Development and Use of Non-FDG PET Radiopharmaceuticals at the Masaryk Memorial Cancer Institute

Vývoj a využití jiných PET radiofarmak než FDG na Masarykově onkologickém ústavu

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Summary
The existence of the cyclotron & PET centre of ÚJV Řež, a.s., at Masaryk Memorial Cancer Institute allows the Masaryk Memorial Cancer Institute and RECAMO researchers to engage in the research, development and application of new radiopharmaceuticals including compounds labelled by short-living positron emitters (especially [^{11}C]). Currently, a [^{11}C]-labelled tracer, L-[*methyl*-^{11}C]methionine, is entering phase I clinical evaluation, and scans with PET radiopharmaceuticals other than fluorodeoxyglucose are performed at the Department of Nuclear Medicine. Continued cooperation will bring new possibilities for PET in the Czech Republic in the future.

Key words
positron emission tomography – radiopharmaceuticals – 3'-deoxy-3'-[^{18}F]fluorothymidine – [^{18}F]fluorocholine – sodium [^{18}F]fluoride – L-[*methyl*-^{11}C]methionine

Souhrn
Existence cyklotronu a PET centra ÚJV Řež, a.s., v Masarykově onkologickém ústavu umožňuje výzkumníkům z RECAMO a Masarykova onkologického ústavu zapojit se do výzkumu, vývoje a využití nových radiofarmak včetně látek označených krátce žijícími pozitronovými zářiči (zejména [^{11}C]). V současnosti zde vstupuje do I. fáze klinického hodnocení [^{11}C]-značený tracer L-[*methyl*-^{11}C]methionin a na oddělení nukleární medicíny jsou prováděny skeny s jinými PET radiofarmaky než fluordeoxyglukózou. Spolupráce by měla pokračovat i nadále a v budoucnu vyústit ve zpřístupnění více možností pro PET zobrazování v České republice.

Klíčová slova
pozitronová emisní tomografie – radiofarmaka –3'-deoxy-3'-[^{18}F]fluorothymidin – [^{18}F]fluorocholin – [^{18}F]fluorid sodný – L-[*methyl*-^{11}C]methionin

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Introduction

Positron emission tomography (PET) is one of the most modern methods of molecular imaging, providing physicians with a non-invasive method of diagnostics, studying and monitoring human organism. Currently it belongs, along with computer tomography and nuclear magnetic resonance, among the main imaging methods used in oncology, cardiology, neurology and other medicinal areas. The idea of PET is a visualisation of desired areas in the patient's body, based on more or less specific interactions of the radiopharmaceutical applied to the patient with processes that occur in their body. The patient is given a compound that contains a positron emitter – an atom whose nucleus undergoes beta-plus decay. Positron, an anti-particle that is a product of such decay, annihilates almost immediately (no more than a few millimetres after emergence) with its counterpart, electron. Detection of the high-energy photons that are simultaneously emitted during the annihilation is the basis of PET image acquisition.

The nuclei that undergo beta-plus decay have usually quite short or very short half-lives. The most commonly used positron source isotopes are fluorine [^{18}F] (half-life 110 min), carbon [^{11}C] (20 min), nitrogen [^{13}N] (10 min) and oxygen [^{15}O] (2 min). Atoms containing these nuclei are chemically bonded to molecules that participate in the usual metabolic processes in the organism – glucose, water, ammonia – or to compounds that are able to specifically bind to some receptor molecules in the tissues. Such molecules are known as radiotracers. By using a well-chosen radiotracer, PET monitoring of almost any compound and biological pathway in the organism is possible, provided that a component of the pathway can be labelled by a positron emitter.

