Intraoperative Tumor Segmentation and Volume Measurement in MRI-Guided Glioma Surgery for Tumor Resection Rate Control[1]

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Rationale and Objectives. Gross-total surgery under intraoperative magnetic resonance imaging (MRI) is a promising method of glioma removal. The purpose of this article is intraoperative measurement of resected tumor volume in MRI-guided glioma surgery using semiautomatic image segmentation to unbiased resection rate control.

Materials and Methods. A newly developed software program based on a fuzzy connectedness (FC) segmentation algorithm was used to achieve fast and semiautomatic tumor segmentation and tumor volume measurement. The program was validated by retrospective study of eight glioma cases and then applied to seven glioma cases. All clinical cases underwent actual MRI-guided surgery using 0.3-T open magnets.

Results. The volume of the tumor before resection ranged from 10.1 to 206.7 mL. A comparison of the results of manual segmentation with those of the semiautomatic FC-based segmentation gave an average dice similarity coefficient of 0.80 and an average match of 76%. Volume measurement combined with a developed software program enabled quantitative monitoring of tumor removal, which was critical in the near-total resection of glioma in MRI-guided surgery.

Conclusion. The FC-based tumor segmentation method can be used for intraoperative tumor segmentation and volume measurement in MRI-guided glioma surgery using 0.3-T open magnets. This method is useful for objective resection rate monitoring, which may ultimately minimize the amount of residual tumor in glioma surgery.

Key Words. *MRI-guided surgery; brain tumor; segmentation;* volume measurement.

The recurrence of glioma can be minimized by total or near-total surgical resection (1,2). Recognizing the importance of total resection of glioma, researchers have been trying to use intraoperative imaging to monitor the extent of tumor resection and ultimately increase the tumor resection rate in neurosurgery. The use of intraoperative imaging enables clear definition of the tumor boundary and observation of the extent of tumor removal during surgery. This real-time intraoperative information is critical to decision-making in tumor resection, which otherwise has to rely on preoperative x-ray computed tomography or magnetic resonance imaging (MRI) scans that do not reflect the current state of the cured lesions.

Intraoperative ultrasound is a widely spread and useful imaging modality for tumor craniotomy. Several studies

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have investigated the effectiveness of intraoperative ultrasound in neurosurgical guidance (3,4). Hammoud and colleagues reported that intraoperative ultrasound facilitated the localization of metastases; however, in their study, the tumor was difficult to define with presurgical radiation therapy in 13 of 34 glioma cases (3). Chacko and colleagues obtained similar results (4) and found that the tumor was poorly defined in low-grade glioma cases. It should also be noted that although the use of three-dimensional (3D) ultrasound has become virtually mandatory in the volumetric observation of tumor removal, its clinical application is still in development (5–7). Mobile computed tomography with its intraoperative imaging capability is another option for guided tumor removal; however, it has not enjoyed widespread application because of the problem of patient and physician exposure to radiation (8).

Gross-total surgery under intraoperative MRI is a promising method of glioma removal. Following the seminal work of Black and colleagues to use open-configuration MRI for guiding craniotomy (9), Schneider and coworkers investigated the effectiveness of MRI-guidance for gross-total resection of glioma and reported an successful average tumor removal rate of 95.7% (10). In their study, total resection of the tumor was possible in 6 of the 12 cases. However, they also warned that the amount of residual tumor could be higher (5.5–15.5%) when the tumor is located close to eloquent areas. In all cases they investigated, the measurement of the tumor volume was an important tool for quantifying the amount of tumor resection, yet no description was given to clarify whether their measurement tool was feasible for intraoperative use (10).

The aim of this study was to develop a system of image processing tools for segmenting intraoperative volumetric images and measure the tumor volume during MRI-guided glioma surgery. Such tools can potentially enhance the location of residual tumor in MRI, facilitate tumor resection, and provide objective estimation of the extent of resection for more precise surgical control. The proposed method is based on a combination of algorithms that enable unbiased, accurate, and reliable measurement of tumor volume in intraoperative MRI. This method also satisfies the time requirements for intraoperative use. The accuracy of the proposed method of image segmentation was evaluated and compared with that of manual segmentation performed by an expert surgeon. The clinical usability of the method was assessed in five intraoperative applications.

Table 1
Patient Data

Case no.	Age	Sex	Grade	Lesion	Eloquent
1	66	F	1	Rt F	V p
2	33	F	3	Lt F	Broca
3	34	F	2	Rt F	CorpusCal
4	32	F	2	Rt T	V p
5	32	F	3	Rt P	CST p
6	48	F	2	RT F	—
7	37	M	3	Lt P	Sensory area
8	34	M	3	Rt F	—
9	55	F	3	Rt T	—
10	16	M	2	Lt T	Memory
11	34	F	3	Lt F	Speech (Broca)
12	39	F	2	Lt Insula	Speech (Broca)
Total/Average	38	F 9; M 3			

F, female; M, male; Rt, right; Lt, left; F, frontal; T, temporal lobe; P, parietal lobe; V, visual; p, pathway; CorpusCal, corpus callosum; CST, cortico-spinal tract.

MATERIALS AND METHODS

Patient Selection

Table 1 summarizes the list of cases discussed in this study. Twelve patients (nine women, three men; mean age 38 years) were diagnosed with glioma by using preoperative 1.5-T MRI. The following histologic diagnoses were obtained using the World Health Organization classification: one Grade 1, five Grade 2, and six Grade 3.

The internal review board of the hospital approved the intraoperative MRI-guided surgery and subsequent analysis by image processing, as well as the procedure for obtaining patient consent. The nature of the procedure was discussed with the patients, and informed consent was obtained following the internal review board guidelines.

Imaging Sequence

All patients underwent MRI-guided craniotomy in a 0.3-T open MRI scanner (AIRIS II TM, Hitachi Medical Co., Tokyo, Japan). The scanner provides intraoperative MRIs in the bore and makes it possible to slide the operative bed into an off-five Gauss-line area where the surgery is performed. Images were taken three times during the surgery: before the resection of the tumor (after craniotomy and dura opening); in the middle of the surgery when the majority of the tumor was thought to have been removed; and before dura closure after the resection of the tumor. Stereotactic navigation based on most recent

Table 2
Accuracy Validation Study

Case no.	True positive (mL) (percent match [%])	False positive (mL)	Dice similarity	Tumor volume	
				Manual (mL)	Automatic (mL)
1	54.6 (83)	17.2	0.79	66.2	71.8
2	6.4 (63)	0.8	0.74	10.1	7.2
3	147.4 (71)	32.1	0.76	206.7	179.5
4	97.4 (80)	2.7	0.88	122.3	100.1
5	84.7 (73)	16.2	0.78	115.4	100.9
6	14.4 (84)	1.1	0.88	17.1	15.5
7	29.0 (76)	6.1	0.79	38.2	35.1
8	42.5 (81)	3.8	0.86	52.4	46.3
Average	(76)		0.80	$r^2 = 0.99$	

intraoperative MR images was used continuously throughout the surgery.

