Evaluation of O-(2-[18F]-Fluoroethyl)-L-Tyrosine in the Diagnosis of Glioblastoma

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Objective: To assess the feasibility of synthesis of O-(2-[18F]-fluoroethyl)-L-tyrosine (FET), a new positron emission tomographic (PET) tracer described in several studies but not yet considered standard in management of glioma, in routine practice and to determine FET uptake in a homogeneous group of patients with suspected high-grade glioma.

Design: Prospective nonrandomized trial.

Patients: Twelve patients with suspicion of high-grade glioma.

Results: The mean (SD) FET uptake ratio was 3.15 (0.72) for the 12 patients and 3.16 (0.75) for the 11 patients with glioblastoma.

Conclusion: The initial results are promising and indicate that FET PET is a valuable and applicable tool for the imaging of high-grade glioma.

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Positron emission tomography (PET), a metabolic imaging modality widely used in systemic cancer, may be a valuable tool for obtaining additional data and for better treatment of patients with glioma.

L-[methyl-11C]-methionine (MET), usually considered the standard method of brain tumor molecular imaging in PET, cannot be used in clinical practice owing to the short half-life of carbon 11; thus, its applications are restricted to academic research centers.1,2 O-(2-[18F]-fluoroethyl)-L-tyrosine (FET) is a recently described amino acid analog radiolabeled with fluorine 18 (18F). It can be synthesized using an automated procedure and can be produced for clinical practice in a satellite concept similar to fludeoxyglucose, which is already widely used in general oncology.3,4 A few studies have already evaluated this new tracer, with promising results in glioma. Uptake and image contrast obtained with FET appear to be very similar to those obtained with MET.5,6 Use of FET has also demonstrated its potential in targeting biopsy sites, delineating extent of glioma, and diagnosing recurrence with a positive predictive value of 84%, as described by Mehrkens et al.7 Baseline FET uptake also seems predictive of outcome in low-grade glioma and may help evaluate therapeutic response.5,10 However, PET using FET is not yet considered routine and is not allowed in French centers in daily practice.

Thus, this prospective study aimed to assess the feasibility of FET synthesis in a conventional PET unit and the suitability of FET-PET in routine practice. We also aimed to consolidate the promising results concerning FET uptake in a homogeneous group of adult patients with newly diagnosed high-grade glioma. We sought to demonstrate clinically significant uptake similar to that described in the literature on high-grade glioma, ie, a tumor-to-brain ratio of 2.6 We consider such results to be indispensable prerequisites for further discussion of FET-PET indications in clinical neurooncology practice.
written informed consent was obtained. The study protocol was approved by the ethics committee of our institution.

Positron emission tomography using FET was performed in 12 patients. In 2 patients, imaging could not be carried out in time owing to a technical problem.

Diagnosis of glioblastoma was histologically confirmed in 11 patients. One patient with brain metastasis of an epidermoid carcinoma was excluded from analysis in accordance with the provisions of the protocol.

Histological analysis was assessed within 10 days of the multidisciplinary session, either by biopsy or surgical resection, using the World Health Organization 2000 classification of tumors of the nervous system.

The amino acid tracer FET was produced according to the method described by Wester et al using a 2-step reaction. The fully automated FET synthesis was performed by the research unit of our university using the Synchrom synthesis module (Raytest GmbH, Straubenhardt, Germany). The total time required for synthesis was about 58 minutes, with radiochemical purity of more than 98% and a radiochemical yield of about 15%.

Positron emission tomography was performed within 10 days of the multidisciplinary session and no more than 10 days before histological confirmation. Images were acquired using an Exact HR+ camera (CTI/Siemens, Knoxville, Tennessee).

The frames were imported into a Mirage console (Segami Corporation, Columbia, Maryland) to draw the regions of interest (ROI). The procedure was robust and brief (<5 minutes). Uptake of FET was determined using the standard uptake value in each ROI according to accepted procedures.

