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A Nationwide Questionnaire Survey on Awake Craniotomy in Japan

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Abstract

The number of awake craniotomies is increasing because of its beneficial features. However, not enough information is available regarding the current status of awake craniotomy in Japan. To evaluate the current status of awake craniotomy in institutes, a nationwide questionnaire survey was conducted. From June to August 2019, we conducted a questionnaire survey on awake craniotomy in the neurosurgery department of 45 institutes that perform awake craniotomies in Japan. Responses were obtained from 39 institutes (response rate, 86.7%). The main methods of awake craniotomy were almost the same in all institutes. Twenty-six institutes (66.7%) had fewer than 10 awake craniotomies (low-volume institutes) per year, and 13 high-volume institutes (33.3%) performed more than 10 awake craniotomies annually. Some institutes experienced a relatively high frequency of adverse events. In 11 institutes (28.2%), the frequency of intraoperative seizures was more than 10%. An intraoperative seizure frequency of 1%-9%, 10%-29%, and over 30% was identified in 12 (92%), 0 (0%), and 1 (8%) of the high-volume institutes, which was significantly less than in 16 (62%), 10 (38%), and 0 (0%) of the low-volume institutes ($p = 0.0059$). The routine usage of preoperative antiepileptic drugs was not different between them, but the old type was used more often in the low-volume institutes ($p = 0.0022$). Taken together, the annual number of awake craniotomies was less than 10 in over two-thirds of the institutes. Fewer intraoperative seizures were reported in the high-volume institutes, which tend not to preoperatively use the old type of antiepileptic drugs.

Keywords: awake craniotomy, Japan, questionnaire investigation, intraoperative seizures, brain tumor

Introduction

Awake craniotomy has been introduced in many institutes because of its beneficial features that minimize the complication risk and enable proper resection of lesions while evaluating the symptoms of the patient. Typical indications include epilepsy, glioma, and cavernous hemangioma.[1)] In 2012, the Japanese Society of Awake Surgery published "Guidelines for Awake Craniotomy."[2)] The guidelines consist of three parts: 1) surgical maneuvers for awake craniotomy, 2) anesthetic management for awake craniotomy, and 3) language assessment during awake craniotomy. These guidelines ensure the safety and precision of an awake craniotomy and describe the method.

In 2014, the Awake Craniotomy Institute Certification System was launched in Japan. The management of brain mapping/monitoring in awake patients with brain tumors is covered by health insurance. Awake craniotomy can contribute to improve the clinical outcome by maximizing safe resection of gliomas.[3,4)] Although awake craniotomy has been performed in many institutes, the current status of awake craniotomy remains unclear, especially regarding whether or not the same methods are used in all institutes. Understanding the overall situation for improving

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Table 1 The current status of awake craniotomy in Japanese institutes

1) Annual number of awake craniotomies (39 institutes responded to the survey)	
Under 10	26 (66.7%)
10-30	8 (20.5%)
Over 30	5 (12.8%)
2) Medical professionals that observe neurological findings (39 institutes responded to the survey; multiple answers possible)	
Surgeons	31 (79.5%)
Speech therapists	24 (61.5%)
Physical therapists	8 (20.5%)
Occupational therapists	2 (5.2%)
Clinical engineers	1 (2.6%)
Nurses	1 (2.6%)
3) Electrophysiological monitoring during awake craniotomy (39 institutes responded to the survey; multiple answers possible)	
High-frequency (50-60 Hz) electrical stimulation mapping (cortex)	37 (94.9%)
High-frequency (50-60 Hz) electrical stimulation mapping (white matter)	32 (82.1%)
Electroencephalography	32 (82.1%)
Motor-evoked potentials	29 (74.4%)
Somatosensory-evoked potentials	20 (51.3%)
Cortico-cortical-evoked potentials	2 (5.2%)

the safety of awake craniotomy is therefore beneficial. In the present study, we conducted a nationwide questionnaire survey to clarify the actual state of awake craniotomy in Japan.

