Use of Language Mapping to Aid in Resection of Gliomas in Eloquent Brain Regions

Matthew C. Garrett, MD, Nader Pouratian, MD, PhD,
Linda M. Liau, MD, PhD*

KEYWORDS

• Glioma • Brain tumor • Language mapping • fMRI • Electrical cortical stimulation

KEY POINTS

- Significant retrospective data exist to support the hypothesis that maximal safe resection benefits patients with glioma in terms of survival, accuracy of diagnosis, and response to chemotherapy.
- There are multiple modalities for preoperatively localizing eloquent language cortex and fibers, including anatomic landmarks, functional magnetic resonance imaging, and diffusion tensor imaging tractography.
- Considerable interpatient variation exists in the location of critical language areas. Thus, intraoperative cortical and subcortical electrostimulation mapping remains the gold standard.
- As our knowledge of human language function advances, our view of the brain will likely evolve from the identification of isolated areas of the cortex to a better understanding of integrated functioning circuits.

INTRODUCTION

It is thought that the cytoreduction of gliomas is a worthy goal and that adjuvant therapies (ie, radiation, chemotherapy, immunotherapy, and so forth) would be more effective with a smaller cell volume leading to delayed recurrence. However, studies looking at resection in high-grade gliomas have had mixed results.[1] Although there is a consensus that obtaining a histologic diagnosis and relieving compression and mass effect are worthwhile goals, the value of further microsurgical resection still remains controversial. This question becomes even more salient when considering a glioma located in eloquent areas, such as the language cortex. The risk of a postoperative language deficit in these surgeries has been reported to be as high as 26%.[2] Thus, the benefit of a gross total or near gross total resection needs to outweigh these risks. Although there is some inconsistency in the literature regarding the impact of the extent of resection on outcomes, an increasing number of reports of both low-grade and high-grade gliomas suggest that extensive resection is beneficial.[1,3,4] As such, it is imperative to use all available strategies to obtain safe and extensive resections to ensure that any benefits of further resection outweigh the risks. The authors briefly review the literature regarding the value of the extent of resection. They proceed to the preoperative and intraoperative tools available to the neurosurgeon to distinguish eloquent from noneloquent language cortex and fibers, including the emerging roles of functional magnetic resonance imaging (fMRI) diffusion tensor imaging (DTI) tractography and direct cortical/subcortical stimulation in the surgical management of tumors in eloquent areas. Finally, the authors evaluate the postoperative course of these

UCLA Department of Neurosurgery, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90096-6901, USA
* Corresponding author. Department of Neurosurgery, UCLA Medical Center, 10833 Le Conte Avenue, CHS 74-145, Los Angeles, CA 90095-6901.
E-mail address: LLiau@mednet.ucla.edu

Neurosurg Clin N Am 23 (2012) 497–506
doi:10.1016/j.nec.2012.05.003
1042-3680/12/$ – see front matter

neurosurgery.theclinics.com

patients and the effect of language deficits on their quality of life.

RATIONALE FOR EXTENSIVE RESECTION

High-Grade Gliomas

One of the earliest and most influential retrospective studies looking at the survival benefits of a gross total microsurgical resection for patients with glioblastomas was performed by Lacroix and colleagues[5] more than a decade ago. In this study, the investigators combined the results of 416 patients with newly diagnosed and recurrent glioblastomas and concluded that a 98% resection was associated with significantly improved survival. This finding has led to the all-or-none mentality that has existed over the last decade. This study, however, was designed to test whether complete or near complete resections had a survival advantage over biopsy and was not designed or powered to discover the threshold value whereby debulking had a survival advantage over biopsy. There were insufficient numbers of subtotal resections to perform this analysis.[1]

Since that time, there was an avalanche of case series attempting to quantify the benefit, if any, of subtotal resection. A recent review identified 28 studies between 1990 and 2007 that compared the outcome of patients with subtotal versus gross total resections.[1] Out of these studies, 16 demonstrated evidence that gross total resection was a significant predictor of overall survival or progression-free survival or both. Twelve studies, however, demonstrated no significant benefit based on extent of resection (EOR). The most quantitative study to date used compiled case series and Kaplan-Meier survival curve analyses, which suggested that a cutoff of 78% tumor resection provides a survival advantage.[4] However, all of these studies were nonrandomized and suffer from the same statistical confounder of selection bias. Despite some studies attempting to control for various tumor characteristics and baseline Karnofsky Performance Status (KPS), the fact remains that larger, more invasive, and difficult tumors in older patients with poor preoperative KPS scores are more likely to be subtotally resected, whereas younger patients with smaller tumors are more likely to get gross total resections.[6–8]

