Table 2 Factors associated with angiographically confirmed obliteration of the arteriovenous malformation nidus after stereotactic radiosurgery

Factor	*p* value
Group A	0.70
Younger patient age	0.13
Hemorrhage before treatment	0.49
Location other than the basal ganglia and thalamus	0.12
Smaller treated volume	0.42

the volume of the nidus. The precise location of the corticospinal tract was confirmed on treatment planning images, and the maximum dose received by the corticospinal tract was restricted to be less than 20 Gy on the basis of previous analyses (Fig. 1) (10–12).

Follow-up and statistical analysis

Serial formal neurologic and radiologic examinations were performed every 6 months after the procedure. The outcomes including motor complications, other adverse events, and complete obliteration confirmed by cerebral angiography were compared between Groups A and B. Statistical analyses were performed using JMP 8 (SAS Institute Inc., Cary, NC). Comparisons of patients' age, nidus volume, and follow-up period were performed by two-sample *t* test. The rate of motor complications and other adverse events and the actuarial obliteration rate were calculated using the Kaplan-Meier method. The rates of adverse events and obliteration rates of patients in both groups were compared using the Cox proportional hazard model.

Results

Comparison of the two groups

The patient characteristics and treatments in both groups are summarized in Table 1. There were no statistical difference between the two groups (Group A vs. Group B) in patients' age at treatment (34 years vs. 33 years, $p = 0.76$), percentage of patients with hemorrhagic events before treatment (50% vs. 29%), or percentage of AVM involving the basal ganglia and thalamus (36% vs. 46%, $p = 0.46$). The treated volume was significantly smaller ($p = 0.026$) in Group A (mean, 4.8 cm^3; range, 0.2–13.7 cm^3) than in Group B (mean, 7.7 cm^3; range, 1.1–22.4 cm^3), and the applied marginal dose was lower in Group B (mean, 19.6 Gy; range, 15–20 Gy) than in Group A (mean, 20.2 Gy; range, 20–25 Gy). The median follow-up period was 62 months (range, 36–113 months) in Group A and 48 months (range, 36–80 months) in Group B ($p = 0.004$).

Nidus obliteration

Angiographically confirmed nidus obliteration rates at 4 years after SRS was 69% in Group A and 76% in Group B. Integration of DTT was not significantly associated with obliteration rate ($p = 0.68$) (Table 2). Latency interval hemorrhage after treatment occurred in 1 patient, in whom no worsening of neurologic symptom was observed.

Complications

During the follow-up period, neurologic events occurred in 9 patients, 6 in Group A and 3 in Group B (Table 3). In Group A, transient hemiparesis was observed in 3 patients, permanent hemiparesis in 1, permanent dysesthesia in 1, and both permanent hemiparesis and dysesthesia in 1 patient. Modified Rankin Scale scores at last follow-up in these 6 patients were 0 in 3 patients, 1 in 1 patient, and 2 in 2 patients. In Group B, transient hemiparesis, permanent dysesthesia, and transient motor aphasia were observed in 1 patient each. Modified Rankin Scale scores at the last follow-up in these 4 patients were 0 in 3 patients and 1 in 1 patient. Deterioration of modified Rankin Scale scores at the last follow-up was observed in 3 patients among the 6 patients in Group A and 1 patient among 3 patients in Group B.

When we analyzed factors associated with the risk of neurologic events after SRS, integration of DTT of the corticospinal tract did not significantly ameliorate the overall risks of any kind of morbidity ($p = 0.18$), and involvement of the basal ganglia or thalamus was solely associated with higher risks ($p = 0.007$) (Table 4).

However, focusing on motor complications, Group A or the use of DTT of the corticospinal tract was significantly associated with a lower rate of motor complications ($p = 0.021$) (Table 5). Namely, it indicated that SRS using DTT of the corticospinal tract at dose planning could significantly reduce those risks (5 patients in Group A vs. 1 in Group B).

Table 3 Characteristics of patients who experienced neurologic deterioration after stereotactic radiosurgery

Age/sex	Group	Nidus location	Nidus volume (cm^3)	Margin dose (Gy)	Timing of obliteration (mo)	Follow-up period (mo)	Kind of morbidity	Timing of morbidity (mo)	MRS at last follow-up
26/F	A	Thalamus	9.2	20	35	60	Hemiparesis/dysesthesia	4	2
64/M	A	Frontal lobe	2.0	20	ND	46	Transient hemiparesis	11	0
24/M	A	Thalamus	2.5	20	36	39	Permanent dysesthesia	1	1
11/M	A	Thalamus	12.3	20	39	87	Permanent hemiparesis	11	2
20/F	A	Basal ganglia	0.4	20	38	38	Transient hemiparesis	16	0
28/M	A	Frontal lobe	8.5	20	36	36	Transient hemiparesis	16	0
48/M	B	Basal ganglia	12.9	20	44	63	Transient aphasia	2	0
14/F	B	Thalamus	5.3	20	46	46	Permanent dysesthesia	10	1
25/F	B	Basal ganglia	13.0	18	24	36	Transient hemiparesis	11	0

Abbreviations: MRS = modified Rankin Score; ND = data not available.

Table 4 Factors associated with any kind of morbidity after stereotactic radiosurgery

Factor	*p* value
Group A	0.18
Older patient age	0.33
Larger treated volume	0.17
Involvement of the basal ganglia or thalamus	0.007

Table 5 Factors associated with motor complications after stereotactic radiosurgery

Factor	*p* value
Group A	0.021
Older patient age	0.71
Larger treated volume	0.091
Involvement of the basal ganglia or thalamus	0.065

In the patient who had transient hemiparesis in Group B, the volume of AVM nidus that was located in the basal ganglia was relatively large: 13.0 cm^3. The lesion was treated with a margin dose of 18 Gy, and the maximum dose delivered to the corticospinal tract was 17 Gy (Fig. 2).

Discussion

Since the introduction of DTT-integrated SRS, we have partially modified treatment dose planning at SRS for AVM (10–12, 16) to restrict the irradiation dose to the adjacent motor fibers, and our early data suggested that SRS with integration of DTT was likely to be useful to prevent radiation-induced adverse events in AVM patients (10, 11, 18). With the accumulation of cases and the follow-up in this study, we evaluated the substantial effects of this technique because two principal concerns still remained unknown: whether integration of DTT could actually eliminate the risk of radiation-induced motor complications in any AVM patients, and how much such dose modifications would affect the other therapeutic effects such as nidus obliteration rates. Our results showed that SRS with DTT of the corticospinal tract could significantly reduce associated radiation-induced motor complications without affecting the nidus obliteration rates, proving that it contributes to preventing one of the most undesirable complications of SRS for AVM.

However, 1 patient had a large nidus involving the basal ganglia and experienced transient hemiparesis after DTT-integrated SRS, which raised another issue. In this patient, the maximum dose received by the corticospinal tract was less than 20 Gy, which had been considered as a tolerable dose to the motor fibers in our preliminary results (10, 11). Larger nidus volume might have exposed the larger portion of the corticospinal tract to a relatively high dose even though the maximum dose did not surpass the tolerable dose, and this might have caused the hemiparesis. Also, the motor fibers passing through the internal capsule, close to the basal ganglia, are assembled in relatively small territories and are more likely to be affected than are fibers close to the cortical areas (10). Therefore, we speculate that the maximum dose to the corticospinal tract is not the only factor in the development of motor complications after SRS, but the extent of irradiated volume of the motor fibers and the irradiated part can be also associated with them as previously analyzed (10).

