

Benefits of ^{18}F -FET PET in preoperative assessment of glioma heterogeneity demonstrated in two case reports

Benefity vyšetření ^{18}F -FET PET v předoperačním posouzení heterogeneity gliálních tumorů demonstrovány na dvou kazuistikách

Dear Editor,

Magnetic resonance imaging is still considered the gold standard of diagnostic algorithms in gliomas. However, especially in gliomas with atypical enhancement patterns, PET could improve evaluation by monitoring processes such as cell proliferation, membrane biosynthesis, and glucose consumption [1]. Radiolabeled amino acids are frequently used PET tracers due to their high signal-to-noise ratio. In contrast to glucose derivatives, the uptake of amino acids in inflammatory cells is lower, which makes them more specific for tumor detection [2]. Moreover, amino acids are accumulated in malignant cells owing to increased expression of type L amino acid transporters in tumor vasculature [3]. Additionally, the counter-transport system A is overexpressed in neoplastic cells and seems to correlate positively with tumor cell growth rate [4]. Elevated transport of amino acids is a result of increased protein synthesis and also reflects the increased demand by tumor cell metabolism [5]. Currently, [^{18}F]-fluoro-ethyl-L-tyrosine (^{18}F -FET) is a promising amino acid radiotracer in diagnosing low-grade glioma and its possible hot spots. Besides diffusion through the impaired blood-brain barrier (BBB), ^{18}F -FET can additionally cross the BBB via endothelial L-transporters [6]. It also retains a relatively long half-life of 109 min. ^{18}F -FET can be produced in large amounts for clinical purposes and is applicable in a satellite concept. In contrast, 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT) is a radiolabeled analog of the DNA nucleoside that enters cells by active trans-

port through nucleoside transporters and by passive diffusion [7]. As it does not cross the intact BBB [8] and reflects tissue proliferation rate [9], the diagnostic yield of ^{18}F -FLT in low-grade gliomas (LGG) is questionable because of their more indolent biological course.

Two cases are presented below, where PET imaging with ^{18}F -FLT and ^{18}F -FET was performed in addition to conventional MRI. The aim of this project was to analyze which of the compared radiotracers was more suitable for glioma evaluation.

A 43-year-old woman suffering from complex partial epileptic seizures was examined. MRI showed a brain tumor in the left parietal lobe with calcifications and no enhancement after contrast administration (Fig. 1). Advanced PET methods were indicated to investigate possible tumor heterogeneity. ^{18}F -FLT PET images were acquired 10 min after tracer injection in a single static image. ^{18}F -FET PET images were acquired as dynamic scanning between 5 min and 45 min after administration, each image acquisition lasting 5 min. Tracer accumulation was evaluated in all images to show tracer kinetics. ^{18}F -FLT PET showed moderately increased accumulation of the radiotracer in a small portion of the tumor (maximal standardized uptake value [SUV_{mad}] 1.75; values of SUV_{mad} above 2.0–2.5 are usually considered significantly pathologic), which supported the diagnosis of LGG. On ^{18}F -FET PET regions with slowly increasing tracer activity representing LGG component, there were regions of tracer kinetics more typical for high-grade glioma,

The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

H. Valeková^{1,2}, J. Vašina³, Z. Řehák³, M. Hodolic^{4,5}, M. Hendrych^{6,7}, T. Kazda⁸, P. Pospíšil⁸, P. Solár^{1,2}, Z. Mackerle^{1,2}, R. Jančálek^{1,2}

¹Department of Neurosurgery – St. Anne's University Hospital Brno, Faculty of Medicine, Masaryk University, Brno, Czech Republic

²Department of Neurosurgery, St. Anne's University Hospital Brno, Brno, Czech Republic

³Department of Nuclear Medicine and PET Center, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czech Republic

⁴Nuclear Medicine Research Department, IASON, Graz, Austria

⁵Department of Nuclear Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic

⁶First Department of Pathology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

⁷First Department of Pathology, St. Anne's University Hospital, Brno, Czech Republic

⁸Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic



Prof. Radim Jančálek, MD, PhD
Department of Neurosurgery
St. Anne's University Hospital
Pekařská 53, 656 91 Brno
Czech Republic
e-mail: radim.jancalek@fnusa.cz

