ABOUT THE USE IN NUCLEAR MEDICINE OF PHARMACEUTICALS ON THE BASIS OF THE ISOTOPE ^{18}F AND ITS ACHIEVEMENTS ON LINEAR ELECTRON ACCELERATORS OF NIK "ACCELERATOR"

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The importance widely used in the world of Radiopharmaceutical: 2-fluoro [^{18}F]-2-deoxy-D-glucose (fluorideglucose, ^{18}F) for the diagnosis of various diseases using PET and CT imaging are shown. Provides information about the levels of specific activity of aqueous solutions containing the isotope ^{18}F, the resulting target irradiation-matrix of Teflon (C_2F_4) on different linear accelerators of electrons NIK "Accelerator". Emphasis on the need to increase the density of the electron flux on the target and find ways of improvement of the methodology for obtaining Radiopharmaceutical, using isotope ^{18}F, produced by the photonuclear method.

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INTRODUCTION

At present, Ukraine's medical institutions that use radionuclide diagnostics have developed a critical situation due to the almost complete absence of radiopharmaceuticals (RFPs) of domestic production based on radioactive nuclides (isotopes). Although most of the diagnostic tools are pharmaceuticals based on technetium ^{99m}Tc, a significant (and in some cases determining) role in the diagnosis of various diseases is allocated to RFPs, "labeled" ultrashort-living (UKZH) radionuclides: ^{11}C, ^{13}N, ^{15}O, ^{18}F.

These positron-active radionuclides are widely used around the world as sources of 511 keV annihilation gamma radiation for positron emission tomographs (PET). The undeniable merit of the PET method, using the UKZh-isotopes, is that, by providing the operation of electronic equipment with high loads (10^5…10^6 s^{-1}), high spatial resolution and a low level of radiation exposure to the patient (fraction of rad) is achieved, and itself the examination procedure lasts a few minutes.

Unfortunately, at the moment there is no universal drug that could detect all tumors, so in PET diagnostics there is a very large number of drugs. The use of UKZh-isotopes isotopes for labeling RFPs administered to a patient provides two main advantages over other types of radioisotope diagnostics.

First, the label with these isotopes, including the isotope ^{11}C, (unlike the isotopes ^{99m}Tc or ^{123}I used in SPECT) does not change the chemical properties of the RFPs, therefore they are functional analogues of natural metabolites, and the distribution in the body of appropriately selected RFPs adequately reflects parameters of the studied biochemical process and/or the functional state of the organism. Secondly, the short half-life of these isotopes allows multiple studies of the same patient, which is of fundamental importance for receptor studies.

1. APPLICATION OF RADIOPHARMA CEUTICAL (RFP) 2-FLUORO [^{18}F] -2-DEOXY-D-GLUCOSE (FLUORODEOXYGLUCOSE, ^{18}F)

It is worthwhile to consider more closely the use of the ^{18}F isotope as a radioactive "tag" when creating RFP for PET diagnostics. Tumors are different in nature and have different cellular composition, and, consequently, have different properties. Unfortunately at the moment there is no universal drug that could detect all tumors, therefore in PET diagnostics there is a very large number of drugs. But among the multitude there is one, the most universal, which works on a large spectrum of tumor pathologies – it is fluorodeoxyglucose or FDG is a molecule of glucose in which one hydroxyl group is replaced by of radioactive fluorine – ^{18}F (Fig. 1).

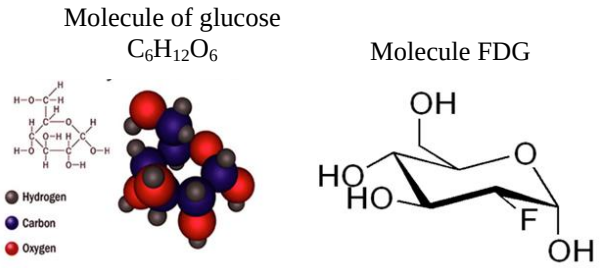

Fig. 1. Molecule of glucose and molecule FDG

How does it work and why does FDG accumulate? Shorter: glucose is energy! All cells need energy, and the cells of the tumor need energy especially, because they quickly divide, and for this, the cells of the tumor need a lot of energy. Therefore, tumor cells accumulate a much larger amount of glucose, and consequently FDG. For this reason, in the PET study, we can see where the tumor cells are located.

