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Current trends in the use of O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) in neurooncology

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Running title: Current trends of FET PET

Abstract

The diagnostic potential of PET using the amino acid analogue O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) in brain tumor diagnostics has been proven in many studies during the last two decades and is still the subject of multiple studies every year. In addition to standard magnetic resonance imaging (MRI), positron emission tomography (PET) using [^{18}F]FET provides important diagnostic data concerning brain tumor delineation, therapy planning, treatment monitoring, and improved differentiation between treatment-related changes and tumor recurrence. The pharmacokinetics, uptake mechanisms and metabolism have been well described in various preclinical studies. The accumulation of [^{18}F]FET in most benign lesions and healthy brain tissue has been shown to be low, thus providing a high contrast between tumor tissue and benign tissue alterations. Based on logistic advantages of F-18 labelling and convincing clinical results, [^{18}F]FET has widely replaced short lived amino acid tracers such as L-[^{11}C]methyl-methionine ([^{11}C]MET) in many centers across Western Europe. This review summarizes the basic knowledge on [^{18}F]FET and its contribution to the care of patients with brain tumors. In particular, recent studies about specificity, possible pitfalls, and the utility of [^{18}F]FET PET in tumor grading and prognostication regarding the revised WHO classification of brain tumors are addressed.

1. Introduction

In recent years, amino acid PET has become an important constituent in brain tumor diagnostics, as it complements conventional MRI, which is considered the gold standard, by adding valuable metabolic data to anatomical images [1]. Using conventional MRI only, it may be difficult to delineate brain tumors and to distinguish treatment related changes from tumor recurrence [2-4]. Consequently, many approaches have been undertaken to find suitable PET tracers providing high tumor-to-brain contrast, reliable tumor delineation, and high specificity for tumor tissue. In this field, radioactively labelled amino acids have emerged as the most powerful tracers and recently, the Response Assessment in Neuro-Oncology (RANO) working group has recommended amino acid PET as a valuable tool to improve the management of brain tumor patients [5, 6]. Among the recommended amino acid tracers, [^{18}F]FET has become one of the most widely used in Western Europe. Due to logistical advantages, ^{18}F-labelled tracers have widely replaced the longer-established L-[^{11}C]methyl-methionine ([^{11}C]MET) [7], which requires an on-site cyclotron owing to short half-life of C-11 of 20 minutes. An advantage of [^{18}F]FET over the less frequently used 3,4- dihydroxy- 6- [^{18}F]fluoro-L- phenylalanine ([^{18}F]FDOPA), is the low accumulation in the striatum [1, 8]. [^{18}F]FET has been approved for brain tumor diagnostics in Switzerland [9] and France and some centers report on more than 10,000 scans so far [10]. Since its development in the 1990s, more than 290 original articles and reviews on [^{18}F]FET PET underline the clinical relevance of this tracer for the diagnosis of brain tumors. Although other F-18 labelled amino acid tracers, such as anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid ([^{18}F]FACBC, fluciclovine) [11], are under consideration, the extensive clinical experience and well-understood behavior of [^{18}F]FET in brain tumors and non-neoplastic lesions remains an advantage and must first be gained with other tracers.

This review summarizes the basic knowledge about [^{18}F]FET and its clinical applications with a focus on more recent studies and discusses the future role of [^{18}F]FET PET in the context of recent developments in neurooncology.

2. Characteristics of [^{18}F]FET

2.1 Radiosynthesis

So far, the radiosyntheses of [^{18}F]FET follows two principle methodologies: via build-up synthesis, using a ^{18}F-fluoroalkylation procedure, or by direct synthesis, using an appropriately protected derivative of tyrosine. Both methods have been optimized for implementation in remote-controlled synthesizers fulfilling GMP-conditions.

