tional propofol was injected immediately, up to a maximum dose of 15 mg in one side. All patients in both groups received equal total propofol injection volumes bilaterally except for one patient in the control group who suffered strong adverse effect after the first propofol dose, and so did not receive a second injection. Total propofol injection volume (mean ± standard deviation) was 22.7 ± 3.8 mg in the methylprednisolone group and 20.8 ± 3.7 mg in the control group.

Clinical characteristics of the two groups were compared using the χ^2 test at a significance level of $p < 0.05$. The results showed no significant difference in underlying disease, sex, history of epilepsy, lesion laterality, speech dominance, or mean age, indicating the control group was appropriate (Table 1).

The adverse effects following propofol injection were grouped into three categories as previously mentioned.[8] Grade 1 adverse effects included eye pain, shivering, face contortion and lacrimation, laughing, or apathy. Grade 2 adverse effects consisted of confusion, involuntary movement, or head and eye version. Grade 3 adverse effects included increased muscle tone with twitching and rhythmic movements or tonic posture. To evaluate the potential risks of propofol injection, the odds ratios and 95% confidence intervals (CIs) associated with various demographic variables were calculated, such as sex, age, history of convulsions, lesion type, lesion laterality, laterality of language function, relationship between the laterality of the lesion and the language center, and injection volume (total, first injection, and second injection), using SAS version 8.2 software (SAS Institute, Cary, N.C., U.S.A.). P values less than 0.05 were considered to be statistically significant in each analysis, whereas p values equal to 0.05 were considered to indicate marginal risks.

Table 1 Clinical characteristics

	Control group	Methyl-prednisolone group	p Value
No. of patients	58	75	
Underlying disease, brain tumor:epilepsy:AVM (no.)	32:13:13	43:18:14	0.8656
Sex, men:women (no.)	36:22	44:31	0.6911
History of epilepsy (no.)	31	51	0.0870
Laterality of the lesion, lt:rt:bil	32:23:3	45:29:1	0.4184
Speech dominant side, lt:rt:bil	50:4:4	68:6:1	0.2443
Age (yrs)			
mean ± SD	38.0 ± 13.4	36.9 ± 15.1	0.3060
range	11–71	10–74	
Total propofol injection volume (mg)			
mean ± SD	20.8 ± 3.7*	22.7 ± 3.8	
range	16–32*	16–30	

*Excludes one patient who stopped the examination and received only 5 mg of propofol. AVM: arteriovenous malformation, SD: standard deviation.

Results

In the methylprednisolone group, 9 of 75 patients experienced adverse effects, all of which were observed immediately after propofol injection. In all of these patients, symptoms disappeared within 5 minutes of injection, and were mild enough to allow continuation of the Wada test as usual. In the control group, 19 of 58 patients had adverse effects. The incidence in the methylprednisolone group was significantly lower, with an odds ratio of 0.280 (95% CI: 0.115–0.679, $p = 0.0036$), yielding a 72% risk reduction (Table 2).

Analysis of the incidence of individual signs and symptoms found that the methylprednisolone group included 1 epilepsy patient with tonic posture (control group 3 patients) and no patients with increased tone with twitching (control group 4 patients) (Fig. 1). These results indicated a significant reduction in Grade 3 adverse effects in the methylprednisolone group, with an odds ratio of 0.084 (95% CI: 0.010–0.712, $p = 0.0052$) and a 92% risk reduction (Table 2). The methylprednisolone group included no patients with involuntary movements and 1 with head and eye version, demonstrating a marked reduction in Grade 2 adverse effects compared with the control group, in which 2 patients showed involuntary movements and 5 exhibited head and eye

Table 2 Adverse effects of intracarotid propofol injection

	Control group (n = 58)	Methylprednisolone group (n = 75)	Odds ratio (95% CIs)	p Value
Adverse effects	19	9	0.280 (0.115–0.679)	0.0036
Grade 3	7	1	0.084 (0.010–0.712)	0.0052
Grade 2	6	4	0.394 (0.105–1.483)	0.1570
Grade 1	6	4	0.394 (0.105–1.483)	0.1570

CIs: confidence intervals.

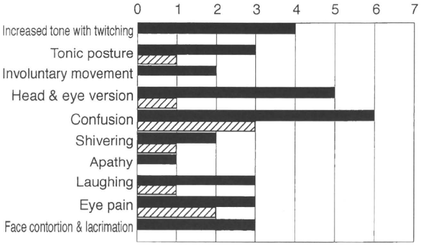

Fig. 1 Comparison of the number of patients with individual adverse effects between the groups with (*shaded columns*) and without (*closed columns*) methylprednisolone injection prior to propofol administration.

version (Fig. 1). The number of patients experiencing confusion in the methylprednisolone group was half that in the control group (3 patients versus 6). Statistical analysis found no significant difference in the effect of methylprednisolone on the incidence of Grade 1 or Grade 2 adverse effects (odds ratio: 0.394, 95% CI: 0.105–1.483, p = 0.1570) (Table 2).

Discussion

Our previous study showed that intracarotid propofol injection is associated with a moderately high risk of side effects. The present study found that intravenous administration of methylprednisolone followed by intracarotid propofol injection significantly reduced the incidence of severe (Grade 3) adverse effects.

Grade 3 adverse effects, which are comparatively rare after amobarbital administration, may result in incompletion or inaccuracy of the Wada test.[8] These adverse effects may be caused by propofol-induced cerebral hyperexcitation.[4] A recent systemic review of studies including intravenous injection of propofol demonstrated that hyperexcitation phenomena were correlated with sudden increases in the cerebral concentrations of propofol, not seizure history.[12] In our previous study, no electroencephalographic seizures or increasing epileptiform discharges were recorded before, during, and after the onset of clinical symptoms.[8] Propofol induces contractions at low concentrations and relaxation at high concentrations in the perfused cerebral artery of the dog,[9] but no in vivo action on cerebral perfusion after intraarterial injection has been described. Transient decrease in arterial blood flow immediately after inadvertent injection of 10 ml propofol into the brachial artery has been reported, suggesting particulate embolization or chemical incompatibility with the blood could be the cause of the decrease in vascular supply following propofol arterial injection.[1] The significant decrease in Grade 3 adverse effects seen in methylprednisolone-treated patients could have involved methylprednisolone effects such as improvement of vascular supply and anti-allergic action, which reduced ischemia-induced brain hyperexcitation.[3] Further electrophysiological or imaging studies during intracarotid propofol injection are needed to elucidate the mechanism of reduction of these severe adverse events with methylprednisolone.

Methohexital[2] and etomidate[6] have been reported as equivalent to amobarbital in terms of the efficacy in the Wada test. However, methohexital was so short-acting that two successive injections were needed for each hemisphere, and no detailed description of adverse effects was provided. Intracarotid injection of etomidate produced shivering-like tremors in approximately half of the patients, and either evidence of contralateral electroencephalography slowing following most injections, or an increase in interictal spike activity in the hemisphere ipsilateral to injection.[6] Moreover, etomidate infusion may be a major risk factor for the development of relative adrenocortical insufficiency in critically ill patients.[7] Future reports of adverse effects in a large number of patients undergoing neurosurgery will provide useful information.

