Published in final edited form as:

J Clin Oncol. 2012 July 10; 30(20): 2437–2440. doi:10.1200/JCO.2011.40.6959.

Pushing the limits of glioma resection using electrophysiological brain mapping

P.R. Lowenstein, MD, PhD and M.G. Castro, PhD

In all affairs it's a healthy thing now and then to hang a question mark on the things you have long taken for granted.

Bertrand Russell

The manuscript by De Witt et al. in this issue of *Journal of Clinical Oncology* proposes that intraoperative stimulatory mapping to determine the location of eloquent brain areas during glioma resection provides increased volume of resection and is associated with reduced late severe neurological deficits (De Witt Hamer et al., *J Clin Oncol* 30:2559–2565, 2012). The report is based on a retrospective systematic meta-analysis of 90 publications describing 8091 glioma patients. As extent of resection and neurological status are two crucial predictors of longer survival in patients with glioblastoma, the authors propose that intraoperative surgical mapping should become part of the standard of care for resective neurosurgery of high grade brain gliomas.

The current standard of care for the treatment of high grade gliomas is neurosurgical resection, followed by radiation and chemotherapy. If tumors can be resected at all, the aim is for the resection to be as complete as possible. Radiation treatment has been standardized for some time now, and the current chemotherapy of choice is temozolomide given in various regimes that have been optimized over the last five years. As long term survival (>2 years) continues to be very low, experimental therapies are administered in tandem with the primary standard of care, or, upon tumor recurrence, which occurs in almost 100% of cases^{1–3}.

Two year survival of high grade glioma at highest complexity medical centers, with optimized standard of care is 38.4%, and median survival is 18–21 months⁴. Longer term survival of the majority of patients continues to be an elusive goal. Predictors of long term survival continue to be classical clinical categories -younger patients (<35yrs of age), with high KPS at presentation, and a tumor which in principle is susceptible to complete neurosurgical excision-. Even in these cases 5 year survival remains below 5%.^{3,5–7}

Whether glioma tumors could ever be cured by surgical resection alone remains anecdotal. Historical classical reports attempting major heroic surgical resections, including hemispherectomies failed to cure patients^{8,9}. Together with the serious consequences of removing eloquent areas of the brain, the neurosurgical consensus shifted to removing as

much tumor as possible –complete resection of tumor visualized on MRI, without damaging eloquent areas of the brain, i.e., those areas involved directly in motor-sensory control, language, vision, and memory functions^{10–16}.

In spite of their clinical importance, there have been no prospective clinical trials evaluating the survival benefits of the extent of surgical resection. Instead, detailed retrospective studies have provided substantial evidence that the extent of tumor resection does provide a measurable survival benefit in high grade gliomas^{14,15,17,18}, as well as in low grade gliomas^{10,12,19–29}. Results published over the last years indicate that increased extent of tumor resection correlates with patient survival. These studies have indicated both the minimum amount of resection necessary to improve survival (i.e., 78%), as well as the improved survival when resection approximates complete resection (i.e., >98%)^{14,17,18,27,30,31}. Complete resection even appears to synergize with other measures of positive outcome as the benefit of increased resection was even stronger in younger patients. Equally impressive is the conclusion that the maximum possible extent of resection provides an increased survival comparable to that of temozolomide. Nevertheless standards of proof in novel clinical therapeutics would eventually require a prospective randomized trial to demonstrate beyond reasonable doubt the absence of potential sources of bias in the interpretation of retrospective multicentric data, i.e., to what extent the ability to safely resect larger tumor portions with clean margins is influenced by exact tumor location, smaller tumor size, better performance status, or even individual surgical skill and the particular genetic makeup of individual tumors -all important factors which risk challenging the intrinsic therapeutic value of aggressive surgical resection-. An example of the independent influence of the genetic makeup of gliomas on outcome is the strong beneficial effect of 1p and/or 19q chromosomal deletions and IDH mutations on survival of patients with low grade tumors.

The studies under discussion support the long held assertion that achieving complete resection in glioma has therapeutic benefit. They have also stimulated the development of techniques to overcome the limitations standing in the way of complete resection. A first limitation is the difficulty in visualizing the true anatomical borders of high grade glioma^{32–41}, which has led to the assertion that the exact identification of such borders during neurosurgical resections may be physically impossible. The justification for this statement is sought in the invasive nature of high grade gliomas, which renders it near impossible to identify an exact border zone.

