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Identification of the Pyramidal Tract by Neuronavigation Based on Intraoperative Diffusion-Weighted Imaging Combined with Subcortical Stimulation

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Key Words

Neuronavigation · Brain shift · Intraoperative magnetic resonance imaging · Subcortical stimulation · Pyramidal tract · Diffusion-weighted imaging · Functional mapping · Fiber tracking

Abstract

Background/Aims: To identify the pyramidal tract by neuronavigation based on intraoperative diffusion-weighted imaging (iDWI) combined with subcortical stimulation. ***Methods:*** Seven patients with brain tumors near the deep white matter underwent resection surgery using neuronavigation based on iDWI to visualize white matter bundles. Subcortical electrical stimulation was performed and electromyography was measured at the extremities when surgical manipulation came near the position corresponding to the depicted bundle. We validated the bundle depicted on iDWI by considering the responses to subcortical stimulation and the distance between the stimulation site and the depicted bundle. ***Results:*** Positive motor-evoked potentials were detected in 5 of 7 patients (8 stimulations) and the distance from the stimulation site to the depicted bundle was 0–4.7 mm (mean ± SD, 1.4 ± 2.1 mm). Negative (no) responses were obtained in all patients when the distance was more than 5 mm. The neuronavigation system had an average error of 0.79 ± 0.25 mm and a maximum error of 2.0 mm (n = 16). ***Conclusion:*** Neuronavigation based on iDWI combined with subcortical stimulation allowed surgeons to identify the pyramidal tract and avoid inadvertent injury. Our findings demonstrate that the white matter bundles depicted by iDWI can contain the pyramidal tract.

Introduction

For resection surgery of brain tumors adjacent to deep white matter, both maximal resection of the lesions and the protection of functional tissues are crucially important [1, 2]. Subcortical mapping, stimulating white matter directly and monitoring neural response, is the most reliable method to localize functionally important white matter bundles such as the pyramidal tract. However, subcortical mapping cannot demonstrate the distance and direction to the tract, although it can indicate if the tract is near the stimulated position [3, 4]. For visualization of the tract, diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI) techniques for fiber-tracking have been investigated [5–7]. These images have been applied to studies incorporating the identification of functionally important tracts with neuronavigation to

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ensure protection of the tracts [8–11]. Fiber-tracking can differentiate and visualize major fiber tracts [12] and has demonstrated clinical usefulness with good accuracy [10, 11, 13, 14]. However, it cannot always estimate correctly the size of the tract because it cannot depict the tract correctly unless ROIs are set properly [13]. A case has been reported in which the size of the pyramidal tract was underestimated and surgical manipulation guided by neuronavigation caused inadvertent complications [15]. In contrast, DWI visualizes not separate tracts but depicts whole bundles running in a given plane, lowering the possibility of underestimation of the tract's size [5]. DWI is obtained with a motion-probing gradient only to one direction and visualizes the bundles as they do not require postprocessing.

The most direct method for validation of the depicted bundle is to estimate the position of the tract with neuronavigation based on these images and to identify it with subcortical stimulation [11, 14]. However, during neurosurgical procedures, brain displacement and deformation caused by the surgical manipulation, known as brain shift, has significant effects on the accuracy of neuronavigation [16–18]. Therefore, validation by subcortical mapping with updating of the navigation image by intraoperative imaging should overcome these problems; however, this has not been reported by other groups to our knowledge [19, 30].

We have developed a neuronavigation system based on intraoperative DWI (iDWI) to preserve the important tracts during neurosurgical procedures [20, 21]. The system minimizes the displacement between the tract image and the real position due to the surgical procedure by incorporating intraoperative DWI using intraoperative MRI, resulting in more precise navigation. It is also expected that the combination of iDWI with subcortical stimulation will allow accurate identification of the tract, resulting in the protection of the patient's motor function while maximizing tumor resection.

The purpose of this study was to identify the white matter bundle containing the pyramidal tract by neuronavigation based on iDWI combined with subcortical stimulation.

For resection surgery of brain tumors in the area of deep white matter, neuronavigation based on iDWI combined with subcortical mapping was performed. Intraoperative imaging corrected the effect of brain shift and DWI was used to avoid underestimation of the tract size. The accuracy of the iDWI navigation system was validated with subcortical mapping.

Materials and Methods

Patient Population

Seven patients with brain tumors near the deep white matter (2 males, 5 females; 18 to 68, 44 ± 17.5 years) gave written informed consent after a full explanation of surgery incorporating intraoperative MRI. Histopathological examination showed the tumors to be grade III, n = 2 (anaplastic astrocytoma and anaplastic oligodendroglioma) and grade IV, n = 5 (glioblastoma) on the World Health Organization (WHO) system. Institutional authorities gave ethical approval for the intraoperative MRI.

Intraoperative MR Imaging

We performed intraoperative imaging using a 0.3-T vertical field MR scanner (AIRIS II®, Hitachi Medical Co., Japan), installed in an operating theater, before and after tumor resection after craniotomy for neuronavigation [17]. A head-holder integrated with a radiofrequency receiver coil was used [20, 21]. Surgical procedures were performed 1.5 m away from the MR scanner and the surgical table with the patient was moved to the scanner for MR imaging.

Intraoperative imaging included positioning, T_2-weighted imaging, T_1-weighted imaging, shimming, DWI. TR/TE values were 27/10 ms for T_1-weighted imaging and 1,000/140 ms for T_2-weighted imaging. DWI was obtained with a peripheral gated multi-shot spin-echo DW echo-planar imaging sequence, TE, 111.1 ms; matrix size, 100 × 92; field of view, 230 mm; slice thickness, 8 mm; slice number, 18; b value, 700 s/mm^2. Delay was set at 300 ms to avoid artifacts due to pulsation [22]. Coronal sections were acquired with a motion probing gradient applied in the anterior-to-posterior direction. Interleaved scanning was performed three times to avoid interference between slices. The intraoperative imaging time was about 25 min, including 10 min for DWI.

Tract Navigation

MR images were DICOM-transferred to a navigation system (PRS navi, Toshiba Co., Tokyo, Japan) and displayed [23]. To provide registration between the navigation coordinates and the spatial coordinates, the surgeons fixed four markers (ALCARE Co., Ltd., Tokyo, Japan) on the skull around surgical field using a pointer device with optical reflection spheres and located them with a positioning system. For visualization of the pyramidal tract, coronal DWI was displayed on the navigation screen in addition to T_1/T_2-weighted images with three sections through the tip of the pointer device [19]. Surgeons were aware of the spatial relationship between the manipulated site and the tumor and performed resection surgery using a microscope. In the vicinity of the pyramidal tract, surgeons referred to iDWI to watch the spatial relationship between the manipulated site and the tract. When motor-evoked potentials (MEPs) were detected by subcortical stimulation around the bundle depicted on DWI, the distance from stimulated position to the depicted bundle was measured by iDWI navigation.

