УДК 616-006-031-073.916
https://doi.org/10.20538/1682-0363-2025-3-149-162

Potential of PSMA-targeted imaging of tumors with various localizations

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ABSTRACT

Diagnosis and therapy of malignant neoplasms are increasingly focused on the use of molecular targets involved in the multistage process of tumor pathogenesis. Prostate-specific membrane antigen (PSMA) is currently one of such molecular markers for prostate cancer, and over the past two decades, there have been active developments in PSMA-directed theranostics for prostate cancer therapy. However, numerous studies in recent years have shown that PSMA, despite its name, is not a specific molecular marker only for prostate cancer screening. It was revealed that the expression of this receptor in other neoplasms is associated with neovascular endothelium, which was the prerequisite for the beginning of studies on the clinical application of PSMA-directed visualization of tumors with various localizations.

This lecture analyzes the possibilities of using PSMA-targeted radionuclide diagnosis for various histologic types of tumors, as well as the features of PSMA expression in some tumors. The authors of the lecture demonstrate existing clinical examples of the results of diagnostic studies and the use of targeted radionuclide therapy. The lecture presents possible applications of PSMA-targeted visualization methods for obtaining additional information about the features of the tumor process.

Keywords: PSMA, PET/CT, cancer, endothelial, radionuclide, therapy, diagnosis

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Medvedeva A.A., Vysotskaya V.V., Muravleva A.V., Zeltchan R.V., Rybina A.N., Gol'dberg V.E., Chernov V.I. Potential of PSMA-targeted imaging of tumors with various localizations. *Bulletin of Siberian Medicine.* 2025;24(3):149–162. https://doi.org/10.20538/1682-0363-2025-3-149-162.

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Потенциал ПСМА-таргетной визуализации опухолей различных локализаций

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РЕЗЮМЕ

Диагностика и терапия злокачественных новообразований в современной онкологии все больше ориентируется на использование молекулярных мишеней, участвующих в многостадийном процессе патогенеза опухолей. Простат-специфический мембранный антиген (ПСМА) является на сегодняшний день одним из таких молекулярных маркеров для рака предстательной железы, и в течение последних двух десятилетий отмечается активное развитие ПСМА-тераностики опухолей простаты. Однако многочисленные исследования последних лет показали, что ПСМА, несмотря на свое название, не является специфичным молекулярным маркером только для ткани предстательной железы. Выявлено, что экспрессия этого рецептора в других новообразованиях ассоциирована в большей степени с неоваскулярным эндотелием, что послужило началу исследований по клиническому применению ПСМА-направленной визуализации опухолей различных локализаций.

В данной лекции проанализированы возможности применения ПСМА-направленной радионуклидной диагностики, главным образом методов позитронной эмиссионной томографии, для различных гистологических вариантов неоплазий, а также особенности ПСМА-экспрессии некоторых опухолей. Авторы лекции демонстрируют существующие клинические примеры не только результатов диагностических исследований, но в ряде случаев и применения таргетной радионуклидной терапии. В лекции представлены возможные точки приложения ПСМА-направленных методов визуализации с точки зрения получения дополнительной информации об особенностях течения опухолевого процесса.

Ключевые слова: ПСМА, ПЭТ/КТ, рак, эндотелиальный, радионуклидный, терапия, диагностика

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Медведева А.А., Высоцкая В.В., Муравлева А.В., Зельчан Р.В., Рыбина А.Н., Гольдберг В.Е., Чернов В.И. Потенциал ПСМА-таргетной визуализации опухолей различных локализаций. *Бюллетень сибирской медицины.* 2025;24(3):149–162. https://doi.org/10.20538/1682-0363-2025-3-149-162.

INTRODUCTION

Diagnosis and therapy of malignant neoplasms in modern oncology are increasingly focused on the use of molecular targets involved in the multistage process of tumor pathogenesis. This was facilitated by numerous studies on the mechanisms of cancer development and the identification of key targets of the pathogenesis of particular carcinogenesis. One of such molecular markers of prostate cancer (PCa) is prostate-specific membrane antigen (PSMA), type II integral membrane glycoprotein (glutamate carboxypeptidase II, or GCPII) [1, 2]. Glutamate carboxypeptidase II was found to consist of three domains: a short N-terminal intracellular portion, a hydrophobic transmembrane region, and an extracellular C-terminal domain [3, 4]. A specific feature of PSMA is its dual nature: it is not only a receptor protein, but also an enzyme that plays a key role in prostate carcinogenesis, glutamatergic neurotransmission (NAALADase), and folic acid absorption (folate hydrolase FOLH1) [5]. Thus, numerous studies have shown that PSMA is characterized as a multifunctional agent involved in the development and course of PCa, in particular in proliferation, apoptosis, and cellular and tissue homeostasis, and also exerting an enzymatic function [6, 7]. Studies have shown a direct correlation between the level of PSMA expression and the degree of prostate tumor malignancy, the stage of the disease, and aggressive behavior of the tumor [8].

