Hybrid $^{18}$F-FET PET and Perfusion MRI to Differentiate Disease Progression from Treatment-Related Changes in Malignant Brain Tumors

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Differentiation between progression of disease (POD) and treatment-related changes (TRCs) in brain tumors remains challenging. Both POD and TRCs can lead to mass effects, perilesional edema, and contrast enhancement in conventional MRI, which presents a major problem in clinical decision-making (1). PET using radiolabeled amino acids and advanced MRI methods such as perfusion-weighted imaging can provide substantial additional information in this crucial situation (2).

PET using radiolabeled amino acids is increasingly being applied in neurooncology, and its benefits have been documented in previous recommendations and guidelines of the PET task force of the Response Assessment in Neuro-Oncology Working Group (3–7). The longest-established amino acid tracer for PET is $[^{11}$C-methyl]-L-methionine, which requires an onsite cyclotron because of the short half-life of $^{11}$C (20 min). Amino acids labeled with $^{18}$F (half-life of 109.8 min) such as $O$-[2-$^{18}$F-fluoroethyl]-L-tyrosine ($^{18}$F-FET), 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine ($^{18}$F-FDOPA), or anti-1-amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid ($^{18}$F-fluciclovine) offer considerable logistic advantages in clinical practice (2). $^{18}$F-FDOPA was initially developed to evaluate dopamine synthesis in the basal ganglia, but the tracer can also be used for brain tumor imaging (7). In the United States and Europe, $^{18}$F-FDOPA is approved for characterization of presynaptic dopaminergic activity in patients with parkinsonian syndromes. Notably, the physiologic uptake of $^{18}$F-FDOPA in the striatum may hamper its use for the evaluation of brain tumor infiltration in this region (7). The synthetic amino acid analog anti-1-amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid has gained clinical interest, particularly for the diagnosis of recurrent prostate cancer, but is now also considered for brain tumor imaging (8). $^{18}$F-fluciclovine has been approved in the United States and Europe for evaluation of recurrent prostate cancer (9) and has orphan drug status for glioma imaging in the United States.

It is assumed that uptake of the mentioned amino acid tracers occurs mainly by facilitated transport via large neutral amino acid transporters of the L-type in gliomas and brain metastases (i.e., subtypes 1 and 2), which are regularly overexpressed in both brain tumor types (7). The tumor-to-brain contrast observed with $^{18}$F-fluciclovine is higher than that of $[^{11}$C-methyl]-L-methionine, $^{18}$F-FET, and $^{18}$F-FDOPA (10), presumably because of the lower transport of $^{18}$F-fluciclovine through the intact blood–brain barrier. Whether this feature is advantageous in brain tumor diagnosis needs to be clarified.

In Europe, $^{18}$F-FET is the most frequently used amino acid tracer for brain tumor imaging, and especially in Germany, some centers have collectively performed more than 20,000 examinations because of the high clinical interest in this method (11,12). Furthermore, the increasing number of publications coming from Australia, China, India, and South Korea indicate a wide acceptance of this method (13–17). For $^{18}$F-FET, approval exists in Switzerland (18) and in France (IASOgli; IASON). Clinical use of $^{18}$F-FET and reimbursement is possible in several European countries depending on the local legislation or exemption for specialized centers.

A particular property of $^{18}$F-FET is the additional information derived from time–activity curve analysis, which is useful for differential diagnosis of brain lesions (11). Several studies reported that high-grade gliomas characterized by older World Health Organization classifications typically show a short time to peak followed by a decreasing time–activity curve, whereas lower-grade gliomas or nonneoplastic lesions usually exhibit delayed and steadily increasing tracer uptake (19–22). Such prominent differences in time–activity curve patterns are not provided by $[^{11}$C-methyl]-L-methionine or $^{18}$F-FDOPA (23,24).

The hybrid PET/MRI study by Smith et al. including 80 patients with gliomas ($n = 42$) or brain metastases ($n = 38$) published in the current issue of The Journal of Nuclear Medicine represents the first study using $^{18}$F-FET PET in the United States (25). The study provides a wide scope of data, and the results concerning the value of $^{18}$F-FET PET for discerning POD from TRCs on MRI are in line with international studies as documented in a recent meta-analysis (26).

Smith et al. report the overall diagnostic performance of hybrid $^{18}$F-FET PET/perfusion-weighted imaging (sensitivity, 86%; specificity, 87%) to differentiate POD from TRCs across all tumor types based on visual reading and analysis of tumor-to-brain ratios. The authors emphasize that $^{18}$F-FET PET outperformed perfusion MRI metrics and positively impacted the routine clinical care of...
challenging malignant brain tumor cases. The authors could not replicate an improvement in overall performance when 18F-FET PET was combined with perfusion-weighted imaging. The use of hybrid PET/MRI offers logistic advantages but seems not essential in this setting. Accordingly, a recent study demonstrated no differences between hybrid and sequential 18F-FET PET MRI in the differentiation of recurrent gliomas (27). On the other hand, hybrid 18F-FET PET/MRI offers essential advantages in pediatric patients by avoiding radiation exposure from the PET/CT scanner and repeated general anesthesia (28).

Special attention should be paid to the analysis of dynamic 18F-FET PET data in the present study. Time to peak and the slope of the late phase of the time–activity curve (SUVslope) yielded results consistent with previous literature. Of note, the authors identified the SUVintercept of the slope extrapolation as a novel parameter. Time to consistent with previous literature. Of note, the authors identified the SUVintercept of the slope extrapolation as a novel parameter. Time to peak and SUVslope influence SUVintercept in the same direction, and the parameter yielded higher accuracies to differentiate POD from that could further improve the use of dynamic 18F-FET PET.

In conclusion, the study by Smith et al. suggests that the time has come to make 18F-FET PET more widely available to U.S. patients. The necessary PET infrastructure is widely available, and the production of this tracer is well established, with costs comparable to those of other tracers routinely used in clinical practice. In addition, the cost-effectiveness of 18F-FET PET has been demonstrated in several studies (29–33). A more reliable diagnostic assessment of recurrent brain tumors is desirable, as the costs of brain tumor therapy options are usually high and an efficient use of these therapies is of utmost importance for both the patient and the treating physician. It is hoped that the study by Smith et al. represents a milestone in this process.

DISCLOSURE

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REFERENCES