EFFICIENCY OF POSITRON EMISSION TOMOGRAPHY WITH ^{18}F-FLUORODEOXYGLUCOSE, ^{11}C-METHIONINE AND ^{82}Rb-CHLORIDE IN DIFFERENTIAL DIAGNOSIS OF LUNG TUMORS AND SOME INFLAMMATORY PULMONARY DISEASES

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The aim of the investigation was to study the informativeness of positron emission tomography (PET) using ^{18}F-FDG, ^{11}C-methionine and ^{82}Rb-chloride in differential diagnosis of tumor and some inflammatory pulmonary diseases.

Materials and Methods. PET findings of 378 patients with lung tumors and inflammatory pulmonary diseases were studied. PET with ^{18}F-FDG and ^{11}C-methionine were performed 120 and 15 min, respectively, after their intravenous administration. PET with ^{82}Rb-chloride was performed 1 min after distant intravenous administration. Quantitative processing of PET findings regardless the medication used included visual image analysis and calculation of Standardized Uptake Value (SUV) in healthy pulmonary parenchyma and in lesion.

Results. SUV in patients with lung cancer in PET with ^{18}F-FDG and ^{11}C-methionine were higher than metabolic activity in an inflammation region, while in PET with ^{82}Rb-chloride, SUV levels were significantly higher in the foci of inflammation than in malignant tumors. The patients with benign tumors and most patients with focal pneumofibrosis in pulmonary tissue consolidation area were recorded to have background distribution of radiopharmaceuticals. It enabled to reliably differentiate benign tumors and focal pneumofibrosis from lung cancer regardless the medications used.

Conclusion. The obtained data on the informativeness of positron emission tomography performed using ^{11}C-methionine suggest high diagnostic value of the technique in the differential diagnosis of lung cancer, neuroendocrine tumors, benign tumors and inflammatory diseases. Despite good imaging potential PET with ^{82}Rb-chloride is unreasonable in differentiation of lung tumors and inflammatory pulmonary diseases.

Key words: positron emission tomography; ^{18}F-FDG; ^{11}C-methionine; ^{82}Rb-chloride; lung tumors and inflammatory pulmonary diseases.

Currently, positron emission tomography (PET) is one of compulsory diagnostic procedures performed in patients with malignant tumors of any localization including pulmonary cancer (PC). It is due to both: high informational content of PET in most oncological diseases, and the introduction of new radioactive preparations (RP). These drugs are biological compounds labeled with positron-emitting radionuclides, which are able to accumulate in some morphological structures and reflect metabolic and dynamic processes. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is currently the most extensively studied and widely used in oncology clinics RP of cyclotron production type. An indubitable advantage of this indicator is relatively large (110 min) half-life period that enables to scan in "the whole body" mode, as well as its capacity to accumulate in an increased amount in malignant tumors. ^{18}F-FDG accumulation in malignant neoplasms is due to two main reasons: increase in the amount of transport proteins delivering RP in an atypical cell and activity rise of hexokinse catalyzing phosphorylation — the change from administered ^{18}F-FDG to ^{18}F-FDG-6-phosphate. The resulting molecule due to its large size and low activity of the following enzyme of glycolytic cascade — phosphohexoisomerase, and falls into a so-called metabolic trap, which promotes imaging of the most malignancies and their metastases as "hot" foci against healthy tissues. However, it is important to note that pathological hyperfixation of RP in pulmonary neoplasm is not always a radiological sign of a malignant process. Sometimes, ^{18}F-FDG accumulation marks inflammatory changes [1–3]. It occurs, primarily, due to a significant increase of glucose transport proteins, as well as the accumulation of macrophages, neutrophils, eosinophils, granulocytes and other blood corpuscles, which are accumulator-cells, in the area of active inflammation. This property of ^{18}F-FDG is certainly to restrain PET feasibility in differential diagnosis between PC and inflammatory diseases. In benign tumors, as well as in the area of cicatrical changes, ^{18}F-FDG metabolic changes do not differ from glycolytic reactions in healthy pulmonary parenchyma. Accordingly, there is no an

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increased ^{18}F-FDG scavenging in these diseases being a reliable differential diagnostic sign that makes it possible in PET with ^{18}F-FDG to differentiate PC, benign tumors and local pulmonary fibrosis.

