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Intraoperative stimulation techniques for functional pathway preservation and glioma resection

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Although a primary tenet of neurosurgical oncology is that survival can improve with greater tumor resection, this principle must be tempered by the potential for functional loss following a radical removal. Preoperative planning with functional and physiological imaging paradigms, combined with intraoperative strategies such as cortical and subcortical stimulation mapping, can effectively reduce the risks associated with operating in eloquent territory. In addition to identifying critical motor pathways, these techniques can be adapted to identify language function reliably. The authors review the technical nuances of intraoperative mapping for low- and high-grade gliomas, demonstrating their efficacy in optimizing resection even in patients with negative mapping data. Collectively, these surgical strategies represent the cornerstone for operating on gliomas in and around functional pathways.
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Key Words • **language mapping** • **motor tract** • **cortical stimulation** • **extent of resection**

Central nervous system tumors are a major cause of morbidity and death, with ~ 18,000 new cases of primary intracranial tumors diagnosed each year in the US. This represents ~ 2% of all tumors found in adults in this country. More than half of these are HGGs. These lesions are extremely aggressive and the vast majority of patients invariably have tumor recurrence, with the median survival time ranging from 1 to 3 years after initial diagnosis. Despite facing a better prognosis when compared with higher-grade glial tumors, 50–75% of patients harboring LGGs eventually die of their disease. Median survival times have been reported to range between 5 and 10 years, and estimates of 10-year survival rates range from 5 to 50%.

Although a primary tenet of neurosurgical oncology is that survival can improve with greater tumor resection, this principle must be tempered by the potential for functional loss following a radical removal. Current neurosurgical innovations aim to improve our anatomical, physiological, and functional understanding of the surgical region of interest to prevent potential neurological morbidity during resection. Emerging imaging technologies, as well as state-of-the-art intraoperative techniques, can facilitate a greater extent of resection while minimizing the associated morbidity profile. Specifically, the value of mapping motor and language pathways is well established for the safe resection of intrinsic tumors.

Interestingly, controversy persists regarding prognostic factors and treatment options for both low- and high-grade hemispheric gliomas. Among the various tumor- and treatment-related parameters—including tumor volume, neurological status, timing of surgical intervention, and the use of adjuvant therapy—patient age and tumor histological characteristics have been identified as primary predictors of patient prognosis. However, location of the tumor in an eloquent area (Fig. 1) has recently emerged as another critical factor affecting outcome, particularly as it relates to tumor extent of resection.[10] Importantly, despite significant advances in operative technique and preoperative planning, the effect of glioma extent of resection in prolonging tumor-free progression and/or survival remains unclear. Although the value of glioma resection in obtaining tissue diagnosis and decompressing mass effect are unquestionable, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection. Even though LGGs and HGGs are distinct in their biological features, clinical behaviors, and outcomes, understanding the effect of surgery remains equally important for both. This is also true for lesions in areas of eloquence, where the proximity of critical pathways, often related to language and motor function, can present a significant challenge to standard operative strategies.

Abbreviations used in this paper: CS = cortical stimulation; DT = diffusion tensor; fMR = functional MR; HGG = high-grade glioma; LGG = low-grade glioma.