The intraoperative MRI was T2 axial imaging (two-dimensional fast spin-echo; repetition time (TR): 1000 millisecond; echo time (TE): 140 milliseconds, number of excitations (NEX): 1; matrix: 256 × 256; field of view: 230 mm × 230 mm; slice thickness: 1.5 mm; slice gap: 3 mm) standard in routine clinical practice at the institution. No contrast agent was administered in any of the cases.

The first eight cases were examined with a goal of postoperative validation to assess the accuracy of automatic segmentation compared with that of manual segmentation. The last seven cases (ie, cases 6–12) involved actual intraoperative image segmentation in the operative theater.

Intraoperative Segmentation and Volume Measurement

We used the fuzzy connectedness (FC) method to perform intraoperative brain tumor segmentation. The FC method (11) was first proposed for application to medical image segmentation (12), followed by reports on tumor segmentation in MRI (13–15). We chose the FC method for the segmentation of brain tumor in intraoperative MRIs for the following reasons. First, the method has proven to be accurate and reliable in brain tumor segmentation using MRI (13). Second, the role of the operator with the FC method is limited to the selection of representative points in the tumor, which means that the method is suitable for intraoperative settings. Starting from the selected seed point in the tissue of interest (ie, tumor), the method calculates the affinity of the neighboring voxels by using two criteria: how close the voxels are spatially and how similar they are in image intensity. The algorithm automatically computes a fuzzy scene (a map of fuzzy connectivity) in 3D from gray-scale images.

The FC algorithm without competition paradigm requires two parameters: a seed point and a threshold for the fuzzy scene. An operator sets the seed point in the region of the tumor by clicking one pixel on the monitor. The operator also limits the region to be analyzed by enclosing the whole tumor in a rectangle and inputting the numbers of the first and last slices. This procedure shortens the processing time. A threshold is then set in the precomputed fuzzy scene.

FC-based software was developed and implemented on a Linux PC (CPU: Pentium 4, 2.53 GHz; RAM: 1024 MB) using the 3D Slicer software program (Brigham and Women's Hospital and Massachusetts Institute of Technology; Boston, MA). The 3D Slicer is a surgical simulation and navigation software program that displays multimodality images three- and two-dimensionally (16,17). The 3D Slicer was used in this study to transfer intraoperative images from the scanner and perform tumor segmentation followed by volume measurement. The Linux PC was set up next to the scanner console in our interventional MRI suite and was used for segmentation, volume measurement, and surgical guidance.

After the segmentation, the total number of the voxels classified to tumor tissue is counted. Multiplying pixel area and slice gap size to this total number of voxels yields the volume of the tumor.

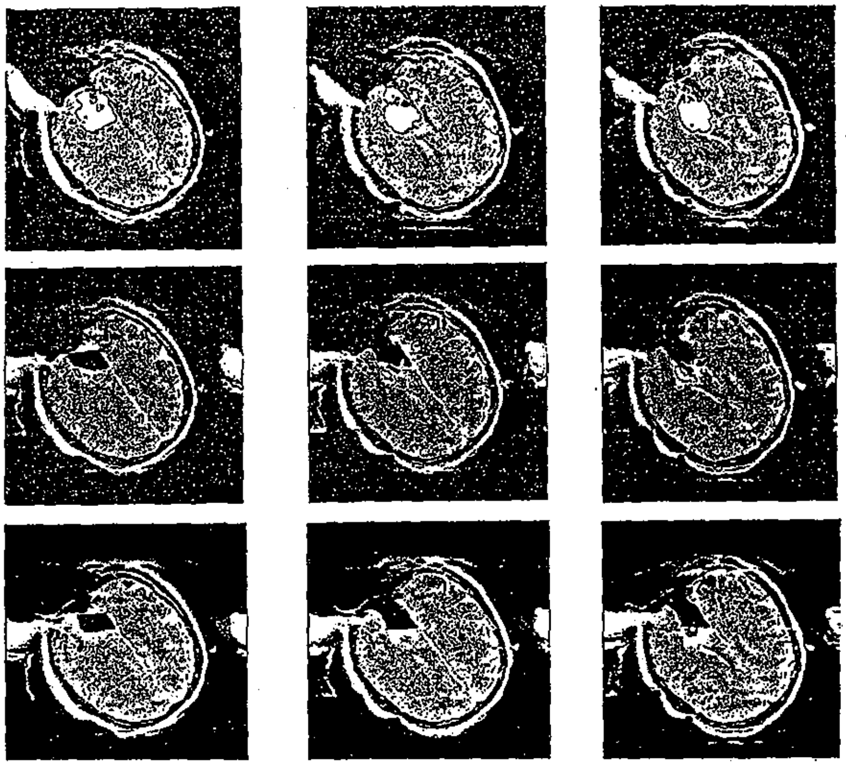

Figure 1. Results of intraoperative tumor segmentation in case 7 performed using T2-weighted magnetic resonance imaging (MRI) (repetition time (TR): 1000 milliseconds; echo time (TE): 140 milliseconds; number of excitations (NEX): 1; matrix: 256 × 256; field of view: 230 mm × 230 mm; slice thickness: 1.5 mm; slice gap 3 mm). Images were obtained after dura opening (top row), initial tumor resection (middle row), and total resection of glioma (bottom row). Residual tumor of 1.9 mL, or 5.4% of the total tumor volume (35.1 mL) remained unresected. It was removed in the second half of the operation as is shown in T2-weighted MRI in the bottom row.

Validation

Two sets of analysis were performed to validate the effectiveness and accuracy of the FC-based segmentation in intraoperative MRI-guided surgery.

The first set of analysis was an unbiased comparison of the results of an actual tumor segmentation performed by the expert neurosurgeons who actually performed the cases and those obtained by the automatic FC-based segmentation. The segmentation results by the expert neurosurgeon were set as gold standard. The goodness of the fit between a gold standard and the results of the automatic segmentation was determined by using an established measure of segmentation accuracy, the dice similarity coefficient (18) and percent match.

The second set of analysis was a detailed examination of intensity profiles obtained around the tumor lesion to determine whether the FC method could be used to enhance the tumor tissue and deemphasize the non–tumor tissue in the fuzzy scene.

RESULTS

Postoperative Image Analysis

In these patients, a hyperintense lesion was observed in T2 MR images and a hypointense signal was observed in T1 MR images. Edema was observed in T2 MR images in four cases (#3, #9, #10, and #11). The volume of the tumor in the first set of images ranged from 10.1 to 206.7 mL. A comparison of the results of manual segmentation with those of the automatic FC-based segmentation gave an average dice similarity coefficient of 0.80 (Table 2). The average match was 76%, ranging from 63% (#2) to 84% (#6). In seven of eight studies, the manual segmentation gave a larger volume than the automatic segmentation.