DTT has been widely used, and its usefulness has been established especially as a diagnostic tool (19). However, the major concern with regard to tractography is its reliability. If the tracts are not shown on the image, that does not always mean that the fibers do not exist (19, 20). By contrast, it has been shown by intraoperative fiber stimulation analysis that the tracts seen on DTT reflect the functioning white matter fibers to some extent (21). Furthermore, those imaging methods are suitable for SRS because SRS has no risk of brain shift caused by craniotomy or

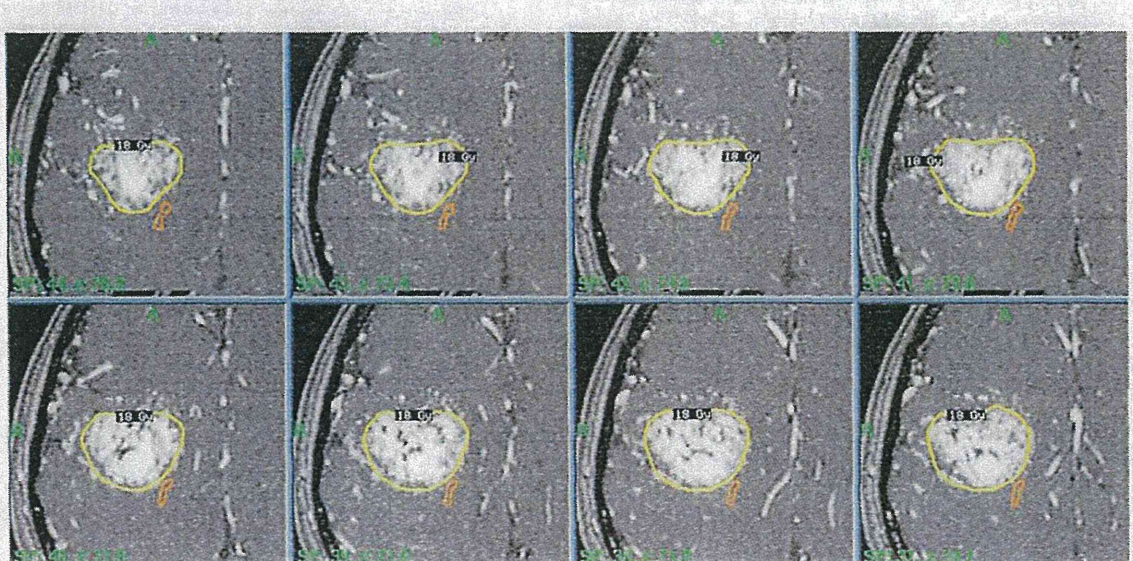

Fig. 2. Treatment planning for a patient with right frontal arteriovenous malformation who experienced transient left hemiparesis after radiosurgery. Long portion of the corticospinal tract (orange) was located adjacent to the large nidus.

tumor removal, which is inevitable in intraoperative applications (22).

The obliteration rates in the cohort in this study, which were 69–76 % at 4 years, were relatively low compared with those previously published (14). Inasmuch as it has been reported that obliteration rates of deeply located AVM have been low, 57–74% within 3 to 4 years (8, 23, 24), and that the lesions in 36–46% of the patients in this study were deeply located AVM, the lower obliteration rates might be explained by patient selection.

Further accumulation of cases with longer follow-up data is awaited to evaluate the effect of integrating tractography into Gamma Knife SRS, but our study disclosed that integrating DTT of the corticospinal tract into treatment planning at SRS contributed to reduction of motor complications and achieved safer treatment without compromising the obliteration rate for AVM adjacent to motor fibers.

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CLINICAL INVESTIGATION **Central Nervous System Tumor**

OUTCOMES OF DIFFUSION TENSOR TRACTOGRAPHY–INTEGRATED STEREOTACTIC RADIOSURGERY

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Purpose: To analyze the effect of use of tractography of the critical brain white matter fibers created from diffusion tensor magnetic resonance imaging on reduction of morbidity associated with radiosurgery.
Methods and Materials: Tractography of the pyramidal tract has been integrated since February 2004 if lesions are adjacent to it, the optic radiation since May 2006, and the arcuate fasciculus since October 2007. By visually confirming the precise location of these fibers, the dose to these fiber tracts was optimized. One hundred forty-four consecutive patients with cerebral arteriovenous malformations who underwent radiosurgery with this technique between February 2004 and December 2009 were analyzed.
Results: Tractography was prospectively integrated in 71 of 155 treatments for 144 patients. The pyramidal tract was visualized in 45, the optic radiation in 22, and the arcuate fasciculus in 13 (two tracts in 9). During the follow-up period of 3 to 72 months (median, 23 months) after the procedure, 1 patient showed permanent worsening of preexisting dysesthesia, and another patient exhibited mild transient hemiparesis 12 months later but fully recovered after oral administration of corticosteroid agents. Two patients had transient speech disturbance before starting integration of the arcuate fasciculus tractography, but no patient thereafter.
Conclusion: Integrating tractography helped prevent morbidity of radiosurgery in patients with brain arteriovenous malformations. © 2012 Elsevier Inc.

Arteriovenous malformation, Diffusion tensor tractography, Gamma knife, Morbidity, Stereotactic radiosurgery.

INTRODUCTION

Stereotactic radiosurgery is one of the principal treatment modalities for various kinds of vascular, neoplastic, or functional disorders of the brain (1–4). Although its efficacy is well known, radiation-induced neuropathy occurs in 5–20% of patients (2, 5–8). To minimize such unignorable risk, we have integrated tractography of the brain white matter based on diffusion tensor magnetic resonance imaging before the procedure into treatment planning of radiosurgery using Gamma Knife (9–11). Diffusion tensor tractography, one of the major recent advancements in magnetic resonance imaging, enables clear visualization of various fibers inside the white matter of the brain, which is not visible with use of conventional imaging modalities (12). Clinical applications of diffusion tensor tractography are mainly reported as diagnostic tools, and reports on its therapeutic application are quite limited (10, 13). In this study, we analyzed the effect of integrating diffusion tensor tractography into treatment planning of stereotactic radiosurgery on the reduction of morbidity in a prospective case series with arteriovenous malformations of the brain.

METHODS AND MATERIALS

Our selection criterion for stereotactic radiosurgery was, in principle, small malformations (<3 cm) in critical, or eloquent, areas of the brain (including sensorimotor, language, or visual cortex; the hypothalamus or thalamus; the internal capsule; the brain stem; the cerebellar peduncles; and the deep cerebellar nuclei) that, if injured, result in disabling neurologic deficits (2, 14). We started integrating diffusion tensor tractography of the pyramidal tract in February 2004 because we considered the pyramidal tract to be the most crucial fiber in preventing morbidity of radiosurgery out of complexity of white matter fibers inside the brain. From May 2006, we added the integration of diffusion tensor tractography of the optic radiation, and diffusion tensor tractography of the arcuate fasciculus tractography from October 2007. One hundred forty-four patients with arteriovenous malformations who have consecutively undergone stereotactic radiosurgery using Gamma Knife with this protocol between February 2004 and December

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Table 1. Baseline characteristics of 144 patients treated

Age (y)	35 (5–77)
Female sex	65 (45)
Details of arteriovenous malformations	
Diameter (cm)	2.7 (0.7–7.9)
Small size	89 (62)
Eloquent brain location	66 (46)
Deep venous drainage	74 (51)
Spetzler-Martin grade	II (I–VI)
Details of radiosurgery	
Target volume (cm^3)	6.9 (0.3–24)
Maximal dose (Gy)	40 (32–50)
Dose to margins (Gy)	20 (15–25)
Follow-up period (mo)	23 (3–72)

Data are number (percentage) or median (range).

2009 were enrolled in this study. All patients were considered as candidates for integrating tractography, but the integration was not carried out if a target lesion was considered to be located more than 1 cm apart from these fiber tracts and risk of injuring them was considered to be sufficiently low. Malformations were located in eloquent brain areas in 66 patients (46%). Detailed treatment parameters are shown in Table 1.

Diffusion tensor magnetic resonance imaging was obtained on the day before treatment. Tractography was created from diffusion tensor imaging by using freely shared programs, according to anatomic landmarks as shown in previous studies (9–12).

On the day of treatment, patients were affixed to the stereotactic coordinate frame and underwent stereotactic magnetic resonance imaging and stereotactic cerebral angiography. Stereotactic magnetic resonance imaging and tractography were registered by using the method reported previously (9–11, 15). After the introduction of Gamma Knife 4C in October 2006, the registration process was automated (16). Tractography-integrated images were imported to treatment planning images on the day of radiosurgery. Conformal treatment planning was made by experienced neurosurgeons and radiation oncologists with use of the treatment planning software GammaPlan (Elekta Instruments AB, Stockholm, Sweden). Generally 20 Gy was given to the margin of lesions by using 40–50% isodose lines. Any portion of the anterior visual pathway and half of the brainstem were designed to receive no more than 10 Gy.

The precise location of the pyramidal tract (Fig. 1), the optic radiation (Fig. 2), or the arcuate fasciculus was confirmed on treatment planning images, and it was attempted that the maximum dose received by each fiber was less than 20 Gy, 8 Gy, or 8 Gy (20 Gy in the frontal fibers), respectively, on the basis of previous analyses (9–11), though this was not possible in some cases.

Serial formal neurologic and radiologic examination was performed every 6 months after the procedure.