The only adverse effects observed in two or more patients in the methylprednisolone group were confusion (3 patients) and eye pain (2 patients), but the incidences were approximately half those in the control group. Confusion is a condition arising from suppression of frontal lobe function and is independent of the type of anesthesia used. Confusion was observed with at least one other adverse effect in 5 of 7 control patients that experienced Grade 3 adverse effects; no patients in this group experienced only confusion. On the other hand, confusion was observed as the only adverse effect in 3 methylprednisolone-treated patients. These results suggest that infusion of methylprednisolone suppressed the occurrence of serious adverse effects. Further studies are needed to clarify the mechanism reducing these moderate adverse events with methylprednisolone. Methylprednisolone did not reduce the incidence of eye pain, a Grade 1 adverse effect, presumably because it does not influence the direct effect of propofol on the ocular arteries.

In our previous study, the risk factors for Grade 3 adverse effects (increased tone with twitching, tonic posture) included age of 55 years or greater, AVM,

Table 3 High-grade adverse effects of intracarotid propofol injection among 113 patients

Age (yrs)	<55	≥55	Odds ratio (95% CIs)	p Value
Total (n=113)	5/97	3/16	4.25 (0.91–19.90)	0.05
Methylprednisolone group (n=67)*	1/57	0/10	—(—)	0.67
Diagnosis	Tumor	AVM	Odds ratio (95% CIs)	p Value
Total (n=88)	2/62	4/26	5.45 (0.93–31.90)	0.04
Methylprednisolone group (n=51)*	0/37	0/14	—(—)	—
Total propofol injection volume (mg)	≤20	>20	Odds ratio (95% CIs)	p Value
Total (n=113)	3/82	5/31	5.06 (1.13–22.66)	0.02
Methylprednisolone group (n=67)*	0/45	1/22	—(—)	0.15

*Excludes 4 patients with Grade 1 and 4 patients with Grade 2 adverse effects. AVM: arteriovenous malformation, CIs: confidence intervals.

and total propofol injection dose greater than 20 mg. In our current study, 113 subjects were selected by eliminating 10 patients with Grade 1 adverse effects and 10 with Grade 2 adverse effects. Analysis conducted on these 113 patients confirmed that risk factors for Grade 3 adverse effects were age of 55 years or greater, AVM, and total propofol injection dose greater than 20 mg (Table 3). Other factors (sex, history of epilepsy, lesion laterality, and speech dominance) did not reach statistical significance. To further clarify the effects of the methylprednisolone, subgroup analysis was performed on 67 patients selected by excluding 4 patients with Grade 1 adverse effects and 4 with Grade 2 adverse effects from the methylprednisolone group. The results showed that none of the 3 factors mentioned above significantly affected the risk of Grade 3 adverse effects (Table 3).

This study suggests that Wada testing using intravenous methylprednisolone administration prior to propofol injection is a safe approach to the preoperative evaluation of brain tumors, epilepsy, and AVMs. Further studies in a large number of patients are needed to compare the adverse effects associated with intracarotid methohexital and etomidate injection during Wada testing.

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Commentary

Mikuni and his colleagues previously reported adverse effects associated with the intracarotid injection of propofol for Wada testing. These adverse effects were divided into three grades: Grade 1 includes eye pain, shivering, face contortion and lacrimation, laughing or apathy. Grade 2 includes confusion, involuntary movement, or head and eye version. Grade 3 includes increased muscle tone with twitching and rhythmic movements or tonic posture. Grade 3 adverse effects are the most clinically relevant since they may result in incompletion or inaccuracy of the Wada test.

The current study is a retrospective comparison of 75 patients who underwent a Wada test from 2006 to 2008 using intracarotid propofol with intravenous methylprednisolone and 58 patients who underwent the Wada test from 2001 to 2005 using intracarotid propofol without methylprednisolone. The comparison was performed to determine if the use of intravenous methylprednisolone decreased the incidence of adverse effects associated with the arterial injection of propofol. The analysis demonstrated that the methylprednisolone group had fewer adverse effects, including a significantly lower incidence of Grade 3 adverse effects.

Although the study is retrospective, the two groups were well matched with regard to demographics, underlying disease and propofol dosage. This study suggests the use of intravenous methylprednisolone may reduce the incidence of adverse effects associated with the use of intracarotid injections of propofol for Wada testing. What this retrospective, non-randomized study does not address is any change in the manufacturing of propofol over the time period of the study that may account for the reduced incidence of side effects.

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Surgical Treatment for Glioma: Extent of Resection Applying Functional Neurosurgery

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Abstract

Current treatments for gliomas, including surgery, chemotherapy, and radiation therapy, frequently result in unsuccessful outcomes. Studies on glioma resection were reviewed to assess better treatment outcomes applying the newest neurosurgical multimodalities. We reviewed reports of surgical removal of gliomas utilizing functional brain mapping, monitoring, and other functional neurosurgery techniques such as neuronavigation and awake surgery. Attempts to maximize the extent of glioma resection improved survival. A close proximity of the resection to the eloquent areas increased the risk of perioperative neurological deficits. However, those deficits often improved during the postoperative rehabilitation and recovery period when the essential or the compensative eloquent areas remained intact. Pre- and intraoperative application of the latest brain function analysis methods promoted safe elimination of gliomas. These methods are expected to help explore the long-term prognosis of glioma treatment and the mechanism for recovery from functional disabilities.

Key words: glioma, resection, brain function, neuronavigation, review

Introduction

Pre- and intraoperative functional brain mapping and monitoring methods have dramatically progressed in the last decade with the advances in medical equipment and computer technology. These methods provide information on brain functions that are helpful for determining surgical strategies, so functional neurosurgery techniques have evolved into the field of general neurosurgery. Parenchymal gliomas infiltrate into the surrounding eloquent areas, so evaluation of brain function is particularly important in determining whether a particular case is suitable for surgery, as well as the optimal surgical strategies when surgery is indicated. In addition, these methods provide useful intraoperative surgical guidance. This review presents the pathophysiology of glioma invasion and cerebral compensation to clarify the current significance and objectives of surgical resection. Multiple safe methods for optimal tumor resection are described, and the results of glioma resection surgery utilizing advanced approaches that integrate these modalities are assessed.

Evaluation of Brain Function for the Surgical Resection of Gliomas

Functional neurosurgery refers to the surgical treatment of functional abnormalities related to the cerebrospinal nervous system, including movement disorders, intractable epilepsy, and chronic pain, among others. Typical examples include stereotactic surgery for Parkinson's disease, epilepsy surgery, and neurovascular decompression for trigeminal neuralgia and hemifacial spasm. With computer-aided developments in diagnostic imaging techniques and nervous function evaluation methods, functional neurosurgery including functional brain mapping and monitoring are now important in the field of general neurosurgery.

Parenchymal glioma, a common intrinsic brain tumor, is characterized by diffuse local invasion of normal brain functional areas. Therefore, evaluation of brain function is very important in the determination of whether a particular case is suitable for surgery, as well as the optimal surgical strategy for cases when surgery is indicated. In addition, evaluation of brain function provides useful intraoperative guidance and increases surgical safety. In practical terms, information on cortical function is extracted by application of magnetic resonance (MR) imaging, functional MR imaging, and magnetoencephalography systems. Neuronal information is obtained by diffusion tensor imaging tractography. Such information is displayed perioperatively in the navigation system, and combined with the results of electrical brain stimulation and awake neurological assessment to make medical decisions.

