Intraoperative Functional Mapping and Monitoring during Glioma Surgery

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Abstract

Glioma surgery represents a significant advance with respect to improving resection rates using new surgical techniques, including intraoperative functional mapping, monitoring, and imaging. Functional mapping under awake craniotomy can be used to detect individual eloquent tissues of speech and/or motor functions in order to prevent unexpected deficits and promote extensive resection. In addition, monitoring the patient's neurological findings during resection is also very useful for maximizing the removal rate and minimizing deficits by alarming that the touched area is close to eloquent regions and fibers. Assessing several types of evoked potentials, including motor evoked potentials (MEPs), sensory evoked potentials (SEPs) and visual evoked potentials (VEPs), is also helpful for performing surgical monitoring in patients under general anesthesia (GA). We herein review the utility of intraoperative mapping and monitoring the assessment of neurological findings, with a particular focus on speech and the motor function, in patients undergoing glioma surgery.

Key words: awake craniotomy, functional mapping, cortico-cortical evoked potential, plasticity, motor evoked potentials

Introduction

In recent years, evidence has accumulated regarding the outcomes of glioma treatment, including improved treatment results with temozolomide (TMZ) and the contribution of molecular markers, such as IDH1 and 1p19q loss of heterozygosity.^{1,2)} However, subanalyses of recent randomized controlled trials of the effectiveness of chemotherapy in treating World Health Organization (WHO) grade 2 and 3 gliomas have demonstrated that the resection rate is more significantly correlated with the survival time.^{3,4)} In 2001, Lacroix et al. reported that removing 98% or more of the brain magnetic resonance imaging (MRI) gadolinium-enhanced portion of the tumor was necessary to achieve a significant increase in patient survival among 416 patients with glioblastoma.⁵⁾ A decade later, Sanai et al. expanded on this conclusion and demonstrated the clinical value of the extent of resection (EOR) of total and subtotal procedures on a percentile-by-percentile basis. Their analysis

of 500 consecutive newly diagnosed patients with glioblastoma demonstrated that an EOR of 78% is the minimum procedure associated with a survival benefit and that this value increases in association with more complete surgical resection (95%, 98% or more, and 100% respectively).⁶⁾ Regarding low-grade gliomas, Smith et al. demonstrated that among 216 patients, those treated with an EOR of at least 90% had 5- and 8-year overall survival (OS) rates of 97% and 91%, respectively, whereas those who received an EOR of less than 90% had 5- and 8-year OS rates of 76% and 60%, respectively.⁷⁾ Recently, we also investigated whether the EOR was associated with progression-free survival (PFS) and OS in 153 patients with low-grade glioma and demonstrated that both the PFS and OS were significantly longer in the patients with an EOR of 90% or more.⁸⁾ These results validate the use of a therapeutic strategy aiming for an EOR of 90% or more in patients with low-grade gliomas.

On the other hand, aggressive resection has the potential to increase the incidence of neurological complications, especially those associated with

regions within or near eloquent language and motor areas. In order to preserve the neurological function in patients undergoing glioma surgery, various intraoperative neurological monitoring have been developed, including motor evoked potentials (MEPs)^{9–11} to detect deterioration of the motor function and sensory evoked potentials (SEPs)^{12,13} to identify the Rolandic cortex. With respect to preserving the language function, awake craniotomy (AC) is a reliable method for ensuring neural integrity during the excision of lesions located within or near eloquent language areas.¹⁴ It is therefore possible to electrically stimulate the cortex and subcortical structure in order to locate functional areas with the patient awake. Furthermore, continuous clinical neurological testing can theoretically be used to detect early deficits in the motor, sensory, or language domains during tumor removal. Intraoperative functional mapping and monitoring thus play important roles in glioma surgery in terms of maximizing the EOR while minimizing the risk of neurological morbidity.