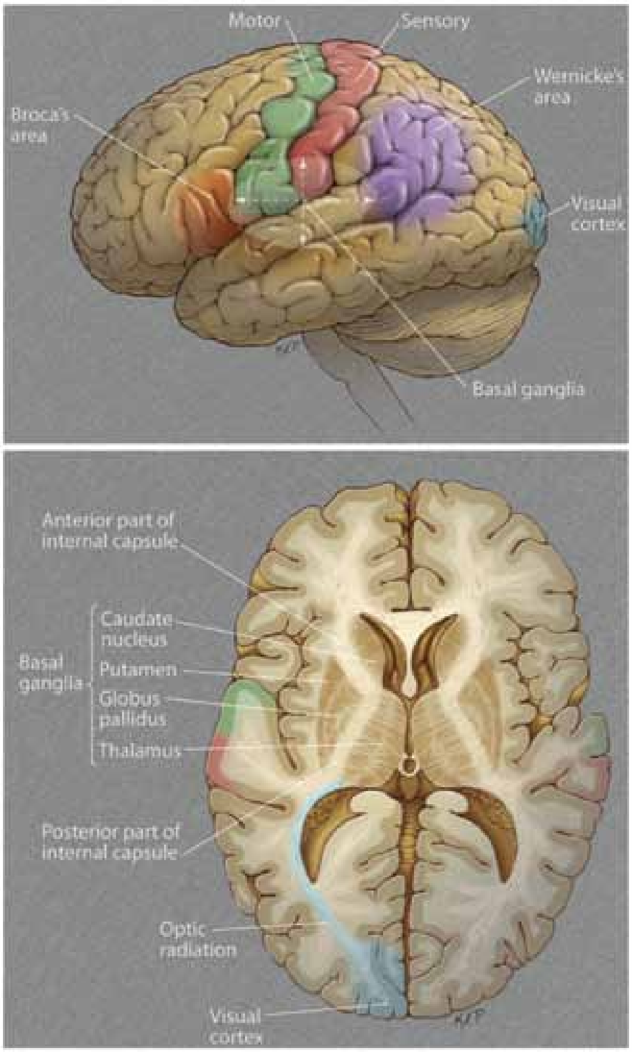

Fig. 1. Illustration of eloquent cortical and subcortical sites in the supratentorial compartment. (Reprinted by permission. Originally published in Chang et al.: Preoperative prognostic classification system for hemispheric low-grade gliomas in adults. **J Neurosurg 109:**817–824, 2008.)

Evolution of Cortical Mapping Strategies

Direct CS has been used in neurosurgery since 1930, first by Foerster,[26] and then later by Penfield and colleagues.[72–74] In recent years, the technique of intraoperative CS has been adopted for the identification and preservation of language function and motor pathways. Stimulation depolarizes a very focal area of cortex, which in turn evokes certain responses. Although the mechanism of stimulation effects on language are poorly understood, the principle is based on the depolarization of local neurons and also of passing pathways, inducing local excitation or inhibition, as well as possible diffusion to more distant areas by way of orthodromic or antidromic propagation.[85] Studies in which optical imaging of bipolar CS was used in monkey and human cortex have shown precise local changes, within 2–3 mm, after the activation of cortical tissue.[30,31] With the advent of the bipolar probe, avoidance of local diffusion and more precise mapping have been enabled with an accuracy estimated to be ~ 5 mm.[30]

Language mapping techniques were historically developed in the context of epilepsy surgery, in which large craniotomies exposed the brain well beyond the region of surgical interest to localize multiple cortical regions containing stimulation-induced language and motor function (that is, "positive" sites) prior to resection. Until recently, it has been thought that such positive site controls must be established during language mapping before any other cortical area could be safely resected. Using this tactic, awake craniotomies traditionally identify positive language sites in 95–100% of the operative exposures. Brain tumor surgery, however, is now evolving toward a different standard of language mapping, in which smaller, tailored craniotomies often expose no positive sites, and tumor resection is therefore directed by the localization of cortical regions that when tested contained no stimulation-induced language or motor function (that is, "negative" sites). This "negative mapping" strategy represents a paradigm shift in language mapping technique by eliminating the neurosurgeon's reliance on the positive site control in the operative exposure, thereby allowing for minimal cortical exposure overlying the tumor, less extensive intraoperative mapping, and a more time-efficient neurosurgical procedure.