Gliomas cause brain damage by infiltration into normal brain tissue and by the creation of a mass effect. The brain area aggressively invaded by high-grade glioma ceases to function properly. When no neurological deficits are detected in the vicinity of a tumor, the tumor is merely causing an anatomical shift to the adjacent areas by physical compression. However, the possibility of cerebral rearrangement by the compensation mechanism remains. However, no neurological deficit is sometimes observed with low-grade gliomas present in areas or neurons controlling major functions. This indicates that the infiltrated tissue continues to function normally, if the local cerebral functions have not been rearranged or compensated.

To investigate the morbidity resulting from the resection of gliomas invading into eloquent cerebral areas, treatment outcomes were compared between surgical cases with glioma resection and with neocortical epilepsy, in which the locations of the epileptogenic lesions were identified. Among 157 cases of glioma resection located in close proximity to eloquent cerebral areas, 57% underwent gross total resection. Transient postoperative deficits were observed in 33% of 81 cases showing no preoperative deficits. Permanent or long-term neurological deficits were reported in 8% and 2.5% of the cases with and without preoperative deficits, respectively. In 76 cases with preoperative neurological deficits, 33% showed complete resolution of these deficits, and 32% improved.[9] In a more recent study on 309 consecutive patients with intracerebral tumors near or within eloquent cortices, 21% had intraoperative neurological deficits. Whereas 39% of these patients experienced worsened neurological outcome at one month, 11% of the patients without intraoperative changes had such outcomes. At one month, 17% of the patients experienced new or worsening neurological deficits. At 3 months, only 7% had a persistent neurological deficit.[25] Another study on the resection of low-grade gliomas in the primary motor and sensory cortices reported that 60% to 100% of the patients who underwent resection experienced transient palsy, but no patients had permanent deficits.[3] On the other hand, in a study of patients with epilepsy undergoing resection surgery involving the primary sensorimotor cortex, post-surgical permanent deficits were reported in 50% of the study cohort.[43] All these studies employed the best available methods for mapping and monitoring to achieve safe, maximal tumor resection. Further analysis is needed to eliminate confounding factors related to surgical indications and patient selection, but these results seem to indicate that gliomas located in or near the eloquent brain areas were treated by the surgical operation relevant for the disease stage that promoted functional recovery. Therefore, functional brain mapping and monitoring should be required in selecting the surgical approaches and in removing tumors appearing as hyperintense on T_2-weighted functional MR imaging (fluid-attenuated inversion recovery).[11,12] Dissection along the circumferential margin of the contrasted tumor image, and elimination of severely damaged or necrotic tissue should carefully avoid impairment of the blood flow and mechanical damage by accidental or unintentional surgical maneuvers to the adjacent brain tissue. However, when the patient presents with preoperative neurological deficits due to tumor invasion, sufficient information may not be obtained from functional brain mapping and monitoring methods that involve voluntary movement and electrical stimulation in awake conditions. Under such circumstances, brain functions should be assessed by a comprehensive analysis of various physiological data.[31,32]

With the development of neuroimaging, functional mapping, and anesthesia studies, lesions in the eloquent area can now be removed with functional recovery.[6,10,13] Functional reorganization, cerebral plasticity, and compensation may contribute to recovery simultaneously or chronologically.[11,12,29,38,49,53] The arguments presented so far are confined to generic postulation of the brain function recovery mechanisms. The nature of these mechanisms, which may be revealed by exploration of the intercortical network between the association area and the damaged areas, remains to be studied.

Significance and Objectives of Surgical Glioma Resection

World Health Organization (WHO) grade II–IV gliomas cannot be completely cured only by surgery. A new modality has been established for the treatment of malignant gliomas that includes chemotherapy plus radiation following administration of temozolomide. In addition, multidisciplinary approaches are being developed that involve the clinical application of gene therapy, cell therapy, molecule-targeted therapy, and immunotherapy. Accumulated evidence suggests that more extensive surgery produces better outcomes for the treatment of WHO grade III and IV gliomas.[26,50] The 5-year survival rate was 68% for WHO grade II astrocytomas, an outcome similar to that for colorectal cancers. In contrast, the 5-year survival rate was below 60% for patients after up to 75% resection of supratentorial astrocytomas, and 73% and 88% for patients with 95% resection and total extirpation, respectively.[7] The progression-free and malignancy-free survival rates for postoperative residual low-grade gliomas were 44% and 74% over 5 years of follow-up, and 24% and 56% over 8 years, respectively.[4] Although reviews published to date failed to identify class I evidence, maximal resection has been stressed as the approach to the treatment of WHO grade II–IV gliomas.[46]

At the same time, intraoperative procedures should be carefully performed to secure safe resection with minimal damage to brain tissue and resulting function. The significance of patient quality of life during the immediate postoperative period and the extent implicated by 'brain functions' depend highly on the course of surgical recovery. Broadly defined, brain functions include higher level activities studied in Systems, Behavioral, and Cognitive Neuroscience. These activities represent important issues to be addressed, especially by neurosurgery as part of human science. At present, there are practical limitations both in the outcomes for the medical treatment of gliomas and in the clinical evaluation of higher-level brain functions. Therefore, voluntary movement, somatic sensation, visual perception, speech, and other parietal functions are the primary foci in relation to brain-tumor resection.

Integrated Functional Neuronavigation and Cortical/Subcortical Electrical Stimulation

The preservation of brain function while maximizing the resection of gliomas is a major goal in neurosurgery. Direct cortical stimulation has been used since 1930 in epilepsy surgery.[16,41,42] Recent studies have developed new methods of presurgical non-invasive functional imaging, including functional MR imaging, and magnetoencephalography, enabling the visualization of cortical areas involved in brain function. The fiber-tracking technique based on diffusion tensor imaging images the three-dimensional macroscopic architecture of fiber tracts.[5,21,33,52,54] Combining these technologies in glioma surgery allows effective and safe resection with anatomo-functional mapping using tractography-integrated functional neuronavigation combined with direct cortical/subcortical electrical stimulation.[22,30,34,38]

I. Electric stimulation

Brain electrical stimulation for functional mapping must maintain efficacy and safety, so the following methods of using probe electrodes and subdural electrodes are recommended.

Probe electrode[48]: Interpolar distance 5 mm, diameter 1 mm, bipolar or diameter 1 mm, monopolar square wave pulses (1 msec) with alternating polarity and frequency of 60 Hz, stimulus duration of up to 4 seconds from 1.5 (or 2) mA to the maximum intensity of 6 mA.

Subdural electrode[15]: Interpolar distance 5 mm to 1 cm, diameter 3 mm, bipolar square wave pulses (0.3 msec) with alternating polarity and frequency of 50 Hz, stimulus duration of up to 10 seconds from 1 mA to the maximum intensity of 15 mA.