Clinical Feasibility Study

In all seven patients who underwent intraoperative segmentation and volume measurement, the FC-based segmentation enhanced the residual tumor, which is

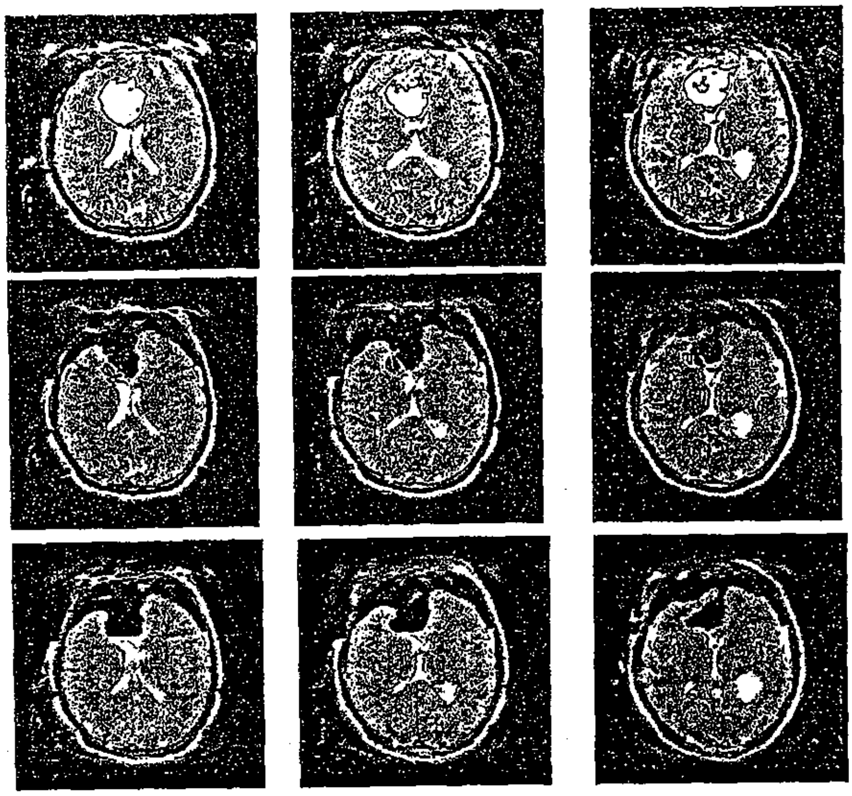

Figure 2. Intraoperative tumor segmentation in T2-weighted magnetic resonance imaging after dura opening (top row), initial tumor resection (middle row), and total resection of glioma (bottom row) in case 8. The images in each row are shown in the inferior-to-superior order. Note that the fuzzy connectedness–based segmentation clearly delineates the tumor and cyst boundary in the first scan (top row). In the second scan (middle row), 2.6 mL, or 6.2%, of the tumor (42.1 mL before the resection) was delineated by segmentation. No tumor was observed in the images obtained before dura closure (bottom row).

difficult to observe directly in MRI or hard to correctly identify by simple thresholding. The tumor volume measurement also facilitated decision-making during tumor resection.

In case 7, segmentation and augmented visualization of residual tumor was particularly important after the first step of tumor resection when the physician was engaged in surgical control, and careful study of images was difficult. After removing most of the tumor (33.2 mL, or 94.6%), a residual tumor of 1.9 mL was delineated by using the proposed segmentation method. In a second step of tumor resection, the tumor was completely removed (Fig. 1).

In case 8, as illustrated in Fig. 2, a frontal tumor of 43.7 mL was removed in the first step of the surgery. However, after T2-weighted MRI scanning, 2.6 mL, or 5.7%, of residual tumor was delineated by segmentation. We then continued the tumor removal toward the nonresected tissue area and achieved total resection.

An illustrative fuzzy scene from case 8 strongly enhanced the site of the tumor over the ventricles; the tumor tissue is classified to tumor by simple thresholding in original T2 images (Fig 3). However, in the fuzzy scene, the intensity of the tumor site was more pronounced than in the neighboring ventricles. The border between the tumor site and the surrounding nontumor tissue in the fuzzy scene also changed more steeply than in the original gray-scale images.

In all the cases, the scanning time was approximately 5 minutes for 100 slices, which was followed by image transfer to the computing workstation. The image processing took approximately 30 seconds. The computing time was short enough not to disturb the operation.

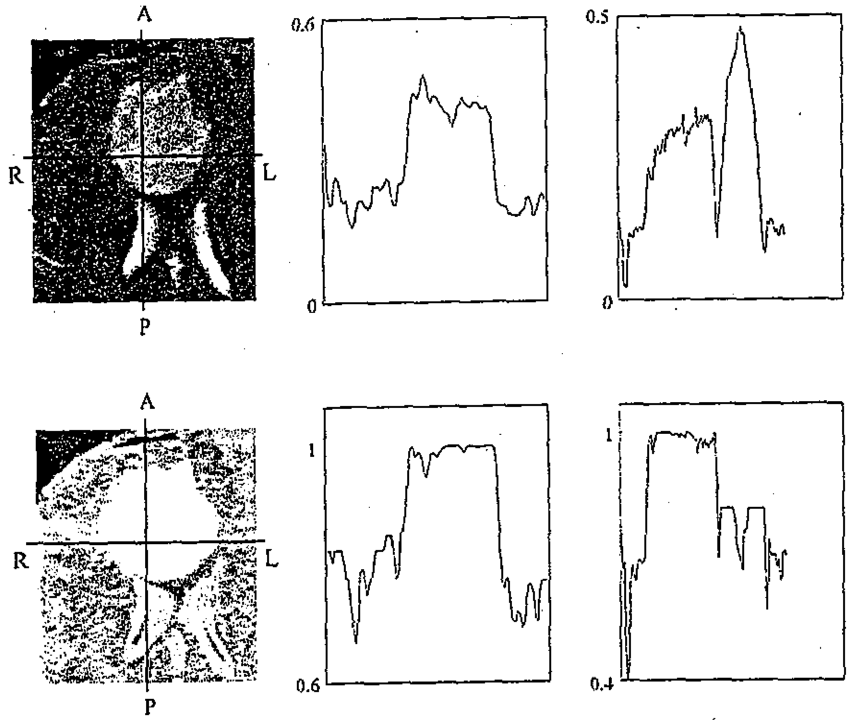

Figure 3. Intensity profiles obtained from original gray-scale T2-weighted magnetic resonance imaging (MRI) (top) and fuzzy science (bottom) after fuzzy connectivity-based segmentation. Compared with the intensity profiles obtained along the right-left line (top middle) and the anterior-posterior line (top right) in gray-scale MRI, the profiles along the right-left line (bottom middle) and the anteroposterior line (bottom right) in fuzzy scene have more distinct tumor delineation.

