ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2018-0122

Neurol Med Chir (Tokyo) 58, 442–452, 2018

Application of Awake Surgery for Epilepsy in Clinical Practice

Satoshi MAESAWA,[1,2] Daisuke NAKATSUBO,[2] Masazumi FUJII,[3]
Kentaro IIJIMA,[2,4] Sachiko KATO,[2,5] Tomotaka ISHIZAKI,[2]
Masashi SHIBATA,[2] and Toshihiko WAKABAYASHI[2]

[1]*Brain and Mind Research Center, Nagoya University, Nagoya, Aichi, Japan;*
[2]*Department of Neurosurgery, Nagoya University School of Medicine, Nagoya, Aichi, Japan;*
[3]*Department of Neurosurgery, Fukushima Medical University, Fukushima, Fukushima, Japan;*
[4]*Department of Neurosurgery, Tosei General Hospital, Seto, Aichi, Japan;*
[5]*Radiosurgery Center, Nagoya Kyoritsu Hospital, Nagoya, Aichi, Japan*

Abstract

Epilepsy surgery aims to control epilepsy by resecting the epileptogenic region while preserving function. In some patients with epileptogenic foci in and around functionally eloquent areas, awake surgery is implemented. We analyzed the surgical outcomes of such patients and discuss the clinical application of awake surgery for epilepsy. We examined five consecutive patients, in whom we performed lesionectomy for epilepsy with awake craniotomy, with postoperative follow-up > 2 years. All patients showed clear lesions on magnetic resonance imaging (MRI) in the right frontal (*n* = 1), left temporal (*n* = 1), and left parietal lobe (*n* = 3). Intraoperatively, under awake conditions, sensorimotor mapping was performed; primary motor and/or sensory areas were successfully identified in four cases, but not in one case of temporal craniotomy. Language mapping was performed in four cases, and language areas were identified in three cases. In one case with a left parietal arteriovenous malformation (AVM) scar, language centers were not identified, probably because of a functional shift. Electrocorticograms (ECoGs) were recorded in all cases, before and after resection. ECoG information changed surgical strategy during surgery in two of five cases. Postoperatively, no patient demonstrated neurological deterioration. Seizure disappeared in four of five cases (Engel class 1), but recurred after 2 years in the remaining patient due to tumor recurrence. Thus, for patients with epileptogenic foci in and around functionally eloquent areas, awake surgery allows maximal resection of the foci; intraoperative ECoG evaluation and functional mapping allow functional preservation. This leads to improved seizure control and functional outcomes.

Key words: awake surgery, electrocorticography (ECoG), epilepsy, intraoperative mapping, lesionectomy

Introduction

The goal of surgery for brain tumors, such as gliomas, is to achieve maximal resection of tumorous tissue while preserving eloquent function as much as possible. On the other hand, in epilepsy patients, the area targeted for resection is the epileptogenic focus, where the tissue may include focal cortical dysplasia (FCD), hippocampal sclerosis, low-grade tumors, vascular malformations, gliosis, etc. Thus, the goals of these surgeries differ, and the goal for epilepsy surgery should be to resect only the epileptogenic zone to control epilepsy while preserving function. Thus, in epilepsy surgery, it is crucial to identify the epileptogenic zone using a combination of electrophysiological and neuroradiological findings. Although non-invasive methods, such as magnetic resonance imaging (MRI) and magnetoencephalography (MEG) have progressed markedly in recent years,[1,2] identification of epileptogenic foci remains challenging, and requires invasive evaluation. Epileptogenic regions often show only subtle histopathological changes, and no imaging abnormalities (FCD type 1). These foci are often located in functionally important areas, such as language and sensorimotor areas, hampering determination of

---

Received May 16, 2018; Accepted August 9, 2018

a resection border. In such situations, awake surgery may be effective.

Awake surgery for epilepsy has certain advantages. First, functional mapping can be performed intraoperatively under awake conditions, allowing identification of eloquent areas, and these functions can be continuously monitored during lesionectomy. Second, intraoperative electrocorticograms (ECoG) can be recorded without being influenced by anesthesia. Therefore, awake surgery provides almost equal ECoG information in the interictal phase to those of step-2 chronic invasive ECoG recording in the patients' ward, which is usually problematic and is an important cause of epilepsy patient drop-out from presurgical evaluation.[3] However, awake surgery has some disadvantages: spatial limitations of craniotomy, limited intraoperative time, and the inability to perform ictal recording. Furthermore, interpretation of ECoG findings is still controversial.[4,5] Another limitation is patients' cooperation for undergoing awake surgery. Some patients cannot sufficiently cooperate because of young age, intellectual disabilities and/or psychiatric problems, which are common characteristics often observed in epilepsy patients.

For clinical application of awake surgery for lesionectomy in epilepsy, we consider three clinical questions that are specific to epilepsy surgery. First, is intraoperative ECoG under awake conditions useful for epilepsy surgery? Second, is it possible to evaluate other higher cognitive functions, such as memory, which are important outcomes in epilepsy surgery, during awake surgery? Finally, does maximal lesionectomy lead to good outcomes in epilepsy surgery? We performed awake surgery in five patients with suspected epileptogenic foci in or around the functionally eloquent areas. We present the results of our experiences in terms of the above-mentioned clinical questions, review previous reports, and discuss the clinical application of awake surgery for epilepsy.

Materials and Methods

Patients' characteristics

Between April 2013 and March 2016, we performed epilepsy surgery including lesionectomy, anterior temporal lobectomy, and selective amygdalohippocampectomy in 31 cases at Nagoya University Hospital (Nagoya, Aichi, Japan). Among them, we performed awake surgery in five patients (three males and two females), and those were followed-up postoperatively for more than 2 years. These patients were subjects of this study. Inclusion criteria for the patients were as follows: The patients suffered from focal epilepsy, which had been uncontrolled by more than two optimal anticonvulsants for more than 1 year. The epileptogenic zone was preoperatively determined to be in or near the functionally dominant areas by routine evaluations, including MRI, functional MRI, MEG, fluoro- deoxyglucose positron emission tomography (FDG-PET), conventional electroencephalogram (EEG), and video-EEG monitoring. The patients had no intellectual disabilities or psychiatric problems, and their general condition was sufficiently good for undergoing awake surgery. The study protocol was approved by the ethical committee of the Nagoya University Graduate School of Medicine and Nagoya University Hospital (2013-0081). The treatment and study protocol were explained to the patients, who understood this and chose to undergo the treatment, and provided written informed consent for their participation.