Stimulation conditions can be varied among electrodes for the purposes of functional mapping. When stimulating the primary motor area under awake conditions, use of low-frequency stimulation or one to five repetitive stimuli is desirable to prevent convulsion. For the identification of false-positive responses to peripherally spreading electrical stimulation which may cause seizure, after-discharges should be monitored. Electrical stimulation may spread 2 to 13 mm.[2,20,23,30] Cortical excitability varies between children and adults, so false-negative results may occur.

II. Evaluation of motor function

The central sulcus is localized based on the polarity inversion of the N20 component of the somatosensory evoked potentials, and cortical motor function is evaluated by electrical stimulation of the precentral gyrus. Images of the subcortical pyramidal tract preoperatively created by the diffusion tensor imaging technique are shown on the navigation system perioperatively with tract activity evaluation by applying subcortical electrical stimulation. These methods can provide accurate intraoperative analysis of the functions of the primary motor area and the originating corticospinal tracts.[11,18,22,30,34]

Motor evoked potentials (MEPs) are generated when electrical stimulation is applied to the primary motor area and the originating corticospinal tracts that form synapses with the spinal anterior horn cells. MEP responses are recorded more commonly from peripheral muscle than from the lumbar spinal cord by placement of epidural electrodes recording descending the corticospinal evoked potentials (D-wave).[55] Patients with MEPs recorded by intraoperative subcortical stimulation are more prone to develop postoperative motor deficits than those without.[24] New, immediate post-surgical motor deficits were documented in 59.3% of patients in whom the subcortical motor tract was identified in close proximity to the surgical site (by positive MEPs) and in 10.9% of those in whom subcortical tracts were not observed (negative MEPs). Among these patients, permanent deficits were documented in 6.5% and 3.5%, respectively.[4] In addition to the primary motor area, stimulation of the somatosensory, supplementary motor, and premotor areas affects voluntary movement. These regions are involved with movement initiation and control. Attention should be paid to the fact that these sites, which have distinct projections to the spinal cord, present different response patterns to electrical stimulation and varying functional deficits after resection.[14,29]

III. Evaluation of language function

In contrast to the identification of areas involved with motor function, the brain areas relevant for language and other parietal-lobe functions are more difficult to locate, particularly so in the presence of brain tumors, which induce adaptive displacements or shifts of brain structures depending on sulci geometry.

In examining language function, the extent of brain areas to apply electrical stimulation and surgically eliminate demands careful attention. First, the region in the language-dominant side of the cortex leading to the inability to name an object when electrical stimulation is applied is wider than Broca's and Wernicke's areas, and extends to the superior, middle, and inferior frontal gyri as well as to the superior and middle temporal gyri.[19,37] Another language area is reported to exist in the basal temporal lobe, called the basal temporal language area.[27] Second, speech production, object naming, repetition, and reading tasks, which are generally included in the testing paradigms, engage different language areas.[8,37] Other language task components include voluntary speech, word recall, word chain formation, repetitive vocalization, auditory comprehension, sentence processing, number counting, and color naming. These functions all relate to different cortical locations.[44,45] Testing paradigms should produce reliable results under the time-limited awake surgery condition. Third, the electrically induced occurrence of anarthria that results from the positive motor response of the tongue and face or from the negative motor response of the tongue must be eliminated.

Care should be taken for the identification of language function regions that are responsive to electrical stimulation of non-physiological origin. Care should also be taken when deciding on the extent of resection. Clinical experience suggests that identification of the cortical regions that contain no stimulation-induced language function (negative language mapping) allow safe tumor resection.[48] In treating 250 consecutive patients with WHO grade II–IV gliomas, the authors strictly adhered to a minimal resection margin of 1 cm from the nearest language site identified by electrical stimulation in excising areas presenting no stimulation-induced language deficits (difficulty with number counting, naming, and speech production tasks). Essential language sites were localized within the operative field in 145 patients (58%). Transient postoperative language deficits emerged in 22%, however, only 1.6% developed a permanent postoperative language deficit.

Subcortical stimulation was used to identify functional language tracts successfully in 59% of patients undergoing glioma resection. Transient postoperative deficits occurred in 67.3% of patients during the resection of lesions located close to or within language areas or pathways, although definitive morbidity was reported in 2.3%.[1] However, several studies have yielded contradicting conclusions on the significance of language pathways. Among the language-association fibers, the articuate fasciculus is well known for its relation to phonological processing. One study reported that the inferior longitudinal fasciculus, located inferolateral to the cerebral ventricle, could be resected, because it produced no language deficits when electrically stimulated, although electrostimulation of the inferior frontooccipital fasciculus impaired word-finding ability.[28] On the other hand, another study demonstrated that the inferior frontooccipital fasciculus, when electrically stimulated, produced speech arrest and compromised word retrieval activity.[1]

Outcomes in Glioma Surgery Applying Functional Neurosurgery

Gliomas selected for treatment by functional neuronavigation and intraoperative electrical stimulation are mainly located in or near the eloquent areas. The results of such operations, therefore, cannot be satisfactorily compared with overall glioma surgery outcomes due to selection bias. A retrospective study reported that subcortical electrical mapping significantly improved the survival rate after resection of low grade gliomas.[11] According to another retrospective analysis, the intraoperative use of brain mapping techniques improved the extent of resection. Preoperative morbidity was also minimized despite temporary postoperative neurological deficits resulting from cerebral edema and compression.[3] Accumulated evidence suggests that more extensive resection of grade II–IV gliomas was associated with more favorable life expectancy, regardless of location near eloquent cerebral areas.[47] Several reports have been published regarding the relationship between the extent of resection and postoperative neurological deficits. In one study, 17 patients underwent resection of cortical or subcortical tumors in motor areas (mean tumoral volumetric resection 89.1 ± 14.2%). A total of 58.8% of the patients had some kind of presurgical motor neurological deficit. The percentage of patients with deficits increased immediately after surgery, but decreased to 47.1% at 1 month postoperatively.[18] In a study of 309 patients with intracerebral tumors adjacent to or within eloquent cortices, gross total resection (≥95%) was obtained in 64%, and minimal resection of 85% was obtained in 77% of the patients. Gross total resection increased the risk of postoperative deficits, and 7% of patients had persistent neurological deficit at 3 months.[25] Comparative investigation evaluated the effect of safety margins around eloquent structures on postoperative outcomes in patients with grade II gliomas, and the rate of permanent deficit was similar with or without a margin (less than 2%). A higher rate of transient neurological worsening in the immediate postsurgical period was associated with no margin, and the extent of resection improved with the absence of a margin.[17]

In addition to various brain functional tests and neuronavigation systems, effective measures for improving glioma surgery include the use of intraoperative MR imaging and photodynamic diagnosis techniques. The application of intraoperative MR imaging system involves several challenging issues such as specific operating environment requirements and prolonged scan time, but enables intraoperative confirmation of the position of the tumor to be removed, and enables extraction of real-time tractography data of displaced brain tissues.[35,40] No significant improvement was noted in the overall survival after photodynamic diagnosis-guided malignant glioma surgery utilizing the 5-amiolevulinic acid (5-ALA) marker. However, the 6-month progression-free survival was 41.1% for patients allocated to the 5-ALA group, higher than that (21.2%) for patients allocated to the white light group. Use of 5-ALA enabled more complete resections of tumor, despite the increased incidence of transient neurological deficits.[51]