Accepted for review: 5. 1. 2021

Accepted for print: 29. 7. 2021

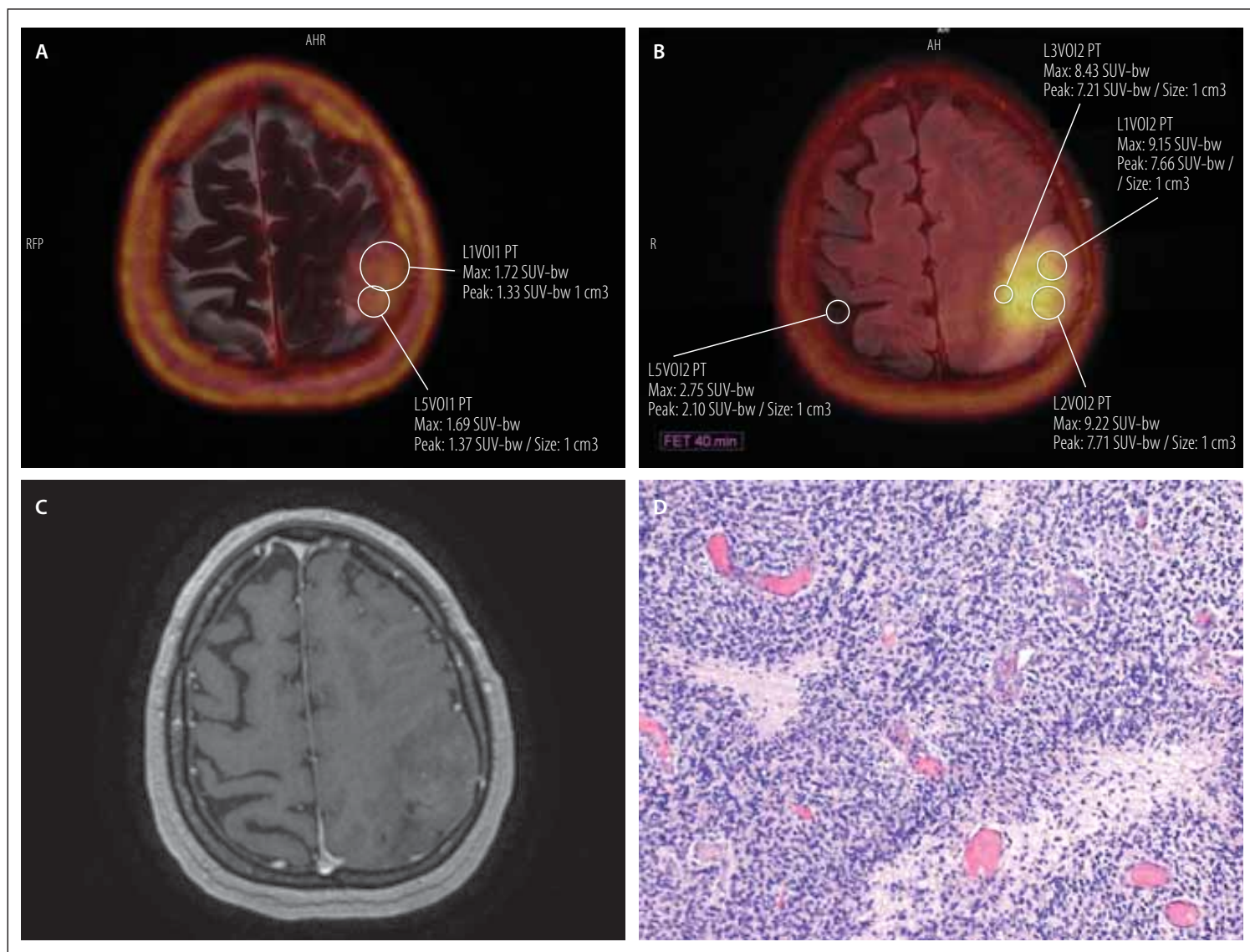


Fig. 1. (A) ¹⁸F-FLT PET/CT 10 min after radiotracer application, subsequently superimposed on anatomical MRI (T2 weighted image) for final evaluation. (B) ¹⁸F-FET PET/CT 40 min after radiotracer application fused with MRI (T2 FLAIR). (C) MRI (T1-weighted image with contrast) – no contrast enhancement detected throughout the tumor. (D) Histological findings – oligodendroglioma, WHO grade 2, IDH-mutant and 1p/19q-codeleted with focal upgrading into anaplastic oligodendroglioma, WHO grade 3, IDH-mutant and 1p/19q-codeleted. A diffuse oligodendroglial proliferation with delicate branching capillary network with focal anaplastic features, brisk mitotic activity and palisading necrosis developed through the progression from pre-existing oligodendroglioma (hematoxylin and eosin-stained; original magnification 100×).

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrosine; ¹⁸F-FLT – [¹⁸F]-fluorothymidine; FLAIR – fluid attenuated inversion recovery; IDH – isocitrate dehydrogenase

Obr. 1. (A) ¹⁸F-FLT PET/CT 10 min po aplikaci radionuklidu, následně fúzované se zobrazením na MR (T2 vážený obraz) k finálnímu zhodnocení. (B) ¹⁸F-FET PET/CT 40 min po aplikaci radionuklidu, fúzované s MR (T2 FLAIR). (C) MR (T1 vážený obraz s kontrastní látkou) – bez detekce patologického syčení po podání kontrastní