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PAPER

Clinical significance of preoperative fibre-tracking to preserve the affected pyramidal tracts during resection of brain tumours in patients with preoperative motor weakness

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Objective: To clarify the clinical usefulness of preoperative fibre-tracking in affected pyramidal tracts for intraoperative monitoring during the removal of brain tumours from patients with motor weakness.
Methods: We operated on 10 patients with mild to moderate motor weakness caused by brain tumours located near the pyramidal tracts under local anaesthesia. Before surgery, we performed fibre-tracking imaging of the pyramidal tracts and then transferred this information to the neuronavigation system. During removal of the tumour, motor function was evaluated with motor evoked potentials elicited by cortical/subcortical electrical stimulation and with voluntary movement.
Results: In eight patients, the locations of the pyramidal tracts were estimated preoperatively by fibre-tracking; motor evoked potentials were elicited on the motor cortex and subcortex close to the predicted pyramidal tracts. In the remaining two patients, in which fibre-tracking of the pyramidal tracts revealed their disruption surrounding the tumour, cortical/subcortical electrical stimulation did not elicit responses clinically sufficient to monitor motor function. In all cases, voluntary movement with mild to moderate motor weakness was extensively evaluated during surgery and was successfully preserved postoperatively with appropriate tumour resection.
Conclusions: Preoperative fibre-tracking could predict the clinical usefulness of intraoperative electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) to preserve affected motor function during removal of brain tumours. In patients for whom fibre-tracking failed preoperatively, awake surgery is more appropriate to evaluate and preserve moderately impaired muscle strength.

A number of anatomo-functional evaluations of the pyramidal tracts have been developed to help preserve motor function while maximising the removal of brain tumours located in close proximity to the pyramidal tracts. Integrated functional neuronavigation and preoperative neuroimaging, such as functional MRI (fMRI), magnetoencephalography (MEG) and fibre-tracking, have been combined with intraoperative electrical stimulation to establish the clinical significance of the findings of each evaluation method.[1–6] Despite these developments in mapping and monitoring techniques, little is known about their clinical utility for patients suffering from motor weakness caused by brain tumours. As the tolerance of affected pyramidal tracts for surgical manipulation is weaker in comparison with that in patients without motor weakness, intraoperative evaluation plays a critical role in the surgeon's ability to maintain motor function. Decreased motor function itself, however, may affect the accuracy of intraoperative evaluation.

White matter fibre-tracking using diffusion tensor imaging is capable of visualising the integrity of white matter.[1 4 7–11] Although fibre-tracking of the pyramidal tracts does not always correlate with the degree of motor weakness, it does reflect the functional condition of the fibres.[16] To predict the clinical usefulness of intraoperative evaluation by presurgical non-invasive fibre-tracking imaging in patients with motor weakness, we compared the results of pyramidal tract fibre-tracking with the results of intraoperative direct electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) and spontaneous movements.

PATIENTS AND METHODS

Patients

We examined 10 patients, aged 28–67 years, who suffered from mild to moderate preoperative motor weakness due to brain tumours located close to the pyramidal tracts (table 1). The tumours included five cases of glioblastoma multiforme, three of anaplastic astrocytoma, one of diffuse astrocytoma and one cavernoma. All lesions were located within the language dominant frontal lobe; before operation, five patients had mild motor aphasia. In response to stimulation of the bilateral median and tibial nerves, scalp somatosensory evoked potentials (SEPs) were recorded in all patients. To evaluate cortical activity during voluntary movement, we evaluated finger/foot tapping during fMRI and MEG studies.

MRI data acquisition and diffusion tensor imaging (DTI) data processing for fibre-tracking and fibre-tractography reconstruction

Detailed methods for fibre-tracking have been described elsewhere.[6 13] Preoperative DTI and anatomical T1/T2 weighted volume imaging used a 3 T MR scanner (Trio; Siemens, Erlangen, Germany). T1 weighted volume data were obtained using a three dimensional magnetisation prepared rapid gradient echo (MPRAGE) sequence. T2 weighted volume data

Abbreviations: DTI, diffusion tensor imaging; fMRI, functional MRI; MEG, magnetoencephalography; MEP, motor evoked potential; MPRAGE, magnetisation prepared rapid gradient echo; ROI, region of interest; SEP, somatosensory evoked potential

Table 1 Clinical characteristics of the 10 patients

Patient No	Age (y)	Sex	Histological type	Location
1	67	M	Glioblastoma multiforme	Left fronto-parietal
2	58	F	Glioblastoma multiforme	Left fronto-insulo-temporo-parietal
3	53	M	Anaplastic astrocytoma	Left fronto-parietal
4	28	M	Glioblastoma multiforme	Left fronto-parietal
5	40	F	Glioblastoma multiforme	Left frontal
6	40	F	Cavernoma	Left fronto-parietal
7	48	M	Diffuse astrocytoma	Left fronto-parietal
8	56	M	Anaplastic astrocytoma	Left frontal
9	60	F	Anaplastic astrocytoma	Left fronto-insulo-temporal
10	50	M	Glioblastoma multiforme	Right fronto-parietal

were obtained using a three dimensional true fast imaging with steady precession sequence. DtiStudio software was used to perform fibre-tractography based on the fibre-assignment by continuous tracking method.[9 14] Fibre-tracking was initiated in both retrograde and orthograde directions according to the direction of the principal eigenvector in each voxel. Results that penetrated the manually segmented regions of interest (ROIs) were assigned to specific tracts. To reconstruct the pyramidal tract, two ROIs were segmented on axial $b = 0$ images: the first ROI at the cerebral peduncles and the second ROI at the precentral gyri.[9 15 16] If the pyramidal tracts were not detected between the two ROIs because of the presence of tumours, the hyperintensity area at the internal capsule on the $b = 0$ image was selected as the second ROI.[11]

Fibre-tractography data processing for navigation system

To convert tractography into a DICOM format dataset, three processing steps were applied. The first step was to change tractography to a voxel dataset. An 8 bit voxel dataset with binary contrast was created from the original tractography using DtiStudio, with the same matrix size as $b = 0$ images. In this voxelised tractography, marked voxels where fibre-tracts penetrate displayed the largest value, and other voxels the smallest ones.[15] The second step was to create merged images of tractography and $b = 0$ images with the same matrix size as the MPRAGE images. The 3-orthogonal coordinates of each voxel in MPRAGE and $b = 0$ images were obtained from the DICOM header information. Trilinear interpolation was applied for voxel value calculation. Merged images were generated from interpolated tractography and interpolated $b = 0$ images. The third step was to convert merged images into DICOM format, according to the MPRAGE header information. DICOM format tractography with the same imaging matrices as MPRAGE were obtained.

Preparation in the navigation system

The MPRAGE images, fast imaging with steady precession images and DICOM format tractography images were transferred to the navigation system (StealthStation TRIA plus, Medtronic Sofamor-Danek, Memphis, Tennessee, USA; or Vector Vision Compact Navigation System, Brain LAB AG Heimstetten, Germany) using Cranial 4.0/VV Cranial 7.5 software. We then applied non-rigid image fusion based on a mutual information algorithm using ImMerge/iPlan2.5 software. The day before the operation, we performed axial whole brain CT with a contiguous slice thickness of 1 mm and six independent scalp point markers for anatomical registration. The CT dataset was also input into the navigation system. CT, MPRAGE and DICOM format tractography were automatically registered; the anatomical registration points were verified to minimise navigation errors. As the differences in distortion between DTI and MPRAGE were within a few millimetres according to a phantom for the neuronavigation system, we determined that the spatial accuracy of the single shot echo planar sequence would be reliable; the potential error of the navigation due to image distortions would be limited to a few millimetres. At navigation setup, the accuracy of image registration was less than 2 mm. Fibre-tracking tractography

Table 2 Results of evaluation of motor function by preoperative and intraoperative assessments

Patient No	Motor weakness	MEG	fMRI	Scalp SEP	Fibre-tracking	MEPs (cortex)	MEPs (subcortex)	Awake surgery
1	Hand 4/5	x	x	x	x	o (unstable)	x	o
	Bracjium 3/5	x	x	x	x	x	x	o
	Leg 2/5	x	x	x	x	x	x	o
2	Hand, bracjium 1/5	x	x	x	x	x	x	o
	Leg 4/5	x	x	x	x	x	o (<1 cm)	o
3	Hand, bracjium 3/5	o	o	o	o	o	o (<1 cm)	o
4	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
5	Hand 4/5	NA	NA	o	o	o	o (<1 cm)	o
6	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
7	Hand, bracjium 4/5	NA	o	o	o	o	o (<1)	o
8	Hand 4/5	NA	NA	o	o	o	x (>2 cm)	o
9	Hand 4/5	o	NA	o	o	o	x (1 cm<<2 cm)	o
10	Hand 4/5	NA	o	o	o	o	x (1 cm<<2 cm)	o

fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MEP, motor evoked potential; NA, not available; o, motor function detected; SEP, somatosensory evoked potentials; x, motor function was undetected.
The distances between points of subcortical stimulation and the fibre-tracking pyramidal tracts are shown as less than 1 cm (<1 cm), between 1 and 2 cm (1 cm<<2 cm) or more than 2 cm (>2 cm).

