Research Square

Preprints are preliminary reports that have not undergone peer review. They should not be considered conclusive, used to inform clinical practice, or referenced by the media as validated information.

On Site Production of [18F]-PSMA1007 Using Different [18F]-fluoride Activities. Practical, Technical and Economical Impact.

Costantina Maisto
Istituto Nazionale Tumori IRCCS Fondazione Pascale https://orcid.org/0000-0001-5772-9909
Anna Morisco
Istituto Nazionale Tumori IRCCS Fondazione Pascale
Roberta de Marino
Istituto Nazionale Tumori IRCCS Fondazione Pascale
Squame Elisabetta
Istituto Nazionale Tumori IRCCS Fondazione Pascale
Valentina Porfidia
Istituto Nazionale Tumori IRCCS Fondazione Pascale
Laura D'ambrosio
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Daria Di Martino
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Paolo Gaballo
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Michela Aurilio
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Monica Buonanno
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Aureliana Esposito
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Marco Raddi
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori
Secondo Lastoria (s.lastoria@istitutotumori.na.it)
Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori

Research article

Keywords: [18F]-Fluoride, time of beam, [18F]-PSMA-1007, RCY, RCP, stability

Posted Date: June 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-652368/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Background

Prostate-Specific Membrane Antigen is overexpressed in prostate cancer and it is considered a good target for staging of primary and recurrences as well as for radioligand therapy. Different PSMA-analogues have been investigated, labeled with [^{68}Ga], showing excellent imaging properties; although, only small amounts can be produced for single synthesis. Recently, a fluorinated PSMA-inhibitor, [^{18}F]-PSMA-1007, has been introduced, ensuring large-scale productions. In this study, the radiosynthesis of [^{18}F]-PSMA-1007 using low (A), medium (B) and high (C) starting activities of [^{18}F]-Fluoride, has been fully tested. The following parameters radiochemical yield, radiochemical purity and stability of [^{18}F]-PSMA-1007 have been measured in 65, consecutive batches to verify the effects of the three different conditions. In addition, the analysis of the costs for the production has been performed.

Results

The radiochemical yield percentage for low and medium range of activities of [^{18}F]-Fluoride was 52%, while for the high range it decreases to 40%. The radiochemical purity was 99% in all three tested starting activities. [^{18}F]-PSMA-1007 did not show radiolysis up to 8 hours after the end of synthesis, confirming that the radiopharmaceutical is stable an suitable for PET studies in humans. Furthermore, stability studies performed in fetal bovine serum demonstrated radiochemical stability at 37°C for 120′.

Conclusions

A starting activity of [^{18}F]-Fluoride of 90 GBq (range B) enables a final amount of [^{18}F]-PSMA-1007 of about 50 GBq, which is powerful for different choices: to perform up to 25 PET/CT scans in a referral institution for prostate cancer, and/or to supply the eventual peripheral PET centers.

Introduction

Prostate cancer (PC) is the major cause of mortality and morbidity worldwide and it is the second, most common, diagnosed cancer in men (Eeles R., Ni Raghallaigh H., 2018; Zhou D., et al 2014, Culp M.B. et al. 2020). Prostate-specific membrane antigen (PSMA) is a transmembrane protein, considered a valuable marker for PC. PSMA is upregulated in poorly differentiated, metastatic, and hormone-refractory PCs (Umbricht CA., et al. 2017). For these reasons PSMA is considered a good target for PC, either for staging or follow-up purposes (Afshar-Oromieh A., et al., 2015), by PET/CT. Different PSMA radiopharmaceuticals have been and are currently investigated (Cardinale J. et al., 2020). [^{68}Ga]-radiolabeled-PSMA synthetic peptides showed excellent imaging properties, accounting excellent results in terms of diagnostic accuracy and resulting superior to conventional imaging tests, currently used in clinics: CT and bone scan (Wurzer A., et al., 2020). The relevance gained in clinical practice reflects its ability in more accurately identifying non metastatic from PC metastatic patients, supporting at the best the choice of the proper, therapeutic, option to select. The only drawback using [^{68}Ga]-radiolabeled-PSMA synthetic peptides is due to the relatively small number of patients who can be imaged by PET/CT at once. Such limitation is consequent to the relatively low amount of [^{68}Ga]-chloride available after each elution from Ge-Ga generators and its short physical half-life (68′). Recently, [^{18}F]-labeled PSMA targeted radiotracers have been introduced increasing by the time their use in clinical practice (Zippel C., et al., 2020; Werner R., et al., 2020). For each radiosynthesis a large amount of [^{18}F]-labeled PSMA may be produced, enabling to study a higher number of patients than those with of [^{68}Ga]-PSMA. The [^{18}F] physical half-life ($T_{1/2}$ = 109′) and larger productions by cyclotron might allow also to provide the distribution to several PET centers distant not more than 4-hours from the producing cyclotron/radiopharmacy facility (Shammi O., et al. 2019). Preliminary clinical reports indicated that fluorinated PSMA offers other, additional, advantages: higher tumor-to-background ratios (Kesch C. et al, 2017) and low renal excretion (Giesel FL, et al., 2017).