DISCUSSION

The preliminary results of the clinical feasibility and validation studies have lead us to believe that FC-based segmentation using intraoperative MRI can be used to accurately measure residual tumor and facilitates gross-total resection of glioma. We believe that this method provides a useful clinical addition to glioma surgery and treatment options aimed at minimizing the recurrence of glioma.

An average dice similarity coefficient of 0.80 agrees with the results obtained in other studies (18) of brain segmentation in MRI. We found that FC-based segmentation is not as effective as manual segmentation when the tumor is close to a surrounding nontumor object/tissue or when the border around the tumor is blurred because of intervention. This poor image quality may have negatively affected the FC-based segmentation in clinical settings. This might also be the cause why average match of 76% obtained in our study was slightly less than that reported previously (19), in which brain tumor was segmented by k-nearest neighbor rule and a semisupervised fuzzy c-means method. A possible solution to overcome these image quality issue is to perform MRI intensity standardization and inhomogeneity correction as preprocessing steps. The former particularly can help improving consistency of performance from one study to another.

We employed the FC method without competition paradigm as opposed to competition paradigm. The FC method without competition can detect only one object at a time and requires thresholding of the connectedness map. The FC method with competition, or relative FC, may be suitable for intraoperative MRI segmentation because it does not require thresholding. Relative FC may also help resolving the issues of incorrect segmentation on fuzzy boundary and incorrect inclusion of nearby nontumor objects into tumor tissue class.

A paucity of material is available on segmentation of a tumor in intraoperative MR images (20). To the authors' best knowledge, this is the first attempt to segment a tumor in series of intraoperative MRI studies.

Therefore, the engineering significance of our study lies in the applicability of the developed tool in real surgical setting in which limited user-software interaction and both speed and robustness of tumor segmentation in poor MRI quality are crucial. This study was also clinically significant because it provided evidence that such tool enables quantitative measurement of the volume of tumor resection and facilitates the resection of tumors.

In conclusion, the FC tumor segmentation method can be used for intraoperative tumor segmentation and volume measurement in MRI-guided glioma surgery using 0.3-T open magnets. The results lead us to conjecture that the method can provide unbiased resection rate of tumor for strategic surgical decision-making, and ultimately minimize the amount of residual tumor.

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Advanced information-guided surgery by integration of data from different modality

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Abstract. We have developed an operating system that provides several kinds of objective information for neurosurgery (intelligent operating theater, IOT). This system mainly detects anatomical, functional, and histological information obtained by intraoperative magnetic resonance (MR) images/navigation, the mapping/monitoring, and frozen section/5-aminolevrin acid (5-ALA), respectively. The intraoperative information contributed 91% of the resection rate and 13% of the complication rate in infiltrative glioma cases. To improve the surgical results, we need not only to improve the quality of each information, but also to integrate the different kinds of information. We here report the data integration system via the navigation to help the decision making process in the surgical procedures. © 2004 CARS and Elsevier B.V. All rights reserved.

Keywords: Brain tumor; Glioma; Navigation; Resection; Brain mapping; Biopsy

1. Introduction

Among primary brain tumors glioma is the most frequently occurring disease and its treatment is difficult. However, recent studies demonstrated correlations between resection rate and prognosis, showing that surgical resection should be the most effective treatment for malignant gliomas [1,2]. In order to increase the resection rate, it is of need to distinguish the glioma boundary and diverse eloquent areas at superior spatial accuracy based on objective evidences. In this sense intraoperative information-guided aging (iMRI) has been of great help to remove exclusively the glioma tissue since 1997 [3–5].

We also have developed a system of an operating theatre (intelligent operating theatre; IOT) to maximize resection rate and minimize neurological deficit in patients with brain tumors [6]. In our system, information necessary for the decision making during surgery is

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obtained by intraoperative magnetic resonance (MR) images and updated navigation (anatomical information), functional mapping and electrophysiological monitoring (functional information) [7], and intraoperative histological examination (histological information). The surgical results of the first 46 patients with glioma were 91% of resection rate and 13% of complication rate.

To improve the surgical result, we need not only to improve the quality of information but also to integrate each data from different modalities. We here report a new system for the integration of different data using the navigation system that was very useful for the decision making of the surgeons during resection.

2. Materials and methods

A total of 36 patients who underwent glioma resection in the IOT were identified for the study of the integration of the anatomical and functional data.

The anatomical data were obtained intraoperatively using an MR scanner (AIRIS-II™, 0.3 T, Hitachi Medical Tokyo, Japan, Fig. 1A) and updated navigation was performed using the intraoperative MR image (photon radiosurgery navigator™, optical tracking, Toshiba, Tokyo, Japan, Fig. 1B). The average errors of the update navigation were 1.4 mm (data not shown).

The functional data were obtained by means of the functional mapping by the electrical stimulation (0.5–10 mA, 50 Hz, Ojemann's stimulator, Medtronic, Minneapolis, MN) under awake craniotomy (Fig. 2A) and/or by the intraoperative monitoring of somatosensory-evoked potential and/or motor-evoked potential (Neuropack™, Nihon Kohden, Tokyo, Japan; epochXP™, Miyuki Giken, Tokyo, Japan). If functional tissues such as motor, speech, or other cognitive function were detected intraoperatively, the updated navigation system checked whether or not the functional tissue located in the tumor showing abnormal intensity.

A total of six patients who underwent intraoperative histological study and navigation during glioblastoma resection in the IOT were identified for the study of the integration of anatomical and histological data. Histological data were collected by the pathological diagnosis of the frozen sections and/or tumor-specific chemical illumination by the 5-aminolevrin acid (5-ALA) [8]. We checked the consistency among the enhanced area of

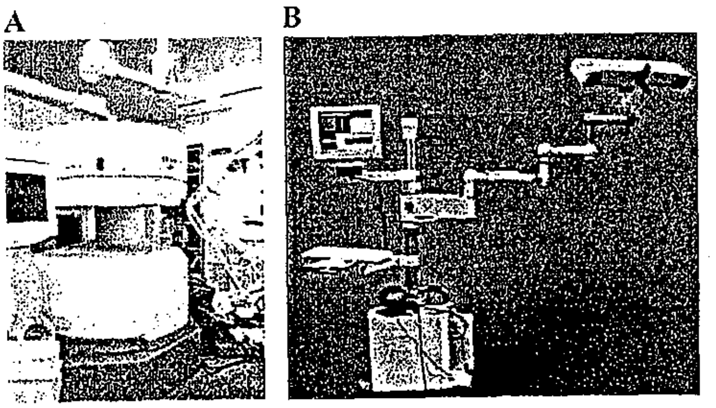

Fig. 1. Open MRI (A, 0.3 T, AIRISII, Hitachi Medical) and navigator (B, PRS navigator, Toshiba).