Awake Craniotomy

Functional mapping under AC offers the potential to accurately localize eloquent brain areas. This procedure allows the surgeon to clearly define language, positive motor, and negative motor areas¹⁵ as well as the position of white matter fibers connected with the speech and motor functions, which helps to prevent unexpected neurological complications. A recent meta-analysis including 90 reports of 8,091 adult patients who underwent resection of supratentorial infiltrative glioma with or without intraoperative stimulation mapping (ISM) demonstrated late severe neurological deficits in 3.4% of the patients who underwent resection with ISM and 8.2% of the patients who underwent resection without ISM.¹⁶ The percentage of radiologically confirmed gross total resection was 75% [95% confidence interval (CI), 66% to 82%] in the patients treated with ISM and 58% (95% CI, 48% to 69%) in those treated without ISM. Most recently, Brown et al. reviewed eight studies comparing the outcomes of craniotomy for tumor resection under general anesthesia (GA) and AC in 951 patients (411 treated with AC and 540 treated with GA).¹⁷ The authors' interpretation of the literature suggests that the mean EOR under awake conditions (41%, $n = 321$) is similar to that of GA (44%, $n = 444$), while the incidence of postoperative deficits is lower under awake conditions (7%, $n = 411$) versus GA (23%, $n = 520$). Given the effectiveness of AC for resecting

eloquent tumors, these data suggest an expanded role for AC in brain tumor surgery, regardless of the tumor location, indicating that ISM should be universally implemented as standard of care for glioma surgery. AC is recommended according to guidelines for the management of low-grade glioma in Europe (Class III level).³ In Japan, "The Guidelines for Awake Craniotomy" were formulated by the Japan Awake Surgery Conference, and AC has since become the basic procedure for performing resection of tumors within or near eloquent areas.¹⁸

I. Language mapping

The purpose of language mapping is to identify language areas and prevent permanent postoperative language dysfunction by preserving these areas. An efficient method is required for intraoperative language mapping to reduce the time necessary to intraoperatively localize eloquent cortical areas. In order to identify language-related areas preoperatively and shorten the time needed to detect language areas intraoperatively, we actively apply the results of functional MRI using a picture-sentence matching task (with active, passive, and scrambled sentences).¹⁹ Our intraoperative mapping procedure follows the dedicated guidelines of the Japan Awake Surgery Conference.¹⁸ For intraoperative brain mapping, electrical stimulation of the cortex is applied with a repetitive square wave biphasic current of alternating polarity (pulse width: 0.5 msec, frequency: 50 Hz, duration: 1–2 seconds) using a bipolar electrode probe. The continuous digital electrocorticogram (ECoG) activity is monitored after discharge, and to detect seizures. The stimulus intensity is then increased steadily from 2 mA in a bipolar fashion using stepwise increments of 1 mA until the effect is obtained or abnormalities are noted on ECoG. The maximum stimulus intensity is 8 mA, which corresponds to 16 mA if a monophasic pulse is used, in concert with the experience and recommendations of others.^{18,20–23} The dedicated intraoperative examination monitor for awake craniotomy (IEMAS) is used to demonstrate the language assessment tasks of the patient.^{24,25} This device allows the real-time visualization, integration, and recording of a wide spectrum of data, including a view of the patient's face during the response, the type of test provided, the position of the cortical stimulator in the surgical field, the anatomical data obtained from the real-time updated neuronavigation system,²⁶ the bispectral index (BIS) monitor, and so forth (Fig. 1).

With the patient counting (from 1 to 30), we first check for sites of speech arrest and delay. Stimulation is then performed in a systematic manner every

Fig. 1 The screen of the dedicated intraoperative examination monitor for awake craniotomy (IEMAS). *Upper left display:* The patient's face. *Lower left display:* The anatomical data obtained from the real-time updated neuronavigation system, which can be used to localize the exact position of the stimulator. *Upper right display:* Four different sets of data for the test object, bispectral index monitor, heart beat monitor, and general view of the operating theater. *Lower right display:* The view of the surgical field through the operative microscope.

8–10 mm along the cortical surface. We subsequently reconfirm the locations of language-related sites using tasks of picture naming, pronouncing written familiar Japanese words, and generating action verbs. During the language mapping procedure, it is important to distinguish the language area from positive (defined as involuntary contractions of the tongue) and negative (defined as impairment of rapid alternating movements of the tongue; arrest of synergic movement) motor areas. After identifying the language areas, we remove the tumor preserving these cortical regions, with subcortical stimulation via the resection cavity directed at clarifying language pathways. The devices used for subcortical stimulation and the parameters of stimulation, including intensity, are similar to those used for cortical mapping. When subcortical stimulation interrupts or disturbs the patient's ability to name a pictured object, the removal procedure is stopped, as we previously confirmed that the responding sites are located very close to the eloquent subcortical fibers (5 mm or less).²⁷⁾ More recently, Trinh et al.²⁸⁾ reported that intraoperative language dysfunction acquired during subcortical dissection is an independent predictor of postoperative deficits in both the immediate postoperative period ($P < 0.001$) and at the 3-month follow-up ($P < 0.001$), as observed in 214 patients undergoing AC. Under awake conditions, the patient's ability to speak freely is constantly monitored during the