Fully automated production of [^{18}F]-PSMA-1007 was established using several, commercially available, synthesizers (Cardinale, J., et al. 2017; Naka S., et al. 2020; Katzschmann I., et al. 2021).

The purpose of this research intended to standardize the best parameters to produce the maximal amount of [^{18}F]-PSMA-1007 for each, single, batch, according to different scenarios: production for the patients of the producing center and production to supply the radioligand to adjacent PET centers. In this setting, we focused our study on the following key points: role of different starting activities

of [^{18}F]-Fluoride on the radiochemical yield (RCY) at end of synthesis (EOS), the stability of the radiolabeled PSMA over a 8-hours period of time and the analysis of the costs of production for a nuclear medicine center with its cyclotron/radiopharmacy facility.

The compliance of the final product and relative quality controls were defined only recently by the monograph on the Edition 10th, 2020, of the European Pharmacopeia.

Materials And Method

Radiolabelling of [^{18}F]-PSMA-1007

[^{18}F]-Fluoride was produced by a 18/9 MeV cyclotron (C18/9 MeV, IBA, Belgium) by irradiating a standard volume of 2.6 mL of [^{18}O] H_2O (≥ 98% of purity; Taiyo-Nippon Sanso Corporation, Japan). The parameters of beam, time (minute) and target current (μA), were adjusted according to the desired, final, activity.

Radiosynthesis of [^{18}F]-PSMA-1007 were performed using a fully automated radiosynthesizer (AllInOne 36, Trasis, Belgium; with 36 manifold actuators and a disposable fluid pathway) as was previously described (Shammi O., et al. 2019). The use of disposable cassettes ensures clean and reproducible operations throughout the whole radiolabeling. This system uses the following, three-purification cartridges: QMA, C18ec and a PS-H^+. Both C18ec and PS-H^+ cartridges, stacked one on the top of the other, must be properly attached to the cassette.

The reagents used for each, individual, synthesis of [^{18}F]-PSMA-1007 are: PSMA-1007 precursor (GMP grade), Dimethyl sulfoxide (DMSO) for precursor, Ethanol, Phosphate Buffered Saline (PBS), TBA-HCO_3 water/ethanol solution 0.075 M. These reagents were purchased as a single kit (ABX, Germany).

Quality Controls on [^{18}F]-PSMA-1007

HPLC analyses were carried out using a LC 20AD Pump with a SPD-20AV UV/VIS detector (Shimadzu, Japan) equipped with a GABI radiometric detector (Raytest, Elysia, Germany). A 5 μm C18 300 Å, 250 x 4.6 mm column (Jupiter®, Phenomenex, Italy) was used with a flow rate of 1mL/min and the following gradient (acetonitrile 0,1% TFA as solvent A, water 0,1% TFA as solvent B): 100% A for 5', A 25% and B 75% in 3', the same gradient for 4' and then 100% B in 3'. The UV/VIS detector was set at 220 nm and 254 nm.

Thin-layer chromatography (TLC), was performed on Alugram silica gel 60 (Mackerey-Nagel, GmbH & Co. KG, Germany) sheets, as stationary phase, and using as mobile phase a v/v mixture of 60% acetonitrile and 40% water, according to European Pharmacopoeia Edition 10th, 2020. TLCs were analyzed by a storage phosphor system (Cyclone Plus, Perkin Elmer, UK).

The assay of tetrabutyl-ammonium (TBA), as possible contaminant impurity of the final product, was performed by iodine-stained TLC, as previously described (Kuntzsch M. et al., 2014); residual solvents (ethanol and DMSO) were quantified by gas-chromatography system (GC 2010 Plus, Shimadzu, Japan) equipped with a flame-ionization detector (FID) and a capillary column (Elite-1301, 6% cyanopropylphenyl 94% dimethyl polysiloxane, L 30m, ID 0.53; Perkin Elmer, UK). The temperature for the split was 240°C and 280°C for the FID.

Radionuclidic purity was determined using multi-channel analyzer (Mucha Star, Raytest, Elysia, Germany) and by half-life measurement by dose calibrator (Atomlab 500, Biodex, USA).

[^{18}F]-PSMA-1007 was also tested for bacterial endotoxin through kinetic chromogenic Limulus Amebocyte Lysate (LAL) method (Endosafe Nexgen-PTS, Charles River, USA).

The radiochemical stability of [^{18}F]-PSMA-1007 was tested using different starting amounts of radioactivity, to verify possible effects, if any, on the final product. Samples from product vial (at room temperature) were analyzed by radio-HPLC, to appreciate the presence of degradation impurities or free [^{18}F]-Fluoride, at different times (2h, 4h, 6h, 8h) after EOS.

In vitro stability studies of [^{18}F]-PSMA-1007 were performed in Fetal Bovine Serum (FBS, Sigma-Aldrich, Germany) at 4°C and 37°C up to 2 h, to simulate *in vivo* conditions.