In literature there are few reports on using another RP in patients with PC — carbon 11 labeled methionine (^{11}C-methionine) [4, 5]. It is important to note that over a number of years this indicator is used for differential diagnosis and treatment efficiency assessment of various brain tumors. However, ^{11}C-methionine is rarely used to detect extracerebral tumors. This is due to the fact that in norm this RP accumulates mainly in internal secretion glands and excretory glands, as well as in bone marrow and spleen. It presents certain problems when estimating tumor extension in cancer patients. Moreover, a short half-life period of ^{11}C (20 min), and, consequently, the problems arising from transporting of the indicator to other laboratories, prevent from its extensive use in isotope facilities with no cyclotron complex.

In its physicochemical properties methionine is a typical aliphatic sulfur-containing amino acid. In norm, after the agent enters blood flow, carrier proteins deliver it inside the cells, where mobile methyl group of amino acid is embedded into purine and pyrimidine bases of DNA molecule. When a normal cell transforms into a malignant one, as a rule, methylation is accompanied by numerous defects resulting in constant methionine deficiency. It is constant demand of atypical cells for methionine that leads to intensive uptake of amino acid exogenous fraction by different malignant tumors [6]. On the other hand, in literature there is information that ^{11}C-methionine, like ^{18}F-FDG accumulates not only in malignant tumors but also in inflammation area [4]. Despite this fact, in literature one can find reports on higher informativeness of ^{11}C-methionine-PET in differentiation between PC and inflammatory diseases compared to ^{18}F-FDG. However, it should be said that literature data on applying ^{11}C-methionine-PET in patients with pulmonary masses of uncertain origin date mainly from the middle of the 90-ies and contain the information on the results of studies carried out in small groups of patients, who frequently had received anti-tumor treatment. In this regard, currently, the role of ^{11}C-methionine-PET in the diagnosis of PC and inflammatory diseases needs elaboration.

Single foreign publications represent data on malignant tumor detection by PET with a generator radiotracer — rubidium-82 chloride (^{82}Rb-chloride). It should be said that this radiotracer is used in cardiology to assess myocardial regional blood flow condition. Meanwhile, some authors performed ^{82}Rb-chloride-PET in patients with cardiovascular pathology report about the accidental detection of malignant pulmonary tumors, breast cancer and other tumors fallen within scanning area [7–9]. Moreover, the researchers note adequate imaging of the masses detected. Currently, there are no reports both in foreign and Russian literature on unequivocal use of ^{82}Rb-chloride in cancer patients.

^{82}Rb-chloride is a normal saline containing nuclide ion ^{82}Rb. By its physicochemical and biological properties ion ^{82}Rb is an analogue of ion K^+. A well known thallium-201 (^{201}Tl) used for perfusion myocardial scintigraphy has similar characteristics. When injected intravenously, ^{82}Rb-chloride, by analogy with ^{201}Tl, is brought by blood flow to organs and tissues, where it is distributed in proportion to flow rate of regional capillary blood flow, as well as to the activity of sodium-potassium ATP-dependent pump. The mechanism of ^{82}Rb-chloride uptake by malignant cells has not been identified yet. There has been only suggested that rubidium, by analogy with ^{201}Tl, can come through membrane of atypical cells providing increased RP accumulation in a malignant tumor, and therefore, its imaging against healthy tissues as a “hot” focus [10].

The current study generalizes the experience of PET with the three above mentioned RP over the period 2011–2014 on the basis of Russian Research Center of Radiology and Surgical Technologies, and with direct participation of several pulmonary and oncology clinics in S. Petersburg.

The aim of the investigation was to study the informativeness of positron emission tomography using ^{18}F-FDG, ^{11}C-methionine and ^{82}Rb-chloride in differential diagnosis of tumor and some inflammatory pulmonary diseases.

Materials and Methods. Chest PET with ^{18}F-FDG, ^{82}Rb-chloride and ^{11}C-methionine was performed in 378 patients with lung tumors and inflammatory pulmonary diseases. In addition to PET, diagnostic examination of patients included bacteriological analysis of sputum or epithelial lining fluid, diaskintest, serological and polymerase chain reaction of blood plasma components to reveal antigens and DNA of Mycobacterium tuberculosis, as well as fibrobronchoscopy, radiography and computed tomography (CT) of chest. In 332 patients (87.8%) a final diagnosis was made relying on cytological and/or morphological analysis. The rest cases were assessed according to dynamic radiological control findings. Table 1 shows the classification of patients depending on a final diagnosis and RP used.

The study complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)) and approved by the Ethics Committee of Russian Research Center of Radiology and Surgical Technologies. Written informed consent was obtained from all patients.

In accordance with a standard program, PET with ^{18}F-FDG and ^{11}C-methionine were performed 120 and 15 min, respectively, after their intravenous administration; ^{82}Rb-chloride-PET was performed 1 min after distant intravenous administration. Quantitative processing of PET findings regardless RP used included visual image analysis and calculation of Standardized Uptake Value (SUV) in healthy pulmonary parenchyma and in lesion.

