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Strategy of Surgical Resection for Glioma Based on Intraoperative Functional Mapping and Monitoring

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Abstract

A growing number of papers have pointed out the relationship between aggressive resection of gliomas and survival prognosis. For maximum resection, the current concept of surgical decision-making is in "information-guided surgery" using multimodal intraoperative information. With this, anatomical information from intraoperative magnetic resonance imaging (MRI) and navigation, functional information from brain mapping and monitoring, and histopathological information must all be taken into account in the new perspective for innovative minimally invasive surgical treatment of glioma. Intraoperative neurofunctional information such as neurophysiological functional monitoring takes the most important part in the process to acquire objective visual data during tumor removal and to integrate these findings as digitized data for intraoperative surgical decision-making. Moreover, the analysis of qualitative data and threshold-setting for quantitative data raise difficult issues in the interpretation and processing of each data type, such as determination of motor evoked potential (MEP) decline, underestimation in tractography, and judgments of patient response for neurofunctional mapping and monitoring during awake craniotomy. Neurofunctional diagnosis of false-positives in these situations may affect the extent of resection, while false-negatives influence intra- and postoperative complication rates. Additionally, even though the various intraoperative visualized data from multiple sources contribute significantly to the reliability of surgical decisions when the information is integrated and provided, it is not uncommon for individual pieces of information to convey opposing suggestions. Such conflicting pieces of information facilitate higher-order decision-making that is dependent on the policies of the facility and the priorities of the patient, as well as the availability of the histopathological characteristics from resected tissue.

Key words: information-guided surgery, decision-making, functional mapping, awake craniotomy, false-positive

Introduction

Visualization of biological information in medicine has at times led to revolutionary changes in diagnosis and treatment. In the field of neurosurgery, computed tomography (CT) and magnetic resonance imaging (MRI), surgical microscopes and endoscopes have slowly but steadily advanced the field, and modern neurosurgery can now achieve higher efficacy and lower risk than before the implementation of these methods.

In recent reports of glioma surgery, the extent of resection (EOR) has reflected positive correlations with survival prognosis.[1–6)] We have also demonstrated that EOR ≥ 90% was significantly associated with progression-free survival and overall survival in low-grade glioma.[7)] On the other hand, aggressive glioma resection carries a risk of causing postoperative complications, so various methods of intraoperative neurophysiological monitoring have been developed to maximize the preservation of motor, sensory, and language functions (Table 1).

Intraoperative neurophysiological monitoring devices provide important visible information for neurofunctional diagnosis. Such visible diagnostic imaging is an important factor in decision-making under various situations, and physicians analyze images based on their rich experience to determine the priority of each as a decision-making factor. New visualization methods have been implemented in recent years, in addition to conventional intraoperative images such as images that appear equal to the naked eye, microscope-enlarged images, and narrow fields of view from endoscopes. Blood flow imaging

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Table 1 Current literature review of intraoperative visible information for glioma surgery

Visible information	Method of examination	Purpose of examination	Parameter of examination	Author	Year	Total cases	Extent of resection (EOR)	Postoperative complication			Evidence level
								Results	False-positive	False-negative	
Anatomical (GA, AC)	iMRI	acurate localization	Updated navigation	Senft et al.54)	2011	49	*0 ml vs. 0.03 ml (residual volume)	13% vs. 8% (with vs. without iMRI)			2
	iUS	acurate localization	Updated navigation	Prada et al.55)	2014	67	NA	NA			
Histological (GA, AC)	Fluorescence	malignancy	Five-aminolevulinic acid (5-ALA)	Stummer et al.68)	2006	251	*65% vs. 36% (complete resection rate)	No difference (with vs. without 5-ALA)			2
	Flow cytometry	malignancy	DNA aneuploidy	Shioyama et al.72)	2013	81	NA	NA			
Functional (GA)	SEP	sensory	Direct cortical stimulation	Thirumala et al.15)	2013	139		3.6%	6/139 (4.3%)	1/139 (0.7%)	
	MEP	motor	Direct cortical stimulaton	Krieg et al.21)	2012	112		30.3% (Trans.+Perm.)	15/39 (38.5%)	10/73 (13.7%)	
				Gempt et al.24)	2013	70		45.7% (MR ischemia)	5/70 (7.1%)	16/70 (22.9%)	
		motor	Direct subcortical stimulation	Neuloh et al.17)	2007	72		27.8% (Trans.+Perm.)	12/32 (37.5%)	0/40 (0%)	
				Szelényi et al.22)	2010	29		44.8% (new motor deficits)	3/15 (20.0%)	1/14 (7.1%)	
		motor	Transcranial stimulation	Zhou and Kelly.30)	2001	50		*16.7% (motor deterioration)	0/8 (0%)	0/40 (0%)	
	iDTI	motor	Tracking with navigation	Maesawa et al.67)	2010	28		42.8% (Trans.), 3.5% (Perm.)			
				Prabhu et al.66)	2011	12		if probe to CST < 5 mm			
	iDWI	motor	Updated navigation	Ozawa et al.65)	2009	7		Positive to CST: 0 mm–4.7 mm			
Functional (AC)	MEP	motor	Direct cortico/ subcortical stimulation	-	-	-		Direct motor monitoring do not show false-negative results			
	Real-time HFO	language	Electrocorticogram (ECoG)	Kamada et al.40)	2014	7		NA			
	CCEP	language	Direct cortical stimulation	Yamao et al.47)	2014	6		33.3% (new symptom)	0/2 (0%)	0/4 (0%)	

(*Continued*)

Table 1 (Continued)