entire procedure with a continuous conversation with a member of the treatment team specialized in assessing the language function who provides specific tasks to evaluate recall, counting, fluency, and comprehension.²⁹⁾

Sanai et al. examined 250 patients with gliomas in order to study the language function after brain-tumor resection using language mapping.²³⁾ Cumulatively, 3,281 cortical sites were stimulated in all patients. A total of 145 of the 250 patients (58.0%) had at least one site with intraoperative stimulation-induced speech arrest, 82 patients had anomia, and 23 patients had alexia. The authors proposed that the lesion can be removed if stimulation with an intensity of 6 mA (using a bipolar electrode, 60 Hz, square wave) elicit no speech arrest or delay, which is called “negative mapping” strategy. Surprisingly, they reported that only 1.6% of surviving patients had a persistent language deficit. In addition, using this strategy, the researchers demonstrated that delineating true functional and nonfunctional areas using intraoperative mapping (in presumed eloquent areas) in high-risk patients to maximize tumor resection dramatically improved the long-term survival of 281 patients with supratentorial low-grade gliomas. However, it should be kept in mind that this strategy was employed in an experienced facility. Therefore, the use of a “positive mapping” strategy, meaning that the tumor is removed after identifying the language areas, is recommended in less experienced facilities.

II. Language monitoring

We consider continuous observation of the patient's intraoperative condition under AC itself to be the most reliable and direct method for monitoring the neurological function. This technique can be used to detect early deficits in the motor, sensory, language, or even higher-order brain functions (e.g., left-right disorientation, acalculia). In addition, continuous direct observation under awake conditions may help the clinician to recognize unexpected neurological complications (e.g., disturbed consciousness due to hemorrhage outside the operative field) in rare cases, thus leading to further imaging studies (e.g., intraoperative MRI or computed tomography), which is useful from the viewpoint of risk management. Importantly, the direct clinical assessments with AC do not show false-negative results, which prevent suboptimal resection in patients undergoing glioma surgery. Consequently, the parallel use of AC and intraoperative neurophysiological monitoring result in more accurate evaluations of the motor and language functions.

III. MEPs during AC

The need for AC to treat gliomas located within or adjacent to the motor eloquent structure is controversial due to differences in the accuracy of MEP monitoring and the goal with respect to the EOR. We actively introduced the use of AC for gliomas located in these areas and have resected such lesions by combining MEP monitoring elicited by direct cortical and transcranial stimulation.³⁰⁾ We apply MEP monitoring with AC to all patients with glioma located in these areas who have indication for AC recommended by “The Guidelines for Awake Craniotomy” in Japan (e.g., patients aged from 15 years to 65 years).¹⁸⁾ On the contrary, we apply MEP monitoring under GA to the patients who do not have indication for AC. The advantages of AC for tumors located in the primary motor cortex or related subcortical fibers is that the surgeon is able to observe the correlations between the results of MEP monitoring, intraoperative voluntary movements, and the involuntary movements elicited by electrical stimulation. Prior studies have reported discrepancies between the results of MEP monitoring and the postoperative or intraoperative neurological status (false-negative and false-positive monitoring).^{10,11,31)} Under awake conditions, even if intraoperative MEP is decreased or absent due to various causes, it is possible to confirm voluntary movements and avoid under-resection. Furthermore, combining MEP monitoring with direct subcortical stimulation and the observation of voluntary movements helps to conduct more accurate evaluations of the intraoperative motor function.

