Resection of Gliomas Using Positron Emission Tomography/Computed Tomography Neuronavigation

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Abstract
Two patients presented with provisional diagnoses of glioma. Computed tomography (CT) and magnetic resonance imaging failed to show the boundaries of the tumor clearly. Positron emission tomography (PET)/CT with [18F]fluorodeoxyglucose and [11C]methionine clearly showed the location, extent, and heterogeneity of the tumors. The tumors were resected under PET/CT neuronavigation guidance. Histological examination of the specimens showed that PET/CT neuronavigation provided reliable distinction between normal brain and glioma, and that the uptake of PET tracers can indicate the degree of proliferation.

Key words: glioma, positron emission tomography/computed tomography neuronavigation, operation

Introduction
The treatment of glioma is one of the most challenging diagnostic and therapeutic problems for the neuro-oncologist. Up to now, the accepted treatment has been surgical excision, followed by radiotherapy and chemotherapy. However, gliomas tend to be diffuse with no sharp border, especially the World Health Organization (WHO) grade II tumors such as diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma, so the tumor is difficult to distinguish from the normal or edematous brain tissue at operation. The percentage of complete removal by routine surgery is disappointing, leading to the poor prognosis. The long-term prognosis is significantly better for cases with total removal compared to partial removal of the tumor, so increasing the ratio of tumor removal is one of the main ways of prolonging patient survival. Genuine biologically total removal of glioma is probably impossible because of the diffuse growth and location. Therefore, excision of the tumor based on visual evidence, and microscopy and neuroimaging findings is the closest available approximation to biologically total removal.

Neuronavigation can precisely delineate the boundaries of a well-defined tumor, and so facilitate the total removal of the tumor. Neuronavigation-guided surgery of 52 primary glioblastomas achieved complete tumor resection in 31% of cases, versus 19% in a series of conventional operations. Therefore, neuronavigation can increase resection of glioblastoma without prolonging operating time, and increase survival time. However, computed tomography (CT) and magnetic resonance (MR) imaging cannot show glioma accurately and completely because of the biological characteristics. The positron emission tomography (PET)/CT technique combines the anatomic data provided by CT with functional and metabolic data related to specific areas of the growth, so may have particular advantages for the visualization of glioma before and during the surgery.

Here we describe our experience with the application of PET/CT neuronavigation to glioma surgery.

Clinical Material and Methods
This study included two male patients, Case 1 aged 65 years and Case 2 aged 55 years, who presented with seizures and loss of consciousness. Neurological examination showed no obvious focal neurological deficits and no symptoms of increased intracranial pressure.
Both patients underwent MR imaging using a 1.5-tesla scanner (1.5T Signa Twin-speed, infinity with Excite I; GE Medical Systems, Milwaukee, Wis., U.S.A.). The conventional imaging protocol consisted of fluid-attenuated inversion recovery sequence T1-weighted imaging (repetition time [TR] 2025 msec, echo time [TE] 8.4 msec, inversion time 750 msec, slice thickness 6.0 mm, slice gap 1.5 mm, field of view 24 × 18 cm, matrix 320 × 224, number of excitations [NEX] 2), fast-recovery fast spin-echo sequence T2-weighted imaging (TR 4000 msec, TE 8.4 msec, slice thickness 6.0 mm, slice gap 1.5 mm, field of view 24 × 24 cm, matrix 512 × 512, NEX 2), spin-echo echo-planar imaging sequence diffusion-weighted imaging (TR 10,000 msec, TE 8.4 msec, slice thickness 6.0 mm, slice gap 1.5 mm, field of view 24 × 24 cm, matrix 128 × 128, NEX 1), and spin-echo sequence T1-weighted imaging (TR 500 msec, TE 8.4 msec, flip angle 75°, slice thickness 6.0 mm, slice gap 1.5 mm, field of view 24 × 24 cm, matrix 256 × 150, NEX 1) 2 minutes after injection of gadolinium-diethylenetriaminepenta-acetic acid (0.1 mmol/kg).

