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Modern methods for radionuclide diagnosis of tumors and non-tumor pathologies of the brain

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ABSTRACT

The review analyzes the global experience in the application of nuclear medicine techniques for diagnosis of tumors and non-tumor pathologies of the brain. The main groups of radiopharmaceuticals currently used for imaging of malignant brain tumors and diagnosis of cognitive impairments and neurotransmitter system disturbances by means of single-photon emission computed tomography and positron emission tomography are described.

Modern approaches to the application of methods for radionuclide diagnosis in neuro-oncology and neurology are compared, and the main trends in production of new, more specific radiopharmaceuticals for visualizing brain tumors of various degrees of malignancy and diagnosing non-tumor pathologies of the brain are described. The review discusses the advantages and disadvantages of currently used techniques and radiopharmaceuticals for imaging of central nervous system disorders, depending on the clinical situation and specific diagnostic tasks.

In addition, the review presents consolidated recommendations of the leading scientific schools in neuro-oncology on the use of nuclear medicine techniques in patients with brain tumors at the stages of treatment and follow-up. The presented article examines the experience of domestic scientific schools in the development of radiopharmaceuticals for neuro-oncology. The features of the development and use of new radiopharmaceuticals in patients with brain tumors and neurodegenerative diseases are highlighted. The review is based on the analysis of literature included in the Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, and RSCI databases.

Key words: nuclear medicine, brain tumor, dementia, radionuclide diagnosis, radiopharmaceutical.

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Современные методы радионуклидной диагностики опухолей и неопухолевой патологии головного мозга

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РЕЗЮМЕ

В обзоре обсуждается мировой опыт применения методов ядерной медицины в диагностике опухолей головного мозга и его неопухолевых изменений. Рассматриваются основные группы применяемых сегодня радиофармацевтических препаратов (РФП) для визуализации злокачественных опухолей головного мозга, диагностики когнитивных нарушений и нарушений системы нейротрансмиссии методом однофотонной эмиссионной компьютерной томографии и позитронно-эмиссионной томографии.

В сравнительном аспекте освещаются современные подходы к применению методов радионуклидной диагностики в нейроонкологии и неврологии, отражаются основные тенденции в производстве новых, более специфичных РФП для визуализации опухолей головного мозга различной степени злокачественности и диагностики неопухолевых заболеваний мозга. Обсуждаются преимущества и недостатки применяемых сегодня методик и РФП для визуализации заболеваний центральной нервной системы в зависимости от клинической ситуации и конкретных диагностических задач.

Представлены консолидированные рекомендации ведущих научных школ нейроонкологии по применению методов ядерной медицины у пациентов с опухолями головного мозга на этапах лечения и динамического наблюдения. Рассмотрен опыт отечественных научных школ в разработке РФП для нейроонкологии. Освещены особенности разработки и применения новых РФП у пациентов с опухолями головного мозга и нейродегенеративных заболеваний. Обзор выполнен на анализе литературы, входящей в базы данных Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health и РИНЦ.

Ключевые слова: ядерная медицина, опухоль головного мозга, деменция, радионуклидная диагностика, радиофармацевтичекий препарат.

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INTRODUCTION

Currently, nuclear medicine technologies are quite firmly entrenched in modern medical science and clinical practice in the world in general and in the Russian Federation in particular. Oncology, neurology, and cardiology remain the main areas of application of nuclear medicine techniques. Radionuclide studies are successfully used for primary diagnosis of brain tumors, assessment of the effectiveness of combination treatment, and as an objective method of disease control at the follow-up stage, as well as for early di-

agnosis of neurotransmitter system disturbances of the central nervous system and various types of dementia [1–3].

These methods make it possible to study the activity of various enzymes, synthesis and metabolism of neurotransmitters, density of receptors, and expression of various genes [4–6]. Modern techniques of radionuclide imaging allow to conduct differential diagnosis of pathological changes in the brain and clarify their biological nature.

