

Editorial

Glioblastoma and surgery

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Glioblastoma is the most common primary brain tumor in adults and also one of the most rapidly fatal tumors of the body. Decades of research on the treatment of this disease has only led to modest increases in patient survival. The current standard of care for primary glioblastoma at presentation consists of surgery, chemotherapy, and stereotactic radiosurgery. However, even with current gold standard treatment, these tumors eventually recur. At the time of recurrence there are no agreed upon treatment modalities. One treatment option is repeat resection of the tumor. Although surgery has been shown to lead to longer survival in primary glioblastoma at the time of presentation, its role in recurrent glioblastoma remains controversial and not well defined.

The study by Chaichana et al.³ presented in this issue is another attempt to tackle the question of whether reoperation for recurrent glioblastoma can increase survival. The authors analyzed the data from 578 patients with primary glioblastoma treated between 1997 and 2007. All of these patients underwent surgery for a primary glioblastoma and 39% underwent between 2 and 4 repeated operations for disease recurrence. The authors found an association between multiple resections and increased survival duration as measured from the time of diagnosis. Furthermore, the length of survival correlated with the number of reoperations. The authors conclude that patients with recurrent glioblastoma can experience longer survival with repeated resections.

This study is the largest one to date addressing the efficacy of repeated surgery in the treatment of recurrent glioblastoma. Nevertheless, it suffers from significant limitations. The reader is left with unanswered questions regarding the selection criteria for reoperation. In comparison to other series on recurrent glioblastoma, the rate of reoperation in this study is slightly higher than the 10%–30% rate reported in the literature,¹ suggesting a more aggressive treatment strategy. Furthermore, whereas the patients were monitored at regular time intervals for progression, it was not clear what factors were used to select patients for reoperation at the time of recurrence. For example, the authors show that patients who were

younger and higher functioning (Karnofsky Performance Scale score > 70) were more likely to undergo multiple resections. These 2 variables have been previously reported to have a positive influence on the outcome of reoperation,¹ making them potentially significant confounding biases. These issues render critical evaluation of the study difficult. Chaichana et al. attempted to control for this selection bias by utilizing a case-control design for which they are to be lauded. This analysis can partially account for selection bias, but it does not address the use of overall survival time from diagnosis as the primary end point of efficacy of the intervention. This is an example of survival time selection bias^{1,5} and it is the largest methodological problem with the study. Patients who live longer are more likely to receive the intervention (reoperation), which is then erroneously attributed to survival. Barker et al.² discussed this problem in detail and attempted to correct for it by using survival from time of recurrence to evaluate the efficacy of reoperation, rather than using time from diagnosis. Similarly, Hau et al.⁶ used the time to progression and survival time from progression as the time intervals used to evaluate the efficacy of reinterventions. Utilization of such time intervals would have strengthened the analysis of Chaichana et al.

The results and limitations presented in this study are shared by previous studies. Previous studies have described an association between longer survival after recurrence and reoperation.^{2,4,6,7,9} Barker et al.² found that there was a significant 19-week survival benefit for those patients undergoing immediate reoperation at the time of recurrence. However, after excluding patients who were likely not eligible for reoperation at the time of recurrence, the survival benefit was found to be 17 weeks and not statistically significant. To control for the effect of selection bias, they used propensity scores for reoperation to show that reoperation was a statistically significant predictor of longer survival after reoperation. Durmaz et al.⁴ found that reoperation had an effect on survival but that effect was not significant after multivariable analysis. Hau et al.⁶ showed a positive survival effect for reintervention, but they did not study the effect of reoperation separately from other forms of reintervention. Mandl et al.⁸ found that reoperation led to an increase in survival only when paired with other treatment modalities in their series. Helseth et al.⁷ found a survival benefit for repeated surgery but acknowledged that selection bias significantly limited their conclusion. Stark et al.⁹ found that reoperation was associated with longer survival from time of diagnosis in univariate analysis data from 267 cases.

In summary, the study by Chaichana et al.³ provides valuable data about the potential role of surgery in the treatment of recurrent glioblastoma but suffers from significant limitations. The authors demonstrate longer survival in patients undergoing reoperation, but the retrospective nature of the study and the failure to appropriately control for the “survivor treatment bias” limits the conclusions that can be drawn from the data. The role of reoperation in the treatment of recurrent glioblastoma will remain difficult to ascertain and will probably continue to be discussed on a case-by-case basis in tumor boards while we wait for an elusive and admittedly difficult-to-perform randomized controlled trial.