Increased expression of PSMA on the cell membrane of PCa has made it a suitable target for molecular imaging and radioligand therapy in patients with PCa [9]. Over the past decades, numerous small-molecule PSMA-binding agents have been developed to create diagnostic and therapeutic radiopharmaceuticals for imaging and treatment of PCa [10–12]. Clinical trials convincingly demonstrate the effectiveness of these radiopharmaceuticals not only in diagnosis, but also in the treatment of this disease.

Further studies have shown that PSMA, despite its name, is not specific to prostate tissue alone. The extracellular domain of PSMA serves as a promising therapeutic target for PCa, but it has also been found to be selectively expressed in the vasculature of other solid tumors [13–16]. This antigen is found in healthy tissues of the salivary glands, duodenal mucosa, renal tubular cells, a subpopulation of neuroendocrine cells in the colonic crypts, as well as in tumor cells – for example, in some subtypes of transitional cell carcinoma, renal cell carcinoma, and colon cancer. However, in contrast to the mechanisms of PSMA expression in PCa cells, its expression in other neoplasms is associated to a greater extent with neovascular endothelium. It should be noted, that this antigen was not detected in the vascular epithelium of healthy tissues or benign formations.

The aim of this lecture was to analyze the current possibilities of using PSMA-targeted radionuclide diagnosis for various histologic types of tumors, taking into account the features of PSMA expression in the tumors. The lecture is intended for researchers and specialists in the field of nuclear medicine and oncology.

FEATURES OF PSMA DIAGNOSIS OF VARIOUS TUMORS

Thyroid cancer (TC) is the most common endocrine malignancy worldwide and its incidence is increasing annually, largely due to improved screening methods [17]. Most newly diagnosed TC are small and asymptomatic papillary lesions, belonging to a significant number of subclinical indolent tumors that would probably not be detected during the patients' lifetime in most cases. However, the increase in the number of newly diagnosed tumors also concerns high-risk TC, aggressive histopathological subtypes, as well as tumors detected at a late stage of the disease, with gross extrathyroidal extension [18]. In this context, the observed increase in mortality rates among patients with advanced TC suggests aggressive postoperative treatment and accurate risk stratification. Post-therapy whole-body imaging after radioactive iodine administration has historically played a significant role in assessing tumor burden and radioiodine sensitivity of residual or recurrent disease [18].

Unfortunately, only approximately 30% of patients with TC metastases demonstrate radioactive iodine uptake. In most cases, metastatic tumors are either initially radioiodine-negative, or lose their ability to accumulate it over time, or progression of the disease is observed after treatment with radioactive iodine, which indicates the development of radioiodine refractoriness [18, 19]. In widespread clinical practice, with the development of TC resistance to radioactive iodine, the main method of radiodiagnosis for detecting relapse of the disease, metastases to the lymph nodes, and distant metastases is contrast-enhanced computed tomography (CT). In addition, this method is also the main tool for assessing the response to treatment with tyrosine kinase inhibitors [18, 20].

In terms of nuclear imaging methods, besides routine radioactive iodine scintigraphy, the most studied method for diagnosing radioiodine-resistant thyroid cancer (rrTC) is fluorine-18 fluorodeoxyglucose ([^{18}F]F-FDG) positron emission tomography (PET). According to the recommendations, this study is advisable for patients with TC with elevated serum thyroglobulin levels and a negative result of whole-body radioactive iodine scintigraphy after therapy [18]. The diagnostic accuracy of this method is influenced by several factors, including dedifferentiation and tumor load – higher sensitivity of the study is observed in patients with aggressive histologic subtypes. High-intensity [^{18}F]F-FDG uptake on PET images is considered an independent prognostic factor for overall survival in patients with TC [20, 21].

In the presence of signs of tumor progression, patients with radioiodine-refractory differentiated TC are recommended to receive targeted therapy with tyrosine kinase inhibitors (lenvatinib, sorafenib) [22–26]. Their mechanism of action on tumors is mediated by suppression of the kinase activity of vascular endothelial growth factor (VEGF) receptors [26, 27]. Since PSMA is frequently expressed on the cell membrane of neovascular endothelial cells of various solid tumors, nuclear imaging methods targeting PSMA may be used as a biomarker of neoangiogenesis and may possibly be involved in predicting the efficacy of antiangiogenic therapy.