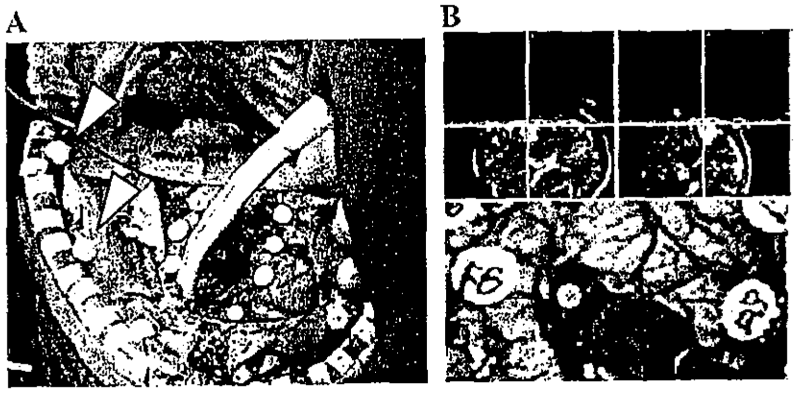

Fig. 2. (A) functional mapping under awake craniotomy. Electrical stimulation by the Ojemann's stimulator on the motor cortex (arrow head; fiducial markers of navigation system). (B) Functional tissue in the tumor. Electrical stimulation caused patient's speech arrest (speech area; red circle, lower column) and update navigation demonstrated that the location of speech arrest (upper column) was in the tumors (T2-high area).

intraoperative MRI, the 5-ALA positive region, and the area revealed as tumor by pathological diagnosis.

3. Results

3.1. Integration of anatomical and functional data

The functional tissue detected by the mapping was difficult to be identified in or out of the tumor area macroscopically, however, the updated navigation demonstrated whether or not the functional tissue located in the tumor. Eleven of thirty-six patients (32%) showed that functional tissues located in the tumor (Fig. 2B) or the manipulation in the tumor caused the peak decrease in the evoked potentials. No functional tissue was detected in the tumor in 23 patents (68%).

3.2. Integration of anatomical and histological data

In all six patients, the updated navigation showed that the histological findings corresponded to the MRI findings. Thus, a lot of tumor cells were detected within the

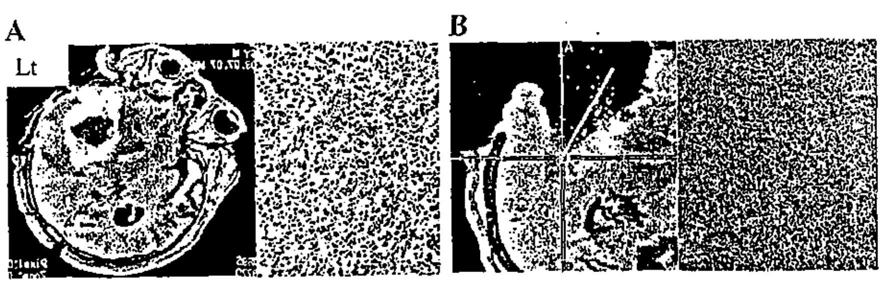

Fig. 3. (A) Glioblastoma in left temporal lobe (left). Histology in the tumor showed high cell density and endovascular proliferation. (B) Integration of navigation (anatomical information) and hisitology (histological information). At the last stage of resection, we stopped resection because navigator based on intraoperative MRI showed resection area was non-enhanced area (left) and the frozen section (right) showed no obvious tumor tissue.

enhanced area and few tumor cells out of the enhanced area (Fig. 2). The illumination of the 5-ALA was very helpful for surgeons to detect the residual tumor, however, the false positive finding of 5-ALA was obtained in two cases (5-ALA-positive, histology-no tumor cell) (Fig. 3).

4. Discussions

In 1990s, an image-guided surgery such as CT-guided or MRI-guided surgery had been introduced in the neurosurgical field. However, the image guidance is not sufficient to achieve precise resection in glioma cases. We proposed the information guidance by integrating various intraoperative examinations to help the critical surgeon's decision of tumor resection at each steps (information-guided surgery [6]).

We here present the usefulness of the integration of various intraoperative data by the updated navigation. It is very difficult to determine whether or not the detected functional tissue is within the tumor especially in the white matter, which collected tissue for histology is from an MRI-enhanced area, non-enhanced area, or iso-intensity. Only updated navigation can show us accurate answers to these critical questions because classical navigation based on the preoperative MRI has the errors by the brain shift.

5. Conclusion

This system that integrates various intraoperative information could help us to resolve a dilemma between the maximal resection of tumor and the minimal complication of surgery.

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専門医に求められる最新の知識

脳腫瘍

神経膠腫摘出のための覚醒下手術

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Ⅰ．はじめに

てんかん外科で考案された覚醒下手術[13)]が近年神経膠腫摘出に用いられるようになった[2,14)]が，日本でもここ数年で全国的な広がりをみせている．新しい手技を導入することのリスクに対する恐れより，できるだけ病変を摘出するという腫瘍外科本来の目的が勝ってきたからだと考える．髄内腫瘍でかつ境界不鮮明な神経膠腫を合併症を抑え最大限に摘出するためには覚醒下手術は有効な方法である．一方，神経膠腫の積極的な摘出には異論もある．

そこで，本稿では神経膠腫の積極的摘出の理論的根拠を述べた後に，覚醒下手術の適応，具体的な方法,注意すべき合併症について述べる．

Ⅱ．Glioma手術の意義

Glioma手術の意義は組織診断，圧迫解除，腫瘍容量減少などである．Malignant glioma (GradeⅢ，Ⅳ)において広範囲腫瘍摘出と予後改善との相関には議論が多い．90年代の代表的な9研究のうちprospective studyを含めた6研究でmalignant gliomaに対する積極的な外科手術が有意に生存率と相関していたが[2)]，3研究では有意差を認めなかった[4)]．

Controversyの原因としてはさまざまな研究方法のbiasや診断基準や分類が研究間で異なることや研究方法の不備が指摘されているが，最も大きな要因は摘出度の評価であると考える．

Albertら[1)]は同一症例で全摘出できたかどうかを外科医の判断，術後CT，術後早期MRIによって判断したが，全摘出率(全症例中全摘出症例の割合)がそれぞれ70%，29%，17%と大きく異なっていた．また外科医の術中判断で全摘出できたとする症例は生存期間が38週で，術後早期MRで全摘出と判断した症例での生存期間が68週とglioma摘出の評価方法によって予後が異なることを示した．