The mean age at surgery was 28.6 ± 6.05 years (mean ± SD). All but one of the patients had focal epilepsy, occasionally followed by generalized tonic convulsion (secondary generalized convulsion). One patient (case 2) had focal epilepsy with impaired awareness and oral/hand automatism (complex partial seizure). The average seizure frequency ranged from three per month to five per day. All patients showed clear lesions on MRI, which included suspected low-grade glioma ($n = 2$), gliosis after arteriovenous malformation (AVM) rupture ($n = 2$), and cavernous malformation; preoperatively, those were presumed to be the epileptogenic lesions. The lesions were located in the right frontal (premotor cortex, $n = 1$), left temporal (superior/middle/inferior temporal gyrus, $n = 1$), and left parietal lobe (anterior transverse parietal gyrus, subcentral gyrus, and marginal/posterior central gyrus, $n = 3$). Patients' characteristics are summarized in Table 1.

Awake surgery and intraoperative brain mapping

All patients underwent awake surgery with direct cortical stimulation, according to the "Guidelines for Awake Craniotomy."[6] We performed partially awake surgery, in which craniotomy was first accomplished under general anesthesia with a laryngeal mask (i-gel, Intersurgical, Wokingham, UK); then, anesthesia agents were withdrawn and the mask removed. Intraoperative brain mapping and monitoring, with direct cortical stimulation, were performed in an awake condition. At the end of the surgery, the patient was re-intubated and cranioplasty with wound closure was performed under general anesthesia. For one patient (case 2), general anesthesia was reintroduced before resecting of mesial temporal structure (see later description). ECoGs were also recorded in and/or around suspected epileptogenic foci with three strip electrodes (18 contacts), during the awake portion of the surgery. The sampling rate was 1000 Hz, and recording was

Table 1 Patients' characteristics

Case	Age/sex	Seizure symptoms	Seizure frequency	R/L	Location of lesion	Pathology	Eloquent area near by
1	30/F	Motor seizure in left arm and leg, occasionally genearalized tonic-clonic convulsion	Five times per day	R	Frontal lobe (premotor cortex)	Oligodendroglioma G2	Motor area
2	38/F	Dyscognitive seizure with oral and hand automatism	Three times per week	L	Temporal lobe (STG, MTG, ITG)	Gliosis after AVM rupture	Language area
3	28/M	Sensorimotor seizure in right hand and leg, occasionally genearalized tonic-clonic convulsion	Three times per day	L	Parietal lobe (ATPG)	PXA G2	Language, motor areas
4	28/M	Sensorimotor seizure in right hand and leg, occasionally genearalized tonic-clonic convulsion	Three times per month	L	Parietal lobe (subcentral gyrus)	Cavernous malformation	Language, motor areas
5	19/M	Sensorimotor seizure in right hand and leg, occasionally genearalized tonic-clonic convulsion	Three times per day	L	Parietal lobe (PCG, marg. G)	Gliosis after AVM rupture	Language, motor areas

ATPG: anterior transeverse parital gyrus, AVM: arteriovenous malformation, ECoG: electroencephalography, F: female, G: grade, ITG: inferior temporal gyrus, L: left, M: male, marg. G: marginal gyrus, MTG: middle temoporal gyrus, PCG: posterior central gyrus, PXA: plemorphic xhantoastrocytoma, R: right, STG: superior temporal gyrus.

performed for about 10 min before as well as after lesionectomy, using a Neuromaster MEE1200 (Nihon Kohden, Tokyo, Japan). Language mapping was performed with a bipolar electrode (Unique Medical, Osaka, Japan). Direct stimulation was applied for less than 4 s with a biphasic current intensity between 2 and 8 mA (60-Hz pulse frequency, 0.5-ms single pulse phase). Picture naming was standard for the language task, and we occasionally added auditory comprehension and repetition of short sentences, if necessary. Sensorimotor mapping was also performed using such direct stimulation, and we checked for motor symptoms, such as weakness and contraction of muscles, and sensory symptoms, such as dysesthesia in the contralateral part of the face and limbs. After-discharges were monitored in ECoG during stimulation for the patient's safety. After determining the eloquent cortical areas, removal of the epileptogenic focus was initiated. For neocortical epilepsy, a gyrectomy approach was used, and subcortical mapping was performed to determine the functional boundary in the deeper area. For subcortical mapping, the electrical stimulation parameters were the same as those used for cortical mapping. Our method for subcortical mapping has been described previously.[7,8]

Recognition-memory mapping

For one patient with temporal lobe epilepsy, recognition-memory mapping was performed. This mapping technique was designed to map the recognition-memory function in the hippocampus, which was originally reported by Coleshill et al.[9] The paradigm involved 4 phases: acquisition, interference, free recall, and recognition. In the acquisition phase, the patient was instructed to memorize three unrelated words for 2 s each after auditory presentation. One word was used as control, without stimulation, and two words were trial words, accompanied by electrical stimulation. In addition, three unrelated pictures were visually presented for 2 s. One picture was used as a control, without stimulation, and the other two were trial pictures, accompanied by electrical stimulation. The parameter of electrical stimulation was the same as for the cortical mapping described earlier, with an intensity of 2 mA. The second phase was used for interference. As a distractor, 60 random kana letters appeared on the monitor for 1 s each, for a total of 60 s. The patient was instructed to verbalize when she saw only the letter "A" or "E". The third phase was for free recall. The patient was instructed to recall the words or pictures presented during the acquisition phase, freely. The last phase was for recognition. Six items, including three targets and three foils, were presented, and the patient answered whether they were truly presented.

The results of intraoperative mapping and ECoG were examined. The postoperative course, including neurological symptoms and seizure outcomes, were evaluated.