Visible information	Method of examination	Purpose of examination	Parameter of examination	Author	Year	Total cases	Extent of resection (EOR)	Postoperative complication			Evidence level
								Results	False-positive	False-negative	
				Saito et al.46)	2014	13	30–100% (median 95%)	61.5% (New symptom)	0/7 (0%)	1/5 (20%)	
	Mapping	motor	Direct cortical stimulation	-	-	-		Direct motor monitoring do not show False-negative relusts			
		language	Task, direct cortical stimulation	Sanai et al.36)	2008	250	59.6% (total resection rate)	1.6% language deficit			
				Duffau et al.38)	2009	24	62.5% (total, subtotal resection rate)	50% (Trans.)			
		language	Task, direct subcortical stimulation	Trinh et al.39)	2013	214		*38% (Immediate), 13% (3M later)			
	Monitoring	motor/ language	Manual muscle testing/direct assesment	-	-	-	See meta-analysis (below)	See meta-analysis (below)			
Functional (AC vs. GA)	meta-analysis			De Witt Hamer et al.31)	2010	8,091	74.8 vs. 58.3% (complete resection rate)	*3.4% vs. 8.3% (AC vs. GA)			2
	meta-analysis			Brown et al.32)	2013	951	41% vs. 44% (tumor mean EOR)	*7% vs. 23% (AC vs. GA)			2

*: statistically significant difference, AC: awake craniotomy, CCEP: cortico-cortical evoked potential, FN: false-negative, FP: false-positive, GA: general anesthesia, HFO: high frequency oscillation, iMRI: intraoperative magnetic resonance imaging, iDTI: intraoperative diffusion tensor imaging, iDWI: intraoperative diffusion weighted imaging, iUS : intraoperative ultrasonography, MEP: motor evoked potential, NA: not applicable, SEP: somatosensory evoked potential, Perm.: permanent, Trans.: transient.

with fluorescein fluorescence, selective fluorescence images of tumors made using 5-aminolevulinic acid (5-ALA) staining, intraoperative X-ray imaging using O-rings or flat panels, and intraoperative MRI are examples of these new modalities, and intraoperative motor evoked potentials (MEPs) and functional mapping/monitoring with awake craniotomy (AC) can also be considered as methods of visualizing brain function.

This article discusses and reviews approaches to integrating intraoperative functional information and making diagnoses in terms of maximizing the EOR while minimizing the risk of neurological impairment. We propose a new concept of using visualized biomedical signals in the surgical decision-making process. Under this concept, visualized data is defined as “information,” and we introduce the basic concepts of information-guided surgery using multimodal information to make decisions. We then describe the mechanisms of how errors in anatomical navigation information arise, and how false-positives (FPs) and false-negatives (FNs) arise in functional information obtained from functional mapping. Using a decision tree, we introduce practical dilemmas in decision-making for glioma resection.

Visualization for Surgical Decision-making

Specifically, we discuss new ways to visualize and objectify changes in biomedical signals that were previously analyzed based on experience, and propose a methodology to extract information to reach more objective and scientific decisions (Fig. 1).

The first step is the *visualization* of the biomedical signals in combination with a medical device alone or in combination with a drug. Intraoperative ultrasonography, CT, MRI, and identification devices with intraoperative fluorescence imaging of 5-ALA for tumor surgery and indocyanine green (ICG) for vascular surgery are all recent examples of successful visualization. In addition, tissue sampling is also a visualization method in tumor surgery, and intraoperative diagnosis is an example of its use.

The second step is the conversion of visualized signal to *digitized data* “*with meaning*.” Visualization alone already provides important material for intraoperative decisions, but if converted into analyzable digitized data, quantification of information becomes possible in a way that is useful for surgical decision-making. This represents a transformation from qualitative data (nominal variables) and semi-quantitative data (ranking variables) to quantitative data (continuous variables) that can be easily manipulated in statistical analyses. In addition, we use the term digitized data “with meaning” to differentiate from regular image data—in recent years all image data have been recorded as digital images, but no analyzable electronic meaning is attached to such images.

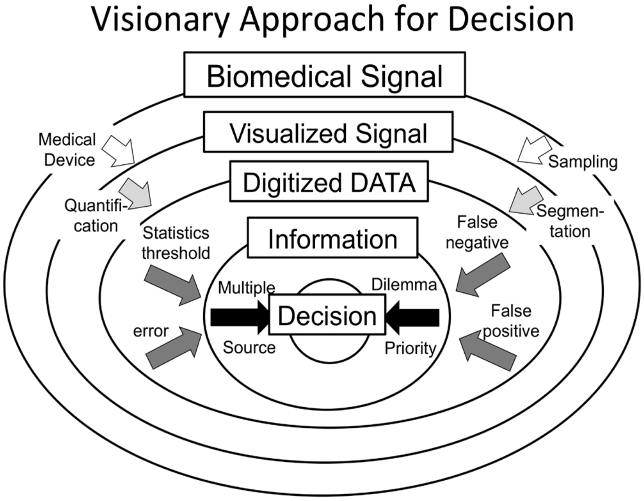


Fig. 1 Visionary approach for intraoperative decision-making. The possibility to visualizing biomedical signals has been a key factor in the dramatic development of medicine since the introduction of computed tomography and magnetic resonance imaging. For analysis of visualized signals, the images should be segmented and digitized data should be quantified. For transformation into clinically relevant information, digitized data should be further statistically processed for minimization of errors, exclusion of false-negative and false-positive values, and establishment of thresholds. The decision based on the data from multiple sources requires evaluation of their concordance and necessitates prioritizing of information from disparate sources. *Quantification*: Transformation to quantitative data (continuous variables). *Segmentation*: The process dividing an image into regions with similar properties such as gray level, color, texture, brightness, and contrast. *Statistics threshold*: The threshold value identified from statistical analyses (adapted from Muragaki et al.[78]).