Materials and Methods

From June to August 2019, we conducted a questionnaire survey on awake craniotomy in the neurosurgery department of 45 institutes that perform awake craniotomy in Japan. A request for cooperation as well as the URL of the questionnaire website, login ID, and password was mailed to each institute.

The questions included (1) the frequency of awake craniotomy, (2) the medical professional who confirms the intraoperative neurological symptoms, (3) the use and method of intraoperative electrophysiological monitoring in awake patients, (4) the type and frequency of adverse events experienced during awake craniotomy, and (5) perioperative seizure management. This questionnaire study, which was carried out as a project of the 17th meeting of the Japan Awake Surgery Society, was approved by the Steering Committee of the Japan Awake Surgery Society and was carried out in accordance with the principles of the Declaration of Helsinki. This study did not require patient consent because no individual information regarding patients was collected.

Statistical analyses were performed using the R project (version 3.3.0, www.r-project.org) software. Categorical variables were compared with the Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results

Responses were obtained from 39 of the 45 institutes to which we sent the cooperation request (response rate, 86.7%).

Current status of awake craniotomy in Japanese institutes

Table 1 shows the frequency of awake craniotomies, the type of medical professional who confirms the intraoperative neurological symptoms, the use of intraoperative electrophysiological monitoring in awake patients, and the survey results of the methods. Twenty-six institutes (66.7%) performed fewer than 10 awake craniotomies annually (low-volume institutes), whereas eight institutes (20.5%) performed 10-30 awake craniotomies, and five institutes (12.8%) performed more than 30 (high-volume institutes) annually.

Physicians were involved in the confirmation of neurological symptoms in awake patients at 31 institutes (79.5%). Of these, medical doctors confirmed neurological symptoms at 12 institutes (30.8%), and a speech therapist confirmed the symptoms in eight institutes (20.5%).

Intraoperative electrophysiological monitoring in awake patients was also performed at all responding institutes. Functional mapping (cortex) of high-frequency (50-60 Hz) stimulation was performed at 37 institutes (94.9%, multiple answers allowed). In addition, functional mapping (white matter) of high-frequency (50-60 Hz) stimulation was performed at 32 institutes (82.1%, multiple answers allowed). Intraoperative electrophysiological monitoring with electro-

encephalography (EEG) was performed at 32 institutes (82.1%, multiple answers allowed). Furthermore, motor-evoked potentials were measured at 29 institutes (74.4%, multiple answers allowed), and somatosensory-evoked potentials were measured at 20 institutes (51.3%, multiple answers allowed). No apparent differences were seen between the low-volume and high-volume institutes regarding the method of local anesthesia, electrical stimulation, and EEG and electrocorticography monitoring during surgery.

Types and frequencies of adverse events experienced during awake craniotomy

Figure 1 shows the frequency of adverse events of seizures, pain, nausea, vomiting, respiratory obstruction, no awakening, and restlessness experienced during awake craniotomy. In 11 institutes (28.2%), the frequency of seizures was more than 10%. Patients experienced "pain" with a frequency of more than 10% in 24 institutes (61.5%), "nausea" of more than 10% in 12 institutes (30.8%), and "vomiting" of more than 10% in 5 institutes (12.8%). "Respiratory obstruction" was experienced at a frequency of 5%-9% in one institute (2.6%) and 1%-4% in eight institutes (20.5%). In no institutes did patients experience "Respiratory obstruction" at a frequency of more than 10%. Fourteen institutes (35.9%) experienced a frequency of more than 10% of "no awakening" in patients who could not perform task tests. Patients experienced "restlessness," which requires re-sedation before completion of the task, at a frequency more than 10% at three institutes (7.7%). At all 39 institutes, if a "seizure" occurred during awake craniotomy, cold water was applied to the brain surface.

