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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 heterogenity 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 transport 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,

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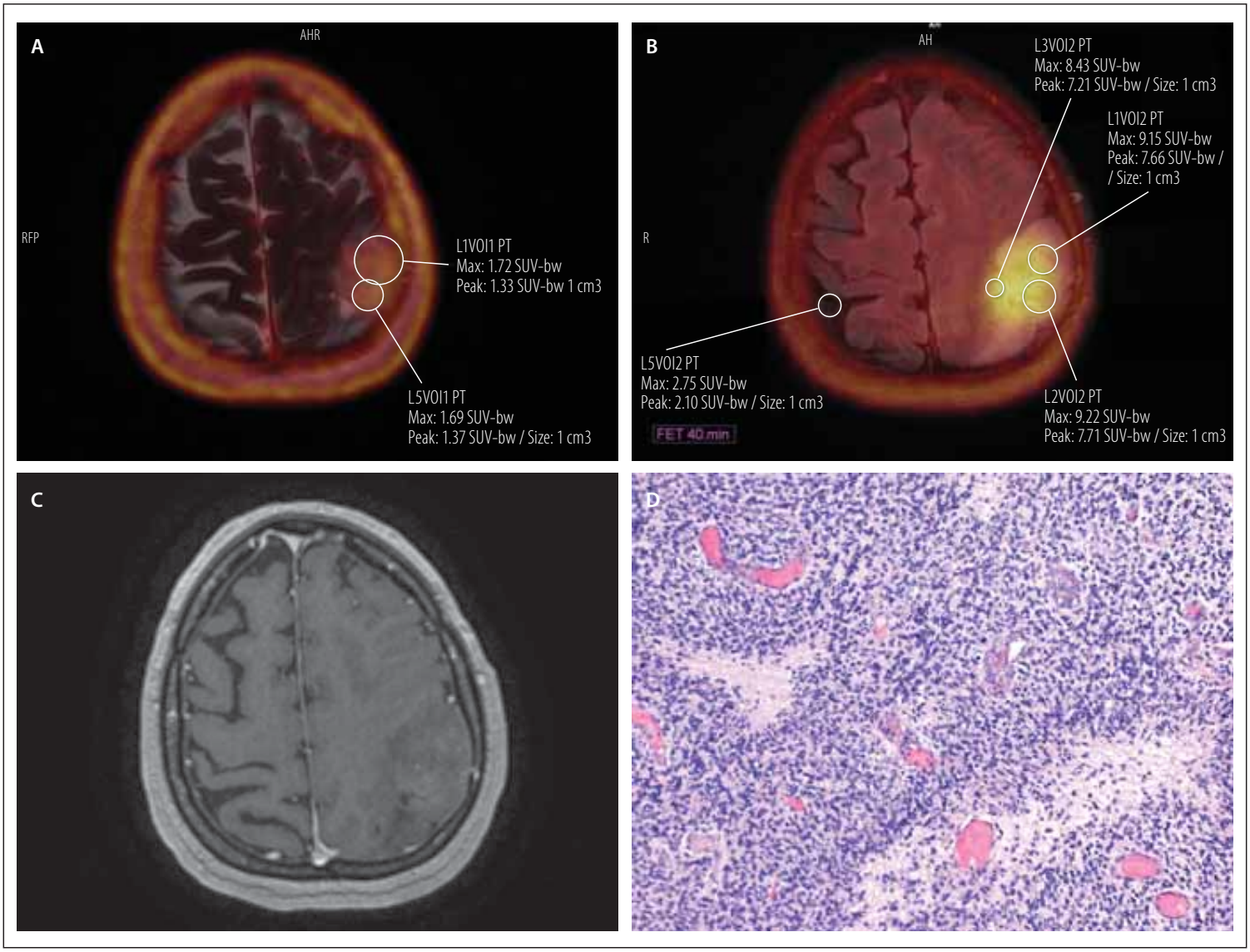


Fig. 1. (A) ^{18}F-FLT PET/CT 10 min after radiotracer application, subsequently superimposed on anatomical MRI (T2 weighted image) for final evaluation. (B) ^{18}F-FET PET/CT 40 min after radiotracer application fused with MRI (T2 FLAIR). (C) MRI (T1-weighted image with contrast) – no contrast enhancement 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×).