IV. Cortico-Cortical Evoked Potentials (CCEPs)

Despite the proven effectiveness and widespread acceptance of direct intraoperative brain mapping using electrical stimulation to evaluate the intraoperative language function, the procedure has some limitations. In particular, intraoperative assessments of the verbal response are generally subjective and may be significantly influenced by the patient's level of consciousness and cooperativeness, as well as the parameters of cortical stimulation. In addition, despite the high level of reliability of intraoperative cortical mapping for determining the anatomical localization of language-related areas, the functional interconnections between these regions generally remain obscure. Therefore, the development of further novel methods to objectively assess the language function during AC is warranted. The technique of cortico-cortical evoked potential (CCEP) monitoring is based on the electrical stimulation of one cortical area while recording the average response

from another, which permits the assessment of functional interconnections.^{32–37)}

Recently, we and Yamao et al. evaluated recordings of intraoperative CCEP as an adjunctive method for assessing the speech function during resection of intraparenchymal brain neoplasms.^{38,39)} In our report, intraoperative monitoring with CCEP was applied in 13 patients (mean age: 34 ± 14 years) during the removal of neoplasms in the dominant cerebral hemisphere located within or around language-related structures.³⁸⁾ For this purpose, strip electrodes were positioned above the frontal language area (FLA) and temporal language area (TLA), which were identified using direct cortical stimulation and/or preliminary mapping with implanted chronic subdural grid electrodes (Fig. 2). No intraoperative CCEP responses were obtained in one case due to technical problems. In the remaining patients, such responses were identified from the FLA during stimulation of the TLA (seven cases) and from the TLA during stimulation of the FLA (five cases), with a mean peak latency of 83 ± 15 ms. The CCEP responses well correlated with the postoperative language function, and the time to recovery of the speech function was significantly associated with

Fig. 2 Intraoperative CCEP monitoring. Changes in CCEP were recognized following stimulation of the frontal language area and recordings of the temporal language area. CCEP: cortico-cortical evoked potential.

the type of intraoperative change on CCEP, specifically unchanged, decreased, or disappeared during resection at 1.8 ± 1.0 months, 5.5 ± 1.0 months, and 11.0 ± 3.6 months on average, respectively ($P < 0.01$). Remarkably, CCEP recordings are task-free and do not require the cooperation of the patient,³⁷⁾ which opens the possibility for monitoring the speech function during neurosurgical procedures performed under GA.

Intraoperative Neurophysiological Monitoring under GA (Particularly MEPs)

The intraoperative monitoring neurological findings obtained during glioma resection under GA are also useful for maximizing the removal rate and minimizing neurological deficits by alarming that the touched area is close to eloquent regions and fibers. Currently, several types of evoked potentials, including MEPs, SEPs, and visual evoked potentials (VEPs), can be assessed during surgical monitoring under GA. In this article, we primarily review the role of intraoperative MEP monitoring for glioma surgery close to motor areas and/or the pyramidal tract.

Direct electrical cortical and subcortical stimulation is the gold standard for localizing and monitoring the motor function, and this readily available intraoperative technique helps to preserve the eloquent structures of the primary motor cortex and pyramidal tract.^{40–43)} Various stimulus parameters of MEP monitoring for glioma surgery have been reported from different facilities, as shown in Table 1 (e.g., the intensity and threshold of deterioration compared to control values). After placing the strip electrode, the median nerve is first stimulated and the central sulcus is identified based on SEP phase reversal.¹³⁾ Continuous MEP monitoring using direct cortical stimulation (DCS) with a strip electrode enables a real-time evaluation of the functional integrity of the pyramidal tract.^{44,45)} Meanwhile, intermittent subcortical mapping of the pyramidal tract with a monopolar or bipolar probe can be used to localize pyramidal tracts in white matter.^{20,46)} The predictive value of signal alterations (amplitude and threshold) of MEP monitoring for motor deficits has been demonstrated in several studies.^{9–11,42,47)}

I. MEP monitoring with direct cortical stimulation under GA

Continuous MEP monitoring of the contralateral upper and lower limb muscle activity using DCS with a strip electrode is widely employed and has been shown to improve the safety of motor eloquent tumor resection.^{10,42,48–52)} In 1993, Taniguchi et al.