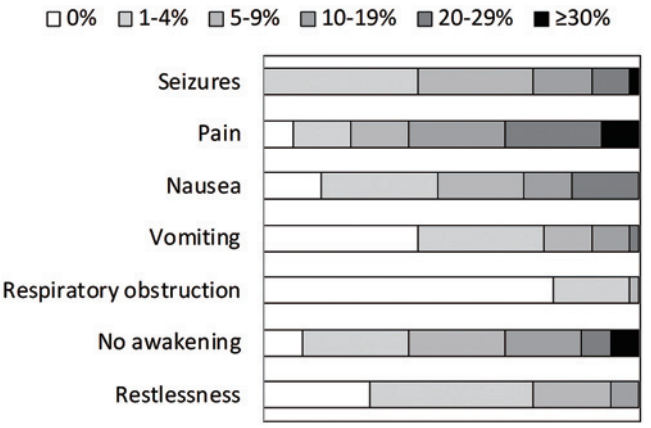

Fig. 1 Frequency of adverse events (39 institutes responded to the survey).
Pain: painkillers were required; Nausea: antiemetics were required; Respiratory obstruction: tracheal intubation and laryngeal mask airway were required; No awakening: Patients could not perform the task; Restlessness: sedation before completion of the task was required.

Perioperative usage of antiepileptic drugs in patients with brain tumors

In patients with brain tumors, all patients were administered prophylactic antiepileptic drugs before awake craniotomy at 26 institutes (66.7%) (Table 2). Only patients with a history of epileptic seizures were administered antiepileptic drugs at 12 institutes (30.8%). Furthermore, levetiracetam, which is the most frequently used antiepileptic drug, was administered at 38 institutes (97.4%, multiple answers allowed) in patients with a history of epileptic seizures. At 24 institutes (61.5%, multiple answers allowed), levetiracetam was also used in patients with no history of epileptic seizures.

Antiepileptic drugs were administered intravenously to all patients during awake craniotomy at 22 institutes (56.4%), whereas they were not used during awake craniotomy at 13 institutes (33.3%). At four institutes (10.2%), antiepileptic drugs were only used in patients with a history of epileptic seizures. Specifically, in patients with a history of epileptic seizures, fosphenytoin was used intraoperatively at 14 institutes (35.9%), whereas levetiracetam was used at 11 institutes (28.2%). Moreover, for patients without a history of epileptic seizures, fosphenytoin was used intraoperatively at 16 institutes (41.0%), whereas levetiracetam was used at 7 institutes (18.0%).

All patients were administered antiepileptic drugs after surgery at 20 institutes (51.3%). Antiepileptic drugs were administered only to patients with a history of epileptic seizures at 19 institutes (48.7%). As a postoperative prophylactic antiepileptic drug, levetiracetam was used at 37 institutes (94.9%) in patients with an epileptic history. Levetiracetam was also used at 19 institutes (48.7%) in patients without an epileptic history.

Intraoperative seizures and antiepileptic drugs in patients with brain tumors

Importantly, a frequency of intraoperative seizures, 1%-9%, 10%-29%, and over 30%, was identified in 12 (92%), 0 (0%), and 1 (8%) of the high-volume institutes, which was significantly less than that in 16 (62%), 10 (38%), and 0 (0%) of the low-volume institutes ($p = 0.017$) (Table 3). Although the routine usage of preoperative antiepileptic drugs was not different between the low-volume institutes (73%) and high-volume institutes (54%) ($p = 0.29$), the routine usage of intraoperative antiepileptic drugs was significantly more frequent in the low-volume institutes (69%) than in the high-volume institutes (31%) ($p = 0.039$) (Table 4).

In comparison between the new type of antiepileptic drugs (levetiracetam, lacosamide, lamotrigine, and perampanel hydrate) and old type (phenytoin, sodium valproate, and carbamazepine), the preoperative usage of the old type was more often in the low-volume institutes than in the high-volume institutes (26% vs. 0% for patients without a history of epilepsy, $p = 0.16$; 18% vs. 5% for patients with a history of epilepsy, $p = 0.018$; total, $p = 0.0022$) (Table 4).

