far no clear line within these diffusely infiltrating lesions separating worthwhile from futile and safe from unsafe, and clinical judgment is still necessary.

Conflict of interest statement. None declared.

Ole Solheim, Sasha Gulati, and Asgeir Store Jakola
Department of Neurosurgery, St. Olavs University Hospital, Trondheim, Norway (O.S.); National Centre for Ultrasound and Image Guided Therapy, Trondheim, Norway (S.G.); MI Lab, Norwegian University of Science and Technology, Trondheim, Norway (A.S.J.)

Corresponding Author: Ole Solheim, MD, PhD, Department of Neurosurgery, St. Olavs University Hospital, N-7006, Trondheim, Norway (ole.solheim@ntnu.no).

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Received 13 December 2013

doi: 10.1093/neuonc/not312

The need to continually redefine the goals of surgery for glioblastoma

The debate over how much to push the limits of surgical resection for malignant gliomas is not a recent controversy. The cost-benefit analysis about increasing survival with more resection at the expense of function has existed for decades. In 1928, Walter Dandy at the Johns Hopkins Hospital performed hemispherectomies for patients with glioblastoma (GB) and found that these tumors still recurred despite this aggressive resection.[1] Over the next decades, the debate continued and led to discussion whether surgical resection was any more effective than needle biopsy. Despite a Cochrane Review demonstrating that there were no well-designed studies to assess the benefit of surgical resection over biopsy,[2] Laws[3] and Buckner[4] in 2003 each independently showed that surgical resection was associated with prolonged survival for patients with high-grade gliomas.[3] This then led to the controversy if more aggressive resection provided better patient outcomes.

While we appreciate and respect the comments by Dr. Solheim and colleagues, we recognize that we did not do a good job explaining the reason for conducting our study. It goes beyond establishing volumetric thresholds for surgical resection of these difficult lesions to also giving hope to patients and health care providers caring for these patients and their families. It is about knowing that we, as health care providers, can do something to influence the course of this devastating disease. It dispels the notion that we need to accomplish 98% resection and, if this is not to be achieved, then we should just do a biopsy. This dichotomy of treatment has unfortunately been a misconception over the last decade in the United States and throughout the world. We recognize that GB is characterized by its ability to invade and infiltrate surrounding parenchyma, making curative resection difficult.[5] Elucidating the role that surgery can play in prolonging the lives of patients who suffer from this devastating disease has been a gradual progress. In 2009, we showed that patients who underwent gross-total resection (GTR) had better outcomes than near-total resection (NTR) and that patients who underwent NTR had better outcomes than subtotal resection (STR).[6] Moreover, we also showed that surgical resection is of benefit to the older patient population, where most of these individuals are only offered biopsies based on their age.[7] Similarly, Solheim and colleagues have shown that early resection of low-grade gliomas is associated with better outcomes than a watchful waiting approach.[8] The beneficial effect of surgery, however, is always tempered by the fact that causing an iatrogenic deficit is associated with worse outcomes independent of extent of resection.[9]

Despite these findings, the ability to truly evaluate the role of extent of resection requires volumetric analyses. Studies using volumetric analyses, however, are few and limited.[10,11] Lacroix et al. in 2001 examined 416 patients with primary and recurrent GB who were operated on from 1993 to 1999 and found that a threshold of 98% was needed to confer a significant survival advantage.[10] More recently, Sanai et al. in 2011 evaluated 500 patients with newly diagnosed GB who were operated on from 1997 to 2009 and identified a survival threshold of 78%.[11] We conducted our study to add to the literature and the ongoing discussion about this important issue since there are several aspects that remain unclear. First, there is a large discrepancy between the 78% and 98% resection thresholds established in these previous studies,[10,11] making it unclear which threshold is more accurate. Second, since residual volume (RV) and percent resection (EOR) can be different, it is unclear if RV is associated with outcome. Third, the patients from previous studies predate current standard of adjuvant care (temozolomide and radiation therapy), so the role of surgery in this more modern context remains unclear. As a result, we studied 259 patients who underwent nonbiopsy surgery of a newly diagnosed intracranial GBM from 2007 to 2011 and found that EOR

and RV were each independently associated with survival and recurrence. The minimum EOR and the maximum RV thresholds that were significantly associated with survival and recurrence were 70% resection and 5 cm^3, respectively.

Solheim and colleagues make several arguments. First, they question whether a biological threshold should not exist and whether established thresholds have clinical significance. Various thresholds have been established from previous studies.[10,11] Since patients with GB typically undergo radiation and chemotherapy, these thresholds may identify postoperative tumor volumes that are responsive to these adjuvant therapies. More importantly, our study, similar to that by Sanai et al.,[11] demonstrates that GTR does not have to be achieved at the risk of causing an irreversible deficit, as has been previously found.[10] Second, they argue whether EOR and RV can be dichotomized since resections that border these thresholds will be difficult to differentiate. We agree, and this is the reason why we first evaluated EOR and RV as continuous variables to first establish their independent importance. A more accurate threshold (and perhaps unnecessary as we recognize it) would require much larger patient numbers with a large distribution of percent resection, which can only be possible if a multi-institutional, multinational study were to be conducted. Lastly, they question the case mix used in our study. We tried to utilize a strict inclusion criteria to make the study population as uniform as possible. The majority of excluded patients were those with recurrent GBM who underwent needle biopsy, which have different biology and survival than patients who present and undergo surgical resection of a primary GBM.[12] Furthermore, patients with multifocal or multicentric lesions or infratentorial tumors, as well as patients lacking pre- and postoperative MRI imaging, were also excluded since their biology is also poorly understood, and they could have led to less accurate conclusions and assumptions.

We believe this study provides several useful insights. This study shows the potential benefits of increased EOR and decreased RV for patients with GBM as a continuous variable. This study establishes a 70% resection threshold, which is the minimum EOR associated with survival in our very clear and established series of selected patients. This volume threshold is lower than previous studies and shows that surgical resection is still important, even when GTR cannot be achieved. It may also reflect advancements in adjuvant therapies and guide us into a new era in which we should attempt to develop technology allowing us to remove more tumor safely. This study is also the first to establish the importance of RV, which may be more important than EOR. Collectively, this study provides useful information to help guide treatment strategies aimed at prolonging survival and delaying recurrence for patients with GBM.

Kaisorn L. Chaichana and Alfredo Quinones-Hinojosa
Department of Neurosurgery, Johns Hopkins University, Baltimore, Maryland (K.L.C. and A.Q.-H.)

Corresponding Author: Kaisorn L. Chaichana, MD, Department of Neurosurgery, Johns Hopkins School of Medicine, 1800 Orleans Street Zayed 6007B, Baltimore, MD 21287 (kaisorn@jhmi.edu).

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Received 24 December 2013, Advance Access publication 30 January 2014

doi: 10.1093/neuonc/not326