According to numerous studies, such radiopharmaceuticals (RP) as a ^{99m}Tc-MIBI, $^{Tl-201}$ chloride, and ^{123}I-labeled amino acids are most commonly used for the diagnosis of brain tumors by single-photon emission computed tomography (SPECT). As a rule, ^{99m}Tc-MIBI SPECT makes it possible to visualize primary malignant brain tumors and hypervascular benign neoplasms [7]. The major limiting factor of ^{99m}Tc-MIBI SPECT in imaging of brain tumors is the intensity of blood flow in the tumor. The degree of ^{99m}Tc-MIBI accumulation in malignant tumors varies widely and does not correlate with the degree of malignancy of the tumor and its histological type [8–10]. Despite this, some authors argue that hyperintense accumulation of ^{99m}Tc-MIBI is characteristic of glioblastoma multiforme, and high values of the drug accumulation index in this type of tumor make it possible to differentiate it from other malignant neoplasms of the brain [11, 12].

Due to the nonspecific accumulation of ^{99m}Tc-MIBI in the zones of post-radiation changes, its use is very limited in the follow-up of patients after radiation therapy of brain tumors [13]. Although some researchers testify to the opposite and admit the use of ^{99m}Tc-MIBI SPECT for assessing the effectiveness of chemoradiotherapy of malignant brain tumors and detecting relapses in this group of patients at early stages [14,15].

Various amino acids labeled with iodine-123 (^{123}I) are still of great interest in terms of diagnosing brain tumors by SPECT. Most of the studies are devoted to the study of the diagnostic capabilities of SPECT with the following amino acids labeled with iodine-123: α-methyl-L-tyrosine and L-phenylalanine [16–18]. It was shown that the level of accumulation of ^{123}I-α-methyl-L-tyrosine in the tumor is slightly higher than that of ^{123}I-L-phenylalanine, and does not depend on the density of tumor cells. SPECT with the indicated iodine-123-labeled amino acids can effectively visualize gliomas of various grades of malignancy (grade I–IV), while metastases to the brain, for example, in lung cancer and non-neoplastic brain lesions, do not accumulate these radioactive tracers.

It was noted that when imaging grade I–II gliomas by SPECT with ^{123}I-L-phenylalanine, false-negative results are more common. Thus, the sensitivity of SPECT with iodine-123-labeled amino acids according to various studies is 78–90%, and the specificity reaches 100% [19– 21].

At the end of the last century, the possibility of using thallium-201 (^{201}Tl) for the diagnosis of brain tumors by SPECT was actively studied. Numerous clinical trials demonstrated the effectiveness of ^{201}Tl SPECT for detecting intracerebral tumors with an average sensitivity and specificity of 95% and 87–93%, respectively. Some authors showed that the degree of ^{201}Tl accumulation in malignant gliomas is significantly higher than in low-grade gliomas and benign brain tumors, which allows for their differential diagnosis [22–27]. It should be noted that ^{201}Tl is currently not used, and large-scale studies on investigating the possibility of using SPECT with another thallium isotope, ^{199}Tl, which favorably differs in low radiation exposure for a patient, have not been carried out in the diagnosis of brain tumors.

In recent years, positron emission tomography (PET) with various radiopharmaceuticals has been the undisputed leader among nuclear medicine techniques for the diagnosis of brain tumors [28–31]. The main radiopharmaceutical for PET is ^{18}F-FDG. The specified RP has physicochemical characteristics that are convenient for the diagnostic process, including a relatively long half-life (110 minutes), which makes it possible to transport it to the nearest PET centers that are not equipped with cyclotrons.

Already in the first studies on the use of ^{18}F-FDG PET in imaging of brain tumors, it was demonstrated that an increase in glucose metabolism in a tumor correlates with the grade of its malignancy and aggressiveness of the course of the disease in general. Based on the results of various studies, a consolidated decision was made to consider the degree of glucose metabolism in the intact gray and white matter of the brain as a background level and rely on it both in visual assessment of the study results and in calculation of quantitative parameters of PET [32, 33].