[18F]fluorodeoxyglucose (FDG) and [11C]-methionine (MET) were produced in a MINItrace cyclotron, with TRACERlab MNFG and TRACERlab FXc synthesizer (GE Medical Systems). PET/CT was performed with a Discovery LS PET/CT unit (GE Medical Systems). Patients fasted for at least 6 hours before the PET/CT examination. A dose of 222–370 MBq (6–10 mCi) FDG and/or 555–740 MBq (15–20 mCi) MET was injected intravenously within 1 minute. Static emission scanning was performed at least 40 minutes after FDG injection or at least 20 minutes after MET injection. PET was performed in three-dimensional (3D) mode (field of view 15 cm, slice thickness 5.0 mm, slice gap 4.25 mm, matrix 128 × 128). The lamellar CT protocol was slice thickness 2.5 mm, slice gap 0, and matrix 512 × 512. Six reference markers were fixed to the scalp around the tumor before the PET/CT investigation.

Intraoperative neuronavigation used a VectorVision® system (Brain LAB AG, Heimstetten, Germany). The PET/CT data were input into the project graphic workstation, the markers were identified, and the 3D PET and CT images rebuilt. The 3D PET image was then coregistered automatically with the 3D CT image using the registration program of the project system, and the fused image adjusted manually. The extent of the operative target was confirmed using the PET/CT image.

The patient was anesthetized, and the head fixed in the Mayfield head frame. The operative project data were input into the neuronavigation workstation, and the markers were registered with an error of ±1.5 mm. The tumor resection was then carried out, directed by the neuronavigation system based on the PET/CT data.

Sections taken from each operation specimen were fixed with formalin, embedded in paraffin, and stained with hematoxylin and eosin. The histological diagnosis was determined by an experienced neuropathologist according to the WHO classification of tumors of the central nervous system.

**Results**

**Case 1:** CT showed the irregular lesion as uniform density, with an unclear border and slight enhancement, deep within the right frontal lobe cortex. Perfusion CT showed the lesion was highly perfused with slightly high permeation. The lesion was surrounded by a large band of edema in the white matter (Fig. 1D, E). MR imaging showed a mass with unclear margins in the right frontal lobe.
Fig. 2 Case 1. Postoperative computed tomography scan, showing the tumor resected completely.

Fig. 3 Case 2. A 55-year-old man with a diffuse lesion in the right frontal lobe. A–C: T1-weighted (A) and T2-weighted (B) magnetic resonance (MR) images, and T1-weighted MR image with contrast medium (C), showing a mass in the right frontal lobe with unclear margin as slightly hypointense on the T1-weighted and hyperintense on the T2-weighted images, with some slightly enhanced spots in the lesion. D: Computed tomography scan, showing the lesion as equal or slightly increased density, with an unclear border, in and below the right frontal lobe cortex. E: \(^{11}C\)-methionine (MET) positron emission tomography (PET) scan, showing an area of high uptake with a clear border in the right frontal lobe. The area of highest MET uptake was in the posterior part of the lesion. F: \(^{18}F\)fluorodeoxyglucose (FDG) PET scan, showing an irregular area of high uptake which was relatively well defined in the frontal lobe. The highest FDG uptake area was in front of the MET hot area.

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Fig. 4 Case 2. Positron emission tomography (PET)-computed tomography (CT) neuronavigation system monitoring images captured during the operation. A: $^{18}$F-fluorodeoxyglucose PET scan; B, C: CT scans; D: $^{11}$C-methionine PET scan. CT provided the anatomic background. PET provided more distinct information about the tumor.

Fig. 5 Case 2. Photomicrograph of the specimen resected from the hot spot demonstrated by $^{11}$C-methionine positron emission tomography showing glioblastoma, World Health Organization grade 4. Nucleus deformation, and cell and vessel proliferation were prominent. Hematoxylin and eosin stain, ×100.