first reported that intraoperative anodal monopolar cortical stimulation causes compound muscle action potentials (CMAPs) in the upper limbs in patients undergoing human glioma surgery.⁵⁰⁾ Subsequently, the authors demonstrated that the intraoperative CMAP changes correlate with the postoperative motor function in subjects undergoing brain tumor surgery.⁵³⁾ However, the impact of CMAP monitoring during glioma surgery had not yet been established. The main reason for criticism was that there were no data regarding the effects of monitoring procedures on the rate of resection of gliomas. Because the resection rate correlates with the survival time, as described above, it is of paramount importance to determine the availability of this procedure. On the other hand, Kombos et al. demonstrated that the resection rate and functional outcomes of tumor resection were not negatively influenced by intraoperative CMAP monitoring in 40 patients with glioma.⁴⁹⁾ Recently, Krieg et al. examined 115 cases of supratentorial glioma located in or close to eloquent motor areas using monitoring of MEP elicited by DCS and found MEP monitoring to be successful in 112 cases (97.4%). This high success rate confirms that the method is very applicable. The authors focused on cases of false-negative results on intraoperative MEP monitoring. In 65.2% of the cases, the MEP were stable throughout surgery, although 8.9% of the patients developed new temporary motor deficits and 4.5% (five) of the patients presented with permanent deteriorations in the motor function representing false-negative monitoring findings. However, these cases were the result of secondary hemorrhage, ischemia, or resection of supplementary motor areas. The authors therefore concluded that continuous MEP monitoring provides reliable information for the motor system, with no false-negative MEP results. Most recently, Gempt et al. aimed to assess the incidence of resection-related ischemia in cases of newly diagnosed or recurrent supratentorial gliomas and determine the sensitivity of intraoperative neuromonitoring of MEPs for detecting such ischemic events and their influence on the neurological motor function in 70 patients with tumors in eloquent motor areas. Nine (69%) of 13 patients with a permanent loss of MEP amplitude exhibited postoperative ischemic lesions. The authors warned that, rather than cortical or subcortical structural damage to eloquent brain tissue alone, the development of peri- and/or postoperative ischemic lesions plays a crucial role in the pathogenesis of surgery-related motor deficits. Based on the findings of several clinical series and recently published data, warning criteria have become more refined based on the addition of a decrement

Table 1 Stimulus parameters of motor evoked potential for glioma surgery

Method of stimulation	Author	Year	Mono or bipolar (Form)	Type of pulse	Duration (ms)	Frequency (Hz)	Intensity	Threshold of deterioration compared to control values
Direct cortical stimulation	Taniguchi et al. ⁵⁰⁾	1993	Monopolar (Rectangle)	Short train (3–5 pulses)	0.2–0.5	300–500 or 50–60	Up to 20 mA	NA
	Suess et al. ⁵¹⁾	2006	Monopolar (Square)	Short train (5–7 pulses)	0.3	400–500	Up to 25 mA	50% (muscle response)
	Kombos et al. ⁴⁹⁾	2009	Monopolar (Rectangle)	Short train (7–10 pulses)	0.1–0.7	400–500	5–20 mA	80% (muscle response)
	Krieg et al. ¹⁰⁾	2012	Bipolar (Square)	Short train (5 pulses)	0.2–0.3	350	6–30 mA	50% (muscle response)
	Seidel et al. ⁵²⁾	2013	Monopolar (Square)	Short train (5 pulses)	0.5	250	Up to 22 mA	60% (muscle response)
	Yamamoto et al. ⁵⁸⁾	2004	Bipolar (Square)	NA	0.2–0.5	2	Up to 25 mA	30% (D wave)
	Fujiki et al. ⁵⁴⁾	2006	Monopolar (Square)	Short train (4 pulses)	0.2–0.5	500	5–20 mA	35% (D wave)
	Our group		Bipolar (Square)	Short train (5 pulses)	0.2	500	Up to 40 mA	50% and/or < 100 μ V (muscle response)
	Yamaguchi et al. ⁶²⁾	2007	Bipolar (Square)	NA	1–2	60	2–16 mA	NA (muscle response)
	Mikuni et al. ⁶⁵⁾	2007	Bipolar (Square)	Short train (5 pulses)	0.2	1	5–15 mA	NA (muscle response)
Transcranial stimulation	Kamada et al. ⁶⁶⁾	2009	Monopolar (Square)	Short train (5 pulses)	0.2	1	8–20 mA	NA (muscle response)
	Fukaya et al. ⁶¹⁾	2011	Monopolar (Square)	NA	0.2–0.4	2–5	Up to 25 mA	NA (D wave)
	Our group		Bipolar (Square)	Short train (5 pulses)	0.5	50	4–16 mA	NA (muscle response)
	Zhou et al. ⁵⁵⁾	2001	Monopolar (Square)	Short train (5 pulses)	NA	0.5–2	40–160 mA	50% (muscle response)
	Szelenyi et al. ¹¹⁾	2010	Monopolar (Square)	Short train (5 pulses)	0.5	250	Up to 220 mA	50% (muscle response)
	Our group		Monopolar (Square)	Short train (5 pulses)	0.05	500	400–600 V	50% and/or < 100 μ V (muscle response)