The third step is the *extraction of information*. Dr. Goldratt defines “data required to reach a decision” as information.[8] Information extraction is recognized as the process of extracting usable information from the digitized data. After recognizing and minimizing measurement errors as much as possible, the possibility of FNs and FPs should be eliminated from the decision-making process as much as possible, then extract data that are as close as possible to true-negatives and true-positives (Fig. 1). Intraoperative data from each case is fed back by comparison to surgical outcomes, and if many cases of intraoperative data are stored, statistical analyses can be conducted. If a certain threshold value that matches the surgical outcome is identified from statistical analyses, "positives" or "negatives" can be determined by comparing subsequent intraoperative data with this threshold, and information is thereby extracted from the data. We will give an example of this flow of visualization, digitization, and information extraction in the section on histological information.

In making decisions using the extracted information, the situation is simple if only a single type of information exists, and even when multiple types of information exist, the decision is confirmed and strengthened if it leads to the same decision. On the other hand, one must be prepared for results leading to different decisions with multiple types of information—for example, some information may indicate tumor removal, while other information might suggest functional preservation. In this case, the relative priority of the information types must be decided in advance.

We define surgery where decisions are made by such information as information-guided surgery.[9,10] For the extirpation of brain tumors, and particularly in the removal of gliomas, anatomical information, functional information, and histological information are all necessary (Fig. 2). Furthermore, metabolic information is also important, although the information can currently only be obtained preoperatively. There is a need for navigation to integrate these pieces of information, and as a rule of thumb, functional information has the highest priority among the

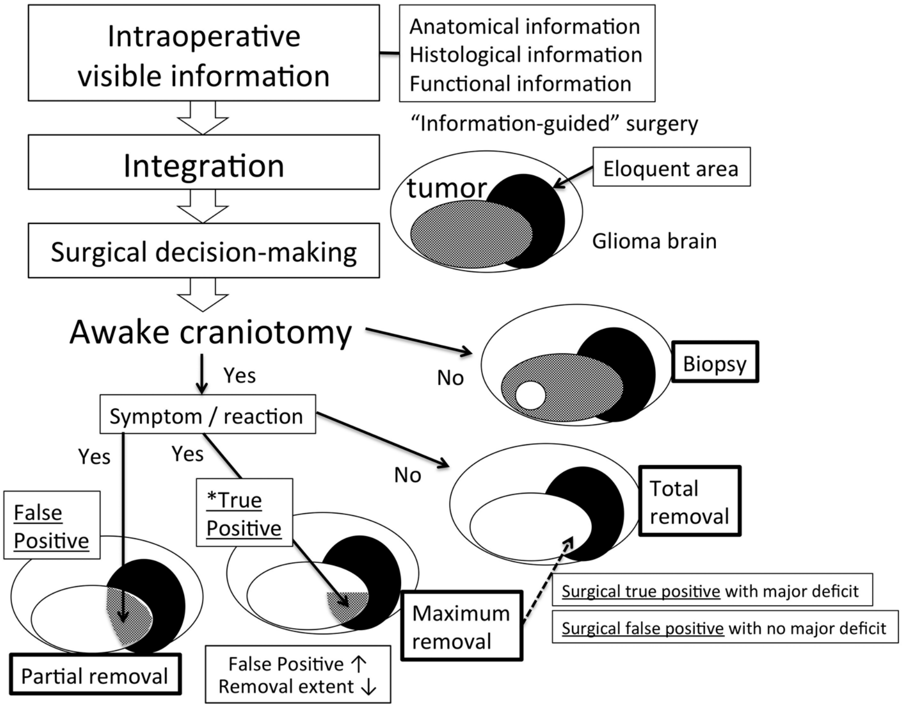


Fig. 2 Effect of intraoperative brain mapping during awake craniotomy on extent of tumor removal. Aggressive and safe tumor removal within or close to language-related structures can be achieved only during awake craniotomy, otherwise only biopsy should be planned. Total removal can be attained in cases without deterioration and/or positive reactions to stimulation within the area of surgical attack; in case of their appearance, removal is suspended. If symptoms and reactions are true-positives (*asterisk*), indicating the presence of functional tissues within the tumor, and those tissues are preserved, maximal possible tumor removal is attained (maximum removal). If symptoms and reactions are false-positives, only partial removal is performed (partial removal). However, even in the latter case, the resection rate is greater than with pure biopsy. Gaining experience with intraoperative brain mapping and monitoring reduces the probability of under-resection of tumors. Even if tumor contains functioning tissue, confirmed by true positive (*) results from brain mapping and monitoring, deep scientific knowledge and adequate surgical experience permit aggressive removal of the neoplasm (surgical false-positive with no major deficit resulting in total removal). For example, during the negative mapping technique, cortical areas non-responding to stimulation current of more than the threshold may be removed. Similarly, areas demonstrating speech arrest caused by stimulation of the subcallosal or uncinate fasciculus could be resected, since areas of frontal or temporal lobectomy include the fasciculus.

information types. In general, the best result of glioma surgery is maximal possible removal of the neoplasm, defined as radiologically total, or as subtotal leaving the residual lesion within the functioning eloquent brain structures. It can be frequently achieved in cases of low-grade gliomas. In high-grade lesions (glioblastoma multiforme) surrounded by prominent peritumoral edema surgery is usually directed on the maximal possible resection of the contrast-enhanced area.

Functional Information, FPs, and FNs

Intraoperative functional information is one of the well-integrated pieces of information in the field of general neurosurgery.

I. Sensory evoked potential (SEP) and MEP monitoring under general anesthesia (GA) (Table 1)

SEPs have been used for a while now, but MEPs have also recently become popular and can use a simpler method than electromyogram with intravenous anesthesia, without the use of muscle relaxants.