It should be noted, that unfortunately this drug is able to detect not all tumors. It depends on the characteristics of the tumor. For example, FDG works great for most lymphomas, many lung tumors, intestinal tumors, breast, melange and many others, but the diagnostic value of FDG in prostate cancer is extremely low. A similar situation with a low diagnostic significance of FDG is observed in most neuroendocrine tumors.

Similarly, the capabilities of the device are limited and we can not identify one or more cells. The resolution of the device is limited and the PET study can visualize tumors ranging from 4…6 mm.

2. PET RESEARCH

Consider PET/CT studies with FDG, since studies with this drug are about 80 percent of all PET research in the world. The first of the presented slides (Fig. 2, top) shows a pure positron tomogram, next – a combined PET/CT image. It can be seen that in this case there is no pronounced pathology.

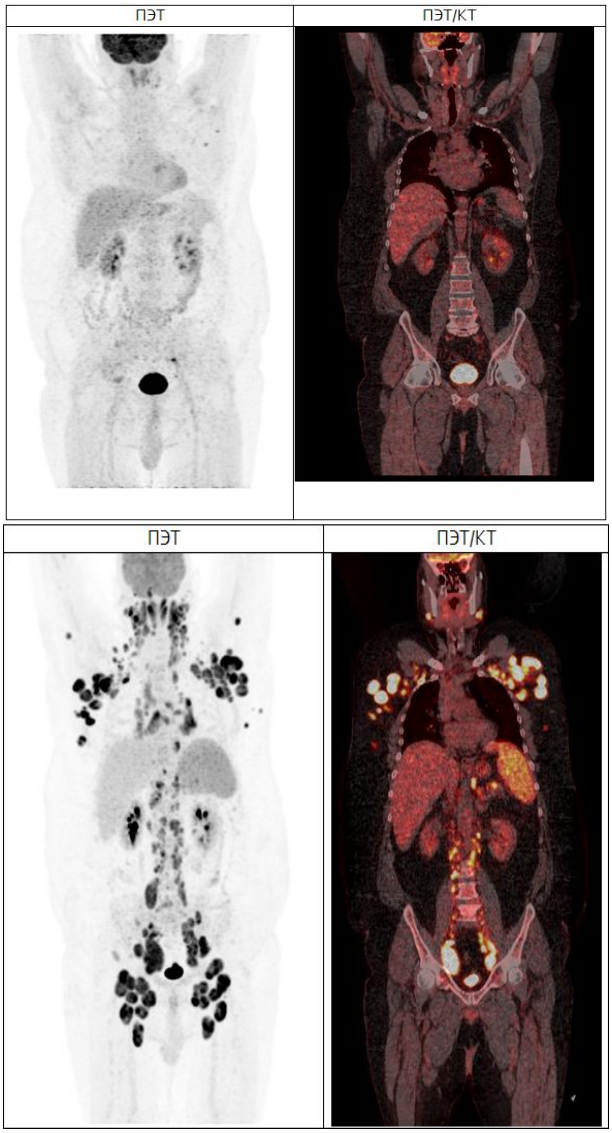

Fig. 2. PET/CT image of the patient

On the slide (Fig. 2, on the bottom) – a patient with Hodgkin's lymphoma, multiple black dots (or red on the next slide) show the affected lymph nodes. It should be noted that the color solution depends on the specific doctor and does not affect the diagnostic value of the study.

How to determine the pathological accumulation of the drug on PET/CT and what is SUV? PET allows not only to see the tumor process, but also to carry out certain measurements. If in X-ray computed tomography (CT) and magnetic resonance imaging (MRI) measurements are performed in centimeters (millimeters) to determine the size of the pathological site. The intensity of accumulation of the drug in the pathological organ – SUV (STANDARDIZED STAGE OF RADIOPHARM PREPARATION ACCUMU-LATION) is determined in PET diagnostics.

It should be noted that there are different SUV parameters and different units of measurement, so in the description protocol there should be a link explaining this data.

Fig. 3 shows, for example, a PET image of the patient's liver patch in a situation with an increased intensity level of the ^{18}F isotope.

