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# Preoperative Prediction of Communication Difficulties during Awake Craniotomy in Glioma Patients: A Retrospective Evaluation of 136 Cases at a Single Institution

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## Abstract

Awake craniotomy has been widely performed in patients with glioma in eloquent areas to minimize postoperative brain dysfunction. However, neurological examination in awake craniotomy is sometimes problematic due to communication difficulties during the intraoperative awake period. We evaluated preoperative predictors of these difficulties in awake craniotomy for patients with glioma. In all, 136 patients with glioma who underwent awake craniotomy at our institution between January 2012 and January 2020 were retrospectively evaluated. Patients were divided into two groups (appropriately awake group and inappropriately awake group) depending on their state during the intraoperative awake period, and the relationship between communication difficulties in awake craniotomy and both clinical and radiological characteristics were assessed. The appropriately awake group included 110 patients, and the inappropriately awake group included 26 patients. Reasons for inclusion in the inappropriately awake group were insufficient wakefulness in 15 patients, restless state in 6, and intraoperative seizures in 5. In multivariate analysis, the likelihood of being inappropriately awake was inversely correlated with preoperative seizures (odds ratio [OR], 0.23; 95% confidence interval [CI], 0.06–0.89;  $p = 0.033$ ) and positively correlated with left-sided lesions (OR, 7.31; 95% CI, 1.54–34.62;  $p = 0.012$ ). Both lack of preoperative seizures and left-sided lesions were identified as risk factors for intraoperative difficulties in awake craniotomy for patients with glioma. Understanding these risk factors may lead to more appropriate determination of eligibility for awake craniotomy.

Keywords: awake craniotomy, glioma, insufficient wakefulness, restless state, intraoperative seizure

## Introduction

Awake craniotomy has been widely performed in patients with brain lesions in eloquent areas, especially those with glioma, to minimize postoperative brain dysfunction and maximize the extent of tumor resection.<sup>1–6</sup> Past studies reported significantly better neurological outcomes and resection extent following

awake craniotomy than after general anesthesia in patients with brain lesions in eloquent areas.<sup>2</sup> In patients with glioma, the extent of tumor resection has been reported to be associated with better outcomes,<sup>7–10</sup> while the development of new perioperative motor or language impairments has been reported to be associated with decreased overall survival, despite no difference in resection extent or adjuvant therapy regimen.<sup>11</sup> Therefore, awake craniotomy has been the standard approach in patients with glioma in eloquent areas. Attempts have been made to further improve perioperative neurological outcomes of awake craniotomy using electrical mapping and motor evoked potentials (MEPs), in addition to conventional neurological examination.<sup>3,4,12</sup>

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Although awake craniotomy has been reported to be useful, neurological examination during this approach is sometimes difficult due to issues such as insufficient wakefulness, restlessness, and intraoperative seizures during the awake period, which may prevent adequate monitoring of motor and language functions. While studies have examined the risk factors of intraoperative seizures in awake craniotomy,<sup>13,14)</sup> only a few have assessed the risk factors of other difficulties during the intraoperative awake period.<sup>15,16)</sup> We hypothesized that clarifying such risk factors would help identify patients most suitable for awake craniotomy, and assist in optimizing preoperative planning when intraoperative difficulties are anticipated. During the 9 years preceding this study, we performed 221 awake craniotomies at our institution. Here, we retrospectively evaluated the risk factors of difficulties during the intraoperative awake period of awake craniotomy for glioma to improve the safety of this approach.

## Materials and Methods

### Patients

This study protocol was approved by the ethics committee of Sapporo Medical University Hospital. As this study had a retrospective design, patient consent was obtained based on an opt-out policy using a website. Therefore, formal consent was not required. From January 2012 to January 2020, consecutive patients who underwent awake craniotomy for glioma at our institution were enrolled in this study. Among patients who underwent awake craniotomy 2 or more times during the study period at our institution, only the first operation was evaluated. At our institution, awake craniotomy was indicated for patients with lesions in eloquent brain areas who could adequately follow the preoperative instructions for intraoperative neurological examination. Therefore, patients who could not follow the instructions due to language impairment were excluded. A total of 136 patients (72 men and 64 women) were examined. The median patient age (interquartile range [IQR]) was 53.5 (38.5–65.0) years (range, 16–84 years). The locations of primary lesions were as follows: right side, 60 patients; left side, 75 patients; midline, 1 patient; frontal lobe, 66 patients; temporal lobe, 33 patients; and other, 37 patients (insular cortex, 12; parietal lobe, 24; and third ventricle, 1). The pathological diagnoses based on morphological characteristics were as follows: oligodendroglioma, 27 patients; diffuse astrocytoma, 21 patients; anaplastic oligodendroglioma, 14 patients; anaplastic astrocytoma, 16 patients; glioblastoma, 49 patients; and other, 9 patients (gliosarcoma, 3; ependymoma, 2; pleomorphic

xanthoastrocytoma, 2; pilocytic astrocytoma, 1; and ganglioglioma, 1). In terms of immunostaining, an IDH-1 mutation was found in 59 patients, and a p53 mutation was found in 93 patients.