Fig. 6 Case 2. Photomicrograph of the specimen resected from the hot spot demonstrated by $^{18}$F-fluorodeoxyglucose positron emission tomography showing the margin of the tumor. Nucleus deformation, and cell and vessel proliferation were similar to that of astrocytoma grade II. Hematoxylin and eosin stain, ×100.

of edema was identified around the tumor. Specimens from the hot spots of MET and FDG uptake were resected separately. Histological examination showed the specimen from the highest MET uptake area was glioblastoma grade IV (Fig. 5), and that from the highest FDG uptake area, and relatively low MET uptake, was the margin of the tumor (Fig. 6). Nucleus deformation, and cell and vessel proliferation were similar to that of astrocytoma grade II. The patient showed no obvious focal neurological deficits after the operation.

Discussion

MR imaging is the first choice to show the position and extent of the tumor. The most malignant part is most likely to be located in the area of breakdown of the blood-brain barrier, so will appear as an area of enhancement on MR imaging with contrast medium. However, T1- and T2-weighted MR imaging cannot definitively show the relationship between the tumor and normal or edematous tissue in the case of lower grade gliomas in WHO grade II and some in grades III and IV. If the blood-brain barrier of the tumor has not broken down, this distinction is not possible, nor can the regional heterogeneity of the tumor be shown. Clinical studies have shown that glioma extends beyond the contrast enhanced margin, and that approximately 80% of tumor relapses occur within a 2-cm margin around the enhanced lesion. Therefore, neuronavigation using only MR imaging cannot be relied upon to outline the target completely.

In addition to CT and MR imaging, MR spectroscopic imaging and metabolic imaging with PET have been considered. PET evaluates the metabolic state of the tumor using radiolabeled tracers such as MET and FDG. PET can estimate the grade and malignancy of the glioma before operation, and
show the tumor extent and heterogeneity.\textsuperscript{1,7,10} Clinical studies using radiolabeled amino acid PET such as MET have shown superior delineation of the glioma mass compared with MR imaging, differentiation between tumor and edema, and recognition of different areas of proliferation in different parts of the tumor. Confirmation of the target of stereotactic biopsy and radiotherapy by PET provides high sensitivity and specificity.\textsuperscript{2,4–6} The new PET/CT technique has significantly improved the precision of PET and combines the advantages of structural and functional imaging.\textsuperscript{8} Both the PET/CT and neuronavigation systems are based on computer systems, so the method is most practical if the input and output formats match. We found that the input/output formats of our two systems were based on Dicom 3.0, so the project graphic workstation of our VectorVision\textsuperscript{62} neuronavigation system could combine the two programs.

We used the PET/CT neuronavigation system to guide the surgery in two patients with glioma that had been difficult to confirm by routine CT and MR imaging. In particular, the actual tumor margin was undefined, and tumor and edema were not distinguished, so the clear and reliable data needed for the neuronavigation system were not available. In contrast, PET/CT clearly identified the extent and invasiveness of the two tumors, and provided the reliable data needed for neuronavigation-guided excision.

The tumor could not be distinguished from the normal brain tissue by visual inspection in Case 1, and the boundary was not visible in the resected specimen. The operation was continued under PET/CT neuronavigation guidance. The tumor was found beneath the cortex in Case 2, but the degree of proliferation in different parts of the tumor could not be distinguished using MR images. In contrast, PET/CT demonstrated distinctly both the tumor extent and the degree of proliferation in the various areas by the different uptakes of FDG and MET. Histological examination of the specimens showed that PET/CT neuronavigation provided reliable distinction between normal brain and glioma, and that the uptake of PET tracers can indicate the degree of proliferation. MET was more effective for this purpose than FDG.