Conclusion

In the last decade, we have observed dramatic development in multidisciplinary modalities involving surgery, chemotherapy, and radiotherapy. Clinical application of gene therapy, cell therapy, molecule-targeted therapy, and immunotherapy is underway, building upon the results of basic research. Increasing amounts of evidence show that favorable treatment outcomes can be achieved by maximal safe resection of tumor. This resection is facilitated by the introduction of medical equipment and technologies including intraoperative neuronavigation, diffusion tensor tractography, and functional brain mapping. Intraoperative visualization of the brain anatomy and function is expected to progress further in the future. However, constant revision of the multidisciplinary surgical approaches and determination of indications seems important, based on the idea that such medical information merely relates to particular aspects of the tumor effects and brain functions. We also propose the importance of pursuing neuroscience research that addresses the dynamic brain networks based on the analysis of local brain functions. Such research will define the compensation mechanisms, so contributing to overall improvement in the outcomes of brain tumor surgery.

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脳機能部位に存在するgliomaの摘出術

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医療機器やPCの進歩に伴い，術前術中脳機能マッピング，モニタリング技術はこの10年間に飛躍的な進歩を遂げてきた．手術方針の決定に信頼できる脳機能情報が得られるようになり，機能的脳神経外科の領域は脳神経外科一般にまで広がるようになった．そのためか，脳腫瘍の手術，特にgliomaの手術では，その手術手技としてよりも脳機能診断法や画像診断法が最近の話題の中心になっている．本稿ではglioma摘出手術を中心として解説する．現時点での摘出の意義と目的を明らかにした後，脳機能の観点からgliomaの病態生理について考察する．大きな腫瘍の場合，術前より神経脱落症状のある場合，そしててんかんを合併している場合に，安全に，時には拡大切除を目指す摘出術の実際を文献・自験例とともに紹介する．

Key Words: 神経膠腫，脳機能，摘出術

Ⅰ．はじめに

「脳機能部位に存在するgliomaの摘出」に関しては，すでに手術支援機器や脳機能診断方法の紹介を中心とした多数の報告がある．日進月歩で新たな知見が紹介されてはいるが，「専門医に求められる知識」として冗長に重複することを避け，周知するべきポイントのみ記載する．

本稿ではまず，現時点で手術摘出の意義を文献的考察から明らかにする．次に，あまり触れられてはいないが根本的な内容，つまりgliomaによる脳機能部位浸潤について，摘出術という視点から考察する．腫瘍が脳機能をすでに浸潤損傷しているのか，単にmass effectによるのか，脳機能代償は皮質間ネットワークを介して生じうるのか，といったことを病態生理の観点から説明する．摘出術においては安全に，時に拡大切除を目指す．大きな腫瘍へのアプローチ，術前神経脱落症状やてんかんのある場合の対処法を紹介し，最後に血流温存についての基本手技を確認する．

Ⅱ．Gliomaに対する摘出術の意義と目的

悪性gliomaの治療では，テモダール®導入後化学療法と放射線治療を組み合わせた新たな治療プロトコールの確立が進み[20)]，さらに遺伝子治療・細胞療法・分子標的療法・免疫療法の臨床応用を含む集学的治療の検討も行われている．手術治療について摘出率が予後改善に寄与するという報告が，glioma WHO（World Health Organization）grade ⅢおよびⅣにおいては蓄積されてきた[8, 19)]．Grade Ⅱ astrocytomaであっても5年生存率は68％にとどまり，大腸がんの予後と同等でしかない．テント上発生の場合，5年生存率は手術なしから75％摘出まではほぼ50％台しか

達しないのに対して，95％摘出では73％，全摘出では88％まで改善する[14]．また，low grade gliomaにおける術後残存腫瘍の再発率，悪性転化率はそれぞれ5年で56％，26％と高い[3]．

これらの報告からgrade Ⅱ～Ⅳ gliomaすべてに対する手術治療において「全摘出を目指して」摘出する意義が認められている[16]．一方でもちろん，脳機能には「安全に」摘出することが求められる．予後良好の場合，不良の場合それぞれで経過中のQOLに対する意義や脳機能という言葉の解釈に違いはある．広義の脳機能部位とはシステム・行動・認知神経科学の分野まで含めた高次脳機能を含み，今後ヒューマンサイエンスの一部として脳神経外科学を位置づけていくうえで重要な課題である．Gliomaの治療成績，臨床上高次脳機能評価，の両者に限界がある現在では，随意的運動・体性感覚・視覚・言語・頭頂葉機能が腫瘍摘出に際して考慮するべき脳機能とするのが一般的である．

Ⅲ．Gliomaによる脳機能部位浸潤

High grade gliomaの場合，少なくとも腫瘍による組織破壊の強い部分にはもはや脳機能は存在しない．脳機能部位近傍に腫瘍があっても神経脱落症状が出現していない場合には，脳機能代償が生じている可能性は残るものの，単に機能部位に対して腫瘍の物理的圧迫による解剖学的シフトが生じたと考えられる．

一方で，low grade gliomaではしばしば脳機能部位内やその神経線維内に病変が存在しているにもかかわらず脱落症状は生じず，脳機能局在の移動・代償の可能性以外に病変そのものが正常な脳機能を有する場合がある．新皮質てんかんでは脳機能が焦点と共存していることが知られており，glioma手術と比較することによってgliomaによる脳機能部位浸潤について推察する．

脳機能部位近傍のglioma手術157例のうち57％でほぼ全摘出を行い，一時的症状悪化は術前症状のない81例中33％で認められたが，永続的症状出現は術前症状のないもので2.5％，術前症状のあるものでは8％であった．術前より症状があった76例中33％で術後症状は消失し，32％で改善している[4]．また，一次運動感覚野近傍のlow grade glioma摘出において60～100％に一過性運動麻痺が生じたが，永続的なものはまったくなかったとする報告もある[2]．

一方で，一次運動感覚野近傍皮質てんかん焦点の摘出では，術後半数で永続的神経症状の出現が報告されている[15]．いずれの報告も，現時点で行いえるマッピング・モニタリングを導入して「安全に多くの病変を摘出」することを図った手術の結果である．手術適応や母集団のバイアスも含まれておりさらに詳細な検討が必要であるが，脳機能部位gliomaでは機能代償の効く段階・術式で手術が行われている，と考えられる．

これらのことから，脳機能マッピング・モニタリングが真に必要になるのは，手術アプローチ選択に際してと，機能野連絡を介する代償機構の検討下でのT2（FLAIR）hyperintensityを示す腫瘍の摘出時[6, 7]である．造影を受ける腫瘍部分あるいは壊死などの組織破壊の強い部分の摘出に際しては，手術操作による周囲脳への機械的障害や血流障害の回避が最も重要である．ただし，造影を受ける腫瘍自身の浸潤のために術前から神経症状が出現している場合には，覚醒下での随意・

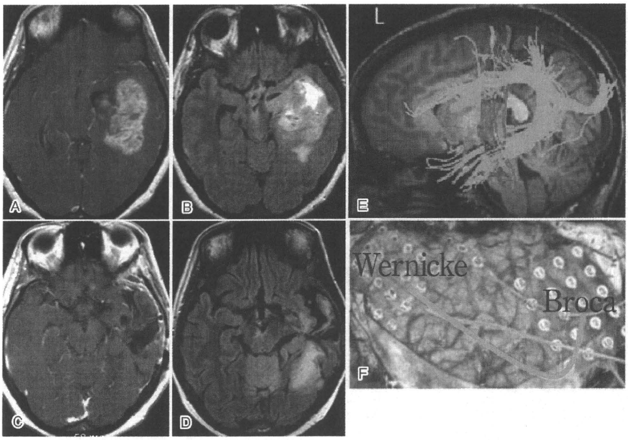

図1 37歳，女性，左側頭葉 glioblastoma
A，B：術前，C，D：術後，E：術前弓状束，F：術中電気刺激で同定したBrocaとWernicke領域を皮質皮質間誘発電位にて確認しながら腫瘍摘出.