The first published synthesis of [^{18}F]FET bases on a two-step reaction, however, requiring two HPLC purification steps and thus is difficult to automate. As a start [^{18}F]fluoroethyl tosylate is synthesized by no-carrier-added (n.c.a.) nucleophilic ^{18}F-fluorination of 1,2-bis(tosyloxy)ethane. Subsequently, reversed phase HPLC-purification and on-line fixation of the ^{18}F-fluoroalkylation reagent is done, which is reacted in the second step with the disodium salt of L-tyrosine. The obtained [^{18}F]FET is purified by HPLC, followed by solid phase extraction and formulation, resulting in a total radiochemical yield (RCY) of 40 % [12]. In order to simplify the process 2-bromoethyl triflate is employed as precursor, enabling purification of the intermediate [^{18}F]fluoroethylbromide by distillation [13]. Alternatively, final isolation of [^{18}F]FET upon the build-up procedure can be performed by means of several cartridge systems saving an HPLC purification step [14].

The less complex direct synthesis proceeds as a one-pot procedure via n.c.a. nucleophilic ^{18}F-fluorination of *O*-(2-tosyloxyethyl)-*N*-trityl-L-tyrosine *tert*-butylester as precursor, followed by deprotection with trifluoroacetic acid in dichloromethane. A combination of a solid phase extraction, coupled with a subsequent HPLC-purification, enables an easy automatable procedure with a RCY of up to 60%, a radiochemical purity of >98%, and a molar activity of

>200 GBq/µmol. The use of ethanol/water (2/98) as HPLC eluent even leads to a ready for application solution of [^{18}F]FET [15]. Usage of hydrochloric acid for deprotection enables an even better automation and GMP-compatibility of the process [16], and again, a tailored set of solid phase cartridges allows the purification of [^{18}F]FET without HPLC [17, 18].

Another one-pot alternative was introduced for direct ^{18}F-labelling, applying a Ni(II) complex of an alkylated (S)-tyrosine Schiff base (Ni-(S)-BPB-(S)-Tyr-OCH_2-CH_2OTs) as precursor, This easy to automate method lead again to a somewhat smaller total RCY of >40 %, but an equal radiochemical purity of >99 % (see [19] and references therein). The purification is here again performed by solid phase extraction methods without the need of HPLC. The use of the nickel-containing precursor as chiral auxiliary provides an enantiomeric excess of 95-96% of L-[^{18}F]FET, while the first two methods provide a stereochemically pure product. Its use, however, seems particularly critical with regard to careful quality evaluation fulfilling given GMP requirements.

In comparison, all three procedures are useful for routine production of [^{18}F]FET, but the second one appears most efficient, considering ease of performance and radiochemical yield.

2.2 Toxicity and dosimetry

The toxicity of FET has been tested in mice in doses up to 150 µg/kg body weight i.v. (Research and Consulting Company Ltd. Itingen/Switzerland, Project 666887). Neither behavioral nor somatic abnormalities were reported and the LD50 is expected to be much higher. According to current guidelines [20], the recommended dose for human application is 185 - 200 MBq of [^{18}F]FET, which corresponds – at a specific radioactivity of 200 GBq/µmol and a molecular weight of 227 g/mol – to approx. 0.23-28 µg [^{18}F]FET per patient, or up to 4 ng/kg for a 70 kg patient. The clinical use of this tracer in more than 10.000 patients in the last 20 years revealed no reported advers events and [^{18}F]FET is generally considered to be safe for human application. The highest radiation dose is observed in the urinary bladder wall with

60 µGy/MBq, the effective dose is 16.5 µSv/MBq i.e. 3.3 mSv after injection of 200 MBq [^{18}F]FET in a 70 kg patient [21].

2.3 Pharmacokinetics

After intravenous injection of [^{18}F]FET the blood activity curve shows an initial peak after 1.5 minutes post injection (p.i.), and reaches a plateau after 20 minutes p.i. with a value of approx. 12±3x10^{-3} % injected dose (ID) per ml. This rather high concentration of [^{18}F]FET in the blood compartment has to be taken into account when evaluating regions near large vessels. Whole body PET scans 70 and 200 minutes p.i. revealed similar distribution of radioactivity in all organs, with a standardized uptake value (SUV) between 0.5 and 1.6. Only the urinary system had higher SUV of up to 2.0 in the kidneys and up to 11.2 in the urinary bladder [21].