In addition, 26 patients (14 men and 12 women) underwent awake craniotomy for epilepsy during the same period at our institution. The median patient age (IQR) was 26.5 (19.5–36.0) years (range, 14–47). The locations were as follows: right side, 5 patients; left side, 19 patients; midline, 1 patient; temporal lobe, 20 patients; frontal lobe, 4 patients; other locations, 2 patients (parietal, 1; corpus callosum, 1). Pathological diagnoses were as follows: cavernoma, 4 patients; ganglioglioma, 1 patient; others, 21 patients.

### Magnetic resonance imaging evaluations

To evaluate the locations and sizes of lesions, magnetic resonance imaging (MRI) was performed using a 3.0-T magnetic resonance system (Signa Excite, Ver. 11; GE Healthcare, Milwaukee, WI, USA). The product of the maximum and perpendicular diameter of each main hyperintense lesion was calculated based on axial, T2-weighted imaging slices according to the Response Assessment in Neuro-Oncology Working Group criteria.<sup>17)</sup> The imaging parameters of T2-weighted MRI were as follows: flip angle = 90°; time of repetition = 5700 msec; echo time = 102.0 msec; bandwidth = 50.0 kHz; field of view = 200 mm × 200 mm; scan thickness = 3.0 mm; slice gap = 1.0 mm; number of slices = 26–30; matrix = 384 × 256; number of signals average = 1; imaging time = 1 min, 5 sec. In addition, functional MRI (fMRI) was performed preoperatively to evaluate hemispheric language dominance. The fMRI imaging parameters were previously described.<sup>18)</sup>

### Anesthesia and operative procedures

Anesthesia was performed using an asleep–awake–asleep technique.<sup>19)</sup> Routine physiological monitoring, including electrocardiography and PO<sub>2</sub>, PCO<sub>2</sub>, and body temperature measurement, was performed while patients breathed 100% oxygen. General anesthesia was induced with a single dose each of propofol (2 mg/kg) and fentanyl (1–2 µg/kg). To facilitate laryngeal mask airway insertion, vecuronium bromide (0.1 mg/kg) or rocuronium bromide (0.6 mg/kg) was injected immediately after loss of consciousness. After induction, bilateral scalp block was performed with ropivacaine 0.375% or levobupivacaine 0.375%. Anesthesia was maintained using a continuous infusion of propofol and remifentanyl. Muscle relaxants were only administered for intubation and were not continued during the surgical procedure. Extubation was performed just before

the resection of the lesion in the eloquent area. During the resection, neurological examination was constantly performed by MEP monitoring. The details of MEP evaluation were previously described.<sup>20)</sup> Patients were divided into two groups (appropriately awake group and inappropriately awake groups) depending on their state during the intraoperative awake period. The appropriately awake group consisted of patients who could follow the instructions necessary for evaluation of their motor and language function during the intraoperative awake period, while the inappropriately awake group comprised the patients who could not follow these instructions. Reasons for inclusion in the inappropriately awake group included insufficient wakefulness, restlessness, and intraoperative seizures. The definitions of these states were as follows: insufficient wakefulness, the patient's level of consciousness made it impossible for him or her to follow instructions (score above 20 on the Japan Coma Scale<sup>21)</sup>); restlessness, the patient could not remain at rest or follow instructions despite a sufficiently high level of consciousness; and intraoperative seizures, the patient experienced one or more partial or generalized seizures and could not follow instructions. Patients who initially could not follow the instructions but who were eventually able to do so were included in the appropriately awake group. Conversely, the inappropriately awake group included patients who were unable to follow the instructions at any point, mainly due to prolongation of insufficient wakefulness or reinduction of general anesthesia for safety reasons such as those related to restlessness or intraoperative seizures. All patients received intraoperative anticonvulsants, while preoperative anticonvulsants were administered only to patients who had a history of seizures. In patients with lesions in the motor or language area, electrical mapping was performed using a Digitimer MultiPulse Stimulator (Neuromaster MEE-1232; Nihon Kohden, Tokyo, Japan), with grid-type electrodes placed on the surface of the precentral gyrus, as well as with MEP analysis, using previously described stimulation parameters.<sup>22)</sup> Electrophysiological evaluation was performed using a combination of electrical mapping and MEP analysis. After resection of the tumor, the patient was reintubated and general anesthesia was reinduced. The bispectral index (BIS) was recorded using a patch electrode positioned on the contra- and ipsilateral nasal bones to the ipsilateral zygomatic bone before the induction of anesthesia and throughout the operative procedure (BIS; Philips, Amsterdam, Netherlands); the maximum values during the intraoperative awake period were evaluated.