Several studies have demonstrated that intense PSMA staining in the endothelium of some TC subtypes, including papillary and follicular cancer, correlated with a more aggressive clinical course. In particular, it was shown, that patients with moderate or strong PSMA expression were more likely to develop rrTC [28–30]. Moreover, anaplastic TC, despite its well-known aggressive behavior, was characterized by lower PSMA expression compared to well-differentiated tumors, which may probably be associated with a lower density of microvessels in this variant of the disease compared to highly differentiated TC [28, 31].

The diagnostic accuracy assessment of PET/CT with PSMA ligands demonstrated relatively weak performance in a number of studies [32–35]. Only two studies reported high incidence of pathological findings (100%) [36, 37]. More intense uptake of PSMA ligands was observed in follicular cancers, whereas low-intensity or absent radiopharmaceutical uptake was observed in dedifferentiated tumors [33, 35, 36]. At the same time, the intensity of PSMA ligand accumulation did not correlate with the results of the immunohistochemical analysis, especially in dedifferentiated TC. Moreover, when analyzing standardized uptake value (SUVmax), all authors noted significant heterogeneity of this parameter (from 1.0 to 39.7). A number of studies also described the comparative analysis of PET findings with PSMA ligands and with [^{18}F]F-FDG and showed that studies with PSMA-targeted radiopharmaceuticals demonstrated lower diagnostic efficiency, however, the histopathologic variants of tumors were not taken into account in the comparison [32–36].

It should be noted that in the presented references, as a rule, [^{68}Ga]Ga-PSMA-11 was used as a diagnostic radiopharmaceutical targeting PSMA receptors. Two studies report theranostics-based use of [^{177}Lu]Lu-PSMA-617 in three patients with rrTC [35, 36]. Two of the included patients exhibited a minor and temporary response to treatment, followed by an increase in serum thyroglobulin levels and disease progression several months after the end of therapy, while one patient experienced disease progression one month after treatment.

Kidney cancer is a common type of tumor, ranking 14th among all newly diagnosed malignant tumors in the world, according to WHO data, and accounting for 3% of the total number of diagnosed tumors [38, 39]. Currently new data are emerging regarding the genomic and molecular characteristics of renal malignancies, but histopathological characteristics are still taken into account when prescribing therapy and analyzing the prognosis of the disease [40, 41]. Clear cell renal cell carcinoma (ccRCC) is the most common histologic type of kidney cancer, characterized by high immunogenicity. In addition, ccRCC is considered to be a highly vascularized tumor due to excessive production of platelet-derived growth factor (PDGF) and VEGF by tumor cells [41]. Standard examination including CT and/or MRI may be considered insufficient since 20–30% of patients with apparently resectable tumors experience progression within a relatively short time after surgery [42].

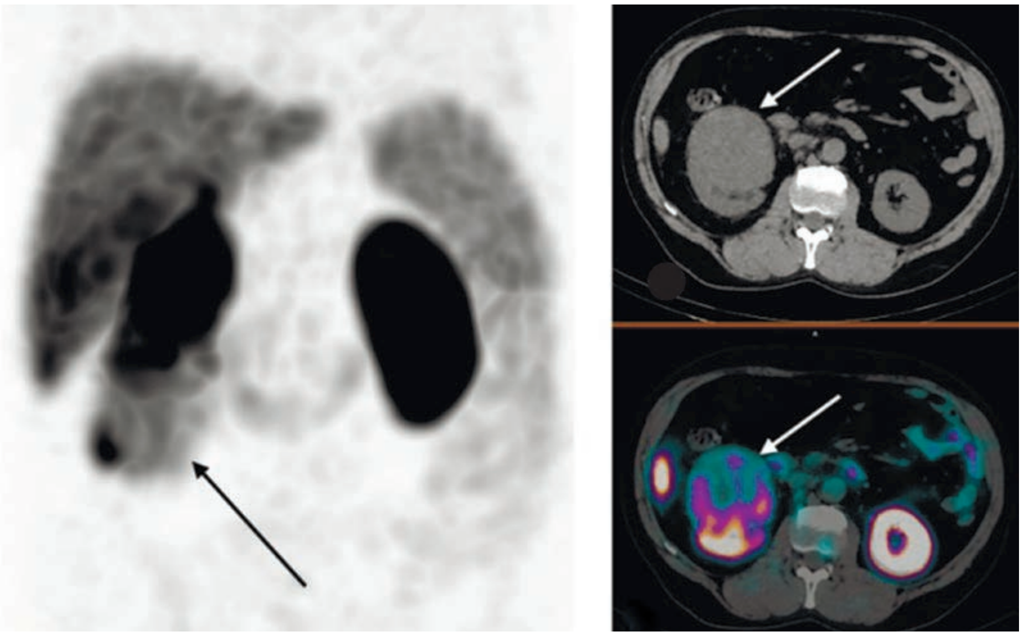
The most studied nuclear medicine method for detecting ccRCC is PET/CT with [^{18}F]F-FDG. [43]. However, this study does not play a key role in the treatment of this category of patients and is currently not recommended as a diagnostic method for ccRCC [44–46]. This limitation is mainly due to the physiological renal excretion of [^{18}F]F-FDG, which naturally complicates visualization of the primary tumor [43]. In addition, ccRCC in general is characterized by a relatively low level of [^{18}F]F-FDG uptake, but the underlying mechanism of this phenomenon is not fully understood. Nevertheless, a recent study showed that [^{18}F]F-FDG uptake reflected the level of FBP1 (fructose-1,6-bisphosphatase 1) expression, which is an essential intermediate of glycolysis. More intense accumulation of FBP1 was observed in ccRCC tumors with low FBP1 expression [48].