Neurophysiological Monitoring

For neurophysiological monitoring, MEPs and sensory-evoked potentials (SEPs) were obtained during surgery. MEPs were monitored transcranially using a MultiPulse Cortical Stimulator D185 (Digitimer Ltd., Hertfordshire, UK) and transcortically for cortical mapping. Electrode locations on the scalp were

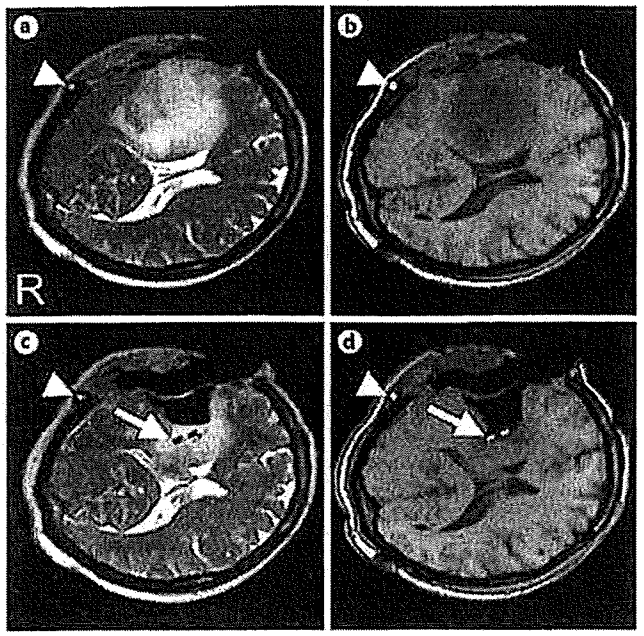

Fig. 1. Intraoperative MR axial images of a 37-year-old female with an anaplastic astrocytoma. T_2- and T_1-weighted images (**a**, **b**) before and (**c**, **d**) after tumor resection. The separate regions in the medial cavity with a high signal in the T_1-weighted image and a low signal in the T_2-weighted image (arrows) were part of doughnut-shaped marker put on the stimulation position for MEPs of the left lower extremity. The small circle with a high signal (arrowheads) in the T_1-weighted images and an iso-signal (arrowheads) in the T_2-weighted images was a fiducial marker.

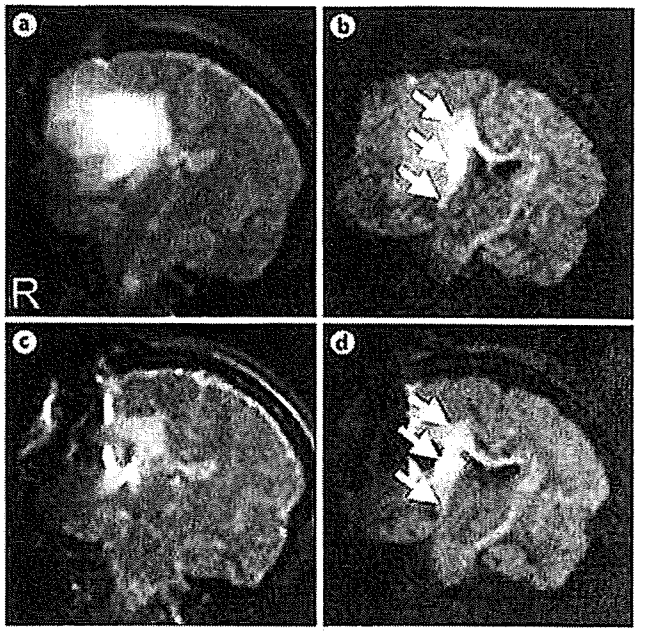

Fig. 2. Intraoperative MR coronal images of a 37-year-old female with an anaplastic astrocytoma. T_2-weighted and DW images (**a**, **b**) before and (**c**, **d**) after tumor resection. DW images demonstrated that the white matter bundles containing the pyramidal tract (arrows) were displaced in the medial direction by the tumor before resection but moved towards the normal position by up to 6.6 mm after resection. The stimulation position for MEPs of the left lower extremity shown in figure 1b and d corresponds to the position displayed by the central arrow in **d**.

C3–C4 specified by the international 10–20 system. Electromyograms were measured at the thenar muscle, the quadriceps femoris muscle, the anterior tibial muscle and the gastrocnemius muscle on both sides. Stimulation conditions for transcranial MEP were 600 V, 50 μs, n = 5. Subcortical direct electrical stimulation was performed in deep white matter using a Model OCS-1 Ojemann Cortical Stimulator (Radionics, Burlington, Mass., USA) with stimulation currents in the range 4–20 mA. While transcranial or transcortical MEP monitoring was done intermittently during surgery, subcortical MEP was done frequently near the pyramidal tract.

Results

The white matter bundle containing the pyramidal tract was clearly visualized in all 7 patients by iDWI. Intraoperative DWI allowed correction for the effect of brain shift, including the shift of the bundle position caused by the surgical procedure. Navigation based on iDWI allowed surgeons to visualize the spatial relationship between the manipulated site and the bundle. Five patients (eight stimulations) had positive responses of MEPs on subcortical stimulation. The distance of the stimulation site to the depicted bundle was 0–4.7 mm (mean ± SD, 1.4 ± 2.1 mm) on neuronavigation. All patients had negative (no) responses when the distance was more than 5 mm. The neuronavigation system had an average error of 0.79 ± 0.25 mm and a maximum error of 2.0 mm (n = 16).

Patient 1

Patient 1 was a 37-year-old female with an anaplastic astrocytoma, close to the corona radiata, from the right frontal and parietal lobe to the insular cortex. The tumor was displayed with high intensity in T_2-weighted images and with low intensity in T_1-weighted images after craniotomy. The intraoperative imaging showed it was mostly resected (fig. 1). Although the white matter bundle in-

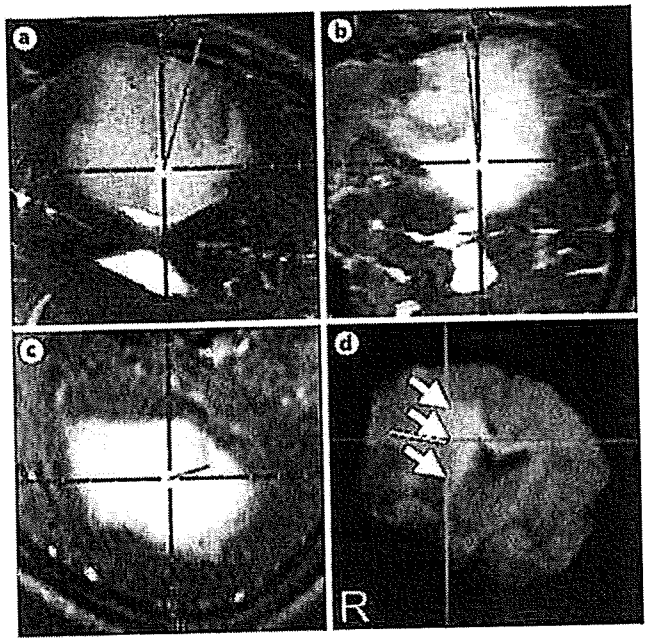

Fig. 3. Navigation images based on intraoperative MR imaging of a 37-year-old female with an anaplastic astrocytoma when MEPs of the left lower extremity were obtained with a 7-mA stimulation current. T_2-weighted images with (**a**) axial section, (**b**) vertical section in the cranio-caudal direction and (**c**) horizontal section and (**d**) coronal DW images. The stimulation site directed by a crosshair cursor is displayed on the lateral boundary of the area (arrows) containing the pyramidal tract with a high signal on the DW images.