### Statistical analysis

Data are expressed as median (IQR). The Mann–Whitney U test, Fisher's exact test, and Pearson's chi-square test were used to compare the two groups. The Kruskal–Wallis test and Fisher–Freeman–Halton exact test were used to compare three or more groups. A simple logistic regression was then used in univariate analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using these models. Each item was selected with stepwise methods (model selection criterion:  $\alpha = 0.10$ ) and multivariate analyses were performed. Receiver operating characteristic (ROC) curve analysis was used to evaluate the area under the curve (AUC), as well as sensitivity and specificity. The statistical analyses were performed using SPSS software (version 26; IBM Corp., Armonk, NY, USA). *p* values less than 0.05 indicated statistical significance. About the evaluated factors, age, sex, and the details of lesion (past operation history, location, multiplicity, size, and pathological diagnosis) were selected as general factors. In addition, preoperative language disorder, preoperative seizure, intraoperative anticonvulsant, electrophysiological evaluation, and immunostaining were selected, because these factors were reported to be associated with communication difficulties during awake craniotomy.<sup>13–16,23)</sup> Furthermore, anesthesia duration before intraoperative awake period, maximum BIS value, and intraoperative posture were selected, because we considered the association between these factors and inappropriately awake group.

### Results

Clinical characteristics of the appropriately and inappropriately awake groups are shown in Table 1. The appropriately awake group included 110 patients (80.9%) and the inappropriately awake group included 26 patients (19.1%). In the inappropriately awake group, 15 patients (11.0%) had insufficient wakefulness, 6 (4.4%) exhibited restlessness, and 5 (3.7%) had intraoperative seizure. Comparing the appropriately and inappropriately awake groups, age (53.0 [36.0–63.0] vs. 64.0 [50.8–77.0] years, respectively,  $p = 0.007$ ) and the incidence of preoperative language impairment (14 [12.7%] vs. 9 [34.6%], respectively,  $p = 0.012$ ), preoperative seizures (48 [43.6%] vs. 5 [19.2%], respectively,  $p = 0.022$ ), and left-sided lesions (53 [48.2] vs. 22 [84.6], respectively,  $p < 0.001$ ) were significantly different between groups, while the other characteristics showed no significant differences. Based on these data, multivariate analysis was performed to assess selection bias (Table 2). A simple logistic regression was used in the univariate analysis, and higher age

**Table 1 Clinical characteristics of the appropriately and inappropriately awake groups**

Characteristics	Appropriately awake group	Inappropriately awake group	<i>p</i> value
Number, patients (%)	110 (80.9)	26 (19.1)	
Age, median (IQR), y	53 (36–63)	64 (50.8–77)	0.007*
Sex, male (%)	56 (50.9)	16 (61.5)	0.329
Preoperative language impairment (%)	14 (12.7)	9 (34.6)	0.012*
Preoperative seizure (%)	48 (43.6)	5 (19.2)	0.022*
Past operation for this lesion (%)	32 (29.1)	5 (19.2)	0.31
Left-sided lesion (%)	53 (48.2)	22 (84.6)	<0.001*
Presence of multiple lesions (%)	3 (2.7)	2 (7.7)	0.243
Deep location (%)	36 (32.7)	7 (26.9)	0.567
Location of lesion			
Frontal lobe (%)	55 (50.0)	11 (42.3)	0.48
Temporal lobe (%)	23 (20.9)	10 (38.5)	0.06
Others (%)	32 (29.1)	5 (19.2)	0.31
Lesion size, cm <sup>2</sup>	24.4 (12.3–41.5)	33.5 (18.3–42.4)	0.129
Intraoperative posture			
Supine (%)	73 (66.4)	20 (76.9)	0.298
Lateral (%)	37 (33.6)	6 (23.1)	
Anesthesia duration before IAP (min)	261.5 (217.3–299.3)	273.5 (239.3–304)	0.34
Intraoperative anticonvulsant			
Phenytoin or fosphenytoin sodium (%)	57 (51.8)	14 (53.8)	0.852
Levetiracetam (%)	53 (48.2)	12 (46.2)	
Electrophysiological evaluation (%)	91 (82.7)	20 (76.9)	0.332
Pathological diagnoses			
Oligodendroglioma (%)	20 (18.2)	7 (26.9)	0.315
Diffuse astrocytoma (%)	18 (16.4)	3 (11.5)	0.394
Anaplastic oligodendroglioma (%)	13 (11.8)	1 (3.8)	0.205
Anaplastic astrocytoma (%)	14 (12.7)	2 (7.7)	0.372
Glioblastoma (%)	37 (33.6)	12 (46.2)	0.232
Others (%)	8 (7.3)	1 (3.8)	0.457
High-grade glioma (%)	66 (60.0)	16 (61.5)	0.885
Genetic characterization			
IDH-1 mutation (%)	49 (45.4)	10 (38.5)	0.524
p53 mutation (%)	75 (69.4)	18 (69.2)	0.983
Maximum BIS value (IQR)	97 (94–98)	96 (92–98)	0.621

\**p* < 0.05. BIS: bispectral index, IAP: intraoperative awake period, IQR: interquartile range.