すなわち，術後早期MRIなどの画像による正確な摘出率評価をしていない研究の場合，extensive removalと予後との関係は論じられないと思われる．

Lacroixら[8)]の416例のglioblastoma (GBM)の報告あるいは日本脳腫瘍全国統計[17)]のGBM症例の検討では，前者は98%以上摘出群，後者は95%以上摘出と全摘群が他群に比較し予後良好との結果であった．またmalignant astrocytoma (anaplastic astrocytoma，以下AA)を加えた6,398例の検討でも全摘出群40%，95%以上摘出群22%，それ以下10～15%と各群間でそれぞれ有意差を認めた．

よくデザインされたprospective studyの結論

を待たなければいけないが，予後を改善するためには全摘近くの摘出が必要であろう．

“良性” glioma (low-grade glioma) でも摘出率が予後と関係しているとの報告が多いが，controversialである．“良性” gliomaでは悪性と比較して長い予後調査期間を必要とするため，最近の報告でも調査開始が古く摘出度の評価が画像でないことが多い．

ヨーロッパのEORTC[15] によるテント上low-grade glioma 288例の予後調査ではtotal removal群が多変量解析では有意差がないという結果だが，外科医が判断した90％以上摘出をtotal removal群としている．

日本脳腫瘍全国統計でのastrocytoma（以下A；Grade Ⅱ）4,460例の検討では全摘群，95％以上摘出群，75％以上摘出群，50％以上摘出群，生検群の5年生存率（5生率）はそれぞれ88％，75％，64％，59％，54％となり，75％以上摘出している3群は他の群と比較して有意差を認め，テント上に限定した2,602例では全摘群と95％以上群がそれ以下の群と比較し有意差を認めたという．

このようにgliomaの積極的な摘出術には異論があるが，“良性” gliomaとよばれることがあるastrocytomaでも5生率は日本全国統計でも67％，EOTRGでもlow-grade gliomaは65％[15]とほかの癌と同等かそれ以下の治療成績である．GBM（Grade Ⅳ）のみ予後の悪さ（6.3％）が強調されているが，“中間型”とよばれるAA（Grade Ⅲ）でも[1]生率は23％と，悲惨な治療成績である．

一方，上記のように全摘出に近い摘出が予後改善を示唆しており，腫瘍細胞をなるべく減らすcytoreductionの立場から，また他臓器転移がまれで再発の9割以上が局所であることから，物理的に取り去る確実な局所治療である手術の役割は大きいと考えられる．脳外科医が最も大きく貢献できるのは手術であり，予後改善の可能性があるならば全摘出を目指すべきと考える．また全摘近い摘出ができた場合，免疫系を強力に抑制するステロイド剤の投与が不要になり，てんかん発作のコントロールも容易になるという利点もある．

さて現状でどれくらいgliomaを全摘出しているかというと，文献上6.2～71％と報告により幅がある．前述のように全摘出の定義や評価方法，また母集団が異なっているからである．例えば母集団に生検例を含めない場合は全摘出率が上昇し，また開頭症例を選択する際にはselection biasが入る危険性がある．生検例も含めた場合，全摘出した症例の割合は6～20％程度と考えられるが，全国統計ではGBM 6.6％，AA 6.7％，A 10％ときわめて低いものであった．従来の方法でいかに困難かが想像できる．

合併症率を低減し，摘出率を上げるためにはgliomaに対する新たな手術戦略が必要と考えられる．

Ⅲ．Glioma手術戦略と覚醒下手術の位置づけ

合併症を抑え摘出率を上げるためには従来と異なる新たな方法と手術戦略が必要である．われわれは客観的な情報によって摘出範囲を決定する“情報誘導手術”を提唱している[6]．術中MRIとナビゲーションによる解剖学的情報，機能マッピングやモニタリングによる機能的情報，術中病理診断や[1]ALAによる組織学的情報を組み合わせ，過不足のない摘出を目指す方法である．

ほかの脳内病変と比較しgliomaでは特に保護すべき部位を同定する機能的情報は重要であ

表1　当科での覚醒下手術の適応

一般条件	覚醒下手術の意義を十分理解できている 15歳以上65歳未満	
除外条件	重篤な頭蓋内圧亢進あり 神経症状がすでに出現 全身合併症あり	
適応	Grade Ⅱ，Ⅲ (海綿状血管腫)	優位半球解剖学的言語野近傍 優位半球頭頂葉外側 優位半球解剖学的言語野近傍白質と弓状線維近傍
相対的適応	Grade Ⅱ，Ⅲ Grade Ⅳ (海綿状血管腫)	運動野近傍（運動野，前運動野） 優位半球解剖学的言語野近傍 優位半球頭頂葉外側 運動野近傍白質（運動野，前運動野）

る．Gliomaでは腫瘍内に機能が共存している可能性が報告されているからである[19]．覚醒下手術は機能的情報を提供する最も信頼できる方法の一つであり，従来は摘出不能と考えられていたeloquent領域のglioma摘出率向上に貢献している．

以下に覚醒下手術の適応と方法を述べるが，重要な点は覚醒下手術が機能的情報を提供する手段の一つであり，ほかの機能的検査の信頼度により覚醒下手術の適応や役割は施設により異なってくることである．例えば，われわれはglioma症例で慢性硬膜下電極によるマッピングを提唱してきたが[11]，埋め込んだ症例で覚醒下手術の役割は結果の再確認とともに，摘出中に変化がないかどうかのモニタリングが主な役割となる．また全身麻酔下MEPの信頼性が高い場合，運動野近傍で覚醒下手術の適応は狭まる．

Ⅳ．覚醒下手術の適応と方法

1．適　応

患者条件を表1に示す．最も大事な点は，覚醒下手術は患者本人が手術に参加するため，積極的な摘出の意義と起こり得る合併症を十分に理解している必要があることである．現在われわれは，原則として15歳以上65歳以下を対象としている．

小児例では慢性硬膜下電極によるマッピングを行う方法があるが，高齢者ではせん妄状態となった患者を経験したことやディプリバンの副作用が高齢者で高率に発現するとの情報から原則年齢制限をしている．無論どちらも経験を積んだ施設では不可能ではないと思われる．

また，中等度以上の症状がすでに発現している症例ではマッピング，モニタリングを行うことが困難なため，施行していない．重篤な全身合併症を有する症例も適応外である．

部位では解剖学的言語野とその近傍の病変，角回を中心とした優位半球頭頂葉外側の病変は適応である．個人差が激しく，覚醒下でしか術中確認できないからである．また，運動性言語野と感覚性言語野を結ぶとされている弓状線維（上縦束）近傍病変でも適応となる．