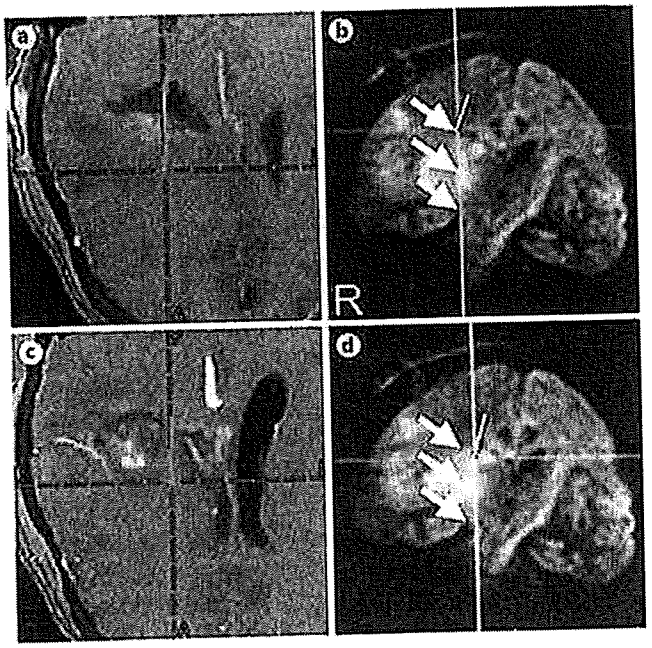

Fig. 4. Navigation images based on intraoperative imaging of a 61-year-old female with a glioblastoma when MEPs of the left lower extremity was obtained with a 6-mA stimulation current. **a** T_2-weighted axial images, and (**b**) DW coronal images after tumor resection. The stimulation site directed by a crosshair cursor is displayed in the lateral boundary of the tract (arrows) on the DW image. **c** T_2-weighted axial image, and **d** DW coronal image after additional resection when MEPs of the left upper and lower extremities were obtained with a 5-mA stimulation current. The stimulation site directed by a crosshair cursor is displayed in the medial boundary of the tract (arrows) on the DW image.

cluding the pyramidal tract was shown on iDWI to be pressed strongly inward by the tumor mass before resection, it moved 6.6 mm towards the normal position after resection (fig. 2). T_2-weighed images could not demonstrate the position of the tract. Surgeons performed tumor resection using neuronavigation based on the T_1-weighted images and were made aware of the distance from the manipulated site to the tract by iDWI navigation near the deep white matter. Subcortical stimulations close to the pyramidal tract depicted on iDWI resulted in positive responses from the corner of the mouth and the left lower extremity (fig. 3) with a 7-mA stimulation current. Both stimulated positions were displayed on the outer boundary of the tract depicted with high intensity on iDWI navigation. The area with a high intensity in the medial cavity on the T_1-weighted images and low intensity on T_2-weighted images was a doughnut-shaped marker put on the stimulated position where a positive response was obtained (fig. 1). Resection was completed with the functional tissue preserved.

Patient 2

Patient 2 was a 61-year-old female with a glioblastoma from the right temporal lobe to the occipital lobe. After tumor resection of the right temporal lobe, the intraoperative MR images demonstrated the complete resection of the tumor and positive motor responses from the left lower extremity were detected after subcortical stimulation with a 6-mA current at the lateral boundary of the pyramidal tract on navigation (fig. 4a, b). After tumor resection from the occipital lobe to the basal ganglia, navigation based on updating images described residual tumor around the basal ganglia, leading to the continuation of resection. Intraoperative DWI navigation showed that the manipulated site was near the pyramidal tract and surgeons performed the resection carefully with subcor-

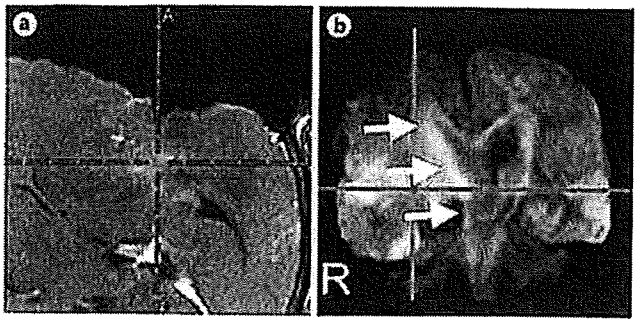

Fig. 5. Navigation images based on intraoperative MR imaging of a 68-year-old female with a glioblastoma when a negative response was obtained after subcortical stimulation. **a** Contrast-enhanced T_1-weighted axial images. **b** DW coronal image. The stimulation site directed by a crosshair cursor was located 18.7 mm away from the tract (arrows) on the DW image.

tical mapping. Positive responses from the left upper and lower extremities were detected with a 5-mA stimulation current at the medial boundary of the pyramidal tract, leading to completion of resection (fig. 4c, d).

Patient 3

Patient 3 was a 68-year-old female with a glioblastoma in the right temporal lobe. After tumor resection, navigation based on intraoperative contrast-enhanced T_1-weighted images demonstrated residual tumor and the surgeon continued resection monitoring transcranial MEPs. No response was detected after subcortical stimulation 18.7 mm away from the pyramidal tract near the thalamus on iDWI navigation.

Discussion

For tumor resection surgery around deep white matter, localization and identification of the pyramidal tract is needed to protect the motor function of the patient. In our study, neuronavigation based on iDWI depicting white matter bundles containing the pyramidal tract allowed surgeons to understand intuitively the spatial relationship between the manipulated site and the position and orientation of the tract. The combination of neuronavigation with subcortical mapping allowed for the identification of the tract, and resulted in the avoidance of inadvertent injury of the tract. Positive motor responses were detected by subcortical stimulation at both the lateral and medial boundary of the tract in patient 2. Although surgeons incorrectly assumed that the manipulated site was well separated from the pyramidal tract in this patient, neuronavigation based on iDWI allowed surgeons to ascertain that the surgery site was close to the medial boundary of the tract, leading to positive responses from left upper and lower extremities after subcortical stimulation. Without the use of iDWI navigation, it is likely that the tract would have been injured in this patient.

Validation of depicted white matter bundles using a combination of neuronavigation with subcortical stimulation should be straightforward. However, displacement between the image and the real position is caused by brain shift during surgery. In this study, intraoperative imaging corrected the effects of brain shift and the combination allowed for image validation. For positive MEPs, the distance from the stimulated site to the tract on the DW image was 0–4.7 mm (1.4 ± 2.1 mm), while negative (no) responses were obtained when the distance was more than 5 mm. The displacement in a right-to-left direction between the DW image and the T_1-weighted image was 1.2 mm in the cortical surface (to the midline) [21] and the accuracy of the navigation system was 0.79 mm, giving a navigation accuracy of about 2 mm with intraoperative DW imaging. The navigation accuracy with intraoperative DW imaging was estimated like this instead of actual measurement [24] because the DW imaging did not have enough contrast of fiducial marker due to large slice thickness of 8 mm. Electrical stimulation operates over a distance around 5 mm; therefore, although our study had a limited number of cases, we have shown that the tracts depicted by DW imaging can contain the pyramidal tract.

The tract depicted on iDWI was not the pyramidal tract itself, but major white matter bundles in the deep area. With application of the MPG pulse along the anteroposterior direction, the contrasting of the pyramidal tract, which is running craniocaudally, was enhanced due to suppression of the signal of the other white matter tracts, such as superior longitudinal fasciculus, which are running anteroposteriorly. The DWI in our study cannot differentiate each tract. As shown in figure 2b, the tract may not be differentiated in DW images from lesions or edema close to the tract. Multiple DW images with motion probe gradients can differentiate the tract from lesions or edema [5]. For visualization of each tract, fiber-tracking [11–13] and a directional color map [25] based on DT imaging would be useful.