Numerous studies demonstrated the differences in the levels of ^{18}F-FDG accumulation in grade I–IV brain tumors. Thus, the level of ^{18}F-FDG accumulation in low-grade tumors is more often the same as in the intact white matter or lower, and the level of accumulation in high-grade tumors is more often equal to

or higher than that in the gray matter of the brain [34]. This feature makes it difficult to visualize low-grade brain tumors and interpret the results of the study. It should also be noted that the specificity of ^{18}F-FDG PET remains low. For example, the level of SUV_{max} in primary cerebral lymphoma is significantly higher than that in glioblastoma [35, 36].

The results of ^{18}F-FDG PET remain ambiguous in the differential diagnosis of grade III–IV gliomas and brain metastases, because the SUV_{max} values in these formations are often the same. According to many authors, ^{18}F-FDG PET has significant limitations in the differentiation of gliomas and various non-neoplastic brain lesions, such as brain abscesses, tumor-like demyelination, inflammatory changes caused by fungal infections, and neurosarcoidosis. All of the above-mentioned pathological processes, as well as tumor damage, one way or another, lead to an increase in glucose metabolism, which complicates interpretation of the study results [37].

At a certain historical stage, ^{18}F-FDG PET of the brain was of great importance for choosing a site of tumor tissue for targeted stereotactic biopsy, because most glial tumors (82%) are characterized by heterogeneity. It should be noted that imaging of such tumor differentiation is absolutely impossible with traditional methods for diagnostic radiology – CT and MRI, even with the use of contrast-enhanced techniques and cutting-edge software algorithms [38–42].

Considering the complexity and multistage nature of the treatment process in patients with brain tumors, assessment of treatment effectiveness and timely detection of relapses remain some of the most important problems in modern neuro-oncology. Studies showed that the change in the level of ^{18}F-FDG accumulation in the brain tumor after radiation therapy or chemoradiation correlates with the tumor response to therapy, which means that a decrease in the level of ^{18}F-FDG metabolism indicates the effectiveness of treatment [43– 46].

It is known that, due to increased proliferation, tumor cells are characterized by increased metabolism, including enhanced protein synthesis, for which a sufficient supply of amino acids is required. It should be noted that amino acids labeled with various isotopes do not differ in their physicochemical properties from natural amino acids and are their complete biological analogs. In neuroimaging, labeled amino acids have a significant advantage over ^{18}F-FDG, which consists in an extremely low level of physiological accumulation in intact brain structures, including the cortex and basal nuclei. Carbon-11-labeled methionine (^{11}C-MET) was the first amino acid-based radiopharmaceutical. Since that time, ^{11}C-MET has become the most commonly used radiopharmaceutical in oncology after ^{18}F-FDG [47, 48].

In most cases, ^{11}C-MET PET makes it possible to visualize brain tumors of various degrees of malignancy (grade I–IV according to the classification of the World Health Organization (WHO)), with a fairly clear definition of the boundaries of the tumor lesion and normal brain tissues, as well as to delimit the area of edema and true tumor infiltration [49]. According to different authors, the averaged indices of the sensitivity and specificity of ^{11}C-MET PET in imaging of brain tumors of various grades of malignancy are 89–90% and 94–100%, respectively [50–52].

Some researchers argue that, when using purely visual assessment of ^{11}C-MET PET without resorting to quantification, the sensitivity and specificity of the method in imaging brain tumors are 94% and 56.5%, respectively. At the same time, the accuracy of the method with this approach is 84.4%, and the level of positive predictive value and negative predictive value is 86.3% and 76.5%, respectively. Determination of semi-quantitative parameters of ^{11}C-MET PET of the brain in most cases contributes to the differential diagnosis between a malignant lesion and benign changes and allows to determine the grade of malignancy of glial brain tumors according to the WHO [53–55].