1. Although intraoperative SEP has been used to localize the somatosensory cortex prior to tumor resection,[11–13] Grant et al. evaluated the use of continuous SEP monitoring to provide a real-time assessment of sensorimotor function during tumor resection and decreasing the patient morbidity.[14] Thirumala et al.[15] studied 139 patients operated using intraoperative SEP monitoring and their results showed a positive predictive value of 45.2% for SEP (FP, 4.3%), while the negative predictive value was 99.2% (FN, 0.7%). These results indicate that continuous SEP monitoring can be helpful in reducing postoperative morbidity when the tumor is closer to the somatosensory pathway with acceptable limits.

2. MEPs differ in terms of stimulating transcranially (transcranial stimulation; TCS) or directly on the cortex (direct cortical stimulation; DCS), and also regarding potential recording from cervical epidural electrodes (D-wave) or intramuscular electrodes (compound muscle action potentials; CMAPs). Besides these differences, stimulation conditions (type, duration, frequency, intensity of pulse stimulated by mono or bipolar forms, etc.) also vary widely, and should be confirmed before interpreting results. Direct electrical cortical and subcortical stimulation are 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.[16,17] After placing the strip electrode, the median nerve is first stimulated and the central sulcus is identified based on SEP phase reversal.[11] Continuous MEP monitoring using DCS with a strip electrode enables real-time evaluation of the functional integrity of the pyramidal tract.[18] Meanwhile, intermittent subcortical mapping of the pyramidal tract with a monopolar or bipolar probe can be used to localize pyramidal tracts in white matter.[19,20] The predictive value of signal alterations (amplitude and threshold) in MEP monitoring for motor deficits has been demonstrated in several studies[17,21–23] and the rate of postoperative motor complications with FP and FN information according to the current literature are listed in Table 1.

- MEP monitoring with DCS under GA

Continuous MEP monitoring of 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.[17,21,23–25] Instead of CMAP monitoring to record MEP, D-waves are also available to allow preservation of motor function in glioma patients.[26,27] In Table 1, Krieg et al.[21] reported the rate of postoperative transient and permanent motor complications was 30.3% (FN, 13.7%) and Gempt et al.[24] indicated a rate for postoperative MRI ischemic change of 45.7% (FN, 22.9%), but both reports lacked the information on EOR and its effects on survival (Table 1). The appropriate warning criteria could detect the complications with a lower FN rate.

- MEP monitoring with subcortical stimulation under GA

Currently, subcortical mapping with a probe for bi- or monopolar stimulation is used beyond cortical stimulation to identify the pyramidal tract. This technique has also been reported as effective for glioma surgery.[17–20] Neuloh et al.[17] reported the incidence of postoperative transient and permanent motor deficits was 27.8% (FN, 0%) and Szelényi et al.[22] mentioned finding new motor deficits in 44.8% (FN, 7.1%) (Table 1). Such direct subcortical mapping is the most reliable method for localizing functionally important white matter bundles. However, subcortical mapping cannot be used to determine distance and direction to the tract, although it does provide information regarding whether the tract is near the stimulated position. With respect to the precise description of the distance and direction to the tract, Mikuni et al.[28] and Kamada et al.[29] had reported as visualizing white matter bundles (please refer to the section 'DTI, tractography').

- MEP monitoring with TCS under GA

While, MEP monitoring by TCS offers some advantages, including that the results can be compared with the contralateral MEP, placement of a strip electrode that could injure the brain surface and/or cortical veins is not required. Zhou and Kelly[30] found postoperative motor deterioration in 16.7% (FN, 0%) and the degree of the worsening was found to correlate significantly with the degree of reduction in intraoperative MEP amplitude (Table 1). The utility of MEP elicited by TCS during glioma surgery remains controversial.[22]

3. MEP under GA and direct motor monitoring under AC

In addition, database is ongoing regarding how to monitor motor function; whether to test MEPs under GA or to test motor function under awake conditions. Given the robustness of the system, we recommend a combination of both (MEP and direct motor monitoring under AC). We have experienced both cases, in which voluntary movement is unchanged even though MEPs were reduced or absent, and cases in which MEPs showed no change even though voluntary movements were reduced or absent. The combination of both may thus detect various clinical situations.

II. 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 areas as well as the positions of white matter fibers connected with speech and motor functions, helping to prevent unexpected neurological deficits. A recent meta-analysis demonstrated late severe neurological deficit in 3.4% of patients who underwent resection with stimulation mapping, compared to 8.3% of patients who underwent resection without mapping.[31] The percentage of radiologically confirmed gross total resection was 74.8% in patients treated with stimulation mapping and 58.3% in those treated without mapping. Brown et al. reviewed eight studies involving a total of 951 patients (411 treated with AC, 540 treated with GA).[32] Their interpretation of the literature reveals that the mean EOR under AC (41%) is similar to that of GA (44%), while the incidence of postoperative complications is lower with AC (7%) than with GA (23%) (Table 1). Given the effectiveness of AC for resecting eloquent tumors, these data suggest an expanded role for AC in brain tumor surgery, regardless of tumor location, indicating that intraoperative stimulation mapping should be universally implemented as the standard of care for glioma surgery. AC is recommended according to the guidelines for the management of low-grade glioma in Europe (Class III level).[2] In Japan, "The Guidelines for Awake Craniotomy" were formulated by the Japan Awake Surgery Conference, and AC has since then become the basic procedure for performing resection of tumors within or near the eloquent areas.[33]

1. Mapping under AC

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. Precise stimulus parameters for MEP in glioma surgery have been mentioned.[20,33–36]

We originally developed an information-sharing device in 2004 that provided an opportunity for all members of the surgical team to visualize a wide spectrum of the integrated intraoperative information related to patient condition, nuances of the surgical procedure, and details of the brain language mapping, practically without interruption of the surgical manipulations (Fig. 3, http://www.iemas.jp).[10,37] Language task examination is performed not only in brain mapping with DCS,[36,38] but also on direct subcortical stimulation[39] to detect language function for the maximum extent of tumor removal and minimum postoperative complication (Table 1).