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

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

18-FET – [^{18}F]-fluoro-ethyl-L-tyrozin; ^{18}F-FLT – [^{18}F]-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). Different 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

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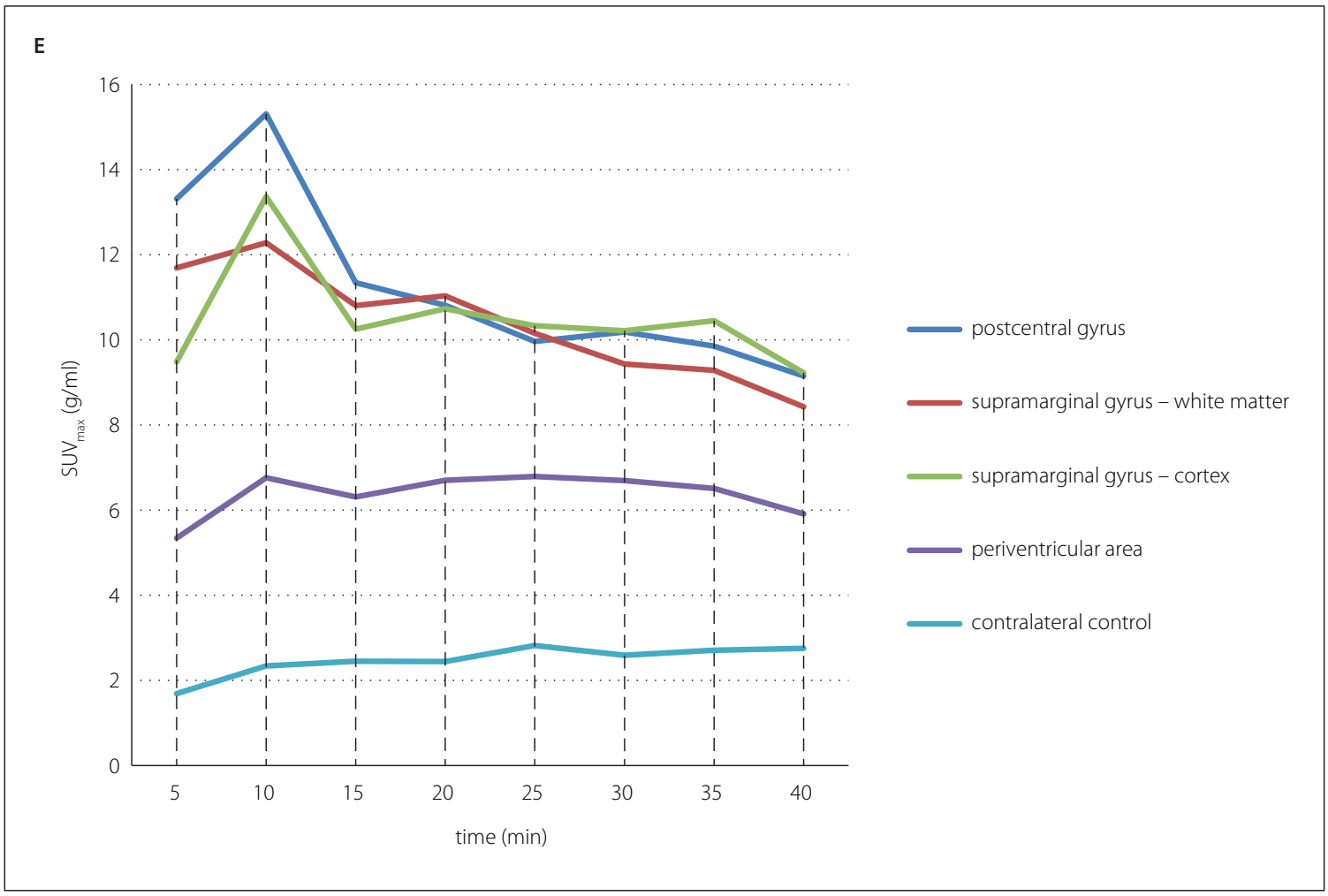


Fig. 1 – continuing. (E) Dynamic ^{18}F-FET PET/CT showed maximal pathologic accumulation of the radiotracer in the left postcentral and supramarginal gyri after 10 min (SUVmax 15.3 and 13.4, respectively) followed by gradual decrease of tracer uptake, a typical pattern for high-grade glioma. The periventricular 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.

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

Obr. 1 – pokračování. (E) Dynamické ^{18}F-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.

18-FET – [^{18}F]-fluoro-ethyl-L-tyrozin; SUV_{max} – maximalní 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 ^{18}F-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 ^{18}F-FLT and ^{18}F-FET PET scans were obtained in the same fashion as in the previous case. ^{18}F-FLT PET showed a homogenous, mildly elevated accumulation of the tracer in the whole lesion (SUV_{mad} 1.4). Interestingly, ^{18}F-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 ^{18}F-FET PET, the patient underwent gross-total resection. The final histopathological diagnosis was anaplastic oligodendroglioma, WHO grade 3, IDH-mutant and 1p/19q-codeleted, originating from oligodendroglioma, WHO grade 2.