Results

Intraoperative mapping in awake surgery

All patients smoothly awoke upon anesthesia withdrawal after craniotomy, and lesionectomy was performed with intraoperative electrical stimulation under the awake condition. Sensorimotor mapping successfully identified the primary motor and/or sensory cortex in four cases, but not in one patient (case 2) who underwent temporal craniotomy. In the primary motor and sensory area, positive reactions, including muscle contraction, motion arrest, and tingling sensations were produced by 2-mA stimulation. After-discharge was often seen in these areas, but was controlled by irrigation with iced lactated Ringer's solution, and anticonvulsant administration was unnecessary. Motor evoked potential monitoring was not necessary, because detailed somatotopy was identified by the low intensity of stimulation in the awake condition. Language mapping was performed in four of the five cases (cases 2, 3, 4, and 5) in which the language-dominant area was suspected to be localized close to the epileptogenic zone. The anterior (Broca's area) and posterior language areas (Wernicke's area) were identified in three cases (cases 2, 3, and 4), at the anatomically predicted locations. In case 5, the language centers were not identified during intraoperative mapping; this patient had previous intracranial hemorrhage due to AVM rupture in the left inferior parietal lobule (see later description). Memory recognition mapping was performed in one case (case 2), for whom the necessity of additional hippocampectomy was under discussion at the time (see later description). Subcortical mapping was applied in all cases. However, since the epileptogenic focus was usually located in the cortex, we did not remove deep subcortical tissues, and this mapping was thus less important. These results are summarized in Table 2.

Intraoperative ECoG in awake surgery

Intraoperative ECoGs were successfully recorded a few times in all cases, before and after resection. In three cases (cases 1, 3, and 4), frequent spikes were observed in and around the epileptogenic zone before lesionectomy. In these cases, ECoG was re-evaluated after lesionectomy. Although a few spikes remained around the resected area, including sensorimotor or language areas, we did not extend the resection, because the number of spikes had decreased markedly and/or some functionally dominant regions were involved. Thus, ECoG information did not change the surgical strategy in these cases. However, case 2 showed frequent spikes in the hippocampus, and therefore, hippocampectomy was also performed. Case 5 demonstrated frequent spike and waves in the posterior central gyrus. Although this area was positive for sensory mapping of the contralateral hand and face, we explained to the patient on the operation table about the risk of dysesthesia and the benefit of seizure control after removal of the posterior central gyrus. The patient agreed to additional resection of this area. Therefore, in these two cases, ECoG information changed the surgical strategy. These results are summarized in Table 2.

Postoperative course and epilepsy outcomes

Postoperatively, no neurological deterioration was seen in any of the patients. Seizure was absent for more than 2 years in four of the five cases. In one case (case 1), seizure had disappeared for 2 years,

Table 2 Intraoperative findings in awake surgery and postopeartive courses

Case	Sensori-motor area identified	Language area identified	Recording of intra-opeartive ECoG	ECoG changes surgical strategy	Follw-up month	Out-comes (Engel class)	Complication
1	Yes	No	Yes	No	52	3b	None
2	No	Yes	Yes	Yes	48	1	Slight memory deterioration
3	Yes	Yes	Yes	No	46	1	None
4	Yes	Yes	Yes	No	36	1	None
5	Yes	No	Yes	Yes	30	1	Transient dysesthesia in right hand

ECoG: electroencephalography.

but recurred in the 25th month of follow-up, along with recurrence of the original tumor (oligodendroglioma, grade 2) in imaging studies. Thus, four of the five cases were Engel class 1 and one case was class 3b (Table 2).

Representative case (case 2)

The patient was a 37-year-old female with left temporal epilepsy. She was right-handed. She experienced generalized tonic seizure for the first time in 2004, and intracranial hemorrhage due to AVM was found in the left anterior temporal area. The AVM was treated with gamma knife radiosurgery and had disappeared 2 years later; however, her seizures remained and occurred frequently. She had focal epilepsy, which started with de-ja-vu and impaired awareness, with oral and hand automatism and was occasionally followed by generalized tonic–clonic convulsion. The seizures occurred 2–5 times per week, despite sufficient administration of antiepileptic drugs. In 2013, she was referred to our hospital. MRI demonstrated a hemorrhagic scar in the left anterior temporal area, extending to the posterior superior temporal gyrus (STG) (Fig. 1). Hippocampal sclerosis was not apparent. FDG-PET demonstrated low-uptake of glucose in the left anterior and medial temporal area (Fig. 1). Interictal EEG showed intermittent spike and waves in F7 and T_1, and ictal EEG with bilateral sphenoidal electrodes (SPs) showed seizure onset in the left medial temporal area (left SP). MEG showed dipoles at the anterior STG. Functional MRI was performed with language tasks, and language dominancy was suspected in the left. Wada test was performed by intracarotid injection of propofol. The dominant side for language was also suspected in the left. For visual and verbal memory function, lateralization was not apparent. Neurocognitive examination was preoperatively performed, and the scores were as follows. In the third version of Wechsler adult intelligence score (WAIS-III), verbal intelligence of quality (VIQ) was 75, performance IQ (PIQ) was 83, and full IQ (FIQ) was 76. In Wechsler memory scale-revised (WMS-R), verbal memory (VeM) was 64, visual memory (ViM) was 113, and generalized memory (GM) was 75. We therefore suspected that the epileptogenic zone was in the AVM scar and surrounding structures, including the anterior and medial temporal areas. Since the posterior edge of the resection area was near the posterior language center, we opted for awake surgery. There was a question whether hippocampectomy should be performed. Ictal onset zone was considered in the mesial temporal structure according to electrophysiological and symptomatic findings, although hippocampal sclerosis was not apparent. Although a further evaluation with invasive video-EEG recording was another option at that time, we considered that cortical mapping and ECoG in the hippocampus also could be performed intraoperatively during awake surgery. If spikes would frequently occur in the hippocampus, we would be able to confirm that the hippocampus was a part of epileptogenic zone, although there would still remain unclear whether the hippocampus was seizure onset. We explained to the patient about these options, and she chose the awake surgery without invasive video-EEG-recording. We therefore skipped this second step.