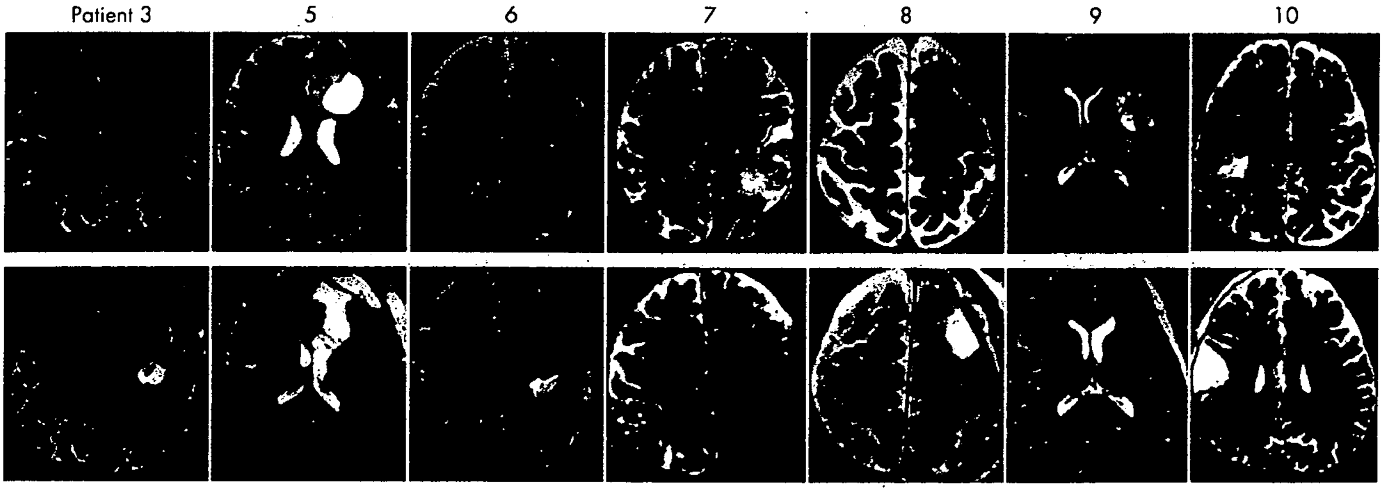

Figure 1 Upper: preoperative T2 weighted MRI in patient Nos 3, 5, 6, 7, 8, 9 and 10, with brain tumours showing a hyperintense area that is close to the pyramidal tracts (red), identified by fibre-tracking. Lower: postoperative T2 weighted MRI demonstrated the extent of tumour removal. Postoperative fibre-tracking in patient Nos 3, 6 and 9 revealed preservation of the pyramidal tracts (red).

of the pyramidal tracts between the cerebral peduncle and the precentral gyrus was successful in 50 surgically treated brain tumour patients without motor weakness (data not shown).

Intraoperative electrical stimulation

The bilateral abductor pollicis brevis, biceps brachialis, deltoid, gastrocnemius, quadriceps femoris and tibialis anterior muscles were chosen for electromyogram recording using neurological monitoring (Epoch XP, Axon Systems, New York, USA). After induction, general anaesthesia was maintained by intravenous infusion with propofol for craniotomy. Muscle relaxants were administered only for intubation and were not continued during surgery. The highest N20–P20 phase reversal of cortical SEPs was recorded using 4×5 subdural electrodes to identify the central sulcus. If SEPs were not sufficient to define the central sulcus, intraoperative visual inspection of the sulci combined with neuronavigation was used to orient the anatomy. After discontinuing the propofol infusion, patients awoke without further deficits.

To monitor motor function of the corticospinal tracts electrophysiologically, we first stimulated the precentral gyrus to identify a positive control motor evoked potential (MEP) and the intensity appropriate to stimulate subcortical fibres. The intensity of cortical stimulation was increased from 5 mA to a maximum of 25 mA. If afterdischarges were induced, we repeated the test at the same intensity or using a 1 mA lower

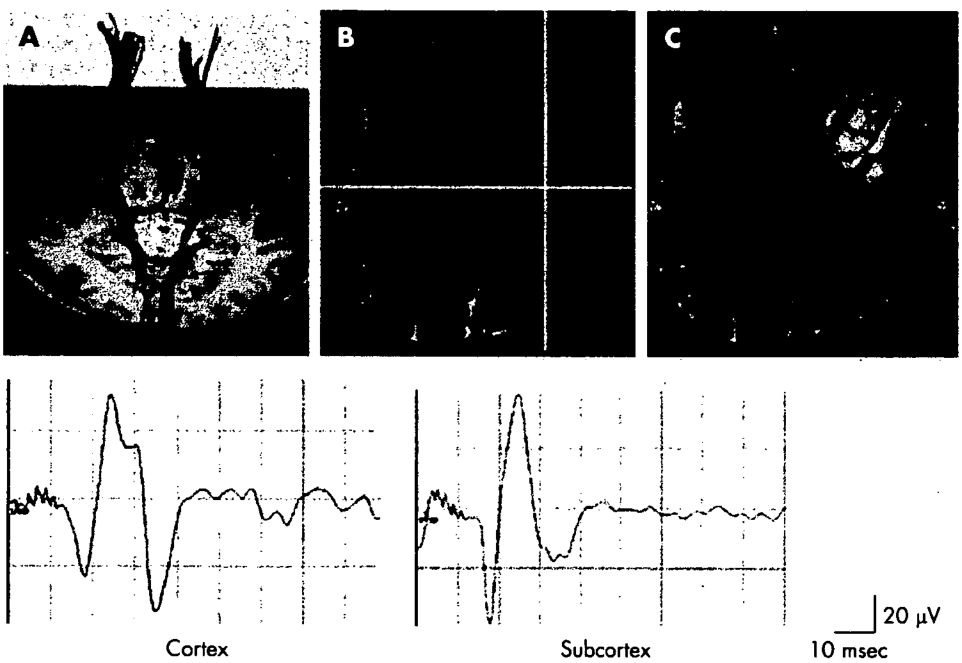

Figure 2 Patient No 4 had a left fronto-parietal glioblastoma multiforme. (A) Preoperative fibre-tracking identified symmetrical pyramidal tracts (red lines) from the cortex to the cerebral peduncles. (B) Brain T2 weighted MRI revealed a hyperintense area in close proximity to the left pyramidal tract, identified by fibre-tracking (red). Cortical stimulation of the left precentral gyrus, which had been defined by a somatosensory evoked potential, elicited a motor evoked potential (MEP) in the right abductor pollicis brevis muscle (Cortex). During removal of the tumour, subcortical stimulation elicited MEPs at the bottom of the tumour (intersection of the yellow lines in the intraoperative navigation image), 1 cm from the edge of the predicted pyramidal tract (red) (Subcortex). To avoid causing additional neurological deficits, no further removal was performed. (C) Postoperative T2 weighted MRI demonstrated preservation of the pyramidal tracts identified by fibre-tracking (red).

