Editorial

F18 FET PET/CT in Brain Tumors

Abdelwahab, M.A and Omar, W.

NCI, Cairo University. Egypt.

18F-fluoro-ethyl-tyrosine (18F-FET) was developed in the late 1990s first synthesized by **Wester and colleagues** [(1)]. Providing an 18F-labeled amino acid PET tracer based on f18- fluro-alkylation of disodium salt of L-Tyrosine, with a (110 minutes) half-life, which is more suitable for routine clinical applications than other C11 labeled PET tracers (eg. C11 methionine) [(2)].

FET is an artificial amino acid taken up into up regulated tumoral cells but not incorporated into proteins (contrary to natural amino acids such as 11C methionine) .18F-FET allows good-contrast images to be obtained in both high- and low-grade tumors [(3)].

After a surge of published clinical studies in the last decade, applications of FET PET in brain tumor imaging have been comprehensively reviewed in many studies [(4, 5 and 6)].

Mechanisms of Tumoral Uptake of Amino Acid PET Radiotracers: System L amino acid transporters (e.g.: LAT1, LAT2, LAT3, and LAT4) transport a variety of neutral amino acids. LAT1 is widely expressed in cancers and plays an essential role in the survival and growth of tumors [(3)] LAT2 is predominantly expressed in other cell types and carries small neutral amino acids [(7)] whereas LAT3 and LAT4 have a narrower substrate selectivity (preferring phenylalanine). Other transport systems, including system A, xCT, glutamine, and cationic amino acid transporters, have been explored for tumor imaging with radiolabeled amino acids [(8,9)] Still, system L currently appears to be the most suitable for brain tumor imaging due to its activity at the blood-brain barrier [(8)].

Corresponding Authors: Abdelwahab, M.A. **E-mail:** mai_4a@yahoo.com.

FET uptake primarily measures the amino acid transport rate because this radiotracer is neither incorporated into proteins nor metabolized after being transported to the cell. FET has lower uptake in inflammatory cells compared to FDG and MET and is more specific to differentiate tumoral tissue from inflammation than MET [10, 11 and 12].

18F-FET PET/CT in Differential Diagnosis of Primary Brain Tumor:

18F-FET has been known to distinguish between proliferative tumor and non-tumoral lesion with reported good sensitivity (82% and 84%) and average specificity (76% and 62%), respectively, for the diagnosis of brain tumor specially glioma [13].

Initial comparison studies demonstrated that 18F-FET uptake ratios correlated with 11C-methionine uptake but with a lesser uptake by inflammatory cells, allowing a better discrimination between infectious and tumoral lesions [14].

Several studies demonstrated that the ability of 18F-FET PET/CT to assess the tumoral brain lesions and seems superior to MRI alone with increased accuracy up to 94 % as reported with ***Floeth et al*** [14,15].

Regarding the ability to distinguish between tumor subgroups, mean tumor/background ratio (TBR) and maximum TBR indices have emerged as measures, allowing inter- and intra-patient comparisons, because the normal brain background is quite variable on consecutive PET examinations even in the same patient. Thresholds (mean TBR >1.6 and maximum TBR > 2.1 for brain tumor) were pinpointed to differentiate high from low grade gliomas with 94% sensitivity, 100% specificity [16, 17].

18F-FET PET/CT in radiotherapy planning:

Of increased interest is the initial assessment of brain lesions by 18F-FET PET/CT and MRI to guide radiotherapy. For instance, ***Weber et al*** [18] compared 18F-FET–based biologic tumor volume for radiotherapy planning in high-grade glioma with conventional MRI–based gross tumor volume.

They found that biologic tumor volume and gross tumor volume differed in size and localization in two thirds of the patients. Similar differences were confirmed in a recent study by ***Niyazi et al*** [19]. They found that the addition of 18F-FET PET/CT resulted in larger target volumes on 3D conformal radiotherapy planning than with MRI alone (P 0.001). Using composite target volumes, ***Weber et al***. demonstrated that 90% of tumor recurrences occurred

Within the 95% is dose line, suggesting that radiotherapy planning with 18F-FET PET and MRI may reduce non-central tumor control failure [18, 19].

18F-FET PET/CT in therapy response:

Piroth et al [20] showed that 18F-FET PET/CT are sensitive at distinguishing between responders and non-responders in patients with Glioblastoma early after radio-chemotherapy.

The value of 18F-FET PET/CT is also established for noninvasively distinguishing between radio necrosis and tumor recurrence.

18F-FET PET/CT can predict therapy response and failure and monitoring of Glioblastoma response to paclitaxel. Thus, pre-treatment baseline 18F-FET PET/CT in patients with brain tumors is important to guide tumor diagnosis and biopsy and is effective for radiotherapy planning and for assessment of tumor response to radiotherapy or chemotherapy [21].

18F-FET PET/CT in differentiating Local Recurrence from Radiation Necrosis

Although, Contrast-enhanced MRI is the method of choice for the evaluation of metastatic brain tumors yet in many patients, the differentiation of local recurrent from radiation necrosis after radiotherapy using contrast-enhanced MRI is difficult. Therefore, new diagnostic methods for the follow-up and management of patients with recurrent brain lesions are needed [18, 22].