Low-Grade Gliomas

The evidence for extensive resection in low-grade gliomas (LGGs) is more persuasive than that for high-grade gliomas. LGGs differ significantly from their higher-grade counterparts in many important respects. A meta-analysis identified 10 studies investigating the benefit of resection in LGGs. Seven of the 10 studies found EOR to be a statistically significant predictor of survival. The survival benefit from gross total resection was approximately 30 months more than subtotal resection, with the average life expectancy increased from 61.1 to 90.5 months.[4,9] In regard to LGGs, although the question of when to observe versus intervene is still controversial, there exists consensus that once the tumor begins to show progression, the extent of resection does correlate with survival and all efforts should be made to obtain extensive resection. Besides the potential impact on survival, other compelling reasons exist for surgical resection, including the treatment of mass effect; potentially increasing the efficacy of adjuvant therapy; and, perhaps most importantly, increasing diagnostic accuracy.

Effect of Resection on Adjuvant Therapy

There is some indication in the literature that patients with extensive resection respond better to adjuvant therapy. There have been 2 prospective, randomized, phase 3 studies that have shown the efficacy of chemotherapy in patients with glioblastomas: one using carmustine (BCNU) wafers (Gliadel)[10] and one using temozolamide[11] in glioblastomas. In the case of BCNU wafers, the treatment was only significantly better than control in those patients who had a greater than 90% tumor resection. The increase in life expectancy was modest (14.8 vs 12. 6 months; $P = .01$) but significant. A similar trend was seen in the trial investigating the effectiveness of concurrent radiation and temozolomide following surgical resection.[11] Although this trial was not designed to examine the extent of resection and postoperative imaging was not mandated, patients were stratified into gross total resection (39%), partial resection (44%), and biopsy (16%). The survival advantage of radiation with concurrent temozolamide was greater in the gross total resection group (+4.1 months) than the partial resection group (+1.8 months) and was nonsignificant in the biopsy-only group (+1.5 months).

Diagnostic Accuracy

Finally, and perhaps most importantly, there is indisputable evidence that resection provides significantly superior diagnostic accuracy over stereotactic biopsy alone. Accurate diagnosis can be evasive when the histologic characteristics are heterogeneous. The grade of a glioma is defined by its most aggressive area, yet the tumor may still contain areas with less malignant features, which, if biopsied, may result in significant sampling and diagnostic error. Stereotactic biopsy series report a diagnostic yield of around 90%; however, a diagnosis made from such a biopsy cannot be confirmed unless the biopsy is followed by an extensive resection. In a series of 64 patients who had undergone stereotactic biopsy followed by a more extensive resection, Sawaya[2] found that the final diagnosis from resection was significantly different, leading to a change in therapy in 34 patients (53%). Further, as our ability to characterize gliomas on a genetic and molecular level increases, having more stored tumor may be vital to perform subsequent analyses and further personalized therapy.

Preventing Symptomatic Mass Effect

In patients who present with symptomatic mass effect, surgical resection is unequivocally indicated, even if the tumor involves eloquent areas. Prior studies have shown that gross total resections are associated with better patient neurologic performance scores than those observed after more limited resections.[12,13] Further, it is unusual for a large high-grade glioma with contrast enhancement to show a significant reduction in size after either radiation or chemotherapy, which, in some cases, requires the surgeon to perform a second surgery for symptomatic debulking.

PREOPERATIVE IMAGING FOR LANGUAGE MAPPING

Given the preponderance of evidence suggesting the importance of extensive resection, it behooves us to identify comprehensive strategies to safely resect gliomas without impairing eloquent function and quality of life. This point is particularly true when resecting tumors near or within canonical language areas. When planning surgery near perisylvian cortices in the dominant hemisphere, the localization of language cortices is of paramount importance in preventing postoperative deficits. The gold standard for locating essential language cortices has been electrical stimulation mapping (ESM). However, this technique is not without obstacles. Unlike intraoperative mapping of motor regions, patients must be awake and able to respond. This requirement leads to longer operative times, a higher chance of intraoperative seizures, and the potential for considerable patient distress. Moreover, awake intraoperative mapping is limited to those patients who have sufficient language ability and behavioral control to participate. Understandably, there is considerable interest in additional noninvasive modalities to identify patients in whom intraoperative awake mapping may be of low yield or not needed at all as well as means to make intraoperative mapping safer and more efficient.

Anatomic Considerations

It has long been recognized that the human brain has a stereotypical pattern of gyri and sulci. As early as 1980, Kido and colleagues[14] described the relationship between the posterior end of the superior frontal sulcus and the precentral sulcus. Similarly in 1997, Yousry and colleagues[15] described the omega sign as a method to identify the hand portion of the precentral gyrus.