Positron emitters are largely generated by controlled bombardment of appropriate target materials in particle accelerators – cyclotrons. A short half-life of said positron emitters limits their usage only to medical facilities that have their own cyclotron facility at their disposal. The exception is fluorine 18, whose almost 2 hours long half-life allows for transportation to medium distances. A good combination in terms of costs and benefits is embodied by the currently most used radiopharmaceutical, 2-deoxy-2-fluoro-D-glucose, FDG for short [1]. Thanks to the fluorine in position 2, the molecule is able to emit positron radiance, and it is also protected from glycolysis (where the presence of oxygen in position 2 is crucial). FDG is therefore an ideal tool for monitoring glucose intake in the organism, especially cells with high metabolic activity that cancer cells usually display. Its' disadvantage lies in rather unspecific intake in the organism (high background), but it is more than compensated by its universality. The development of more specific and specialised tracers is, however, almost as old as the method. PET radiochemists aim at labelling of biologically active compounds that express higher specificity than FDG – substrates of important receptors or intermediates of important biological pathways. An apt choice of radiotracer and the labelling isotope (the half-life of the emitter isotope and the velocity of the interaction must be considered) allows for possibilities of monitoring of many previously unmonitorable processes.

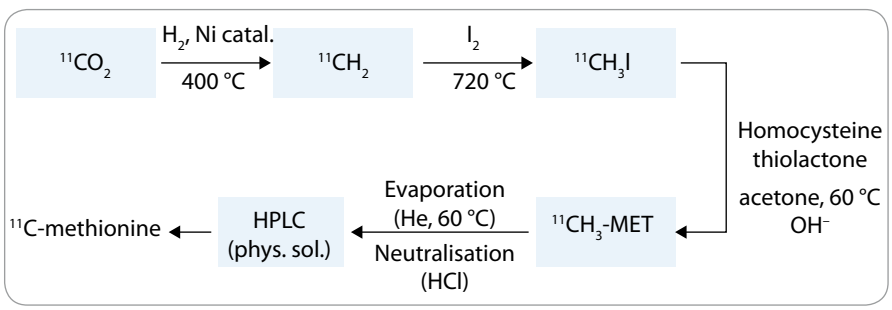

Fig. 1. Schematics of L-[*methyl*-^{11}C]methionine synthesis.

Under the framework of RECAMO, scans were performed with commercially available non-FDG radiopharmaceuticals (3'-deoxy-3'-[^{18}F]fluorothymidine, [^{18}F]fluorocholine, [^{18}F]fluoride), as well as in-house development of a [^{11}C]-tracer for on-site use in the cooperation of RECAMO and ÚJV Řež – ^{11}C-methionine, a labelled amino acid that is currently entering the stage of clinical evaluation as of October 2012.

Development of L-[*methyl*-^{11}C]methionine ([^{11}C]MET)

L-[*methyl*-^{11}C]methionine belongs to the group of labelled amino acids used in PET for detection of brain tumours [2,3]. Most brain tumours show an increased uptake of amino acids as compared with normal brain, whereas the amino acids are retained in tumour cells due to their higher metabolic activities including incorporation into proteins [4]. This radiopharmaceutical has applications in oncology, neurology and paediatric oncology. The radiopharmaceutical is produced in the PET Centre Brno by synthesising [^{11}C]methyl iodide from $^{11}CO_2$ and subsequently L-[*methyl*-^{11}C]methionine from [^{11}C]methyl iodide and L-S-benzyl-homocysteine, with HPLC as the final purification method (see Fig. 1). The synthesis takes 25 minutes and produces about 10 GBq of [^{11}C]MET with a volume activity of about 2.0 GBq/ml at the end of synthesis. Achieved radiochemical purity is > 96%. The procedure was performed on the TracerLab FXC synthesis module (GE Healthcare). Provided that the logistics of synthesis, quality control and transport are optimised, it is possible to provide approximately 3 GBq (2 ml at maximum volume activity) for the injection, therefore allowing for short-distance transports as well. It is the first case of [^{11}C]-labelled radiopharmaceutical to enter clinical evaluation in the Czech Republic. The evaluation is planned to be concluded in 2013, with a total of 16 patients.