Different volumes of [^{18}F]-PSMA-1007 were added to FBS to reach a final volume of 1 mL, keeping a constant activity of 37 ± 3,7MBq, and the radio-HPLC was performed at different times (5', 30', 60', 120') for both temperatures.

Results

In a series of sixty-five, consecutive, syntheses of [^{18}F]-PSMA-1007 and relative quality controls we have evaluated the use of three different ranges of starting [^{18}F]-Fluoride activity, identified as: low (A, 55,91 GBq ± 6,69 GBq), medium (B, 89,06 GBq ± 4,02 GBq) and high activity (C, 162,38 GBq ± 6,46 GBq). These three ranges of [^{18}F]-Fluoride activities were obtained monitoring both essential parameters of the cyclotron: time/lenght of the beam (20', 30' and 55' respectively for A, B and C) and constant target current at 60 mA.

The final volume [^{18}F]-PSMA-1007 at the EOS was of 19 mL, with a mean activity of 28,71 ± 0,56 GBq for range A, 46,84 ± 2,54 GBq for range B and 65,70 ± 4,23 GBq for range C and appeared clear, colorless, particle-free, sterile with a pH ranging between 5 and 7.

The radiolabeling procedure of [^{18}F]-PSMA-1007, that is fully automated, has been shown to be very reliable. In fact, the measured RCY at EOS, not corrected for decay and related to a synthesis time of ≃ 40', was similar for the range A (52,09% ± 7,10) and B (52,66% ± 3,40), while for range C it decreased to 40,26% ± 1,76, as resumed in Table 1.

Radiochemical purity (RCP), performed by radio-HPLC after each production, was ³ 99% (Table 2); the retention time was ≃ 13,6' and no significant [^{18}F]-Fluoride was detectable at EOS.

RCP, by TLC, was > 97% for the ranges A and B, and 96,7% for the range C.

Residual TBA was £ 2.6 µg/mL; the amount of ethanol was £ 10% v/v was, the residual DMSO was £ 5000 ppm, according to Ph Eur method 2.4.24.

Radionuclidic purity evaluation achieved values between 490 KeV-531 KeV for g-spectrometry assay and 105'-115' for half-life measurement. The endotoxin value was less than 2.5 EU/mL.

The radiochemical stability of [^{18}F]-PSMA-1007 was analyzed up to 8 hours after EOS, being in all time points > 99%; with no evidence, on the chromatograms, of degradation impurities and detectable amounts of free [^{18}F]-Fluoride (Figures 1 and 2).

In order to verify the radiochemical stability *in vivo*, it was tested in FBS up to 120', at 4°C and 37°C, with lack of measurable radiolysis in both conditions, as shown by radio-HPLC analysis in Figure 3. The results of these tests were furtherly confirmed in patients administered and scanned within 2 hours from EOS.

No differences in the [^{18}F]-PSMA-1007 biodistribution, by PET/CT, were found in patients who received the radioligand at different times from EOS (figures 3 and 4), confirming that no degradation occurred by the time.

Discussion

PSMA-PET/CT represents a ground-breaking diagnostic approach to stage and follow-up patients with recurrent PC. In particular, [^{18}F]-PSMA-1007 gained great interest for clinical applications, because of the physical decay advantages over [^{68}Ga]-PSMA, for the opportunity to study a greater number of patients daily and for the relatively low excretion by the urinary system and high tumor to background ratios (Sprute K. et al., 2021; Ioppolo J.A. et al., 2020). In addition, preliminary papers described elevated sensitivities also in small or tiny tumor deposits. A larger use of [^{18}F]-PSMA-1007 is expected for diagnostic purposes as alternative to [^{68}Ga]-PSMA-11, having, at least, a non-inferior diagnostic accuracy, but also because it is the perfect option for selecting patients to treat by radioligand therapy with [^{177}Lu]-PSMA-617.

Thus, analysis and optimization to clarify and to optimize all possible variables in the process of [^{18}F]-PSMA-1007 radiosynthesis, may be helpful for those who are planning to start. The labeling process to obtain [^{18}F]-PSMA-1007 is extremely reliable and it is characterized by elevated yield; a radiolabeling failure occurred only in two cases. Both these two failures were characterized by a complete lack of reaction, more likely related to mechanical errors within the module rather than to chemical failure during radiosynthesis, being the final yield equal to 0%.

The trend of RCY and RCP, using three different activities of [^{18}F]-Fluoride did not show significant differences. In details, RCY was 52% for batches labeled with activities included in range A and B, resulting slightly higher than the average of [^{18}F]-PSMA-1007 yield, declared by module's manufacturer: [3] 40±10% (not corrected for decay); whilst a RCY was reduced to 40% for batches labeled with activities included in range C to 40%.

The RCP values were substantially similar for all the three different ranges of starting activities of [^{18}F]-Fluoride, showing values $\geq$ 99% (99,49% for range A; 99,85% for range B; 99,66% for range C). Moreover, stability studies were serially performed on [^{18}F]-PSMA-1007 in the period included from 2 to 8 hours after EOS, showing no degradation of the radiolabeled PSMA.