Kamada et al. [11] validated tract depiction using a combination of 1.5T fiber-tracking with subcortical stim-

ulation. Okada et al. [14] combined 3T fiber-tracking with subcortical stimulation. However, it is difficult to determine accurately the tract position using navigation based on preoperative fiber-tracking because the navigation is affected by brain shift in both the deep white matter and the cortex [18]. Evaluation based on intraoperative imaging requires discussion. Kinoshita et al. [15] found displacement between the position of the pyramidal tract determined by fiber-tracking in 1.5-T MR and the position determined by subcortical stimulations giving positive responses and concluded that fiber-tracking cannot estimate accurately the size of the tract. Visualization of the tract using fiber-tracking depends on user-defined processes such as setting of seed ROIs and target ROIs. The combination of iDWI-based navigation with subcortical stimulation is a direct validation because of the correcting of brain shift effects and requiring no postprocessing. There have been trials using 3-T MR for intraoperative imaging, allowing the collection of images with high SNR in short acquisition times [26]. However, EPI for DWI or DTI can cause image distortion due to susceptibility artifacts, leading to positional errors on navigation.

A combination of iDWI with subcortical stimulation can be used to predict the position of the pyramidal tract and identify it for protection of motor function during tumor resection surgery in deep white matter. Intraoperative DWI navigation can display visually the positional relationship between the manipulated site and the tract and call the neurosurgeon's attention to potential problems. Displaying the tract and lesions separated with colors can enhance their visibility [11]. Setting safety margins at a suitable distance around the tract may reduce the risk of injuring the tract [27]. Making a warning beep sound when surgical tools come within the safety margins would be a useful adjunct to prevent inadvertent injury of the tract [28, 29]. Furthermore, the method presented can be used for the validation of tracts depicted on DW images.

Conclusion

In conclusion, we identified the pyramidal tract by combining neuronavigation based on iDWI with subcortical stimulation. The white matter bundles depicted on iDWI can contain the pyramidal tract. The combination of iDWI navigation with subcortical stimulation should be useful in protecting motor function during neurosurgical procedures.

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Shift of the Pyramidal Tract During Resection of the Intraaxial Brain Tumors Estimated by Intraoperative Diffusion-Weighted Imaging

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Abstract

The present study evaluated the shift of the pyramidal tract during resection of 17 proximal intraaxial brain tumors. In each case intraoperative diffusion-weighted (iDW) magnetic resonance imaging with a motion-probing gradient applied in the anteroposterior direction was performed using a scanner with a 0.3 T vertical magnetic field. The position of the white matter bundles containing the pyramidal tract was estimated on the coronal images before and after resection of the neoplasm, and both quantitative and directional evaluation of its displacement was done. In all cases iDW imaging provided visualization of the structure of interest. The magnitude of the pyramidal tract displacement due to removal of the neoplasm varied from 0.5 to 8.7 mm (mean 4.4 ± 2.5 mm) on the lesion side and from 0 to 3.6 mm (mean 1.3 ± 1.1 mm) on the normal side ($p < 0.001$). Tumor location in regards to the pyramidal tract was significantly associated with the direction of the pyramidal tract displacement ($p < 0.05$). Outward shift occurred in 10 out of 13 cases of the lateral neoplasms, whereas in all 4 supromedial tumors inward shift was marked. In conclusion, the direction of the pyramidal tract displacement during resection of the proximal intraaxial brain tumors is mainly determined by position of the neoplasm, but can be unpredictable in some cases, which necessitates use of subcortical brain mapping and intraoperative imaging, particularly iDW imaging with updated neuronavigation.

Key words: brain shift, pyramidal tract, functional mapping, diffusion-weighted magnetic resonance imaging, intraoperative magnetic resonance imaging, neuronavigation

Introduction

Identification of the pyramidal tract is extremely important to protect motor function during resection of brain tumor in the proximal structures. Functional mapping using electrical stimulation can identify the nerve fiber locally, but cannot visualize the position and course of the fiber tract.[24,26] Diffusion-weighted (DW)[9] and diffusion tensor (DT) magnetic resonance (MR) imaging[21] can depict the course of the major fiber tracts and are widely used for surgical planning and neurosurgical navigation. However, brain displacement and deformation, known as "brain shift," may cause discrepancies between the image and the true brain position.[5,11,12]

Color-coded fractional anisotropy (FA) is a technique to visualize fiber tracts running in the mediolateral, craniocaudal, and anteroposterior directions as different colors, commonly red, blue, and green. However, the color of each tract can be abnormal in intraoperative color-coded FA, and may appear disorientating because the patient's head is usually fixed facing to the right or left, depending on the position of the lesion. In addition, the visibility of fiber tracking depends on the size and the position of the user-defined seed point,[3] and may not estimate correctly the size of the tract.[8]

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Coronal DW imaging with a motion-probing gradient applied to the anteroposterior direction can display white matter bundles containing the pyramidal tract.[4,9] Such DW imaging does not need post-processing and the visibility of the tract does not depend on user choices.

In the present study intraoperative DW (iDW) MR imaging was used for quantitative and directional evaluation of the displacement of the pyramidal tract during resection of the proximal intraaxial brain tumors.

Materials and Methods

Study was done in 7 male and 10 female patients aged from 18 to 68 years (mean 42.8 ± 15.1 years), who underwent surgery for intraaxial brain tumor located in the vicinity to the pyramidal tract. There were 2 oligodendrogliomas (World Health Organization [WHO] grade II), 5 anaplastic astrocytomas and 2 anaplastic oligodendrogliomas (WHO grade III), 6 glioblastomas (WHO grade IV), metastatic carcinoma and cavernous malformation (one case each). According to the relation of the tumor to the pyramidal tract as was estimated on preoperative imaging all neoplasms were divided into two groups: lateral, located in the temporal lobe, lateral part of the frontal and parietal lobes, insula and putamen (13 cases); and superomedial, located in the posteromedial part of the frontal lobe and medial part of the parietal lobe (4 cases). Use of iDW imaging during surgery for intracranial neoplasms was approved by responsible authorities of the Department of Neurosurgery of the Tokyo Women's Medical University. Before operative procedure all patients were fully informed about nuances of their treatment with the use of intraoperative MR (iMR) imaging and provided a signed consent.

The main principles of the surgical management of parenchymal brain tumors in the Intelligent Operating Theater of the Tokyo Women's Medical University had been provided in details elsewhere.[10] iMR imaging was performed with the use of 0.3 T vertical magnetic field scanner (AIRIS II®; Hitachi Medical Corp., Tokyo), which provides a maximum gradient field of 15 mT/m and through rate of 17.6 T/m/sec.[6] An original radiofrequency receiver coil integrated with a modified Sugita head holder (Head-holder coil; Mizuho Ltd., Tokyo) was used.[17,18] During routine procedure iMR imaging was usually performed at least twice: after craniotomy and completeness of the approach to the tumor and after resection of the neoplasm. If additional removal of the lesion is required iMR imaging investigation was repeated.

In the present study intraoperative imaging protocol included T_2-weighted imaging, T_1-weighted imaging with contrast medium, additional shimming and DW imaging. The latter was done in coronal plane using peripheral-gated multi-shot DW spin-echo echo-planar imaging sequence with echo time 111.1 msec, matrix size 100 × 92, field of view 250 mm, slice thickness 8 mm, slice interval 3 mm, slice number 18, and b-value 700 sec/mm^2. The delay time was set at 300 msec to prevent pulsatile artifacts.[7] A motion-probing gradient was applied in the anteroposterior direction. iDW imaging was performed as three interleaved scans to prevent slice interference. The total scan time was about 25 minutes including 10 minutes for DW imaging.

