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CLINICAL INVESTIGATION **Brain**

AN INTERINDIVIDUAL COMPARISON OF O-(2- [^{18}F]FLUOROETHYL)-L-TYROSINE (FET)– AND L-[METHYL-^{11}C]METHIONINE (MET)–PET IN PATIENTS WITH BRAIN GLIOMAS AND METASTASES

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Purpose: L-[methyl-^{11}C]methionine (MET)–positron emission tomography (PET) has a high sensitivity and specificity for imaging of gliomas and metastatic brain tumors. The short half-life of ^{11}C (20 minutes) limits the use of MET-PET to institutions with onsite cyclotron. O-(2- [^{18}F]fluoroethyl)-L-tyrosine (FET) is labeled with ^{18}F (half-life, 120 minutes) and could be used much more broadly. This study compares the uptake of FET and MET in gliomas and metastases, as well as treatment-induced changes. Furthermore, it evaluates the gross tumor volume (GTV) of gliomas defined on PET and magnetic resonance imaging (MRI).

Methods and Materials: We examined 42 patients with pretreated gliomas (29 patients) or brain metastases (13 patients) prospectively by FET- and MET-PET on the same day. Uptake of FET and MET was quantified by standardized uptake values. Imaging contrast was assessed by calculating lesion–to–gray matter ratios. Tumor extension was quantified by contouring GTV in 17 patients with brain gliomas. Gross tumor volume on PET was compared with GTV on MRI. Sensitivity and specificity of MET- and FET-PET for differentiation of viable tumor from benign changes were evaluated by comparing the PET result with histology or clinical follow-up.

Results: There was a strong linear correlation between standardized uptake values calculated for both tracers in cortex and lesions: $r = 0.78$ ($p = 0.001$) and $r = 0.84$ ($p < 0.001$), respectively. Image contrast was similar for MET- and FET-PET (lesion–to–gray matter ratios of 2.36 ± 1.01 and 2.33 ± 0.77, respectively). Mean GTV in 17 glioma patients was not significantly different on MET- and FET-PET. Both MET- and FET-PET delineated tumor tissue outside of MRI changes. Both tracers provided differentiated tumor tissue and treatment-related changes with a sensitivity of 91% at a specificity of 100%.

Conclusions: O-(2- [^{18}F]fluoroethyl)-L-tyrosine–PET and MET-PET provide comparable diagnostic information on gliomas and brain metastases. Like MET-PET, FET-PET can be used for differentiation of residual or recurrent tumor from treatment-related changes/pseudoprogression, as well as for delineation of gliomas.

FET-PET, MET-PET, Brain tumors, Pseudoprogression, Gross tumor volume.

INTRODUCTION

In brain tumors treatment planning and evaluation of local response to therapy are usually based on magnetic resonance imaging (MRI) and computed tomography (CT). These investigations show the anatomy of the brain with high accuracy. However, the correlation between real tumor extension and the radiologic imaging of the malignant tissue on CT or MRI is quite different for gliomas and brain metastases. In brain gliomas stereotactic biopsy specimens showed that malignant tissue could be located far beyond the margins of the tumor visualized on MRI or CT (1–4). In contrast, in brain metastases the correlation between real tumor extension and the imaging of the lesions on MRI or CT is very high (5–7). In both gliomas and metastases treatment-related changes (TRCs) (after radiochemotherapy, also called ''pseudoprogression'') such as blood–brain barrier (BBB) disturbance or edema can generally not be differentiated from viable tumor tissue (8, 9).

Several studies suggest that because of its high sensitivity and specificity for tumor tissue, L-[methyl-^{11}C]methionine

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(MET)–positron emission tomography (PET) is a useful tool for the visualization of brain tumors (10–15). MET is transported across the BBB by the L-type amino acid transport system and intensely accumulated by tumor cells. Disruption of the BBB is therefore not necessary for MET accumulation in the tumor tissue. In a intracellular manner, MET can enter multiple metabolic pathways. However, studies have indicated that at the time of PET imaging, tumor uptake of MET mainly reflects AA transport (16). When we compare CT, MRI, and MET-PET with stereotactic biopsy in brain gliomas, MET-PET has shown a significantly higher accuracy in defining the extent of tumor than CT and MRI (10–15). Therefore MET-PET can improve tumor delineation for surgery (17, 18) or radiation therapy planning (19–21) and could have an impact on the evaluation of treatment outcome. Nevertheless, the application of MET-PET has been limited to a small number of research centers, because the short physical half-life of ^{11}C (20 minutes) necessitates an onsite cyclotron for MET-PET examinations.