látky. (D) Histologický nález – oligodendrogliom, WHO G2, IDH-mutovaný s 1p/19q-kodelečí s fokálním upgradingem na anaplastický oligodendrogliom, WHO G3, IDH-mutovaný s 1p/19q-kodelečí. Je patrna difúzní oligodendroglialní proliferace s větvičí se sítí kapilár, ložiskově přítomny anaplastické elementy, mitotická aktivita a palisádující nekrózy charakteristické pro progresi z původního oligodendrogliomu (barvení hematoxylin-eozin; zvětšení 100×).

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrozin; ¹⁸F-FLT – [¹⁸F]-fluorothymidin; FLAIR – fluid attenuated inversion recovery; IDH – isocitrátdehydrogenáza

i.e., an early tracer activity peak followed by its gradual decrease (Fig. 1E). The maximal SUV_{mad} was detected 10 min after tracer injection in the postcentral gyrus (SUV_{mad} 15.3). Increased tracer uptake was also noticed in the supramarginal gyrus (SUV_{mad} 13.4). Dif-

ferent dynamics were detected in the periventricular area of the left occipital horn, where mildly elevated values (mean value of SUV_{mad} for the 5th to the 40th min was 6.4) remained stable during the whole scanning time. This area could correspond to a low-

-grade portion of the tumor. The patient underwent 5-ALA navigated surgery with intraoperative monitoring. Histological diagnosis of oligodendroglioma, WHO grade 2, isocitrate dehydrogenase (IDH)-mutant and 1p/19q-codeleted with focal upgrading into anaplastic