18F-FDG PET/CT is not sensitive enough to differentiate viable brain tumors from radiation necrosis [22]. In contrast to 18F-FDG uptake, amino acid uptake has been shown to be increased relative to normal brain tissue in most low- and high-grade tumors, and radio labeled amino acids might therefore be preferable for evaluating recurrent tumors. Previously, it has been shown that PET using L-[methyl-11C] methionine (11C-MET) may be effective however, remains restricted to centers with an on-site cyclotron because of the short half-life of the 11C isotope (20 min) [2]. 18F-FET /CT exhibit high in vivo stability, low uptake in inflammatory tissue, and suitable uptake kinetics for clinical imaging. Contrast-enhancing non-tumoral tissue on MRI, for example, due to radio necrosis, is usually negative on 18F-FET PET/CT .In many studies 18F-FET was able to distinguish between recurrent tumor and therapy-induced benign changes with 100% accuracy.

Focal and high 18F-FET uptake was considered suggestive of tumor recurrence, whereas low and homogeneous Uptake around the resection cavity was considered a benign post treatment change [23, 24, 25 and 26]. ***Figure 1;*** showed recurrence primary tumor in LT tempro-parietal region with central necrosis**.**

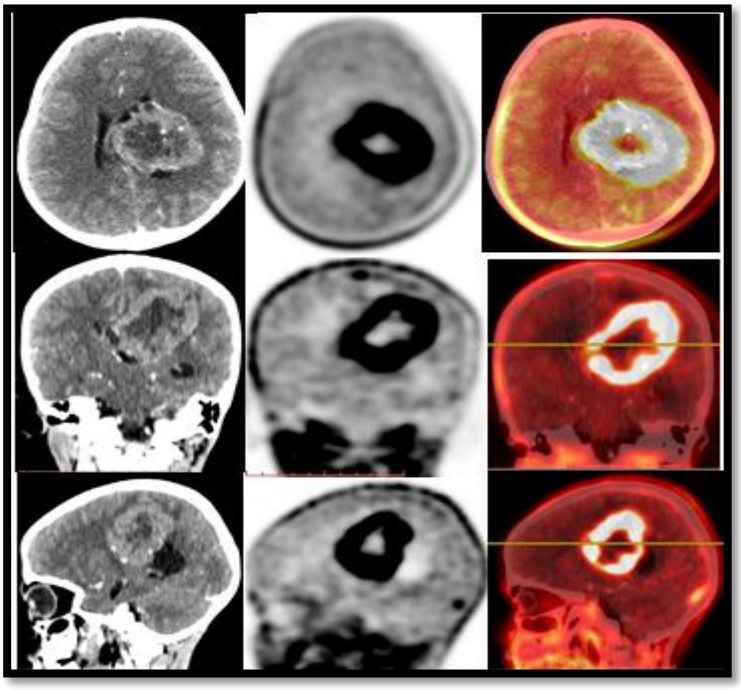

Figure (1): 18F-FET PET avid left tempro-parietal lesion with high grade Glioblastoma (A case reported in Children Hospital of Pediatric Oncology CCHE).

REFRENCES:

1) ***Wester HJ, Herz M, Weber W, et al.*** Synthesis and radio pharmacology of O-(2-[18F]fluoroethyl)-L-tyrosine for tumor imaging. J. Nucl. Med. 40:205–12. [PubMed: 9935078]; 1999.

2) ***Glaudemans AW, Enting RH, Heesters MA, et al.*** Value of 11C-methionine PET in imaging brain Tumors and metastases. Eur. J. Nucl. Med. Mol. Imaging. 40:615–35. doi: 10.1007/ s00259-012-2295-5. [PubMed: 23232505]; 2013.

3) ***Heiss P, Mayer S, Herz M, et al.*** Investigation of transport mechanism and uptake kinetics of O-2-[18F] fluoro-ethyl -L-tyrosine in vitro and in vivo. J. Nucl. Med. 40:1367–73. [PubMed: 10450690]; 1999.

4) ***Gotz I, Grosu AL.*** [18F] FET-PET imaging for treatment and response monitoring of radiation therapy in malignant glioma patients - a review. Front Oncol. : 104.doi:10.3389/fonc.2013.00104. [PubMed: 23630666]; 2013.

5) ***Weber WA, Wester HJ, Grosu AL, et al.*** O-2-[18F] fluoro-ethyl -L-tyrosine and L-[methyl-11C] methionine uptake in brain tumors: initial results of a comparative study. Eur. J. Nucl. Med. 27:542–549; 2000.

6) Huang C, McConathy J. Fluorine-18 labeled amino acids for oncologic imaging with positron emission tomography. Curr. Top Med. Chem. 13:871–91. doi: 10.2174/1568026611313080002.PubMed: 23590170]; 2013

7) del Amo EM, Urtti A, Yliperttula M. Pharmacokinetic role of L-type amino acid transporters LAT1 and LAT2. Eu.r J. Pharm. Sci. 35:161–74. doi:10.1016/j.ejps.2008.06.015. [PubMed: 18656534]; 2008.