O-(2- [^{18}F]fluoroethyl)-L-tyrosine (FET) is an analog of tyrosine that is not metabolized and not incorporated into proteins. The uptake by tumor cells is mediated by the L-type AA transport system (22, 23). The sensitivity and specificity for tumor tissue, evaluated by use of stereotactic biopsy specimens, are higher for FET-PET than for MRI and CT (24–26). In contrast to MET the physical half-life for ^{18}F (110 minutes) allows FET-PET studies to be performed in centers without an onsite cyclotron. Similar transport characteristics for FET and MET were shown in studies using F98 rat glioma cells (27). In a previous clinical study we observed a close correlation between the intensity of MET and FET uptake in tumoral and non-tumoral cerebral lesions (28). However, this trial included only 16 patients and did not assess differences in tumor extension between the two imaging modalities.

The aim of this study was to perform an intraindividual comparison of FET-PET and MET-PET in patients with brain gliomas or metastases. Tracer uptake in normal and tumor tissue, sensitivity and specificity for differentiation of tumor tissue vs. TRCs, and macroscopic tumor extension were compared for FET-PET and MET-PET.

METHODS AND MATERIALS

Patients

Forty-two consecutive patients were included in the study within 24 months. All patients had previously been treated for gliomas or brain metastases (Table 1) and now presented with MRI findings suggesting the presence of residual or recurrent tumor tissue. Of the patients, 29 had a high-grade (n = 25) or low-grade (n = 4) glioma and 13 had had brain metastases. The patient population includes 16 patients who were reported on previously (28).

In all patients the two FET- and MET-PET studies were performed on the same day.

The institutional review board approved the study protocol, and written informed consent was obtained from all patients.

MRI procedure

Magnetic resonance imaging was performed by use of a Philips 1.5-T Gyroscan ACS-NT scanner (Philips Medical Systems, Andover, MA). The acquisition was done with a standard head coil. Axial T1-native and post–contrast material application (gadolinium–diethylenetriamine pentaacetic acid, 0.1 mmol/kg of body weight) images and T2-weighted images were acquired from the foramen magnum to the vertex, orthogonal to the holder plate of the mask. The slice thickness was 1.5 mm, without a gap.

The PET/MRI image fusion was performed with a program developed by Pietrzyk *et al.* (29). The MRI studies were evaluated by an expert neuroradiologist and a radiation oncologist (A.L.G.) with training in neuroradiology.

PET procedure

Positron emission tomography studies were acquired with an ECAT EXACT PET scanner (CTI/Siemens, Eulangen, Germany) (30). Patients fasted for at least 4 hours before PET imaging to ensure standardized metabolic conditions. Before tracer injection, a transmission scan was acquired to correct for absorption. Emission data were acquired in two-dimensional mode and corrected for attenuation, scatter, and random coincidences. Reconstruction was performed by filtered backprojection by use of a Hanning filter with a cutoff frequency of 0.5 cycles per bin.

MET-PET procedure

Carrier-free MET (specific activity >18.5 GBq/μmol) was synthesized from [^{11}C]methyl iodide and homocysteine (31). Patients were injected with 185 to 370 MBq of MET, and a dynamic emission scan was performed over a period of 30 minutes (five 1–minute and five 5–minute frames). For visual image analysis and placement of regions of interest, MET-PET studies were summed between 10 and 30 minutes.

FET-PET procedure

To avoid contamination by [^{11}C]methionine activity, FET-PET was performed 3 hours (6 half-lives) after MET-PET. O-(2- [^{18}F]fluoroethyl)-L-tyrosine is synthesized by [^{18}F]fluoralkylation of tyrosine (22).

Mean activity injected was 185 to 370 MBq of carrier-free FET (specific activity >18.5 GBq/μmol), and it was administered intravenously. Starting with tracer injection, a dynamic acquisition was performed for 60 minutes (five 1–minute and eleven 5–minute frames). For visual image analysis and placement of regions of interest, FET-PET studies were summed between 20 and 40 minutes.

Analysis of PET scans

The FET- and MET-PET scans were evaluated by one investigator (W.A.W.) who was blinded to the results of the other imaging studies as well as to patient follow-up data. Uptake of MET and FET was quantified by standardized uptake values (SUVs) normalized to the patient's body weight. Tracer uptake was measured in the lesions (SUV-l) and in contralateral gray matter (SUV-g) as previously described (28). To assess image contrast, the ratio between tracer uptake in the tumor and contralateral gray matter was determined (lesion–to–gray matter ratio [l/g]).

Positron emission tomography studies were considered as ''positive'' for tumor tissue when there was focal MET uptake with an l/g of more than 1.5. Linear tracer uptake around a resection cavity was not considered as evidence of tumor tissue but was considered as treatment related even if the l/g was higher than 1.5.