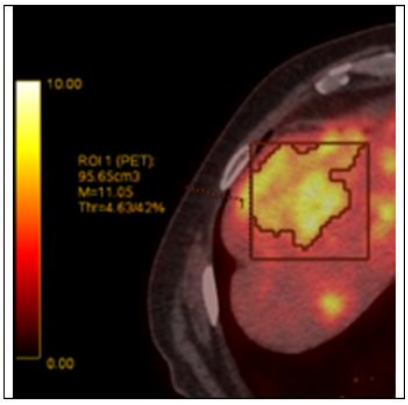

Fig. 3. SUV=11

Thus, this parameter shows how many RFPs accumulated in the volume of the tumor focus. What is it for?

First, there are threshold values for which doctors are oriented, for a conditional differentiation of the norm and pathology.

Second – the change in SUV against the background of treatment helps doctors to conclude on its effectiveness. That is, if the treatment of SUV is reduced against the background, then the treatment works and vice versa, by how significantly the SUV changes, a conclusion is made about the continuation or change of therapeutic tactics.

3. EXPERIMENT

In the world, a technique for obtaining the ^{18}F isotope is widely used by irradiating protons with energy 10…20 MeV water enriched with a stable isotope of oxygen ^{18}O according to the reaction ^{18}O(p, np)^{18}F, which makes it possible to obtain fluorinated compounds, for example, fluorodeoxyglucose, ^{18}F.

The task of this study at the initial stage was to determine the feasibility of the ^{18}F isotope production by the photonuclear method at various linear accelerators of electrons existing in the NIC "Accelerator" (NSC KIPT AN NASU). As a criterion, the specific activity of aqueous solutions, containing the isotope ^{18}F, was determined, which is formed as a result of irradiation of target matrices from fluoroplastic (fluoropolimer) (C_2F_4) by a gamma-ray beam from a linear electron accelerator. An experimental verification of this possibility was carried out at accelerators: LU-10, «EPOS», LU-40m.

3.1. ACCELERATOR LU-10

The study of the ^{18}F isotope production on the LU-10 accelerator was carried out, using the output device schematically depicted in Fig. 4.

The output device includes the Bremsstrahlung converter K, the Φ1 filter (4 duralumin plates 2 mm thick each) and additional polyethylene filter Φ2 with a thickness of ~ 50 mm. Target M1 includes two capsules of duralumin, into which a coiled film of fluoroplastic with a mass of 1.020 g is placed in water (distillate) – in one capsule in the other – a coarse-grained powder of fluoroplastic with a mass of 1.000 g.

Two pieces of dosimetric film are placed on each capsule from the side of the beam. The target M1 con-

sists samples of In, Au, Cd, Hf and Sn, used for dosimetry of bremsstrahlung of the accelerator.

At the accelerator LU-10, a mode of 12…13 MeV is obtained at the maximum of the spectrum.

An output device is installed according to the experimental design.

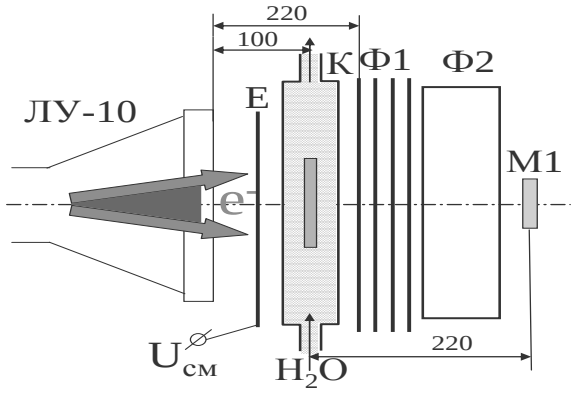

Fig. 4. The circuit of the output device

The targets were irradiated with a scanned beam with a mean current of 200 μA for 30 minutes.

Results of the experiment:

1. Weight loss of each ampoule was 0.5 g.

2. The activity (according to the isotope ^{18}F) of an aqueous solution of 1 cm^3, extracted from the capsule with the film (C_2F_4) was 1.85 KBq/g.

3. The activity (according to the isotope ^{18}F) of an aqueous solution of 1cm^3, extracted from the capsule with powder (C_2F_4) was 1.66 KBq/g.

4. Considering the different amount of water in the capsule, we can conclude that the isotope ^{18}F is more efficiently released to the aqueous phase from the powder.