The findings were statistically processed using

MedCalc 11.0.1 for Windows. In addition, we used parametric and nonparametric techniques including estimated mean (M), mean error (m). Critical significance level of a zero statistical hypothesis was taken equal to 0.05. Sensitivity, specificity, diagnostic accuracy, positive and negative prognostic value were determined using characteristic curve analysis (Receiver Operating Characteristic, ROC). In addition, SUV were cut-off values or numeral classifiers.

Table 1

Study design (n=378)

Final diagnosis	^{18}F-FDG-PET (n=182)		^{82}Rb-chloride-PET (n=80)		^{11}C-methionine-PET (n=116)	
	Absolute number	%	Absolute number	%	Absolute number	%
Pulmonary cancer	90	49.4	29	36.3	54	46.5
Neuroendocrine tumors	7	3.9	2	2.5	11	9.5
Benign tumors	15	8.2	21	26.2	9	7.8
Inflammatory diseases	56	30.8	21	26.2	35	30.2
Focal pneumofibrosis (post-tuberculosis)	14	7.7	7	8.8	7	6.0

Results. Image analysis of tomograms obtained by using ^{18}F-FDG showed pathological RP uptake in all patients with PC and the patients with inflammatory diseases. No increased accumulation of ^{18}F–FDG was found in pulmonary benign tumors. No RP accumulation was also recorded in 3 out of 7 patients with neuro-endocrine tumors (NET) and in 7 out of 14 patients with post-tuberculosis pneumofibrosis.

^{82}Rb-chloride-PET revealed foci of increased RP accumulation in the lung in 45 out of 80 patients. In 26 cases the changes were due to PC, in 2 cases — due to NET, in 17 — active tuberculosis. There was recorded no pathological ^{82}Rb-chloride hyperfixation in all patients with benign pulmonary tumors and focal pneumofibrosis, in 3 PC patients, as well as in 4 cases of infiltrative tuberculosis.

Visual analysis of tomoscintigrams taken by chest scanning using ^{11}C-methionine showed foci of pathological RP accumulation in all patients with PC and NET, in 31 out of 35 patients with inflammatory diseases, as well as in 2 out of 7 cases of focal pneumofibrosis. The rest patients were recorded to have background (consistent with intact pulmonary parenchyma) RP distribution in the tumor view. No signs of focal uptake were revealed.

Analysis of SUV recorded in patients with pulmonary tumors and inflammatory diseases detected by PET with focal RP uptake (Table 2) showed SUV recorded in PET with ^{18}F-FDG and ^{11}C-methionine to be significantly higher in patients with PC than in patients with inflammatory diseases and focal pneumofibrosis ($p \leqslant 0.05$). In addition, ^{82}Rb-chloride-PET showed the opposite results: SUV above the inflammatory foci had significantly higher metabolic activity than those recorded in malignant pulmonary tumors (p=0.0012). ^{18}F-FDG-PET in patients with NET demonstrated significantly lower SUV than in patients with PC (p=0.0026). However, SUV levels in NET patients did not differ from metabolic activity in foci of inflammation (p=0.1941). Similar findings were obtained in the study with ^{11}C-methionine in patients with PC and NET. The comparison of SUV levels in these patients showed no significant differences (p=0.1341).

Thus, imaging findings, as well as the results of comparing mean SUV calculated in PET with ^{18}F-FDG, ^{11}C-methionine and ^{82}Rb-chloride indicated similar semiotic manifestations and quantitative characteristics in patients with pulmonary tumors and pulmonary inflammatory diseases. In this regard, we performed ROC analysis to determine numerical differential diagnostic criteria, as well as to calculate PET informativeness. Threshold SUV and informativeness of PET with ^{18}F-FDG, ^{82}Rb-chloride and ^{11}C-methionine in differential diagnosis of pulmonary tumors and inflammatory diseases (Table 3) indicate that maximum values of diagnostic accuracy of PET in differential diagnosis of pulmonary tumor and inflammatory diseases were found in ^{11}C-methionine-PET. And specificity values in ^{18}F-FDG and ^{11}C-methionine-PET were comparable. Informativeness indices in differentiation of malignant and inflammatory

Table 2

SUV levels recorded in patients with pulmonary tumors and inflammatory diseases in PET with ^{18}F-FDG, ^{82}Rb-chloride and ^{11}C-methionine manifested by focal RP uptake (M±m)

Diagnosis	^{18}F-FDG-PET	^{82}Rb-chloride-PET	^{11}C-methionine-PET
Pulmonary tumors	9.92±1.05	5.66±0.20	4.05±0.27
NET	3.10±0.81	4.1; 3.8*	3.81±0.31
Inflammatory diseases	3.68±0.38	7.36±0.37	1.92±0.12
Focal pneumofibrosis	1.12±0.08	—	1.21±0.04
Intact pulmonary parenchyma	0.79±0.10	3.18±0.33	1.06±0.06

* — total two observations.