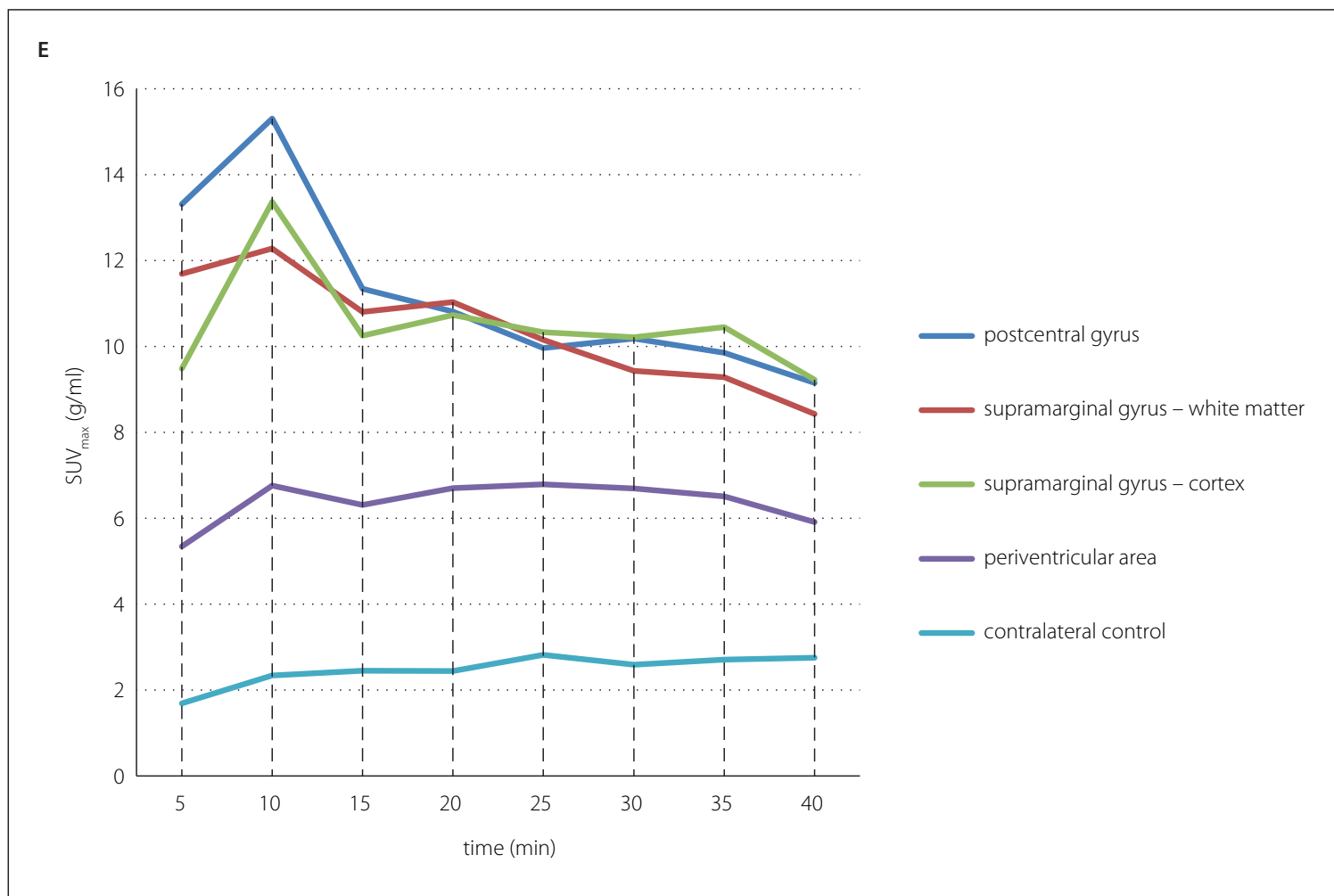


Fig. 1 – continuing. (E) Dynamic ¹⁸F-FET PET/CT showed maximal pathologic accumulation of the radiotracer in the left postcentral and supramarginal gyri after 10 min (SUV_{max} 15.3 and 13.4, respectively) followed by gradual decrease of tracer uptake, a typical pattern for high-grade glioma. The periventricular area showed a more stable curve with peak value (SUV_{max} 6.8) at 25 min after tracer injection, suggesting low-grade character. The contralateral supramarginal gyrus was used for comparison with a maximal SUV_{max} value of 2.8 and linear dynamics of radiotracer uptake.

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrosine; SUV_{max} – maximal standardized uptake value

Obr. 1 – pokračování. (E) Dynamické ¹⁸F-FET PET/CT zobrazila maximum patologické akumulace radionuklidu v levém postcentrálním (SUV_{max} 15,3) a supramarginálním (SUV_{max} 13,4) gyru v časné fázi (po 10 minutách od aplikace) s následným postupným poklesem vychytávání radionuklidu, obraz typický pro high-grade gliomy. Periventrikulární oblast vykazovala lineárnější průběh křivky akumulace radionuklidu s nejvyšší hodnotou SUV_{max} 6,8 25 minut po aplikaci, což odpovídá obrazu u low-grade gliomů. Jako referenci nepatologické tkáně ke srovnání hodnot byl využit kontralaterální supramarginální gyrus s maximální SUV_{max} 2,8 s lineární dynamikou vychytávání radionuklidu.