NA: not applicable.

in amplitude of 50%.^{45,53–55)} We therefore adopted this criterion also. Furthermore, it should be kept in mind that the use of anesthesia significantly influences the reliability of CMAP monitoring, including inhalation anesthetics as well as residual muscle relaxants. Hence, anesthesia should be induced and maintained with continuous intravenous anesthetic administration (e.g., propofol).

DCS of the motor cortex can be used to record the MEP evoked from the epidural space in the spinal cord.^{56,57)} The corticospinal MEP response recorded using this procedure consists of a D-wave and a later I-wave. As described above, CMAP monitoring is significantly influenced by anesthesia, whereas the D-wave is resistant to the effects of anesthetics and muscle relaxants. Yamamoto et al. reported the availability of D-wave monitoring using bipolar stimulation with a multicontact plate electrode to preserve the motor function in 37 patients with glioma.⁵⁸⁾ The authors identified that the critical point for eliciting a persistent motor disturbance was a 30% to 40% decrease in the amplitude of the D-wave and decided to halt the tumor resection procedure before the decrease in amplitude reached 30%; no permanent motor deficits were subsequently identified in their report.

In 1990, Berger et al. described a modification of the bipolar technique using a handheld probe already employed by Penfield.⁵⁹⁾ This modification enables the application of intermittent direct electrical cortex stimulation, even during surgery under GA. Although this method does not permit the use of a qualitative analysis, this bipolar stimulation technique has since become the standard method for performing intraoperative cortical stimulation and mapping of motor areas under GA.

II. Subcortical motor mapping with subcortical stimulation under GA

Currently, subcortical mapping with a probe for bipolar and monopolar stimulation is used beyond cortical stimulation to identify the pyramidal tract. This technique has also been reported to be effective for glioma surgery.^{20,42,44,46)} Recently, Szelenyi et al. compared monopolar and bipolar stimulation aiming to identify the pyramidal tract.⁶⁰⁾ The stimulation intensity (2–25 mA) for eliciting MEP was found to be significantly lower for monopolar multipulse stimulation. Therefore, the authors concluded that monopolar cathode stimulation is more effective for activating the subcortical region of the pyramidal tract than bipolar cathode stimulation. Fukaya et al. also reported that monopolar stimulation more clearly evokes subcortical D-waves from the spinal epidural space than bipolar stimulation.⁶¹⁾ In contrast,

Yamaguchi et al. developed a novel bipolar needle electrode that enables the identification of motor pathways following insertion of the device into the white matter and reported the efficacy of this instrument in preserving the motor function.⁶²⁾

Subcortical mapping, in which the white matter is directly stimulated and the neural response is monitored, is the most reliable method for localizing functionally important white matter bundles, such as those in the pyramidal tract. However, subcortical mapping cannot be used to determine the distance and direction to the tract, although it does provide information as to whether the tract is near the stimulated position. With respect to visualizing the tract, the effectiveness of diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI) techniques for fiber tracking has been investigated.^{63,64)} Mikuni et al. directly compared the results of fiber tracking based on preoperative images and subcortical electrical stimulation during intraoperative neuronavigation in 40 patients with brain tumors located near the pyramidal tract.⁶⁵⁾ Their results suggest that MEP are elicited from the subcortex when the distance between the stimulated subcortex and the estimated pyramidal tract on tractography-integrated intraoperative neuronavigation is within 1 cm. Kamada et al. also studied the association between the characteristics of the pyramidal tract on tractography and subcortical electrical stimulation and found that a minimum stimulus intensity of 20 mA, 15 mA, 10 mA, and 5 mA was associated with stimulus points approximately 16 mm, 13.2 mm, 9.6 mm, and 4.8 mm from the pyramidal tract, respectively.⁶⁶⁾ However, navigation with only preoperative images lacks precision, due to brain shift during tumor resection. In order to address this problem, we developed a neuronavigation system based on intraoperative DWI (iDWI),^{27,67)} while Prabhu et al. and Maesawa et al. examined the correlations between the results of subcortical stimulation and the course of the pyramidal tract on tractography using intraoperative DTI (iDTI).^{68,69)} We validated the bundle depicted on iDWI by considering the responses to subcortical stimulation (range: 4–16 mA) and the distance between the site of stimulation and the depicted bundle (Fig. 3). Positive MEPs were detected in five of seven patients and the distance from the stimulation site to the depicted bundle was 0–4.7 mm (mean: $\pm$ SD, 1.4 ± 2.1 mm). Negative (no) responses were obtained in all patients when the distance was greater than 5 mm. These findings suggest that the white matter bundles depicted on iDWI may contain the pyramidal tract. Similarly, Prabhu et al. noted a trend toward worsening of neurological

