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Surgical Treatment for Glioma: Extent of Resection Applying Functional Neurosurgery

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Abstract

Current treatments for gliomas, including surgery, chemotherapy, and radiation therapy, frequently result in unsuccessful outcomes. Studies on glioma resection were reviewed to assess better treatment outcomes applying the newest neurosurgical multimodalities. We reviewed reports of surgical removal of gliomas utilizing functional brain mapping, monitoring, and other functional neurosurgery techniques such as neuronavigation and awake surgery. Attempts to maximize the extent of glioma resection improved survival. A close proximity of the resection to the eloquent areas increased the risk of perioperative neurological deficits. However, those deficits often improved during the postoperative rehabilitation and recovery period when the essential or the compensative eloquent areas remained intact. Pre- and intraoperative application of the latest brain function analysis methods promoted safe elimination of gliomas. These methods are expected to help explore the long-term prognosis of glioma treatment and the mechanism for recovery from functional disabilities.

Key words: glioma, resection, brain function, neuronavigation, review

Introduction

Pre- and intraoperative functional brain mapping and monitoring methods have dramatically progressed in the last decade with the advances in medical equipment and computer technology. These methods provide information on brain functions that are helpful for determining surgical strategies, so functional neurosurgery techniques have evolved into the field of general neurosurgery. Parenchymal gliomas infiltrate into the surrounding eloquent areas, so evaluation of brain function is particularly important in determining whether a particular case is suitable for surgery, as well as the optimal surgical strategies when surgery is indicated. In addition, these methods provide useful intraoperative surgical guidance. This review presents the pathophysiology of glioma invasion and cerebral compensation to clarify the current significance and objectives of surgical resection. Multiple safe methods for optimal tumor resection are described, and the results of glioma resection surgery utilizing advanced approaches that integrate these modalities are assessed.

Evaluation of Brain Function for the Surgical Resection of Gliomas

Functional neurosurgery refers to the surgical treatment of functional abnormalities related to the cerebrospinal nervous system, including movement disorders, intractable epilepsy, and chronic pain, among others. Typical examples include stereotactic surgery for Parkinson's disease, epilepsy surgery, and neurovascular decompression for trigeminal neuralgia and hemifacial spasm. With computer-aided developments in diagnostic imaging techniques and nervous function evaluation methods, functional neurosurgery including functional brain mapping and monitoring are now important in the field of general neurosurgery.

Parenchymal glioma, a common intrinsic brain tumor, is characterized by diffuse local invasion of normal brain functional areas. Therefore, evaluation of brain function is very important in the determination of whether a particular case is suitable for surgery, as well as the optimal surgical strategy for cases when surgery is indicated. In addition, evaluation of brain function provides useful intraoperative guidance and increases surgical safety. In practical terms, information on cortical function is extracted by application of magnetic resonance (MR) imaging, functional MR imaging, and magnetoencephalography systems. Neuronal information is obtained by diffusion tensor imaging tractography. Such information is displayed perioperatively in the navigation system, and combined with the results of electrical brain stimulation and awake neurological assessment to make medical decisions.

Gliomas cause brain damage by infiltration into normal brain tissue and by the creation of a mass effect. The brain area aggressively invaded by high-grade glioma ceases to function properly. When no neurological deficits are detected in the vicinity of a tumor, the tumor is merely causing an anatomical shift to the adjacent areas by physical compression. However, the possibility of cerebral rearrangement by the compensation mechanism remains. However, no neurological deficit is sometimes observed with low-grade gliomas present in areas or neurons controlling major functions. This indicates that the infiltrated tissue continues to function normally, if the local cerebral functions have not been rearranged or compensated.