Awake surgery was performed in April 2014. Intraoperatively, Broca's and Wernicke's areas were identified by cortical mapping under awake conditions, and the posterior edge of the resection area was determined (Fig. 2A). After opening the inferior horn of the ventricle, hippocampal ECoG was recorded. Frequent spikes were observed in the

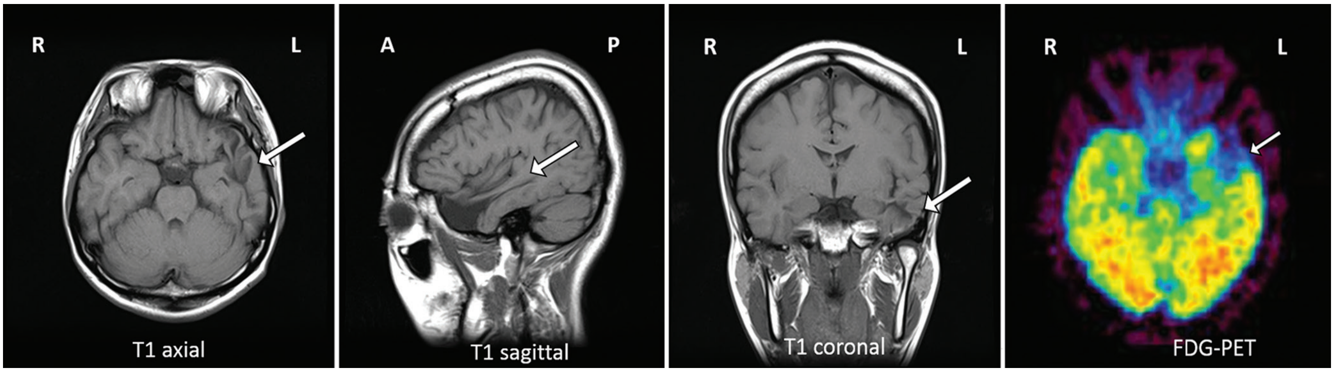

Fig. 1 Preoperative magnetic resonance image and FDG-PET of case 2. A hemorrhagic scar of a ruptured arteriovenous malformation was seen in the left anterior temporal area, which extended to the posterior superior temporal gyrus. FDG-PET demonstrated low glucose uptake in the left anterior and medial temporal area. A: anterior, L: left, P: posterior, R: right.

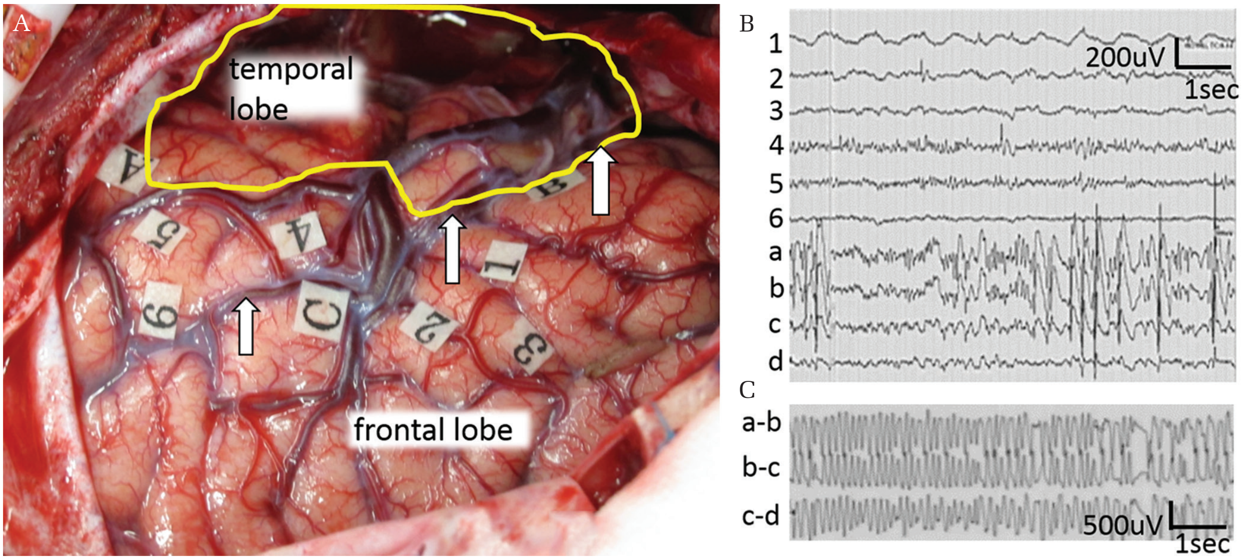

Fig. 2 (A) Intraoperative cortical mapping in case 2. Tags 1, 2, and 3 represent the anterior language center (Broca's area). Tags 4, 5, and 6 represent the posterior language center (Wernicke's area). Tags B C, and the *white arrow* represent the Sylvian fissure. Tag A represents the posterior margin of the arteriovenous malformation scar. The *solid yellow line* represents the area targeted for lesionectomy. (B) Intraoperative electrocorticography (ECoG) in case 2. Electrodes 1–6 were placed on the superior temporal gyrus (1; anterior, 6; posterior). Electrodes a–d were placed on the hippocampus (a; anterior, d; posterior). Frequent spikes were observed in the anterior hippocampus. (C) Electrodes a–d were placed on the hippocampus (a; anterior, d; posterior). The hippocampal electrodes were shown with a bipolar montage. After-discharge was observed in the whole hippocampus.

anterior hippocampus, independent of the spikes in the superior temporal gyrus (Fig. 2B). Therefore, we also performed hippocampectomy. We applied memory-recognition mapping with electrical stimulation for the hippocampus. We started the acquisition phase by word presentation. Surprisingly, severe after-discharge was evoked by a short period of electrical stimulation in the hippocampus (Fig. 2C). Irrigation with iced lactated Ringer's was immediately performed, but the discharge lasted for 30 s. Fortunately, symptomatic seizure did not occur, and she completed all tasks, including acquisition, interference, free-call, and recognition. She could correctly recall presented words and correctly answered questionnaires for recognition. This implied that the left hippocampus was not involved in memory-recognition in this case, but we needed to check reproducibility prior to drawing a conclusion. However, we abandoned further mapping for safety reasons. Lateral areas of the temporal lobe were resected to the posterior border demarcated by the language mapping, and the patient did not show any changes in speech and motor function. Before starting resection of mesial structures including the hippocampus, the patient was re-intubated, and general anesthesia was introduced again. For one reason, we considered the risk of unexpected injuries during microsurgical manipulation around the brain stem, which may be caused by tiny movement of the patient under awake condition. For the second reason, we do not know what would happen to patient after the hippocampectomy under awake condition. There was no consensus for this procedure. Therefore, resection of mesial structure including the hippocampus was performed under general anesthesia. Finally, cranioplasty was performed.

