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Editorial

# The value of extended glioblastoma resection: Insights from randomized controlled trials

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## BACKGROUND

The relationship between the extent of glioblastoma resection (EOR) and clinical benefit remains a critical question in neuro-oncology.[3,7-9,20] It is generally agreed that glioblastoma is intrinsically an aggressively infiltrative disease[1] and that microscopic total resection is not possible without significant morbidity.[11] What remains unclear is whether reduction of tumor burden enhances efficacy of subsequent chemo-radiation treatment. The extreme chemo-resistance of glioma cells have led some to speculate that any residual tumor will lead to fatality and that EOR is irrelevant.[4,5] In contrast, proponents of extended EOR point to data that suggest the therapeutic efficacy of chemotherapy is largely a function of tumor burden.[16,19] Resolution of this controversy remains elusive in the existing literature. Here, we provide pertinent datasets derived from randomized controlled trials (RCTs) as well as expert opinions on the matter.

## RANDOMIZED CONTROLLED TRIALS

The only prospective randomized study to directly examine the issue of EOR was reported by Vuorinen *et al.*[17] The authors randomized patients over the age of 65 years with radiographically diagnosed glioblastoma to either surgical debulking or stereotactic biopsy. Of the 30 patients enrolled, histologic diagnosis of malignant glioma was confirmed in 10 surgical patients (all glioblastoma) and 13 biopsied patients (4 anaplastic astrocytomas and 9 glioblastomas). The primary end-points of the study included overall survival and time to clinical deterioration. Preoperative Karnofsky Performance Status (KPS), age, tumor location, and tumor sizes were comparable between the two study arms. The median survival for the surgically treated patients was longer than that of the biopsy patients (171 days vs. 85 days, $P = 0.035$). This difference persisted after adjustment for tumor grades (HR = 2.621, $P = 0.042$). Surgically treated patients also had longer times to clinical deterioration than did the biopsied patients (105 days vs. 72 days, $P = 0.057$, grade adjusted HR = 2.8, $P = 0.049$). Limitations of the study were the small number of patients, the lack of details pertaining to postsurgical treatment, and the exclusion of younger patients.

There are five other randomized prospective trials that indirectly offer insight into the issue of EOR for glioblastomas.[10,13,16,18,19]

The first study was a multicenter, prospective, randomized trial designed to determine whether the use of 5-aminolevulinic acid (5-ALA) enhanced the EOR in glioblastoma patients.[13] Glioblastoma patients were enrolled only if the surgeon felt that

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gross total resection (GTR) was possible based on preoperative imaging. The primary end-points of the trial were: GTR on postoperative magnetic resonance imaging (MRI) (defined by contrast enhancing lesion <0.175 cc) and the 6-month progression free survival (PFS) (assessed by MRI). The randomized groups were comparable in terms of age, KPS, and tumor locations. Central reviewers of radiological outcomes were masked as to the treatment allocations. The frequency of GTR was higher among the 5-ALA group ($n$ = 139) relative to the conventional surgery group ($n$ = 139; 65% vs. 36%, $P$ < 0.0001). The 5-ALA group also exhibited improved 6-month PFS (6mPFS) relative to the conventional surgery group (6mPFS: 41% vs. 21%, $P$ = 0.0003). However, no difference in overall survival was noted between the two groups (median survival 15.2 months vs. 13.5 months, $P$ = 0.1).[14]

The second study was designed to evaluate whether intraoperative MRI guidance could enhance the EOR for glioma surgeries.[10] Patients were enrolled only if the surgeon felt that GTR was possible based on preoperative imaging. The primary end point of the study was the frequency of GTR (defined by contrast enhancing lesion <0.175 cc). Central reviewers of radiological outcomes were masked as to the treatment allocations. The randomized groups were comparable in terms of age, gender, and KPS. The frequency of GTR was higher in the intraoperative MRI group ($n$ = 24) relative to the conventional surgery group ($n$ = 25; 96% vs. 68%, $P$ = 0.0023). 6mPFS was also longer in the intraoperative MRI group relative to the conventional surgery group (67% vs. 36%, $P$ = 0.046). However, no difference was noted between the groups in terms of overall survival (median 202 days vs. 115 days, $P$ = 0.38).