Variability in Cortical Language Localization

Prediction of cortical language sites based on classic anatomical criteria is inadequate in light of the significant individual variability of cortical organization,[35,64,66,70] the distortion of cerebral topography from tumor mass effect, and the possibility of functional reorganization through plasticity mechanisms.[71,95,121] A consistent finding of language stimulation studies has been the identification of significant individual variability among patients.[64] Speech arrest is variably located and can go well beyond the classic anatomical boundaries of the Broca area for motor speech. It typically involves an area contiguous with the face-motor cortex, and yet in some cases is seen several centimeters from the sylvian fissure. This variability has also been suggested by studies designed to predict the location of speech arrest preoperatively, based on the type of frontal opercular anatomy[83] or by using functional neuroimaging.[15,43,94,105,111–113] Similarly, for temporal lobe language sites, one study of temporal lobe resections assisted by subdural grids demonstrated that the distance from the temporal pole to the area of language function varied from 3 to 9 cm.[14] Functional imaging studies have also corroborated such variability.[25] Furthermore, because functional tissue can be located within the tumor nidus,[102] the standard surgical principle of debulking tumor from within to avoid neurological deficits is not always safe. Consequently, the use of intraoperative cortical and subcortical stimulation to detect functional regions and pathways accurately is essential for safely removing dominant-hemisphere gliomas to the greatest extent possible.

Preservation of Functional Pathways by Using Intraoperative Stimulation Mapping

Intraoperative CS has yielded critical data regarding essential language sites, which seem to be organized in discrete mosaics that occupy a much smaller area of cortex than described by traditional language maps.[65,67,69] Interestingly, the majority of these language sites are surrounded by cortex that, when stimulated, produce no language errors.[68] In the temporal lobe, identification of speech areas within the superior and middle temporal gyri has been documented within 3 cm of the temporal lobe tip.[64] In this region, the distance of the resection margin from the nearest language site is the most important variable in predicting the improvement of preoperative language deficits. Accordingly, if the distance to the resection margin from the nearest language site is > 1 cm, significantly fewer permanent language deficits occur.[29] Strict adherence to this principle when operating in any region of the dominant hemisphere can substantially reduce the risk of inadvertently resecting functional tissue.

The Role of Functional Imaging for Eloquent Tissue Localization

Because the need to preserve cortical language function must be balanced with the goal of maximal tumor resection, intraoperative language mapping is advocated by some as the rule, rather than the exception.[108] The greatest risk of tumor recurrence is located within 2 cm of the contrast-enhancing rim on imaging studies,[37,117] supporting the concept that the resection should ideally go beyond the gross tumor margin apparent on preoperative imaging. However, because of the infiltrating nature of gliomas, it is more than likely that a portion of the mass will occupy, or be continuous with, functional tissue. Again, this emphasizes the need for CS mapping to avoid injuring these critical areas, particularly language pathways. Although it was classically thought that patients who were neurologically intact or minimally affected preoperatively had their functional pathways either displaced or obliterated by infiltrative tumors, we now know that normally functioning language, motor, or sensory tissue can blend with tumor.[102] Therefore, it is not only patients with tumors located within the frontal operculum who benefit from intraoperative language mapping, but also those with lesions in proximity to this region, because there is significant variability in this region's anatomical and functional organization.[23,83]

Functional imaging has advanced considerably in both technology and availability, raising the question of whether it may supplant intraoperative CS mapping. Devices such as fMR imaging, PET, and magnetoencephalography units may aid in the preoperative planning of the resection strategy, but these techniques remain too imprecise for complex functions such as language mapping: their sensitivity (PET, 75%; fMR imaging, 81%) and specificity (PET, 81%; fMR imaging, 53%) are suboptimal.[25,34] These modalities highlight language-associated areas of indeterminate significance,[7] and they do not offer real-time information intraoperatively. To this end, MR neuronavigational techniques not only facilitate greater resection, but embedding of DT imaging–based tractography can prevent inadvertent resection of adjacent subcortical pathways.[107,120] In a recent study of 238 patients with glioma who were randomized to DT imaging–based imaging versus traditional MR neuronavigation with DT imaging, postoperative motor deterioration occurred in 32.8% of control cases, whereas it occurred in only 15.3% of the study cases. Although the use of DT imaging–based tractography has not been shown to impact patient survival directly, the literature highlights the utility of this technology in maximizing tumor resection while minimizing morbidity. Nevertheless, for the identification of functional language pathways and guidance of safe tumor removal, these diagnostic imaging tools are still only supplements, not substitutes, for direct intraoperative stimulation mapping.