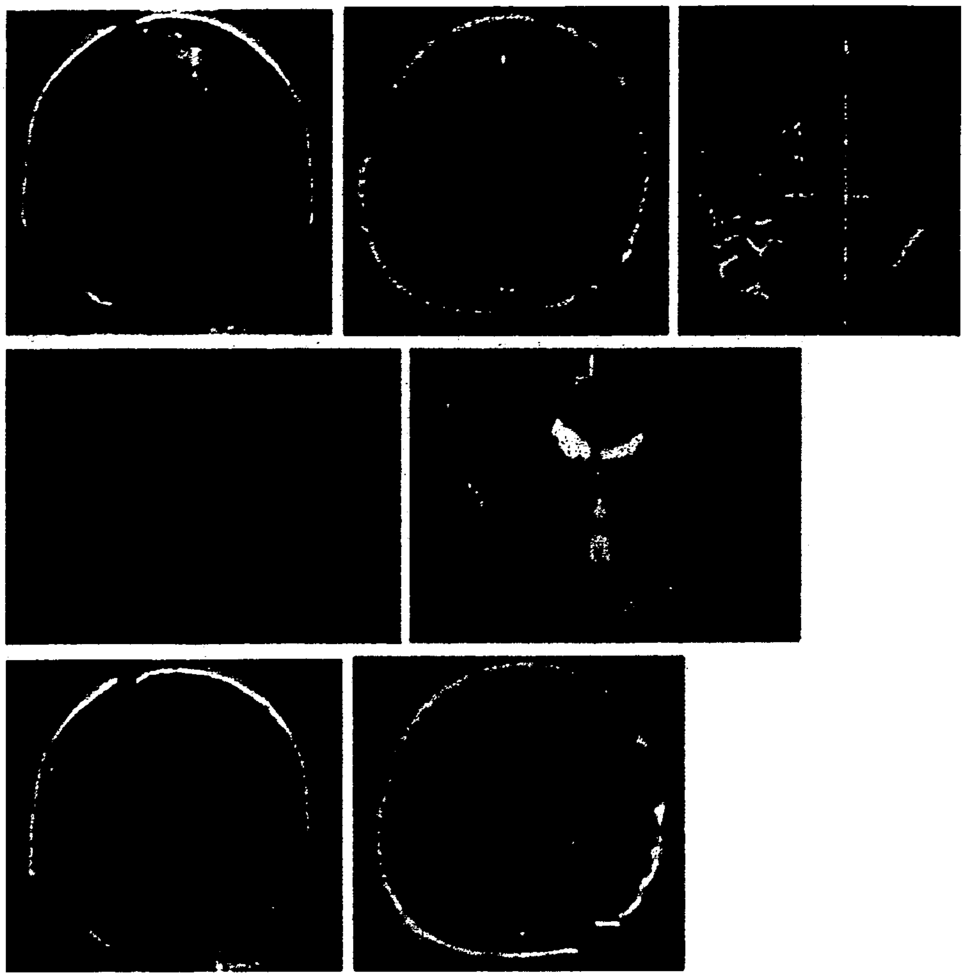

Figure 3 Patient No 1. Fibre-tracking of the pyramidal tracts was disrupted in a 67-year-old man with a left fronto-parietal glioblastoma multiforme. Upper: preoperative T2 weighted MRI identified a focus of hyperintensity in the left perirolandic region with gadolinium enhancement of the rostral precentral cortex. Stimulation of the left cortex rarely elicited weak motor evoked potential (MEP) responses on the right abductor pollicis brevis muscle. Subcortical stimuli, even on the approximated posterior bank of the precentral gyrus on neuronavigation (intersection of the yellow lines in the intraoperative navigation image), did not elicit MEPs. Middle: a relative anisotropy map indicated the principal eigenvector (green, anterior–posterior; red, right–left; and blue, inferior–superior). Fibre-tracking of the left pyramidal tracts (red lines) near the tumour was disrupted during its course to the cortex. Lower: postoperative MRI with gadolinium enhancement.

current. During removal of tumour tissue within 2 cm of the pyramidal tracts by intraoperative neuronavigation, we performed repetitive subcortical electrical stimulations. Electrical stimuli were applied across a relatively wide area to avoid any anatomical shift caused by the tumour. Five trains of monophasic square waves with a duration of 0.2 ms were applied. Current was delivered by a pair of adjacent electrodes (3 mm in diameter) with a centre-to-centre inter-electrode distance of 1 cm.[3] A 50 Hz electric current was delivered for language and sensory testing. Language functions were assessed by the reading of a paragraph, spontaneous speech, naming and comprehension activities.[17] We confirmed the points of stimulation by visualisation using the navigation system. In all patients, the minimum distances between points of stimulation and the fibre-tracking pyramidal tracts were measured using three dimensional MRI by intraoperative neuronavigation.

Surgery

All patients underwent removal of their tumour under local anaesthesia using the combination of tractography integrated functional neuronavigation and direct cortical/subcortical stimulation. During removal of the tumours around the pyramidal tracts, motor function of all four extremities was continuously monitored using the muscle manoeuvre test.[18] Language function was evaluated using similar testing as that used for electrical stimulation, depending on the location of the tumour. In three patients in whom part of the tumour extended into the left angular gyrus, single digit multiplication was evaluated. All procedures were approved by the ethics committee (No 542); written informed consent was obtained from all patients. As the presence of subcortical MEPs during resection of the tumour is an important sign warning of permanent motor weakness, we avoided further resection after obtaining the first MEP response.[19 20]

RESULTS

Results of evaluation of motor function by preoperative and intraoperative assessments are summarised in table 2. Preoperative fibre-tracking identified the pyramidal tracts of eight patients, including seven with mild hand motor weakness (patient Nos 4–10) and one with moderate motor weakness (3/5) of his upper limb (patient No 3) (figs 1, 2). In all patients, MEPs were elicited for all of the muscles evaluated, including the weakened muscles, by electrical stimulation of both the precentral gyrus and the subcortex within 1 cm of the pyramidal tracts, identified by intraoperative functional neuronavigation. The tumours were removed while confirming stable MEP responses by repetitive electrical stimulation. Motor function was either

Figure 4 Patient No 2. Left: fibre-tracking of the pyramidal tracts (red lines) demonstrated disruption around a left fronto-insulo-temporo-parietal glioblastoma multiforme. Middle: during removal of the tumour, cortical stimuli did not elicit any motor evoked potentials (MEPs). Subcortical stimuli very close to the predicted pyramidal tracts (red) on neuronavigation (intersection of the yellow lines in an intraoperative navigation image), however, elicited MEPs of her affected right lower extremities, but not her right upper extremities. Right: Postoperative T2 weighted MRI demonstrated that the pyramidal tracts identified by fibre-tracking (red) were preserved.

maintained or improved both during and after the operation. In addition, we demonstrated preservation of the pyramidal tracts by postoperative fibre-tracking (patient Nos 3, 4, 6 and 9).

In two patients (patient Nos 1 and 2), fibre-tracking of the pyramidal tracts around the tumour failed. Patient No 1 (fig 3) suffered from preoperative right hemiparesis (3/5 on the brachium, 4/5 on the hand and 2/5 on the leg) because of left fronto-parietal glioblastoma multiforme. Cortical SEPs exhibited weak responses on stimulation of the right median nerve; no response was observed after stimulation of the right tibial and sural nerves. Cortical stimulation of the anatomically confirmed precentral gyrus by neuronavigation elicited a rare MEP in his abductor pollicis brevis muscle; no MEPs were elicited in his biceps brachialis, deltoid, gastrocnemius, quadriceps femoris or tibialis anterior muscles. Neurological examinations soon after the patient recovered from general anaesthesia demonstrated no additional deficits. As the tumour was removed piece by piece, continuous evaluation of muscle strength helped preserve motor function of the lower extremities and improve motor function of the upper extremities to 4/5. Subcortical electrical stimulation did not elicit MEPs at any point during resection of the tumour. Patient No 2 (fig 4) exhibited right hemiparesis (1/5 on the upper extremity and 4/5 on the leg) preoperatively, caused by a left fronto-insulo-temporo-parietal glioblastoma multiforme. We operated on this patient with the goal of preserving motor function of the lower extremities. She also displayed mild motor aphasia. Cortical SEPs could not be elicited. Despite the absence of MEP responses following cortical stimulation of the wide area surrounding the anatomically identified precentral gyrus by neuronavigation, subcortical stimulation elicited MEPs of her lower but not upper extremities. Through continuous evaluation of muscle strength intraoperatively, motor function of the lower extremities was preserved during removal of the tumour. Postoperatively, she exhibited adequate removal of the tumour without any further neurological deficits.

DISCUSSION

To maintain the quality of life of patients with motor weakness undergoing surgical treatment of brain tumours, it is essential to evaluate motor function intraoperatively. The damage done to the pyramidal tracts, however, may affect the results of the evaluation. As MEPs elicited by direct intraoperative electrical stimulation remain the most reliable index of motor function,[21–23] it is important to predict if MEP responses will be elicited from the affected motor cortex and the pyramidal tracts during removal of the tumour. Presurgical evaluations, such as the degree of motor weakness (muscle strength), MEG, fMRI, positron emission tomography, transcranial magnetic stimulation and fibre-tracking are all potential candidates for predicting intraoperative MEP responses.

In this study, the degree of preoperative motor weakness did not always correlate with the incidence of intraoperative MEP responses. Muscles that were moderately affected by compression caused by the tumour elicited MEPs following cortical/subcortical stimulation (patient No 3), a result that is consistent with previous case reports.[2 24] MEP responses, however, could not be elicited from only mildly affected muscles in two patients (patient Nos 1 and 2). MEG, fMRI and positron emission tomography images provide information concerning motor function at the cortical, but not subcortical, level. Repetitive voluntary movements are often necessary to elicit motor evoked fields by MEG and bold effects by fMRI. While preoperative scalp SEPs correlated with the incidence of MEP responses in our patients, the results of SEP assessments do not directly reflect motor function.

Fibre-tracking of the affected pyramidal tracts was first compared with the incidence of intraoperative MEP responses by direct cortical/subcortical electrical stimulation. Subcortical MEPs were always elicited in regions in close proximity to the pyramidal tracts that had been predicted by fibre-tracking in patients with mild to moderate preoperative motor weakness. In addition, continuous fibre-tracking of the pyramidal tracts from the motor cortex to the cerebral peduncle indicated the positive response of cortical MEPs. On the other hand, cortical MEPs were never elicited as reliable responses in patients with disrupted fibre-tracking pyramidal tracts. These data suggest that preoperative fibre-tracking of the pyramidal tracts provides anatomical information as well as functional information in predicting the clinical usefulness of intraoperative cortical/subcortical electrical stimulation.