When studying the possibility of using ^{11}C-MET PET in the differential diagnosis between low-grade (grade I–II) and high-grade (grade III–IV) gliomas according to the classification of the WHO, the researchers also focused on the level of ^{11}C-MET accumulation in the tumor. It turned out that the degree of ^{11}C-MET accumulation in grade III–IV gliomas is significantly higher than in low-grade tumors.

Another important aspect in the use of ^{11}C-MET PET in the diagnosis of brain tumors is the possibility of using the level of RP accumulation in the tumor as a prognostic factor for the course of the disease. It was found that a high level of ^{11}C-MET uptake in the primary brain tumor before treatment indicates a poor prognosis of the disease. It should also be noted that a decrease in the level of ^{11}C-MET uptake in the course of conservative therapy reliably reflects the effectiveness of treatment [56–58].

According to literature, ^{11}C-MET PET is effectively used in follow-up of patients with benign brain gliomas, and the index of RP accumulation in the tumor reflects the grade of its malignancy. It is believed that

when the threshold value of the ^{11}C-MET accumulation index in the tumor is reached, it indicates its transition to the group of malignant gliomas, which requires a change in patient management strategy from a passive to an active radical approach [59–62].

Timely detection of recurrent malignant gliomas is still an important aspect in the treatment of patients with brain tumors. Most authors claim that ^{11}C-MET PET is capable of detecting tumor recurrence even against the background of post-therapeutic changes with sensitivity of 88% and specificity of 85% [63].

Therefore, ^{11}C-MET PET is widely used today in the oncological practice at all stages of treatment and follow-up of patients with brain tumors. This method is now considered routine and quite effective, and its availability for the population is constantly growing.

18F-fluoroethyl-L-tyrosine (^{18}F-FET) is another RP based on labeled amino acids, which has proven to be effective in diagnosing brain tumors. The indicated RP, as well as ^{11}C-MET, is characterized by low-intensity background accumulation in unchanged structures and parts of the brain. In addition, ^{18}F-FET is less accumulated in macrophages and granulocytes than ^{11}C-MET, which, in turn, leads to an increase in the specificity of ^{18}F-FET PET in detecting brain tumors [64].

The main diagnostic difference in the use of ^{18}F-FET PET for imaging of brain masses is the ability to assess the dynamic characteristics of drug accumulation in the tumor in addition to the usual accumulation indices in the area of interest. The use of data from a dynamic scanning protocol in ^{18}F-FET PET allows for differential diagnosis between grade I–II and grade III–IV gliomas and indicates the presence of tumor relapse, reliably differentiating it from the zones of radiation necrosis [65, 66].

This is of particular importance in clinical situations when a patient with suspected grade II glioma does not show contrast agent accumulation on MRI. In about 40% of these patients, an anaplastic lesion is found on a ^{18}F-FET PET scan. Application of the kinetic characteristics of the method increases its sensitivity and specificity up to 95% [67]. According to different authors, the averaged indicators of the sensitivity and specificity for ^{18}F-FET PET in the diagnosis of brain tumors are 94% and 100%, respectively.

Many authors also suggest focusing on the index of RP accumulation in the tumor during ^{18}F-FET PET. A number of studies highlight the role of ^{18}F-FET PET in planning radiation therapy in patients with brain tumors. The authors argue that the use of ^{18}F-FET in planning radiation therapy reduces the error in determining tumor boundaries and, thereby, increases the effectiveness of radiation therapy [68–70].

In recent years, the possibility of using a synthetic analog of the amino acid, L-6- [^{18}F] fluoro-3,4-dioxyphenylalanine (^{18}F-DOPA), for the diagnosis of brain tumors has been studied [71]. Studies have shown that the sensitivity of ^{18}F-DOPA PET in detecting malignant and benign brain tumors is 96%, and the specificity is about 40%. At the same time, the specificity of the method allows to significantly increase the use of threshold values of the accumulation index – tumor / striatum. It has also been shown that ^{18}F-DOPA PET can be used to differentiate the relapse of malignant gliomas and radiation necrosis [72].