(OR, 1.04; 95% CI, 1.01–1.07; *p* = 0.010), preoperative language impairment (OR, 1.54; 95% CI, 0.64–3.70; *p* = 0.010), preoperative seizures (OR, 0.31; 95% CI, 0.11–0.88; *p* = 0.027), and left-sided lesions (OR, 7.89; 95% CI, 2.23–27.89; *p* = 0.001) were significantly associated with the inappropriately awake group. Two items were selected using

stepwise methods and the following significant differences were noted in the multivariate analysis: preoperative seizures (OR, 0.23; 95% CI, 0.06–0.89; *p* = 0.033) and left-sided lesions (OR, 7.31; 95% CI, 1.54–34.62; *p* = 0.012). The AUC of the analysis was 0.719 (95% CI, 0.606–0.832; *p* = 0.001), and the sensitivity and specificity were 69.2% and

**Table 2** Univariate and multivariate analyses for detecting inappropriately awake group in 136 patients

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Age	1.04 (1.01–1.07)	0.01*		
Sex, male	1.54 (0.64–3.70)	0.331		
Preoperative language disorder	3.63 (1.36–9.71)	0.01*		
Preoperative seizure	0.31 (0.11–0.88)	0.027*	0.23 (0.06–0.89)	0.033*
Past operation for this lesion	0.58 (0.20–1.67)	0.314		
Left-sided lesion	7.89 (2.23–27.89)	0.001*	7.31 (1.54–34.62)	0.012*
Presence of multiple lesions	2.97 (0.47–18.77)	0.247		
Deep location	0.76 (0.29–1.97)	0.568		
Location of lesion (frontal lobe/temporal lobe/other)	0.97 (0.58–1.61)	0.906		
Lesion size	1.00 (1.00–1.00)	0.238		
Intraoperative posture, lateral	0.59 (0.22–1.60)	0.301		
Anesthesia duration before intraoperative awake period	1.00 (1.00–1.01)	0.329		
Intraoperative anticonvulsant, LEV	0.92 (0.39–2.17)	0.852		
Electrophysiological evaluation	0.70 (0.25–1.96)	0.494		
High-grade glioma (grade 3, 4)	1.07 (0.44–2.57)	0.885		
GBM	1.69 (0.71–4.02)	0.235		
IDH-1 mutation	0.75 (0.31–1.81)	0.525		
p53 mutation	0.99 (0.39–2.50)	0.983		
Maximum BIS value	0.97 (0.90–1.04)	0.381		

\**p* < 0.05. CI: confidence interval, BIS: bispectral index, GBM: glioblastoma, LEV: levetiracetam.

74.5%, respectively. Furthermore, patients with and without preoperative seizures differed significantly regarding preoperative language impairment (3 [5.7%] vs. 20 [24.1%], respectively, *p* = 0.005) but not regarding lesion size (26.5 [12.9–39.8] vs. 27.5 [17.5–43.7] cm<sup>2</sup>, respectively, *p* = 0.398). Among 49 patients with glioblastoma, left- and right-sided lesions were present in 20 (40.8%) and 17 (34.7%) patients in the appropriately awake group, respectively, compared with 11 (22.4%) and 1 (2.0%) patients in the inappropriately awake group, respectively. Furthermore, univariate and multivariate analyses for detecting inappropriately awake group in 87 patients except for patients with glioblastoma (GBM) were performed to assess the confounding of GBM (Supplementary material 1). Left-sided lesions (OR, 6.67; 95% CI, 1.38–32.22; *p* = 0.018), anesthesia duration before intraoperative awake period (OR, 1.01; 95% CI, 1.00–1.03; *p* = 0.029), and maximum BIS value (OR, 0.92; 95% CI, 0.84–1.00; *p* = 0.049) were significantly associated with inappropriately awake group in univariate analysis, while no factor was detected in multivariate analysis due to small

number of patients. In addition, hemispheric language dominance was successfully evaluated in 106 (77.9%) patients using fMRI. Right hemispheric dominance was present in three patients with right-sided lesions, and therefore language tasks were added during the intraoperative awake period in these cases. In terms of the purpose of awake craniotomy, language function evaluation (73/136 [53.7%]) was a less common objective in the appropriately awake group than in the inappropriately awake group (50 [45.5%] vs. 23 [88.5%], respectively, *p* < 0.001), while motor function evaluation (121/136 [89.0%]) was the objective in similar percentages of patients in the two groups (99 [90.0%] vs. 22 [84.6%], respectively, *p* = 0.314).

In our cases, the main causes of difficulty with neurological examination in the inappropriately awake group were (1) insufficient wakefulness, (2) restlessness, and (3) intraoperative seizures. We compared the appropriately awake group and these subgroups of the inappropriately awake group (Table 3). Age (53 [36.0–63.0] vs. 67.0 [59.0–78.0] vs. 66.5 [45.5–77.5] vs. 45.0 [31.5–51.5], respectively, *p* = 0.001), preoperative language impairment (14 [12.7%]