2. Monitoring under AC

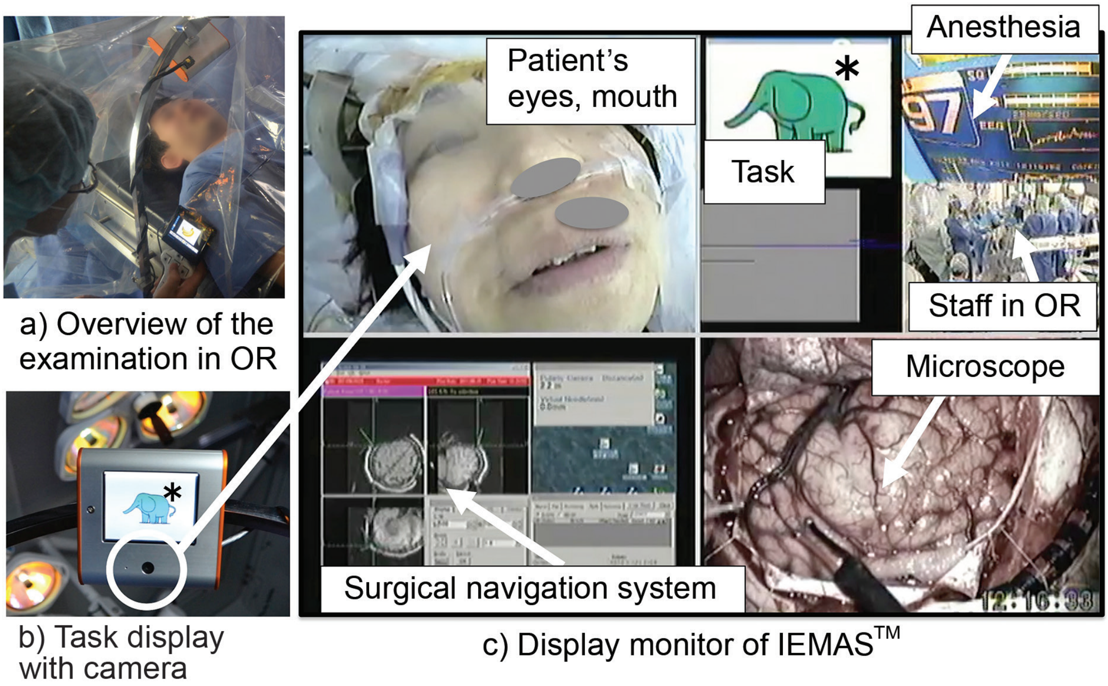
Under awake conditions, the ability of the patient to speak freely is constantly monitored during the entire procedure through continuous conversation with a member of the treatment team specialized in assessing language function, who provides specific tasks to evaluate recall, counting, fluency, and comprehension. Importantly, the findings of direct assessments do not show FN results, which prevent under-resection in patients undergoing glioma extirpation. Consequently, the parallel use of AC and intraoperative neurophysiological monitoring results in more accurate evaluation of motor and language functions.

3. Motor evoked potentials under AC

Prior studies have reported discrepancies between the results of MEP monitoring and the post- or intraoperative neurological status (FN and FP monitoring).[21,22] Furthermore, combining MEP monitoring with direct subcortical stimulation and the observation of voluntary movements helps to conduct more accurate evaluations of intraoperative motor function.

4. Real-time high-frequency oscillation (HFO) under AC

Kamada et al. developed a novel technique to visualize the electrophysiological phenomenon of HFO in real-time for intraoperative monitoring during AC.[40] Real-time HFO mapping can rapidly indicate eloquent epicenters of the motor and language functions and significantly shorten the AC.


a) Overview of the examination in OR

b) Task display with camera

c) Display monitor of IEMAS™

Fig. 3 Integration of multiple intraoperative parameters on the display monitor of the intraoperative examination monitor for awake surgery (IEMAS™). a: Overview of the language mapping with task examination in the operating theater in awake craniotomy. b: Language task display shows an adequate task (*) controlled by the examiner, viewing the eyes, mouth, and face of the patient as well as recording verbal responses. c: Display monitor of IEMAS™. Upper left display: The face and eyes of the patient can be seen to facilitate checking of consciousness status and performance during response-to-test tasks. Lower left display: Anatomical information from the real-time updated neuronavigation system is shown, allowing localization of the exact position of the cortical stimulator. Lower right display: The surgical field through the operative microscope during brain functional mapping is seen, facilitating precise identification of the timing of stimulation. Upper right display: Three different types of information are presented, which are (from clockwise): a naming task (*); parameters of the bispectral index monitor reflecting awake state; and general view of the operating room (OR). In total, six different intraoperative parameters are integrated and synchronized in real-time on a signal screen.

5. Cortico-cortical evoked potential (CCEP) under AC

The technique of CCEP monitoring is based on electrical stimulation of one cortical area while recording average response from another, permitting the assessment of functional interconnections.[41–45] Both we and Yamao et al. recently evaluated the recordings of intraoperative CCEP as an adjunctive method for assessing speech function during resection of intraparenchymal brain neoplasms.[46,47] Remarkably, CCEP recordings are task-free and do not require patient cooperation,[44] opening the possibility of monitoring speech function during neurosurgical procedures performed under GA.