Current Intraoperative Language and Motor Mapping Techniques

In general, a limited craniotomy should expose the tumor and up to 2 cm of surrounding brain. Using bipolar electrodes, cortical mapping is started at a low stimulus (1.5 mA) and increased to a maximum of 6 mA, if necessary. A constant-current generator delivers biphasic square wave pulses (each phase, 1.25 msec) in 4-second trains at 60 Hz across 1-mm bipolar electrodes separated by 5 mm. Stimulation sites (~ 10–20 per patient) can be marked with sterile numbered tickets. Throughout motor and language mapping, continuous electrocorticography should be used to monitor afterdischarge potentials, and therefore eliminate the chance that speech or naming errors are caused by subclinical seizure activity.

Awake CS and Impact of Language Mapping

Speech arrest is based on blocking number counting without simultaneous motor response in the mouth or pharynx. Dysarthria can be distinguished from speech arrest by the absence of perceived or visible involuntary muscle contraction affecting speech. For naming or reading sites, CS is applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings or words, respectively. All tested language sites should be repeatedly stimulated at least 3 times. A positive essential site can be defined as an inability to name objects or read words in 66% or more of the testing per site. In all cases, a 1-cm margin of tissue should be measured and preserved around each positive language site to protect functional tissue from the resection.[49] The extent of resection is directed by targeting contrast-enhancing regions for high-grade lesions and T2-hyperintense areas for low-grade lesions. Some groups advocate the use of language mapping along subcortical white matter pathways as well.[19,21]

Despite the considerable evidence supporting the use of intraoperative CS mapping of language function, the efficacy of this technique in preserving functional outcome following aggressive glioma resection remains poorly understood. Nevertheless, it is important to define the long-term neurological effects after using this tech-