**Table 3** Clinical characteristics of the appropriately awake group and subgroups of the inappropriately awake group

Characteristics	Appropriately awake group	Insufficient wakefulness	Restlessness	Intraoperative seizure	<i>p</i> value
Number, patients (%)	110 (80.9)	15 (11.0)	6 (4.4)	5 (3.7)	
Age, median (IQR), y	53 (36–63)	67 (59–78)	66.5 (45.5–77.5)	45 (31.5–51.5)	0.001*
Sex, male (%)	56 (50.9)	7 (46.7)	5 (83.3)	4 (80.0)	0.257
Preoperative language impairment (%)	14 (12.7)	4 (26.7)	4 (66.7)	1 (20.0)	0.008*
Preoperative seizure (%)	48 (43.6)	2 (13.3)	0 (0)	3 (60.0)	0.012*
Past operation for this lesion (%)	32 (29.1)	4 (26.7)	1 (16.7)	0 (0)	0.681
Left-sided lesion (%)	53 (48.2)	13 (86.7)	5 (100.0)	4 (80.0)	0.001*
Presence of multiple lesions (%)	3 (2.7)	2 (13.3)	0 (0)	0 (0)	0.243
Deep location (%)	36 (32.7)	6 (40.0)	1 (16.7)	0 (0)	0.416
Location of lesion					
Frontal lobe (%)	55 (50.0)	5 (33.3)	1 (16.7)	5 (100.0)	0.021*
Temporal lobe (%)	23 (20.9)	6 (40.0)	4 (66.7)	0 (0)	0.020*
Other (%)	32 (29.1)	4 (26.7)	1 (16.7)	0 (0)	0.681
Lesion size, cm <sup>2</sup>	24.4 (12.3–41.5)	29.2 (18.2–39.3)	33.6 (19.9–43.3)	41.3 (24.9–54.0)	0.386
Intraoperative posture					
Supine (%)	73 (66.4)	12 (80.0)	3 (50.0)	5 (0)	0.233
Lateral (%)	37 (33.6)	3 (20.0)	3 (50.0)	0 (0)	
Anesthesia duration before IAP (min)	261.5 (217.3–299.3)	276 (241–304)	252 (217–277)	288 (254–337)	0.371
Intraoperative anticonvulsant					
Phenytoin or fosphenytoin sodium (%)	57 (51.8)	10 (66.7)	1 (16.7)	3 (60.0)	0.229
Levetiracetam (%)	53 (48.2)	5 (33.3)	5 (83.3)	2 (40.0)	
Electrophysiological evaluation (%)	91 (82.7)	12 (80.0)	4 (66.7)	4 (80.0)	0.641
Pathological diagnoses					
Oligodendroglioma (%)	20 (18.2)	5 (33.3)	0 (0)	2 (40.0)	0.182
Diffuse astrocytoma (%)	18 (16.4)	0 (0)	2 (33.3)	1 (20.0)	0.126
Anaplastic oligodendroglioma (%)	13 (11.8)	0 (0)	0 (0)	1 (20.0)	0.361
Anaplastic astrocytoma (%)	14 (12.7)	2 (13.3)	0 (0)	0 (0)	1.000
Glioblastoma (%)	37 (33.6)	7 (46.7)	4 (66.7)	1 (20.0)	0.292
Others (%)	8 (7.3)	1 (6.7)	0 (0)	0 (0)	1.000
High-grade glioma (%)	66 (60.0)	10 (66.7)	4 (66.7)	2 (40.0)	0.792
Genetic characterizations					
IDH-1 mutation (%)	49 (45.4)	5 (33.3)	1 (16.7)	4 (80.0)	0.169
p53 mutation (%)	75 (69.4)	8 (53.3)	6 (100.0)	4 (80.0)	0.201
Maximum BIS values (IQR)	97 (94–98)	94 (87–97.5)	96.5 (88.3–98)	98 (92–98)	0.612

\**p* < 0.05. BIS: bispectral index, IQR: interquartile range, IAP: intraoperative awake period.

vs. 4 [26.7] vs. 4 [66.7%] vs. 1 [20.0%], respectively,  $p = 0.008$ ), preoperative seizure (48 [43.6%] vs. 2 [13.3] vs. 0 [0%] vs. 3 [60.0%], respectively,  $p = 0.012$ ), left-sided lesion (53 [48.2%] vs. 13 [86.7] vs. 5 [100.0%] vs. 4 [80.0%], respectively,  $p = 0.001$ ), frontal lobe lesion (55 [50.0%] vs. 5 [33.3] vs. 1 [16.7%] vs. 5 [100.0%], respectively,  $p = 0.021$ ), and temporal lobe lesion (23 [20.9%] vs. 6 [40.0] vs. 4 [66.7%] vs. 0 [0%], respectively,  $p = 0.021$ ) were significantly different. In addition, the other notable findings of patients with restlessness were as follows: male sex, five patients (83.3%); lateral position three (50.0%); and high-grade glioma, four (66.7%). Those of patients with intraoperative seizures were as follows: male sex, 4 (80.0%); frontal lobe lesion, 5 (100.0%); levetiracetam treatment (intraoperative anticonvulsant), 3 (60.0%); electrophysiological evaluation, 4 (80.0%); low-grade glioma, 3 (60.0%); and p53 mutation, 4 (80.0%). In two patients with intraoperative seizure, electrical mapping stimulation elicited a seizure. As the most common cause of inclusion in the inappropriately awake group, univariate and multivariate analyses for detecting insufficient wakefulness were performed (Table 4). A simple logistic regression was used in the univariate analysis, and age (OR, 1.07; 95% CI, 1.03–1.12;  $p = 0.002$ ) and the incidences of preoperative seizures (OR, 0.21; 95% CI, 0.05–0.98;  $p = 0.047$ ) and left-sided lesions (OR, 6.08; 95% CI, 1.32–28.11;  $p = 0.021$ ) were significantly associated with insufficient wakefulness. In multivariate analysis, preoperative seizure was selected using stepwise methods, although there was no significant difference between groups (OR, 0.15; 95% CI, 0.02–1.23;  $p = 0.077$ ). The AUC of the analysis was 0.644 (95% CI, 0.512–0.776;  $p = 0.069$ ), and the sensitivity and specificity were 86.7% and 42.1%, respectively. A summary of the inappropriately awake patients who presented with restlessness or intraoperative seizures during the intraoperative awake period is shown in Table 5, and a summary of patients with insufficient wakefulness is shown in supplementary material 2.