According to these results, the medium range (B) coupled two advantages: a relatively short time of beam/radiolabeling and a better synthesis performance in terms of RCY (Table 3). Increasing starting activity of [^{18}F]-Fluoride is not directly proportional to the final [^{18}F]-PSMA-1007 amount. In fact, labeling PSMA with the high starting activity of [^{18}F]-Fluoride (range C), a decrease of RCY along with an increase of the time of beam was observed, without a substantial gain in the amount of available [^{18}F]-PSMA-1007.

Thus, the suggested option to adopt for clinical purposes in a center with a cyclotron/radiopharmacy facility is to produce a final amount of [^{18}F]-PSMA-1007 of about 50 GBq, which allows to perform up to 25 PET/CT scans per day in a referral institution for PC. The high radiochemical stability measured within 8 hours after EOS justifies and supports the choice of using fluorinated PSMA for an entire working day, without degradation and loss of binding ability. Furthermore, it allows also to justify the transfer from producing cyclotron/radiopharmacy facility to PET centers located at a distance reachable in 3-4 hours. The starting amount of cold precursor of PSMA-1007 is fixed in 1.6 mg in commercially available kits used in our experience. Such amount is in excess, and it enables sufficient radioligand product to image prostate cancer lesions in humans, being not a limit for the clinical use, also varying the starting activities of [^{18}F]-Fluoride.

The costs for on site production of batches of 46,84 GBq of [^{18}F]-PSMA-1007 have been estimated in 5454€ (4.31€/37 MBq). These costs include the complete process, from cyclotron beam to dispensation of [^{18}F]-PSMA-1007, disposable/reagents, personnel, technologies and maintenance, radioactive waste dismission and general costs. On these bases a providing price of 10-15 € for 37 MBq should be justified.

In the analysis of the costs, we accounted also those related to the wasting of the disposables used for the synthesis of [^{18}F]-PSMA-1007. In fact, they showed, in addition to ^{18}F, other radioactive contaminants with longer physical half-lives, including: [^{58}Co], [^{57}Co], [^{51}Cr], [^{54}Mn], etc. Thus, according to the current laws in European countries (Euratom BSS Council Directive 2013/59/Euratom), the removal and wasting of these disposables follows very restricted rules. In fact, they cannot be eliminated very quickly, but can be released after gamma ray spectrometry analysis and a prolonged stockage or release to authorized, specialized, companies.

Conclusions

Methodological aspects for an optimal production of [^{18}F]-PSMA-1007 have been evaluated in order to define the best operating procedures. Suggested starting activity of [^{18}F]-Fluoride should range from to 55 to 90 GBq, showing the following advantages:

- Short time of beam (30').
- Highest radiochemical yield (> 50%) and purity (> 99%) at EOS.
- Relatively low costs of production with many available doses of [^{18}F]-PSMA-1007.

All these aspects strongly indicate that [^{18}F]-PSMA-1007 produced following this approach, may satisfy the growing requests of PSMA PET/CT in clinical practice, guaranteeing high quality radiopharmaceutical.

Declarations

ACKNOWLEDGEMENTS: At this point, want to thank the contribute of *PLATT* project, financed by Regione Campania.

DECLARATIONS

Not applicable.

References

Afshar-Oromieh A., Avtzi E., Giesel F.L., Holland-Letz T., Linhart H.G., Eder M., Eisenhut M., Boxler S., Hadaschik A., Kratochwill C., Weichert W., Kopka K., Debus J., Haberkorn U. The diagnostic value of PET/CT imaging with the [^{68}Ga]-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur. J. Nucl. Med. Mol. Imaging. 2015;42(2):197-209.

Cardinale J., Martin R., Remde Y., Schäfer M., Hienzsch A., Hübner S., Zerges A.-M., Marx H., Hesse R., Weber K. Procedures for the GMP-Compliant Production and Quality Control of [^{18}F]PSMA-1007: A Next Generation Radiofluorinated Tracer for the Detection of Prostate Cancer. Pharmaceuticals. 2017;10(4):77.

Cardinale J., Roscher M., Schäfer M., Geerlings M., Benešová M., Bauder-Wüst U., Remde Y., Eder M., Nováková Z., Motlová L., Barinka C., Giesel F.L., Kopka K. Development of PSMA-1007-Related Series of ^{18}F-Labeled Glu-Ureido-Type PSMA Inhibitors. J. Med. Chem. 2020; 63(19):10897–10907.

Culp M.B., Soerjomataram I., Efstathiou J.,Bray F. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. European Urology. 2020;77(1):38-52.

Eeles R., Ni Raghallaigh H. Men with a susceptibility to prostate cancer and the role of genetic based screening. Transl. Androl. Urol. 2018;7(1):61-69.

Giesel FL., Hadaschik B., Cardinale J.,Radtke J., Vinsensia M.,Lehnert W., Kesch C., Tolstov Y., Singer S., Grabe N., Duensing S., Schäfer M., Neels O.C., Mier W., Haberkorn U., Kopka K., Kratochwil C. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur. J. Nucl. Med. Mol. Imaging. 2017;44(4):678-688.