It was initially hoped that this link between structure and function would provide surgeons with much-needed guidance to distinguish an eloquent from a noneloquent cortex. However, with advances in neuro-functional imaging, we are finding more interpatient neuroanatomical variability even among typical patients. For example, the aforementioned omega sign can either represent a primary motor or premotor cortex.[16] Other groups have also reported variability in the functional organization of the primary sensorimotor cortices. For example, within the precentral gyrus, the stimulation of individual cortical sites has been shown to recruit both sensory and motor phenomenon; in other cases, stimulation has been shown to recruit motor movements in more than 1 motor group.[17–19]

The language cortices are even more variable. While performing cortical stimulation mapping on patients with gliomas undergoing resection, Quinones and colleagues[20] found more than 4 cm of variability in the localization of speech arrest when using classical anatomic landmarks. This finding may be because the cortical representation of speech is more complex than the motor cortex, with multiple essential and nonessential speech areas throughout the frontal, temporal, and parietal lobes. Fortunately, although the location of essential speech areas is variable among individuals, once it is found it is typically small and discrete.[21]

However, the difficulty still remains in predicting where the essential language areas will be in any individual patient. Although it is difficult to positively predict where vital areas will be, it is easier to define where they will not be. Ojemann and colleagues[22] reported that the posterior inferior frontal region is essential in 79% of patients, whereas the anterior middle temporal gyrus is essential in only 5% of patients. In perhaps the most extensive study of intraoperative mapping, Sanai and colleagues[23] tested 3281 cortical sites in 250 patients. In the 151 patients in whom the frontal lobe was tested, only 92 (60.9%) had essential areas of language that were identified on ESM. Further subdividing the frontal lobe squares revealed that even the most prevalent areas only yielded speech arrest in less than 25% of the stimulations.

The presence of an intracranial neoplasm seems to further compound this variability. Intracranial lesions can affect functional localization in 3 ways. First, developmental and vascular lesions may affect how the overlying cortex develops and which functions it assumes. Two studies have noted a greater preponderance of right-sided language lateralization in patients with cerebrovascular malformations.[24,25] Further, in patients with left temporal lobe epilepsy, earlier age of onset has been associated with a greater likelihood of right-sided or bilateral language lateralization.[26,27]

Second, intracranial pathologic conditions can lead to functional reassignment. Developmental lesions, destructive injuries, and malignancies acquired in adulthood can all lead the brain to compensate by reassigning neurologic functions to other areas of the cortex.[28] Lucas and colleagues compared language maps in patients with acquired pathologic conditions (gliomas, subarachnoid hemorrhage, and traumatic brain injury) with age-matched controls and found significant migration of language function to the nondamaged cortex in the pathologic group. The best evidence for this phenomenon is that, in stark contrast to ischemic stroke, LGGs rarely present with acute neurologic deficits. In fact, language mapping of patients with LGGs demonstrate multiple patterns of reorganization and compensation.[29] Robles and colleagues[30] reported on 2 patients in whom maps of eloquent language cortices changed between surgeries spaced by several years, allowing a multistage surgical approach for the resection of LGGs in eloquent cortices.

Third, the effect of intracranial disease on the accuracy of the imaging modality is unclear, possibly leading to disease-related imaging artifacts. It has long been suspected that fMRI cannot be used to map eloquent cortices adjacent to arteriovenous malformations (AVMs) because AVMs may alter the perfusion-dependent response that fMRI relies on or because AVMs cause susceptibility artifacts that can interfere with the detection of the blood oxygen level–dependent fMRI response. To investigate this claim, the authors' group specifically tested the accuracy and reliability of blood oxygen level–dependent fMRI mapping in patients with vascular malformations and found that fMRI is highly sensitive and specific for determining language localization in patients with vascular malformations, even directly adjacent to these lesions.[31] In the authors' practice at the University of California, Los Angeles, it was found that relying on anatomic localization alone fails to identify up to 25% of the cases in which preoperative mapping (described later) suggested that awake intraoperative ESM mapping was necessary to achieve extensive resection.

fMRI

Recently, the use of fMRI has increased in prevalence. The use of the technology has expanded from simple language lateralization to specific language localization. fMRI works by detecting localized changes in blood flow and metabolism that is coupled to neuronal activity, such as during word language exercises. In contrast to ESM in which only essential cortices are identified, fMRI detects changes in all cortices (essential or not) that are activated during language tasks, resulting in an overly sensitive but nonspecific language map. A recent meta-analysis by Giussani and colleagues[32] identified 9 reports in the literature of case series in which patients with surgical lesions in the eloquent language cortex underwent preoperative fMRI followed by intraoperative electrocortical stimulation (ECS). Of the 9 studies cited, 5 of them computed a sensitivity and specificity of fMRI in comparison with ECS as a gold standard. The sensitivities ranged from 59% to 100% and the specificities ranged from 0% to 97%. The investigators stated that the varied methods and results used in these studies precluded any definitive conclusions about the utility of fMRI in preoperative planning. At this point, fMRI is not universally reliable and depends largely on the quality of the equipment and expert analysis and interpretation. Besides variability across institutions, the variability within a subject across cortices (frontal vs temporal vs parietal) is also not fully understood.