Fig. 3 A, B: Magnetic resonance (MR) images obtained before the second surgery demonstrating regrowth of the residual tumor just posterior to the prior resection cavity located in the frontal operculum. The tumor is hyperintense on axial T₂-weighted image (T₂WI) (A) and sagittal fluid attenuated inversion recovery (FLAIR) image (B). C, D: MR images obtained after the second surgery showing that the tumor had been subtotally removed on T₂WI (C) and FLAIR (D).

deficits if the distance from the stimulus probe to the pyramidal tract is short (< 5 mm), indicating the close proximity of the resection cavity to the pyramidal tract based on subcortical stimulation and iDTI tractography.⁶⁹⁾ Meanwhile, Maesawa et al. demonstrated that the distance from intraoperative tractography of the pyramidal tract to the motor-evoked area exhibits a positive correlation with the intensity of stimulation.⁶⁸⁾ However, the distance from preoperative tractography did not display a positive correlation with the stimulation intensity. These results indicate that intraoperative tractography and DWI show the location of the pyramidal tract more accurately than preoperative tractography. The combination of MEP monitoring and intraoperative tractography or DWI therefore enhances the quality of surgery for gliomas located in motor-eloquent areas.

III. MEP monitoring with transcranial stimulation under GA

The utility of MEP elicited by transcranial electric stimulation (TCS) during glioma surgery remains

controversial. While, MEP monitoring by TCS has some advantages including that it can be compared with the contralateral MEP, it does not require the placement of a strip electrode which could injure the brain surface and/or cortical veins. Prior reports have studied MEP elicited by TCS using various stimulus parameters during brain tumor surgery (Table 1). Zhou and Kelly monitored the MEP elicited by TCS in 50 patients undergoing brain tumor resection.⁵⁵⁾ The degree of postoperative worsening of the motor status was found to significantly correlate with the degree of reduction in the intraoperative MEP amplitude. The authors indicated that persistent intraoperative MEP reductions of more than 50% are associated with postoperative motor deficits. We also studied MEP using transcranial stimulation in 196 patients with brain tumors. In that study, monitoring of MEPs elicited by transcranial stimulation was successful in 98% of the patients. In 10 of 196 patients, we compared the findings of MEP elicited by TCS with DCS. In all patients, MEP alterations elicited by TCS were consistent with that obtained using DCS. These results support the efficacy of MEP monitoring using TCS during brain tumor surgery. In contrast, Li et al. reported that the MEP elicited by DCS, and not TCS, could be used to detect brain ischemia during brain tumor resection.⁷⁰⁾ The authors thus insisted that MEP monitoring with DCS is superior to that of TCS in patients undergoing brain tumor resection. Recently, Szelenyi et al. demonstrated that MEP loss elicited by TCS bears a higher risk than MEP deterioration (> 50% amplitude decrease and/or motor threshold increase) for postoperative motor deficits resulting from subcortical postoperative magnetic resonance changes in the pyramidal tract.¹¹⁾ In contrast, the detection of MEP deterioration points to the presence of motor cortex lesions. Therefore, MEP deterioration should be considered as a warning sign during surgery performed close to the motor cortex. Although the availability of MEP monitoring with TCS remains controversial, we believe that the parallel use of TCS and DCS mutually improves the sensitivity of the intraoperative detection of motor impairment.