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrozin; SUV_{max} – maximální standardizovaná hodnota absorpce

oligodendroglioma, and WHO grade 3, IDH-mutant and 1p/19q-codeleted, was confirmed (Fig. 1D). This corresponded with different SUV_{mad} curves in different tumor parts on ¹⁸F-FET PET.

A 44-year-old man with headache and lower limb dysesthesias was diagnosed (CT scan) with a large tumor of the left frontal lobe with vast calcifications. MRI showed a non-enhancing non-homogeneous lesion infiltrating the corpus callosum and basal ganglia (Fig. 2). Both ¹⁸F-FLT and ¹⁸F-FET PET scans were obtained in the same fashion as in the previous case.

¹⁸F-FLT PET showed a homogenous, mildly elevated accumulation of the tracer in the whole lesion (SUV_{mad} 1.4). Interestingly, ¹⁸F-FET PET showed pathologic accumulation of a radiotracer in the central tumor area (SUV_{mad} 9.9 after 5 min) and its caudal part (SUV_{mad} 8.6 after 5 min). Moreover, the SUV curve showed an early peak and a slow decrease of accumulation with time (to SUV_{mad} 6.4 in both of these areas), whereas the rest of the tumor had more stable dynamics. With the knowledge of possible upgrading according to ¹⁸F-FET PET, the patient underwent gross-total resec-

tion. The final histopathological diagnosis was anaplastic oligodendroglioma, WHO grade 3, IDH-mutant and 1p/19q-codeleted, originating from oligodendroglioma, WHO grade 2.

¹⁸F-FLT is a suitable radiotracer in diagnostics of glioblastoma, WHO grade 4, since its uptake is highly related to BBB disruption and reflects tissue proliferation [10]. However, it is unable to detect the aggressive tissue transformation before the BBB is damaged. Therefore, it has a limited diagnostic efficiency in LGs where BBB usually remains intact [8]. It also has a high positivity in the bone