Despite its potential limitations, fMRI has been demonstrated at several institutions to be of value in identifying patients who require awake intraoperative language mapping and in identifying cortical regions that must be specifically interrogated intraoperatively for eloquence, thereby facilitating intraoperative awake mapping and making it more time efficient.

DTI Tractography

Gliomas often grow along white matter tracts in an infiltrative fashion. The method of DTI is a modification of diffusion-weighted imaging that is sensitive to the preferential diffusion of water along white matter fibers and can detect subtle changes in white matter structure and integrity.[33] Over the past 5 years, the authors have routinely integrated

DTI into the preoperative evaluation of patients harboring brain tumors (**Fig. 1**). This imaging modality can be used in a variety of capacities. For example, DTI can be used to differentiate normal white matter from edematous brain and nonenhancing tumor margins. More commonly, however, DTI has been used to evaluate the effect of intraparenchymal tumors on adjacent white matter tracts, including displacement, infiltration, and possible disruption by the tumor. Likewise, combined with functional imaging data (eg, fMRI), DTI has been used to identify the subcortical connections between essential eloquent cortices. This identification provides the surgeon with invaluable 3-dimensional information about spatial relationships of eloquent structures and their connectivity intraoperatively. It should be noted that DTI provides only anatomic and not functional information. Despite this limitation, the use of this technology can be useful in aiding the resection of tumors in the eloquent brain.[34,35] For instance, DTI, when combined with 3-dimensional intraoperative guidance, may be used to locate the pyramidal tracts in patients with insular gliomas or the arcuate fasciculus between the Broca area and Wernicke area.

INTRAOPERATIVE LANGUAGE TESTING AND ESM

ECS

Penfield introduced the method of direct cortical stimulation to assess motor function in the clinical setting in 1961.[36] Electric stimulation was delivered to the brain under local anesthesia to determine if there were any visible muscle contractions. Since that time, the awake craniotomy has become more sophisticated and allows the neurosurgeon to perform intraoperative electrical brain mapping with minimal risk (**Fig. 2**). Several studies have shown effective resection in eloquent areas previously thought to be inaccessible.[37–40] In a clinical case series by De Benedictis and colleagues,[36] the investigators reviewed the literature for 13 case series of patients with gliomas who underwent resection with intraoperative awake ECS mapping.[36] Of the 1460 patients reviewed, the severe permanent postoperative complication

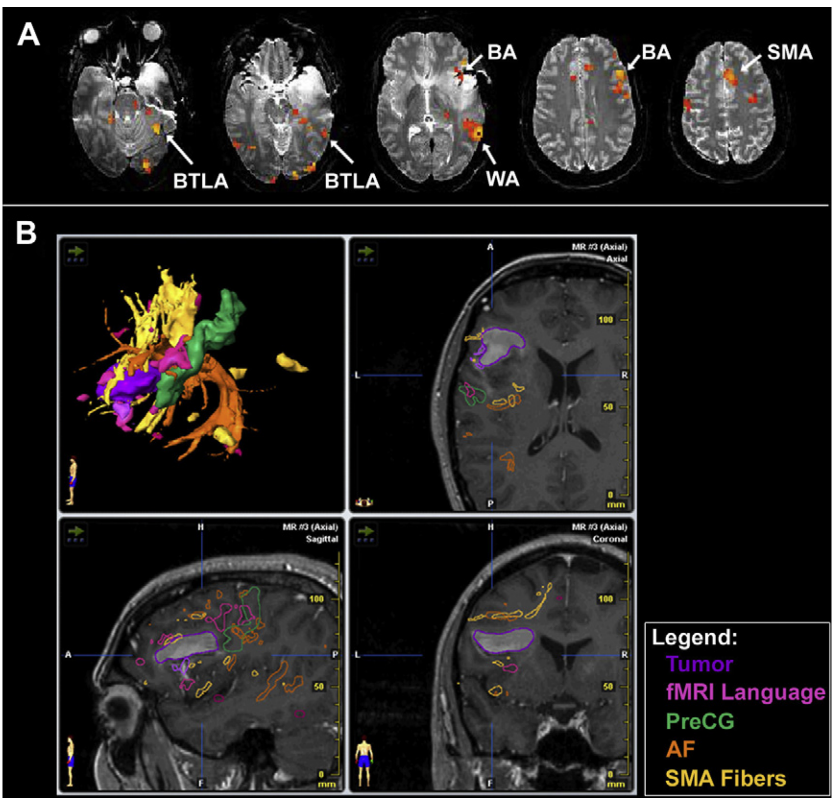

Fig. 1. fMRI and DTI tractography. (*A*) fMRI demonstrates areas of activation during language exercises. (*B*) Preoperative neuro-navigational imaging showing fMRI and DTI tractography fused to anatomic MRI to demonstrate important areas for intraoperative navigation. AF, arcuate fasciculus; BA, Broca area; BTLA, basal temporal language area; PreCG, precentral gyrus; SMA, supplementary motor area; WA, Wernicke area.