Brain Functional Plasticity

Low-grade gliomas are frequently located within or close to eloquent motor and language-related areas. Therefore, the EOR is limited by functional boundaries. Prior reports have suggested that slow-growing lesions, such as low-grade gliomas, induce functional reshaping due to plasticity.^{71–78)} These reports suggest that brain functional plasticity is induced by slow-growing lesions, as the

slow time course of cerebral injury is a critical factor in neuroplasticity. For example, Robles et al. described two patients with low-grade gliomas located in the left dominant middle frontal gyrus who experienced language functional plasticity during the interval between two separate resection procedures.⁷⁹⁾ The authors proposed that functional plasticity enables the surgeon to obtain an increased EOR during a second or even third surgery, while simultaneously facilitating preservation of the brain function in patients with low-grade gliomas located in eloquent areas. The following mechanisms of brain functional plasticity have been suggested by Robles et al.: (1) the slow infiltrative nature of low-grade glioma makes it possible to find functional areas within the tumor; (2) eloquent areas can be redistributed immediately around the tumor (perilesional plasticity); (3) other distant areas of the network within the same hemisphere can be activated; and (4) the contralateral homolog areas can also be recruited.⁷⁹⁾ Recently, we reported a patient with oligoastrocytoma in the left inferior frontal gyrus in whom the functional plasticity of language was confirmed via intraoperative functional mapping and updated neuronavigation based on intraoperative MRI performed between two consecutive surgeries.⁸⁰⁾ This case shows that language areas and related subcortical fibers cross the pre-central sulcus during tumor progression as a result of functional plasticity. Consequently, we were able to achieve subtotal removal of the recurrent tumor (Fig. 3). Most recently, Hayashi et al. described a functional shift in the motor area of a patient with an oligodendroglial tumor located in the right primary motor cortex.⁸¹⁾ The findings of intraoperative direct electrical stimulation under AC indicated that the motor region had shifted posteriorly and reorganized beyond the central sulcus. The results of these cases suggest that the second mechanism plays an important role in functional reorganization and contributes to maximal resection with functional preservation.

Several reports have suggested that brain function plasticity occurs preoperatively in patients with low-grade gliomas, based on the findings of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).^{82–88)} Prior fMRI and PET studies have demonstrated activation of motor and language areas within and around the tumor.^{89,90)} These reports indicate that the infiltrative characteristics of low-grade gliomas may make it possible for the neurologic function to persist within the tumor, while the slow rate of tumor invasion likely promotes functional plasticity.

Furthermore, activated areas have been recognized in distant areas within the same and contralateral hemisphere.^{90–92)} These phenomena suggest that slow-growing lesions affect functional networks and induce rewiring and the formation of new connections. These mechanisms may explain why most patients with low-grade gliomas have normal or only slightly impaired neurological outcomes.

Based on these findings, a multistage approach with intraoperative neurophysiological monitoring and AC for low-grade gliomas in eloquent areas is sustainable, while the combination of functional imaging and intraoperative electrical mapping can help to characterize brain functional plasticity. Additional studies with larger patient populations are needed to optimize this approach and validate treatment outcomes.

Conclusion

Intraoperative functional mapping and monitoring under AC have become increasingly widespread as a standard procedure for preserving the motor and language functions, maximizing the resection rate, and prolonging survival in glioma patients. On the other hand, less experienced facilities should seek to increase the learning curve for AC by visiting experienced facilities and referring to the appropriate guidelines. A facility authorization system and training courses have recently been developed by the Japan Neurosurgical Society and Japan Awake Surgery Society.

The new monitoring method using CCEP is feasible and useful for objectively evaluating the speech function, including direct assessments during AC. Intraoperative MEP monitoring during glioma resection under GA is also useful for maximizing the removal rate and minimizing neurological deficits by alarming that the touched area is close to eloquent motor areas and fibers.

Several papers have reported that brain function plasticity is induced during the interval between two surgeries for low-grade gliomas. This phenomenon indicates that functional plasticity may enable the surgeon to obtain an increased EOR during a second or even third surgery, while simultaneously facilitating preservation of the brain function in patients with low-grade gliomas located within eloquent areas.

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Conflicts of Interest Disclosure

No conflict of interest exists. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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