RESULTS

Diffusion tensor–based tractography was prospectively integrated in 71 (46%) of 155 treatment sessions. Integrated fiber tracts were the pyramidal tract in 45, the optic radiation in 22, and the arcuate fasciculus in 13 sessions, including 9 in which two tracts were integrated (the pyramidal tract and the optic radiation in 2, the pyramidal tract and the arcuate fasciculus in 3, the optic radiation and the arcuate fasciculus in 4). The optic radiation could not be depicted in 1 patient, and only arcuate fasciculus was drawn. Of 71 treatments with integration of tractography, the distance between the lesion and critical white matter fibers was less than 5 mm in 43 (60%); thus, tighter treatment planning was mandatory. Consequently, 39 sessions (55%) necessitated any modification in treatment planning by reducing the radiation dose to the visualized tracts. Until December 2007, 38% of treatments (37 of 98 sessions) were performed with integration of tractography, whereas tractography was integrated for 60% (34 of 57) thereafter. This difference in frequency was statistically significant according to χ^2 test ($p = 0.008$).

Two patients died of unknown cause after the procedure. The other 142 patients were followed for 3–72 months (median, 23 months) after radiosurgery. During this period, transient speech disturbance was observed in 2 patients. They were treated before 2007, when we started integrating arcuate fasciculus tractography. One patient with right thalamic arteriovenous malformation showed gradual worsening of pre-existing dysesthesia of left upper and lower extremities after treatment, and this symptom lasted until the last

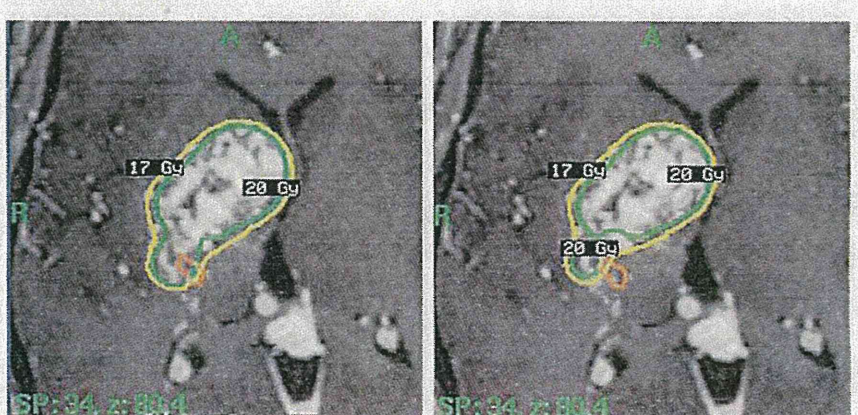

Fig. 1. Radiosurgical dosimetry of 23-year-old woman with ruptured arteriovenous malformation in the right basal ganglia. Dose delivered to the corticospinal tract before referring to tractography (a) was intentionally reduced after its integration (b).

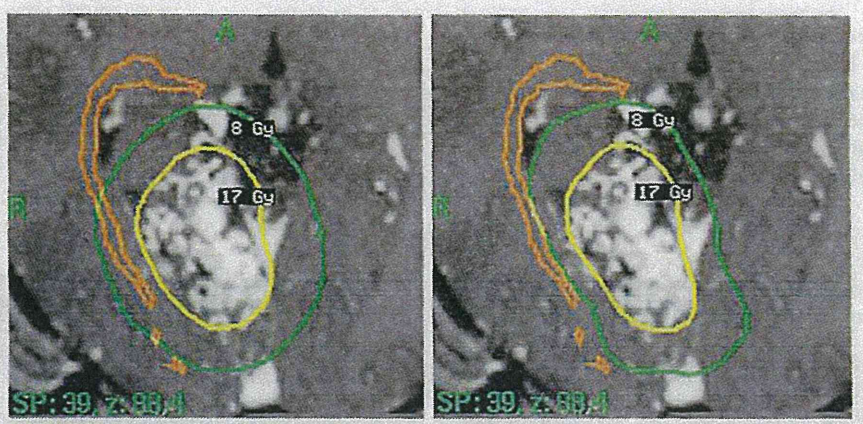

Fig. 2. Radiosurgical dosimetry of 33-year-old woman with unruptured arteriovenous malformation in the right occipital lobe. Dose delivered to the optic radiation before referring to tractography (a) was intentionally reduced after its integration (b).

follow-up at 45 months. This was the only patient who developed permanent morbidity after the prospective integration of tractography. Another patient exhibited mild transient hemiparesis 12 months after treatment prospectively integrating pyramidal tractography but fully recovered after administration of oral corticosteroid agents. Frequency of pre-existing epileptic attacks increased in 3 patients, and new onset of convulsive seizure was observed in 1 patient after radiosurgery. Nidus obliteration was confirmed by magnetic resonance imaging or angiography in 42 patients (29%) until last follow-up. Posttreatment hemorrhage was observed in 2 patients during 319 patient-years. Neither of them exhibited radiation-induced neuropathy before their subsequent hemorrhage. The other patients had no complications throughout the follow-up period.

DISCUSSION

By integrating diffusion tensor tractography of the brain white matter to radiosurgery, permanent and transient morbidity could be reliably prevented in our patients with brain arteriovenous malformations. Although many results of utilizing diffusion tensor–based tractography for diagnostic purposes have been reported (17), its integration into treatment planning of radiosurgery is our original technique and has not been performed at any other institute. Therefore, though this is a retrospective case series, reporting our results would be the most appropriate means to evaluate its efficacy.

Although there are a variety of white matter fiber tracts, we considered that the pyramidal tract would be the most important tract in preventing morbidity of radiosurgery because its injury causes motor paresis and leads to decline of activities of daily living (18, 19). At the same time, the pyramidal tract was practically the easiest one to draw from the technical point of view (17). The optic radiation and the arcuate fasciculus would be next important and are more difficult to draw (20, 21). Injury of the optic radiation causes visual disturbance. Verbal function requires participation of a distributed neural system in the dominant hemisphere, and we integrated the arcuate fasciculus tractography to preserve this function as much as practically possible. For the time being, we are introducing the above three tracts, considering them as critical white matter structures to be preserved. Technical difficulty is also a consideration, as mentioned above. Confirming above three tracts along with anatomically identifiable critical structures of the brain would be sufficient to prevent major disabling morbidity.

Integration of tractography into intraoperative navigation was also developed at our institute (13). However, it contains risks of inevitable brain shift caused by craniotomy or tumor removal, thus leading to poorer accuracy. On the other hand, such a shift does not occur in the setting of integration of tractography into radiosurgery. Therefore, we believe this would be the most suitable clinical application of diffusion tensor tractography in treating brain disorders.

Our study has several potential limitations. Our follow-up period was not long enough to evaluate late adverse events after radiosurgery (6), although it would be appropriate to observe early radiation injury that usually occurs 6 months to 2 years after radiosurgery (2, 6). Longer follow-up would be necessary to investigate whether delayed radiation-induced neuropathy does not affect our result.

Furthermore, the obliteration rate in this study group was low, probably because the median follow-up period of 23 months was shorter than that usually necessary for nidus obliteration, which is 3–5 years (22). One concern is that obliteration on imaging or subsequent prevention of future hemorrhage, which is the therapeutic goal of radiosurgery for arteriovenous malformations, can be compromised by modification of treatment planning by referring to tractography. Therefore, we need to prove, by longer follow-up, that this technique can provide morbidity prevention without lowering the obliteration rate.

Another limitation of tractography is its reliability. There is no guarantee that fibers do not exist where the tracts is not drawn (17, 23). However, tractography has been

proven to reflect anatomic pyramidal tract functioning in intraoperative fiber stimulation analysis (24). Therefore, as indicated in this study, irradiation while paying attention to firmly depicted fibers could sufficiently prevent morbidity, and practically this is the best and the only way to prevent morbidity.

The fact that the rate of tractography integration was higher in the last 2 years suggests the feasibility and usefulness of the procedure. We hope our technique will also be applied to future treatment planning software so that even physicians who are unfamiliar with complicated imaging processing can utilize our methodology (10).

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The Guidelines for Awake Craniotomy

Guidelines Committee of The Japan Awake Surgery Conference

Preface

Cortical mapping by awake craniotomy has become frequently used worldwide as part of the treatment strategy for brain lesions located near language areas. However, no systematic guidelines have been established for this surgery. The Japan Awake Surgery Conference has now created guidelines for awake craniotomy for brain lesions near language areas.