Several limitations to fibre-tracking as a preoperative evaluation, however, should be mentioned. Selection of the seed ROIs and the thresholding of fractional anisotropy, which define the parameter of the algorithm used in the procedure, may subjectively affect the errors in track trajectories.[8 25 26] In the present study, individual muscle maintained various degrees of motor activity preoperatively instead of disruption on the fibre-tracking pyramidal tracts, which may reflect the limitations of fibre-tracking from technical errors and pathological conditions. Part of the pyramidal fibres tracking from the precentral gyrus in lower convexity may fail to trace the precise course because the pyramidal tract intersects with callosal fibres and the superior longitudinal fasciculus at the level of the centrum semiovale.[3 27 28] Lack of visualisation of some upper limb fibres would account for some of the discrepancies between extent of weakness and ability to visualise fibres. To compare the pyramidal fibres tracking and MEP responses more precisely, taking intraoperative brain shift[29] into consideration, DTI image processing during the course of surgery with the use of intraoperative MRI is needed.[5 30 31] In addition, individual pathophysiological factors resulting from the brain tumours may affect the results of fibre-tracking,[2 10 20 32 33] although it is controversial whether the tumour itself or peritumoral oedema on the pyramidal tracts can be distinguished by DTI metrics.[34 35] In the two such patients evaluated in this study, preservation of motor function indicated that secondary effects, such as oedema or mass effect, rather than tumour infiltration, caused the motor deficits. Relatively large amounts of peritumoral oedema in these patients compared with the other eight patients might cause unsuccessful fibre-tracking of the pyramidal tracts. Although a wide area was stimulated electrically, a portion of the pyramidal tracts may have been shifted by compression of the tumour. Further studies with a larger number of patients will be necessary to study the physiological significance of fibre-tracking of affected pyramidal tracts and to clarify the clinical relationship between preoperative fibre-tracking and intraoperative cortical/subcortical electrical stimulation. The tendency for patients not to be operated on until they begin to suffer from moderate motor weakness due to growing brain tumours may, however, limit these studies. In addition, postoperative fibre-tracking of the pyramidal tracts and neurological status should be compared with the extent of tumour resection for further verification of the clinical value of preoperative fibre-tracking.

Despite the clinical utility of complete pyramidal tract fibre-tracking in reliable MEPs of the motor cortex and pyramidal tracts, disruption of estimated pyramidal tracts suggested that electrical stimulation is insufficient to permit the preservation of motor function during tumour removal. For patients with mild to moderate motor weakness in whom pyramidal tract fibre-tracking failed preoperatively, awake surgery would be better suited to evaluate motor function by voluntary movement during removal of the tumour. As awake surgery allows spontaneous movements to be easily monitored continuously, it would be useful for a subset of pathological conditions.[36] During removal of a tumour under local anaesthesia, injuries to motor associated areas must also be considered. Motor weakness is not observed immediately after resection of the supplementary motor area[37] whereas an injury to the negative motor area after resection would cause an immediate and transient disturbance in fine movement.[17]

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Clinical impact of integrated functional neuronavigation and subcortical electrical stimulation to preserve motor function during resection of brain tumors

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Object. The authors evaluated the clinical impact of combining functional neuronavigation with subcortical electrical stimulation to preserve motor function following the removal of brain tumors.

Methods. Forty patients underwent surgery for treatment of brain tumors located near pyramidal tracts that had been identified by fiber tracking. The distances between the electrically stimulated white matter and the pyramidal tracts were measured intraoperatively with tractography-integrated functional neuronavigation, and correlated with subcortical motor evoked potentials (MEPs) and clinical symptoms during and after resection of the tumors.

Motor function was preserved after appropriate tumor resection in all cases. In 18 of 20 patients, MEPs were elicited from the subcortex within 1 cm of the pyramidal tracts as measured using intraoperative neuronavigation. During resection, improvement of motor weakness was observed in two patients, whereas transient mild motor weakness occurred in two other patients. In 20 patients, the distances between the stimulated subcortex and the estimated pyramidal tracts were more than 1 cm, and MEPs were detected in only three of these patients following stimulation.

Conclusions. Intraoperative functional neuronavigation and subcortical electrical stimulation are complementary techniques that may facilitate the preservation of pyramidal tracts around 1 cm of resected tumors.

KEY WORDS • **pyramidal tract** • **fiber tracking** • **motor evoked potential** • **motor function** • **neuronavigation**

PRESERVING motor function while maximizing brain tumor resection is a major goal of neurosurgery. Presurgical noninvasive functional imaging, including positron emission tomography, functional MR imaging, and magnetoencephalography, enables the visualization of cortical areas involved in motor function, and has been integrated into functional neuronavigation. Cortical and subcortical functional connectivity can be clarified using intraoperative electrical stimulation.[9] To define the subcortical fibers from the primary motor cortex (the pyramidal tracts) as well as to monitor their motor function, MEPs elicited by direct electrical stimulation remain the most reliable index. Despite the use of presurgical cortical functional mapping and evaluation of MEPs, 7 to 20% of patients with perirolandic tumors suffer permanent motor weakness postoperatively, mainly due to resection of subcortical lesions near the pyramidal tracts.[3,8,15]

The fiber-tracking technique based on DT imaging shows the 3D macroscopic architecture of fiber tracts.[6,12,21,30,31] Recently, investigators have developed a new method for anatomofunctional mapping, using tractography-integrated functional neuronavigation combined with direct fiber electrical stimulation (MEP recording).[5,14,24] We have reported on the use of this method by using 3-tesla MR imaging.[26] To understand the clinical impact of this new technique on motor outcome during the resection of brain tumors located near the pyramidal tracts, we have directly compared the results of fiber tracking and subcortical electrical stimulation during intraoperative neuronavigation. Neurological evaluations of motor function were performed during the surgery and postoperatively.

Clinical Material and Methods

All procedures were approved by the ethics committee, and written informed consent was obtained from all patients.

Patient History

We examined 40 patients, 15 to 69 years of age, with

Abbreviations used in this paper: CT = computed tomography; DICOM = digital imaging and communications in medicine; DT = diffusion-tensor; MEP = motor evoked potential; MPRAGE = magnetization prepared rapid gradient echo; MR = magnetic resonance; ROI = region of interest.

tumors located close to the pyramidal tracts. These tumors included one pilocytic astrocytoma, 10 diffuse astrocytomas, 14 anaplastic astrocytomas, eight glioblastomas multiforme, two oligodendrogliomas, one ependymoma, and four cavernomas (Table 1). In all patients, the lesion margins were less than 2 cm from the pyramidal tracts identified by preoperative fiber tracking. Mild motor weakness was observed preoperatively in five patients.

Diffusion-Tensor Data Acquisition and Processing for Fiber Tracking

Detailed methods used in fiber tracking have been described elsewhere by one of the authors.[25,26] A whole-body 3-tesla MR imager (Trio, Siemens) was used to perform preoperative DT imaging as well as anatomical T_1- and T_2-weighted volume imaging. The T_1-weighted volume data were obtained using a 3D MPRAGE sequence, and the T_2-weighted volume data were obtained using a 3D true fast imaging with steady-state precession sequence.

Fiber Tractography Data Processing for use in the Navigation System

Fiber tracking was performed using all pixels inside the brain (that is, with the brute force approach) and was begun in both the orthograde and retrograde directions, according to the direction of the principal eigenvector in each voxel. Results that penetrated the manually segmented ROIs based on the known anatomical distributions of tracts were assigned to those specific tracts. To reconstruct the pyramidal tract using tractography, two ROIs were segmented on axial non–diffusion weighted images: the first ROI at both cerebral peduncles, and the second ROI at both precentral gyri.[21,26,31]

In the process of converting tractography data into a DICOM-format data set, three steps were used. In the first step, tractography data were changed into a voxel data set. Using DtiStudio software version 2.02 (H. Jiang, S. Mori: Department of Radiology, Johns Hopkins University), an 8-bit voxel data set with binary contrast was created from the original tractography data with the same matrix size as non–diffusion weighted images. In this voxelized tractography data set, marked voxels (where fiber tracts showed penetration) showed the largest value, whereas other voxels displayed the smallest value.[19]

In the second step, tractographic images and non–diffusion weighted images were merged, using the same matrix size as that for MPRAGE images. The three orthogonal coordinates of each voxel on MPRAGE and non–diffusion weighted images were obtained from the DICOM header information. To calculate voxel values, trilinear interpolation was used. Merged images were generated from interpolated tractographic images and interpolated non–diffusion weighted images.

In the third step, merged images were converted into DICOM format according to the MPRAGE header information. Tractography studies in DICOM format with the same imaging matrices as MPRAGE studies were obtained.

Preparation in the Navigation System

The MPRAGE images, fast imaging with steady-state precession images, and DICOM-format tractography images were transferred to the navigation system (StealthStation TRIA plus with Cranial 4.0 software, Medtronic Sofamor-Danek; or Vector Vision Compact Navigation System with VV Cranial 7.5 software, BrainLab AG). We applied nonrigid image fusion to the images using ImMerge or iPlan 2.5 software, based on a mutual information algorithm. The day before the operation, we performed axial whole brain CT with a contiguous slice thickness of 1 mm by attaching six independent scalp point markers to the patient for anatomical registration. The CT image data set was also transferred to the navigation system. Computed tomography images, MPRAGE images, and DICOM-format tractography were registered automatically, and the anatomical registration points were verified to minimize navigation error. The differences in distortions between DT imaging and MPRAGE imaging were within a few millimeters according to our study using a phantom for the neuronavigation system, and therefore spatial accuracy of the single-shot echo planar sequence would be reliable. The potential for error during neuronavigation due to image distortions would be limited to a few millimeters. The accuracy of image registration was within 2 mm at navigation setup.