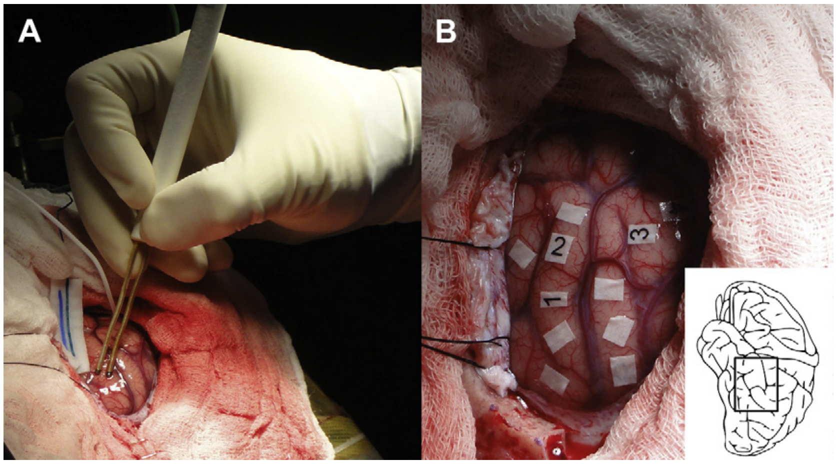

Fig. 2. ECS mapping. (*A*) Intraoperative photograph of ECS. (*B*) Results of intraoperative testing demonstrating essential (*letters*) and nonessential (*blank*) areas of cortex.

rate was 4.1% compared with a historical control of 19.0%.[41] Only 3 studies compared intraoperative mapping with traditional resection.

In the first of these studies, Reithmeier and colleagues[42] compared 42 patients who underwent ECS with 28 pair-matched controls who underwent resection between 1994 and 1997. The investigators noted a 14% incidence of postoperative deficit compared with a 29% incidence in the control group. In a study by Duffau and colleagues,[41] the investigators compared 100 patients with supratentorial LGGs undergoing traditional resection from 1985 to 1996 with 122 patients with similar tumors undergoing resection with intraoperative ECS mapping from 1996 to 2003 by the same surgical faculty. The investigators noted a 6% gross total resection rate and 17% severe permanent deficit rate in the control group compared with 25.4% and 6.5% in the awake intraoperative mapping group. In the third study, the investigators performed a re-resection using ECS on 9 patients who had undergone subtotal resections at another hospital for gliomas in the eloquent (defined as language or sensory motor) cortex. Five of the 9 patients were able to receive gross total resections. The investigators further noted that although only 6 of the 9 were able to work before surgery, all 9 were able to work after surgery.[43]

Negative Mapping

The first surgeries to use ECS mapping techniques were for epilepsy. These surgeries were typically done with large craniotomies to expose not only the region of surgical interest but also multiple other cortical sites involved in language production (positive sites). 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% to 100% of the operative exposures.[23] However, the current trend is toward the identification of negative sites in which smaller tailored craniotomies often expose no positive functional language sites. Tumor resection is, therefore, directed by the localization of cortical regions that, when tested, contain no stimulation-induced language or motor function, which has led to less-extensive intraoperative mapping and a more time-efficient neurosurgical procedure.[44]

Direct Subcortical Stimulation

In addition to the identification of eloquent cortical brain areas, there is increased interest in using intraoperative direct subcortical stimulation (DSS) to functionally identify critical and eloquent white matter tracts that also must be preserved. DSS is similar to ECS in that it is performed intraoperatively with a awake patients; but instead of stimulating the cortex, the underlying white matter at the depths of the tumor resection cavity are interrogated. Because of the increased time required for the mapping of subcortical structures (relative to that required just for cortical mapping), subcortical mapping is often limited with respect to the number of tasks that can be performed before patients become too fatigued to cooperate. As an application of this concept, Lang and colleagues[45] used DSS on a series of insular gliomas but asserted that the technique did not give sufficient warning for the surgeon to alter his or her technique but rather served to inform the surgeon of damage that was already done. It should be noted that the surgeons stated that the "subcortical stimulation was used infrequently during tumor resection."[45] As such, critical damage may have occurred in between stimulations. Regardless of this experience, ECS associated with DSS is a potentially useful technique for preserving function and has been used by several surgeons to establish functional boundaries of tumors to guide maximal and safe resections to minimize both residual tumor and postoperative deficits.[46]

Neuropsychological Testing

As our technology of functional mapping improves, so does our understanding of the neuro-functional organization of the ability to understand and produce language. This, in turn, guides our clinical use of neuropsychological testing. By studying patients with strokes and traumatic brain injuries, it is clear that the language system can be separated into distinct subfunctions that can be selectively damaged or spared during surgical resections.