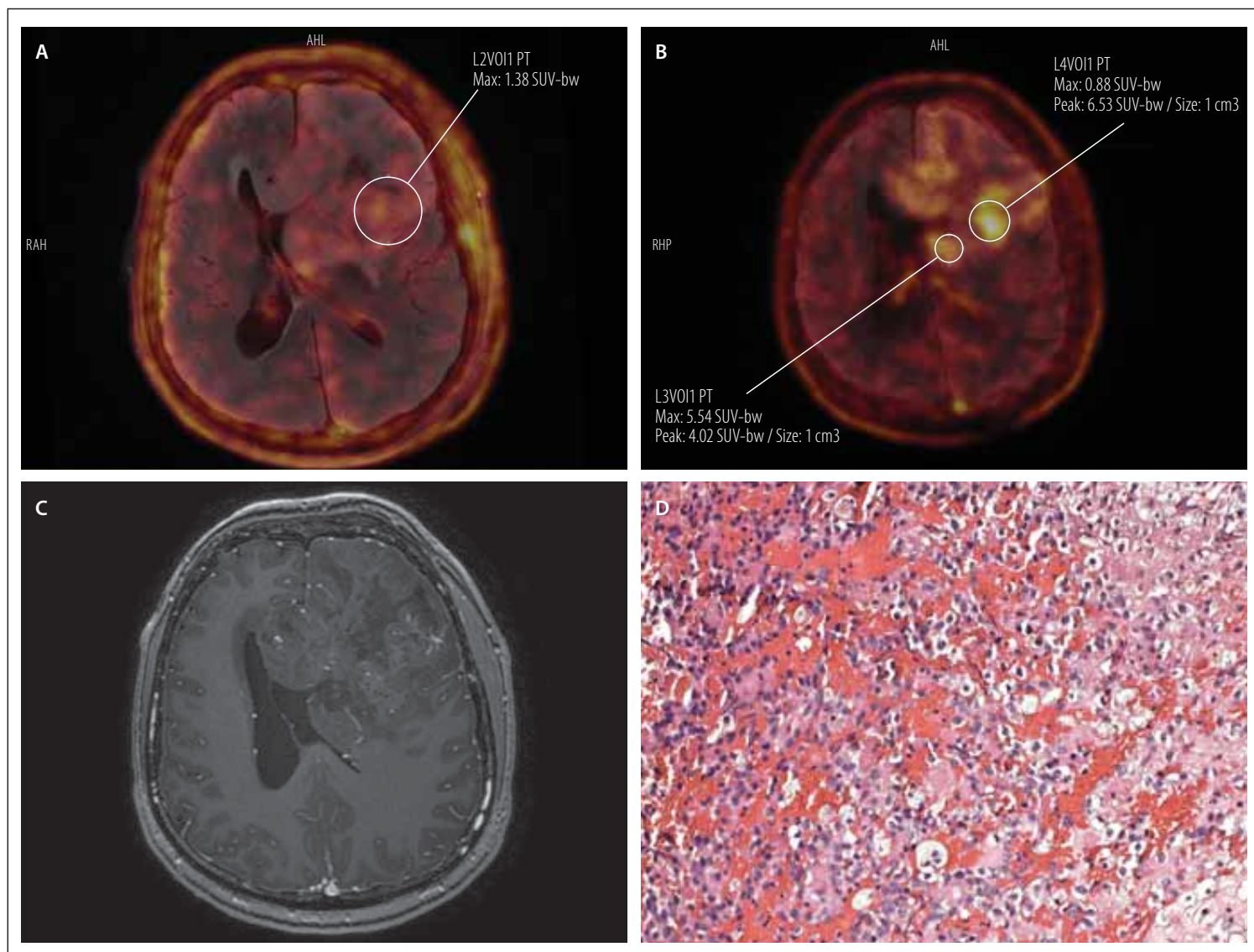


Fig. 2. (A) ¹⁸F-FLT PET/CT 10 min after radiotracer application, fused with MRI (T2 FLAIR). (B) ¹⁸F-FET PET/CT 5 min after radiotracer application, fused with MRI (T2 FLAIR). (C) MRI (T1 weighted image with contrast) – no contrast enhancement detected throughout the tumor. (D) Histological findings – anaplastic oligodendroglioma, WHO grade 3, IDH-mutant and 1p/19q-codeleted (hematoxylin and eosin-stained; original magnification 200×).

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrosine; ¹⁸F-FLT – [¹⁸F]-fluorothymidine; FLAIR – fluid attenuated inversion recovery; IDH – isocitrate dehydrogenase

Obr. 2. (A) ¹⁸F-FLT PET/CT 10 min po aplikaci radionuklidu, fúzovaná s MR (T2 FLAIR). (B) ¹⁸F-FET PET/CT 5 min po aplikaci radionuklidu, fúzovaná s MR (T2 FLAIR). (C) MR (T1 vážený obraz s kontrastní látkou) – bez detekce patologického syčení po podání kontrastní látky. (D) Histologický nálezn – anaplastický oligodendrogliom, WHO G3, IDH-mutovaný s 1p/19q-kodelečí (barvení hematoxylin-eozin; zvětšení 200×).

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrozin; ¹⁸F-FLT – [¹⁸F]-fluorothymidin; FLAIR – fluid attenuated inversion recovery; IDH – isocitrátdehydrogenáza

marrow of the skull, causing an unsatisfying signal-to-noise ratio. Although ¹⁸F-FET is not yet a part of widely used diagnostic protocols in the Czech Republic, it has some advantages over ¹⁸F-FLT that makes it applicable in clinical practice. ¹⁸F-FET easily crosses the intact BBB using the combination of passive diffusion and active transport mechanisms and has a relatively long half-life that makes its clinical use more convenient. Lesions in ¹⁸F-FET PET images demonstrated higher tumor to background ratio than in ¹⁸F-FLT PET images.

Also, the change of accumulation in time as shown in ¹⁸F-FET PET provided additional information compared to ¹⁸F-FLT PET.

In conclusion, the results of PET/CT imaging in both case reports suggest the superiority of ¹⁸F-FET over ¹⁸F-FLT in revealing focal areas of possible upgrading in suspected LGG. According to the authors' experience with PET imaging, the use of ¹⁸F-FET PET in a routine diagnostic protocol of gliomas is recommended, especially in the case of suspected LGG to rule out possible upgrading.