TABLE 1
Summary of the clinical characteristics of 40 patients with brain tumors

Tumor Type & Location	No. of Patients
histological type	
pilocytic astrocytoma	1
diffuse astrocytoma	10
anaplastic astrocytoma	14
glioblastoma multiforme	8
oligodendroglioma	2
ependymoma	1
cavernoma	4
anatomical location (rt/lt)	
frontal lobe	4/16
temporal lobe	2/5
insular cortex	2/5
parietal lobe	2/2
brainstem	2

Intraoperative Electrical Stimulation

The bilateral abductor pollicis brevis, biceps, brachialis, deltoid, gastrocnemius, quadriceps femoris, and tibialis anterior muscles were selected for electromyographic recording by using neurological monitoring (Epoch XP, Axon Systems). General anesthesia was induced and maintained with intravenous infusion of propofol during the craniotomy. Muscle relaxants were administered only for intubation procedures and not during surgery. A peripheral nerve stimulator was used to confirm train-of-four muscle contractions. To identify the central sulcus, the highest N20 to P20 phase reversal of somatosensory evoked potentials was recorded using 4 × 5 subdural electrodes. For electrophysiologically monitoring the motor function of corticospinal tracts, the precentral gyrus was first stimulated to identify a positive control MEP as well as the intensity that was to be further used to stimulate the subcortical fiber. The intensity for cortical stimulation was increased by 1-mA increments, from 5 mA to a maximum of 15 mA. If afterdischarges were induced, the test was repeated with the same current level intensity or at a current level 1 mA lower.

During the removal of tumors within 3 cm of the pyramidal tracts using intraoperative neuronavigation, subcortical electrical stimulations were carried out repetitively. Bipolar stimulation of five trains with monophasic square waves and a duration of 0.2 msec were applied with a frequency of 1 Hz. For language and sensory testing, a 50-Hz electrical current was delivered.[20] Language functions were assessed during spontaneous speech, naming, reading a paragraph, and were also based on reading comprehension.[20] Sensory function of both positive and negative symptoms was evaluated by the examiner.

We confirmed the points of stimulation by visualization on the neuronavigation system. In all patients, the minimum distances between the points of stimulation and the fiber tracking of the pyramidal tracts were measured with 3D MR imaging during intraoperative neuronavigation.

Surgical Procedures

All of the patients underwent tumor removal with the combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. After the administration of local anesthetic agent, motor function of the four extremities in 28 patients was continuously monitored using the muscle maneuver test[7] during removal of tumors near the pyramidal tracts. In these patients, language function was evaluated with the same testing procedures as those used for electrical stimulation, depending on the location of the tumor. Single-digit multiplication was performed by three patients in whom part of the tumor extended to the left parietal lobe. Resection of the lesions was ceased when a subcortical stimulation elicited an MEP response or language dysfunction. All elicited responses were recorded on video and later confirmed.

Results

Motor function was preserved postoperatively in all patients. In five patients with preoperative mild motor weakness in the upper or lower extremities, motor ability improved to full strength on the 2nd postoperative day (Table 2). Three resections were terminated due to the appearance of a disturbance in reading and naming ability caused by electrical stimulation.

Among 21 patients in whom MEPs were elicited, the distance between the estimated pyramidal tracts and the site of the positive MEPs was 1 cm or less in 18 patients (Fig. 1). Mild preoperative motor weakness in the upper extremities improved intraoperatively in two of four patients overall. Mild and transient motor weakness of the contralateral hand occurred when the first MEP was observed in the other two patients.

The distance between the estimated pyramidal tracts and the site of stimulation was 1 to 2 cm in 15 patients, and MEP recordings were negative in 12 of these patients. Two of these 15 patients suffered postoperative supplementary motor area syndrome,[10] which lasted for 2 weeks. In the remaining five patients, MEPs were never elicited by stimuli more than 2 cm from the estimated pyramidal tracts.

Discussion

This study showed the clinical impact of integrated functional neuronavigation and subcortical electrical stimulation for preserving motor function while attaining adequate tumor resection. Various methods, including positron emission tomography, functional MR imaging, magnetoencephalography, and electrical stimulation, have been shown to be effective for functional mapping and monitoring to preserve motor function at the cortical level. For better surgical outcomes, DT fiber tractography and/or subcortical electrical stimulation have been used to evaluate both the anatomical and functional condition of the pyramidal tracts. Several limitations to these approaches, however, have not been resolved.

Errors in track trajectories estimated by fiber tracking are

TABLE 2

*Relationships among distance, MEP response, and motor function in 40 patients with brain tumors**

Distance (cm)†	No. of Patients	MEP Recordings (no. of patients)	Preop Motor Weakness (no. of patients)‡	Intraop Change in Motor Function (no. of patients)§	Postop Motor Function Results (no. of patients)‖
0–1	20	positive (18)	present (3)		
			upper, Grade 4/5	improved to Grade 4+/5	improved to Grade 5/5
			upper, Grade 4/5	improved to Grade 4+/5	improved to Grade 5/5
			lower, Grade 4/5	no change	improved to Grade 5/5
			none (15)	no change (8), worsened (2)	no deficits (15)
		negative (2)	none (2)	no change (2)	no deficits (2)
1–2	15	positive (3)	none (3)	no change (3)	no deficits (3)
		negative (12)	present (1)		
			upper, Grade 4/5	no change	improved to Grade 5/5
			none (11)	no change (6)	SMA syndrome (2), no deficits (9)
2–3	5	positive (0)	NA	NA	NA
		negative (5)	present (1)		
			upper, Grade 4/5	no change	improved to Grade 5/5
			none (4)	no change (2)	no deficits (4)

* NA = not available; SMA = supplementary motor area.
† Distance between the electrically stimulated white matter and the pyramidal tracts on intraoperative neuronavigation.
‡ Motor function graded according to the Dejong scale.
§ Intraoperative change in motor function is the change in clinical symptoms during awake surgery (in 28 patients) caused by tumor resection, not by electrical stimulation.
‖ Postoperative motor function was compared with preoperative motor function on the 2nd day after the operation.

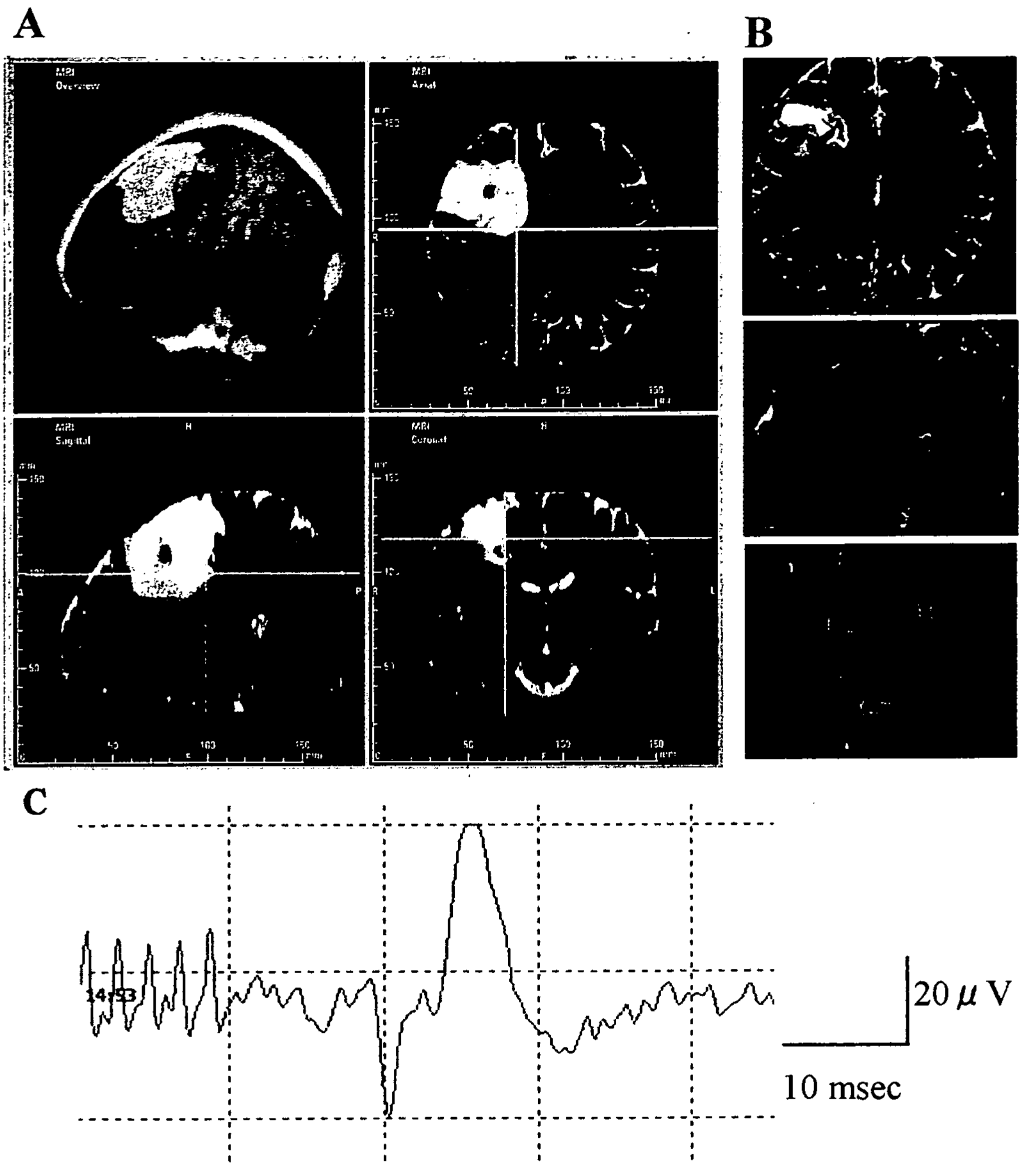

FIG. 1. Subcortical MEPs elicited intraoperatively in a 36-year-old woman with a right frontal diffuse astrocytoma. Her neurological examination was normal preoperatively. A: Intraoperative T_2-weighted MR images showing a hyperintense area (yellow area in *upper left panel*) close to the pyramidal tract identified by fiber tracking (green). During the removal of the tumor, subcortical stimulation elicited MEPs at the bottom of the tumor (intersection of *yellow lines*) 8 mm from the edge of the estimated pyramidal tract. No further removal was performed to avoid causing neurological deficits. B: Postoperative MR images demonstrating that the pyramidal tracts identified by fiber tracking (red) are preserved. C: A typical waveform of MEP response elicited from the left biceps muscle by subcortical stimulation during tumor removal.