Surgeons and neuropsychologists have traditionally focused on naming exercises during intraoperative testing. However, the use of language requires numerous subcategories of function: semantics, pronunciation, inflection, prosody, connotation, sublexical procedures, reading, and writing. Further, each of these subcategories can have varying degrees of dysfunction. For these reasons, a thorough preoperative neuropsychiatric language evaluation is crucial before any surgical resection in eloquent brain areas.[47]

The first goal of neuropsychological testing is to provide a baseline for intraoperative and all postoperative evaluations. At a minimum, these evaluations should include sublexical processing, semantic and lexical knowledge, syntax, verbal short-term memory, and the ability to process auditory and visual stimuli as well as produce written and oral responses.

The second goal is to identify the most critical and feasible tasks for intraoperative testing. The list of tasks tested intraoperatively should include those that are both likely to be at risk during the surgery and functional at baseline. In regard to the former, when approaching a lesion in the superior temporal gyrus, a phoneme-discrimination task or a word picture with phonological foils will be appropriate considering the role played by this region in speech perception.[48] In other areas, simple picture naming may be sufficient or naming may need to be combined with comprehension, such as pairing an object with its intended action or naming an object both verbally and in written form. Of note, the tested function need not be completely unimpaired. Making a preoperative deficit worse may be more devastating in some cases than causing a new postoperative deficit. Many language functions are not all-or-none phenomena but rather have different gradations of function. For example, a patient may have a mild lexical impairment for nouns (pure anomia). This type of deficit affects uncommonly used nouns more often that commonly used ones. Preoperatively, a list can be made of nouns that patients can name without error for use during the manipulation of suspected eloquent areas. Finally, the list of tasks must be defined and finite in length and performed in a reasonable amount of time so as to not excessively extend the operative time or cause patient fatigue.

Technical Considerations

The sensitivity and specificity of intraoperative language mapping also depends heavily on the neurosurgeon's skill. First and most simply, the intensity of the stimulation can affect the map produced. Low-intensity stimulation may be insufficient to affect the target, whereas high-intensity stimulation can excite neighboring areas, which leads to afterpotentials and false positives. Second, although most surgeons stimulate each area more than once, the number of stimulations differs among practitioners, as does the number and types of errors tolerated to define an essential language area. The electrical stimulation may produce an error at any of a variety of levels from simple dysarthria to true lexical semantic errors (tip-of-the-tongue states). Thus, the usefulness and benefit of intraoperative ECS and DSS mapping and, hence, the functional outcome of patients may vary depending on the experience of the surgeon with these techniques.

POSTOPERATIVE GOALS AND ASSESSMENT

The aim of any brain tumor treatment extends well beyond increasing survival. Palliation of symptoms and the maintenance/improvement of quality of life are important goals of any therapeutic intervention. Thus, the benefits of existing or new treatments need to be weighed against the side effects and possible impairment of patients' quality of life.

Aphasia and related language disabilities have wide-ranging impacts on the lives of those impaired and their families. These impacts can affect employment, social interactions, and familial roles regardless of how severe the linguistic impairment may be. Adults with aphasia and their relatives report numerous negative consequences of aphasia: changes in communication situations, changes in interpersonal relationships, difficulty controlling emotions, physical dependency, loss of autonomy, restricted activities, fewer social contacts, and recurring feelings of loneliness and despair.[49]

Surgeons tend to follow their patients throughout their inpatient course and for variable periods of time after discharge. As such, many surgeons may underestimate the potential for rehabilitation in the acute postoperative period. For many years, treatment of high-grade gliomas was considered palliative and neurologic rehabilitation was neglected. However, it is increasingly recognized that many patients who have undergone resection of gliomas in eloquent regions have significant functional impairment. Furthermore, these impairments can be responsive to rehabilitative physical, occupational, and speech therapy with corresponding improvements in functional status. Recently, studies have begun to compare the rehabilitative potential of patients with gliomas with those of patients who have had a stroke and found these two populations to be comparable in functional recovery.[50] Although many of these studies have used outcome tests that include language disturbances as a parameter, none have been sufficiently powered to look at language deficits specifically. Further outcome studies in the area of functional language recovery following glioma surgery are warranted.