The quantitative and directional evaluation of the displacement of the white matter bundle containing the pyramidal tract was done by comparison of its position on coronal iDW imaging before and after resection of the neoplasm both on the lesion and normal sides. The maximum displacement between the medial position of the tract contour segmented manually in the direction vertical to the craniocaudal axis from the vertex to the middle of midbrain was measured. To mark the shift of the tract positive and negative values were given if its displacement was directed outward and inward, respectively.

A two-tailed t-test and chi-square test with continuity correction were used for statistical analysis. The level of significance was determined at $p < 0.05$.

Results

In all cases of the present series iDW imaging demonstrated the white matter bundle containing the pyramidal tract both before and after tumor resection (Fig. 1). While image artifacts in the echo-planar sequence caused by brain fixation pins and susceptibility artifacts on the tissue-air interface were not uncommon, those were localized on the brain surface and did not interfere with visualization of the deep white matter structures.

The magnitude of the pyramidal tract displacement due to tumor resection varied from 0.5 to 8.7 mm (mean 4.4 ± 2.5 mm) on the lesion side and from 0 to 3.6 mm (mean 1.3 ± 1.1 mm) on the normal side ($p < 0.001$). On the lesion side the outward and inward displacements of the tract were noted in 10 and 7 cases, respectively. On the normal side the outward and inward displacements of the tract were noted in 9 and 6 cases, respectively, whereas in 2 cases tract displacement was not identified. The range of the shift varied from −8.0 to +8.7 mm on

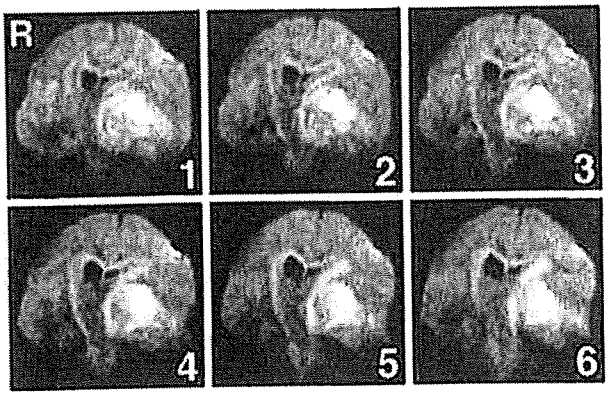

Fig. 1 Serial coronal intraoperative diffusion-weighted magnetic resonance images (from 1 to 6) at 3-mm slice intervals before resection of the left frontotemporal glioblastoma. The white matter bundle containing the pyramidal tract is strongly compressed by the tumor and shifted inwards. The spatial interrelationship between the neoplasm and the tract is clearly demonstrated.

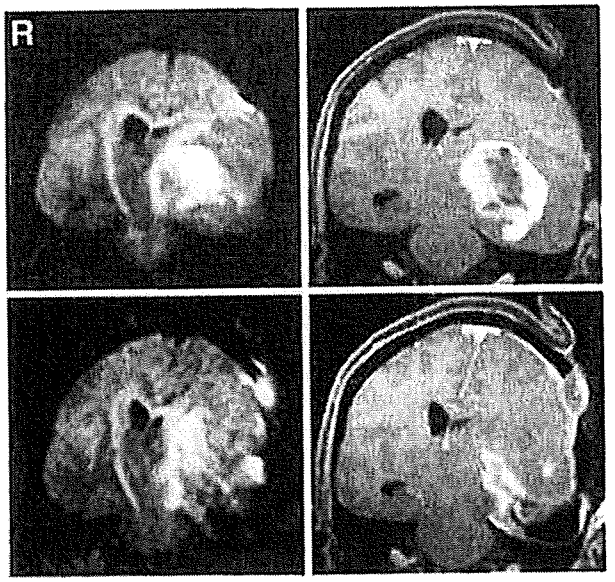

Fig. 2 Coronal intraoperative diffusion-weighted (*left column*) and postcontrast T_1-weighted magnetic resonance images (*right column*) before (*upper row*) and after resection of the left frontotemporal glioblastoma (*lower row*). Removal of the neoplasm was accompanied by outward displacement (maximum 4.8 mm) of the white matter bundle containing the pyramidal tract. Note that T_1-weighted images clearly demonstrate the position and size of the tumor, but not the pyramidal tract.

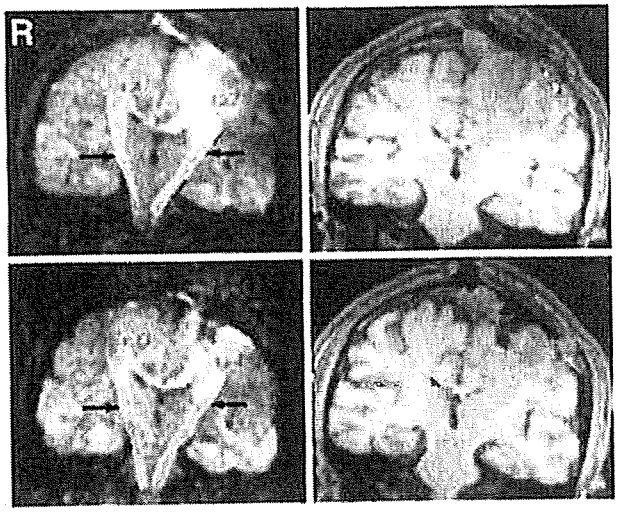

Fig. 3 Coronal intraoperative diffusion-weighted (*left column*) and T_1-weighted magnetic resonance images (*right column*) before (*upper row*) and after resection of the frontal lobe glioblastoma (*lower row*). The white matter bundle containing the pyramidal tract was shifted laterally by the superomedial tumor, whereas removal of the neoplasm was accompanied by its inward displacement (maximum 2.7 mm). The maximum displacement was measured between the medial position of the tract contour (*arrows*) segmented manually on the diffusion-weighted images before and after resection, in the direction vertical to the craniocaudal axis from the vertex to the center of the midbrain. Note that T_1-weighted images demonstrate only hypointense tumor and resection cavity, but not the pyramidal tract.

the lesion side and from −3.0 to +3.6 mm on the normal side.

In the group of lateral neoplasms the magnitude of the pyramidal tract displacement due to tumor resection varied from 1.5 to 8.7 mm (mean 4.8 ± 2.2 mm). Outward tract displacement was marked in 10 out of 13 cases (Fig. 2). The inward shift was observed in 3 cases and was caused either by fenestration of the lateral ventricle, or by anterolateral or posterolateral tumor position in relation to the pyramidal tract. The range of the shift varied from −4.5 to +8.7 mm.

In the group of superomedial neoplasms the magnitude of the pyramidal tract displacement due to tumor resection varied from 0.5 to 8.0 mm (mean 3.3 ± 3.3 mm). In all 4 cases inward shift of the tract was observed (Fig. 3). The range of the shift varied from −8.0 to −0.5 mm. Comparison of two defined

groups of neoplasms did not reveal statistically significant difference of the magnitude of the pyramidal tract displacement due to tumor resection, but its direction was significantly different ($p < 0.05$).

Discussion

The present study showed that iDW imaging with a low field scanner could clearly visualize the white matter bundle containing the pyramidal tract and allow measurement of the displacement during resection surgery. Although visualization of the white matter bundle using iDW imaging was not always enough clear in cases which had edema around the lesions, identification of the bundle and evaluation of the shift was able to be performed. Bello et al. reported that many low grade gliomas can include the tracts inside, which are different from that of high grade gliomas.[1] iDW imaging did not have enough image contrast and resolution to demonstrate if the bundle runs through the lesions. iDW imaging did not depend on the orientation of the patient's head or user-defined processes, in contrast to color-coded FA and fiber tracking with DT imaging.