^{18}F-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 LGGs where BBB usually remains intact [8]. It also has a high positivity in the bone

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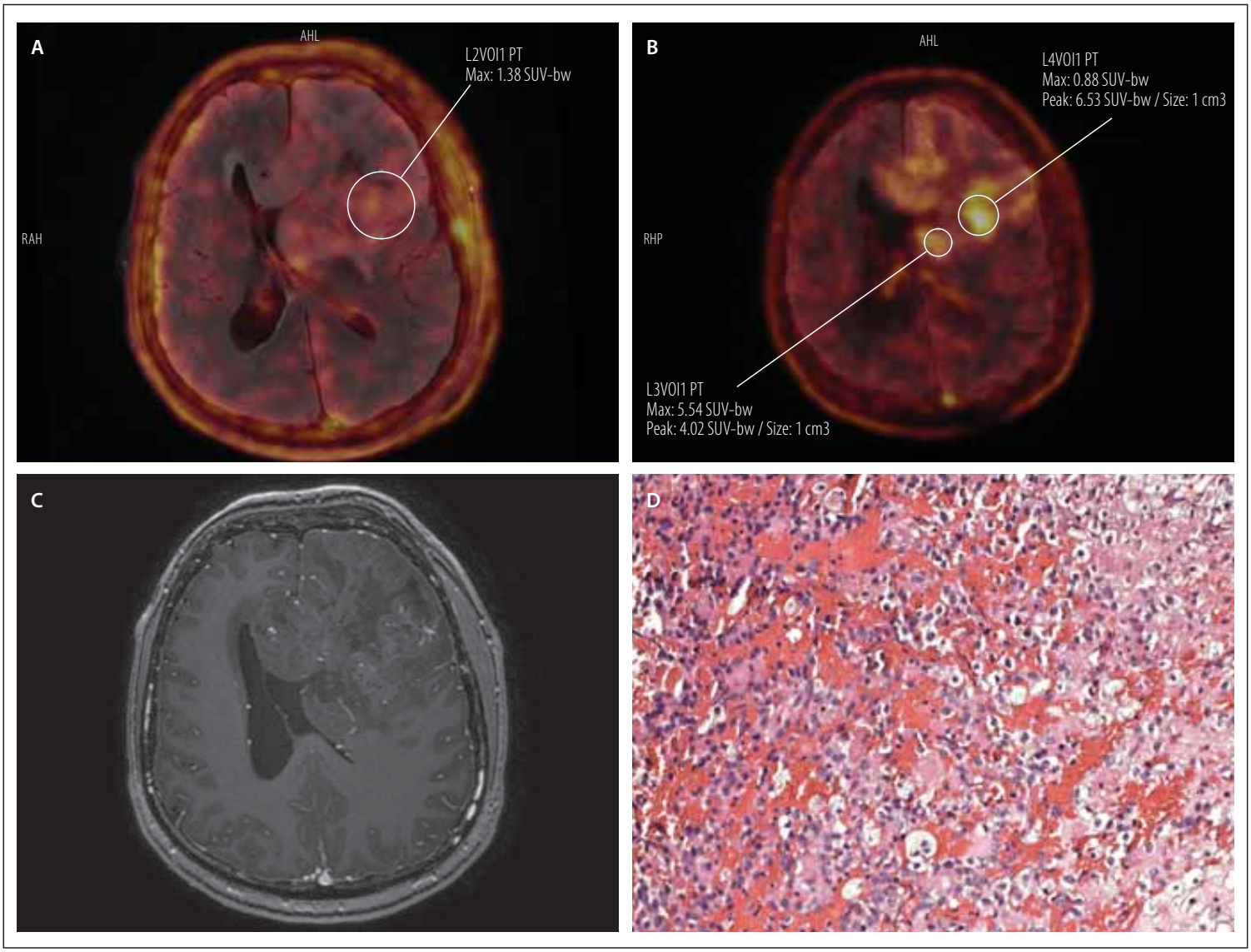


Fig. 2. (A) ^{18}F-FLT PET/CT 10 min after radiotracer application, fused with MRI (T2 FLAIR). (B) ^{18}F-FET PET/CT 5 min after radiotracer application, fused with MRI (T2 FLAIR). (C) MRI (T1 weighted image with contrast) – no contrast enhancement detected throughout the tumor. (D) Histological findings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

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

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

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

marrow of the skull, causing an unsatisfying signal-to-noise ratio. Although ^{18}F-FET is not yet a part of widely used diagnostic protocols in the Czech Republic, it has some advantages over ^{18}F-FLT that makes it applicable in clinical practice. ^{18}F-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 ^{18}F-FET PET images demonstrated higher tumor to background ratio than in ^{18}F-FLT PET images. Also, the change of accumulation in time as shown in ^{18}F-FET PET provided additional information compared to ^{18}F-FLT PET.