Among patients who underwent awake craniotomy for epilepsy, the appropriately awake group comprised 20 patients (76.9%) and the inappropriately awake group consisted of 6 patients (23.1%); this distribution was not significantly different compared with the glioma patients ( $p = 0.642$ ). In the inappropriately awake group, one patient (3.8%) had insufficient wakefulness, five (19.2%) exhibited restlessness, and none had intraoperative seizures. Among five patients with restlessness, three with temporal lobe epilepsy may have experienced it due to intraoperative pain during manipulation of the dura mater

and vessels, and in one patient it may have been related to preoperative emotional disturbance.

## Discussion

### The importance of preoperative seizures and lesion side

In this study, we evaluated risk factors for difficulties with neurological examination during the intraoperative awake period in awake craniotomy for glioma. In the multivariate analyses, a lack of preoperative seizures and left-sided lesions were identified as risk factors for these difficulties. A past report mentioned that preoperative seizures and right-sided lesions might be associated with successful awake craniotomy, although these factors were not statistically significant.<sup>16)</sup> It is possible that our findings were significant due to the larger number of patients in this study.

Patients with preoperative seizures might have milder impairments than patients without seizures. Preoperative seizures were reported to be the most common presenting symptoms in patients with low-grade glioma, and might be the only symptom for months or years in the initial disease phase<sup>24–26)</sup>; these patients may therefore be investigated before they present with significant motor or language impairments. In this study, preoperative language impairment was significantly less common in patients with preoperative seizures than in those without (3 [5.7%] vs. 20 [24.1%], respectively,  $p = 0.005$ ). Furthermore, the lesion size was smaller in patients with preoperative seizures than in those without, although this difference was not significant (26.5 [12.9–39.8] vs. 27.5 [17.5–43.7] cm<sup>2</sup>, respectively,  $p = 0.398$ ). In past reports, there was an inverse correlation between seizure risk and tumor growth rate.<sup>25,27)</sup> Moreover, seizures at presentation are also associated with longer median survival.<sup>28)</sup> Milder impairments in patients with preoperative seizures might decrease the rate of difficulties during the intraoperative awake period. On the other hand, a history of seizures is related to failed awake craniotomy due to intraoperative seizures.<sup>15)</sup> Furthermore, in our study, the development of intraoperative seizures was associated with a higher likelihood of preoperative seizures (60%), although this finding was not significant.

Compared to patients with right-sided lesions, those with left-sided lesions might present with more severe disability, mainly in the form of language impairment. In a past report, preoperative language impairment was reported to be associated with a higher rate of failed awake craniotomy due to inability to communicate during the intraoperative



**Table 4 Univariate and multivariate analyses for detecting insufficient wakefulness in 136 patients**

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Age	1.07 (1.03–1.12)	0.002*		
Sex, male	0.75 (0.26–2.21)	0.607		
Preoperative language impairment	1.95 (0.56–6.78)	0.292		
Preoperative seizure	0.21 (0.05–0.98)	0.047*	0.15 (0.02–1.23)	0.077
Past operation for this lesion	0.97 (0.29–3.26)	0.96		
Left-sided lesion	6.08 (1.32–28.11)	0.021*		
Presence of multiple lesions	6.05 (0.93–39.6)	0.06		
Deep location	1.51 (0.50–4.56)	0.461		
Location of lesion (frontal lobe/ temporal lobe/other)	1.25 (0.67–2.34)	0.477		
Lesion size	1.00 (1.00–1.00)	0.623		
Intraoperative posture, lateral	0.51 (0.14–1.90)	0.312		
Anesthesia duration before intraoperative awake period	1.00 (0.99–1.01)	0.426		
Intraoperative anticonvulsant, LEV	0.51 (0.16–1.58)	0.241		
Electrophysiological evaluation	0.89 (0.23–3.42)	0.864		
High-grade glioma (grade 3, 4)	1.36 (0.44–4.23)	0.594		
GBM	1.65 (0.56–4.85)	0.366		
IDH-1 mutation	0.60 (0.19–1.87)	0.38		
p53 mutation	0.46 (0.15–1.36)	0.159		
Maximum BIS value	0.96 (0.88–1.05)	0.374		

\**p* < 0.05. BIS: bispectral index, CIs: confidence interval, GBM: glioblastoma, LEV: levetiracetam.