The Japan Awake Surgery Conference was established in 2002 for the purpose of continuing research into neurocognitive functions as well as establishing and promoting safe methods of awake craniotomy. The 4th annual meeting of this conference decided to establish guidelines for awake craniotomy and organized a guidelines committee. Members specializing in the fields of neurosurgery, neurology, and anesthesiology took part in discussions, a systematic review was carried out, and the guidelines committee attempted to create guidelines in compliance with evidence-based medicine methods as far as possible. However, the absence of randomized control trials of awake craniotomy forced the guidelines committee to use "de facto standards" to create the guidelines.

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. The guidelines are not intended to override the methods of experienced practitioners, and are not intended to exclude methods other than those included. We hope that these guidelines will improve the safety of awake surgeries and promote the development of the neuroscience of neurocognitive function.

President of The Japan Awake Surgery Conference
Takamasa KAYAMA, MD

I. SURGICAL MANEUVERS FOR AWAKE CRANIOTOMY

Indications

1. Age

[Recommendation]

While there is no specific upper age limit, an anesthesiologist, surgeon, and speech therapist should consider the condition of each patient carefully. Surgeons with little experience of awake craniotomy should try to perform awake surgery only in patients aged from 15 to 65 years.

[Commentary]

Awake surgery is usually performed in patients aged from 15 to 65 years. However, patients indicated for such surgery are not only specified by age. If the required tasks can be handled correctly, awake surgery can be performed in persons younger than 15 years and older than 65 years. Patients can undergo such surgery at any age if they are considered to be suitable candidates after other factors have been assessed. The cortex is difficult to excite by electrical stimulation in children aged 7 years or younger, so they do not fulfill the criteria for cortical electrical stimulation.[1] Patients older than 70 years, who may develop delirium or marked emergent increase in blood pressure, require especial attention.

Reference

1) Berger MS, Ojemann GA, Lettich E: Neurophysiological monitoring during astrocytoma surgery. *Neurosurg Clin N Am* 1: 65–80, 1990

These guidelines are approved by The Japan Neurosurgical Society. The part on anesthetic management is approved by the Japan Society of Anesthesiology and the part on language assessment during awake craniotomy is approved by the Neuropsychology Association of Japan.

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2. Diseases

[Recommendation]

In principle, the indication is for intramedullary diseases that can be treated surgically.

[Commentary]

Epilepsy without macroscopic demarcation between the normal brain tissue and the lesion, gliomatosis with indistinct borders, and cavernous hemangiomas that can only be reached through normal brain regions are typical indications.[1] Metastatic brain tumors are sometimes an indication. Extramedullary tumors such as meningioma are a less common indication, depending on the case.[2] For example, extramedullary tumor corresponding to brain disease with extended motor nerve involvement may be an indication.

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3. Sites

[Recommendation]

Areas indicated for awake surgery are locations where surgical procedures may lead to worsening of neurological symptoms, but can be assessed by the performance of intraoperative tasks.

[Commentary]

Lesions in and around the anatomical language areas, lesions in the lateral parietal lobe of the dominant hemisphere (mainly including the angular gyrus), lesions adjacent to the arcuate fibers (superior longitudinal fasciculus), lesions adjacent to the motor cortex, etc.

Awake surgery is indicated for lesions affecting the triangular and opercular regions of the posterior part of the inferior frontal gyrus (Brodmann's areas 44 and 45) or the inferior part of the precentral gyrus with respect to the language motor center, as well as lesions in the posterior half of the superior, middle, and inferior temporal gyri of the temporal lobe (areas 41, 42, 22, and 37) or the supramarginal and angular gyri of the parietal lobe (areas 40 and 39) with respect to the sensory language center. Awake surgery is also indicated for lesions adjacent to the arcuate fibers (superior longitudinal fasciculus) that appear to connect the motor and sensory language areas. The hippocampus is located deep inside the temporal lobe, and is associated with verbal memory, and includes the insular gyri.[1] If a lesion is located near any of the above sites in the dominant hemisphere or if the lesion cannot be confirmed to affect the nondominant hemisphere, identify the functional areas by stimulation.

Reference

1) Muragaki Y, Maruyama T, Iseki H, Takakura K, Hori T: [Functional brain mapping and electrophysiological monitoring during awake craniotomy for intraaxial brain lesions]. *No Shinkei Geka Journal* 17: 38–47, 2008 (Japanese)

4. Other indications such as neurological symptoms

[Recommendation and commentary]

The patient has to participate in awake surgery, so the patient, assessors, surgeons, and anesthesiologists must all fully understand the meaning of aggressive resection and possible complications, and be able to recognize whether or not the patient can tolerate awake anesthesia.

If patients have already developed moderate or severe symptoms, mapping and monitoring are difficult to perform. For example, patients with impairment of language functions, such as understanding, reading, repetition, and object naming, are not suitable for awake surgery. Among patients who cannot speak fluently but have no disorders of understanding, those with minor naming disorders and decreased word enumeration are candidates, although severe disorders may develop during surgery.[1]

Patients with serious intracranial hypertension and those with serious systemic complications are not suitable.

Reference

1) Berger MS, Ojemann GA, Lettich E: Neurophysiological monitoring during astrocytoma surgery. *Neurosurg Clin N Am* 1: 65–80, 1990

5. Determination of the dominant hemisphere

[Recommendation]

Performance of a provocation test (Wada test) by cerebral angiography is desirable. If determination of the dominant hemisphere is done by noninvasive tests such as functional magnetic resonance imaging (fMRI), the therapeutic strategy should be defined after considering the possibility of pseudolocalization.

[Commentary]

Various advanced procedures such as fMRI, mag-

netoencephalography (MEG), and near infrared spectroscopy (NIRS) have been developed as functional tests. These procedures are noninvasive and have made substantial contributions to neuroscience and neurology. However, for decision-making about surgical resection, the "gold standard," which is the most reliable procedure available (the procedure used to define the "correct answer" as the standard for comparison with new procedures), should be used. The gold standards for identification of the dominant hemisphere, functional areas, and neuronal functions are the provocation test (Wada test), that involves infusion of anesthetic during cerebral angiography, identification of functional sites by electrical stimulation, and neurological testing, respectively. Although the anesthetic for the Wada test was amobarbital in the original proposal, propofol is primarily used these days because amobarbital is not currently marketed in Japan.[3] These "gold standard" procedures should be used despite being more invasive because, if less invasive but less reliable procedures are used and an incorrect result is obtained, the invasiveness of surgery may become greater than necessary. Determination of the dominant hemisphere in patients with tumors causing compression based on fMRI may have left-right errors (pseudolocalization) in 14%.[4] The surgical strategy largely depends on whether or not a lesion affects the dominant hemisphere and incorrect information naturally increases the risk, so performing the Wada test (the gold standard preoperative procedure) is considered to be necessary. Although textbooks state that 99% of right-handed persons are left hemisphere dominant, a meta-analysis of 734 patients undergoing the Wada test (including 121 of our patients)[2] revealed that the dominant hemisphere for right-handed persons was the left hemisphere in 88%, the right in 5%, and both in 7%.[1] The dominant hemisphere determined by electrical stimulation is the left hemisphere in 91% and the right in 9%. Thus, around 90% of right-handed persons are left hemisphere dominant and around 10% are right hemisphere dominant, which is not a low prevalence, suggesting that careful attention should be paid during surgery to lesions in functional areas of the dominant hemisphere. The results of the Wada test in left-handed people have shown that the left dominant:right dominant ratio ranges from 1:1 to 3:1, with a slightly higher rate of left dominance.

In recent years, the increasing accuracy of noninvasive procedures such as fMRI, MEG, and NIRS has provided us with more and more knowledge. In addition, when a gradual transition from invasive to noninvasive procedures occurs because of the risk of complications of cerebral angiography, including the Wada test, the risk of pseudolocalization should be accepted. Feedback with respect to comparison of the results of the Wada test and those of mapping by electrical stimulation is needed.

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Methods

1. Preoperative treatment

1-1. Status and details of simulation

[Recommendation]

The tasks that will be performed during surgery should be preoperatively rehearsed in the ward. Simulation of the surgical posture, equipment set-up, and role sharing, as well as rehearsal of the tasks for the patient, surgeons, anesthesiologists, and other surgical staff (such as nurses) should also be performed in the operating room.

[Commentary]

For successful intraoperative mapping with awake anesthesia, it is important to reduce the patient's anxiety as much as possible by maintaining a comfortable environment during surgery. Bring the patient to the operating room on the day before surgery, and take enough time to explain what will be done on the next day (including the posture that the patient will be placed in by the surgeon, anesthesiologists, and nurses). Then have the patient actually adopt that posture. If possible, show the patient a video of surgery on previous patients for better understanding. If functional language mapping is performed, conduct higher function exami-

nation before surgery, perform the tasks that will done during surgery in the ward in advance, and select intraoperative tasks, for example, by showing the patient pictures or photographs of common objects used in object naming and selecting some that the patient can answer correctly. If there has been a long interval between examination and surgery in a patient with progressive symptoms due to a tumor adjacent to the language areas, the tasks should be selected immediately before surgery.