Ioppolo J.A., Nezich R.A., Richardson K.L., Morandeau L., Leedman P., Price R.I. Direct *in vivo* comparison of [^{18}F]PSMA-1007 with [^{68}Ga]Ga-PSMA-11 and [^{18}F]AlF-PSMA-11 in mice bearing PSMA-expressing xenografts. Applied Radiation and Isotopes 2020;161.

Katzschmann I., Marx H., Kopka K., Hennrich U. Development and Validation of a GMP-Compliant High-Pressure Liquid Chromatography Method for the Determination of the Chemical and Radiochemical Purity of [18F]PSMA-1007, a PET Tracer for the Imaging of Prostate Cancer. Pharmaceuticals. 2021;14(3):188.

Kesch C., Kratochwil C., Mier W., Kopka K., Giesel FL. ^{68}Ga or ^{18}F for Prostate Cancer Imaging? J. Nucl. Med. 2017; 58(5):687-688.

Kuntzsch M., Lamparter D., Brüggener N., Müller M., Kienzle G. Development of Kryptofix 2.2.2 and Tetrabutylammonium in [^{18}F]-labeled Radiopharmaceutical. Pharmaceuticals. 2014;(7):621-633.

Naka S., Watabe T., Kurimoto K., Uemura M., Soeda, F., Neels O.C., Kopka K., Tatsumi M., Kato H., Nonomura N., Shimosegawa E., Cardinale j., Giesel F.L., Hatazawa J. Automated [^{18}F]PSMA-1007 production by a single use cassette-type synthesizer for clinical examination. Eur. J. Nucl. Med. Mol. Imaging: Radiopharm. Chem. 2020;(5):18.

Shammi O., Nebeling B., Grievink H., Mishani E. Fine-tuning of the automated [^{18}F]PSMA-1007. J.Label. Comp. Radiopharm. 2019; (62):252-258.

Sprute K., Kramer V., Koerber S.A., Meneses M., Fernandez R., Soza-Ried C., Eiber M., Weber W.A., Rauscher I., Rahbar K., Schaefers M., Watabe T., Uemura M., Naka S., Nonomura N., Hatazawa J., Schwab C., Schutz V., Hohenfellner M., Holland-Letz T., Debus J., Kratochwil C., Amaral H.,Choyke P.L., Haberkorn U., Sandoval C, Giesel F.L.

Diagnostic Accuracy of 18F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence. J. Nucl. Med 2021; (62):208-213.

Umbricht C.A., Benešová M., Schmid R.M., Türler A., Schibli R., Van der Meulen N., Müller C. [^{44}Sc]-PSMA-617 for radiotheragnostics in tandem with [^{177}Lu]-PSMA-617-preclinical investigations in comparison with [^{68}Ga]-PSMA-11 and [^{68}Ga]-PSMA-617. Eur. J. Nucl. Med. Mol. Imaging. Res. 2017;7(1):9.

Werner R., Derlin T., Lapa C., Sheikbahaei S., Higuchi T., Giesel F., Behr S., Drzezga A., Kimura H., Buck A., Bengel F., Pomper M., Gorin M., Rowe S. [^{18}F]-Labeled, PSMA-Targeted Radiotracers: Leveraging the Advantages of Radiofluorination for Prostate Cancer Molecular Imaging. Theranostics. 2020;10(1):1-16.

Wurzer A., Di Carlo D., Schmidt A., Beck R., Eiber M., Schwaiger M., Jurgen Wester H. Radiohybrid Ligands: A Novel Tracer Concept Exemplified by [^{18}F]- or [^{68}Ga]-Labeled rhPSMA Inhibitors. J. Nucl. Med. 2020;(61):735–742.

Zhou D., Lin M., Yasui N., Al-Qahtani M., Dence S., Schwarz S., Katzenellenbogen J. Optimization of the preparation of fluorine-18-labeled steroid receptor ligands 16alpha-[^{18}F] fluoroestradiol (FES), [^{18}F]fluoro furanyl norprogesterone (FFNP), and 16beta-[^{18}F]fluoro-5alpha-dihydrotestosterone (FDHT) as radiopharmaceuticals. J. Labelled Comp. Radiopharm. 2014;57(5):371-377.

Zippel C., Ronski S., Bohnet-Joschko S., Giesel F., Kopka K. Current Status of PSMA-Radiotracers for Prostate Cancer: Data Analysis of Prospective Trials Listed on ClinicalTrials.gov. Pharmaceuticals (Basel). 2020;13(1):12.

Monograph “PSMA-1007 (18F) Injection” (Monograph Number: 07/2021:3116). European Pharmacopeia, 10th Edition. 2020. Available online: https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-10th-edition (accessed on 19 April 2021).

Tables

Table 1. Comparison of [^{18}F]-Fluoride (GBq) starting activity and related RCY(%) at EOS.