In addition to amino acids labeled with various isotopes that have proven their effectiveness, other synthetic analogs of biological molecules are also used for imaging of brain tumors. Thus, to assess the proliferative activity of tumor cells, an RP based on thymidine, 3-deoxy-3- [^{18}F] -fluorothymidine (^{18}F-FLT), was proposed. Studies have shown that the degree of ^{18}F-FLT accumulation in the tumor correlates with the level of Ki-67 expression [73]. ^{18}F-FLT PET can be used to assess the malignancy grade of gliomas, predict the course of the disease, and plan radiation therapy. ^{18}F-FLT PET is of particular importance in determining the prognosis in patients with malignant brain gliomas [74]. The main disadvantage of ^{18}F-FLT is the dependence of its accumulation on the degree of damage to the blood – brain barrier and the intensity of blood flow in the tumor.

In addition, there are currently RPs for imaging brain tumors, the use of which is based on the assessment of tumor cell hypoxia, for example, [^{18}F] -fluoromisonidazole (^{18} F-FMISO). In studies on a group of patients with malignant gliomas before surgical and radiation treatment, the effectiveness of this RP was shown in determining the exact boundaries of the tumor, as well as in assessing the severity of hypoxia [75]. The disadvantages of ^{18}F-FMISO include high background accumulation of the RP, due to which there is a need for a delayed study, 2–4 hours after intravenous administration.

Currently, several RPs have been synthesized to assess the expression level of VEGF receptors. First of all, these are [^{64}Cu]-DOTA-VEGF (DEE), [^{89}Zr] -ranibizumab, as well as [^{11}C]-gefitinib ([^{11}C]-iressa) [76, 77]. Preliminary studies showed the effectiveness of these RPs in the diagnosis of tumors of various localization, including the brain, as well as in

assessing the effectiveness of their treatment. Along with the above-mentioned radioactive tracers, RPs are currently being developed to assess the state of adhesion receptors of the αVβ3integrin class. RPs with high tropism for αVβ3integrins include, in particular, [^{18}F]-galacto-arginylglycylaspartic acid, ^{64}Cu-DOTAE {E [c (RGDfK)] 2} 2, as well as a number of arginylglycylaspartic acid derivatives [78, 79]. Currently, these RPs are at different stages of development and study, so they have not yet found widespread use in the clinical practice.

Analyzing the above-presented information, we can say that PET with various RPs is firmly entrenched in the algorithms for diagnosing brain tumors at all stages of treatment and follow-up of patients with such lesions. The undisputed leaders among all RPs used in neuro-oncology today are drugs based on labeled amino acids. This is confirmed by the recommendations of the European Association of Neuro-Oncology (EANO) on the clinical use of PET in brain gliomas at various stages of patient management (Figure).