Our study using DW imaging estimated the shift of the white matter bundles containing the pyramidal tract and not the shift of the tract. Color-coded FA based on DT imaging was previously used to evaluate the white matter bundles.[14,15] These methods are less likely to underestimate the tract size. Fiber tracking would be useful for evaluation of the shift of the tract and the course of the tract,[25] but may underestimate the size of the tract. In either case, validation of the tract depicted on the images is required. Simultaneous confirmation of the tract position using subcortical stimulation and neuronavigation would provide such validation.[2,16] Intraoperative imaging would facilitate correct validation without the effect of brain shift.[19]

White matter bundle shift was previously measured as -8 to $+15$ mm ($+2.7 \pm 6.0$ mm) in 37 cases of glioma surgery and the direction was unpredictable.[14] In our study, outward shift occurred in 10 of 13 cases of lateral lesions and inward shift occurred in all 4 cases of superomedial lesions. Decreased compression caused by the lesion apparently resulted in shift of the tract. Unexpected inward shift for lateral lesions occurred in a case with cerebrospinal fluid leakage from the cerebral ventricle and in two cases in which the lesion compressed the tract from the anterolateral or posterolateral side. Therefore, the direction of tract shift was unpredictable, but mainly depended on the location of the lesion. Localization of the tract based only on preoperative images or surgeon's experience may result in false recognition of the tract. Therefore, identification of the tract using intraoperative imaging and subcortical mapping is essential.

The present study measured a mean displacement of 4.4 mm for the tract shift, which is not negligible during neurosurgery near eloquent regions. Such a shift may affect the accuracy of neuronavigation with fiber tracking acquired preoperatively. The pyramidal tract depicted by preoperative fiber tracking showed a considerable discrepancy with the findings of intraoperative subcortical white matter stimulation, suggesting that the size of the tract was not estimated correctly under pathological conditions.[8] The discrepancy between the apparent and actual positions depends on the resolution and distortion of the DT image,[22] and the procedures of fiber tracking such as setting seed regions of interest.[3] In addition, brain shift increases the positional error during neurosurgery as shown in our study. The direction of tract shift was unexpected in some cases. Therefore, image updating is needed during surgical procedures. The risk of positional error could be reduced by setting safety margins around the depicted tract, which could be displayed in color on the DW images to guide the surgeon.[13,20] Neuronavigation integrated with auditory feedback would be effective to prevent surgical manipulation within the safety margin.[20,23]

In conclusion, comparison of iDW imaging before and after tumor resection demonstrated considerable shift of the white matter bundles containing the pyramidal tract during neurosurgery in the eloquent area. The direction of tract shift mainly depended on the position of the lesion, but was unpredictable in some cases. These findings can be obtained only by iMR imaging and will benefit all neurosurgeons, including those not using such a system. Neuronavigation with intraoperative updating of DW imaging not requiring post-processing has the potential to protect functional areas during surgery to resect deep white matter lesions.

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Commentary

The authors address a matter that is very important and up to date. Intraoperative imaging, in brain tumor surgery, has recently attracted the attention and oriented the work of several surgeons, with the double aim of more radically resecting neoplasms, and of avoiding additional damage to cortical eloquent areas and subcortical functional tracts. Dr. Ozawa and coworkers demonstrate, in this paper, that the pyramidal and other motor tracts shift significantly after resection of the tumors; therefore, as other authors suggest as well, the new more superficial position may expose the tracts to inadvertent surgical damage. One of the most interesting results is that the displacement of the tracts may be unpredictable in some cases, even though in most instances the position of the neoplasm determines the direction of the shift. To resolve this problem, the authors suggest to update the navigation with intraoperative imaging, and this is certainly effective. The other possibility is to couple anatomical mapping with functional neurophysiological monitoring, as it is done in some neurosurgical centers (see for instance Bello et al., Neuroimage 2008, as quoted by the authors). In my opinion, only neurophysiological monitoring is not sufficient to solve the question, but coupled with anatomical MRI mapping may achieve the best results.

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Ozawa and collaborators present magnetic resonance findings in patients with tumors near the pyramidal tract before and after surgical removal of the tumor. They depict the morphological pathway of the pyramidal tract with intraoperative diffusion-weighted imaging techniques using a vertical 0.3 tesla magnetic field scanner. With great diligence the authors analyzed the space occupying effect of the tumor and the subsequent effect of its removal. The images presented are convincing, as they clearly show the change of the displacement before and after surgery. Although we are not told the clinical outcome, this paper undoubtedly is a significant further step in avoiding lesions to functionally highly important structures during tumor surgery. The authors are to be congratulated on their work. Further progress is to be expected from further advancement of imaging prior to and during our surgical procedures.

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Original

Assessment of Effect and Toxicity of Temozolomide Combined with Radiation Therapy for Newly-Diagnosed Glioblastoma in Japan

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Objective: Temozolomide has been used since 1999 in North America and Europe. However, it has been used in Japan for 3 years, resulting in a lack of sufficient efficacy and toxicity data for Japanese. We summarized the result of temozolomide treatment in our institute, focusing on toxicity. **Methods:** The 26 newly-diagnosed glioblastoma patients with concomitant and adjuvant radiation and temozolomide were included. Adverse events, overall survival and prograssion-free survival were assessed. **Results:** The median age was 57 years old and 66% were men. The overall and the progression-free survival were 19.8 months and 10.3 months, respectively. Adverse events of grade 3 and higher were observed in 23% of the patients, if hematologic toxicity was evaluated by leukopenia. Lymphopenia was seen in 35%, resulting in all adverse events seen being 46%. Three had severe gastrointestinal toxicity and four showed mental toxicity. Almost all patients suffered mild constipation (grade 2). There was no incidence of *Pneumocystis* pneumonia. **Conclusion:** Our incidence of adverse events of grade 3 and higher seemed comparable to other reports. Severe gastrointestinal toxicity or mental toxicity was not reported before. Considering racial/ethnic difference of reaction to the drugs, collecting and sharing data from Japanese patients will be necessary.

Key words: brain tumor, toxicities, Japanese, GI bleeding, depression

Introduction

Malignant gliomas in general are considered to have poor prognoses. In particular, the most malignant type, glioblastoma, shows only 12 months of median survival time even with surgical resection, radiation therapy and chemotherapy.

Since the 1970s, a number of chemotherapeutic agents have been introduced to treat malignant gliomas, such as nitrosoureas (lomustine: CCNU, nimustine: ACNU, carmustine wafers: BCNU), carboplatin, cisplatin, etoposide, procarbazine, vincristine and so on. However, therapeutic effects of those agents had been insignificant. After the introduction of those agents, no agent for gliomas was clinically approved for 20 years and finally, an oral alkylating agent, temozolomide (TMZ), was approved in North America and Europe. Then in 2005, it was first proven effective to malignant gliomas in the multi-centered phase III studies by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC)[1].

Subsequently, TMZ was approved for clinical application in Japan in September 2006 for malignant gliomas after clinical trial for recurrent grade III gliomas in Japan and also based on the results of clinical evidences in North America and Europe. At that time, the clinical trials were performed for re-

current patients based on the adjuvant therapeutic protocol by Stupp et al (5 days TMZ on, 23 days off), and patients suffered little toxicity. However, Stupp's concomitant therapeutic protocol for newly diagnosed cases assigned a different dosage; 42 days consecutive administration of TMZ along with concomitant radiation therapy, followed by an adjuvant protocol of 6 courses of 5 days with TMZ on, 23 days without. The whole initial therapy seemed to show stronger toxicity.