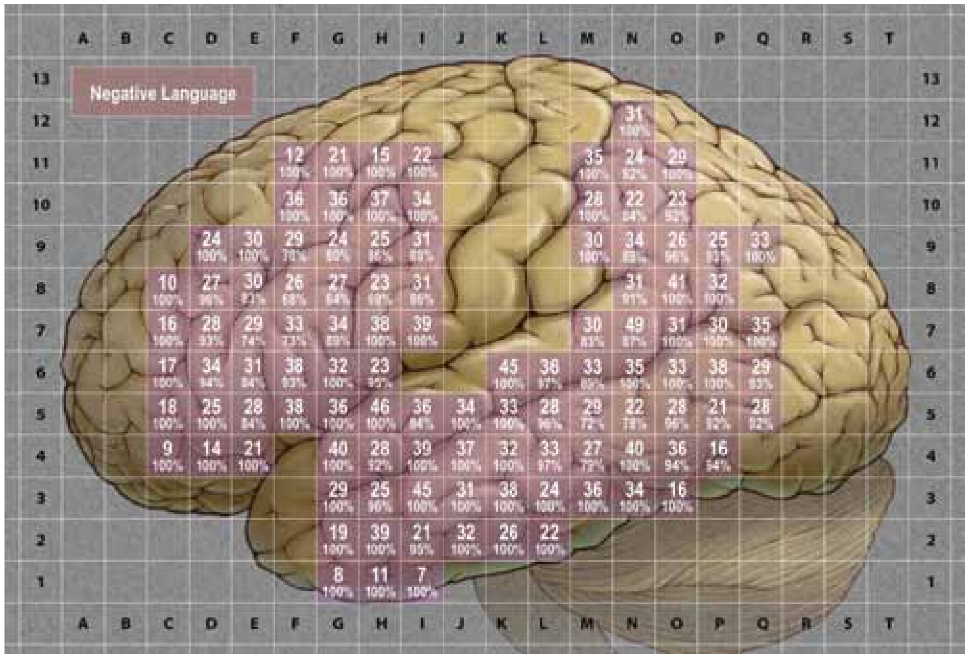

Fig. 2. Negative language map indicating the percentage of negative stimulations per square centimeter of the dominant cerebral hemisphere. (Reprinted by permission. Adapted with permission from Fig. 2 in Sanai et al.: Functional outcome after language mapping for glioma resection. **N Engl J Med 358:**18–27, 2008. Copyright © 2008, Massachusetts Medical Society. All rights reserved.)

nique for large, dominant-hemisphere gliomas to advocate its use accurately.[88]

Our experience with 250 consecutive patients with dominant-hemisphere glioma (WHO Grades II–IV) suggests that functional language outcome following awake mapping can be favorable, even in the case of an aggressive resection.[89] Overall, 159 of these 250 patients (63.6%) had intact speech preoperatively. At 1 week postoperatively, 194 (77.6%) remained at their baseline language function, whereas 21 (8.4%) worsened and 35 (14.0%) had new speech deficits. However, by 6 months, 52 (92.8%) of 56 patients with new or worsened language deficits returned to baseline or better, and the remaining 4 (7.1%) were left with a permanent deficit. Interestingly, among these patients, any additional language deficit incurred as a result of the surgery had either improved by 3 months or not all (Fig. 1). Thus, using language mapping, only 1.6% (4 of 243 survivors) of all glioma patients develop a permanent postoperative language deficit. One explanation for this favorable postoperative language profile may be our strict adherence to the "one-centimeter rule," first described by Haglund et al.,[29] which demonstrated that, for temporal lobe tumors, a resection margin of 1 cm or more from a language site significantly reduces postoperative language deficits.

Cortical and Subcortical Motor Mapping Techniques

For patients with gliomas that are located within or adjacent to the rolandic cortex, and thus the descending motor tracts, stimulation mapping of cortical and subcortical motor pathways enables the surgeon to identify these descending motor pathways during tumor removal and to achieve an acceptable rate of permanent morbidity in these high-risk functional areas.[8,20,47] In a recent study, new immediate postoperative motor deficits were documented in 59.3% of patients in whom a subcortical motor tract was identified intraoperatively and in 10.9% of those in whom subcortical tracts were not observed. However, permanent deficits were observed in 6.5% and 3.5%, respectively.[8] In another study of subcortical motor pathways in 294 patients who underwent surgery for hemispheric gliomas, 14 patients (4.8%) had a persistent motor deficit after 3 months. Interestingly, patients whose subcortical pathways were identified intraoperatively were more prone to develop an additional transient or permanent motor deficit (27.5 vs 13.1%).[47] In another study with an 87% gross- or subtotal resection rate, the overall neurological morbidity was 5% after using cortical motor mapping.[20] Thus, collectively the recent literature suggests that intraoperative cortical and subcortical motor mapping can safely identify corridors for resection, as well as define the limits of tumor resection.

Tailored Craniotomies and the Value of Negative Mapping

In contrast to the classic mapping principles practiced in epilepsy surgery, where 95–100% of operative fields contain a positive language site, a paradigm shift is emerging in brain tumor language mapping, where positive language sites are not always found prior to resection (Fig. 2). In our practice, because of our use of tailored cortical exposures, < 58% of patients have essential language sites localized within the operative field. Our experience suggests that it is safe to use a minimal exposure of the tumor and resect based on a negative language map, rather