The third study was designed to test whether the Gliadel wafer prolonged survival in patients with *de novo* glioblastoma.[19] In this trial, 240 patients were randomized to either 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) or placebo wafer at the time of surgical resection. The primary end point of the study was overall survival. The randomized groups were comparable in terms of age, gender, and KPS. The study reports a median survival of 13.9 months for the BCNU group relative to 11.6 months for the placebo treated group ($P$ = 0.03). *Post hoc* analysis revealed that median survival was improved in patients who received >90% tumor resection with the carmustine (BCNU) wafer placement intraoperatively (14.5 vs. 12.4 months, $P$ = 0.02) but not in patients with a partial resection (11.7 vs. 10.6 months, $P$ = 0.98).[19]

The fourth study was designed to test the efficacy of combined temozolomide/radiation relative to radiation treatment alone.[16] In this trial, malignant glioma patients (93% GBMs) were randomized to the two treatment arms. The primary end point of the study was overall survival. The randomized groups were comparable in terms of all demographic characteristics. The study reports a median survival of 14.6 months for the temozolomide/radiation group and 12.1 months for the radiation group. *Post hoc* analysis found that the treatment effect of temozolomide was significant in the resected groups (HR = 0.63, $P$ < 0.0001) but not among the biopsied patients (HR = 0.69, $P$ = 0.084).[15]

Another clinical trial, conducted by the Brain Tumor Study Group (69-01), was designed to evaluate the effectiveness of including BCNU in the treatment of high grade gliomas (grade III and IV).[2,18] In this trial, 303 patients (90% GBM) were randomized to receive either BCNU alone, BCNU with radiotherapy, radiotherapy alone, or supportive care only as adjuncts after surgery, with overall survival as the primary endpoint. The randomized groups were comparable in terms of age, gender, location of tumor, symptoms of tumor, amount of corticosteroid use, and extents of resection. The study reported improved median survival with BCNU treatment relative to supportive care alone (18.5 weeks vs. 14 weeks) but found no significant difference between combined BCNU and radiotherapy compared with radiotherapy alone (35 weeks vs. 34.5 weeks).[18] *Post hoc* analysis of 225 patients from the study revealed that the patients who had biopsy ($n$ = 12) had significantly worsened survival when compared with the patients who underwent bulk resection ($n$ = 213, $P$ = 0.01).[2] However, on step-wise regression analysis, a bulk resection was associated with survival only when the variable of treatment group was not included.

## A case against extended resection

"We need to get over our medieval tendencies to 'torture' the data until they confess…" Peter Warnke, University of Chicago.

The analysis of RCTs to determine the effect of EOR on clinical outcome in glioblastoma patients is a wonderful example of the triumph of strong beliefs over evidence. In cases with mass effect, surgical debulking is indisputable in terms of therapeutic benefits. For the remaining glioblastoma patients – and this group grows due to better diagnostic tools resulting in earlier detection – the situation is more complex than can be distilled from the literature. All RCTs in glioblastoma looking at the issue of EOR and overall survival have inherent statistical flaws reaching from low sample size[17] to elaborate data fitting by regrouping of data for a separate analysis (the *post hoc* dilemma). Even the determination of EOR is completely oversimplified in most studies. As shown elegantly by Kubben *et al.*,[6] postoperative assessment of residual glioblastoma volume is highly subjective and prone to observer bias as well as inter-observer disagreement. Further, any correlation between EOR and overall survival was *post hoc*, and this form of analysis is particularly prone to statistical artifacts. Multiple comparisons are

typically made in the *post hoc* setting, and these analyses rarely incorporate statistics that correct for multiple comparisons. Additionally, the *post hoc* subgroups are not randomized in the original study design. As such, both known and unknown prognostic variables are no longer balanced in the comparison groups. Finally, the original study design of RCT do not factor into consideration statistical power of the *post hoc* subgroup analysis. Thus, the sample sizes in the *post hoc* subgoups are rarely sufficient for statistical comparison.[12] Pertaining to EOR, an analogy can be drawn to the issue of radical mastectomy versus lumpectomy followed by radiation in surgical oncology. After hundreds of retrospective studies demonstrating the superiority of radical mastectomy relative to lumpectomy followed by radiation, this superstition of superiority, treasured by many heathen surgeons, was shattered by a few randomized trials. So, we need to get over our medieval tendencies to "torture" the data until they confess – if we want to truly answer the question what role extent of resection plays.