Acknowledgement

This work was supported by the Grant Agency of Masaryk University: MUNI/A/1429/2019 and by the Ministry of Health, Czech Republic – Conceptual Development of Research Organization (MMCI 00209805). Fluoro-ethyl-tyrosine (¹⁸F-FET) radiotracer used in patients presented in this case report was kindly provided by IASON, GmbH.

References

1. la Fougere C, Suchorska B, Bartenstein P et al. Molecular imaging of gliomas with PET: opportunities and limitations. *Neuro Oncol* 2011; 13(8): 806–819. doi: 10.1093/neuonc/nor054.

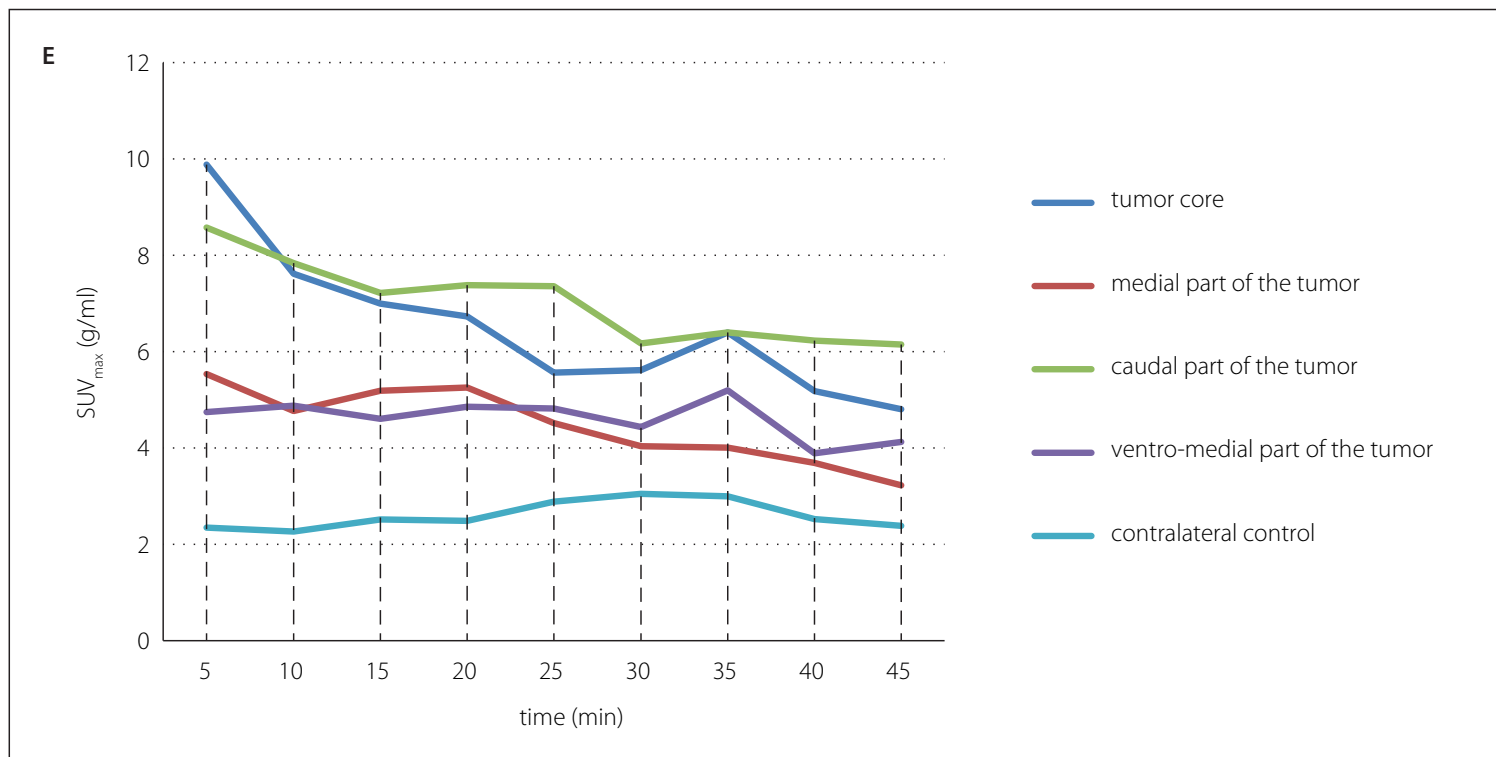


Fig. 2 – continuing. (E) Dynamic ¹⁸F-FET PET/CT acquisition showed an early peak of pathologic accumulation of ¹⁸F-FET 5 min after the radiotracer application in the central tumor area (SUV_{max} 9.9) and its caudal part (SUV_{max} 8.6). Maximal tracer uptake was followed by its slow gradual decrease after 45 min in the tumor core, as well as in its caudal and medial parts (SUV_{max} 4.8, 6.2, and 3.2, respectively). In contrast, the antero-medial part of the tumor showed more stable dynamics (SUV_{max} 4.8 after 5 min and SUV_{max} 4.13 after 45 min) and could represent a low-grade portion of the tumor.

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrosine; SUV_{max} – maximal standardized uptake value

Obr. 2 – pokračování. (E) Dynamické ¹⁸F-FET PET/CT snímání detekovalo časný peak akumulace radionuklidu 5 min po aplikaci v centrální (SUV_{max} 9,9) a kaudální (SUV_{max} 8,6) části tumoru. Následoval pozvolný pokles akumulace v průběhu 45 min sledování (SUV_{max} v jádru tumoru 4,8, v kaudální části 6,2, v mediální části 3,2). Antero-mediální část tumoru vykazovala naopak stabilnější dynamiku (SUV_{max} 4,8 po 5 min a 4,13 po 45 min) a pravděpodobně odpovídala low-grade komponentě tumoru.