The transaxial slice showing the highest activity was chosen, and an isocountour region was automatically drawn around the maximal intensity of uptake ($C_{max}$) and around regions corresponding to 85% and 75% of $C_{max}$ ($C_{85}$ and $C_{75}$). As a reference, similarly sized ROI were drawn in analogous, normal-appearing regions of the contralateral hemisphere ($N_{max}$, $N_{85}$, and $N_{75}$, respectively). Tumor to brain ratios were calculated and called, respectively, $R_{max}$, $R_{85}$, and $R_{75}$.

An isocontour region corresponding to $C_{max}$ was also drawn in healthy gray matter, using the contralateral cortical band ($N_{gm}$) and used to calculate a brain to tumor ratio ($R_{gmax}$).

STATISTICAL ANALYSIS

All standard uptake value to normal brain ratios were tested for normality and are given as mean (standard deviation). To estimate whether standard uptake value ratios were higher than the theoretical value of 2 previously reported by Weber et al, we used a 1-tailed t test. Mean comparisons between standard uptake value ratios were done using balanced repeated-measures analyses of variance to take into account intra-individual variability.

The time to peak uptake was defined for each subject as the time to maximal uptake. We estimated the decreasing slope from peak uptake to the last frame using a mixed model analysis with random intercepts. Analysis was performed using Stata 9.0 software (Stata Corporation, College Station, Texas).

RESULTS

All patients showed significantly higher FET uptake in intracerebral lesions than in normal gray matter (Figure) or the contralateral hemisphere.

The tumor to brain ratio was significantly different from the theoretical value of 2 for all patients. The ratio for $R_{75}$ was 3.16 (0.76) ($P < .001$); $R_{85}$, 3.31 (0.71) ($P < .001$); $R_{max}$, 3.33 (0.64) ($P < .001$); and $R_{gmax}$, 3.20 (0.92) ($P = .002$).

COMMENT

This study confirms that FET synthesis is feasible and that FET-PET can be carried out during a routine diagnostic procedure for patients with glioma. Synthesis of FET requires a radiopharmaceutical unit, but FET can also be purchased and is already commercialized in Europe. Unlike carbon 11–labeled methionine, the 109.7-minute half-life of this 18F-radiolabeled tracer allows its application under similar conditions to the widely used fludeoxyglucose, with centralized synthesis and distribution to the PET center without an on-site cyclotron. The radiation burden is low (mean effective dose, 3 mSv for each examination).8

In this homogeneous group of patients, we confirm the promising results previously reported in the literature with this radiolabeled tracer.3,6,13,15 Uptake of FET in malignant brain tumors is elevated, with an $R_{75}$ of 3.16.

Figure. Visual evaluation of O-(2-[18F]-fluoroethyl)-L-tyrosine uptake in a patient with glioblastoma (A) and magnetic resonance imaging of the same patient (B) are shown with coregistered images (C).
(95% confidence interval, 2.70-3.61), and is significantly higher than the theoretical value of 2. These results suggest that FET-PET may be as clinically useful as MET-PET in the imaging of glioma.

Merkhens et al7 have demonstrated promising results, with a positive predictive value of 84%, for diagnosis of glioma progression. The population of patients evaluated in this study (31 patients with suspicion of glioma recurrence after various forms of treatment) is different from ours (newly diagnosed patients included before any treatment). However, their results strengthen the interest of FET-PET in the management of glioma.

The most appropriate method of calculating tumor to brain ratio must also be discussed. Various methods have been described in the literature; we have used several to measure FET uptake (several ROI were considered, and uptake ratio was defined using either gray matter or contralateral, same-sized, mirrored ROI as a reference). The results did not significantly differ with either method (P = .44).

In our study, the Cmax ROI represented a single pixel for all patients. The possibility that a quantification procedure based on a single pixel could be inaccurate must be considered, so R85 or R75 seemed to be the most relevant choice.

Our findings confirm that radiosynthesis of FET is effective and can be routinely used in a PET center. We demonstrate, in a homogeneous group of patients with newly diagnosed, histologically proven glioblastoma, that FET uptake is highly discriminant with respect to the normal brain. This study may be considered preliminary, and a multicenter trial aiming to pursue these possibilities is currently under way.

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REFERENCES