Over the last several decades, neuroscientists and neurosurgeons have moved from a localizationist view of language in which language function was contained in discreet areas of neuronal cortex to an associationist view in which the visual and auditory linguistic information was processed in discreet cortical sites and then transported through subcortical white matter connections that are equally important.[51] As our white matter tractography imaging and DSS techniques improve and we are better able to map out and test functional connections, we may find that language follows a connectionist model, with multiple centers processing information in parallel. From Mesulam's large-scale neural network model of language in particular, it seems that there are 2 parallel pathways, the dorsal phonological stream and the ventral semantic stream, which converge to a common final tract allowing speech production.[52] Furthermore, the network is modulated by cortico-striato-pallido-thalamo-cortical loops. The next step to progress in the understanding of the brain connectivity might be a more accurate analysis of the interactions between the language circuit and the networks underlying the other cognitive functions, in particular the visuospatial component in which the role of the superior fronto-occipital fasciculus has been emphasized.[53]

The future neurosurgeon will need to be aware of how these different systems function in concert and identify which are peripherally involved with function versus essential to function. Additionally, neurosurgeons will need to understand and respect the role of subcortical structures and their associated connections because studies of stroke have taught us that lesions in the white matter can be significantly more damaging and debilitating than those found on the overlying cortex.[46]

SUMMARY

Although a clinical trial comparing biopsy with resection is not feasible, there exists sufficient retrospective uncontrolled evidence to conclude that a safe maximal resection will lead to the best outcome in most patients with glioma. A postoperative deficit in addition to an already debilitating disease can have serious and devastating consequences on a patient's quality of life. Identification and preservation of eloquent language regions in the brain are of critical importance to the neurosurgeon. As our understanding of the mechanisms of human speech and language expands, it is hoped that we will be better able to use current and future noninvasive imaging techniques to predict which areas of cortex and white matter are likely essential for speech production and language comprehension.

REFERENCES

1. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008; 62(4):753–64 [discussion: 264–6].
2. Sawaya R. Extent of resection in malignant gliomas: a critical summary. J Neurooncol 1999;42(3):303–5.
3. Sanai N, Berger MS. Extent of resection influences outcomes for patients with gliomas. Rev Neurol 2011;167(10):648–54.
4. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115(1):3–8.
5. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95(2):190–8.
6. Stummer W, van den Bent MJ, Westphal M. Cytoreductive surgery of glioblastoma as the key to successful adjuvant therapies: new arguments in an old discussion. Acta Neurochir 2011;153(6): 1211–8.
7. Albert FK, Forsting M, Sartor K, et al. Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual

tumor and its influence on regrowth and prognosis. Neurosurgery 1994;34(1):45–60 [discussion: 60–1].
8. Stummer W, Reulen HJ, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008;62(3):564–76 [discussion: 564–76].
9. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. J Neurosurg 2010;112(1): 1–9.
10. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003; 5(2):79–88.
11. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10): 987–96.
12. Ammirati M, Vick N, Liao YL, et al. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. Neurosurgery 1987; 21(2):201–6.
13. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 1998;42(5):1044–55 [discussion: 1055–6].
14. Kido DK, LeMay M, Levinson AW, et al. Computed tomographic localization of the precentral gyrus. Radiology 1980;135(2):373–7.
15. Yousry TA, Schmid UD, Alkadhi H, et al. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 1997;120(Pt 1): 141–57.
16. Shinoura N, Suzuki Y, Yamada R, et al. Precentral knob corresponds to the primary motor and premotor area. Can J Neurol Sci 2009;36(2):227–33.
17. Branco DM, Coelho TM, Branco BM, et al. Functional variability of the human cortical motor map: electrical stimulation findings in perirolandic epilepsy surgery. J Clin Neurophysiol 2003;20(1):17–25.
18. Farrell DF, Burbank N, Lettich E, et al. Individual variation in human motor-sensory (rolandic) cortex. J Clin Neurophysiol 2007;24(3):286–93.
19. Sanes JN, Donoghue JP, Thangaraj V, et al. Shared neural substrates controlling hand movements in human motor cortex. Science 1995;268(5218): 1775–7.
20. Quinones-Hinojosa A, Ojemann SG, Sanai N, et al. Preoperative correlation of intraoperative cortical mapping with magnetic resonance imaging landmarks to predict localization of the Broca area. J Neurosurg 2003;99(2):311–8.
21. Pouratian N, Bookheimer SY. The reliability of neuroanatomy as a predictor of eloquence: a review. Neurosurg Focus 2010;28(2):E3.
22. Ojemann G, Ojemann J, Lettich E, et al. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71(3):316–26.
23. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med 2008;358(1):18–27.
24. Lehericy S, Biondi A, Sourour N, et al. Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. Radiology 2002; 223(3):672–82.
25. Vikingstad EM, Cao Y, Thomas AJ, et al. Language hemispheric dominance in patients with congenital lesions of eloquent brain. Neurosurgery 2000; 47(3):562–70.
26. Brazdil M, Chlebus P, Mikl M, et al. Reorganization of language-related neuronal networks in patients with left temporal lobe epilepsy - an fMRI study. Eur J Neurol 2005;12(4):268–75.
27. Janszky J, Mertens M, Janszky I, et al. Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: an fMRI study. Epilepsia 2006;47(5):921–7.
28. Lucas TH 2nd, Drane DL, Dodrill CB, et al. Language reorganization in aphasics: an electrical stimulation mapping investigation. Neurosurgery 2008; 63(3):487–97 [discussion: 497].
29. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain 2007;130(Pt 4):898–914.
30. Robles SG, Gatignol P, Lehericy S, et al. Long-term brain plasticity allowing a multistage surgical approach to World Health Organization grade II gliomas in eloquent areas. J Neurosurg 2008;109(4): 615–24.
31. Pouratian N, Bookheimer SY, Rex DE, et al. Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. Neurosurg Focus 2002; 13(4):e4.
32. Giussani C, Roux FE, Ojemann J, et al. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. Neurosurgery 2010;66(1):113–20.
33. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003;4(6):469–80.
34. Coenen VA, Krings T, Axer H, et al. Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (PTV) reliably predicts true position of principal motor pathways. Surg Neurol 2003;60(5):381–90 [discussion: 390].
35. Holodny AI, Schwartz TH, Ollenschleger M, et al. Tumor involvement of the corticospinal tract: diffusion