Metabolic analyses revealed a high stability of [^{18}F]FET in the plasma. Between 5 to 120 minutes p.i., the percentage of stable [^{18}F]FET in relation to total plasma activity decreased from 95±9% to 87±13% ID. Few metabolites are found in plasma and the percentage of stable [^{18}F]FET in urine is lower, i.e. 61±3 % ID 150 minutes p.i., suggesting that most metabolites are rapidly excreted by the kidneys, while overall excretion with a rate of 5.3% ID/h is rather low [21]. Furthermore, no significant participation of [^{18}F]FET into protein synthesis has been found [12, 22, 23], nor is there evidence for the tracer to be part of the catecholamine pathway [21] or to be a substrate of tyrosine hydroxylase [24].

[^{18}F]FET, as its natural analogue L-tyrosine, belongs to the class of large neutral amino acids, which are predominantly transported by the system L amino acid transporters (LAT). Today, it is assumed that [^{18}F]FET transport into the brain is mainly mediated by Na^+-independent LAT1, since LAT2 and Na^+-dependent transporters are not expressed at the luminal side of the blood-brain barrier [25]. This conclusion is based on several *in vitro* studies using tumor cells [22, 23], *Xenopus* oocytes [26, 27] or other cell lines [28, 29] which express different

types of amino acid transporters. [^{18}F]FET uptake can be displaced by other amino acids transported by the LAT transporter or by 2-aminobicyclo-[2,2,1]heptane-2-carboxylic acid (BCH), an inhibitor of the system L transporter. While the main route via LAT1 into the brain seems to be elucidated, the studies also point to other uptake mechanisms like the Na^+-dependent amino acid transporters $B^{0,+}$ and B^0, depending on the specific cell line and intra- and extracellular amino acid concentrations. This rather complex mechanism might account for unexpected findings such as low [^{18}F]FET uptake in peripheral tumors despite high LAT1 expression [30].

Kinetic modelling of [^{18}F]FET uptake has been applied in few clinical [31, 32] and preclinical studies [33, 34], using 1-tissue and 2-tissue compartment models as well as the model-independent Patlak analysis. So far, no clinical benefit of using kinetic modelling over simpler approaches as tumor-to-brain ratios (TBR) has been reported.

3. Clinical applications

3.1 Methods: Static and dynamic scans

A detailed description of the methodological aspects of [^{18}F]FET PET has been presented in an earlier publication [35]. Data evaluation is usually based on static scans from 20-40 minutes p.i. of [^{18}F]FET [20, 36, 37]. The tracer uptake in the tumors and in the normal brain is quantified by the SUV by dividing the radioactivity (kBq/ml) in the tissue by the radioactivity injected per gram of body weight. Important parameters are the maximum or mean tumor-to-brain ratio (TBR_{max}, TBR_{mean}) and the biological tumor volume (BTV) which corresponds to the [^{18}F]FET positive tumor by application of a cut-off TBR of more than 1.6 [38, 39]. Caution has to be taken when patients are under dexamethasone therapy, especially during treatment monitoring, as [^{18}F]FET uptake in normal brain tissue and thus the TBR and the BTV might be influenced [40]. To ensure stable metabolic conditions, fasting for more than 4 h prior to the scan is recommended, although preclinical results suggest that only high

doses of amino acids in the blood pool alter the [^{18}F]FET uptake [41]. It has been reported that for glioma grading based on histology early scans from 5-15 minutes p.i. may be more accurate [42]. Further information may be derived from dynamic PET scans for up to 50 minutes p.i. and analyzing the time-activity-curves (TAC) of brain lesions [43], as high-grade tumors often show an early peak and subsequently a decreasing TAC, while low-grade tumors classified according the WHO classification of 2007 [44] and non-neoplastic lesions exhibit slowly increasing uptake patterns [45-47]. In heterogeneous tumors, selected regions may exhibit different curve patterns, indicating locally a higher tumor grade than in the whole tumor area [48, 49]. Besides qualitative descriptions of the TAC [46], quantitative parameters like time-to-peak (TTP) [50], the slope in the phase from 15-40 minutes p.i. [51, 52] and TBR from different phases of the scan [46, 53] may be helpful for comparative assessment. Dynamic scans and evaluation, however, are more time consuming and consequently more expensive; therefore, the cost-value ratio depends on the specific clinical question.