Table 2 Perioperative usage of antiepileptic drugs in patients with brain tumors (39 institutes responded to the survey)

	Preoperative usage		Intraoperative usage		Postoperative usage	
	No epileptic history	Epileptic history	No epileptic history	Epileptic history	No epileptic history	Epileptic history
No usage of antiepileptic drugs	13 (33.3%)	1 (2.6%)	17 (43.6%)	13 (33.3%)	19 (48.7%)	0 (0%)
Usage of antiepileptic drugs	26 (66.7%)	38 (97.4%)	22 (56.4%)	26 (66.7%)	20 (51.3%)	39 (100%)
Breakdown list (multiple answers possible)						
LEV	24	38	7 (div)	11 (div)	19	37
LCM	3	14	0	1 (div)	7	20
PHT (fosPHT)	3	5	16 (div)	14 (div)	3	3
VPA	3	4	0	0	2	4
CBZ	1	10	0	0	3	5
LTG	1	3	0	0	2	2
PER	1	6	0	0	3	11

LEV, Levetiracetam; LCM, Lacosamide; PHT, Phenytoin; fosPHT, Fosphenytoin; VPA, Sodium valproate; CBZ, Carbamazepine; LTG, Lamotrigine; PER, Perampanel hydrate; div, drip infusion in vein

Table 3 Frequencies of intraoperative seizures based on the annual number of awake craniotomies

Frequency of seizures	Awake craniotomies <10 (26)	Awake craniotomies ≥10 (13)
1%-4%	9 (35%)	7 (54%)
5%-9%	7 (27%)	5 (38%)
10%-19%	6 (23%)	0 (0%)
20%-29%	4 (15%)	0 (0%)
Over 30%	0 (0%)	1 (8%)

However, the intraoperative antiepileptic drugs were not different between them (50% vs. 67% for patients without a history of epilepsy, $p > 0.999$; 68% vs. 75% for patients with a history of epilepsy, $p = 0.65$; total; $p = 0.72$) (Table 4).

The routine usage of postoperative antiepileptic drugs was not different between the low-volume institutes (50%) and high-volume institutes (54%). As for preoperative antiepileptic drugs, the postoperative usage of the old type tends to be more often in the low-volume institutes (Table 4).

Discussion

A nationwide questionnaire survey was conducted to reveal the actual conditions of awake craniotomy in Japan. Twenty-six institutes (66%) performed fewer than 10 awake craniotomies annually, and 13 institutes (33%) performed more than 10 awake craniotomies annually. In Europe, the survey of awake diffuse low-grade gliomas (DLGG) surgery within the European Low-Grade Glioma Network centers showed that a median of 15 (range, 2-165) DLGG patients were annually operated on in each center.[5] In the United Kingdom, approximately 33.5 awake craniotomies per year were performed in a single neurosurgical center.[6] Awake craniotomy is carried out at a relatively large number of institutes in Japan, but the annual number of awake craniotomies in over two-thirds of the institutes was less than 10.

Although the basic methods of anesthesia, surgery, and intraoperative brain function examinations are unified, clearly some differences are present in the details. Most institutes involved surgeons to confirm the neurological symptoms during awake craniotomy. In addition, more than 25 of 39 institutes involved speech therapists or physical therapists for this. Some institutes involved only speech therapists or physical therapists for assessing neurological symptoms without involving surgeons. Building a good relationship of trust between the patient and the surgical staff when performing an awake craniotomy is most important[7] and shows that the participation of medical professionals is reliable when performing an awake craniotomy. Moreover, electrophysiological monitoring was performed at all institutes, with the majority performing functional mapping (cortex or white matter) with high-frequency (50-60 Hz) stimulation. For this feature, no apparent difference among the institutes was observed. Electric cortical stimulation during awake craniotomy has been the gold standard for reversible cortical perturbation, which is valuable for functional cortical mapping and safe surgical resections.[8-10] Modern functional mapping can support a more patient-specific approach.[11]

Awake craniotomy is a well-defined procedure with a

Table 4 Usage of antiepileptic drugs based on the annual number of awake craniotomies