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Commentary

Our ability to more safely and accurately resect glial neoplasms has been greatly enhanced during the past decade by increasing reliance on high resolution neurodiagnostic imaging. First using CT, and more recently using high resolution MRI using both contrast enhanced and long TR imaging sequences, we have been able to more clearly define resectable tumors. When combined with various neuronavigation tools, we can now more precisely define the anatomy, restrict the size of our craniotomy approaches, and more accurately resect tumors from a wide variety of brain locations. Despite these great advances, there are several caveats that must be kept in mind when combining these powerful neurodiagnostic imaging tools, now supplemented by PET imaging, and bear this in mind as we continue to debate the merits of aggressive resection of glial neoplasms.

There is a wide spectrum of the morphology of glial tumors. Some, predominantly the Daumas-Dupont Type I tumors, have sharp borders, and when located in polar or lobar locations can achieve significant cytoreductive efforts. Examples include juvenile pilocytic astrocytomas, some oligodendrogliomas, and some oligoastrocytomas (as in Case 1 in the present report). It is certainly likely that both metabolic imaging as well as structural imaging provide a greater level of input to help the surgeon achieve a greater resectability of such resectable tumors.

Unfortunately, the vast majority of the tumors that present clinically are Daumas-Dupont Type II tumors. Those with a large area of actively growing tumor, surrounded by an area of brain adjacent to tumor which is grossly infiltrated with tumor cells, and which represents long TR imaging sequence, are often confused with “edema.” For a tumor that contains $30\times10^6$ cells at the time of presentation, a 90% resection of this tumor leaves $3\times10^8$ cells, and a 99% cytoreductive effort leaves $3\times10^7$ cells remaining. We can argue that this represents a significant cytoreductive surgery, but we are faced with the fact that surgery per se is never sufficient for such tumors, may be helpful for some patients, may be harmful to some patients, and unfortunately is never curative. The concept that such aggressive cytoreductive surgery improves outcomes is an interesting hypothesis, which to date has defined scientific validation. In order to define a 20% increase in survival for such patients undergoing aggressive cytoreductive surgery, hundreds of patients would be needed in a randomized prospective study with patients followed up for 7 to 20 years. This is not to be fatalistic, it is simply to realize that continued arguments over how to do the best operation must be put into the perspective of, “we do not cure gliomas of the Type II variant by cytoreductive surgery.” All patients should require adjuvant management usually consisting of radiation therapy, and in some cases chemotherapy. Patients with Daumas-Dupont Type III tumors, diffusely infiltrative tumors such as gliomatosis cerebri, are not eligible for and do not benefit from cytoreductive surgery. Stereotactic biopsy is the appropriate management followed by adjuvant radiation and chemotherapeutic options.

Imaging adjuvants that improve the reliability, quality, safety, and efficacy of surgery are admirable. Surgery remains a mainstay of management for properly selected patients with tumors eligible for aggressive surgery, those in polar or lobar locations. True advances in the management of glial neoplasms must await other more effective treatment options applied outside the operating room.

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Clinical usefulness of PET is widely accepted, and precise diagnostic accuracy for glioma and good surgical results have been reported. In the present paper, the authors described the usefulness of neuronavigation using co-registered positron emission tomography and computerized tomography (PET/CT neuronavigation) in two cases of low grade glioma. It is very difficult to distinguish perifocal edema from low grade glioma by MR imaging. The authors demonstrate the possibility to differentiate these pathologies using intraoperative PET/CT neuronavigation. However, the authors should pay attention to certain brain shifts during the surgery, because they noted that they could not distinguish the tumor from the brain tissue by visual inspection in Case 1 and by MR imaging in Case 2. They performed successful surgery and complete excision of tumor was achieved using this navigation system. However, postoperative PET study was not yet made. Moreover, a long-term follow up is also necessary whether there is a possible recurrence or not during the long-term course after surgery. The authors are encouraged to publish a further study which covers these problems with acquired cases.

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Yang et al. present their preliminary results on resection of glioma using PET/CT neuronavigation. They evaluated the validity of PET scan in combination with CT, as an additional tool for localization and resection of tumor tissue during open surgery. They provided new data and new methodological insights, which could be helpful for neurosurgical practice.

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