^{18}F-labeled non-FDG Radiopharmaceuticals

Besides the development of **L-[*methyl*-^{11}C]methionine**, scans were performed at the Department of Nuclear Me-

dicine with commercially available [^{18}F]--labelled tracers, such as 3'-deoxy-3'--[^{18}F]fluorothymidine, sodium [^{18}F]fluoride (provided by RadioMedic company) or ^{18}F-fluorocholine (provided by IASON company), in order to assess their usability and practical applicability at the Masaryk Memorial Cancer Institute. The results from the scans were also used in other RECAMO research programmes.

3'-deoxy-3'-[^{18}F]fluorothymidine (FLT)

Unchecked proliferation is characteristic for tumour cells. Characterising the proliferation rate of cancer cells is important to differentiate benign from malignant tumours as well as characterise malignant tumours within normal tissues. As mentioned before, FDG has been widely used in cancer imaging – however, besides tumour cells, increased uptake of FDG occurs in inflammatory cells and lesions as well. Thymidine and its analogues are the standard markers for DNA synthesis, and is why 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) was developed for PET imaging to monitor proliferation [5,6].

FLT, an analogue of the nucleoside thymidine, is phosphorylated by thymidine kinase-1 (TK-1), an enzyme expressed during the DNA synthesis phase of the cell cycle. Most cancer cells have a much higher TK-1 activity than normal cells. Thanks to the fluorine labelling, FLT monophosphate is not incorporated into DNA and as a result is metabolically trapped inside the cells. The uptake of FLT is used as an index of cellular proliferation [7,8]. FLT-PET has been widely used to detect and monitor tumour proliferation, staging and detection of metastases. Applications of FLT in various types of tumours are described in the literature, such as lung tumours [10–13], lymphoma [14,15], breast tumours [16], head and neck tumours [17], soft tissue sarcoma [18] or colorectal cancer [19].

In three years, 32 scans using FLT were performed. The radiopharmaceutical proved capable of identifying proliferative regions in patients, as well as brain metastases, as illustrated in Fig. 2 and 3. This was beneficial in evaluation of therapy response, where persisting proliferation of the tumour tissue can be distinguished from reparatory or inflammatory processes. It is planned to perform more scans with this radiopharmaceutical in the future.