III. FPs and FNs

Brain function mapping by electrical stimulation and brain function monitoring by neurological examination in AC is also spreading rapidly as a method for obtaining functional information. Functional information is required for functional preservation, but is also necessary for aggressive removal. For example, if the anatomical language areas are involved in a tumor, biopsy is the only means in facilities that do not use awake surgery, but in facilities with the possibility of awake surgery, aggressive excision of the tumor is possible if tumor and functional tissue do not coincide (Fig. 2).[48] Even with awake functional testing, tumor coexisting with functional tissue will lead to biopsy, but the reported incidence is low, at only 7%.[49]

Although brain function monitoring with awake surgery is an excellent method leading to few FNs (no intraoperative symptoms, but persistent deficits continuing after surgery), FPs (some intraoperative symptoms present, but no persistent postoperative deficit) are common, and require attention at less experienced centers. For example, if too much anesthetic is given and awakening is poor, the inability to respond to a task may lead to a judgment of deficit. Furthermore, the use of brain retractors to remove tumors surrounding the eloquent areas may lead to compression of the eloquent areas leading to positive symptoms, and a decision to terminate removal due to attribution of the false symptom to excessive removal. Even with such FPs, more tissue can often be removed compared to the biopsy method, and it is possible to maximize excision margins and eliminate FPs through facility-wide technical improvements (Fig. 2).

IV. Surgical true-positive and surgical FP

As an advanced discussion, there is the issue of whether a "true positive" with mapping/monitoring (M/M) is surgically a true positive. That is, whether excision will lead to permanent deficits. Excising tissue that is truly positive in M/M will lead to deficits and therefore preservation is standard; in other words, M/M serves to determine what to preserve. On the other hand, from many recent cases and from historical observations in neurosurgery, in many cases excision of M/M-positive tissue may be possible, and may result in only minimal or absent deficits (surgical FP). For example, Sanai et al. propose a negative mapping technique,[36] where excision is performed if there is no reaction under certain stimulus conditions (60-Hz bipolar stimulation at up to 6 mA; of note, absolute thresholds differ with stimulus conditions). This is an example of such concerns, and means that response with stimulation over a threshold current intensity yields a positive in terms of M/M, but is judged as surgically FP. We have also encountered cases of clear speech arrest in the deep anterior temporal lobe and frontal lobe lateral anterior horn in the dominant hemisphere. The former deficit was attributed to stimulation of the uncinate fasciculus (note the difference from the arcuate fasciculus), the latter to the subcallosal fasciculus, with both tracts involving language-related fibers.[50] However, both sites are surgically removable, and indeed, excision showed no significant postoperative complications in either case (Fig. 2). We identified three grammar-related circuits in the process of measuring grammar-task activated areas in fMRI[51] and tracing their fiber connections with diffusion tensor imaging (DTI).[52] The three identified circuits were the longitudinal fasciculus itself in the dominant hemisphere, a large circuit in the dominant hemisphere consisting of inferior fronto-occipital fasciculus and corticocerebellar connecting fibers, and a circuit connecting the left and right hemispheres through the corpus callosum.[52] These findings in neuroscience suggest that language-related fibers not involved in these circuits such as the uncinate fasciculus and the subcallosal fasciculus may be excised without incurring major deficits.

V. Positive motor, negative motor, and language area

Areas that cause speech arrest in cortical mapping include positive motor areas, negative motor areas, and language areas (anterior language area, posterior language area) (Fig. 4). Negative motor areas show

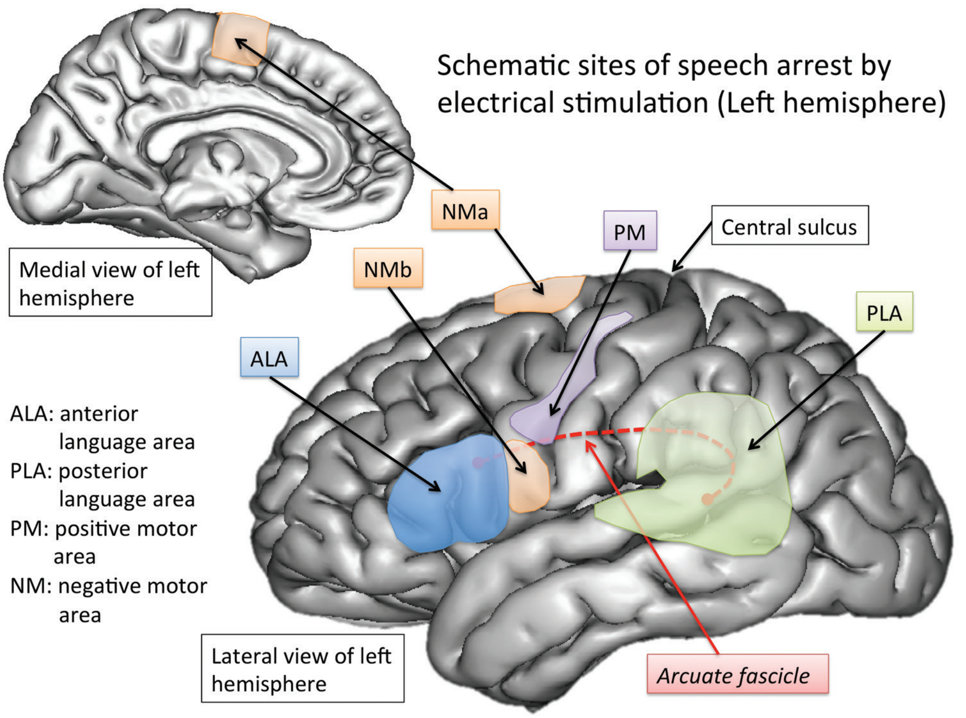


Fig. 4 Schematic sites of speech arrest by electrical stimulation (left hemisphere). Lateral and medial cortical surface of left hemisphere on which speech arrest can be induced by electrical stimulation. These schematic sites provide three types of speech arrest that is, positive motor (PM) area, negative motor (NM) area, and language area including anterior language area (ALA) or posterior language area (PLA), as well as their subcortical connections (arcuate fascicle). NMb is approximately located in the posterior part of ALA. NMa: Negative motor area located in the supplementary motor area in the medial superior frontal gyrus and NMb: negative motor area in the lateral pre-central gyrus near the Sylvian fissure.