1-2. Monitoring of anticonvulsants

[Recommendation]

In patients who are scheduled to undergo awake surgery, it is desirable to initiate the administration of anticonvulsants in advance and maintain effective blood concentrations if enough time is available. Phenytoin can be administered and the concentration increased to the upper limit of the effective range (target level 20 mg/dl) by the day before surgery.

[Commentary]

Even if an effective blood concentration of an anticonvulsant has been maintained since before surgery, there is some risk of convulsions during awake surgery (as described below). Therefore, sufficient preoperative antiepileptic drug saturation is desirable to prevent intraoperative convulsions and for easy drug loading after the onset of convulsions. Regarding the selection of drugs, phenytoin is recommended, since intravenous administration can be performed immediately before or during surgery when oral administration is not possible, rapid saturation is easy, a steady-state blood concentration can be obtained after a relatively short time (4–5 days), and regulation of the blood concentration is easy.

The bioavailability of phenytoin is high (98%) and there is little difference between systemic absorption after intravenous and oral administration. If there are 3 or more days before surgery, it is desirable to achieve the target blood concentration by oral administration to reduce patient discomfort. If rapid saturation immediately before surgery is selected, the target blood concentration can be obtained promptly by intravenous administration of phenytoin.

Especially for patients with tumors located near the motor cortex, after obtaining an adequate preoperative blood concentration of phenytoin, the blood level should be monitored every 2 hours during surgery. If the concentration is low, intravenous administration of 250 mg of phenytoin should be given to raise the concentration to the normal upper limit (this dose increases the blood level by approximately 6 mg/dl in a patient weighing 60 kg), or 100–200 mg of phenytoin should be given every 4 hours during surgery (this dose will increase the blood level by approximately 2.4–4.7 mg/dl in a patient weighing 60 kg).

Sixteen (16%) of the 100 patients who underwent awake surgery at Tokyo Women's Medical University from 2004 to the present developed seizures under awake conditions, whereas 48 (48%) of these 100 patients had a history of seizures before surgery. Twelve (24.5%) of the 49 patients with tumors near the motor cortex developed seizures during awake surgery and this rate was higher than at other sites. Occurrence of seizures during awake surgery is defined as clinically obvious convulsions and does not include patients who only have afterdischarges.

Among the 80% or more of our 100 patients who had received preoperative antiepileptic drug therapy, patients with lesions near the motor cortex and a preoperative blood level within or above the effective range accounted for 70% of patients both with and without intraoperative convulsions, although the blood level was not measured in all patients. Thus, even if the blood level of an antiepileptic drug is within the effective concentration range, there is no improvement of the preventative effect against intraoperative seizures, which is more likely to depend on the conditions of electrical stimulation.

Preoperative phenytoin loading is not performed at Tokyo Women's Medical University, so its efficacy has not been demonstrated there. Therefore, the frequency of intraoperative convulsions in patients with brain lesions at each site should be compared with that determined at institutions where rapid preoperative phenytoin saturation is performed to assess the usefulness of this procedure. It may also be necessary to assess the conditions employed for electrical stimulation, especially for the motor cortex, as well as the use of rapid anticonvulsant saturation.

[Saturation][1,2]

Initial loading dose [mg]: target blood concentration [mg/dl] × volume of distribution Vd [l/kg] × body weight [kg] = 20 × 0.7 × body weight [kg]..(a)

Additional loading dose [mg]: {target blood concentration − measured value [mg/dl]} × volume of distribution Vd [l/kg] × body weight [kg] = (20 − measured value) × 0.7 × body weight [kg].....(b)

Where target blood concentration is 20 mg/dl, and Vd is specific value for each drug: phenytoin 0.6–0.8 (approximately 0.7) l/kg.

For example, in a patient weighing 60 kg, the initial loading dose calculated using (a) is 840 mg, which is administered as three divided doses every 2

to 4 hours. This will avoid cardiovascular adverse reactions such as hypotension, bradycardia, and arrhythmia, as well as gastrointestinal symptoms. After 12 to 24 hours of administration at the above dose, initiate therapy at the usual maintenance dose (200–400 mg/day). Measure the blood concentration 2 to 3 days after finishing the initial loading dose for oral administration, and at 24 hours after or immediately before surgery when rapid saturation has been achieved by intravenous administration, and calculate the additional loading dose using (b).

The saturation period for phenytoin should be within the range of 3 to 5 days to avoid the development of adverse reactions when the blood level is maintained at the upper limit of the effective concentration range for too long (1 week or more) before surgery. There have been many reports about phenytoin-induced skin disorders such as disseminated erythematous papules after approximately 2 weeks and serious drug-induced hypersensitivity syndrome after 2 to 6 weeks in most cases.[3]

Because the protein-binding rate of phenytoin is high (90–95%), even if the blood level of the drug is within the effective range in patients who have a low serum albumin concentration, the concentration of free drug (not bound to albumin) will be increased and measured values may not reflect the actual levels. If the serum albumin is 3 g/dl or lower, free phenytoin should be simultaneously measured or the effective phenytoin concentration estimated using the following formula for correction: Measured phenytoin level/{(0.2 × albumin level) + 0.1} .....(c)

Where target range for free phenytoin is 2 to 2.5 mg/dl.

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2. Various intraoperative methods

2-1. Sites and methods of local scalp anesthesia

[Recommendation]

For local anesthesia of the scalp, it is common to use long-acting local anesthetics in combination with invasive anesthesia and nerve blocks.

[Commentary]

Analgesia by local anesthesia is often performed by the combination of infiltration with local anesthetic and nerve blocks. At some institutions, anesthesia is performed only by local injection or only by nerve block. Long-acting local anesthetics such as ropivacaine and bupivacaine are often used and these are combined with lidocaine at some institutions.[3] Supraorbital nerve block is used if the skin incision is primarily located in the frontal region, whereas auriculotemporal nerve block is used for an incision in the temporal region. Greater or lesser occipital nerve blocks can be added to these blocks. If head fixation is used, an anesthetic is administered at the sites of the pins in addition to the skin incision sites. Sufficient anesthetic should be provided at the pin sites because many patients complain of pain at these sites during emergence.

Preoperative simulation of temporary pseudo-emergence can be performed after fixing the head in a specific posture before the initiation of surgery, to confirm whether tasks can be performed or whether there are any problems with the removal and reinsertion of a laryngeal mask.[1,2]

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2-2. Head fixation and posture setting

[Recommendation]

Successful awake functional brain mapping/monitoring depends on whether the patient's cooperation can be maintained for a long time. Therefore, head fixation and posture setting are important to keep the patient in a comfortable position for a long period.

Although there is no definitive method of head fixation and posture setting, continuous feedback is essential about whether functional brain mapping/monitoring is successful or not, and whether or not the patient can comfortably cooperate with surgery and functional brain mapping/monitoring, and the surgeon should continue to assess whether the selected method is correct or not.

The basic procedure is as follows:

i) Preoperative explanation: It is important to create an image of surgery for the patient and family. If

this is not done, the patient will not understand what to do and how to cooperate, and will be uneasy during the surgery. The preoperative explanation should include basic issues related to brain functional differentiation, association of the extent of tumor invasion with functional areas, neurosurgical procedures, and functional brain mapping/monitoring procedures, and be illustrated with pictures, slides, and videos. Also, bring the patient to the actual operating room before surgery, perform head fixation and posture setting, and allow enough time to perform surgical simulation that includes meeting with the surgeons and nurses.

ii) Head fixation: Whether complete restriction of movement of the head by pin fixation or to allow movement of the head by not performing fixation is better has not been decided. The purpose of surgery is to safely and reliably resect the tumor, and the method should be established at each institution that both maintains patient comfort and allows surgery to achieve its purpose.

iii) Posture setting: To perform functional mapping of motor and sensory areas including functional language mapping, craniotomy must extend to sites that include normal brain tissue as well as the tumor. A posture that allows the performance of wide frontal-temporal-parietal craniotomy is generally used. For posture setting, given that the body weight is supported by various parts of the body, individual differences with regard to a comfortable posture and how painful maintaining the same posture for a long time can be for patients must be fully understood. Setting a posture that is only tolerable for a short time and attempting to maintain it for a long time leads to pain at unexpected sites. How many times the posture can be changed during surgery and the patient's desired temperature (hot or cold) must also be confirmed.