5. The neutron flux measured by Au-threshold detectors was: fast neutrons – $4.49 \cdot 10^5$ $n \cdot s^{-1}$, slow neutrons – $2.23 \cdot 10^6$ $n \cdot s^{-1}$.

3.2. ACCELERATOR "EPOS"

The scheme of the experiment is shown in Fig. 5.

The accelerator worked in the mode of scanning an electron beam: energy – 25 MeV, I_{av}= 450 мкА, the time of irradiation is 110 min.

A Pb converter, 10 mm thick, was used to obtain the flux of gamma rays, which was placed just before the irradiated capsule. The current density on the converter is 0.25 μA/cm^2.

Capsules of duralumin, fluoroplast and copper filled with water and fluoroplastic in the form of a film with a thickness of 20 μm and coarse-grained powder were irradiated.

To cool the capsules, a "rainwater" flow of water was technologically used.

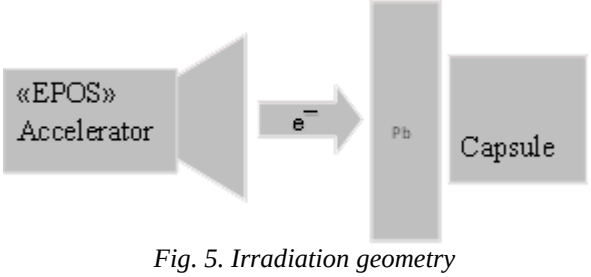

Fig. 5. Irradiation geometry

The results obtained in the irradiation geometry shown in Fig. 5 during the exposure time 110 min, at

E = 25 MeV and I_{av} = 450 μA:

- the activity of ^{18}F in the aqueous phase is $4.1 \cdot 10^4$ Bq/g;
- the activity of ^{18}F in the matrix film is $1.01 \cdot 10^6$ Bq/g;
- the activity of ^{18}F in the plate-matrix is $1.05 \cdot 10^6$ Bq/g.

The yield of the isotope ^{18}F in water was 4%.

3.3. ACCELERATOR LU-40m

The study of the ^{18}F isotope run on the LU-40m accelerator [1] is performed in geometry irradiation of the capsule-target containing fluorine plastic, depicted in Fig. 6.

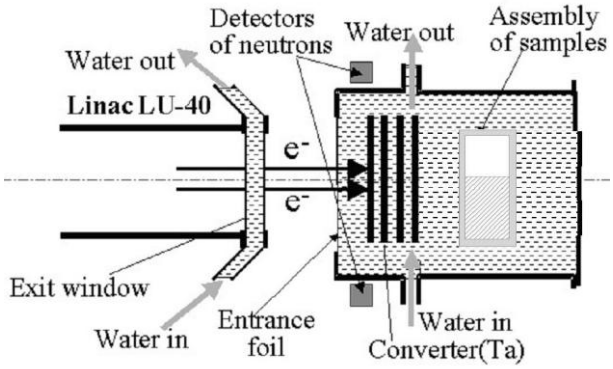

Fig. 6. The irradiation scheme of the capsule-target at the accelerator LU-40m with water cooling of the converter and capsule

Irradiation regime: energy-36 MeV. The average current I_{av}=4.8 μA. The irradiation time is 30 minutes. Converter: Ta (4 plates with gaps total thickness 4mm). Target: capsule of fluoroplastic (C_2F_4), filled with fluorine plastic film with a thickness of 20 μm (weight 1.82 g) and water (mass – 1.27 g).

The total mass of the capsule in the collection: before irradiation – 30.48 g, after irradiation – 30.27 g.

The "mass defect" of the capsule after irradiation is explained by the leakage of heated (up to vapor) water from the capsule.

1. After irradiation, an aqueous "concentrate", activated with the ^{18}F isotope, was extracted from the capsule, with a mass of 0.225 g.

2. The small amount of the extracted "concentrate" is explained (presumably) by the "absorption" of water by a fluoroplastic film, under the action of irradiation (visually it looked "swollen"). Total mass of the capsule in the collection: before irradiation – 30.48 g, after irradiation – 30.27 g.

The "mass defect" of the capsule after irradiation is explained by the leakage of heated (up to vapor) water from the capsule.

3. Specific activity of the ^{18}F isotope contained in the aqueous medium, calculated for the 60 min irradiation with regard to: the irradiation time, the measurement time, the change in activity during the measurement time and the "holding" (or cooling) time was equal $1.42 \cdot 10^6$ Bq/g.