3.2 Differential diagnosis, grading, and prognostication

The differential diagnosis of cerebral lesions includes non-neoplastic lesions like inflammatory processes, hemorrhage and infarction, as well as primary and secondary brain tumors. [^{18}F]FET PET has a sensitivity between 82-92% and a specificity between 57-76% to distinguish a tumor from a non-neoplastic lesion with a positive predictive value of 98% for neoplastic tissue [54-56]. A TBR_{mean} threshold of 1.6 and a TBR_{max} of 2.1-2.5 provided the best results to separate these entities. Nevertheless, histological evaluation after biopsy or surgery remains the gold standard to provide an accurate histological and molecular characterization of the lesions.

By merely evaluating the [^{18}F]FET uptake, high-grade tumors classified according the WHO classification of 2007 [44]are not well distinguishable from low-grade tumors. The sensitivity and specificity ranges between 71-80 and 56-85%, respectively [55, 57-59]. One cause is the

relatively high uptake in oligodendrogliomas which comprise up to 15-28% of all gliomas [55, 58, 59] and which have a better prognosis than other gliomas of the same grade [47, 60]. The accuracy for the differentiation between low- and high-grade gliomas classified according to the WHO classification of 2007 can be increased by using dynamic parameters of [^{18}F]FET uptake [42, 61-63]. In more recent studies, the revised WHO classification 2016 has been taken into account [64], and the relationship between [^{18}F]FET uptake and molecular markers such as gene mutation encoding for the isocitrate dehydrogenase enzyme (IDH) has been investigated [65-67]. These studies demonstrated a relationship between [^{18}F]FET kinetics and IDH mutation status which may be helpful to predict these molecular parameters non-invasively.

Studies on the prognostic significance of [^{18}F]FET PET are controversial. On the one hand, there is some evidence for better prognosis in gliomas with low [^{18}F]FET uptake [68, 69] on the other hand gliomas with a photopenic appearance in [^{18}F]FET PET can have an unfavorable prognosis [39, 70]. One study identified prognostically relevant information of [^{18}F]FET kinetics beyond molecular markers [71]. Another approach is to measure uptake heterogeneity of amino acids using textural features analyses of tracer distribution, which shows potential to improve tumor grading and prognostication [72-74]. Furthermore, the BTV of [^{18}F]FET uptake at primary diagnosis of gliomas has been reported to be a prognostic factor [75-77]. In low grade-gliomas, the kinetic analysis may help to identify areas of malignant transformation and thus adds prognostic information [39, 49, 57, 78, 79].

3.3 Treatment planning

The ability of [^{18}F]FET to delineate the BTV and to identify metabolically active parts beyond the enhancement of MRI contrast agents (Fig. 1) provides advantages for tumor treatment planning compared with conventional MRI. The potential of [^{18}F]FET to detect the tumor extent in malignant gliomas and even in non-enhancing gliomas without BBB leakage has

been demonstrated in several studies [38, 56, 80, 81]. Furthermore, a sensitivity of 72-79% has been reported for detecting a local maximum for biopsy guidance in gliomas [56, 82], which may be helpful to minimize false-negative results. Tissue samples from the most active tumor parts obtained by biopsies are crucial for histological and molecular characterization of the tumors and hence for determining the best treatment options. Optimized planning for radiation therapy is provided by improved tumor delineation using [^{18}F]FET PET, though no prolonged survival compared to standard MRI-based planning has been reported so far [83, 84]. A prospective phase II clinical trial with recurrent glioblastoma patients is currently ongoing [85]. Biopsy controlled studies have provided evidence that [^{18}F]FET PET depicts the solid and metabolically active tumor mass more reliable than conventional MRI [38, 48, 80, 86, 87].

Studies using [^{18}F]FET report a higher sensitivity than MRI alone for the detection of residual tumor after resection and PET has been recommended additionally to MRI for postoperative assessment [88-90]. An experimental study demonstrated a slightly increased [^{18}F]FET accumulation at the rim of the resection cavity, which could be attributed to reactive astrocytosis [91] However, the accumulation was lower than in tumor tissue and decreased significantly after 2 weeks. Therefore, it was recommended to assess residual tumor after surgery after a time interval of 2 weeks.