[Commentary on approach without head fixation]
Posture setting

What surprised us most when we visited the institution of Berger et al., who are pioneers in the use of this method for maximum resection of gliomas, is that Dr. Berger himself took time to carefully set each patient's posture with pads that were tailor-made for size, shape, and thickness. Their stock of prepared pads and linen was much larger than ours. Awake surgery provides us with a good opportunity to realize how inadequate our previous posture setting is for general anesthesia. The following posture setting and head fixation procedures are basically according to the method of Berger et al.[1-3]

Preparation on the day before surgery: Bring the patient to the actual operating room on the day before surgery, and take enough time to explain what will be done on the next day, including posture setting. It is important for the patient to meet the surgeons, assistants, anesthesiologists, and nurses. At that time, detailed explanation of the patient's pathological condition, and explanation using videos about tumor resection in combination with awake functional brain mapping/monitoring should be provided to the patient (permission for the use of videos should be obtained because they contain personal information). It is as important for the patient to have an understanding of the surgery as it is for the surgeons to develop an image of the procedure.

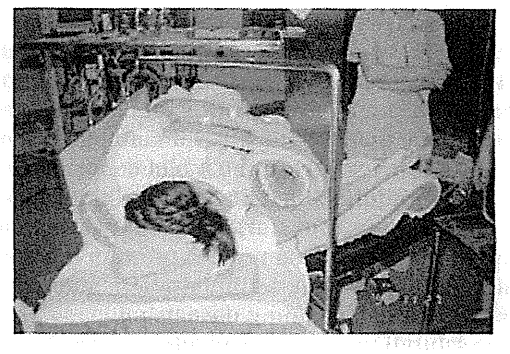

Fig. 1 Posture setting in the Department of Neurosurgery of Tohoku University.

To perform functional mapping of motor and sensory areas, including functional language mapping, craniotomy needs to expose normal brain tissue as well as the tumor. In general, to allow for wide frontal-temporal-parietal craniotomy, the head is tilted 75° to the opposite side. The next section covers whether head fixation should be performed or not. Place a large pad supporting the whole body from the shoulder to the waist to avoid torsion of the shoulders and head. To improve venous return, slightly raise the upper part of the body. Find the most comfortable positions for both the upper and lower extremities, and be careful not to overload any part of the body. It is desirable to fill little empty spaces with small pads. During posture setting, maintain an environment similar to that during the actual surgery as far as possible, continue conversation, and take time to check for the presence or absence of pain and to be careful not to have any body part unsupported (Fig. 1).

To perform mapping, you need to have a clear space in front of the patient's eyes and to have enough space to place a portable computer within the vision, which is used for object naming in functional language mapping. At our hospital, this space is created with L-shaped bars and infusion stands

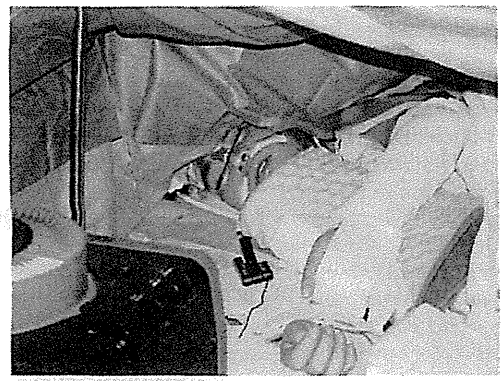

Fig. 2 Conditions used for the first case in the Department of Neurosurgery of Tohoku University (1996).

(Fig. 2), and transparent drapes may be used to allow vision.[6] Surgery takes a long time and osmotic diuretics such as mannitol may be used because of the inability to employ hyperventilation to control brain swelling, so continuous urine flow is required.

If intraoperative motor functional mapping is done under general anesthesia, unlike awake anesthesia, freer setting of the posture and head position (including use of the prone position) is available. However, functional brain mapping takes time to perform without administration of muscle relaxants, so whether the patient will feel comfortable in an unforced posture should be considered when setting the posture.

Posture setting on the day of surgery: Even if the posture has already been confirmed on the day before surgery, take enough time to set the patient's posture again and ensure that he/she is comfortable. To confirm whether the patient feels comfortable or not, hold a conversation and do not induce anesthesia until the completion of posture setting.

Head fixation

There is no consensus at this time about whether head fixation should be done or not. If we give first priority to the patient's comfort, no fixation would seem to be more desirable. However, lack of fixation will lead to constant movement of the surgical field. To continually respond to unexpected movements for a long time when manipulating deep brain regions or blood vessels is very stressful for surgeons. For surgery combined with awake functional brain mapping/monitoring, which is based on cooperation and achieving a balance between the surgeons and the patient, determine whether head fixation should be used or not after careful consideration at each institution. Even without head fixation, continuous navigation is available[5] by fixing the reference points to the skull.[4]

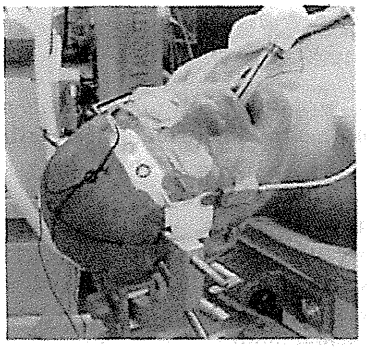

Fig. 3 Approach with head fixation.

[Commentary on approach with head fixation]

The advantages of head fixation include a fixed operating field and complete fixation of the conventional navigation system, retractor, electroencephalograph, or other instruments, so that the surgeon can operate as under general anesthesia. The disadvantages of this approach include more patient discomfort compared with the absence of head fixation, due to pain at the pin fixation sites, and difficulty of moving the body and changing the head position. Also, treatment of vomiting or convulsions and reintubation may be difficult, so sufficient simulation is necessary. A patient with a left frontal lobe glioma receives 4-point fixation after insertion of a laryngeal mask (Fig. 3). As with 3-point fixation, it is difficult to rotate and move the head after application of 4-point fixation, so simulation of emergency situations is very important.

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2-3. Awake state and surgery: Status of anesthesia and status of electrical stimulation during resection

[Recommendation]

Resection is often performed under anesthesia or sedation, and the methods vary among institutions. With subcortical mapping, electrical stimulation needs to be continued even during resection. There is no established method at this time and the value of the procedure is uncertain.

[Commentary]

Although the use of sedation is common during resection of the lesion, it is done on a case-by-case basis or never performed at some institutions because it is still controversial. Propofol is often used, but dexmedetomidine, sevoflurane, nitrous oxide, etc., can also be employed.

For subcortical mapping, electrical stimulation needs to be continued even during resection. However, there is no established method of subcortical stimulation and the methods employed vary among institutions at present. For subcortical mapping of the corticospinal tract, the method of recording the electromyogram by using Ojemann-type bipolar electrodes as in cortical mapping seems to be employed relatively often. With bipolar recording, however, the stimulation range is limited to the immediate vicinity of the electrodes and injury has often already occurred when a response is detected. If the presence of the corticospinal tract cannot be predicted at a certain distance, subcortical mapping may well be useless. A method of recording corticospinal motor-evoked potentials (D-wave) that descend through the corticospinal tract from spinal epidural electrodes for subcortical mapping is being discussed. The amplitude of D-waves evoked by monopolar stimulation may reflect the distance between the stimulation points and the corticospinal tract to some degree, so the method of recording the D-wave amplitude under given stimulus conditions seems to be promising.

Also, in subcortical mapping of language functions, conventional bipolar stimulation limits the range as for mapping the corticospinal tract, so whether language area-derived speech arrest can be certainly detected is unclear and the reliability of subcortical electrical stimulation during resection is difficult to determine.

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2-4. Conditions and timing of stimulation

2-4-1. Cortical stimulation: type of electrode, intensity of stimulation, and duration

[Recommendation]

In the setting of brain electrical stimulation for functional mapping, because of its effect and to maintain the safety of the brain tissues, the following methods of using probe electrodes and subdural electrodes are recommended:

Probe electrodes: Interpolar distance of 5 mm and diameter of 1 mm for bipolar electrodes or diameter of 1 mm for monopolar electrodes; square wave pulses (0.2 or 0.3 or 1 msec) with alternating polarity and frequency of 50 or 60 Hz, and stimulus duration of up to 4 seconds; and current from 1.5 (or 2) mA with maximum intensity of 16 mA.