known to be caused by low signal-to-noise ratios, the selection of the seed ROIs, the setting of thresholds for fractional anisotropy, the algorithm used in the procedure, or the effects of crossing fibers.[2,4,18] Intraoperative brain shift during surgery should also be considered.[28] In addition to the technical factors mentioned, other factors such as preoperative motor weakness and tumor-related edema can also affect the results of fiber tracking and MEP responses.[16] Additionally, MEP responses are affected by the condition of electrical stimulation;[13] the type of electrodes;[22] and errors in electrical stimulation due to current spread, electrical conductivity, and resistance.[3,11,27,29] These possible errors in the results of MEP recordings may cause postoperative motor deficits following resection of subcortical lesions near the pyramidal tract.[3,8]

Taking these limitations into consideration, complementary use of fiber tracking and subcortical MEPs in the present study offers clinical anatomical–functional information that aids in the preservation of pyramidal tracts. Combined use of these two methods in the present study has shown better surgical outcome in the preservation of motor function than outcomes repeated following MEP monitoring alone[3,8,15] or fiber tracking alone.[1,32] From the neurooncological point of view, subcortical electrical mapping has significantly improved the survival rate of patients undergoing low-grade glioma resections.[8] We believe that combined functional neuronavigation and subcortical electrical stimulation during removal of nonmalignant gliomas will contribute to further improvement of the survival rate and maintenance of a high quality of life.

Because intraoperative MR imaging frequently cannot be performed during tumor resection, evaluation of the distance between the site of resection and the pyramidal tracts on intraoperative neuronavigation would be important for determining the optimal time to apply subcortical stimulation. During the removal of tumors located approximately 1 cm from the pyramidal tracts in the course of neuronavigation, repetitive subcortical electrical stimulation should be applied. The presence of subcortical MEPs during resection of a tumor is an important warning sign of the occurrence of permanent motor weakness, and therefore further resection after obtaining the first MEP response should be avoided.[15,16] Alternatively, lesions could be removed without injury to the pyramidal tracts if the estimated fibers were more than 2 cm away on intraoperative neuronavigation. To clarify the critical distance between the subcortex to be electrically stimulated and the estimated pyramidal tracts, further studies with DT image processing during the course of surgery with the use of intraoperative MR imaging are needed.[24] In addition to its use in subcortical mapping of the pyramidal tracts, MEP monitoring using cortical or transcranial electrical stimulation should also be considered as a way to preserve motor function.[17,23,32,33]

Conclusions

In 40 patients with brain tumors located near the pyramidal tracts, MEPs were elicited from the subcortex in 18 of 20 patients when the distance between the stimulated subcortex and the estimated pyramidal tracts on tractography-integrated intraoperative neuronavigation was within 1 cm. In the other 20 patients, with distances greater than 1 cm between the stimulated subcortex and the estimated pyramidal tracts, MEPs were elicited in only three patients. During removal of tumors located within 1 cm from the pyramidal tracts on functional neuronavigation, subcortical electrical stimulation should be applied to preserve motor function.

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脳腫瘍の診断

渋井壮一郎*

はじめに

「頭痛があれば脳腫瘍を疑う」というのは間違いではない．しかしながら，頭痛を経験したことのない人はほとんどいないといえるが，脳腫瘍の発生頻度は10万人に12～14人程度であり，およそ8,000人に1人というわずかな人数である．確率としてはかなり低いが，脳腫瘍の診断はまず「その存在を疑う」ことから始まる．

症　状

脳腫瘍の症状は，頭蓋内圧亢進症状と巣症状とに分けられる．前者は頭蓋骨という閉鎖空間に異物があることで起こる症状である．良性腫瘍のようにゆっくりと大きくなる腫瘍の場合は，脳自体の変形や脳脊髄液腔の縮小などにより，頭蓋内圧は上がらず，その結果，直径が5cmを越えるような大きな腫瘍でも頭痛や嘔気を生じないこともある．一方，悪性腫瘍では増大する速度が速く，さらに周囲に広範な脳浮腫を伴うことが多いため，小さな腫瘍でも頭痛で発症することも珍しくない．これに対し，巣症状は腫瘍の占める部位による症状である．脳は，機能局在がはっきりしており，前頭葉と頭頂葉の境界をなす中心溝のすぐ前の障害では反対側の運動麻痺，中心溝の後の障害では反対側の感覚障害，後頭葉では，反対側の視野障害(同名半盲)，優位半球(多くは左側)前頭葉では運動性失語(理解はできるが発語が困難)，側頭葉では感覚性失語(言語理解不能)を来たす．脳腫瘍ではこれらの症状が数週間あるいは数ヵ月かかって徐々に進行するのが特徴であるが，痙攣や腫瘍内出血を伴い，急性発症する場合もあるため注意を要する．

疫　学

原発性脳腫瘍の発生原因は不明である．神経線維腫症，ヒッペル・リンドウ病，結節性硬化症など遺伝的素因がわかっているものもあるが，大半の原発性脳腫瘍については，環境的素因を含め，因果関係が証明されているものはない．脳腫瘍全国統計による脳腫瘍の組織別頻度を表1に示す．最も多いのが神経膠腫(グリオーマ)，次に髄膜腫，下垂体腺腫，神経鞘腫，頭蓋咽頭腫などの良性腫瘍が続く．近年の特徴として，髄膜腫や下垂体腫瘍が増加の傾向にあり，グリーマの比率は減少していること，中枢神経原発の悪性リンパ腫が急激に増加していることなどがあげられる．

画像診断

脳腫瘍の確定診断を得るためには，摘出した腫瘍に対する組織診断である．通常のHE(ヘマトキシリン・エオジン)染色で大半の診断は可能であるが，免疫組織化学的染色を追加することで，細分類も可能になる．さらに最近では遺伝子情報も診断に応用されるようになっている．しかしながら，臨床の場では，治療方針を立てる意味でも術前の診断が必要であり，実際にはかなりの腫瘍が画像から組織診断を推測することが可能である．

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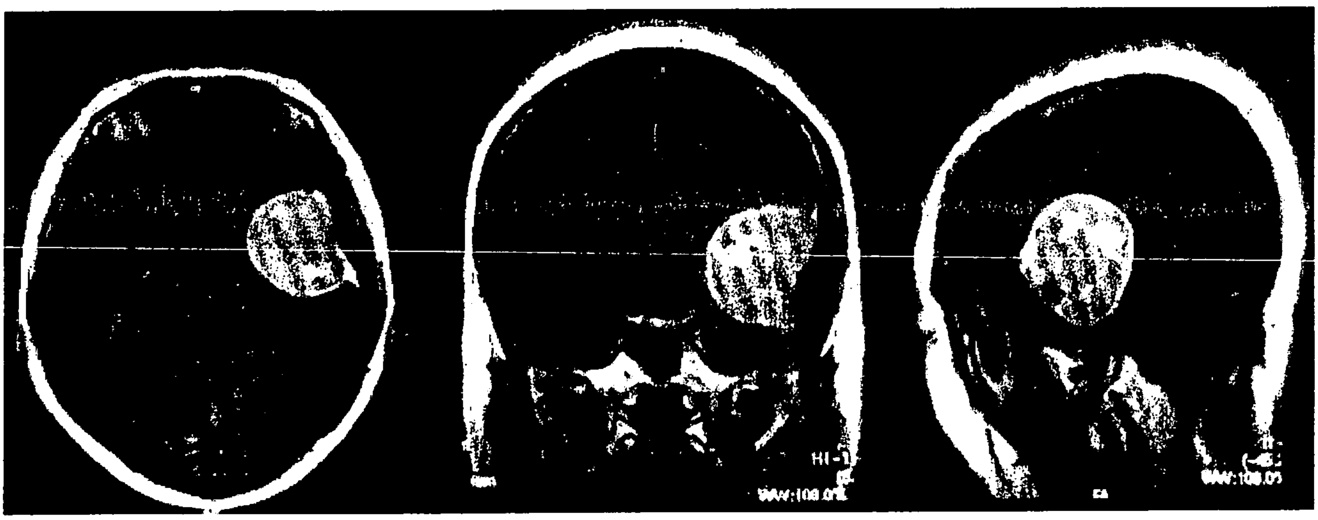
▶表1　脳腫瘍全国統計による原発性脳腫瘍の頻度(1991－1996年登録症例)