awake period.<sup>15)</sup> Some reports and guidelines also state that patients with language impairment are not good candidates for awake craniotomy.<sup>29–31)</sup> In our study, preoperative language impairment was associated with neurological examination difficulties in the univariate analysis, although this association was not detected in the multivariate analysis. Patients who could not follow the preoperatively presented instructions concerning intraoperative neurological examinations were excluded in this study; however, mild language impairment, which would still allow patients to process preoperative instructions, might increase the risk of difficulties intraoperatively. Since patients with left-sided lesions and associated language impairment might have increased difficulty communicating during the intraoperative awake period, they may require more attention during surgery than those with right-sided lesions. In addition, fMRI is performed preoperatively at our institution to evaluate hemispheric language dominance. However, in this study only three patients (2.2%) with right-sided lesions demonstrated right hemispheric dominance, and the effect was less

enough. Furthermore, regarding the reason for performing awake craniotomy, assessment of language function was a less frequent objective in the appropriately awake group than in the inappropriately awake group (50 [45.5%] vs. 23 [88.5%], respectively, *p* < 0.001). This is probably because patients who required evaluation of language function were likely to have left-sided lesions and preoperative language impairment, both of which were more common in the inappropriately awake group.

Regarding factors other than preoperative seizures and left-sided lesions, univariate analysis showed that higher age was significantly associated with neurological examination difficulties in this study. In past studies, the metabolism of propofol was reported to be lower in older patients.<sup>32,33)</sup> This could help explain our result, although we could not evaluate propofol blood concentrations in this study. Given that a 90-year-old patient successfully underwent awake craniotomy,<sup>34)</sup> we consider patient cooperation to be more important than numerical age for awake craniotomy. From the viewpoint of pathological diagnosis, patients in the inappropriately

Table 5 Summary of patients with restlessness or intraoperative seizures

Case No.	State	Age, y	Sex	PO LD	PO S	PO OH	Past OH	Location of lesion	Lat. of lesion	Lesion mult.	Deep location	Lesion size, cm <sup>2</sup>	IO Pos.	AD, min	IO AC	EE	PD	Maximum BIS value	IDH-1 mutation	p53 mutation
1	R	17	M	(-)	(-)	(+)	(+)	Third ventricle	Midline	(-)	(+)	7.6	Supine	341	PHT	(+)	DA	71	(-)	(+)
2	R	69	M	(+)	(-)	(-)	(-)	Temporal	Left	(-)	(-)	38.8	Supine	256	LEV	(-)	GBM	98	(-)	(+)
3	R	64	F	(+)	(-)	(-)	(-)	Temporal	Left	(-)	(-)	57.1	Lateral	179	LEV	(+)	GBM	95	(-)	(+)
4	R	82	M	(+)	(-)	(-)	(-)	Frontal	Left	(-)	(-)	34.6	Supine	230	LEV	(+)	GBM	98	(-)	(+)
5	R	76	M	(+)	(-)	(-)	(-)	Temporal	Left	(-)	(-)	32.7	Lateral	248	LEV	(-)	GBM	98	(-)	(+)
6	R	55	M	(-)	(-)	(-)	(-)	Temporal	Left	(-)	(-)	24	Lateral	256	LEV	(+)	DA	94	(+)	(+)
7	I	34	M	(-)	(+)	(-)	(-)	Frontal	Left	(-)	(-)	41.3	Supine	332	PHT	(+)	AO	98	(+)	(+)
8	I	51	F	(-)	(-)	(-)	(-)	Frontal	Left	(-)	(-)	62.1	Supine	288	LEV	(+)	DA	92	(+)	(+)
9	I	29	M	(-)	(+)	(-)	(-)	Frontal	Left	(-)	(-)	45.8	Supine	342	LEV	(+)	OD	98	(+)	(+)
10	I	52	M	(+)	(-)	(-)	(-)	Frontal	Left	(-)	(-)	36.4	Supine	273	LEV	(+)	GBM	NA	(-)	(+)
11	I	45	M	(-)	(+)	(-)	(-)	Frontal	Right	(-)	(-)	13.4	Supine	234	PHT	(-)	OD	NA	(+)	(-)

BIS: bispectral index, AC: anticonvulsant, AD: anesthetic duration before intraoperative awake period, AO: anaplastic oligodendroglioma, DA: diffuse astrocytoma, EE: electrophysiological evaluation, F: female, GBM: glioblastoma, I: intraoperative seizure, IO: intraoperative seizure, IO: intraoperative, Lat.: laterality, LD: language disorder, LEV: levetiracetam, M: male, NA: not available, OD: oligodendroglioma, OH: operation history, PD: pathological diagnosis, PHT: phenytoin or fosphenytoin sodium, PO: postoperative, Pos.: posture, R: restlessness, S: seizure.