## A case for extended surgical resection

"It is unlikely that additional, large-scale prospective randomized studies are either necessary or practical in the face of such overwhelming evidence," Nader Sanai, Barrow Neurological Institute.

Decoding the glioblastoma extent of resection dilemma is less about the fallibility of human nature and more about the quality of the existing data. Technical and biological limitations inherent to glioma surgery may preclude classical randomized study design, but the current literature still strongly suggests a progression-free and overall survival benefit for newly diagnosed patients. Perhaps the clearest evidence to date comes from the 5-ALA Study Group,[13] whose multicenter randomized trial was powered to detect an improvement in progression-free survival (which it did). The case for an overall survival benefit associated with greater extent of resection is admittedly less direct, but high-quality, large-scale retrospective studies cannot be overlooked.[7,9] Taken together, the aggregate literature is clear in its current conclusion – reduction of tumor burden does help. Like the lumpectomy, radiographic resection of newly diagnosed glioblastoma is an essential first-step in modern neurosurgical oncology. As such, the radical mastectomy analogy is better applied to the emerging question of supra-total glioma resection.[22] Thus, it is unlikely that additional, large-scale prospective randomized studies are either necessary or practical in the face of such evidence, although comparable efforts within the recurrent glioblastoma population remain a logical next-step.

## Editorial summary

GTR and 6mPFS: There is Level 1 evidence[21] that GTR is associated with improved 6mPFS (from 36% to 65%) based on the 5-ALA RCT study.[13] Though the RCT by Senft *et al*.[10] also demonstrated improved 6mPFS in patients who underwent GTR, the trial was not designed with 6mPFS as a primary end point. As such, we consider this as Level II evidence.[21]

GTR and OS: While the RCT by Vuorinen *et al*.[12] demonstrated an association between GTR and OS, this study was limited in sample size. As such, we consider this as Level II evidence.[21] It is striking that GTR was consistently associated with improved OS in three independent RCTs,[14,16,19] though these associations were observed only in *post hoc* subgroup analysis. The association between GTR and OS reached statistical significance in two studies[16,19] and showed a trend toward significance in the third study.[14] The duration of the improved OS was consistently 2–3 months in all three studies,[14,16,19] suggesting that the benefit may be limited in most patients.

Overall Assessment: Since microscopic total resection of glioblastoma cells is not possible without significant morbidity, meaningful clinical impact of the resection fundamentally rests on whether the residual tumor (microscopic or macroscopic) will respond to the subsequent therapy. Insights from RCT reinforced this central principle, where the benefit of GTR is most evident in patients who responded to temozolomide or BCNU treatment.[16,19] However, it is currently impossible to accurately identify these responders. Since we should not strip any patients of the potential benefit of our surgical resection, the goal of surgical resection should remain GTR whenever this can be achieved without significant morbidity – for every patient. Future studies should be directed toward (1) developing molecular technologies that afford the identification of the patient subset most likely to respond to temozolomide treatment, because these patients are the ones most likely to benefit from a GTR; (2) assessing the quality of life in patients who underwent GTRs; and (3) understanding the economic and health impacts of the various adjunct technologies used to achieve GTR, including intraoperative MRI and cortical mapping.

## Solicitation of input

What are your thoughts on the matter? How strongly do you think RCT data justified extended glioblastoma resection? Please voice your thoughts by visiting http://neurosurgery.ucsd.edu/survey

The first hundred responses will be recorded and the results will be presented in a future issue. Select opinions may also be published.

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