(<http://thejns.org/doi/abs/10.3171/2012.5.JNS12690>)

Disclosure

The authors report no conflict of interest.

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Response

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There has been a growing body of evidence that extent of resection, without causing an iatrogenic deficit, will

prolong survival in patients with glioblastoma.^{5,6} However, regardless of the extent of resection, these tumors will continually recur and patients will continue to have a poor prognosis. The question that plagues surgeons, oncologists, and families is whether to offer repeat resection, because nearly all patients with glioblastoma will inevitably experience recurrence and the risks of repeated surgery must be taken into consideration. We attempted to address this important clinical question by reviewing all patients who underwent primary glioblastoma resection at a single institution from 1997 to 2007. Five hundred seventy-eight patients with primary glioblastoma met the inclusion/exclusion criteria, and 354, 168, 41, and 15 patients underwent 1, 2, 3, or 4 resections, respectively. This study is the largest study to date to evaluate the role of repeated glioblastoma resection. Using multivariate proportional hazards regression analysis to control for already known factors of survival, log-rank analysis to compare survival curves, and case-control evaluation to minimize inherent surgical biases, we show that patients with an increasing number of resections had prolonged survival.

Shaikhouni and Chiocca raise some important and interesting issues. The reoperation rate in our series (39%) is higher than in previous studies (10%–30%).¹ Our institution has adopted an aggressive approach towards patients who present with recurrent glioblastoma. We believe that if a patient is a surgical candidate, repeat surgery may optimize a patient’s chances of improving symptoms, maintaining or improving quality of life, and improving response to adjuvant therapies. Our study shows that repeat surgery may also prolong survival.

In addition to a higher reoperation rate, Shaikhouni and Chiocca also note that our study may be subject to survival-time selection bias, in which patients who live longer are more likely to be offered repeat surgery. Another consideration for patients who survive longer is simply that the biology of these tumors is different and less infiltrative/proliferative, and as a consequence these patients will survive longer. While this is an obvious bias in any retrospective analysis, we have tried to minimize this bias by using multivariate proportional hazards regression analysis and case-control evaluation. In the multivariate analyses, we controlled for factors known to affect survival, namely younger age and improved neurological function. Moreover, we used case-control evaluation to try to select for identical populations among patients who had single and repeat surgeries. We believe that these measures have minimized this bias in order to draw the most accurate conclusions on the efficacy of repeated surgery given the nature of this retrospective study design. Lastly, Shaikhouni and Chiocca also identify several studies that have^{4,7} and have not found any advantages to repeat surgery.^{2,3} Our study, however, is different. Our patient population is much larger, and our study uses multivariate analyses, separates cohorts by number of resections rather than single versus repeat resection, and uses case-control evaluation.

Ultimately, we believe our findings offer useful insights into the role that repeat surgery has for patients with glioblastoma, and equally important, repeated surgery will hopefully make it into every case-by-case discussion in tu-

mor boards so that patients can benefit from repeated surgery if they are surgical candidates. We acknowledge that there may be an inherent bias associated with patient selection, in which patients who were offered repeated surgeries may have a propensity for better outcomes. However, we tried to create a uniform patient population by utilizing strict inclusion and exclusion criteria, thus providing more relevant information for patients undergoing repeat resections for glioblastoma. We included only patients who underwent nonbiopsy resection of active intracranial tumors. Furthermore, we performed multivariate analyses to control for potential confounding variables, which included disparate treatment regimens and factors associated with survival. We also performed case-control analysis to try to minimize these biases. Given these statistical controls and a relatively precise outcome measure, we believe our findings show that repeated resection may improve survival for patients with glioblastoma. However, to provide better data to guide clinical decision making, multiinstitutional prospective studies are needed in which other factors such as tumor types are taken into consideration.

Disclosure

Dr. Quiñones-Hinojosa serves as a consultant to Stryker.

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Please include this information when citing this paper: published online October 19, 2012; DOI: 10.3171/2012.5.JNS12690.