To investigate the morbidity resulting from the resection of gliomas invading into eloquent cerebral areas, treatment outcomes were compared between surgical cases with glioma resection and with neocortical epilepsy, in which the locations of the epileptogenic lesions were identified. Among 157 cases of glioma resection located in close proximity to eloquent cerebral areas, 57% underwent gross total resection. Transient postoperative deficits were observed in 33% of 81 cases showing no preoperative deficits. Permanent or long-term neurological deficits were reported in 8% and 2.5% of the cases with and without preoperative deficits, respectively. In 76 cases with preoperative neurological deficits, 33% showed complete resolution of these deficits, and 32% improved.9) In a more recent study on 309 consecutive patients with intracerebral tumors near or within eloquent cortices, 21% had intraoperative neurological deficits. Whereas 39% of these patients experienced worsened neurological outcome at one month, 11% of the patients without intraoperative changes had such outcomes. At one month, 17% of the patients experienced new or worsening neurological deficits. At 3 months, only 7% had a persistent neurological deficit.25) Another study on the resection of low-grade gliomas in the primary motor and sensory cortices reported that 60% to 100% of the patients who underwent resection experienced transient palsy, but no patients had permanent deficits.3) On the other hand, in a study of patients with epilepsy undergoing resection surgery involving the primary sensorimotor cortex, post-surgical permanent deficits were reported in 50% of the study cohort.43) All these studies employed the best available methods for mapping and monitoring to achieve safe, maximal tumor resection. Further analysis is needed to eliminate confounding factors related to surgical indications and patient selection, but these results seem to indicate that gliomas located in or near the eloquent brain areas were treated by the surgical operation relevant for the disease stage that promoted functional recovery. Therefore, functional brain mapping and monitoring should be required in selecting the surgical approaches and in removing tumors appearing as hyperintense on T_2-weighted functional MR imaging (fluid-attenuated inversion recovery).11,12) Dissection along the circumferential margin of the contrasted tumor image, and elimination of severely damaged or necrotic tissue should carefully avoid impairment of the blood flow and mechanical damage by accidental or unintentional surgical maneuvers to the adjacent brain tissue. However, when the patient presents with preoperative neurological deficits due to tumor invasion, sufficient information may not be obtained from functional brain mapping and monitoring methods that involve voluntary movement and electrical stimulation in awake conditions. Under such circumstances, brain functions should be assessed by a comprehensive analysis of various physiological data.31,32)

With the development of neuroimaging, functional mapping, and anesthesia studies, lesions in the eloquent area can now be removed with functional recovery.6,10,13) Functional reorganization, cerebral plasticity, and compensation may contribute to recovery simultaneously or chronologically.11,12,29,38,49,53) The arguments presented so far are confined to generic postulation of the brain function recovery mechanisms. The nature of these mechanisms, which may be revealed by exploration of the intercortical network between the association area and the damaged areas, remains to be studied.

Significance and Objectives of Surgical Glioma Resection

World Health Organization (WHO) grade II–IV gliomas cannot be completely cured only by surgery. A new modality has been established for the treatment of malignant gliomas that includes chemotherapy plus radiation following administration of temozolomide. In addition, multidisciplinary approaches are being developed that involve the clinical application of gene therapy, cell therapy, molecule-targeted therapy, and immunotherapy. Accumulated evidence suggests that more extensive surgery produces better outcomes for the treatment of WHO grade III and IV gliomas.26,50) The 5-year survival rate was 68% for WHO grade II astrocytomas, an outcome similar to that for colorectal cancers. In contrast, the 5-year survival rate was below 60% for patients after up to 75% resection of supratentorial astrocytomas, and 73% and 88% for patients with 95% resection and total extirpation, respectively.7) The progression-free and malignancy-free survival rates for postoperative residual low-grade gliomas were 44% and 74% over 5 years of follow-up, and 24% and 56% over 8 years, respectively.4) Although reviews published to date failed to identify class I evidence, maximal resection has been stressed as the approach to the treatment of WHO grade II–IV gliomas.46)

At the same time, intraoperative procedures should be carefully performed to secure safe resection with minimal damage to brain tissue and resulting function. The significance of patient quality of life during the immediate postoperative period and the extent implicated by 'brain functions' depend highly on the course of surgical recovery. Broadly defined, brain functions include higher level activities studied in Systems, Behavioral, and Cognitive Neuroscience. These activities represent important issues to be addressed, especially by neurosurgery as part of human science. At present, there are practical limitations both in the outcomes for the medical treatment of gliomas and in the clinical evaluation of higher-level brain functions. Therefore, voluntary movement, somatic sensation, visual perception, speech, and other parietal functions are the primary foci in relation to brain-tumor resection.

Integrated Functional Neuronavigation and Cortical/Subcortical Electrical Stimulation

The preservation of brain function while maximizing the resection of gliomas is a major goal in neurosurgery. Direct cortical stimulation has been used since 1930 in epilepsy surgery.16,41,42) Recent studies have developed new methods of presurgical non-invasive functional imaging, including functional MR imaging, and magnetoencephalography, enabling the visualization of cortical areas involved in brain function. The fiber-tracking technique based on diffusion tensor imaging images the three-dimensional macroscopic architecture of fiber tracts.5,21,33,52,54) Combining these technologies in glioma surgery allows effective and safe resection with anatomo-functional mapping using tractography-integrated functional neuronavigation combined with direct cortical/subcortical electrical stimulation.22,30,34,38)

I. Electric stimulation

Brain electrical stimulation for functional mapping must maintain efficacy and safety, so the following methods of using probe electrodes and subdural electrodes are recommended.