Low Range (A)		Medium Range (B)		High Range (C)	
[^{18}F]-Fluoride Starting Activity (GBq)	Radiochemical Yield (%)	[^{18}F]-Fluoride Starting Activity (GBq)	Radiochemical Yield (%)	[^{18}F]-Fluoride Starting Activity (GBq)	Radiochemical Yield (%)
46,80	63,24	86,77	54,15	153,55	41,69
52,54	53,52	86,95	56,59	159,10	38,89
55,50	51,33	87,32	54,24	162,54	41,98
61,42	46,38	88,06	48,32	166,50	38,56
63,27	45,61	96,20	50,00	170,20	38,50
55,91*	**52,09***	**89,06***	**52,66***	**162,38***	**40,26***
6,69**	**7,10****	**4,02****	**3,4****	**6,46****	**1,76****

RCY average values (%) estimated at EOS, not corrected for decay and related to a synthesis time of ≃ 40'. For range A and B, RCY score is 52%, for range C it decreases to 40%. *Average; **Standard Deviation

Table 2. Comparison of produced [^{18}F]-PSMA-1007 activities (GBq) and related RCP(%). *Averages, **Standard deviation

Low Range (A)		Medium Range (B)		High Range (C)	
[^{18}F]-PSMA-1007 Final Activity (GBq)	Radiochemical purity (%RCP)	[^{18}F]-PSMA-1007 Final Activity (GBq)	Radiochemical purity (%RCP)	[^{18}F]-PSMA-1007 Final Activity (GBq)	Radiochemical purity (%RCP)
29,60	99,80	46,99	99,81	72,89	99,64
28,12	99,40	49,21	99,97	61,86	99,81
28,49	99,37	47,36	99,97	64,01	99,63
28,49	99,51	42,55	99,57	64,19	99,67
28,86	99,39	48,10	99,93	65,53	99,53
28,71*	**99,49***	**46,84***	**99,85***	**65,70***	**99,66***
0,56**	**0,18****	**2,54****	**0,17****	**4,23****	**0,10****

In red, RCP average values (%) related to three ranges (A, B and C) of the obtained [^{18}F]-PSMA-1007. RCP is >99% and it is independent from the amount of final product at EOS. *Average; **Standard Deviation

Table 3. Parameters employed in the synthesis of [^{18}F]-PSMA-1007 for three different ranges of activity

	Starting Activity (GBq)	Time of Beam (min)	Final Activity (GBq)	Radiochemical Yield (RCY%)	Radiochemical Purity (RCP%)
A	55,91	20	28,71	52,09	99,49
B	89,06	30	46,84	52,66	99,85
C	162,38	55	65,70	40,26	99,66

The table shows the variable parameters of the synthesis process: [^{18}F]-Fluoride starting activity by cyclotron, time of beam, final [^{18}F]-PSMA-1007 activity, RCY and RCP. The best values of RCY and RCP were obtained for range B, although the starting activity and the time of beam werere not optimal. The best range is B because it has no unfavorable conditions

Legend of colors: ¨ unfavorable conditions, ¨ optimal conditions, ¨ intermediate conditions.