awake group in this study were more frequently diagnosed with oligodendroglioma than anaplastic oligodendroglioma (7/27 [25.9%] vs. 1/14 [7.1%], respectively,  $p = 0.153$ ), despite the similar genetic features, although the difference was not statistically significant. Left-sided lesions were more common in oligodendroglioma than in anaplastic oligodendroglioma (15/27 [55.6%] vs. 4/14 [28.6%], respectively,  $p = 0.100$ ), and this difference may have affected the results. In addition, univariate and multivariate analyses for detecting inappropriately awake group in 87 patients except for patients with GBM were performed to assess the confounding of GBM, and no factor was detected in multivariate analysis due to small number of patients. However, preoperative seizures and left-sided lesions were detected in multivariate analysis for all 136 patients, while GBM was not detected. Therefore, the confounding of GBM was considered to be deniable. Another study showed that phenytoin treatment was related to failed awake craniotomy due to lack of communication, and multiple antiepileptic drugs were related to increased incidences of intraoperative seizures.<sup>15)</sup> In our study, the types of anticonvulsants administered did not differ significantly between the two groups, and the number of antiepileptic drugs administered to each patient was not evaluated. Remifentanyl administration was previously reported to be associated with failed awake craniotomy in a multivariate analysis.<sup>16)</sup> We adopted the same anesthesia method as that study, and remifentanyl was administered to all patients.

### Considerations regarding insufficient wakefulness, restlessness, and intraoperative seizures

Three factors, specifically insufficient wakefulness, restlessness, and intraoperative seizures, might lead to difficulties when performing awake craniotomy because of challenges in communicating with patients.

Insufficient wakefulness was the main cause of communication difficulties in our study. In the multivariate analysis, insufficient wakefulness occurred significantly more frequently in patients with preoperative seizures than in those without. In the univariate analysis, higher age and left-sided lesions were significantly associated with insufficient wakefulness, although these associations disappeared in the multivariate analysis. Plausible explanations for the correlations of the above factors with insufficient wakefulness are as follows: individuals with preoperative seizures have milder symptoms, older patients have a reduced rate of anesthetic metabolism, and left-sided lesions produce more severe symptoms than right-sided lesions.

Regarding restlessness, we could not perform sufficient statistical analysis due to the small number of relevant patients. Preoperative language impairment, left-sided lesions, and lateral position showed a nonsignificant association with restless state during the intraoperative awake period. We considered that unpleasant sensations such as uncomfortable posture, pain, and difficulty communicating might lead to restlessness, although no previous reports have supported these theories.

Although we could not perform sufficient statistical analysis of intraoperative seizures, they may be associated with younger age, frontal lobe lesions, preoperative seizures, low-grade glioma, and p53 mutation; furthermore, electrical mapping stimulation elicited a seizure in two patients. In the literature, intraoperative seizures have been associated with younger age, history of seizure, frontal lobe tumors, and brain mapping and stimulation patterns.<sup>13,14,35,36)</sup> In particular, stimulation during brain mapping was reported to induce intraoperative seizures at a high rate (8.2–20.0%).<sup>14,35,36)</sup> Our results mostly confirmed the aforementioned findings. With respect to brain mapping of the motor area, short-train stimulation was reported to be associated with a significantly lower risk of seizures than 50–60 Hz stimulation, due to the shorter stimulus duration.<sup>36)</sup> At our institution, electrical mapping is performed using constant-current stimuli at 50–60 Hz for 10 sec, and this might have increased the risk of intraoperative seizure. With respect to pathological findings, low-grade glioma was previously found to be associated with higher rate of preoperative seizure,<sup>24–26)</sup> and p53 mutation was associated with drug-resistant epilepsy in low-grade glioma.<sup>23)</sup> Our results also suggest an association between pathological findings and intraoperative seizures.

In addition, we compared patients with glioma to those with epilepsy, and found that they accounted for similar percentages of the inappropriately awake group (26/136 [19.1%] vs. 6/26 [23.1%],  $p = 0.642$ ). Relative to patients with glioma, those with epilepsy were less likely to have insufficient wakefulness and intraoperative seizures but were more likely to demonstrate restlessness. The main cause of inappropriate wakefulness in patients with epilepsy was restlessness (5/26 [19.2%]), in which three patients with temporal lobe epilepsy may have been due to intraoperative pain secondary to manipulation of the dura mater and vessels. By contrast, no patients with glioma demonstrated restlessness that was obviously caused by pain. One patient with epilepsy exhibited emotional disturbance. Relatively younger age, emotional disturbance, and manipulation of the dura mater and vessels in epilepsy patients

might be associated with the difference, although we identified no previous studies that supported this theory.

### Limitations and future work

This study had several limitations. First, the anesthetics used in this study may have affected the results, particularly since their metabolism can vary from patient to patient. However, we attempted to minimize their effects by adopting the same anesthesia protocol in all patients. Second, there was a lack of detailed data about preoperative impairments in language, cognition, and other neurological functions, although we did preoperatively confirm that patients could follow the instructions needed for the intraoperative neurological examination. Finally, the sample size was not large enough to perform detailed statistical analysis of each subgroup; thus, we described only the notable findings. To overcome these limitations, in the future it will be necessary to confirm our results in prospective studies with large sample sizes.

### Conclusions

In this study, we evaluated the risk factors of difficulties with neurological examination during the intraoperative awake period in awake craniotomy for glioma. The lack of preoperative seizures and left-sided lesions conferred increased risk of difficulties. Understanding these risk factors may lead to more appropriate identification of patients eligible for awake craniotomy and help define the optimal preoperative preparation for this procedure, thus improving outcomes.

### Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest.

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