Postoperatively, epilepsy has been absent for 4 years to date. The patient did not show any neurological deterioration of speech, motor, or sensory function. She complained of slight difficulty in recalling names of unfamiliar relatives or TV stars. Neurocognitive examination were postoperatively examined at 3-month follow-up. In the WAIS-III, VIQ was 82, PIQ was 92, and FIQ was 85. In the WMS-R, VeM was 59, ViM was 101, and GM was 67. Neurocognitive examination showed slight memory deterioration, although intelligence was preserved. These did not hamper her activities of daily life, and she has returned to full-time work.

Representative case (case 5)

The patient was a 19-year-old male with left parietal epilepsy. He had suffered from intracranial hemorrhage in the left parietal lobe due to AVM in 2008, and emergency craniotomy with hematoma removal was performed. Gamma knife radiosurgery was performed for residual AVM three months later. Thereafter, he started having frequent focal seizures. His seizures were of the sensorimotor type, often starting with a tingling and burning sensation in the right hand and arm, followed by muscle contraction to tonic convulsion. The seizure often extended to the face, leg, and whole right side, and was occasionally followed by generalized tonic convulsion. Seizures occurred three times per day, on average, and were not controlled by sufficient amounts of anticonvulsants. He was referred to our hospital for surgical treatment in 2015. Imaging studies demonstrated an intracerebral hemorrhage scar in the left parietal lobe. FLAIR images showed low-intensity signals for a hematoma cavity, with a surrounding high-intensity signal, suspected to be gliosis changes (Fig. 3A). This area extended anteriorly to the central sulcus, and inferiorly to the Sylvian fissure. FDG-PET showed low uptake in this area. Interictal EEG showed frequent spikes in C3 and P3. Ictal EEG demonstrated that seizure activity started at C3 and P3. Functional MRI was performed with the tasks of verb generation and picture naming, and we found left temporal activation. We could not decide the dominant side for the anterior language area, because no significant activation was observed in

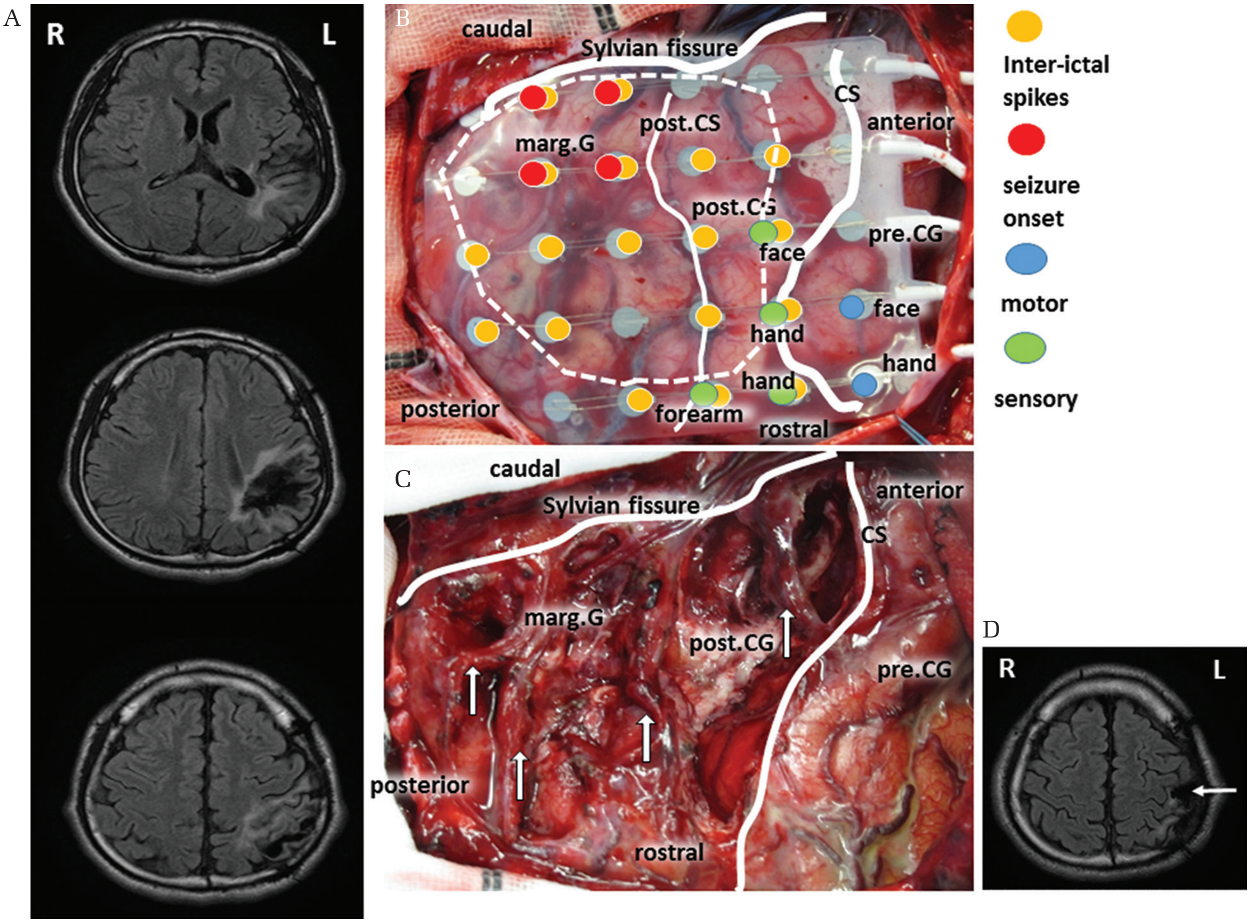

Fig. 3 **(A) Preoperative MRI in case 5. FLAIR images showed a low-intensity signal for hematoma cavity, with surrounding high-intensity signals, which was suspected of representing gliosis changes. This area extended anteriorly to the central sulcus, and inferiorly to the Sylvian fissure. (B) Results of intracranial electrocorticography (ECoG) and functional mapping in case 5. The *Dodd line* demonstrates the abnormal area in magnetic resonance images. During ECoG recording in the patient's ward, interictal spikes were frequently seen in the posterior central gyrus, the inferior parietal lobule (the marginal gyrus), and the superior parietal gyrus. The ictal activity started at the marginal gyrus. Functional mapping revealed the sensorimotor areas. However, language mapping was negative in the areas covered. CS: central sulcus, CG: central gurus, marg. G: marginal gyrus. (C) Intraoperative image of case 5 after lesionectomy. We first performed gyrectomy in the cortices on the hematoma cavity at first, followed by the superior parietal gyrus, the marginal gyrus, and the posterior central gyrus. The vessels running in the sulcus were retained (*arrow*). CS: central sulcus, CG: central gurus, marg. G: marginal gyrus. (D) Postoperative MRI demonstrated that the posterior central gyrus was resected dorsally just reaching the hand area (*arrow*).**

bilateral frontal areas. Wada test was also performed by intracarotid injection of propofol. The score of the object naming was slightly better in the left injection than right one, which may imply that language dominancy was the right hemisphere, but other scores were almost equal. Therefore, language dominancy remained unclear.