刺激活動を含めた脳機能マッピング・モニタリングを総動員しても十分な情報が得られないこともあり，さまざまな生理的側面から脳機能を総合的に判断する必要がある[11, 12].

Ⅳ. 摘出術における工夫

A）脳機能部位温存摘出

術前に脳機能部位近くに病変が存在していてもそれぞれが離れている場合には，腫瘍境界での摘出，あるいは術中navigationや電気刺激の結果を参考にすれば安全な摘出が可能である．WHO grade Ⅲ，Ⅳ gliomaにおいて，造影を受ける部分には機能部位はないがその周囲のFLAIR（T2）hyperintensityを示す部分には脳機能が存在すると予測される場合，造影部分の摘出を安全かつ確実に行うことが外科治療の必要条件となる．脳機能温存を第一に考える際には，hyperintensityを示す部分は電気刺激で症状が出現または随意活動が低下すれば摘出中止を考慮する.

症例は37歳，女性，左側頭葉glioblastomaで，術前のfiber trackingでは弓状束が腫瘍造影部分を囲むように，FLAIR（T2）hyperintensity内に抽出された（図1）．覚醒下手術術中検査では電気刺激で言語（呼称および自発会話）障害が生じる皮質の下に腫瘍は存在していた．この皮質を温存して腫瘍に到達し術中navigationで弓状束を解剖学的に温存し，かつBroca野とWernicke野との皮質間機能連絡を電気刺激によって確認しながら症状悪化させることなく造影部分の摘出を行った.

電気刺激によるMEP（motor evoked potential，運動誘発電位）誘発では，ほぼ完全かつ正確に脳機能野を同定できる．一方で，言語や頭頂葉機能はしばしばその担当する脳が完全には同定できない．特に脳腫瘍の場合には，物理的影響で脳機能

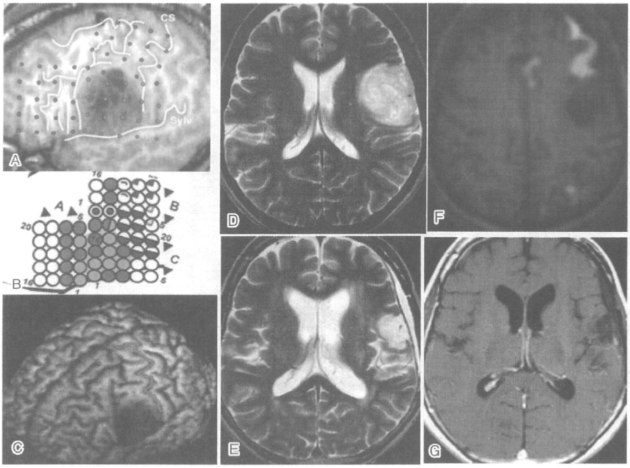

図2　53歳，女性，左前頭葉 diffuse astrocytoma

A，B：慢性硬膜下電極電気刺激による腫瘍内の言語野（赤）と陰性運動野（緑），C：3D MRI による中心溝（赤線）と腫瘍（黒）との位置関係，D：術前 MRI，E：f-MRI による腫瘍内前方の言語野，F，G：術後 MRI.

皮質が脳溝内に移動するために同定困難になりやすい．電気刺激で言語障害が誘発されない皮質部位，つまり negative mapping を確信すれば安全に脳腫瘍摘出を行えると報告されている．250人の脳腫瘍症例を対象として，言語野が同定できればそこから1 cm のマージンを残して摘出，電気刺激により言語（カウンティング，呼称，音読課題）障害が生じなければその腫瘍は摘出する，という方針で手術を行った[17]．言語野皮質が同定可能であったのは145例58%，術後一時的言語障害は22%で出現したが，永続的な言語障害の出現は1.6%にとどまったとしている．

B）拡大摘出

術前神経脱落症状がないにもかかわらず，腫瘍内に脳機能が存在することがある．この部分の摘出に伴う正確なリスクは不明であるが，摘出可能であることをしばしば経験する．

症例は53歳，女性，左前頭葉 diffuse astrocytoma（**図2**）．術前しりとり・語想起課題での f-MRI にて腫瘍内に言語機能部位の一部を認め，術中脳電気刺激によって運動性失語が同部位に確認された．肉眼的に腫瘍境界がわかる術中所見であり，T2 hyperintensity 部の全摘出を覚醒下手術にて目指した．言語機能部位の摘出時には脱落症状は生じなかった．陰性運動野摘出時に一過性の右手巧緻運動障害が生じるも，画像上全摘出を行い，その後新たな症状や再発を認めていない．広がりを持つ脳機能部位の一部が腫瘍内に存在する場合，腫瘍拡大摘出の可能性を示しており皮質代償機構の関与が考えられる．

C）機能部位を含む大きな腫瘍

言語機能温存には覚醒下手術が望ましいが，時

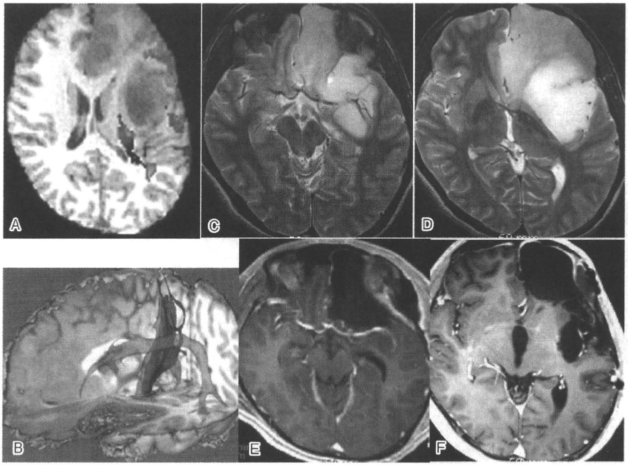

図3　28歳，男性，左insulaから前側頭葉に広がるdiffuse astrocytoma
A，B：術前上縦束（黄），錐体路（緑：顔面，赤：手），C，D：術前，E，F：術後．