At the histological level the potential border between tumor proper and normal brain is the zone of normal brain tissue that surrounds the tumor and which is being infiltrated to varying degrees by tumor cells. Precise identification of this border zone at the histological level also remains an outstanding challenge of glioma neuropathology, and resective neurosurgery^{33–41}. The lack of a unique cytological marker of glioma cells, availability of MRI-identified border zones available for histological study, and neuropathological methods that separate beyond doubt normal from neoplastic cells, has until now precluded a precise description and in depth neuroanatomical understanding of the tumor border zone.

A further clinico-pathological complexity is that in a very high percentage of cases tumors will recur within the tumor border “left behind” after the resection. A detailed neuroanatomical investigation and the establishment of MRI-histological correlations of the complex areas surrounding glioma tumors will be necessary to understand the nature of glioma infiltration of normal brain tissue, as well as the cellular mechanisms underlying glioma recurrence from marginal zones left behind after surgical resection. Nevertheless, as indicated by the clinical prospective correlations, increased resection improves survival, even if the maximum survival provided remains limited. These studies also support the development of improved visualization of tumor extent during neurosurgery, intra-operative MRI, 5-aminolevulinic acid-induced fluorescence, are likely to stimulate the search for improved ways of detecting tumor tissue remaining unresected during ongoing neurosurgery^{33–41}. Even if we accept that complete resection will not cure brain gliomas, the short overall survival of patients supports the development of better methods to resect as much of the tumor as possible.

The second main limitation standing in the way of complete resection is tumor infiltration of eloquent areas which is the main topic addressed by the paper under discussion. Eloquent brain regions are forebrain areas that play important roles in the control of movement, sensation, language, memory, or vision. Glioma tumors located within or close to motor-sensory cortex in the parietal lobe, the language areas in the temporal lobe, or areas of the brain involved in memory such as the hippocampus, or primary visual cortex, will limit the extent of neurosurgical resection. Though ablation of eloquent areas is surgically possible, the immediate post-surgical decline of the patient, added to the relatively small improvement in overall survival makes such resections impractical. Therefore, a precise delineation of eloquent brain areas located close to the tumors aims to improve extent of resection while preserving the function of eloquent brain areas, thus improving immediate post-surgical patient outcome. A particular challenge is the subcortical location of pathways relaying the information from eloquent brain areas to other brain regions. Their precise location and preservation constitutes a further limitation to optimal preservation of eloquent brain areas^{10–13,15,19–21,23–25,35,42–52}.

The manuscript by DeWitt et al. performed a detailed study of the neurosurgical literature encompassing 90 publications and 8091 patients operated on with or without intraoperative stimulation brain mapping. Such a study is crucial to determine whether currently utilized methods to delineate the location of eloquent brain areas are of use in improving the extent of resection while preserving the function of eloquent brain areas. As lesions (resections) of eloquent brain areas will lead to long term neurological deficits, the authors asked whether the use of intraoperative stimulation brain mapping effectively reduces long term neurological deficits.

The authors conclude that the use of intraoperative stimulation mapping increased the number of confirmed total resections from 48–69% (mean: 58%) without mapping, to 66–82% (mean: 75%) with mapping, and reduced the incidence of late severe neurological deficits from 5.7–11.4% (mean: 8.2%) without mapping, to 2.3–4.8% (mean: 3.4% when mapping was used. Also, eloquent locations were more frequent amongst the studies utilizing intraoperative mapping. The authors propose the universal addition of

intraoperative stimulation mapping to the standard of care for the neurosurgical excision of high grade gliomas. How well justified are these conclusions?

Several factors might have contributed to the variance observed in the results, including type of intraoperative mapping used (electrostimulation vs. evoked potentials); the geographical locations (North America vs. Europe); and whether the study was performed in an academic setting. Nevertheless, it is reassuring that the statistical analyses used by the authors were designed to control for such factors. Of clinical interest, the early severe deficits were observed more frequently in patients following resections that utilized intraoperative mapping (24.9–49.1%, mean: 36% when stimulation was used, vs., 5.9–20.2%, mean: 11.3% without stimulation mapping); however, as patients evolved, these resolved and late neurological deficits were substantially reduced in patients in whom intraoperative mapping had been used. It is likely that the procedure itself has side effects that interfere with normal brain function, the majority of which appear to be transitory.

