much can be learned from the authors' techniques. First, all of the "survival curves" in this manuscript include data on "censored" patients—patients who have not reached the study end point. This allows a rigorous risk assessment at any point along the survival curve. In addition, the authors attempt to control for known prognostic factors in their multivariate analyses by using the proportional hazards model developed by Cox.[2] This does allow stronger conclusions in the background of patient heterogeneity. Finally, they control for the multiple statistical comparisons performed, even in their prespecified analyses. We must always remember that the definition of statistical significance at $p < 0.05$ is not magical. The p value represents nothing more than a probability value that the observed outcome has occurred by chance. When $p = 0.05$ it means that there is a 1 in 20 chance that the outcome has occurred by chance. As such, if 20 different analyses are performed, we would be almost certain to see one result that at least appeared to be statistically significant. These multiple comparison errors are most important to protect against when datasets become large and statistical power can outweigh reason. We must always remember that statistical significance itself only becomes important when the differences are clinically meaningful in magnitude, especially in large data sets; the differences the authors show here are large enough to be important to patients.

Placebo-controlled, double-blinded RCTs remain the gold standard for medical evidence. Unfortunately, application of this standard to evaluating treatment strategies in patients with LGGs is difficult for several reasons. The ability of RCTs to provide definitive answers depends primarily on the magnitude of the difference between 2 treatment arms and the period of time over which that difference will become evident. While many of us believe that the impact of radical resection on the outcome of patients with LGG may be large, others are less convinced. In addition, given the long-term survival of these patients, even without any intervention, the time required to see a treatment effect would be extraordinarily long. As such, a thousand or more patients might be required for such a trial along with a decade or more of follow-up. It is also important to note, however, that sometimes surgical manipulations have such a dramatic impact that fewer patients are required to demonstrate a clinically significant effect than might be expected. Take for example the RCT of surgery for temporal lobe epilepsy. In this trial, only 80 patients needed to be enrolled and randomized to provide definitive conclusions in favor of surgery.[4] An alternative to an RCT for LGG might be to conduct rigorously matched case-controlled studies, perhaps across institutions with different biases for treatment strategy. Thus, the task of evaluating various treatment strategies in patients with LGGs should not be abandoned.

In the end, regardless of whether one is convinced that resection of LGGs is efficacious or not, an important rationale for tumor resection these days, when it can be done safely, will be to provide additional tumor samples, whereby we can leverage the explosion of genetic informatics currently becoming available to more accurately and reproducibly predict patient prognosis and even someday precisely direct patient therapy.

References

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Response

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We would like to thank Dr. Sampson for his in-depth and thorough review. The impetus for this study arose from a simple observation that, despite the frequent and well-known invasion of eloquent brain regions by LGGs, remarkably few studies to date have actually considered this an important prognosticator affecting survival. We first reported this association in our UCSF LGG Scoring System,[2] and then validated it in an external multiinstitutional cohort.[1]

As Dr. Sampson points out, the majority of studies carried out in the modern era using quantitative volumetric measurements and multivariate analyses have demonstrated a survival benefit for greater extent of resection. Surgery in eloquent brain locations is considered by some to be particularly controversial, as the greater risks of creating a neurological deficit must be weighed against the potential survival benefits of resection.

Our current study critically extends our earlier observations by demonstrating that intraoperative functional mapping can powerfully improve survival estimates by de-

lineating those patients whose tumors truly are in eloquent areas while also maximizing the extent of safe resection. We show that presuming eloquence based on anatomical criteria alone results in smaller subtotal resections and therefore shorter survival; with intraoperative functional mapping with electrocortical stimulation, the opposite can be achieved. This is the first demonstration that mapping as a surgical adjunct can lead to a significant reduction in long-term mortality.

We should carefully consider eloquence in surgical decision making and adjust for it in future studies on the long-term prognosis of LGGs. Hopefully, more widespread use of intraoperative mapping as well as development of improved noninvasive preoperative imaging tools will assist with achieving this goal.

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