no reaction such as muscle contraction (as is seen with stimulation of the positive motor areas), but exhibit a characteristic arrest of coordinated hand movements as well as speech arrest during task performance. These are said to be present in the supplementary motor area in the medial superior frontal gyrus, and in the lateral pre-central gyrus near the Sylvian fissure located in the posterior part of anterior language areas. It has not yet been determined whether excision is possible, but Mikuni et al. have reported only transient deficiency symptoms after removal,[53] and Kumabe et al. have made a conference report of a case in which removal lead to persistent dysarthria. Having experience with both cases ourselves, further consideration is awaited in the future.

Surgical resection of gliomas located within or in close vicinity to language-related cerebral structures represents significant challenge. To minimize the risk of permanent postoperative speech dysfunction detailed localization of the anterior language area (ALA) and posterior language area (PLA), as well as their subcortical connections, is critical. However, the most effective and precise method is direct brain mapping using electrical stimulation, which can be accomplished either after implantation of the chronic subdural grid electrodes, or during AC. During examination speech production, repetition, object naming, verb generation, and reading tasks are used with simultaneous stimulation of the different language areas. According to CCEPs study that described the connection between the ALA and PLA in the language dominant hemisphere, it was rather difficult to detect speech function in PLA than in ALA because of a rather broad neuronal network, indicated smaller number of projection fibers excited by single pulse stimulation.[44]

Accuracy and Risks of Anatomical Information

In general, anatomical information is often used for navigation with preoperative MRI, but use of navigation that is updated with intraoperative MRI (updated navigation) is preferable. This gives higher accuracy, for instance regarding intraoperative brain shift, which will be described later. It also allows identification of residual tumor and complications such as bleeding, and therefore contains an extremely large amount of information. Senft et al. reported a significant advantage of using intraoperative MRI with regard to EOR[54] (in Table 1, anatomical information also indicates the usage of intraoperative ultrasonography[55]).

I. DTI, tractography

In neuroscience, the development of tractography using DTI, which suggests the directions of white matter fibers, has exerted a major impact on functional MRI (which suggests cortical function). It has become the target of a large number of studies on its correlation with disease/symptoms, in relevant clinical fields such as neurosurgery as well as neurology, psychiatry, and others. In particular, there are active efforts to superimpose tractography data onto navigation systems in the field of neurosurgery, and is used to try to preserve the pyramidal tract and superior longitudinal fasciculus. With respect to visualizing the tract, the effectiveness of diffusion-weighted imaging (DWI) and DTI techniques for fiber tracking has been investigated.[56] Mikuni et al. directly compared the results of fiber tracking based on preoperative images and subcortical electrical stimulation during intraoperative neuronavigation.[28] Their results suggest that MEPs 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 characteristics of the pyramidal tract on tractography and subcortical electrical stimulation and found that a minimum stimulus intensities of 20 mA, 15 mA, 10 mA, and 5 mA were associated with stimulus points approximately 16 mm, 13.2 mm, 9.6 mm, and 4.8 mm from the pyramidal tract, respectively.[29]

II. Errors and underestimation in DTI

In principle, the method allows unification of anatomical information with functionally suggestive fiber bundle/functional information. However, one must be aware of multiple sources of error. The most significant factor is the inherent inter-investigator variance in tractography, appearing as differences in fiber measurement depending upon the operator. The software for this method requires specification of a region of interest (ROI) as a transit point for the fibers, but studies of the same patient analyzed by different groups have demonstrated that differences in software and differences in specified points can lead to great variations in the results of analysis.[57] The major problem from a surgical perspective is that the fibers present may be underestimated and not rendered (FNs), leading to the possibility of unexpected complications from removal in accordance with the FN navigation results.[58] Indeed, one case report has described paralysis after extracting distant from the pyramidal tract based on tractography navigation. One must pay attention to careful visualization with the appropriate ROI specification, but tractography is also plagued by the fundamental characteristic that crossing fibers cannot be visualized. The fibers of the upper limbs and face are well known to be unable to be visualized due to the pyramidal tract intersecting the superior longitudinal fasciculus. New methods such as diffusion spectrum magnetic resonance imaging (DSI)[59)] and Q ball imaging[60)] have now made it possible to visualize the crossing fibers.[61)] To avoid underestimation errors, however, it is necessary to be aware of the rough distance between the tumor and critical fibers, using original images such as DTI color maps and DWI focused on specific fibers.