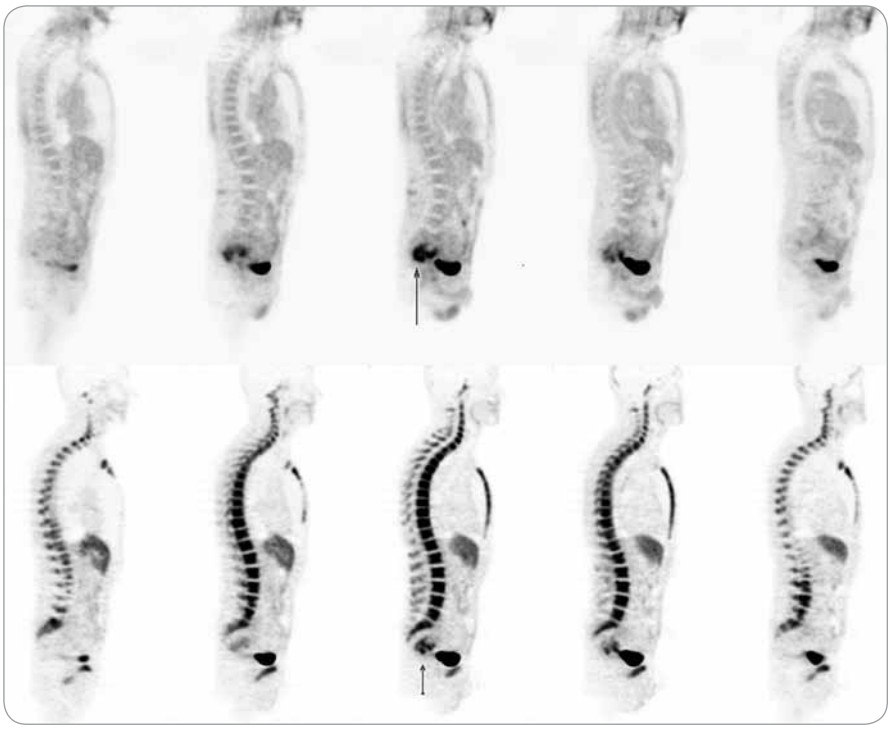

Fig. 2. Example of FLT-PET combined with FDG-PET. Large presacral infiltrate (marked with black arrow) with high metabolic activity (top row, FDG PET) and high proliferative activity (bottom row, FLT PET) in a patient after colorectal carcinoma therapy, hinting at local relapse of tumour.

[^{18}F]fluorocholine (FCH)

Choline is an important component of cellular membranes. Tissues with increased metabolism rate usually exhibit high uptake of choline. Choline is phosphorylated by choline kinases to phosphorylcholine and subsequently integrated into the phospholipidic membranes. The fluorine-labelled analogue of choline, FCH – [^{18}F]fluorocholine, is used for visualisation of heightened choline kinase activity that is typical for proliferating tumours. The use of FCH encompasses brain tumours, breast carcinoma

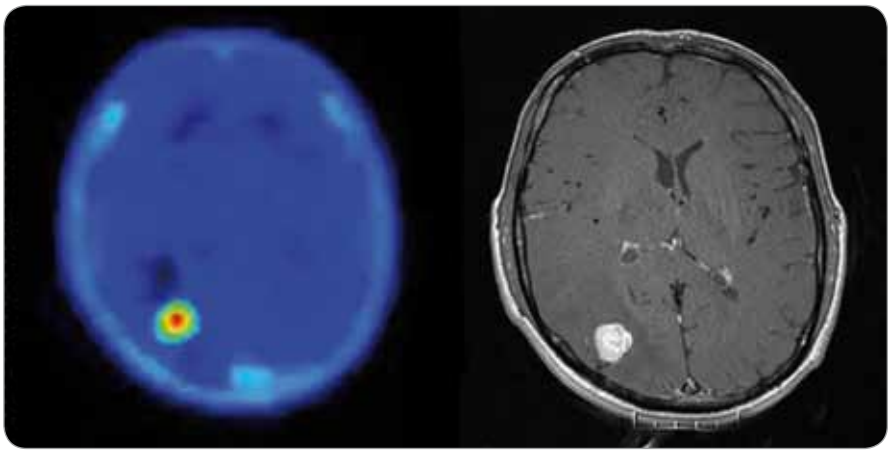

Fig. 3. Example of FLT-PET. Solitary metastasis in brain, right occipital lobe, in a patient with thigh soft tissue sarcoma. Left image: FLT – PET, right image: brain MRI. No clinical symptoms.

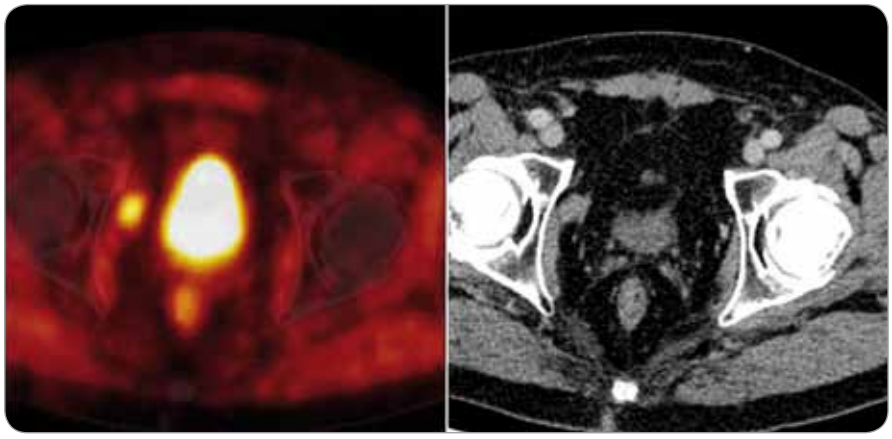

Fig. 4. Example of FCH PET/CT. Prostate carcinoma. Patient after prostatectomia, with suspected relapse. FCH PET/CT detects metastatic involvement of right pre-iliac lymph node. Left image: FCH-PET, right image: CT.