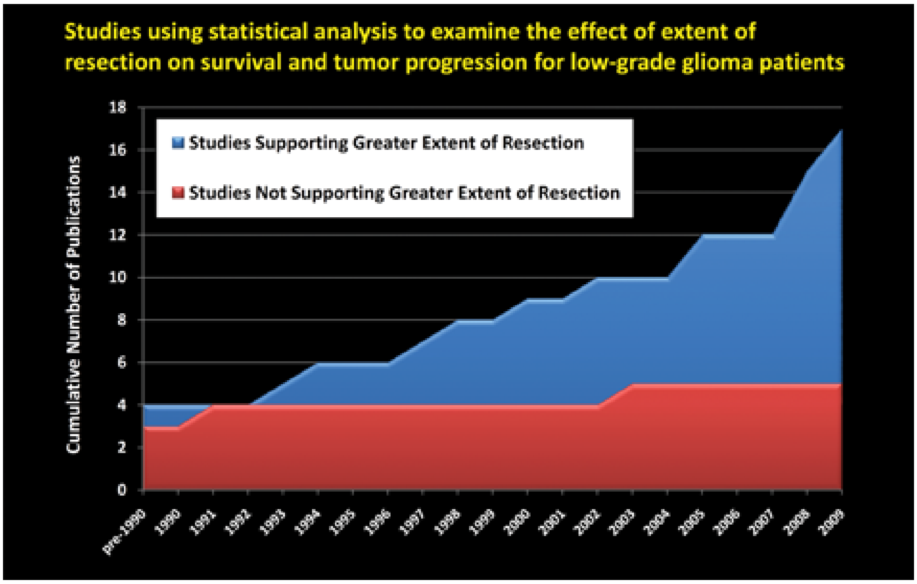

Fig. 3. Chart showing absolute number of LGG studies in the neurosurgical literature from 1990 to 2009 that statistically examined the effect of extent of resection on patient survival.

than rely on a wide craniotomy to find positive language sites well beyond the lesion. However, language mapping techniques such as this are generally more successful and safer at high-volume neurosurgical centers.

Negative language mapping, however, does not necessarily guarantee the absence of eloquent sites (Fig. 2). Despite negative brain mapping, permanent postoperative neurological deficits have been reported.[108] In our experience with 250 consecutive patients with dominant-hemisphere glioma, all 4 of our patients with permanent postoperative neurological deficits had no positive sites detected prior to their resections. Other cases of unexpected postoperative deficits have also been attributed to progressive tumor infiltration into functional areas.[3] Furthermore, both intraoperative stimulation and functional imaging techniques have provided evidence for redistribution of functional neural networks in cases of stroke,[11,95,118] congenital malformations,[54,56] brain injury,[27] and tumor progression.[24,95,121] Not surprisingly, it has been hypothesized that brain infiltration by gliomas leads to reshaping or local reorganization of functional networks as well as neosynaptogenesis.[18,109] This would explain the frequent lack of clinical deficit despite glioma growth into eloquent brain areas,[17,24,95] as well as the transient nature of many postoperative deficits. In the case of language function located in the dominant insula, the brain's capacity for compensation of functional loss has also been associated with recruitment of the left superior temporal gyrus and left putamen.[17]

Assessing the Value of Glioma Extent of Resection

Microsurgical resection remains a critical therapeutic modality for all gliomas.[4,28,45,122] However, there remains no general consensus in the literature regarding the efficacy of extent of resection in improving patient outcome.[32,36,60,78,81,87,92] With the exception of WHO Grade I tumors, gliomas are difficult to cure with surgery alone, and the majority of patients will experience some form of tumor recurrence. Patients with glioblastomas have median survival rates of 12.2–18.2 months,[33] whereas those with anaplastic astrocytomas can expect to survive 41 months, on average.[46] Low-grade gliomas carry a better prognosis, although the vast majority of patients eventually die of their disease and 5-year survival percentages range from 42 to 92% in the literature.[51,52,59,76,84,96,97,123]

For all gliomas, the identification of universally applicable prognostic factors and treatment options remains a great challenge. Among the many tumor- and treatment-related parameters, only patient age and tumor histological characteristics have been identified as reliable predictors of patient prognosis, although tumor location in an eloquent area and a patient's functional status can also be statistically significant. Surprisingly, despite significant advances in brain tumor imaging and intraoperative technology during the last 15 years, the effect of glioma resection in extending tumor-free progression and patient survival remains unknown.