III. Brain shift in DTI, intraoperative DWI (iDWI), and intraoperative DTI (iDTI)

One source of error in navigation from preoperative tractography images is the aforementioned brain shift. Although intraoperative displacement of fibers due to brain shift has been measured by intraoperative tractography (fiber-tracking) as 2.7 mm on average,[62)] not only do some cases sink inward, but examples also exist where the brain shifts and "floats" up outwards, indicating difficulties in simulation and prediction. To minimize errors caused by brain shift, navigation with intraoperative images is the only possibility. In order to address errors caused by operator differences and brain shift in tractography, we had developed a navigation system using low-field iDWI in 2003,[63,64)] and intraoperative displacement of the pyramidal tract in this study was a means of 4.4 mm,[65)] while Prabhu et al.[66)] and Maesawa et al.[67)] examined the correlations between the results of subcortical stimulation and the course of the pyramidal tract on tractography using intraoperative DTI (iDTI) (Table 1). Prabhu et al. noted a trend toward worsening of neurological deficits if the distance from the stimulus probe to the pyramidal tract was short (< 5 mm), indicating the close proximity of the resection cavity to the pyramidal tract based on subcortical stimulation and iDTI tractography.[66)] 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.[67)] 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. Tractography is an extremely important new technology for the brain surgeon to visualize nerve fibers. Based on an understanding of FNs and error issues, this method should be used actively in preoperative simulations, intraoperative decision-making, and postoperative evaluation.

Visualization and Extraction of Histological Information

Histological information is important when determining excision margins for the removal of gliomas with unclear boundaries. Although the contrast-enhanced areas in glioblastoma and imaging areas of relative clear boundary can be determined under the operating microscope with experience, this is limited to only some cases and certain areas, so there is a need for an intraoperative diagnostic method with high reliability. Rapid intraoperative diagnosis with frozen sections and smears is a histological visualization method with a long history, and is currently the most reliable gold standard. On the other hand, even though this method provides information to determine surgical strategy, it does suffer from certain drawbacks that may lead to errors, such as difficulties with extremely small sample of tissue, low morphological quality compared to formalin-fixed specimens, and pressure on the pathologist to provide a rapid report.

New technologies for visualizing histological information have been developed, and a representative example is intraoperative photodynamic diagnosis with 5-ALA. In this method, the porphyrin IX metabolized in cells is excited, and the tumor cells "glow" in a specific manner and become visible. The approach is particularly useful for contrast-opaque glioblastoma, and a randomized trial has shown that when compared to excision under natural light, more cases achieve total excision (65% vs. 36%) and 6-month progression-free survival (41% vs. 21%).[68)] In the field, the results of this method are qualitative, with interpretations such as strongly positive, weakly positive, and negative. Devices are therefore under development to determine a threshold and drive the suction device based on the results.[69)] A method for discriminating tumor by Raman spectroscopy, which does not require drug application, has also been reported.[70)] Photodynamic diagnosis with 5-ALA offers a simple and useful method capable of imaging the entire operative fields in real-time, but issues have been identified, such as a tendency towards FPs in the case of recurrence, and FNs in cases of low-grade glioma using the standard protocol. On the other hand, attempts to utilize methods conventionally conducted in the laboratory for intraoperative diagnosis by rapidly performing these methods on excised tissue have gained popularity. Examples include rapid immunohistochemistry devices and rapid isocitrate dehydrogenase (IDH) mutation analyses.[71)] We have also developed an apparatus capable of DNA analysis by flow cytometry within

8 minutes, in an intraoperative context.[72] Not only is the cell cycle of the tissue visualized, we devised a malignancy index and digitized the histogram to a single value. Comparing this value to 328 cases along with malignancy index from pathological diagnoses, we were able to determine the threshold between normal tissue and tumor, thereby converting the data into information. This method is useful in the differentiation of low-grade glioma from cortical dysplasia, and also in determining the excision margins for glioma.

Integration of Multimodal Information for Decision-making and Priorities

Information-guided surgery allows overall decision-making using visualized data converted into information, but also presents a dilemma due to the wide range of information types (Figs. 1, 2). The biggest dilemma is seen when abnormalities persist in the anatomical information from intraoperative MRI, but functional information from functional mapping demonstrates a tissue as an important eloquent area. The former suggests excision, whereas the latter suggests preservation. The solution is to use other information, such as histological information from intraoperative rapid tissue diagnosis, etc., or on occasion, to use information from methionine positron emission tomography (PET), which can only provide preoperative information.

Brain functional plasticity

Histological information suggesting the absence of tumor mass argues for preservation, but whether to excise an area or give priority to functional information and preserve the tissue can be debated when a tumor mass is present. One theoretical basis for the decision to conserve tissue is that reorganization of functional fields within the tumor has been observed on recurrence,[73–77] and excision can be performed upon relapse, when the tumor does not include a functional area. This strategy is reasonable for low-grade or anaplastic gliomas, but for glioblastoma, given that reorganization is mainly reported as requiring re-operation after 2–3 years and that the possibility of functional areas coexisting within the tumor is lower, excision should be given priority. The most important point is to determine basic policies within the facility and team, and then to take into account the patients' preferences regarding preservation or removal.

In this manner, intraoperative decisions vary from important decisions such as excision margins as described above, to determination of skin incisions. The factors involved in the decision-making process are often unknown even to the individual surgeon, and may be totally unclear to many staff members. This is why these factors are referred to as tacit knowledge, but we believe that determination of the factors and visualization of the decision tree allows visualization (formalization) of the decision process, and that highly reproducible decisions closer to those of an experienced surgeon are thereby possible. In addition, visualization and digitization of judgment factors also allows statistical analysis, providing feedback for better decisions in the future.

Conclusion

In this article, we started from the visualization of intraoperative biomedical signals, and discussed digitization and conversion into information, as well as the accuracy and errors inherent in anatomical, functional, and histological information. Furthermore, we described an example of functional information-guided surgery in which this information is integrated for intraoperative decisions, and we presented a decision tree leading to the diagnosis of excision margins.

In information-guided surgery, it is possible to link various types of information using navigation as an information-hub, and incorporation of a decision process that formalizes various types of information will allow more accurate intraoperative surgical decision-making.

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Conflicts of Interest Disclosure

The authors report no conflicts of interest concerning the materials or methods used in this article.

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