3.4 Diagnosis of tumor recurrence and treatment monitoring

The most frequent indication for the use of [^{18}F]FET PET in neuro-oncology is the differentiation between tumor progression on the one hand and treatment-related changes on the other hand. Contrast enhancement in MRI is frequently observed after radiotherapy and/or chemotherapy owing to treatment related changes. During the first 12 weeks after chemoradiation of malignant gliomas with temozolomide, progressive contrast-enhancing lesions are frequently observed on MRI, which are not related to tumor progression, but

remain stable or regress during further follow-up. This phenomenon is observed in 15-30% of patients with malignant gliomas and is referred as pseudoprogression. [92-94]. [^{18}F]FET PET has been shown to differentiate pseudoprogression from recurrence with an accuracy of up to 90% [95-97]. In the course of the disease further treatment-related changes such as radionecrosis may occur even up to years after radiotherapy [98]. A number of studies have examined the significance of [^{18}F]FET PET for differentiating tumor recurrence from treatment-related changes in glioma patients. The diagnostic accuracy of these examinations varies between 80% and 90% and is therefore clearly superior to conventional MRI [99-105]. Similar results of up to 88% have been reported for the differentiation of recurrent brain metastasis from radiation necrosis using dynamic [^{18}F]FET PET [51, 106-108]. In this context, the evaluation of textural parameters derived from static [^{18}F]FET PET appears to be promising as well [109].

Another diagnostic problem is the so-called pseudoresponse, which is frequently observed in MRI during anti-angiogenic therapy due to rapid restoration of the BBB [110]. Anti-angiogenic drugs can rapidly decrease contrast enhancement after initiation of treatment, producing an apparent response with persistent non-enhancing tumor. [^{18}F]FET PET has been shown to discriminate responders from non-responders much earlier than MRI alone [111-115].

In the assessment of early treatment response, reduction of [^{18}F]FET uptake has been reported to be a good prognostic factor after postoperative chemoradiation [116, 117]. A reduction of 10% uptake, referred to as [^{18}F]FET PET responders, correlated with a significantly longer progression-free survival compared to stable or increasing tracer uptake after therapy. Similar results have been reported for other approaches like radioimmunotherapy and convection-enhanced delivery of paclitaxel [118, 119]. In a recently published review the previous applications of [^{18}F]FET PET in therapy monitoring have been described in detail. [120] .

4. Pitfalls

[^{18}F]FET uptake in benign brain lesions is usually low and does not exceed tracer uptake in malignant gliomas [56]. Preclinical studies confirm generally low uptake of [^{18}F]FET in inflammatory lesions, abscesses, ischemia, and hematoma. Slightly increased uptake is observed in reactive gliosis which usually can be well distinguished from tumor uptake [121-124]. Only in rare cases high [^{18}F]FET uptake has been reported in abscesses, demyelination and other active inflammatory processes as well as postischemic lesions and cortical malformations [55, 125, 126]. Furthermore, a recent study [127] reported about a subgroup of seizure patients with high gyral [^{18}F]FET uptake in epileptic foci, mimicking tumor tissue. In those patients, upregulation of LAT1/2 in neurons rather than reactive astrogliosis was found to be the reason for the elevated uptake. A recent study in two different rat models of seizures and a group of patient with different kinds of epilepsy, showed no increased [^{18}F]FET uptake post- and interictally. The authors concluded that [^{18}F]FET uptake due to seizure activity is a very rare phenomenon and not a major pitfall in brain tumor diagnostics (Stegmayr et al., manuscript submitted). Taken together, unspecific [^{18}F]FET uptake in non-neoplastic lesions is not frequent, but has to be considered in clinical routine.