Preoperative AED	Awake craniotomies <10 (26)		Awake craniotomies ≥10 (13)	
All patients	19 (73%)		7 (54%)	
Selective	6 (23%)		6 (46%)	
None	1 (4%)		0 (0%)	
	No epileptic history	Epileptic history	No epileptic history	Epileptic history
LEV	17	25	7	13
LCM	2	10	1	4
LTG	1	2	0	1
PER	0	4	1	2
New type AEDs	20 (74%)	41 (69%)	9 (100%)	20 (95%)
PHT (fosPHT)	3	5	0	0
VPA	3	4	0	0
CBZ	1	9	0	1
Old type AEDs	7 (26%)	18 (31%)	0 (0%)	1 (5%)
Intraoperative AED	Awake craniotomies <10 (26)		Awake craniotomies ≥10 (13)	
All patients	18 (69%)		4 (31%)	
Selective	2 (8%)		2 (15%)	
None	6 (23%)		7 (54%)	
	No epileptic history	Epileptic history	No epileptic history	Epileptic history
LEV	6	9	1	2
LCM	0	1	0	0
LTG	0	0	0	0
PER	0	0	0	0
New type AEDs	6 (32%)	10 (50%)	1 (25%)	2 (33%)
PHT (fosPHT)	13	10	3	4
VPA	0	0	0	0
CBZ	0	0	0	0
Old type AEDs	13 (68%)	10 (50%)	3 (75%)	4 (67%)
Postoperative AED	Awake craniotomies <10 (26)		Awake craniotomies ≥10 (13)	
All patients	13 (50%)		7 (54%)	
Selective	13 (50%)		6 (46%)	
None	0 (0%)		0 (0%)	
	No epileptic history	Epileptic history	No epileptic history	Epileptic history
LEV	13	25	6	12
LCM	4	15	3	5
LTG	2	2	0	0
PER	1	6	2	5
New type AEDs	20 (77%)	48 (83%)	11 (85%)	22 (92%)
PHT (fosPHT)	2	2	1	1
VPA	2	4	0	0
CBZ	2	4	1	1
Old type AEDs	6 (23%)	10 (17%)	2 (15%)	2 (8%)

AED: antiepileptic drug

very low rate of complications.[11] The guidelines, which were published in 2012, describe complications and their countermeasures.[2] In the present study, we investigated the frequency of adverse events that required drug administration or that led to the inability to perform tasks, and each institution clearly experienced a relatively high frequency of adverse events. Some institutes reported that the frequency of seizures, pain, and no awakening was more than 20%, which is also an issue for proper awake craniotomy. In a cohort study of 609 awake craniotomies by Takami et al., intraoperative adverse events with impossible awake condition were identified in 21 patients, including emotional intolerance in 3 (0.5%), air embolism in 3 (0.5%), generalized seizures in 4 (0.7%), and unexpected subarachnoid hemorrhage in 1 (0.2%).[12] Preoperative cognitive decline, dysphasia, and low performance status (poor Karnofsky Performance Status score) were risk factors for emotional intolerance. Intraoperative adverse events tended to cause inpatient admission, longer hospital stay, and difficult discharge to home.[12] Kuribara et al. reported that the inappropriately awake conditions were identified in 26 of 136 patients with awake craniotomy (19%) because of insufficient wakefulness in 15 patients, restless state in 6, and intraoperative seizures in 5. The lack of preoperative seizures and left-sided lesions were identified as risk factors for inappropriately awake condition.[13] On the basis of these results, preoperative conditions are important to select patients for awake craniotomy.