We have treated 26 newly-diagnosed Japanese glioblastoma patients with TMZ based on Stupp's protocol and observed adverse events of grade 3 and higher for 23% of the patients. A not insignificant number of patients suffered from severe gastrointestinal (GI) toxicity and/or mood alteration that featured a depressive state. There has been no report on racial/ethnic variation of the toxicity of TMZ and we felt it important to report on toxicities that might to be distinctive to Japanese patients.

Patients and Methods

1. Patients

All the patients, who were newly diagnosed with glioblastoma [World Health Organization (WHO) grade IV astrocytoma] by their surgical specimens or clinical/radiological manifestations in the Tokyo Women's Medical University from September 2006 through March 2008, and who were treated with the standard radiotherapy plus concomitant daily TMZ followed by the adjuvant regimen according to the EORTC/NCIC protocol, were included in this study.

2. Treatment

The patients received temozolomide according to the EORTC/NCIC protocol of concomitant and adjuvant temozolomide: the concomitant chemotherapy consisted of temozolomide at a dose of 75 mg per square meter per day, given 7 days per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 days. After a 4 weeks break, the patients were then to receive adjuvant temozolomide according to the standard 5 days schedule every 28 days. The dose was 150 mg per square meter for the first cycle and was increased to 200 mg per square meter beginning with the second cycle, so long as there were no severe toxic effects.

Radiotherapy consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily 5 days per week (Monday through Friday) over a period of 6 weeks, for a total dose of 60 Gy.

Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist was administered 1 hour before taking TMZ. The patients presented lymphopenia (800/μl and fewer, or 1,000/μl or fewer if corticosteroids were given) was administered prophylaxis against *Pneumocystis* pneumonia with oral trimethoprim-sulfamethoxazole (160 mg trimethoprim per day every other day).

3. Evaluation of toxicity and efficacy

Adverse events during concomitant and adjuvant therapy were retrospectively investigated and evaluated according to the CTCAE Ver.3[2]. The overall survival (OS) and the progression-free survival (PFS) times were calculated by using the Kaplan-Meier methods.

Results

1. Patient Characteristics

There were 26 patients entered in this study. The median age was 57 years old (range 22-71) and 66% were men. Of these 26 patients, 25 were surgically operated on (5 received surgery in other institutes) and one was diagnosed according to clinical and radiological manifestations. Of those who received surgical resection, 16 patients (61%) had total (more than 98% contrast-enhanced area by MRI) resection and 9 (35%) had partial resection (Table 1).

2. Treatment

Of all 26 patients, 25 patients (96%) completed the concomitant therapy without discontinuation. One had to discontinue the therapy because of fever of unknown origin. The median number of the adjuvant courses was 5 (range 0-18). Eight patients (31%) had to discontinue the adjuvant therapy. Of these, 6 showed progression of the disease, one had GI toxicity because of the therapy and one patient voluntarily discontinued (Table 2).

3. Survival and Progression

The median observation time was 11 months.

Table 1 Patient characteristics (n=26)

Age (median, range=57 years, 22-71)		
< 50	9	34%
> 50	17	66%
Sex		
Men	17	66%
Women	9	34%
Karnofsky performance status		
> 80	21	81%
< 80	5	19%
Extent of surgery*		
Total	16	61%
Partial	9	35%
(one patient had no surgery, diagnosed by MRI)		
Use of corticosteroids		
Yes	3	12%
No	23	88%

*Total resection; > 98% contrast-enhanced area by MRI.

Table 2 Adjuvant therapy (n=26)*

Radiation therapy	Median dose given (Gy)=60 (50-60)
Temozolomide (TMZ)**	
Concomitant TMZ (75 mg/m^2, given daily)	
Median days given=42 (27-48)	
Discontinuation=1 patient	
Adjuvant TMZ (150-200 mg/m^2×5 days/28 days in 1 course)	
Median courses given=5 (0-18)	
Discontinuation=8 patients***	

*Numbers in parentheses after median numbers represent ranges.
**15 patients (58%) received prophylaxis for *Pneumocystis carinii* pneumonia.
***6 patients due to progression of the disease, 1 due to toxicity, 1 voluntarily.

Table 3 Adverse events (n=26)

	Number of patients (percent)	
	All	grade > 3
Total (by leukopenia)*	26 (100)	6 (23)
Total (by lymphopenia)**	26 (100)	12 (46)
Hematologic		
Leukopenia	9 (35)	0
Neutropenia	2 (8)	0
Lymphopenia	18 (69)	9 (35)
Anemia	3 (12)	1 (4)
Thrombopenia	1 (4)	0
Gastrointestinal		
Abdominal pain	1 (4)	1 (4)
Constipation	21 (81)	0
Diarrhea	2 (8)	2 (8)
Nausea/vomiting***	3 (12)	0
Mental		
Mood changes	4 (15)	0
General		
Anorexia	9 (35)	0
Fatigue	3 (12)	0
Fever	1 (4)	0
Musculoskeletal		
Myalgia	1 (4)	0
Hepatic		
AST/ALT	6 (23)	1 (4)
γ-GTP	6 (23)	4 (15)
Hypoalbumin	1 (4)	0
Respiratory		
Coughing	3 (12)	0

*Hematologic toxicity was evaluated by total leukocyte loss.
**Lymphopenia was counted as independent ematologic toxicity.
***All patients were on antiemetic prophylaxis with 5-HT antagonist.

The OS was 19.8 months and the PFS was 10.3 months.

4. Safety and Tolerability (Table 3)

Adverse events of grade 3 and higher were observed in 6 (patients (23%), if hematologic toxicity was evaluated by leukopenia.

The number of lymphocytes decreased in all the patients at various levels and grade 3 and higher toxicity was detected in 9 patients (35%). The average decrease of individual patient from the pretreatment level to the nadir was 49%. We administered sulfamethozazole/trimethoprim to 15 patients (58%) in order to prevent *Pneumocystis* pneumonia.

Severe GI adverse events of grade 3 and higher were detected in 2 patients, including one with abdominal pain and hemorrhagic diarrhea and the other with severe non-hemorrhagic diarrhea. For those with diarrhea, stool culture was performed and all negative for clostridium difficile, norovirus and rotavirus. Continuous nausea and loss of appetite was seen in 9 patients (23%). Almost all patients suffered mild constipation (grade 2) and elevated hepatic transaminase (grade 2).

We detected mood changes in 4 patients. All these presented a depressive state. They were diagnosed by psychiatrists and given medication. There was no incidence of *Pneumocystis* pneumonia.

5. A Notable Case

There was one patient who presented severe GI toxicity. The patient was a 37 years old woman who presented no history of GI diseases. She started to present coughing and abdominal pain several days before completion of concomitant therapy (60 Gy radiation and 42 days TMZ). Two days after comple-

tion, she presented severe abdominal pain and repetitive hemorrhagic diarrhea for more than 20 times. She was treated by fasting and hydration for a month and it took 48 days for her to be discharged. At discharge, she was still having soft stool and was on a soft-meal diet and it took 4 months for her to be completely recovered.