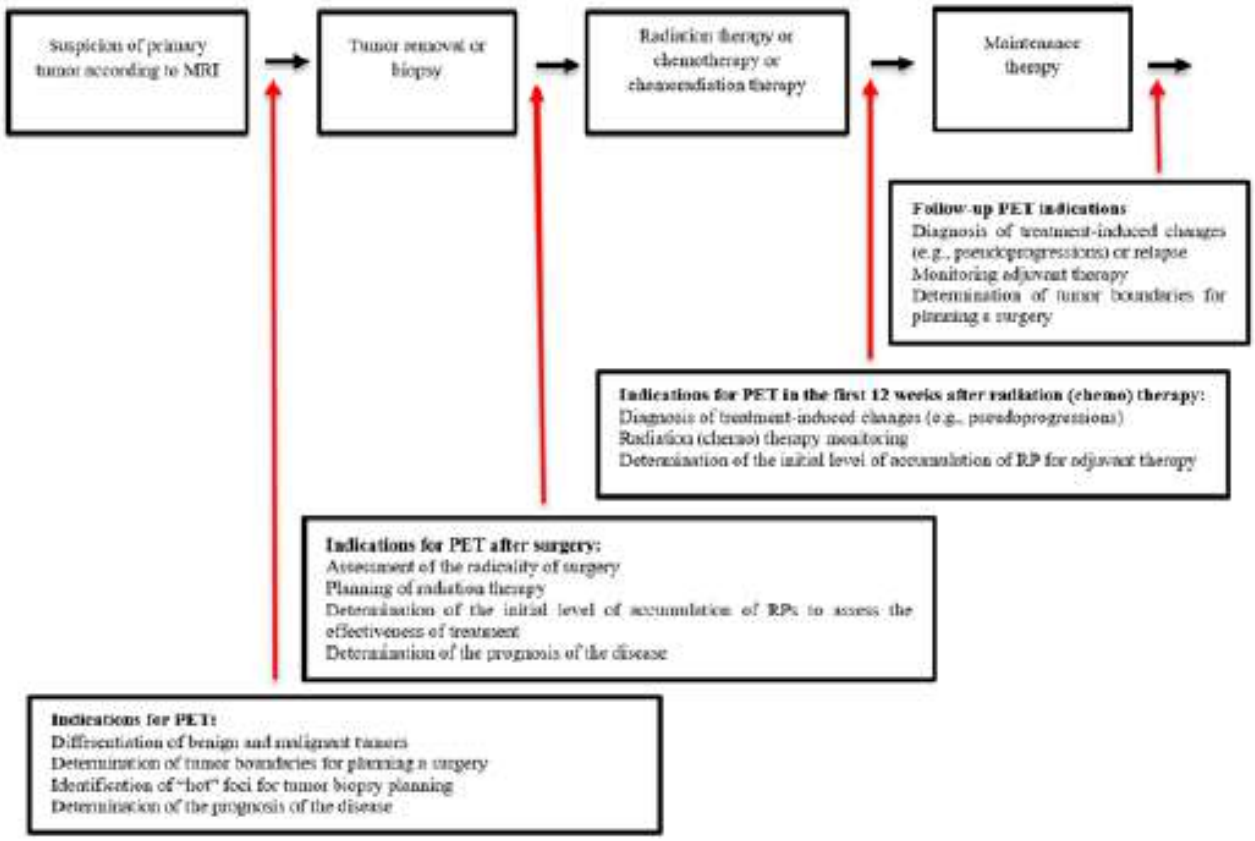

Figure. EANO General Guidelines for the Clinical Use of PET with Labeled Amino Acids in Brain Gliomas, 2016

Despite high diagnostic effectiveness of PET with various RPs, the widespread use of this method in our country is limited due to the high cost of the diagnostic procedure and the complexity of the cycle of manufacturing RPs in cyclotron facilities. From this point of view, it is of interest to develop new RPs based on technetium-99m, which is widely used in numerous SPECT centers. For example, the use of glucose-based RPs labeled with technetium-99m will make it possible to study the biochemical processes occurring in the body at the molecular level due to inclusion of glucose derivatives in normal and pathological metabolic processes, as well as to obtain information in terms of uniqueness and reliability that is not inferior to PET studies.

A number of studies found that the most promising glucose derivatives for being labeled with the ^{99m}Tc radioactive isotope, which retain the biochemical properties of glucose itself, are: 1-thio-D-glucose, 5-thio-D-glucose, glucosamine, as well as their salts or hydrates [80–83]. The available literature describes the results of the experimental use of various ^{99m}Tc-labeled glucose derivatives in animal models of a tumor lesion. At the same time, the authors note high efficiency of such drugs [84, 85].

Based on global trends in the production of RPs and our own experience in the development of drugs for radionuclide diagnosis, a team of authors from Cancer Research Institute of Tomsk NRMC in close cooperation with National Research Tomsk Polytechnic University developed a new drug based on a technetium-99m-labeled glucose derivative for radionuclide diagnosis of malignant neoplasms – "^{99m}Tc-1-thio-D-glucose" [86–88]. During phase I clinical trials, both safety and efficacy of ^{99m}Tc-1-thio-D-glucose for imaging of brain tumors by SPECT was demonstrated [89].