Probe electrode48): Interpolar distance 5 mm, diameter 1 mm, bipolar or diameter 1 mm, monopolar square wave pulses (1 msec) with alternating polarity and frequency of 60 Hz, stimulus duration of up to 4 seconds from 1.5 (or 2) mA to the maximum intensity of 6 mA.

Subdural electrode15): Interpolar distance 5 mm to 1 cm, diameter 3 mm, bipolar square wave pulses (0.3 msec) with alternating polarity and frequency of 50 Hz, stimulus duration of up to 10 seconds from 1 mA to the maximum intensity of 15 mA.

Stimulation conditions can be varied among electrodes for the purposes of functional mapping. When stimulating the primary motor area under awake conditions, use of low-frequency stimulation or one to five repetitive stimuli is desirable to prevent convulsion. For the identification of false-positive responses to peripherally spreading electrical stimulation which may cause seizure, after-discharges should be monitored. Electrical stimulation may spread 2 to 13 mm.2,20,23,30) Cortical excitability varies between children and adults, so false-negative results may occur.

II. Evaluation of motor function

The central sulcus is localized based on the polarity inversion of the N20 component of the somatosensory evoked potentials, and cortical motor function is evaluated by electrical stimulation of the precentral gyrus. Images of the subcortical pyramidal tract preoperatively created by the diffusion tensor imaging technique are shown on the navigation system perioperatively with tract activity evaluation by applying subcortical electrical stimulation. These methods can provide accurate intraoperative analysis of the functions of the primary motor area and the originating corticospinal tracts.11,18,22,30,34)

Motor evoked potentials (MEPs) are generated when electrical stimulation is applied to the primary motor area and the originating corticospinal tracts that form synapses with the spinal anterior horn cells. MEP responses are recorded more commonly from peripheral muscle than from the lumbar spinal cord by placement of epidural electrodes recording descending the corticospinal evoked potentials (D-wave).55) Patients with MEPs recorded by intraoperative subcortical stimulation are more prone to develop postoperative motor deficits than those without.24) New, immediate post-surgical motor deficits were documented in 59.3% of patients in whom the subcortical motor tract was identified in close proximity to the surgical site (by positive MEPs) and in 10.9% of those in whom subcortical tracts were not observed (negative MEPs). Among these patients, permanent deficits were documented in 6.5% and 3.5%, respectively.4) In addition to the primary motor area, stimulation of the somatosensory, supplementary motor, and premotor areas affects voluntary movement. These regions are involved with movement initiation and control. Attention should be paid to the fact that these sites, which have distinct projections to the spinal cord, present different response patterns to electrical stimulation and varying functional deficits after resection.14,29)

III. Evaluation of language function

In contrast to the identification of areas involved with motor function, the brain areas relevant for language and other parietal-lobe functions are more difficult to locate, particularly so in the presence of brain tumors, which induce adaptive displacements or shifts of brain structures depending on sulci geometry.

In examining language function, the extent of brain areas to apply electrical stimulation and surgically eliminate demands careful attention. First, the region in the language-dominant side of the cortex leading to the inability to name an object when electrical stimulation is applied is wider than Broca's and Wernicke's areas, and extends to the superior, middle, and inferior frontal gyri as well as to the superior and middle temporal gyri.19,37) Another language area is reported to exist in the basal temporal lobe, called the basal temporal language area.27) Second, speech production, object naming, repetition, and reading tasks, which are generally included in the testing paradigms, engage different language areas.8,37) Other language task components include voluntary speech, word recall, word chain formation, repetitive vocalization, auditory comprehension, sentence processing, number counting, and color naming. These functions all relate to different cortical locations.44,45) Testing paradigms should produce reliable results under the time-limited awake surgery condition. Third, the electrically induced occurrence of anarthria that results from the positive motor response of the tongue and face or from the negative motor response of the tongue must be eliminated.

Care should be taken for the identification of language function regions that are responsive to electrical stimulation of non-physiological origin. Care should also be taken when deciding on the extent of resection. Clinical experience suggests that identification of the cortical regions that contain no stimulation-induced language function (negative language mapping) allow safe tumor resection.48) In treating 250 consecutive patients with WHO grade II–IV gliomas, the authors strictly adhered to a minimal resection margin of 1 cm from the nearest language site identified by electrical stimulation in excising areas presenting no stimulation-induced language deficits (difficulty with number counting, naming, and speech production tasks). Essential language sites were localized within the operative field in 145 patients (58%). Transient postoperative language deficits emerged in 22%, however, only 1.6% developed a permanent postoperative language deficit.