Although LGGs and HGGs are distinct in their biology, clinical behavior, and outcome, understanding the efficacy of surgery remains equally important for each. With this in mind, an examination of the modern neurosurgical literature (1990 to present) reveals clues as to the role of extent of resection in outcome for glioma patients (Fig. 3).

Extent of Resection Studies for LGG

In the last 2 decades, mounting evidence in the literature suggests that a more extensive resection of an LGG is associated with a more favorable life expectancy (Fig. 3). In addition to providing longer overall survival, more aggressive resections for LGG can also influence the risk of malignant transformation, raising the possibility that a surgical intervention can alter the natural history of the disease.[87] These associations are evident not only within the population with general hemispheric LGGs,[9,103] but also for those with specific LGGs limited to specific eloquent subregions, such as insular LGGs.[90,100] An overall review of the modern neurosurgical literature reveals 23 studies[2,12,40,42,44,52,55,57,59,61,63,75,76,84,86,90,93,96,98,103,115,119,123] since 1990 that have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among patients with LGG. Six of these studies included volumetric analysis of extent of resection.[12,44,90,98,103,115] Of the nonvolumetric studies, 14 demonstrated evidence supporting extent of resection as a statistically significant predictor of either 5-year survival or 5-year progression-free survival. These studies were published between 1990 and 2009, and most commonly used a combination of multivariate and univariate analyses to determine statistical significance. Interestingly, of the 3 nonvolumetric studies that did not support extent of resection as a predictor of patient outcome, none of these reports evaluated progression-free survival, but instead focused solely on 5-year survival.

Extent of Resection Studies for HGG

Twenty-nine studies[1,5,6,13,16,22,38,39,41,45,46,48–50,53,58,62,77,79,80,82,91,99,101,104,106,110,114,116] since 1990 have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among patients with HGG. Four of these studies included volumetric analysis of extent of resection.[45,46,49,79] Of the nonvolumetric studies, 16 demonstrated evidence supporting extent of resection as a statistically significant predictor of either time to tumor progression or overall survival. Although some of these reports showed extent of resection to have a significant effect on both tumor progression and overall survival, every study showed a survival benefit. Ten studies, however, demonstrated no significant benefit based on extent of resection. Notably, the distribution of adjuvant chemotherapy and radiation treatment was comparable among all extent of resection studies for HGG. Echoing the nonvolumetric study results, half of all HGG volumetric studies showed a significant survival advantage with greater extent of resection.

Conclusions

Intraoperative stimulation for cortical and subcortical mapping is a reliable, robust method to maximize resection and minimize morbidity, even when removing gliomas within or near adjacent functional pathways. Unlike motor function, speech and language are variably distributed and widely represented, thus emphasizing the utility of language mapping in this particular patient population. Gliomas located in eloquent territories can displace predicted fiber pathways in unpredictable conformations. The combination of advanced imaging paradigms, such as neuronavigational DT imaging–based tractography, with intraoperative mapping techniques can best assure preservation of critical function. Using this approach, and in conjunction with standardized neuroanesthesia and neuromonitoring, the postoperative motor and language resolution profiles following glioma resection may be predictable. Specifically, in our experience, any additional language deficit incurred as a result of the surgery will improve by 3 months or not all. Our experience also emphasizes the value of negative language mapping in a patient with a tailored cortical exposure. Although the value of extent of resection remains less clear, the available literature for both low-grade and high-grade hemispheric gliomas demonstrates mounting evidence that a more extensive resection is associated with a more favorable life expectancy for patients with both LGG and HGG. This objective should be cautiously pursued for all gliomas, even those in an eloquent location.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: N Sanai, MS Berger. Drafting the article: N Sanai, MS Berger.

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