In neurology, ^{18}F-FDG PET is also quite effectively used to diagnose various pathological changes in the brain. In recent years, it has been demonstrated that the sensitivity and specificity of ^{18}F-FDG PET in the diagnosis of Alzheimer's disease (AD) reach 94% and 73%, respectively. The role of ^{18}F-FDG PET in predicting the development of cognitive impairments is also great [90]. In this case, an important diagnostic feature is a decrease in the accumulation of ^{18}F-FDG in the association cortex.

AD is characterized by a decrease in ^{18}F-FDG metabolism in the cortex of the temporal and parietal lobes, posterior cingulate gyri, while dementia with Lewy bodies is characterized by hypometabolism in the occipital cortex. Huntington's disease is characterized by changes in glucose metabolism in the lenticular nuclei and the heads of the caudate nuclei. Post-stroke dementia, which is characterized by multiple foci of hypometabolism in the cerebral cortex and cerebellum, also has specific presentation in ^{18}F-FDG PET. An early diagnostic sign of Pick's disease and other frontotemporal dementias is a pronounced decrease in glucose metabolism in the cortex of the frontal lobes of the brain [91–93].

PET is used quite successfully for the differential diagnosis of various types of dementia. It is known that dementia with Lewy bodies is accompanied by the development of parkinsonism, in contrast to AD. Therefore, when using ^{18}F-DOPA (dihydroxyphenylalanine), in most cases it is possible to differentiate between AD and dementia with Lewy bodies [94].

The possibility of studying the state of the presynaptic dopaminergic system during ^{18}F-DOPA PET allows to diagnose Parkinson's disease (PD) at the preclinical stage. The main diagnostic criterion is a decrease in the metabolic rate of ^{18}F-DOPA in the striatum. This drug reflects the activity of the enzyme dopadecarboxylase and the level of dopamine in neurons of the striatum [95]. Some authors argue that ^{18}F-DOPA PET allows not only to detect a decrease in the number of neurons in the striatonigral system in PD patients, but also to predict the development of this disease. This is possible due to the fact that clinical manifestations of PD occur when about 60–70% of dopaminergic neurons die [96]. ^{18}F-DOPA PET is also used to assess the effectiveness of PD treatment; in addition, the level of ^{18}F-DOPA accumulation depends on the severity of motor impairments, but does not in any way reflect the severity of cognitive impairments in such patients.

Currently, the most promising RPs for diagnosing AD and other neurodegenerative disorders are markers of β-amyloid peptide (Aβ), the increased deposition of which is the main component in the pathogenesis of AD. The carbon-11-labeled RP substance B-[^{11}C] PiB, proposed by the Pittsburgh scientists, became the first Aβ-selective radioligand for PET imaging of amyloid deposits in the association cortex. Additionally, it was shown in clinical trials that patients without dementia also had accumulation of [^{11}C] PiB in the association cortex, which, in turn, further confirmed the predictive role of [^{11}C] PiB PET in the diagnosis of AD. Currently, the development of specific RPs for the radionuclide diagnosis of neurodegenerative disorders is being actively pursued.

It is known that the second generation of PET markers of Aβ has been developed – benzofuran, benzoxazole, imidazobenzothiazole derivatives, etc. Some compounds have been labeled with ^{18}F, which will simplify their clinical use. Most of the compounds have shown their effectiveness in preclinical studies and are at the stage of clinical trials. Therefore, there is still no comprehensive information on the effectiveness of such compounds in the available literature.

CONCLUSION

Therefore, analyzing the information presented, it can be stated that high-tech nuclear medicine techniques have integrated into the development trends in modern neurology and neuro-oncology. Not a single clinic dealing with the problems of treating tumors of the central nervous system or various types of dementia can do without methods of radionuclide diagnosis in its clinical practice. It is also important that the research teams of the Russian scientific schools of physics, oncology, and nuclear medicine manage to keep up with the times in their scientific research and in some areas are ahead of the world-class leaders.

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Authors contribution

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