5. Cost effectiveness

As described in the previous chapters, the additive diagnostic value of [^{18}F]FET PET compared to conventional MRI has been demonstrated in numerous studies. The effect of additional [^{18}F]FET PET on patient-relevant parameters like survival or increased quality of life, however, is difficult to assess since these endpoints are influenced by a wide range of factors and long-lasting prospective studies with large numbers of patients are needed to answer these questions. Alternatively, some studies have addressed the cost effectiveness of [^{18}F]FET PET using model-based approaches addressing the number needed to diagnose in order to avoid wrong diagnosis. In one study comparing [^{18}F]FET PET and MRI to MRI alone

in selecting the biopsy site for the diagnosis of gliomas resulted in a cost-effectiveness ratio of € 6,405 from the perspective of the German statutory health insurance [128]. Again considering the German statutory health insurance a cost-effectiveness ratio of € 5,725 year was calculated in a study evaluating [^{18}F]FET PET in addition to MRI in patients with recurrent high-grade glioma under anti-angiogenic treatment [129]. A calculation concerning the cost-efficiency ratios for progression-free and overall survival in glioblastoma patients after surgery and before temozolomide maintenance treatment based on cost calculations from the perspective of the National Institute for Health and Disability Insurance in Belgium, resulted in a cost-effectiveness ratio of € 1,357.38 per life-year for every identified non-responder [130]. Hence, [^{18}F]FET PET seems to be well justified not only for clinical accuracy but also with respect to reducing costs.

5. Conclusion

The potential of [^{18}F]FET PET in modern brain tumor diagnostics has been well documented in multiple studies in the last two decades. The production of the tracer is very efficient and so far, no side effects have been observed in tens of thousands of applications. The improved delineation of tumor extent allows a more accurate treatment planning and the high accuracy in the differentiation of tumor progression from treatment-related changes is very helpful to tailor an optimal treatment strategy for each individual patient. Besides amino acid PET, advanced MRI sequences are applied in many centers to overcome the shortcomings of conventional anatomical MR imaging. The fact that [^{18}F]FET PET is widely used in those centers that have access to the full spectrum of advanced MRI methods emphasizes the value of the method beyond these alternative MRI methods. The costs of [^{18}F]FET PET appear justified in terms of clinical benefit, especially since newer therapeutic approaches are very cost-intensive and reliable diagnostics are required in order to be able to use them in a targeted manner.

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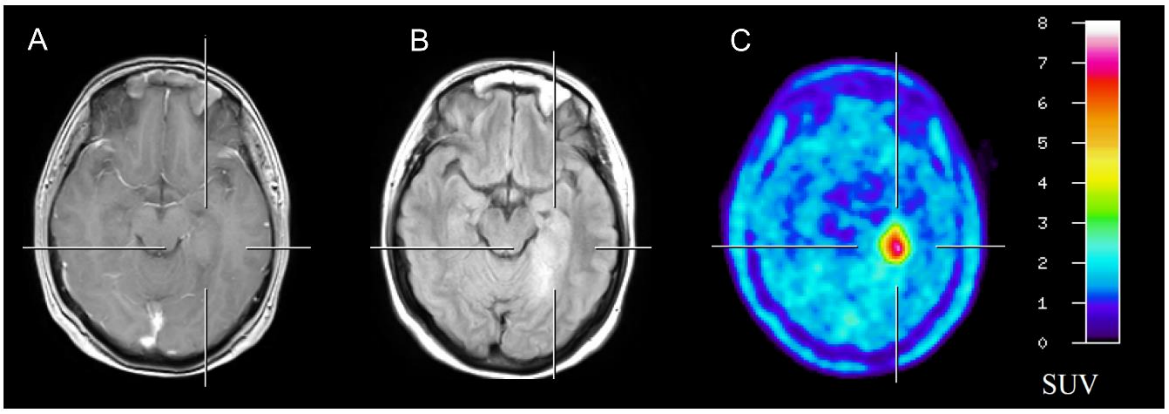

Figure 1: Patient with an unclear non-enhancing lesion in the left temporal lobe. The true extent of the tumor and the metabolically most active tumor parts for biopsy guidance are difficult to identify in the contrast-enhanced T1-weighted (A) and in T2-weighted MRI (B) but clearly depicted in [^{18}F]-FET- PET (C). Neuropathological evaluation of tissue obtained by biopsy revealed the diagnosis of glioblastoma.