Figures

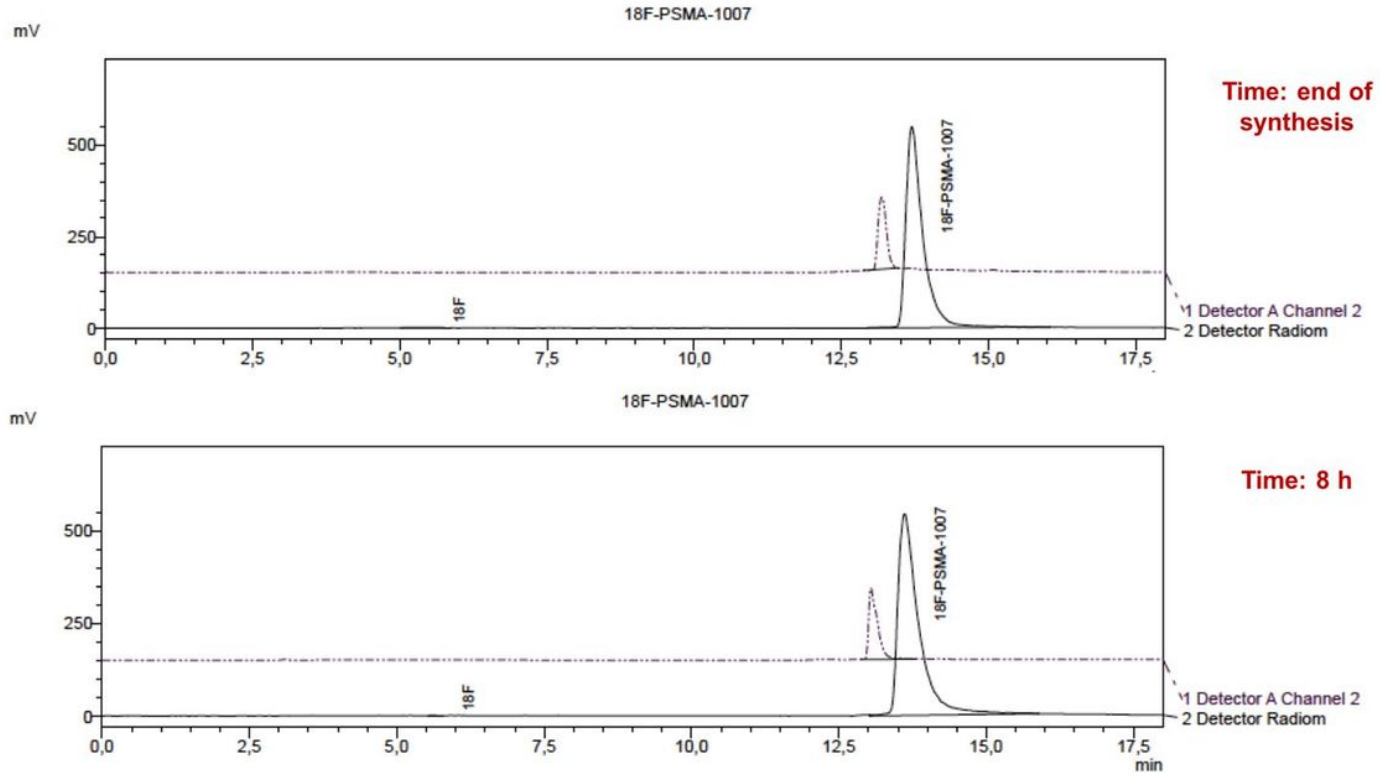

Figure 1

Radio-HPLC chromatograms performed at the EOS and after 8 hours. The UV signal (Detector A Channel 2, 220 nm) of the PSMA-1007 and the radiometric of [18F]-PSMA-1007 (Detector Radiom) due to the radiolabeled compound overlapped. The stability of radiolabeled peptide is confirmed up to 8 hours after EOS.