Subdural electrodes: Interpolar distance of 5 mm to 1 cm and diameter of 3 mm for bipolar electrodes; square wave pulses (0.2 or 0.3 msec) with alternating polarity and frequency of 50 or 60 Hz, and stimulus duration of up to 10 seconds; and current from 1 mA with maximum intensity of 16 mA.

[Commentary]

Stimulation conditions vary among the types of electrode and purposes of functional mapping. The recommendations cover typical methods for cortical language mapping. When stimulating the primary motor area under awake conditions, use of low fre-

quency stimulation or one to five repetitive stimuli is desirable to prevent convulsions.

For identification of false-positive responses to peripherally spreading electrical stimulation, afterdischarges should be monitored.[1,2] Cortical excitability differs between children and adults and also varies between individuals, so false-negative results can occur.

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2-4-2. Subcortical stimulation: type of electrode, intensity of stimulation, and duration

[Recommendation]

The conditions for stimulation are the same as those for "cortical stimulation."

Alternative method for stimulation (subcortical): 0.2 msec, 50 Hz, stimulus duration of up to 4 seconds, from 1 mA to maximum intensity of 20 mA.

Implanted subdural electrode (deep electrode): Used for hippocampal lesions. The interpolar distance is 1 cm or 5 mm.

[Commentary]

Experience shows that responses are often identified by the same tasks and current intensity as with cortical stimulation. If maximum resection is performed while checking the response to subcortical stimulation, 80% of patients develop transient neurological symptoms, but 94% of them recover within 3 months.[1] Subcortical stimulation also allows identification of the following language-related fibers, by which various findings have been obtained[2,3]: superior longitudinal fasciculus, arcuate fasciculus, subcallosal fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, orofacial motor fibers, etc.

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2-5. Treatment of convulsions

Risk: Convulsion can develop during intraoperative mapping and tumor resection.

Measures: Reduce the stimulus intensity. Do not persist with mapping. For tumors near the motor cortex, raise the concentrations of phenobal and phenytoin to the upper normal limits and check the levels every 2 hours during surgery. If the levels are lower than the limits, appropriately administer 250 mg of intravenous phenytoin and 100 mg of intramuscular phenobal to increase the concentrations to the upper limits. If convulsions occur, put cold water or cold artificial cerebrospinal fluid (e.g., Artcereb®; Otsuka Pharmaceutical Factory, Inc., Tokyo) on the brain surface and wait until the convulsions cease. If convulsions occur frequently, switch to general anesthesia and then switch back to awake surgery if possible after adequately raising the concentrations of anticonvulsants. (For tumors near the motor cortex, surgery can continue while checking the motor-evoked potentials [second best method].)

2-6. Necessity and usefulness of confirming afterdischarges: methods and evaluation

[Recommendation]

Confirmation of stimulation-induced convulsions by evaluating the occurrence of afterdischarges on the electrocorticogram should be a basic procedure.[2] At the very least, until the number of cases experienced by the institution increases, it is essential that the stimulation conditions are standardized, and the method of functional evaluation is established. The risk of mistakenly identifying motor, sensory, and language disorders induced by development of brain dysfunction at distant sites because of stimulation-induced afterdischarges should be avoided. To confirm whether electrical stimulation is actually being delivered (i.e., the current is flowing), electroencephalography is useful. Position the electrocorticographic electrodes and record the electrocorticogram without stimulation (Fig. 4). Place small pieces of paper with numbers, etc. on the brain surface so that surgeons, staff performing electrophysiological mapping, and staff performing higher function examination can mutually confirm the stimulation sites. Stimulate the brain surface for 2 to 3 seconds by applying biphasic rectangular pulses of 50 Hz and 0.3 msec pulse width with

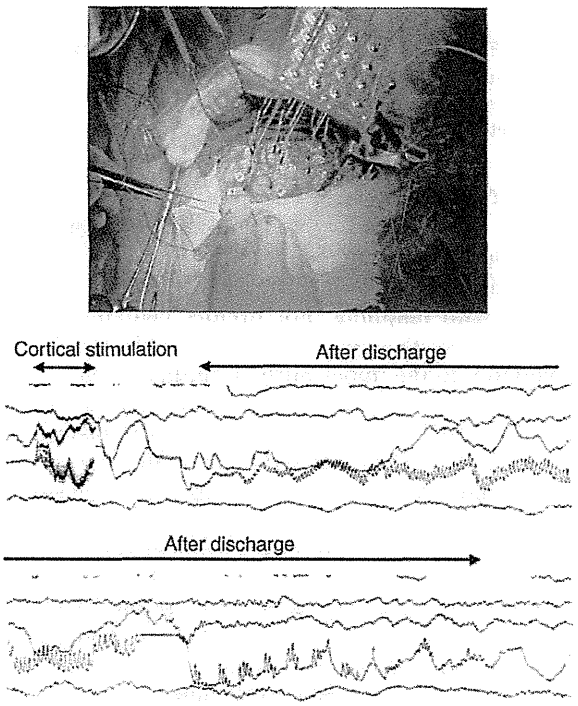

Fig. 4 Setting the electrocorticograph and electrocorticographic stimulation with bipolar electrodes.

bipolar electrodes using an inter-electrode distance of 5 mm. For stable stimulation, the brain surface should be kept moist by using a nebulizer. Increase the stimulus current from 4 mA in increments of 1 mA and determine the optimal current for achieving stable muscle contraction without afterdischarges in the cortical electroencephalogram. Under the above conditions (which we use), effective stimulation is often obtained at 8–11 mA. Under awake anesthesia, a lower stimulus current is optimal and 4–8 mA is often used. For the sensory areas, because instantaneous brain-surface stimulation with a low current leads to complaints of numbness and discomfort by the patient, it is desirable to initiate mapping of the sensory areas first. Stimulation is done at the sites predicted using the neuronavigation system or from anatomical landmarks such as sulci, gyri, and superficial veins, and from the somatosensory-evoked potentials obtained by median nerve stimulation or labial stimulation, and the aim is to achieve effective results from the first stimulus. The motor cortex does not cover all of the precentral gyrus, but lies between the anteroposterior regions on the side of the central sulcus. Therefore, stimulation should be applied along the central sulcus first. Bipolar electrodes are used to apply stimulation perpendicular to the central sulcus. If the craniotomy does not extend as far as the finger area during tumor resection in the frontal opercular region, you can place strip electrodes across the central sulcus underneath the dura for stimulation. Electromyography[3] is not performed for all muscles, so the extremities and face must be carefully observed at sites where stimulation is expected to induce movement.

After completion of mapping of the motor and sensory areas, initiate functional language mapping. First, ask the patient to count from 1 to 50 continuously. At this time, increase the stimulus current in increments of 1 mA, while confirming that there are no afterdischarges in the cortical electroencephalogram. A current of up to about 16 mA may be used. Record the sites associated with speech arrest and hesitation. When stimulating the lower portion of the precentral gyrus, a negative motor response[1] may inhibit speech. One of the methods for confirming this is to apply stimulation to the brain surface i) while instructing the patient to project the tongue and move it from side to side, ii) while continuing countermovement of the thumb and forefinger, and iii) while bending and extending the ankle joints. If arrest of movement of the tongue or countermovement of the fingers and movement of the ankle joints is observed, the inhibition is associated with a negative motor response and not with language dysfunction. By these procedures, the optimal stimulus current can be determined and the frontal language areas identified to some extent. Then, perform object naming while continuing stimulation.

No abnormalities of counting does not always correspond with no disorders of object naming. Show the patient slides for approximately 2–3 seconds each. Assess whether there is speech arrest, hesitation, or wrong answers after presenting the stimulus. If these occur, you always need to confirm whether they are induced by actual stimulation of language function areas, fatigue, inability to see the slides, or the development of seizures. Using the sentence pattern for naming "This is ###" allows us to determine whether abnormalities are associated with arrest of speech itself by stimulation of the tongue motor areas or negative motor areas, or are due to stimulation of language function areas. Because identification of language areas needs repeated confirmation of the results, patients have to expend a large amount of energy. Therefore, functional brain mapping/monitoring requires complete cooperation of the patient.

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2-7. Complications other than convulsions and countermeasures

2-7-1. Pain

Risk: Pain can develop in the skin, muscles, dura mater, and sites on the underside of the body.

Measures: Ask the patient about painful sites and treat with local anesthesia as far as possible. Fix the head with 3 or 4 pins (if you use a head frame) and place something soft under the body to allow for movement. For surgery on the temporal lobe, turn the waist up as far as possible to prevent pain caused by compression of the underside of the waist, which often occurs in the lateral position.

