Glioblastoma (GBM) remains an incurable cancer; nonetheless, incremental gains in patient survival have been seen over the past few decades associated with improvements in surgical technique, use of combined chemoradiation, and the advent of novel antitumor technologies. For newly diagnosed GBM, there is a paucity of evidence generated from prospective, randomized clinical trials demonstrating a benefit from resection of enhancing tumor. Multiple retrospective studies have demonstrated that a more extensive surgical resection of the enhancing tumor component of the disease is associated with a longer survival.1–8 Whether using a resection percentage-based approach or more biologically relevant measurements of residual enhancing disease, these studies indicate that removal of the bulk tumor can be associated with 3 to 5 months of benefit.3,5,8 In select cases, removal of tumor-infiltrated tissue outside of the enhancing bulk tumor is associated with additional survival benefit.9 Furthermore, several novel investigational therapeutics (eg, vaccines, viral gene therapies) require extensive tumor debulking in order to provide sufficient material for generation of a tumor-derived vaccine, reduce the need for steroids, and/or provide time for viral replication to occur or an immune response to be mounted. In recognition of the benefit that can accrue from an extensive tumor resection, multiple tools and adjuvants have been developed to help neurosurgeons maximize their ability to remove enhancing tumor, including intraoperative use of conventional imaging modalities7,10,11 and use of novel tumor-specific fluorophores.9 Yet, not all patients can benefit from an extensive tumor resection, as involvement of eloquent and/or deep neurological structures, medical comorbidity, and diffuse disease (eg, gliomatosis cerebri) may introduce unacceptable levels of risk to the patient of neurological deterioration if the neurosurgeon does not exercise appropriate discretion.6 This body of evidence has led most neurosurgical oncologists to employ an approach of “maximally safe resection” for newly diagnosed GBM.

While it may logically follow that the same positive relationship between completeness of tumor resection and outcome should apply to recurrent GBM, there are additional concerns that need to be considered in the recurrent setting. Patients with suspected recurrent GBM have undergone cranial radiotherapy and likely systemic chemotherapy, both of which suppress immune system functioning12 and increase the chances of wound dehiscence and consequent infection. Patients with known GBM also are imaged frequently and many recurrences are radiographic in nature only, without obvious mass effect or clinical progression; surgical resection may not be needed as often to relieve symptoms related to mass effect, as is the case for surgery in the newly diagnosed GBM setting. With the demonstrably increased risk associated with surgery in the recurrent setting, we owe it to our patients, and to ourselves, to fully evaluate whether tumor debulking carries a meaningful clinical benefit.

DIRECTOR was an investigator-initiated, prospective clinical trial that randomized patients with recurrent GBM (first progression) to a rechallenge with 2 different dose-intensified regimens of temozolomide chemotherapy.13 While the overall trial results showed no meaningful difference in outcome between the 2 chemotherapy regimens, the study team recognized that they had a well-annotated dataset that would be valuable for addressing other questions, including that of the relationship between surgical resection and outcome in the recurrent GBM setting. For this retrospective analysis, the authors employed volumetric tools to examine the extent of resection (%) and residual tumor volume (cc) with secondary tumor resection and examined the impact of these variables on overall survival, progression-free survival, and quality of life.

Approximately two-thirds of the patients in the DIRECTOR trial underwent surgery prior to study entry, which provided a reasonably large subset for this analysis. Remarkably, there were no statistically significant differences in incidence of O6-DNA methylguanine-methyltransferase promoter methylation, KPS, tumor volume prior to surgery, steroid use, or time to first progression for patients who did or did not undergo surgery. It may be difficult to interpret the significance of this finding, as the investigators did not evaluate why patients did or did not undergo surgery prior to enrollment in the DIRECTOR trial; the decision as to whether a patient underwent surgery was made locally, prior to enrollment in the trial, and some of the nonsurgical patients might have been taken to surgery at other institutions involved in the trial. For patients who

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underwent surgery, complete resection of enhancing tumor (CRET) was achieved in about 68%, and the median residual tumor volume for the surgical group was substantially smaller than the median tumor volume at study entry for the nonsurgical patients. Surgery was well tolerated in this population, with only one complication that prevented continuation of protocol therapy—this is a remarkable result that speaks to the skill of this very experienced study team.

To evaluate the impact of surgery on outcome, the investigators evaluated the relationship between extent of resection and outcome for the surgical patients, as well as whether the outcomes were different for patients who did or did not undergo surgery. Similar to what has been observed in the newly diagnosed GBM setting, CRET was associated with improved postresection survival compared with incomplete tumor resection for the group that underwent any surgery. Compared with patients who did not undergo surgery at all, there were trends toward improved survival for patients who underwent CRET and, remarkably, worsened outcome for those who underwent incomplete resection; however, these comparisons were not statistically significant, likely due to the small size of the study. Furthermore, on multivariate analysis, CRET was found to be an independent predictor for postresection survival. Finally, the authors found that a strong relationship existed between the presence of enhancing tumor at study entry and survival, independent of whether surgery was performed. Taken together, these results further reinforce the concept that the presence of bulky, enhancing GBM tumor impacts negatively on patient outcome, and surgical resection of this component of the disease, even at recurrence, is an important element in the comprehensive treatment of patients with GBM.

References