Subcortical stimulation was used to identify functional language tracts successfully in 59% of patients undergoing glioma resection. Transient postoperative deficits occurred in 67.3% of patients during the resection of lesions located close to or within language areas or pathways, although definitive morbidity was reported in 2.3%.1) However, several studies have yielded contradicting conclusions on the significance of language pathways. Among the language-association fibers, the articuate fasciculus is well known for its relation to phonological processing. One study reported that the inferior longitudinal fasciculus, located inferolateral to the cerebral ventricle, could be resected, because it produced no language deficits when electrically stimulated, although electrostimulation of the inferior frontooccipital fasciculus impaired word-finding ability.28) On the other hand, another study demonstrated that the inferior frontooccipital fasciculus, when electrically stimulated, produced speech arrest and compromised word retrieval activity.1)

Outcomes in Glioma Surgery Applying Functional Neurosurgery

Gliomas selected for treatment by functional neuronavigation and intraoperative electrical stimulation are mainly located in or near the eloquent areas. The results of such operations, therefore, cannot be satisfactorily compared with overall glioma surgery outcomes due to selection bias. A retrospective study reported that subcortical electrical mapping significantly improved the survival rate after resection of low grade gliomas.11) According to another retrospective analysis, the intraoperative use of brain mapping techniques improved the extent of resection. Preoperative morbidity was also minimized despite temporary postoperative neurological deficits resulting from cerebral edema and compression.3) Accumulated evidence suggests that more extensive resection of grade II–IV gliomas was associated with more favorable life expectancy, regardless of location near eloquent cerebral areas.[47] Several reports have been published regarding the relationship between the extent of resection and postoperative neurological deficits. In one study, 17 patients underwent resection of cortical or subcortical tumors in motor areas (mean tumoral volumetric resection 89.1 ± 14.2%). A total of 58.8% of the patients had some kind of presurgical motor neurological deficit. The percentage of patients with deficits increased immediately after surgery, but decreased to 47.1% at 1 month postoperatively.[18] In a study of 309 patients with intracerebral tumors adjacent to or within eloquent cortices, gross total resection ($\geq$95%) was obtained in 64%, and minimal resection of 85% was obtained in 77% of the patients. Gross total resection increased the risk of postoperative deficits, and 7% of patients had persistent neurological deficit at 3 months.[25] Comparative investigation evaluated the effect of safety margins around eloquent structures on postoperative outcomes in patients with grade II gliomas, and the rate of permanent deficit was similar with or without a margin (less than 2%). A higher rate of transient neurological worsening in the immediate postsurgical period was associated with no margin, and the extent of resection improved with the absence of a margin.[17]

In addition to various brain functional tests and neuronavigation systems, effective measures for improving glioma surgery include the use of intraoperative MR imaging and photodynamic diagnosis techniques. The application of intraoperative MR imaging system involves several challenging issues such as specific operating environment requirements and prolonged scan time, but enables intraoperative confirmation of the position of the tumor to be removed, and enables extraction of real-time tractography data of displaced brain tissues.[35,40] No significant improvement was noted in the overall survival after photodynamic diagnosis-guided malignant glioma surgery utilizing the 5-amiolevulinic acid (5-ALA) marker. However, the 6-month progression-free survival was 41.1% for patients allocated to the 5-ALA group, higher than that (21.2%) for patients allocated to the white light group. Use of 5-ALA enabled more complete resections of tumor, despite the increased incidence of transient neurological deficits.[51]

Conclusion

In the last decade, we have observed dramatic development in multidisciplinary modalities involving surgery, chemotherapy, and radiotherapy. Clinical application of gene therapy, cell therapy, molecule-targeted therapy, and immunotherapy is underway, building upon the results of basic research. Increasing amounts of evidence show that favorable treatment outcomes can be achieved by maximal safe resection of tumor. This resection is facilitated by the introduction of medical equipment and technologies including intraoperative neuronavigation, diffusion tensor tractography, and functional brain mapping. Intraoperative visualization of the brain anatomy and function is expected to progress further in the future. However, constant revision of the multidisciplinary surgical approaches and determination of indications seems important, based on the idea that such medical information merely relates to particular aspects of the tumor effects and brain functions. We also propose the importance of pursuing neuroscience research that addresses the dynamic brain networks based on the analysis of local brain functions. Such research will define the compensation mechanisms, so contributing to overall improvement in the outcomes of brain tumor surgery.

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