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

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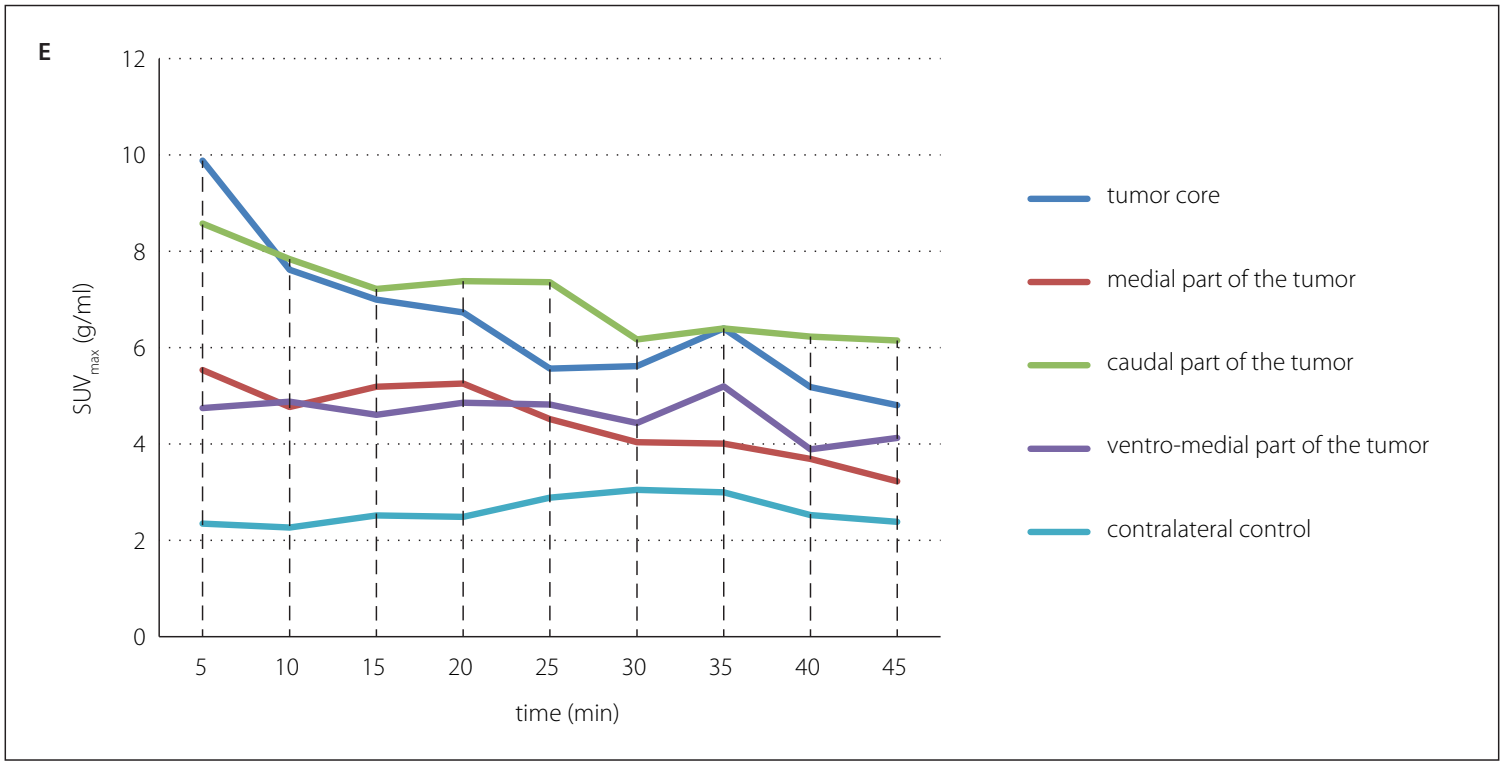


Fig. 2 – continuing. (E) Dynamic ^{18}F-FET PET/CT acquisition showed an early peak of pathologic accumulation of ^{18}F-FET 5 min after the radiotracer application in the central tumor area (SUV_{max} 9.9) and its caudal part (SUV_{max} 8.6). Maximal tracer uptake was followed by its slow gradual decrease 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.

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

Obr. 2 – pokračování. (E) Dynamické ^{18}F-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.

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

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