In particular, the frequency of intraoperative seizures during awake craniotomy has been reported to be approximately 0%-24%, although it depends on the target disease and its definition.[12-17] Afterdischarges, which are defined as repetitive epileptiform discharges provoked by a stimulus,[18] are also identified on electrocorticography.[19] In recommendations for intraoperative seizures in the guidelines, surgical operations, especially electrical stimulation, were discontinued, and cold water was applied to the brain surface at the site of the seizure. Boetto et al. reported that all intraoperative seizures identified in 13 (3.4%) of 374 patients were partial seizures, which quickly resolved by irrigation with cold Ringer lactate.[20]

In the analysis of 477 patients with awake craniotomy by Nossek et al., intraoperative seizures were associated with younger patients, frontal lobe involvement, and a history of seizures.[21] In the other analysis of the same institute, history of seizures and treatment with multiple antiepileptic drugs were related to intraoperative seizures.[22] Abecassis et al. identified intraoperative seizures in 35 patients (15%) and afterdischarges in 40 patients (18%) in 229 patients undergoing awake craniotomy, which were commonly observed during intraoperative stimulation for brain mapping.[19] They found that patients (23%) with intraoperative seizures had afterdischarges prior to their seizure, although intraoperative seizures and afterdischarges were not statistically associated. Stimulation-induced seizures happen on lower stimulation intensities than afterdischarge thresholds detected by concurrent electrocorticography.[8,18] Zanello et al. reported that intraoperative seizures occurred in 3.5% of patients during cortical stimulation and no predictor of intraoperative seizures was identified in 202 patients with diffuse glioma.[16] Failures of awake craniotomy were associated with a lower incidence of gross-total resection and increased postoperative morbidity.[22] The review of literature in 2020 indicated that stimulation-related intraoperative seizures do not always cause permanent and severe postoperative deficits, but they can affect the patient's perioperative status and the duration of hospitalization.[17]

Regarding antiepileptic drugs, the guideline states,[2] "in cases where awake craniotomy is planned, it is desirable to start administration of anticonvulsants in advance and maintain the effective blood concentration if there is time to surgery." However, a previous report suggested that even if the blood concentration of antiepileptic drugs is within the effective range, no difference is present in the preventive effect of intraoperative convulsive seizures, and intraoperative seizures depend on the conditions of electrical stimulation.[23] In this study, the low-volume institutes experienced more frequent intraoperative seizures than the high-volume institutes. The methods of local anesthesia, electrical stimulation, cold water, and EEG and electrocorticography monitoring during surgery were almost the same between the low-volume and high-volume institutes. The routine usage of intraoperative antiepileptic drugs was significantly more frequent in the low-volume institutes. However, as the preoperative antiepileptic drugs, the old type tends not to be used in the high-volume institutes. Recently, some molecular aberrations associated with drug-resistant epilepsy in gliomas have been reported.[24] Therefore, these findings are needed to evaluate in a future large cohort study.

This study has limitations. It was an analysis of a questionnaire survey with limited numbers of questions. Therefore, accurate investigation of the relationship among the patient's characteristics, methods, medications, and adverse events was difficult.

This questionnaire survey revealed that the frequency of adverse events such as seizures, pain, and no awakening is different from 0% to over 30% among the institutes. This fact suggests that it is necessary to identify the technical and operational causes of adverse events, which should be reflected in training courses and guidelines in professional societies to realize the equalization of the best management in awake craniotomy.

Conclusions

Considering the results of the present questionnaire study, the main methods used during awake craniotomy are the same, but a few differences were noted among the

institutes, including functional evaluation methods, antiepileptic drugs, local anesthesia, and postwake management. The annual number of awake craniotomies was less than 10 in over two-thirds of the institutes. Some institutes experienced a relatively high frequency of adverse events. Fewer intraoperative seizures were reported in the high-volume institutes. Although its reason was not clear in the present survey, the high-volume institutes tend not to preoperatively use the old type of antiepileptic drugs. These clinical questions are needed to evaluate in a future large cohort study.

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List of Abbreviations

EEG: Electroencephalography
MEP: Motor-evoked potential
SEP: Somatosensory-evoked potential

Ethics Approval and Consent to Participate

This questionnaire plan, which was carried out as a project of the 17th meeting of the Japan Awake Surgery Society, was approved by the Steering Committee of the Japan Awake Surgery Society.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest Disclosure

All authors have no conflict of interest for this study.

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