As total resections increased with the use of intraoperative mapping, the advantages outweighed the disadvantages in a clinically relevant and significant manner. Furthermore, the value of intraoperative mapping of course increases when surgery will involve known eloquent brain areas, while it may be dispensable when operating on brain areas known not to contain eloquent areas.

The authors propose the adoption of intraoperative surgical mapping as standard of care in the neurosurgical treatment of high grade gliomas that are shown to involve potentially eloquent areas of the brain. Though this proposal is certainly supported by the authors' findings, a question remains regarding whether a prospective clinical trial should be performed preceding universal adoption of intraoperative mapping. A prospective trial would be justified since this is the gold standard of clinical translational science and is designed to overcome any biases in retrospective analysis. The shortcomings are also obvious. It has been difficult to perform surgical phase III clinical trials, as in many cases such trials will involve a comparison between complete resection and partial resection, or omit the use of intraoperative mapping in patients with tumors encroaching on eloquent brain areas, and therefore might not gain wide acceptance by physicians and patients who have a bias for one approach over the other. The alternative has been to perform large, careful, detailed prospective studies, and advances have been made both concerning the advantages of extent of resection 78%, and now the use of intraoperative mapping. As an alternative to Phase III trials it will be important that individual centers continue to monitor and evaluate in a prospective manner how the introduction of these techniques affects their ongoing neurosurgical outcomes.

In which directions will intraoperative mapping evolve? Future developments in mapping techniques and instrumentation and functional intraoperative imaging are likely to improve the general utility of intraoperative neurosurgical charting of eloquent brain areas. While at this time most mapping consists in an intraoperative study of the effects of transient cortical inactivation and the mapping of evoked potential from cortical areas predicted to affect motor or sensory behavior, it is likely that future mapping and life imaging technologies will permit the mapping of higher functions of the brain, such as memory functions sustained by

the hippocampus⁵³, or higher cognitive functions^{54,55}, such as those carried out by the frontal lobes^{56–59}. Equally, improvements in the mapping of subcortical pathways^{11,15,34,35,39,44,60} impinged upon by growing tumors will improve the capacity of neurosurgeons to increase resection while maintaining essential neuronal pathways^{44,60,61}. Detailed intraoperative mapping will eventually be combined with improved imaging technologies to explore the floor of the resection cavity in search of normal brain tissue infiltrated and thus already functionally compromised by the growing tumor.

It is likely that over the next decade neurosurgical techniques will be pushed to achieve the maximum possible resection in the majority of patients undergoing neurosurgical treatment for gliomas. As this goal is achieved it will be of great clinical importance to determine whether survival benefits provided by temozolomide will be sustained once complete resection becomes a routine goal. The same caveat will apply to other novel therapeutics, as currently age, general status of the patient, and extent of resection offer the best predictors for improved survival. How total resection's improved survival interacts with molecular subtypes of high grade gliomas^{62–70} will also have to be evaluated in the future.

As our intraoperative mapping capabilities move towards total brain mapping, we will also need to explore whether “supratotal” resections²⁵ ought to become a new neurosurgical aim in both low and high grade gliomas, i.e., to resect beyond identifiable tumor areas to eliminate as much as possible of the tumor border from where gliomas eventually recur. Such approaches will allow the detailed neuropathological study of the tumor resection cavity border to determine whether effectively this area contains the tumor cells that will originate tumor recurrence.

In closing we should remind ourselves that in spite of achieving the heroic goal of total resection in all surgical patients we need to continue to develop novel treatments. Complete resection and even supratotal resections will be unlikely to extend life much beyond currently obtained limits. As improved surgery allows a better and deeper analysis of brain gliomas, parallel advances in associated neuropathological, molecular, immunological and ultrastructural studies of tumor borders, the resection cavity and glioma infiltration, will improve our understanding on how brain tumors grow, disseminate and ultimately kill patients. It is our hope that these advances will reveal gliomas' Achilles heel, and thus help us improve the prognosis, and develop effective treatments that will improve the quality of life and achieve long term survival for patients suffering from currently lethal brain tumors.

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