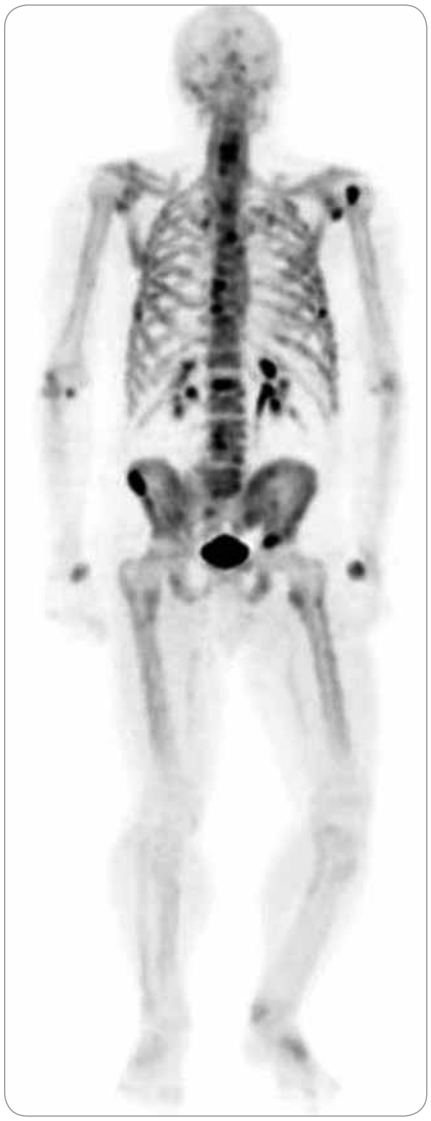

Fig. 5. Example of NaF-PET. Multiple bone metastases in patient with prostate carcinoma.

and primarily, prostate tumours [20,21]. 32 scans were performed in the year 2012 and the results were used in management of therapy of prostate cancer patients. An example of FCH PET scan is provided in Fig. 4. Further scans using [^{18}F]fluorocholine scans are planned in the future.

Sodium [^{18}F]fluoride

Sodium [^{18}F]fluoride (NaF) is a bone remodelling marker usable for detecting bone metastases, as well as other bone defects. It was used for bone scintigraphy as early as the 1960's [22,23], but was quickly replaced by technetium diphosphonates [24]. In the last decade, its' potential contribution to nuclear medicine was re-evaluated, mainly because of the PET/CT technology [25,26]. It has desirable characteristics as a bone-imaging agent – a high and rapid uptake in the bone with rapid blood clearance, producing a high bone-to-background ratio in a short time. Combined with PET/CT scanners ability to provide quantitatively accurate, high resolution images with improved sensitivity compared to SPECT or planar scanners, this makes NaF PET/CT imaging a very attractive alternative to ^{99m}Tc-methylenediphosphonate bone scintigraphy [27–30]. An example of NaF scan is provided in Fig. 5.

A total 12 scans were performed. The very high sensitivity of NaF PET can be often double-edged, because the scan is able to identify regions with any increased bone turnover, e.g. post-traumatic bone defects and/or degenerative changes. As for the current state, no NaF scans are planned.

Conclusions

Under the RECAMO framework, researchers from Masaryk Memorial Cancer Institute participate in the development and clinical evaluation of a novel ^{11}C-labelled radiopharmaceutical. Besides that, the Department of Nuclear Medicine performs scans with other non-FDG radiopharmaceuticals as well. RECAMO is going to cooperate further with the researchers from ÚJV Řež in the development and introduction of a broader range of PET tracers to Czech patients, by participating in research of new methods of synthesis, labelling and use of tracers.

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