8) Imai H, Kaira K, Oriuchi N, et al. Inhibition of L-type amino acid transporter 1 has antitumor activity in non-small cell lung cancer. Anticancer Res. 2010; 30:4819–28. [PubMed: 21187458] Juhasz et al. Page 14 *Mol Imaging*. Author manuscript; available in PMC 16 October; 2014.

9) Baek S, Choi CM, Ahn SH, et al. Exploratory clinical trial of (4S)-4-(3-[18F] fluoro-propyl - glutamate for imaging xC-transporter using positron emission tomography in patients with non-small cell lung or breast cancer. Clin. Cancer. Res. 18:5427–37. doi: 10.1158/1078-0432.CCR-12-0214. [PubMed: 22893629]; 2012.

10) Alkonyi B, Mittal S, Zitron I, et al. Increased tryptophan transport in epileptogenic dys-embryoplastic neuroepithelial tumors. J Neurooncol. 107:365–72. Doi: 10.1007/s11060-011-0750-y. [PubMed: 22048879]; 2012.

11) Zitron IM, Kamson DO, Kiousis S, et al. In vivo metabolism of tryptophan in meningiomas is mediated by indoleamine 2, 3-dioxygenase 1. Cancer Biol Ther.14:333–9. Doi: 10.4161/cbt. 23624. [PubMed: 23358471]; 2013.

12) Rossier G, Meier C, Bauch C, et al. LAT2, a new basolateral 4F2hc/CD98-associated amino acid transporter of kidney and intestine. J. Biol. Chem. 274:34948–54. Doi: 10.1074/jbc. 274.49.34948. [PubMed: 10574970]; 1999.

13) Stober B, Tanase U, Herz M, et al. Differentiation of tumor and inflammation: characterization of [methyl-3H] methionine (MET) and O-2-[18F] fluoro-ethyl -L-tyrosine (FET) uptake in human tumor and inflammatory cells. Eur. J. Nucl. Med. Mol. Imaging.33:932–9. Doi: 10.1007/s00259-005-0047-5. [PubMed: 16604346]; 2006.

14) Jager PL, Vaalburg W, Pruim J, et al. Radiolabeled amino acids: basic aspects and clinical applications in oncology. J. Nucl. Med. 42:432–445; 2001.

15) Laverman P, Boerman OC, Corstens FH, Oyen WJ. Fluorinated amino acids for tumour imaging with positron emission tomography. Eur. J. Nucl. Med. Mol. Imaging. 29:681–690; 2002.

16) Pauleit D, Floeth F, Hamacher K, et al. O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain. 128:678–687; 2005.

17) Floeth FW, Pauleit D, Wittsack HJ, et al. Multimodal metabolic imaging of cerebral gliomas: positron emission tomography with [18F] fluoroethyl-L-tyrosine and magnetic resonance spectroscopy. J Neurosurg.102:318– 327; 2005.

18) Grosu AL, Weber WA, Franz M, et al. Re-irradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractional radiotherapy. Int J. Rad. Oncol. Biol. Phys. 63:511–519; 2005.

19) Tralins KS, Douglas JG, Stelzer KJ, et al. Volumetric analysis of 18F-FDG PET in Glioblastoma multiform: prognostic information and possible role in definition of target volumes in radiation dose escalation. J Nucl Med. 43: 1667–1673; 2002.

20) Piroth MD, Pinkawa M, Holy R, et al. Prognostic value of early [18f] fluoroethyltyrosine positron emission tomography after radio-chemotherapy in Glioblastoma multiform. Int J. Rad. Oncol. Biol. Phys. 80:176–184; 2011.

21) Po¨pperl G, Goldbrunner R, Gildehaus FJ, et al. O-2-[18F] fluoroethyl -L-tyrosine PET for monitoring the effects of convection-enhanced delivery of paclitaxel in patients with recurrent Glioblastoma. Eur. J. Nucl. Med. Mol. Imaging.32: 1018–1025; 2005.

22) Levivier M, Goldman S, Pirotte B, et al. Diagnostic yield of stereotactic brain biopsy guided by positron emission tomography with [18F] fluorodeoxy glucose. J. Neurosurg.. 82:445–452; 1995.

23) Langleben DD, Segall GM. PET in differentiation of recurrent brain tumor from radiation injury. J. Nucl. Med.41:1861–1867; 2000.

24) Spaeth N, Wyss MT, Weber B, et al. Uptake of 18F-fluorocholine, 18F-fluoroehtyl-L-tyrosine, and 18F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumor recurrence. J. Nucl. Med. 45:1931–1938; 2004.

25) Popperl G, Gotz C, Rachinger W, et al. Value of O-2-[18F] fluoroethyl -Ltyrosine PET for the diagnosis of recurrent glioma. Eur J. Nucl. Med. Mol. Imaging. 31:1464–1470; 2004.

26) Rachinger W, Goetz C, Popperl G, et al. Positron emission tomography with O-2-[18F] fluoroethyl -L-tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas. Neurosurgery.57:505–511; 2005.