当科では運動野近傍病変も上記条件が許せば積極的に覚醒下手術としている．一方運動野近傍の手術では全麻下MEPでモニタリングとして十分であり，逆に覚醒下では例えば補助運動

表2　覚醒下手術のさまざまな方法

	開頭	マッピング	腫瘍摘出 モニタリング	閉頭	利　点	欠　点
awake craniotomy[2, 13]	覚醒*	覚醒	覚醒	覚醒	スムーズにマッピング可能	長時間で術者・患者に負担
変法1	覚醒	覚醒	挿管	挿管	負担軽く，少人数で可能	摘出中モニタリングなし
wake-up procedure[3]	咽頭マスク	覚醒	覚醒	覚醒 or 咽頭マスク	患者・術者の負担軽い	覚醒までLoss timeあり
変法2[10]	挿管	覚醒	覚醒	覚醒	一般病院でも可能	覚醒までLoss time長い

＊覚醒：この表では気道確保されていない状態を指し，実際は静脈麻酔下にあり，覚醒レベルはStageによって異なる．

野摘出による一過性麻痺などにより摘出できる部分を取り残すとの意見もある．われわれは覚醒下手術が最も鋭敏な方法であること，麻痺出現時はMEPでモニタリングできることや23例で画像上平均97％摘出率を得ていることから適応としている．各施設でのmodalityごとの経験と治療成績によると思われる．

組織型でみるとGrade Ⅱ，Ⅲが疑われる場合は適応である．Grade Ⅳが疑われる場合には現在適応としていない．組織学的にみても造影領域内に機能がある可能性は非常に少なく，実際造影領域の摘出で予想外の神経学的合併症は経験していない．ただGrade Ⅳでも機能が共存するとの報告があり，また造影領域のみの摘出を目指しても周囲正常組織を分離できない場合もあるため，注意が必要である．

本稿とは外れるが，glioma以外の適応疾患としては海綿状血管腫がある．病変自体に機能はないが，脳白質にあること，周囲gliosis摘出が痙攣コントロールに重要であることが機能野周辺病変では問題となる．すなわち病変へ到達する経路を選択するときに機能野を損傷しないため，周囲gliosis部分を摘出する場合に重要な神経線維を損傷しないためにはマッピング・モニタリングが必要であり，覚醒下手術を用いる．

2. 方　法

覚醒下手術には二つの役割がある．電気刺激で機能領（皮質・白質）を同定するマッピングと摘出の手術手技により神経症候が出現していないかを確認するモニタリングである．現在覚醒下手術は各施設でさまざまな変法が用いられているが[3, 7]，開頭，マッピング，腫瘍摘出（モニタリング），閉頭と四つのStageに分け，その概略と利点，問題点を表2に示す．

覚醒下手術（awake craniotomy）は，皮切から閉頭まで気道確保を行わず全過程を“覚醒下”（正確には気道確保を行っていない状態）で手術を施行する方法である（表2）．途中で覚醒させるという作業が必要なく，スムーズにマッピングを施行でき，エキスパートにはよい方法と思われるが，覚醒下での時間が長いため，術者・患者負担が大きい．

そこでマッピング以外の時間を気道確保したうえで麻酔深度を深くし，全身麻酔と類似の状況で手術する種々の変法が考案されている（表2）．マッピングまで覚醒下でそれ以降挿管して摘出を行う方法（変法1），咽頭マスク（Laryngeal mask）下で開頭し，その後抜管してマッピング・モニタリングを行う方法（wake-up procedure）[3]，挿管し全麻下で開頭した後抜管し，覚醒下でその後の手術を行う方法（変法2）[10]などである．

変法1はスタッフの少ない施設でも可能であるが，摘出中のモニタリングや白質マッピング

表3 覚醒下麻酔プロトコール（文献[12]より改変）

	操作	propofol	fentanyl	local anesthesia	その他（BISモニター値）
入室	モニター装着				
		3〜4μg/mL	2μg/kg静注		
麻酔導入	Laryngeal mask挿入				入眠時propofol濃度＊確認
		2〜3μg/mL	1μg/kg/h		
	各種ライン挿入				
					高齢者では調節呼吸可能 自発呼吸あれば補助呼吸
頭部固定				浸潤麻酔 神経ブロック ロピバカイン〜40mL	適切な局所麻酔が重要
手術開始		直前	1μg/kg静注		
開頭			1〜2μg/kg/h （ESC 2ng/mL）		（BIS 50〜60） CO_2濃度に注意
硬膜切開		入眠濃度＊	0.5〜1μg/kg/h （ESC 1ng/mL）		
覚醒下マッピング	Laryngeal mask抜去 鼻カニューレ 酸素マスク	0.6〜1.0μg/mL	0.5〜1μg/kg/h （ESC 1ng/mL）	適宜追加 （ピンや皮膚折返部）	（BIS ＞80） 高次機能の場合 propofolさらに低い濃度に 長時間の場合も低い濃度で
腫瘍摘出 （モニタリング）					
閉頭		2.2〜3.0μg/mL	1〜2μg/kg/h （ESC 1.5〜2ng/mL）	追加 （皮切，皮膚折返部） 20〜30mL	（BIS 40〜60） 必要ならばAirway Laryngeal mask挿入
手術終了 退室		off	off		
術中対応					
痙攣発作	電気刺激中止 術野に冷リンゲル液撒布	一時的に2.0μg/mLの上昇			無効時 ジアゼパム投与
体動時		一時的1.0μg/mLの上昇	0.5μg/kg静注	疼痛時追加	
嘔気・嘔吐	頭位回転				メトクロプラミド10mg静注 無効時オンダンセトロン考慮

ができない．変法2は特殊な道具が必要なく，全麻手術での抜管を閉頭後に行うところを開頭後に行うと考えれば，覚醒下手術導入時に抵抗感が少ない．本法で麻酔法に習熟することも一法であり，詳しくは開頭後術野をドレーピングし，頭部固定器の頭部固定部分以外を緩めた後抜管する．抜管後はpropofolによる静脈麻酔とし，固定器を再設定後にマッピングを施行し摘出する．

現在われわれは，初発例では抜管時のloss timeが比較的少なくマッピング・モニタリングが施行できるwake-up procedureを用いている．慢性硬膜下電極を埋め込んだ症例や再発例では原法を用いている．閉頭時は再度咽頭マスクを挿入する方法もあるが，腫瘍摘出により十分に減圧され低換気による頭蓋内圧亢進の可能

性が少ないため，われわれは酸素マスクのみで閉頭している．

V．麻酔法と合併症対策（表3）

覚醒下手術の麻酔で最も大事な点は，患者に疼痛や不安を与えずに，すなわち十分な鎮静と鎮痛の下，マッピング・モニタリングを行うことである．開閉頭時には深い鎮静・鎮痛下に手術を行い，摘出時には覚醒に近い状態での手術にすることである．この覚醒下手術の隆盛に最も貢献したのは即効性の静脈性麻酔剤propofol（ディプリバン®，アストラゼネカ）の開発とTCI (Target controlled infusion）を可能にしたポンプ（アストラゼネカ）の開発である．