As step 2 evaluation, a subdural electrode was implanted in the left parietal lobe, and invasive video-ECoG monitoring was performed in an inpatients' ward for 1 week. Interictal spikes were frequently seen in the posterior central gyrus, the inferior parietal lobule (the marginal gyrus), and the superior parietal gyrus (Fig. 3B). During seizure, ictal activity started at the marginal gyrus. Cortical mapping with electrical stimulation was also performed, and we could identify the sensorimotor areas. However, language mapping was negative in the areas covered, including the marginal and angular gyrus. At this point, we considered that the seizure onset zone was the marginal gyrus; the posterior central gyrus was an irritative and symptomatic zone, and large areas surrounding the hematoma cavity were irritative zones. The irritative zones showed gliosis on MRI, and therefore we planned to include this in the resection target. However, there were two concerns at that time: whether the marginal gyrus truly had no language function, and whether the posterior central gyrus could be resected safely. We therefore opted for awake surgery.

After craniotomy, the patient smoothly awakened upon withdrawal of general anesthesia agents. We performed ECoG in the awake condition, and found similar patterns as obtained in the ward, with frequent interictal spikes in the posterior central gyrus, marginal gyrus, and superior parietal gyrus. Sensorimotor and language mapping was performed, with the same results as obtained in the ward. Therefore, we started lesionectomy in the scheduled area while monitoring for language function by continued conversation, and for sensorimotor function by active and passive movements. We first performed gyrectomy in the cortices at the hematoma cavity, followed by the superior parietal gyrus, marginal gyrus, and posterior central gyrus. The vessels running in the sulcus were retained (Fig. 3C). Although the patient transiently complained of a tingling sensation in the right hand and arm when we removed the posterior central gyrus, he did not show any apparent neurological deterioration. There was no obvious change in his speech. We assumed that the language-dominant area had shifted to atypical anatomical areas because of the congenital disease (AVM).[10]

Postoperatively, the patient complained of a little dysesthesia in the right hand, but otherwise experienced no neurological deficit. Deep sensation (sense of positon and vibration) was within normal limit in the right hand and arm. Postoperative MRI demonstrated that the posterior central gyrus was resected dorsally just reaching the hand area (Fig. 3D). His epilepsy disappeared for 2 and a half years, and he went back to school.

Discussion

Is intraoperative ECoG under awake conditions useful in epilepsy surgery?

We obtained intraoperative ECoGs in all cases under awake conditions. In two of the five cases, the surgical strategy was changed by the ECoG findings (cases 2 and 5). Regardless of whether surgery is performed under awake conditions or generalized anesthesia, intraoperative ECoG permits precise localization of the irritative zone in the selected cortex. The intraoperative procedure has two advantages over in-ward chronic ECoG recording: the mobility of electrodes during the procedure, and repeated recording at different time points, before and after lesionectomy. On the other hand, intraoperative ECoG has the disadvantage that the seizure onset zone cannot be identified. Intraoperatively, only interictal epileptic discharges can be recorded, and only the irritative zone can be observed. Therefore, intraoperative ECoG cannot completely substitute the extraoperative ECoG, and the seizure onset zone should be evaluated before surgery by non-invasive and/or invasive studies.

The most intense controversy about the application of ECoG is the correlation between the extent of resection of the irritative zone and seizure outcomes.[4] Studies have yielded conflicting results in terms of the correlation between the extent of resection in the irritative zone, observed by intraoperative ECoG, and epilepsy outcomes.[11–14] Wyllie et al. reported that complete resection of the irritative zone led to a good seizure outcome in 86% of surgery cases, as compared to 51% for incomplete resection.[11] Sugano et al. examined 35 cases with focal epilepsy with demarcated lesions, and found a seizure-freedom rate of 77% in cases treated with lesionectomy alone, and 91% in those who underwent lesionectomy plus irritative zone resection.[13] However, recent studies have suggested that there is no correlation between resection of the irritative zone identified in ECoG and epilepsy outcome.[14,15] There is no agreement about whether residual spikes in the post-resection ECoG predicts seizure outcome.[12] To interpret post-resection ECoG, in addition to the residual spikes from residual epileptogenesis, newly developed spikes should be considered, including a spike burst–suppression pattern caused by cortical isolation,[16] surgical injury of the cortex,[17] activation of a secondary focus by partial resection of the major focus.[17] In summary, not all residual spikes are related to epileptogenesis, and it is necessary to distinguish between epileptogenesis-related spikes, termed red spikes, and unrelated spikes, termed green spikes.[18] High frequent oscillation in intraoperative ECoG has recently attracted much attention as a specific biomarker of epileptogenesis, and may contribute to the resolution of this issue.[19–22]

Compared to general anesthesia, awake surgery does not require much consideration of the influence of anesthesia agents on ECoG recordings. Anesthesia agents used during ECoG recording may affect its findings. In children, the frequency of spikes decreases markedly in intraoperative ECoG under general anesthesia as compared to extraoperative ECoG.[23] Beta activity initially increases with most anesthesia agents, followed by diffusely appearing theta and delta activity.[24] Fentanyl, alfentanil, propofol, and thiopental enhance epileptiform activity.[25–27] On the other hand, isoflurane and sevoflurane decrease this activity.[28,29] Chassoux et al. reported that pseudo-rhythmic activity in FCD type 2, which is frequently seen across a wide area in the light sleep stage, localizes to the epileptic focus with the administration of diazepam.[30] In summary, ECoG findings are influenced by anesthesia conditions; ECoG recordings during awake surgery may provide more accurate and reliable information, although no such comparative study has been reported to date. We performed ECoG in both extraoperative and intraoperative awake conditions only in one case, and found that the trends were similar. Further comparative studies are necessary.