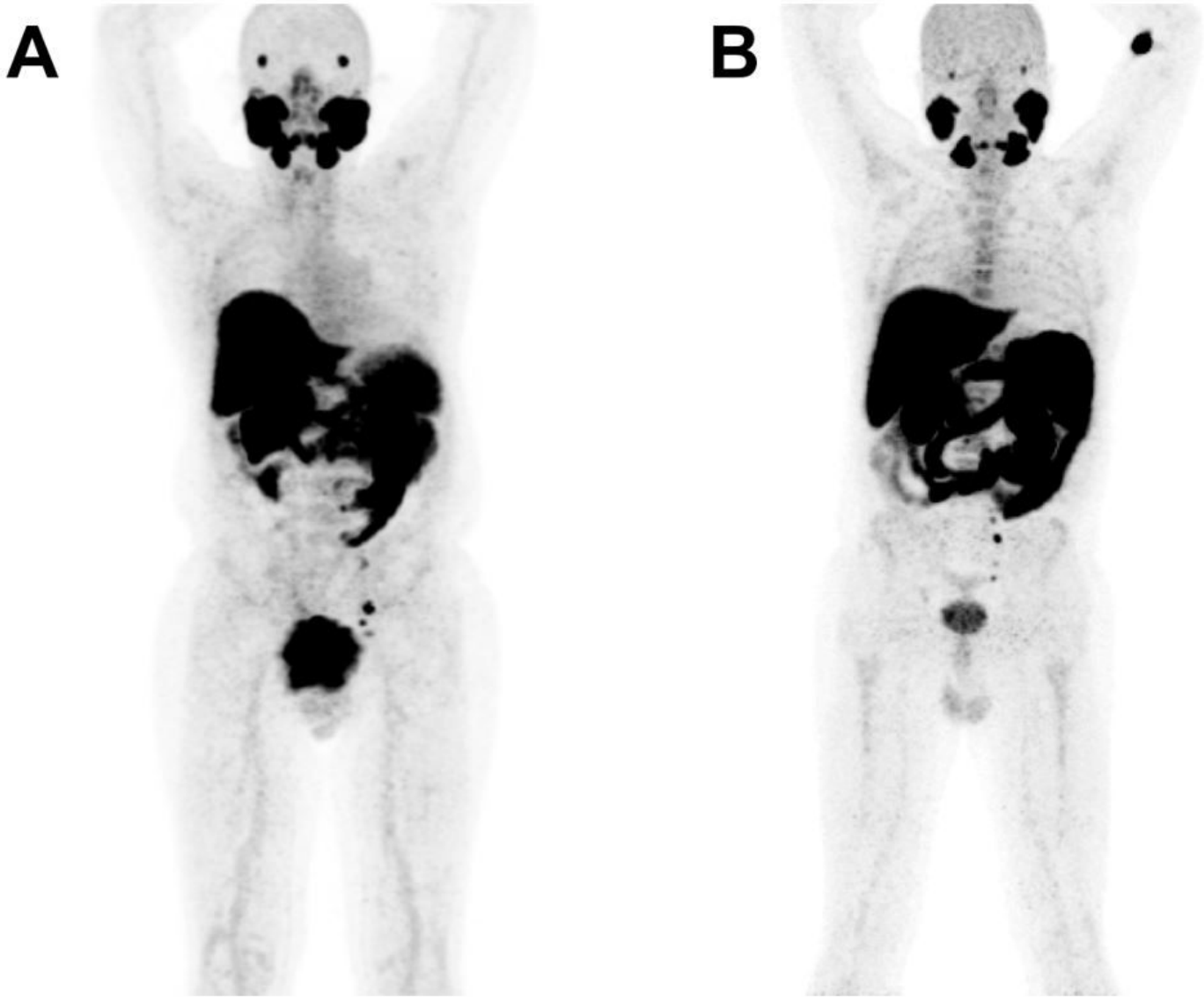

Figure 2

Example of different patients, with similar tumor burden, acquired on the same date, but receiving the injection at different times after the EOS. Patient A was injected about one hour after the [18F]-PSMA-1007 EOS, and patient B six hours later.

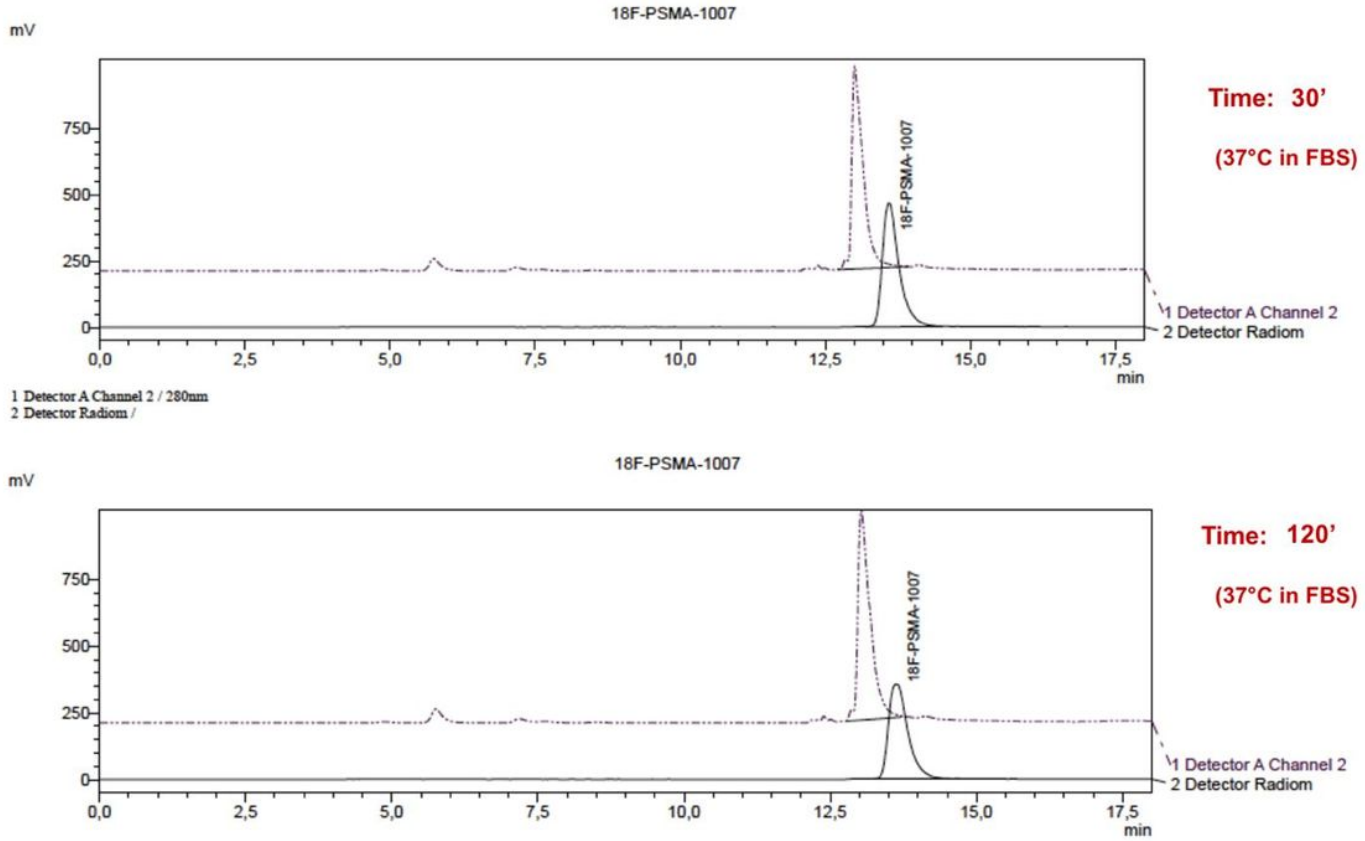

Figure 3

Studies of stability were performed by incubating of [18F]-PSMA-1007 at 37°C in FBS at the concentration of 37MBq/mL. The chromatograms confirm the stability of the radiolabeled compound up to 120'.

Figure 4

A patient with nodal and bone metastasis, administered and scanned within 2 hours from EOS.