	全例	年齢(歳)		
		<15	15–69	>70
神経膠腫	27.3%	57.7%	24.3%	26.9%
髄膜腫	26.2	2.0	26.2	42.3
下垂体腺腫	15.2	1.9	17.2	10.1
神経鞘腫	10.4	1.1	11.8	7.1
頭蓋咽頭腫	3.5	9.0	3.3	1.6
悪性リンパ腫	2.9	0.4	2.6	6.7
血管芽腫	1.7	0.4	2.0	1.0
類表皮嚢胞・類皮嚢胞	1.6	1.6	1.7	0.5
胚細胞腫	2.8	15.4	2.0	0.0
その他	8.4	10.5	8.9	3.8
合　計	100.0 (n＝51,818)	100.0 (n＝4,070)	100.0 (n＝41,653)	100.0 (n＝6,095)

(脳腫瘍全国統計委員会：Neuro Med Chir 43(suppl), 2003)



▲図1　髄膜腫のMRI T1強調画像(ガドリニウム造影)

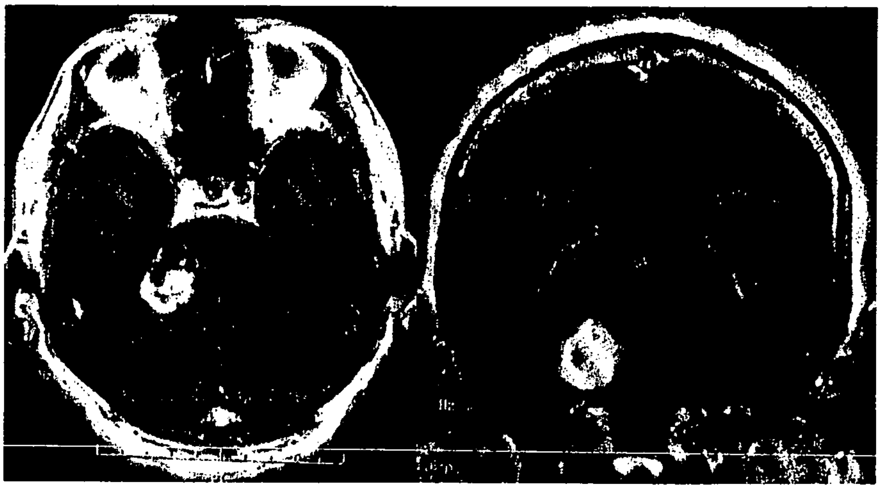
髄膜腫(図1)

髄膜(硬膜，クモ膜，軟膜)より発生するため，通常は脳表に見られる．良性腫瘍であり，MRIでは境界鮮明で，造影剤(ガドリニウム)にて強く造影される．男女比1：2.7で女性に多い．好発部位として，傍矢状部，大脳鎌，大脳半球円蓋部，蝶形骨縁，嗅窩，鞍結節部などがある．全摘により治癒するが，部位により摘出が困難な場合はガンマナイフ治療も行われる．

下垂体腺腫(図2)

脳下垂体より発生する良性腫瘍で，ホルモン非分泌性腫瘍とホルモン分泌性腫瘍(プロラクチン，成長ホルモン，副腎皮質刺激ホルモン，甲状腺刺激ホルモン，卵胞ホルモン，黄体ホルモン)に分けられる．前者はホルモンの分泌障害，後者は分泌過多による症状を呈する．脳下垂体の直上は視交叉部にあたり，腫瘍が上方に進展するに従い，視力・視野障害を来たす．典型的には両耳側半盲(左右とも外側半分の視野欠損)を呈する．治療として，上歯肉を切

◀図 2　下垂体腺腫の MRI



◀図 3　聴神経腫瘍(神経鞘腫)の MRI

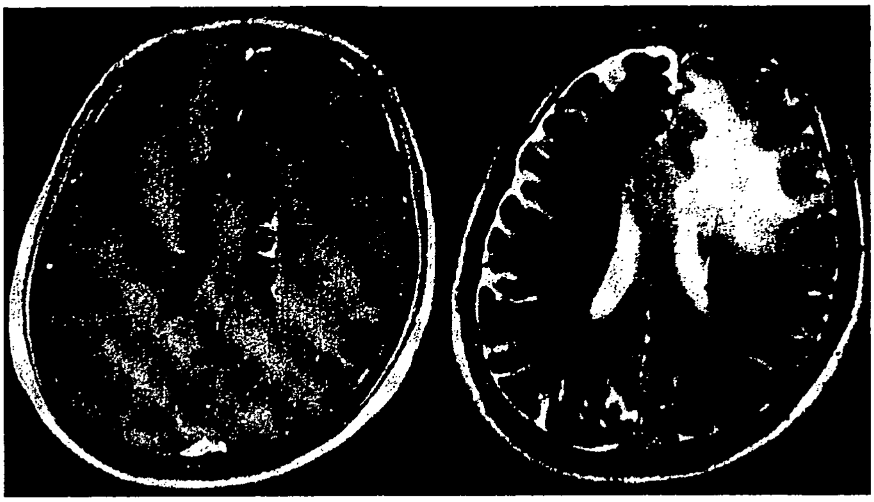
開し経蝶形骨的な手術が行われることが多いが，最近は内視鏡を用いた経鼻的手術も行われている．残存腫瘍に対しては放射線治療も行われる．プロラクチン産生性の腫瘍にはブロモクリプチンやカベルゴリンが著効する．

神経鞘腫(図 3)

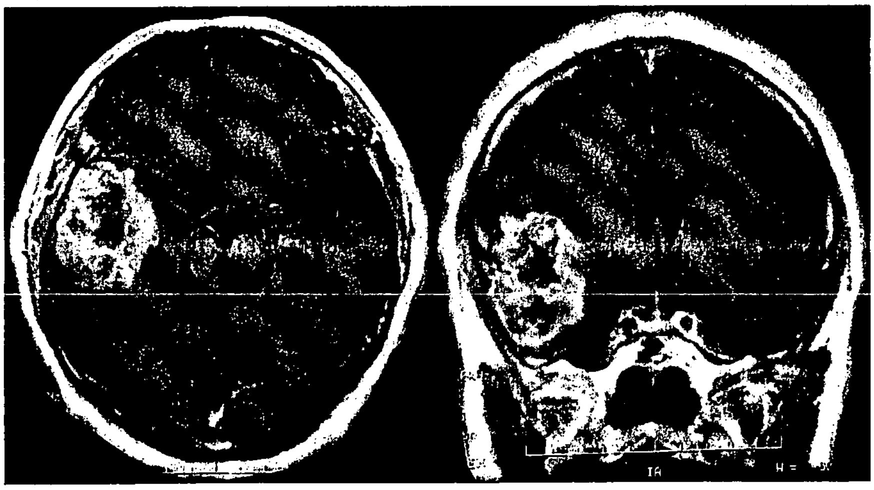
頭蓋内神経鞘腫の大半は，小脳橋角部に発生する聴神経腫瘍である．ガドリニウムにて造影される境界鮮明な腫瘍で，嚢胞を形成することもある．聴神経を構成する前庭神経側から発生することが多いので，かなり大きな腫瘍でも聴力が残っていることがある．その他，三叉神経，頸静脈孔(舌咽・迷走・副神経)，顔面神経にも見られる．治療としては手術が主体であるが，直径 3 cm 以下の腫瘍に対してはガンマナイフも用いられている．治療に伴う合併症として，聴神経腫瘍では顔面神経麻痺，頸静脈孔腫瘍では，嗄声・嚥下障害などが問題になる．特殊型として神経線維腫症に伴う両側聴神経腫瘍がある．

神経膠腫(グリオーマ)

脳実質内のグリア細胞から発生する腫瘍で，星細胞腫が80％程度を占める．星細胞腫は悪性度により grade 1 から 4 までに分類されており，grade 1 は毛様細胞性星細胞腫，grade 2 はびまん性星細胞腫，grade 3 は退形成性星細胞腫，grade 4 は膠芽腫と呼ばれ，grade 1 以外は悪性腫瘍の範疇に入る．Grade 1 は小児の小脳に発生することが多いが，その他は成人が主体である．Grade 2 は MRI の T1 強調画像では黒く，T2 および FLAIR 法にて白く描出され，造影剤による増強が少ない(図 4)．これに対し，



▶図 4　びまん性星細胞腫
左：造影 MRI T1 強調画像，右：T2 強調画像



▶図 5　膠芽腫の MRI

grade 3 および 4 は，造影剤に増強されることが多い(図 5)．Grade 3, 4 に対しては，手術，放射線，化学療法を組み合わせた治療が行われているが，前者の 5 年生存率は 23%，後者は 7%程度である．最も悪性度の高い膠芽腫でも，手術的に摘出できたものの生存率が高いため，可能な限り摘出を行い，腫瘍の周囲の脳浮腫を含めた領域に 50～60 Gy の放射線照射が行われる．この際，通常は化学療法剤を併用する．

転移性脳腫瘍(図 6)