magnetic resonance tractography with intraoperative correlation. J Neurosurg 2001;95(6):1082.
36. De Benedictis A, Moritz-Gasser S, Duffau H. Awake mapping optimizes the extent of resection for low-grade gliomas in eloquent areas. Neurosurgery 2010;66(6):1074–84 [discussion: 1084].
37. Bello L, Acerbi F, Giussani C, et al. Intraoperative language localization in multilingual patients with gliomas. Neurosurgery 2006;59(1):115–25 [discussion: 115–25].
38. Bello L, Gallucci M, Fava M, et al. Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. Neurosurgery 2007;60(1):67–80 [discussion: 80–2].
39. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 2008;108(2):227–35.
40. Duffau H. Intraoperative cortico-subcortical stimulations in surgery of low-grade gliomas. Expert Rev Neurother 2005;5(4):473–85.
41. Duffau H, Lopes M, Arthuis F, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. J Neurol Neurosurg Psychiatr 2005;76(6):845–51.
42. Reithmeier T, Krammer M, Gumprecht H, et al. Neuronavigation combined with electrophysiological monitoring for surgery of lesions in eloquent brain areas in 42 cases: a retrospective comparison of the neurological outcome and the quality of resection with a control group with similar lesions. Minim Invasive Neurosurg 2003;46(2):65–71.
43. Amorim RL, Almeida AN, Aguiar PH, et al. Cortical stimulation of language fields under local anesthesia: optimizing removal of brain lesions adjacent to speech areas. Arq Neuropsiquiatr 2008;66(3A):534–8.
44. Sanai N, Berger MS. Intraoperative stimulation techniques for functional pathway preservation and glioma resection. Neurosurg Focus 2010;28(2):E1.
45. Lang FF, Olansen NE, DeMonte F, et al. Surgical resection of intrinsic insular tumors: complication avoidance. J Neurosurg 2001;95(4):638–50.
46. Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity–a review. J Neurooncol 2006;79(1):77–115.
47. Pillon A, d'Honincthun P. The organization of the conceptual system: the case of the "object versus action" dimension. Cogn Neuropsychol 2011;27(7):587–613.
48. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007;8(5):393–402.
49. Cruice M, Worrall L, Hickson L. Health-related quality of life in people with aphasia: implications for fluency disorders quality of life research. J Fluency Disord 2010;35(3):173–89.
50. Geler-Kulcu D, Gulsen G, Buyukbaba E, et al. Functional recovery of patients with brain tumor or acute stroke after rehabilitation: a comparative study. J Clin Neurosci 2009;16(1):74–8.
51. Geschwind N. The organization of language and the brain. Science 1970;170(961):940–4.
52. McClelland JL, Rogers TT. The parallel distributed processing approach to semantic cognition. Nat Rev Neurosci 2003;4(4):310–22.
53. Thiebaut de Schotten M, Urbanski M, Duffau H, et al. Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. Science 2005;309(5744):2226–8.