間的制限があるため術前手術計画が重要である．特に大きな腫瘍でマイクロ操作が長くなる場合にはマイクロ操作の手順，覚醒にするタイミング，そして覚醒下で評価・摘出する病変の範囲をあらかじめ決めておくのがよい．

症例は28歳，男性，左insular diffuse astrocytomaが前側頭葉に広がる（**図3**）．手術手技経過中温存すべきは，脳表言語野，MCAおよびその穿通枝，言語神経線維（上縦束），錐体路である．手術中覚醒の時間を短縮するために，まずSEP（somatosensory evoked potential，体性感覚誘発電位）にて中心溝確認後precentral gyrusの電気刺激により上肢MEP陽性運動野を同定．Sylvian fissureを開放しMCA本幹を確保後に覚醒状態とし，脳表電気刺激によって言語野，陰性運動野および顔面一次運動野を同定．言語野を温存して前頭葉腫瘍を摘出し術中迅速診断を得る．次いでMCA branchの合間からperforatorを確認温存し，覚醒下でinsular tumorを随意運動と皮質MEPの変化がないことを確認しながら摘出．腫瘍後上方に電気刺激によって言語障害（名前の質問に年齢や自分と違う名前を答える）が出現し，navigationにてSLF（上縦束）近傍であることを確認したためinsulaの腫瘍摘出は摘出限界と判断．その後，覚醒状態は終了して深麻酔下で前頭葉前部腫瘍をinterhemispheric fissureまで摘出した．

D）術前神経脱落症状のある患者

術前症状のある場合には，①腫瘍内部に機能が存在する場合，②脳機能部位が外から腫瘍の物理的障害を受けている場合，がある．どちらの機序であるかを術前に診断することは，治療方針決定に重要である．症状が軽微の場合にはDTI trac-

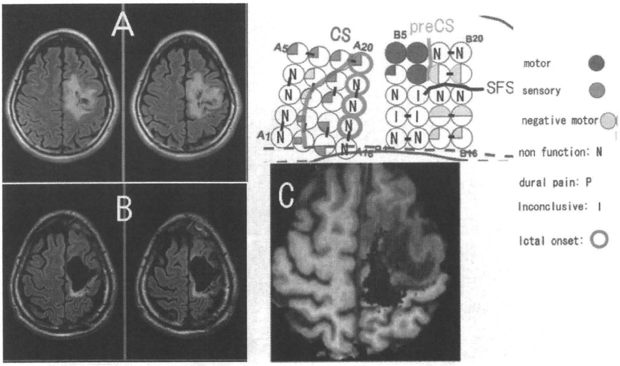

図4 34歳，男性，左 paracentral anaplastic astrocytoma
A：術前，B：術後，C：電気刺激マッピングとDTI tractographyにて腫瘍内部に手の運動野（繊維）（赤）および下肢運動野（繊維）（青）を腫瘍内に認める．薄青は電気刺激による感覚野．

tographyやf-MRIあるいはMRIの解剖情報によって予測可能なことが多く，神経機能が中等度以上障害されている場合には正確な鑑別は困難である．DTI tractographyは腫瘍浸潤や浮腫のため抽出不良となり，f-MRIは随意運動障害のために検査施行困難となっている．このような症例はhigh grade gliomaであることが多く，その予後の観点からも個々の病態での慎重な手術適応，摘出範囲決定が要求される．手術を行う場合には，すでに障害されている脳機能は手術操作によって悪化しやすいが，術中MEPなど脳機能モニターの信頼性が保証されないため，手術の目的および評価するべき機能を明確にして，その説明を術前に行っておく必要がある．①，②それぞれの一例を示す．

①腫瘍内部に機能が存在する場合

34歳，男性．左 paracentral anaplastic astrocytoma（**図4**）で右上下肢進行性麻痺のため，自立歩行が徐々に困難となっており，食事は左手で行っている．また，薬剤難治の症候性てんかんを合併している．病変は左中心前回に存在しており，DTI tractographyと脳電気刺激のいずれによっても上下肢一次運動感覚機能を示す部分が，FLAIR（T2）hyperintensityを示す腫瘍内部に存在している．皮質下MEP，上下肢SEPおよび随意運動機能評価を覚醒下手術にて行いながら腫瘍をほぼ摘出した．

本症例では上下肢SEPおよび随意運動機能評価が術中有用であった．術後中等度の運動感覚麻痺を生じたが，リハビリにて自立歩行の距離が徐々に伸びてきている．腫瘍と一緒にてんかん焦点同定切除も行っており，術後は発作消失している．腫瘍内部に機能が存在する場合，術中に生じる機能低下をどのように術後機能経過の指標として評価するかは今後の課題である．

②脳機能部位が外から腫瘍の物理的障害を受けている場合

54歳，男性．左 paracentral anaplastic astro-

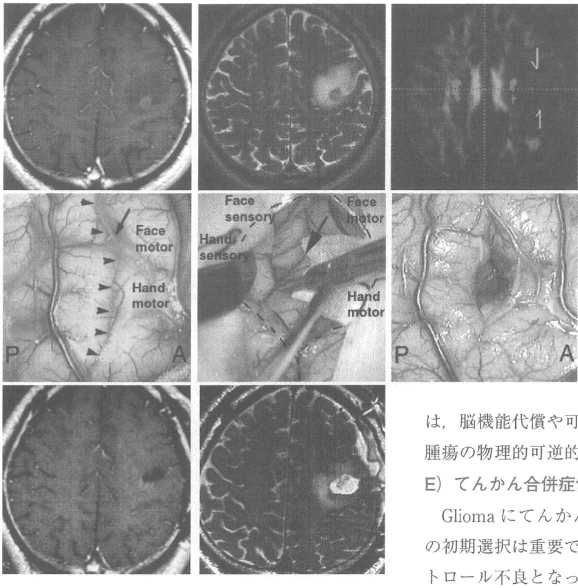

図5　54歳，男性，左 paracentral anaplastic astrocytoma

上段：術前 MRI にて中心溝最下部に造影を受ける腫瘍を認め，周囲の T2 hyperintensity 内は DTI にて神経線維抽出不良となっている．中段：術中所見，中心溝開放による腫瘍摘出．下段：術後 MRI．

cytoma（**図5**）にて術前より中等度の右上肢運動麻痺を認める．造影病変は中心溝直下に存在しており，周囲白質を中心に T2 hyperintensity を伴う．さきに述べたように，造影病変には脳機能は存在していないが，周囲にはやや障害を受けた錐体路が存在すると予想される．術中皮質電気刺激により顔面・手の一次運動感覚野を確認後，中心溝を開放して造影部分摘出中に上肢運動は著明に改善した．上肢 MEP の定性的波形では運動機能の改善は評価できなかった．造影部分の摘出・術中病理組織診断後，症状を悪化させない範囲で周囲の腫瘍摘出を行った．

このようにリアルタイムで症状改善する場合には，脳機能代償や可塑性よりもむしろ外部からの腫瘍の物理的可逆的障害の解除が考えられる．

E）てんかん合併症例

Glioma にてんかんが生じた際，抗てんかん薬の初期選択は重要である．適切な薬で発作がコントロール不良となった場合には，腫瘍外科とてんかん外科，両方の観点による早期治療が望ましい．