転移性脳腫瘍は，がん患者の 20～40%にみられるといわれ，原発性脳腫瘍の 10 倍程度発生するとされている．原発がんとして最も多いのが肺がん(52%)，続いて乳がん(9%)，大腸がん(9%)，腎がん(5%)，胃がん(5%)があげられる．半数以上は多発である．転移性脳腫瘍に対する治療は一様でない．原発巣は比較的よくコントロールされており，6 ヵ月程度の生命予後が期待され，直径 3 cm を越える大きな単発性腫瘍に対しては積極的に手術を行い，術後放射線治療を行う．小さな腫瘍，多発性腫瘍については放射線治療が優先される．通常の放射線以外に，最近ではガンマナイフやリニアックによる定位放射線治療が取り入れられている．転移性脳腫瘍は強い脳浮腫により，比較的急激に神経症状が進行するが，あくまで全身疾患の一部であることを念頭に置き，治療にあたる必要がある．

▲図 6　肺原発多発性脳転移の MRI

おわりに

最近は，国内のどの医療機関にも CT や MRI の設備があり，非侵襲性の検査ができるようになった．その結果，症状の軽微なうちに腫瘍が発見されることが多くなっている．脳腫瘍の診断の第一歩は「疑う」ことであり，実際にうつ病とか加齢に伴う記銘力障害として見過ごされている場合も少なくないので注意を要する．

●文　献

1)　脳腫瘍全国統計委員会：Brain Tumor Registry of Japan. Neurol Med Chir 43(suppl), 2003

脳腫瘍の放射線治療・化学療法

渋井壮一郎*

はじめに

悪性脳腫瘍は浸潤性に発育するため，手術による摘出のみでは通常再発を来たす．そこで，術後の放射線治療が行われるが，その効果を高めるため化学療法が併用されることが多い．とくに悪性神経膠腫(グリオーマ)では，ニトロソウレア系の抗がん剤との併用が多く，化学放射線治療としてその効果が評価される．

標準治療

標準治療とは，科学的証拠(エビデンス)に裏付けされ，現時点で最も治療効果の期待できる治療と定義される．本来，どの施設においても標準治療がなされるべきであるが，悪性グリオーマについては，絶対的効果の期待できる薬剤がなく，各施設でまちまちな治療が行われているのが現状である．標準治療を構築していくためには，一定の基準に従った臨床試験が必要である．とくに大規模なランダム化比較試験はエビデンスのレベルが高く，信頼性の高い結果を導き出すことができる(表1)．ランダム化比較試験は第Ⅲ相試験とも言われ，従来の標準治療に対し，有効性の期待できる新治療の効果を比較するものである．通常は，第1次の評価項目(エンドポイント)として生存率あるいは生存期間が選ばれ，両者を統計的に比較する．第2次の評価項目としては奏効率(CTやMRIでの縮小率)や有害事象発生率などが選ばれる．両者の比較の結果，統計的に優っているものが次の標準治療として残ることになる．ただし，エンドポイントのわずかな差から有意差を証明するには，多くの症例数が必要となり，多施設共同の臨床試験が必須となる．

▼表1　エビデンスレベルと推奨グレード(米国臨床腫瘍学会：ASCO)

エビデンスレベル
Ⅰ．多数の良質比較試験のメタアナリシス，大規模無作為化比較試験
Ⅱ．1つ以上の良質の実験的研究，小規模無作為化比較試験
Ⅲ．良質の準実験的研究(非無作為化，コホートなど)
Ⅳ．よいデザインの非実験的比較試験，症例研究
Ⅴ．症例報告
推　奨　度
A．Level Ⅰ，または複数のLevel Ⅱ，Ⅲ，Ⅳの結果が一致(強く勧められる)
B．Level Ⅱ，Ⅲ，Ⅳの結果が一致(行うよう勧められる)
C．Level Ⅱ，Ⅲ，Ⅳの結果が不一致(勧める根拠がない)
D．Evidence なし(行わないよう勧められる)

悪性グリオーマ治療のエビデンス

欧米では，1970年代後半より，大規模な臨床試験が実施されており，悪性グリオーマの治療に関するエビデンスが確立してきたといえる．その結果，放射線単独照射において，45 Gyより60 Gyまで徐々に照射量を上げるに従い，平均生存期間が統計的に有意に延長し，さらに，ニトロソウレア系抗がん剤のBCNU(カルムスチン)を併用するこ

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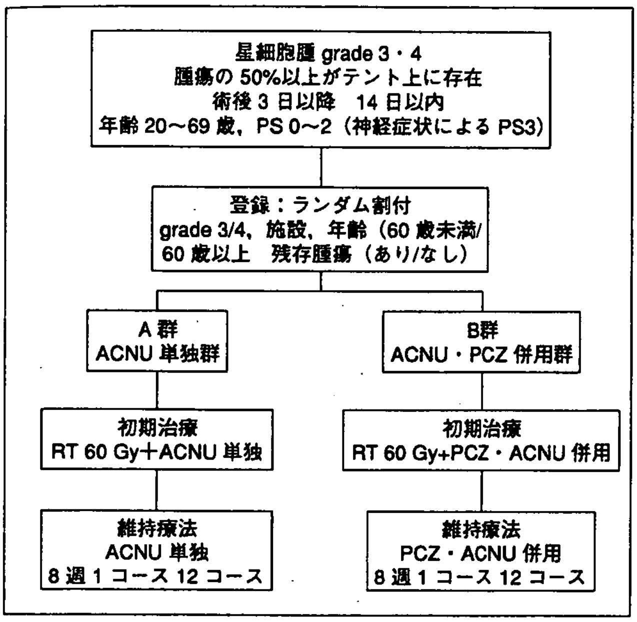

▲図 1　星細胞腫 grade 3–4 に対する JCOG 臨床試験のシェーマ

とで，いっそうその効果が高まることが証明された．この試験を含め 12 のランダム化臨床試験の結果をまとめた報告でも，ニトロソウレア系抗がん剤を併用することで，放射線単独治療に比べ，1 年生存で 6％，2 年生存で 5％の上昇が示され，放射線＋ニトロソウレアが標準治療とされるようになった．化学療法剤としては BCNU 以来，いろいろな薬剤が用いられてきたが，それ以上の効果を示すものがなかった．国内では，放射線単独治療と放射線＋ACNU（ニムスチン）の効果を比較した高倉らの報告が唯一のエビデンスといわれるものであるが，集められた症例数の問題もあり，奏効率において後者が優ったものの，生存率に有意な差が認められなかった．その後，国内での大規模な臨床試験結果の発表はないまま今日に至っているが，現在，日本臨床腫瘍研究グループ（JCOG）の脳腫瘍グループが，国内での標準治療を確立することを目的として，放射線＋ACNU と放射線＋ACNU＋プロカルバジンの第Ⅱ/Ⅲ相試験を行っている．これは，ACNU に対する耐性機構のひとつである O6-methylguanine DNA-methyltransferase (MGMT) という酵素をプロカルバジンが低下させるということを利用し，これを ACNU 投与より 1 週間前から開始する方法と従来の ACNU 単独による化学放射線治療を比較するものである（図 1）．

テモゾロミドによる治療

2005 年に，ヨーロッパとカナダの共同研究グループ (EORTC/NCIC) から今後の悪性グリオーマ治療の方向付けをする報告がなされた．これは，膠芽腫に対し，経口抗がん剤テモゾロミドを併用した放射線治療と放射線単独治療との効果を比較したランダム化試験であるが，おのおの 280 例を超える登録数による生存期間中央値は，放射線単独が 12.1 ヵ月であったのに対し，テモゾロミド併用群では 14.6 ヵ月となり，2 年生存率も前者が 10.4％，後者が 26.5％と，膠芽腫に対する治療としては，初めて放射線単独を有意に上回ったというものである（図 2）．この報告により，欧米での悪性グリオーマに対する標準治療はテモゾロミドとなり，次の段階として，その投与方法あるいは，他の薬剤との組み合わせの工夫が始まっている．国内でも 2006（平成 18）年 9 月に保険診療での使用が可能になり，いっせいに使われるようになった．一般的な使用方法は，腫瘍摘出後，放射線治療と同時に 1 日 1 回空腹時に 75 mg/m² のテモゾロミドを開始し，6 週間の放射線治療期間中服用を継続する．放射線治療終了後は，4 週間後に 1 日 150 mg/m² を 5 日間服用し 23 日間休薬する．その後は，有害事象の程度に応じた増量基準，減量基準に従い，28 日ごとに 5 日間服用する治療を 6 回繰り返す（図 3）．テモゾロミドは，経口投与によって速やかに吸収され，生理的 pH で加水分解されて抗腫瘍効果を発揮するため，人種差もほとんどないといわれている薬剤で，しかも脳脊髄液への移行も優れていると報告されている．さらに，化学療法剤の使用においての重要な副作用である骨髄抑制が軽度であり，治療が予定通りに実施できる利点もある．もちろん，副作用が全くないわけではなく，骨髄抑制とくにリンパ球減少が半数例に認められ，それも誘因のひとつと考えられるカリニ肺炎例が報告されており，その予防対策が必要である．

放射線治療

悪性グリオーマに対する放射線治療は，通常，化学療法剤との併用で行われる．かつての欧米の臨床試験では全脳