¹⁸F-FET – [¹⁸F]-fluoro-ethyl-L-tyrosin; SUV_{max} – maximální standardizovaná hodnota absorpce

2. Del Sole A, Falini A, Ravasi L et al. Anatomical and biochemical investigation of primary brain tumours. *Eur J Nucl Med* 2001; 28(12): 1851–1872. doi: 10.1007/s002590100604.

3. Miyagawa T, Oku T, Uehara H et al. "Facilitated" amino acid transport is upregulated in brain tumors. *J Cereb Blood Flow Metab* 1998; 18(5): 500–509. doi: 10.1097/00004647-199805000-00005.

4. Bading JR, Kan-Mitchell J, Conti PS. System A amino acid transport in cultured human tumor cells: implications for tumor imaging with PET. *Nucl Med Biol* 1996; 23(6): 779–786. doi: 10.1016/0969-8051(96)00073-x.

5. Heiss W-D. Clinical impact of amino acid PET in gliomas. *J Nucl Med* 2014; 55(8): 1219–1220. doi: 10.2967/jnumed.114.142661.

6. Wyss MT, Spaeth N, Biollaz G et al. Uptake of 18F-fluorocholine, 18F-FET, and 18F-FDG in C6 gliomas and correlation with 131I-SIP(L19), a marker of angiogenesis. *J Nucl Med* 2007; 48(4): 608–614. doi: 10.2967/jnumed.106.036251.

7. Langen K-J, Hamacher K, Weckesser M et al. O-(2-[18F]fluoroethyl)-L-tyrosine: uptake mechanisms and clinical applications. *Nucl Med Biol* 2006; 33(3): 287–294. doi: 10.1016/j.nucmedbio.2006.01.002.

8. Saga T, Kawashima H, Araki N et al. Evaluation of primary brain tumors with FLT-PET: usefulness and limitations. *Clin Nucl Med* 2006; 31(12): 774–780. doi: 10.1097/01.rlu.0000246820.14892.d2.

9. Salskov A, Tamisetti VS, Grierson J et al. FLT: measuring tumor cell proliferation in vivo with positron emission tomography and 3'-deoxy-3'-[18F]fluorothymidine. *Semin Nucl Med* 2007; 37(6): 429–439. doi: 10.1053/j.seminuclmed.2007.08.001.

10. Galldiks N, Lohmann P, Albert NL et al. Current status of PET imaging in neuro-oncology. *Neurooncol Adv* 2019; 1(1): vdz010. doi: 10.1093/oaajnl/vdz010.