Summary table of ^{18}F production

Accelerators	LU-10 Accelerator	«EPOS» Accelerator	LU-40m Accelerator
The accumulated specific activity of the ^{18}F isotope in the aqueous phase	$1.85 \cdot 10^3$ Bq/g	$4.1 \cdot 10^4$ Bq/g	$1.42 \cdot 10^6$ Bq/g

Reserve possibilities for increasing the amount of isotope ^{18}F:

- increase in the irradiation time (440 minutes,
- $4T_{1/2}$) – factor ~ 2;
- increase in the mass of irradiated fluoroplastic-factor ~ 10;
-increase in the yield of the ^{18}F isotope in water-factor ~ 5;
- increase in the average current – factor ~ 100.

The total factor for increasing the amount of isotope^{18}F in the aquatic environment can be ~ 10^4.

With the activity of the ^{18}F isotope in an aqueous medium amounting to ~ Curie, we can speak of "opening opportunities" that provide the creation of the pharmaceutical preparation "Fluodeoxyglucose, ^{18}F"

CONCLUSIONS

1. As shown by the conducted studies, at the linear accelerators of electrons available in the NSC KIPT, the production of specific activities of the ^{18}F isotope in an aqueous medium (~ Curie) sufficient to create RFP "Fluorodeoxyglucose, ^{18}F" is possible only under the condition of optimizing all the factors that determine the amount of the ^{18}F isotope.

2. One of the main factors ensuring the value of the ^{18}F isotope under the conditions, described above, is the current density on the target.

REFERENCES

1. M.I. Ayzatsky, V.I. Beloglasov, V.N. Boriskin, et al. State and prospects of the linac of nuclear-physics complex with energy of electrons up to 100 MeV // *Problems of Atomic Science and Technology. Series "Nuclear Physics Investigations"*. 2014, № 3, p. 60-63.

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ОБ ИСПОЛЬЗОВАНИИ В ЯДЕРНОЙ МЕДИЦИНЕ РФП НА ОСНОВЕ ИЗОТОПА ^{18}F И ВОЗМОЖНОСТИ ЕГО НАРАБОТКИ НА ЛИНЕЙНЫХ УСКОРИТЕЛЯХ ЭЛЕКТРОНОВ НИК «УСКОРИТЕЛЬ»

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Показана значимость широко используемого в мире РФП: 2-фтор[^{18}F-2-дезокси-D-глюкозы (фтордезоксиглюкозы, ^{18}F) для диагностики различных заболеваний с применением ПЭТ и КТ-томографии. Приведены сведения об уровнях удельной активности водных растворов, содержащих изотоп ^{18}F, образующийся в результате облучения мишеней-матриц из фторопласта (C_2F_4) на различных линейных ускорителях электронов НИК «Ускоритель». Делается ударение на необходимости повышения плотности потока электронов на мишени и поиска путей усовершенствования методологии получения РФП-фтордезоксиглюкозы с использованием изотопа ^{18}F, нарабатываемого фотоядерным методом.

ПРО ВИКОРИСТАННЯ В ЯДЕРНІЙ МЕДИЦИНІ РФП НА ОСНОВІ ІЗОТОПУ ^{18}F ТА МОЖЛИВОСТІ ЙОГО НАПРАЦЮВАННЯ НА ЛІНІЙНИХ ПРИСКОРЮВАЧАХ ЕЛЕКТРОНІВ НДК «ПРИСКОРЮВАЧ»

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Показана значимість широко використовуваного в світі РФП: 2-фтор[^{18}F]-2-дезоксі-D-глюкози (фтордезоксіглюкози, ^{18}F) для діагностики різних захворювань із застосуванням ПЕТ і КТ-томографії. Приведені відомості про рівні питомої активності водних розчинів, що містять ізотоп ^{18}F, що утворюється в результаті опромінення мішеней-матриць з фторопласту (C_2F_4) на різних лінійних прискорювачах електронів НДК «Прискорювач». Робиться наголос на необхідності підвищення щільності потоку електронів на мішені і пошуку шляхів удосконалення методології отримання РФП-фтордезоксіглюкози з використанням ізотопу ^{18}F, напрацьованого фотоядерним методом.