2-7-2. Air embolism

Risk: Tumors of the inner motor cortex are associated with a risk of air embolism because the surgical field is placed in the highest position.

Measures: Bend the head forward without affecting respiration, raise the lower extremities, and bend the abdomen slightly forward to increase the jugular venous pressure. Cover the skull with fibrin, thrombin, and Calcicol immediately after opening the skull. Keep the head down until the dura mater is opened and then gradually raise the head while observing SaO_2. If there are symptoms such as cough and a decrease of SaO_2, immediately put the head down and hold the neck.

2-7-3. Delirium and emotional incontinence

Risk: There are some reports of delirium developing when anesthesia is stopped to obtain the awake state. Intraoperative anxiety and pain may also cause emotional incontinence.

Measures: Avoid decreasing the level of consciousness by use of local anesthetic as far as possible. Play the patient's favorite music or take measures to avoid anything that makes the patient uncomfortable so that the patient can undergo surgery easily. Depending on the patient's condition and the progress of surgery, decide whether it should be continued under awake conditions, should be continued without awake conditions, or should be discontinued. If continuation of awake conditions is needed, deal with the patient's complaints (primarily pain) as far as possible, but sometimes encourage the patient to tolerate the discomfort.

2-7-4. Increased intracranial pressure

Risk: Increased intracranial pressure may develop in patients with brain tumors, but seldom in those with epilepsy. During awake surgery, arterial carbon dioxide tension ($PaCO_2$) tends to be higher than under general anesthesia, leading to a higher risk of increased intracranial pressure.

Measures: If there is evidence of increased intracranial pressure on imaging studies, general anesthesia should be employed. If awake surgery is considered to be absolutely necessary, the decision can be made after dural incision following standard intubation. If there is no brain swelling induced by increased intracranial pressure, switch to awake surgery after extubation. If brain swelling occurs during awake surgery, consider switching to general anesthesia.

2-7-5. Others

There are reports about the development of air embolism and pneumonia, although whether these are characteristic problems of awake surgery is controversial. Air embolism can be caused by raising the head excessively (for example, locating the operating field at the highest position in the motor cortex 1). As with general anesthesia, bend the head forward without affecting the respiration, raise the lower extremities, and bend the abdomen slightly forward to increase the jugular venous pressure. Cover the skull with bone wax, fibrin, and thrombin immediately after opening the bone. Keep the head down until the dura mater is opened and then gradually raise the head while observing arterial oxygen percent saturation (SaO_2). If there are symptoms such as cough and decrease of SaO_2, immediately put the head down and hold the neck. Also, for prevention of pneumonia, it seems to be important to prevent lowering of consciousness and vomiting (refer to the section on anesthetic management for details about dealing with nausea and vomiting).

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2-8. Decision-making based on the results of stimulation

2-8-1. Epilepsy

[Recommendation]

In the case of epilepsy, consider whether the results of functional brain mapping by electrical stimulation are reliable. Epileptic foci often include functional brain sites and the extent of resection influences postoperative seizure control. It is desirable to fully assess the extent and overlap of epileptogenic foci and functional sites, and then carefully discuss the indications for resection of functional areas in individual cases depending on the pathological condition.

[Commentary]

Epilepsy is a functional disease, and the presence or absence of functional disorders associated with surgery influences the indications for surgery. For decision-making about additional surgical treatment and the extent of resection in individual cases, it is important to fully understand the pathology of epilepsy. Assessment of the results obtained by functional brain mapping with electrical stimulation requires attention to the following points. In patients with epilepsy, cortical excitability at functional sites is variable and both false-positive and false-negative results of electrical stimulation can occur.[1] Displacement of brain function sites from their anatomical positions can also occur. Therefore, functional brain mapping by electrical stimulation should be performed carefully, and it is desirable to undertake subdural electrode placement with reference to the results of various noninvasive physiological tests, such as fMRI, positron emission tomography, and MEG, for detailed mapping. The use of brain surface electrodes allows for complementary cortical function testing to assess the development of symptoms and to measure evoked potentials during voluntary activity after electrical stimulation. Epileptogenic foci often overlap with functional sites in the brain. In such a situation, resection of the focus is superior to multiple subpial transection and more complete resection results in better postoperative control of epileptic seizures.[2] It is reported that 0% to 63% of patients develop persistent functional disorders after resection of functional brain areas involved by epileptic foci. However, due to the small number of cases, it is unclear whether we should resect all the functional sites, whether we should consider the resection of sites with a possible compensatory function, and how to decide on the discontinuation of resection.

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2-8-2. Brain tumors

[Recommendation]

Functional tissues revealed by mapping should be preserved unless consent giving priority to resection is obtained or the surgeon determines that resection is feasible. Accumulate experience with mapping and pay careful attention to false-positive results (nonfunctional brain tissues despite positive findings on stimulation).

[Commentary]

Intraoperative functional testing during awake surgery involves mapping by electrical stimulation and monitoring to observe neurological findings. Mapping is performed to identify functional brain tissues and to prevent neurological complications induced by resection and damage to functional tissues during brain tumor removal. Therefore, the sites where symptoms occur during mapping should be preserved in principle because they are likely to be functional tissues. If they are not preserved, we see no point in performing awake surgery. However, if tumors coexist with functional tissues[2] and preoperative consent has been obtained, functional tissues may not be preserved if the decision is confirmed to give priority to tumor resection after accepting the risk of complications and the fact that postoperative symptoms are likely to develop even with a response (e.g., negative motor areas in the supplementary motor cortex). Because responses are sometimes false-positive, you should acquire proficiency in mapping. False-positive findings are primarily obtained because awake conditions are poor and do not allow patients to perform their tasks, and sometimes because the basic conditions for the tasks are poor (e.g., the patient cannot see the screen because a drape covers his/her eyes). At our hospital, some patients could not perform the naming task due to inability to see the screen because of conjugate deviation induced by stimulation of oculomotor fibers, but they were regarded as having language arrest (the truth was recognized by reviewing videos). Recently, Berger et al.[1] have insisted on the validity of a "negative mapping strategy," suggest-

ing that language areas do not have to be identified as a positive control (and major craniotomy does not have to be performed for identification), and that resection can be performed if language areas do not exist within the resection zone under certain conditions (60 Hz, maximum 6 mA). Given that this is a report from the most experienced institution, resection after identifying the language areas seems to be safer at less experienced institutions. It is significant that their report indicates that awake language mapping allows us to perform even aggressive resection with a very low incidence of complications and that a report on language mapping was published in a top clinical journal, suggesting that evaluation of its usefulness as a surgical procedure for glioma has been established.

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II. Anesthetic Management for Awake Craniotomy

1. Introduction

In the 1800s, resection of foci in epileptic patients was performed by craniotomy under local anesthesia.[6] With no electroencephalogram, direct stimulation of the cortex was employed to detect the epileptic focus and identify functionally important sites, which seems to be the prototype of current awake craniotomy. In the 1900s, with addition of sedation, surgery became more comfortable for patients.[8] Using codeine, thiopental, and meperidine, management was conducted under spontaneous respiration or partially by tracheal intubation. Epileptic surgery then came to emphasize intraoperative electroencephalography.[9] In the 1960s, neuroleptanalgesia was introduced into anesthesia, and the combination of droperidol and fentanyl was considered especially useful for surgery in patients with temporal lobe epilepsy because it had less influence on the intraoperative electroencephalogram.[5] In addition, the development of a long-acting local anesthetic, bupivacaine, facilitated awake craniotomy. As a result, many procedures for intractable epilepsy employed neuroleptanalgesia.[1,7] Thereafter, short-acting analgesics such as sufentanil and alfentanil were introduced.[4] Propofol was introduced for awake craniotomy because it is short-acting and has anticonvulsant and antiemetic effects.[10] It is now widely used as the main sedative. Recently, new anesthetics such as dexmedetomidine[2] and remifentanil[3] have been introduced, while use of a laryngeal mask has been initiated for airway management.[11] Because procedures that are not necessary during ordinary general anesthesia, such as airway management and treatment of intraoperative convulsions, are required, we would like you to refer to these guidelines for reliable and safe anesthetic management. There is limited evidence about anesthetic management during awake craniotomy, so the methods in actual use and those recommended by the review committee are presented. Also, because there is "awake surgery" in the cardiac surgery field and the "wake-up test" in orthopedic surgery, we are using the term "awake craniotomy" here to distinguish awake brain surgery from those procedures.

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