このpropofolの最大の特徴は用量依存性の鎮静作用をもつことである．鎮静・覚醒のコントロールが短時間で可能であり，頭蓋内圧低下作用をもつことも脳神経外科の覚醒下手術に適している．注意すべき点は，血圧低下作用による過度の低血圧と大量使用による肝機能障害である．また，TCI用Infusionポンプによって短時間でかつ低用量（従来法の1／2～1／3量）で目的とする血中濃度に到達し，さらに血中濃度を安定して維持することができ，覚醒下手術の麻酔をより安全に施行することが可能になった．またBIS (Bispectral index）モニター（Aspect Medical）は脳波を周波数解析することにより覚醒状態を数値で表示するモニターであり，propofolの投与量決定に非常に有用である．

当科における各Stageでの麻酔薬の容量その他を表3[12]に示す．

さて，実際の覚醒下手術の麻酔において留意する点は，①患者の不安・疼痛の除去，②気道確保，③痙攣予防，④嘔吐，嘔気予防，⑤頭蓋内圧亢進の予防などである．

まず疼痛対策であるが，propofolは鎮痛作用をもたないため,十分な局所麻酔が必要である．Fentanylの併用も有効であるが，過量により覚醒不良となり，マッピングの信頼性が低くなるので，十分な注意が必要である．局所麻酔は，皮膚切開部とヘッドピン周囲の浸潤麻酔のみならず頭皮神経のブロックを施行する．具体的には開頭前にブピバカインかエピネフリン添加キシロカインを用いてsupraorbital nerve（Ⅵ）を眉毛部周辺で，zygomatic-temporal nerveやauriculo-temporal nerveを耳介前部で，greater and lesser occipital nervesをsuperior nuchal line周辺でブロックする．

開頭後もSylvian fissure下方からtemporal tip周辺の硬膜は過敏なので麻酔を十分に行うべきとされている[16]．自験例でもこの部位の電気凝固で疼痛を訴えた患者を経験している．

また長時間の手術となった場合，皮弁の折り返しでの痛みを訴えることが多いため，局所麻酔を早めに追加し，極量に注意しながら閉頭前にも追加する．最近では長時間作用型のロピバカイン（アナペイン®，アストラゼネカ）を使用して良好な鎮痛管理を得ている．

次に，覚醒下では常に緊急で気道確保が必要になることを想定しなければならない．文献上全身麻酔への移行は2～6％であるが，挿管のためのシミュレーションを麻酔科医とともに施行し，ドレープ・覆布などのセッティングを皮切前に検討することも重要である．またある程度の摘出を施行するまで，特に開頭時は二酸化炭素濃度に注意する．

嘔吐・嘔気は比較的頻度の高い症状（8～50％）である．患者の不快感をあおり覚醒下手術の継続が困難になるばかりでなく，突然の脳圧亢進をきたし危険な状態となる可能性がある．Propofol濃度を下げた後に吐気が出ることが多く，積極的な予防投与も行っている．第一

選択はメトクロパミド（プリンペラン®）であるが，保険外治療の5-HT3阻害薬の投与も準備している．

また胃管の挿入は異論のあるところであるが，以前は胃管を挿入していたが，それ自体が刺激になることがあり．挿入せずに管理している．われわれは4点の杉田式頭部固定器を用いているが，簡便に頭位を回転できることは緊急挿管の場合や嘔吐時の誤嚥予防に非常に有用である．

術中の痙攣発作は文献上16～18％の発生率である．特にマッピングのための電気刺激時に注意が必要である（後述）．

最も注意すべきは頭蓋内圧亢進や脳腫脹であるが，上記に示した方法すべてが対策である．すなわちpropofol，fentanyl，局所麻酔薬を最大の鎮静鎮痛効果が得られ最小の呼吸抑制となるように適切に投与し，二酸化炭素濃度が上昇しないよう呼吸管理を行い，痙攣や嘔吐を予防することである．

看護スタッフの役割のなかでは術野以外の不快感の対処と精神的なサポートが重要である．頻度の高い腰痛，口渇，顔面のかゆみ，感情失禁に対してそれぞれ体位変換やクッション挿入，水を浸したガーゼ挿入，言葉による励ましなどで対処する．われわれは，長時間の覚醒下状態が予想される場合には患者の好きな音楽CDを持ち込み摘出中に流している．

Ⅵ. 脳機能マッピング・モニタリング

患者の覚醒が得られた後にマッピングを施行する．まず病変とその周辺の皮質脳波をシート状電極で記録し，てんかん焦点を検索する．その後，われわれはOjemann刺激装置（OCS-1，Radionics）を用いてマッピングのための電気刺激を行う．

電気刺激条件は2相，矩形波とし，0.2ms，50Hzで，20mA以下を原則としている．まずbipolarでスクリーニングした後，陽性所見が出た部位はmonopolarで刺激する．

運動野や感覚野では刺激症状（運動野を刺激すると対応する筋肉が収縮する）が出現し，言語野などの高次機能では停止症状（電気刺激に発語が停止する）が出現する．運動・感覚野は電気刺激に対する反応が直接的でマッピングが比較的容易であるが，言語野は注意が必要である．というのは従来電気刺激により言語停止する部位が言語野とされていたが，それらには①陽性運動反応（発語に関連する筋肉の収縮），②陰性運動反応（電気刺激をすると共同運動が停止する反応），③言語野が含まれているので，実際の言語野を同定することが必要である[5]．

さらに，呼称と自発言語課題だけでは言語野全体のなかで約20％の部位では見逃してしまうとされている．これらを識別するためにマッピングに時間を要するため，われわれは慢性硬膜下電極によるマッピングを推奨している[11]．星田ら[5]は，覚醒下手術のマッピングのみで切除範囲を決定する場合，言語野同定に物品呼称と反応性呼称の組み合わせを推奨している．

電気刺激による痙攣発作の予防対策を述べる．まず刺激を低電流（1mA；刺激器の表示は0.5mAだが矩形波のため最大振幅は1mA）から始め，徐々に上げていく（1～4mA程度）．導入初期は刺激間で30秒以上の間隔をあけるべきだが，経験により十分な監視のもと刺激間隔を短縮していく．皮質脳波で棘波が得られた部位の刺激は十分に注意する．

ストリップ電極でafter dischargeをチェックし，発生した場合には刺激間隔をさらにあけるか，一旦ほかの部位の刺激をすべきである．しかしafter dischargeが続くときやpartial seizure