Is it possible to evaluate other higher cognition functions, such as memory, during awake surgery?

In a case in this series, we performed memory-recognition mapping in the hippocampus, intraoperatively. This was performed as a preliminary trial, to examine whether the hippocampus, suspected as part of the epileptogenic zone, retained memory function. We found a negative response to free-recall and recognition after electrical stimulation during the acquisition period in this case, but we could not continue the trial for safety reasons. Hippocampectomy was finally performed, and the patient demonstrated slight deterioration of generalized memory and verbal memory postoperatively. It is difficult to conclude the correlation between memory mapping and functional outcome from only this case.

There has been no report about intraoperative memory mapping in the hippocampus to date. Some previous studies conducted memory mapping in-ward in patients with implanted subdural and deep electrodes.[9,31,32] Coleshill et al. reported that left hippocampal stimulation produced word-recognition memory deficits, while right hippocampal stimulation produced face-recognition memory deficits.[9] Tani et al. reported that electrical stimulation at the parahippocampus can predict functional outcomes for memory.[32] According to these reports, functional mapping of memory function may be possible, but it is limited by the short time in an intraoperative setting. Safety is also important, considering the susceptibility of the hippocampus to electrical stimulation, as in our case.

Another higher cognitive function that is of interest for intraoperative mapping is working memory.[33,34] Kho et al. reported that, in a patient with an epileptogenic lesion in the left dorsolateral prefrontal cortex (DLPFC), working memory mapping was performed during in-ward chronic ECoG recording.[33] They revealed positive areas for some tasks for working-memory, such as an n-back task. However, because those areas were considered the epileptogenic zone, they were resected. Postoperatively, the patient demonstrated deterioration of working memory. They concluded that their working memory mapping correlated with surgical outcomes, and thus it was justified. Matsui et al. reported that intraoperative DLPFC stimulation caused positive responses in some attention tasks, such as the color Stroop test, which may be related to working memory.[34] In summary, it remains challenging to perform intraoperative mapping for higher cognition. There is a need for improvement of tasks that can be performed during the short intraoperative period with high sensitivity, high specificity, high reproducibility, and safety. Furthermore, even if a higher cognitive area is identified, whether it should be resected or retained remains an issue, which depends on whether higher cognitive function or seizure control is the priority.

Does maximal lesionectomy lead to a good outcome in epilepsy surgery?

In our study, we achieved a complete resection of imaging-demarcated lesions in all cases using awake surgery with MRI-guided navigation. Awake surgery was helpful for identification of functionally eloquent areas, so that we could determine functional borders and perform maximal lesionectomy while preserving functional areas. In four of the five cases, Engel class 1 status for epilepsy control was achieved for more than 2 years. These results are good, even though the patient cohort in our study was small. We assumed that good seizure control may be obtained by the maximal lesionectomy that can be achieved in awake surgery. In awake surgery for gliomas, supra-total resection based on functional borders were reported by Yordanova and Duffau.[35] Similar effects can be expected in awake surgery for epilepsy. Kresk et al. examined 149 cases surgically treated for focal epilepsy, and reported that complete resection of MRI-demarcated lesion is the best predictive factor for good seizure control.[36] Another study reported that complete resection of the tissue manifesting ECoG abnormalities and MRI abnormalities are independent predictors of seizure freedom.[37] In addition, the surgical outcomes of 50 cases with FCD type IIb were reported from the University of Bonn; these patients underwent expanded lesionectomy, which included not only the MRI-documented lesions, but also a further 5–10 mm extensions. The seizure freedom rate was 92% after complete resection, but was 8% after incomplete resection.[38] In summary, maximal resection of the epileptogenic zone is an important factor for seizure freedom. Since awake surgery allows maximal resection with identification of functional borders, it contributes to improved seizure outcomes.

Conclusions

Our study was limited by the small number of patients, disease heterogeneity (lack of FCD), and lack of meticulous analysis of ECoG findings using high-frequency oscillations. However, our results demonstrated one possibility that, for patients with epileptogenic foci in and around the functionally eloquent areas, awake surgery may lead to improved seizure control and minimize neurological complications by facilitating maximal lesionectomy while preserving dominant functions by means of intraoperative ECoG and mapping information. Further studies should be conducted in large number of patients with improved methods for intraoperative ECoG analysis and higher cognitive function mapping, to clarify the importance of applying awake surgery for epilepsy in a clinical context.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research (KAKENHI, no. 17K10890). This study was presented in part at the 41st Annual Meeting of the Epilepsy Surgery Society of Japan, and was recommended for publication by the editorial board of *Neurologia Medico-Chirurgica* (Tokyo).

Conflicts of Interest Disclosure

All authors declare that there are no conflicts of interest (COIs) regarding this article according to the criteria of The Japan Neurosurgical Society. They have completed the self-reported registration of their COI status to the Society.

References

1) Englot DJ, Konrad PE, Morgan VL: Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. *Epilepsia* 57: 1546–1557, 2016
2) Maesawa S, Bagarinao E, Fujii M, Futamura M, Wakabayashi T: Use of network analysis to establish neurosurgical parameters in gliomas and epilepsy. *Neurol Med Chir* (*Tokyo*) 56: 158–169, 2016
3) Berg AT, Vickrey BG, Langfitt JT, et al.; Multicenter Study of Epilepsy Surgery: The multicenter study of epilepsy surgery: recruitment and selection for surgery. *Epilepsia* 44: 1425–1433, 2003
4) Fernández IS, Loddenkemper T: Electrocorticography for seizure foci mapping in epilepsy surgery. *J Clin Neurophysiol* 30: 554–570, 2013
5) Yang T, Hakimian S, Schwartz TH: Intraoperative ElectroCorticoGraphy (ECog): indications, techniques, and utility in epilepsy surgery. *Epileptic Disord* 16: 271–279, 2014
6) Kayama T; Guidelines committee of the Japan awake surgery conference: The guidelines for awake craniotomy guidelines committee of the Japan awake surgery conference. *Neurol Med Chir* (*Tokyo*) 52: 119–141, 2012
7) Fujii M, Maesawa S, Motomura K, et al.: Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma. *J Neurosurg* 122: 1390–1396, 2015
8) Maesawa S, Fujii M, Futamura M, Hayashi Y, Iijima K, Wakabayashi T: A case of secondary somatosensory epilepsy with a left deep parietal opercular lesion: successful tumor resection using a transsubcentral gyral approach during awake surgery. *J Neurosurg* 124: 791–798, 2016
9) Coleshill SG, Binnie CD, Morris RG, et al.: Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. *J Neurosci* 24: 1612–1616, 2004
10) Deng X, Zhang Y, Xu L, et al.: Comparison of language cortex reorganization patterns between cerebral arteriovenous malformations and gliomas: a functional MRI study. *J Neurosurg* 122: 996–1003, 2015
11) Wyllie E, Lüders H, Morris HH, et al.: Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 37: 1634–1641, 1987