Discussion

The comparison of our study vs. Stupp's study (insert reference) is as follows: median age 57 (range 22-71) vs. 56 (19-70); proportion of older patients (> 50 years) 66 vs. 69%; sex (proportion of men) 66 vs. 64%; proportion of patients with good PS 81 (KPS > 80) vs. 86% (PS > 1); proportion with total resection 61 vs. 39%; administration of corticosteroids 12 vs. 67%. The backgrounds were similar except for the extent of surgery and use of corticosteroids[1].

In this study, the OS was 19.8 months and the PFS was 10.3 months. Before TMZ was introduced, we performed ACNU-based chemotherapy and the OS was 16 months and the PFS was 8.5 months[3]. There was no significant difference compared to TMZ-treated cases.

Both were longer than the results of the clinical study by Stupp et al, which reported an OS of 14.6 months and a PFS of 6.9 months[1]. The final report by the EORTC/NCIC in 2009 showed OS of 14.6 months, which was not that longer than the ad interim report[1]. Compared to their report, out result showed much longer OS. The EORTC/NCIC report concluded that the higher the resection rate was, the longer the OS was and our result shows the similar tendency (total resection, which was defined to be the resection of 98% or higher of the Gd-contrast area, was 61% of patients in our institute and 39% for the report of the EORTC/NCIC). One of the reasons that dedicated to the higher resection rate might have been use of 5-ALA in our institute[3].

The incidence of adverse events was 23% in our study, if hematologic toxicity was evaluated by leukopenia, lower than the previous report (28% of the concomitant phase and 37% of the adjuvant phase) (data of the Food and Drug Administration (FDA))[6].

However, if lymphopenia (seen in 35%), was independently evaluated, 46% of the patients showed adverse events of grade 3 and higher. The FDA summarized the EORTC/NCIC study and reported that 37% of the patients experienced adverse events of grade 3 and higher, though this result did not include lymphopenia[6].

There is a report (Stupp, Journal of Clinical Oncology, 2002) in which grade 3 and higher lymphopenia was observed in 79 and 64% of the glioblastoma patients during the concomitant and adjuvant phase, respectively. Of those, 3 patients suffered from infectious disease and two developed *Pneumocystis* pneumonia. Both of these patients were receiving corticosteroids and presented simultaneous grade 3 or 4 neutropenia and lymphopenia at the time of infection[7]. We did not experience any infectious complication. Besides having fewer patients presenting lymphopenia (35%), we administered prophylaxis as soon as we detected lymphocytopenia. It should be fairly critical to monitor changes of lymphocytes, as well as to take efforts to prevent loss of lymphocytes.

One measurement that could be recommended to prevent loss of lymphocytes is to avoid use of corticosteroids as much as possible. At the beginning of this discussion, we mentioned that we used corticosteroids on fewer patients compared to Stupp's report (12 vs. 67%). Another thing that was outstanding in that comparison was that we achieved total resection for more patients than in Stupp's report (61 vs. 39%). We assume that the extensive surgical resection we usually perform contributed to bulk reduction of intracranial volume, then resulted in little necessity of administering corticosteroids. Extensive surgical resection may be one approach to suppress complications of TMZ.

As for GI toxicities, nausea/vomiting was observed in 3 patients (12%), which is a much lower incidence than in Stupp's report (nausea 36–49%, vomiting 20–29%)[6]. We administered antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist to all the patients and instructed them to take TMZ before bedtime to reduce nausea during day-

time. Constipation was observed in 21 (81%) patients, which seemed to be a higher incidence compared to previous reports (around 22%), but we could manage all of these with mild laxative agents.

We reported a case of a patient who suffered from GI toxicity who presented GI hemorrhage and severe diarrhea and was hospitalized for 48 days. We also experienced another case in which the patient had to receive intravenous fluid infusion because of severe diarrhea. The post-marketing surveillance study of TMZ in Japan (April 2007, data not published) showed a case from Japan in which the patient died of severe hemorrhagic GI toxicity. Stupp reported 2 patients (1%) who had diarrhea of grade 3 and higher during adjuvant therapy[6]. There was no report of any case from other countries that required hospitalization.

We observed mood changes for 4 patients (15%). All of these presented a depressive state. Stupp et al. have reported no such complications. There has been no such complication resulting from ACNU applied to glioblastomas reported in this country. Psychological complications such as depressive state or anxious state (2 patients out of 143 patients or 1.4%) were detected in the post-marketing surveillance study of TMZ in Japan (April 2007, data not published). It might be speculated that no such complications were detected in the previous reports and our results may be the first to suggest that TMZ has the potential to cause a depressive state.

On the other hand, it has been reported that the incidence of depression in patients during cancer therapy is 13%, and that 15% of high-grade glioma patients will show depressive mental status in the post-operative period[8,9]. These incidences resemble our reports on TMZ treatment and therefore, the depressive state shown in the middle of TMZ treatment might be merely the result of cancer-bearing patients' general psychological reaction.

However, we may have to pay attention to the patients' psychological status to elucidate a cause-and-effect relationship of TMZ and depressive status. Also, we should carefully observe the patients being treated with TMZ for the possibility that this treatment may initiate depression.

Conclusion

Adverse events of grade 3 and higher were observed in 23% of the patients. Lymphopenia was almost inevitable, but prevention of *Pneumocystis* pneumonia can be achieved by prophylactic use of antibiotics (or anti-microorganisms) and avoidance of corticosteroids. We experienced more patients with GI toxicity and mental toxicity compared to the reports from North America and Europe. Accumulating toxicity data from Japanese patients and sharing those with other investigators, especially discussing racial/ethnic variation of toxicities, will be necessary.

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日本人における初発膠芽腫に対するテモゾロミドを用いた初期放射線化学療法の治療成績と有害事象

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〔背景〕膠芽腫標準治療薬である temozolomide（テモダール™：TZM）は，1999年より使用開始されている欧米では効果・副作用に関する充分なデータの蓄積がなされつつあるが，国内では市販後調査が行われ始めてわずか3年が経過したに過ぎず，数年後と予測されるその解析が待たれているところである．我々の施設での初発膠芽腫患者における temozolomide を用いた初期放射線化学療法の使用成績を，特に有害作用に重点をおいて報告する．またTZMとの因果関係が否定できない重篤な消化管障害を誘発した1例を報告する．〔方法〕2006年9月～2008年3月までに temozolomide 併用初期放射線化学療法を受けた膠芽腫全患者を対象とし，初期治療中の有害事象，Kaplan-Meier 法を用いて平均生存期間を算出した．〔結果〕対象となった患者26例，年齢中央値57歳，男女比2対1，全生存期間19.8ヵ月，無増悪生存期間10.3ヵ月であった．初期治療終了までに，TZMとの因果関係が否定できない有害事象が46%（12/26例）の患者に生じ，そのうちリンパ球減少症を取り上げると35%（9/26例），また grade 3（CTCAE Ver.3）以上の重篤な有害事象を生じたものは23%（6/26例）に見られた．また重篤な例として48日間の入院加療を要した消化管出血を伴う消化管壊死（grade3），輸液を必要とする下痢（grade2）それぞれ1例があった．持続する悪心・食欲不振35%（9/26例），ほぼ全例にみられた便秘，肝機能値の上昇はいずれも軽度（grade2）であり，また *Pneumocystis* 肺炎の発症はなかった．今回これまでになかった有害事象として抑うつ状態15%（4/26例）も報告した．〔結語〕我々の調査ではTMZによる grade3 以上の有害事象は，これまでに報告されてきた以上の頻度で発生していたことがわかった．また今回報告するTMZによる重篤な消化管障害や抑うつ状態はこれまでに報告されていない．人種差の検討も含めて今後日本人データの蓄積と共有が必要である．