Table 3

Threshold SUV and informativeness of PET with ^{18}F-FDG, ^{82}Rb-chloride and ^{11}C-methionine in differential diagnosis of pulmonary tumor and inflammatory diseases, %

Study type, SUV threshold value	Sensitivity	Specificity	Diagnostic accuracy	Positive prognostic value	Negative prognostic value
^{18}F-FDG-PET, SUV>4.3	70.3	86.2	80.8	86.7	77.1
^{11}C-methionine-PET, SUV>2.4	89.5	87.5	86.9	87.1	86.7
^{82}Rb-chloride-PET, SUV⩽6.47	74.4	46.4	58.7	52.0	69.9

changes in the lungs using ^{82}Rb-chloride-PET were significantly lower than those obtained in ^{18}F-FDG and ^{11}C-methionine-PET.

Discussion. Currently, ^{18}F-FDG-PET is widely used in patients with pulmonary masses of uncertain origin. The main advantage of the technique is the possibility to perform differential diagnosis of malignant and benign pulmonary tumors, as well as determine the stage of a tumor process in patients with verified PC. However, despite a long-term experience of using ^{18}F-FDG-PET in such patients, it would be incorrect to consider the problem of differentiation of PC and inflammatory disease to be resolved. Unfortunately, ^{18}F-FDG-PET shows malignant and inflammatory processes in the ling as equally increased RP accumulation. So, the search and introduction of more specific radiotracers are required.

For that purpose we compared informativeness of PET performed with a widely used ^{18}F-FDG with the efficiency of the method using other tracers: ^{11}C-methionine and ^{82}Rb-chloride. The results of visual analysis of PET with ^{18}F-FDG, ^{11}C-methionine and ^{82}Rb-chloride indicated similar semiotic manifestations of pulmonary tumor and inflammatory diseases. In patients with benign tumors and the most patients with focal pneumofibrosis there was recorded background RP distribution in the pulmonary tissue consolidation area. It enabled to classify reliably benign tumors and focal pneumofibrosis from PC regardless of RP used. However, in PET with ^{18}F-FDG, ^{11}C-methionine and ^{82}Rb-chloride the most patients with inflammatory diseases, as well as the patients with malignant pulmonary tumors had RP accumulation of different intensity degree in the tumor area. The comparison of SUV levels in patients with PC and inflammatory diseases revealed significant differences between metabolic activity indices using all the tracers under study. SUV were higher than metabolic activity in the inflammation area in PET with ^{18}F-FDG and ^{11}C-methionine in PC patients. On ^{82}Rb-chloride-PET, SUV levels in inflammatory foci were significantly higher than in malignant tumors. In addition, despite the stated significant differences between SUV levels in patients with PC and inflammatory diseases, and good imaging of pathological masses on ^{82}Rb-chloride-PET, informativeness indices indicated inadequate differential and diagnostic properties of this radiotracer.

The results of ^{18}F-FDG-PET and ^{11}C-methionine-PET comparison appeared to be more satisfactory. On ^{18}F-FDG-PET in 3 out of 7 patients with typical pulmonary carcinoids there were recorded no increased accumulation of RP in tumor, i.e. we received false-negative results. Moreover, on ^{11}C-methionine-PET in all patients with NET, RP accumulation was observed in pathological mass of the lung that helped to diagnose a malignant tumor. In addition, on ^{11}C-methionine-PET compared to ^{18}F-FDG-PET in 4 tuberculosis patients the process in the lung was correctly estimated as inflammatory changes due to the lack of increased RP accumulation in the tumor area. ROC-analysis of ^{11}C-methionine-PET findings enabled to state that the highest informativeness indices in differentiation between pulmonary tumors and pulmonary inflammatory diseases were recorded when using this radiotracer.

Conclusion. The findings on informativeness of positron emission tomography using ^{11}C-methionine suggest high diagnostic accuracy of the technique in differential diagnosis of pulmonary cancer, neuro-endocrine tumors, benign tumors and inflammatory diseases. ^{82}Rb-chloride-PET in spite of good imaging possibilities is unreasonable to use for differentiating pulmonary tumors from pulmonary inflammatory diseases.

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