12) McKhann GM, Schoenfeld-McNeill J, Born DE, Haglund MM, Ojemann GA: Intraoperative hippocampal electrocorticography to predict the extent of hippocampal resection in temporal lobe epilepsy surgery. *J Neurosurg* 93: 44–52, 2000

13) Sugano H, Shimizu H, Sunaga S: Efficacy of intraoperative electrocorticography for assessing seizure outcomes in intractable epilepsy patients with temporal-lobe-mass lesions. *Seizure* 16: 120–127, 2007

14) Asano E, Juhász C, Shah A, Sood S, Chugani HT: Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery. *Brain* 132: 1038–1047, 2009

15) Benifla M, Otsubo H, Ochi A, et al.: Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. *Neurosurgery* 59: 1203–1213; discussion 1213–1214, 2006

16) Hosain S, Burton L, Fraser R, Labar D: Focal suppression-burst on electrocorticography after temporal lobectomy. *Neurology* 45: 2276–2278, 1995

17) Schwartz TH, Bazil CW, Forgione M, Bruce JN, Goodman RR: Do reactive post-resection "injury" spikes exist? *Epilepsia* 41: 1463–1468, 2000

18) Rasmussen T: Characteristics of a pure culture of frontal lobe epilepsy. *Epilepsia* 24: 482–493, 1983

19) Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J: Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia* 49: 1893–1907, 2008

20) Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW: Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology* 75: 1686–1694, 2010

21) Urrestarazu E, Chander R, Dubeau F, Gotman J: Interictal high-frequency oscillations (100-500 Hz) in the intracerebral EEG of epileptic patients. *Brain* 130: 2354–2366, 2007

22) Andrade-Valença L, Mari F, Jacobs J, et al.: Interictal high frequency oscillations (HFOs) in patients with focal epilepsy and normal MRI. *Clin Neurophysiol* 123: 100–105, 2012

23) Asano E, Benedek K, Shah A, et al.: Is intraoperative electrocorticography reliable in children with intractable neocortical epilepsy? *Epilepsia* 45: 1091–1099, 2004

24) Blume WT, Holloway GM: Electrocorticography. In Koubeissi MZ, Maciunas RJ (eds): *Extratemporal lobe epilepsy surgery*. Surrey, John Libbey, 2011, pp. 345–351

25) Manninen PH, Burke SJ, Wennberg R, Lozano AM, El Beheiry H: Intraoperative localization of an epileptogenic focus with alfentanil and fentanyl. *Anesth Analg* 88: 1101–1106, 1999

26) Keene DL, Roberts D, Splinter WM, Higgins M, Ventureyra E: Alfentanil mediated activation of epileptiform activity in the electrocorticogram during resection of epileptogenic foci. *Can J Neurol Sci* 24: 37–39, 1997

27) Hewitt PB, Chu DL, Polkey CE, Binnie CD: Effect of propofol on the electrocorticogram in epileptic patients undergoing cortical resection. *Br J Anaesth* 82: 199–202, 1999

28) Endo T, Sato K, Shamoto H, Yoshimoto T: Effects of sevoflurane on electrocorticography in patients with intractable temporal lobe epilepsy. *J Neurosurg Anesthesiol* 14: 59–62, 2002

29) Ito BM, Sato S, Kufta CV, Tran D: Effect of isoflurane and enflurane on the electrocorticogram of epileptic patients. *Neurology* 38: 924–928, 1988

30) Chassoux F, Landré E, Mellerio C, et al.: Type II focal cortical dysplasia: electroclinical phenotype and surgical outcome related to imaging. *Epilepsia* 53: 349–358, 2012

31) Lacruz ME, Valentín A, Seoane JJ, Morris RG, Selway RP, Alarcón G: Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. *Neuroscience* 170: 623–632, 2010

32) Tani N, Kishima H, Khoo HM, et al.: Electrical stimulation of the parahippocampal gyrus for prediction of posthippocampectomy verbal memory decline. *J Neurosurg* 125: 1053–1060, 2016

33) Kho KH, Rutten GJ, Leijten FS, van der Schaaf A, van Rijen PC, Ramsey NF: Working memory deficits after resection of the dorsolateral prefrontal cortex predicted by functional magnetic resonance imaging and electrocortical stimulation mapping. Case report. *J Neurosurg* 106: 501–505, 2007

34) Matsui Y, Maesawa S, Futamura M, Tobinaga M, Fujii M: Challenging for preservation of higher cognitive functions during awake surgery—a case demonstrating the association of attention in the dorsolateral prefrontal cortex in dominant hemisphere. *Hr Brain Funct Res* 35: 1–8, 2015 (Japanese)

35) Yordanova YN, Duffau H: Supratotal resection of diffuse gliomas - an overview of its multifaceted implications. *Neurochirurgie* 63: 243–249, 2017

36) Krsek P, Maton B, Jayakar P, et al.: Incomplete resection of focal cortical dysplasia is the main predictor of poor postsurgical outcome. *Neurology* 72: 217–223, 2009

37) Chang EF, Wang DD, Barkovich AJ, et al.: Predictors of seizure freedom after surgery for malformations of cortical development. *Ann Neurol* 70: 151–162, 2011

38) Wagner J, Urbach H, Niehusmann P, von Lehe M, Elger CE, Wellmer J: Focal cortical dysplasia type IIb: completeness of cortical, not subcortical, resection is necessary for seizure freedom. *Epilepsia* 52: 1418–1424, 2011

Address reprint requests to: Satoshi Maesawa, MD, PhD,
Department of Neurosurgery, Nagoya University School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8550, Japan.
e-mail: smaesawa@med.nagoya-u.ac.jp