WHO grade I に分類される ganglioglioma や dysembryoplastic neuroepithelial tumor（DNT）はいずれも 80％以上の症例でてんかんを合併しており，腫瘍に合併する皮質形成異常にてんかん原性が存在することが多い[5]．その他の通常の glioma では，腫瘍により二次的にてんかんが生じることが多い．抗てんかん薬服用で発作が生じていない場合には腫瘍のみの切除で発作コントロールは良好であるが，薬剤難治性の場合には腫瘍内あるいは腫瘍外近傍にてんかん焦点を形成している場合があり，適切に焦点検索を行うことが推奨される．腫瘍とは離れた皮質や海馬が焦点とな

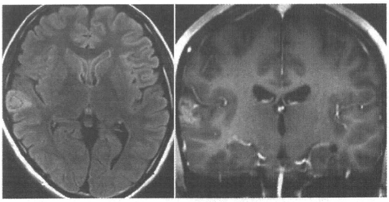

図6　20歳，女性，薬剤難治性てんかんを持つ右側頭葉 oligodendroglioma

上側頭回の病変周囲以外に右海馬にてんかん焦点を形成していた．

ることがあり，それぞれ co-existence，dual pathology と病態が定義されている．

当院で薬剤難治性てんかんを伴う脳腫瘍に対して腫瘍切除かつ焦点検索切除（てんかん外科）を行った38症例のうち，10例で腫瘍内，25例で腫瘍外近傍，3例で腫瘍外遠方にてんかん焦点を形成していた．薬剤難治性てんかんの罹患期間が長いと腫瘍外焦点を形成しやすく，手術によるてんかんコントロールの成績が落ちることが報告されている[1, 13, 18]．

症例は20歳，女性，13年間の薬剤難治性てんかんを持つ右側頭葉 oligodendroglioma（**図6**）．7歳時より音や会話の判別ができなくなる単純部分発作を毎日数回生じており，徐々に複雑部分発作を生じて薬剤難治となりさらに悪化してきた．右聴覚野近傍の病変をMRI上指摘され，20歳になり紹介受診となる．さまざまなてんかん焦点検索を行い，術中覚醒下脳波にてMRI病変近傍だけではなく，右側海馬からも発作が生じる（dual pathology）ことを確認後病変および焦点切除を行った．術後1年半発作は完全消失している．

F）手術手技

脳機能部位近傍 glioma 摘出の際，正常脳および計画的に残存させる腫瘍に存在する脳機能を損傷しないことが重要である．最先端の医療機器・診断技術をもっても，手術原則の知識がなければ外科治療成績の向上は望めない．なかでも血流障害の回避を常に念頭に置くべきであり，自然と脳回単位の摘出法（gyrectomy）を原則とすることになる．脳機能部位は脳回が基本的単位，脳腫瘍の広がりやその周囲のてんかん焦点における軟膜下 glial limitting membrane の存在，てんかん焦点となりうる皮質形成異常は脳回単位での発生異常，という事実においても gyrectomy が理にかなう．ただし，同一 gyrus でも precentral gyrus のように，前半（Brodmann の area 6）と後半（Brodmann の area 4）では機能やその損傷症状が異なる場合もある．

Gyrectomy を施行する際には病変部位への血管支配，脳溝の構造，白質部の処理について検討することが重要である（**図7**）[21]．軟膜下摘出でも脳溝を開放した摘出でもよいが，当施設では脳溝を開放して細い血管の走行を追って腫瘍を摘出する手技を基本としている[9]．脳溝を走る主要血管から病変部位への feeding artery は同定後凝固切断するが，腫瘍栄養血管を分枝し病変部を通過して遠位で正常脳を栄養している transit artery や病変部を通過するだけの passing artery の温存が必要である．太い栄養血管であれば術前血管撮影で診断できることもある．正中近くでは ACA 分枝，insula 近くでは MCA 分枝，特に穿通枝の走行には注意を要する．静脈に関しては，腫瘍と正常脳の還流パターンおよび側副還流の発達を認識して

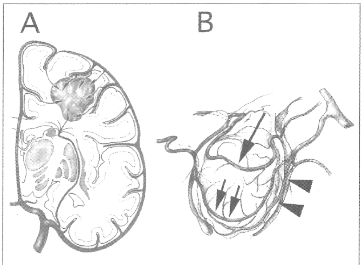

図7　グリオーマに関する血流動態[21)]
A:腫瘍への栄養血流, B:腫瘍へ栄養血管を分枝する脳表（矢印）および脳溝（2本矢印）の動脈（transit artery）は正常脳への血液供給も担当している．脳溝を走行する皮質静脈（矢頭）は正常脳と腫瘍両者からの血液還流を受けている．

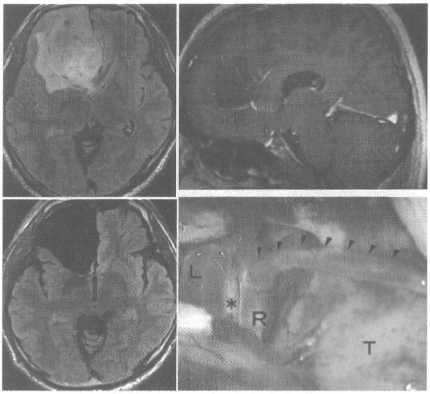

図8　32歳，男性，右前頭葉 anaplastic astrocytoma
上段：術前，下段左：術後，下段右：脳梁 genu（*）直後で分岐する callosomarginal artery（矢頭）は transit artery となって腫瘍（T）へと多数の小栄養血管を分枝していた．
R, L: right and left pericallosal artery

おく．腫瘍が pia を破って隣接した脳回に浸潤している場合など，腫瘍内の脳溝で transit artery や vein が腫瘍に強く癒着している際には残すべき動静脈の迅速で正確な判断が必要であり，ふだんから血流に留意した手術を心掛けている．

図8は ACA から feeder がある左前頭葉 anaplastic astrocytoma．まず interhemispheric fissure を分けて本幹および腫瘍へ向かう分枝を確認し，腫瘍から剥離して transit・passing artery を確認して早期に feeder を処理後腫瘍摘出を行った．

図9のように脳表の draining vein が red vein となってシャントを形成している場合，腫瘍への栄養血管を処理して静脈血色となってから摘出の最後に凝固切断する．Red vein 裏に最後の feeder が存在することが多い．

V．おわりに

手術ナビゲーション，tractography，MEP と，5，6年前では目新しかった医療機器・技術が今では当然のように使用されている．手術顕微鏡が導入されて，病変や血管が「見える」ようになった時代からマイクロサージェリーは進歩してきた．さまざまな脳の信号を PC によって視覚化できるようになった現在，病変や脳の状態を術中リアルタイムであたかも見えるように感じることができる．今後さらに 3D，誘起信号，脳波の視覚化や音声化といった技術が進むことが予想され，安全かつ最大限摘出，という現時点での目的にさらに近づくことが期待される．

一方で，見えているのは何か，つまり，腫瘍や脳機能の一側面を見ているという意識を持って手術の本質を常に考えていく姿勢が，より望まれる．また，薬剤や放射線治療などの治療法の進歩に伴