As already mentioned, ccRCC is considered to be a highly vascularized tumor and this may be a rationale for the use of nuclear medicine methods with radiopharmaceuticals targeting PSMA receptors, which are expressed, among other things, on the surface of neovascular endothelial cells [13–16]. This is especially relevant in light of the fact that the combination of immunotherapy and antineoangiogenetic therapy is the standard of care for metastatic ccRCC. This means that PSMA-guided PET/CT may become a valuable tool for predicting treatment outcomes and assessing the response to this therapy in patients with ccRCC [44–46].

Besides, it should be noted, that surgical treatment with radical or partial nephrectomy remains the only effective method of treating localized renal cancer and postoperative changes may complicate the differentiation of local tumor recurrence from postoperative changes using [^{18}F]F-FDG PET, since accumulation of this radiopharmaceutical can also be observed in foci of inflammation, abscesses, and areas of fat necrosis [46]. In a number of studies, PET/CT with PSMA ligands demonstrated higher accuracy in determining tumor burden in patients with ccRCC, visualizing more metastatic foci than conventional diagnostic methods, thus leading to a reduction in false-positive results and changing patient treatment strategy in a significant percentage of cases [49–55].

The few studies on this topic have analyzed the level of [^{68}Ga]Ga-PSMA-11 accumulation depending on the stage of the disease and histopathological type of ccRCC and it was shown that SUVmax was significantly higher in tumors with a more aggressive phenotype [49–52]. In the study by Y. Liu et al. [56], comparison of the results of PET studies with [^{18}F]F-FDG and [^{18}F]F-DCFPyL showed the advantage of using PSMA ligand in detecting bone metastases and disease recurrence. Regarding the visualization of metastatic lesions in visceral organs and lymph nodes, the higher detection rate with [^{18}F]F-DCFPyL was not statistically significant, but SUVmax and tumor-to-background ratio were significantly higher than those of [^{18}F]F-FDG.

Similar results were presented in the works by V. S. Ilyakov et al. [57, 58], where the authors analyzed comparative PET studies with [^{18}F]F-PSMA-1007 and [^{18}F]F-FDG in patients with locally advanced, metastatic ccRCC and suspected local recurrence after surgical treatment. Regarding the use of [^{99m}Tc]Tc-HYNIC-PSMA, its high physiological accumulation in the kidneys is likely to be a limiting factor for the use of this radiopharmaceutical in the diagnosis of primary renal tumor (Fig. 1). However, the use of single-photon emission computed tomography (SPECT) with PSMA ligands can also be considered as an alternative method for identifying advanced forms of the disease, or, in the future, as a method for selecting patients for therapy.



a *b*

Fig. 1. MIP- reconstruction (*a*), CT and combined SPECT / CT images (*b*) at 2 h after administration of [^{99m}Tc]Tc-HYNIC-PSMA in a patient with ccRCC, grade2: the arrow indicates the tumor, SUVmax 7.72 (self-reported).

Breast cancer (BC) is one of the leading malignant tumors in the world in terms of incidence, ranking fifth in terms of deaths. Over the past 10 years, the annual standardized growth rate of incidence has amounted to 1.97% in Russia [59]. Breast cancer diagnosis requires a personalized and multimodal approach taking into account age, medical history, heredity, and the structure of the mammary glands. The use of conventional imaging methods is included in the standards for examining patients with BC, as well as nuclear medicine methods, which have already become a routine method for examining this category of patients. In recent years, [^{18}F]F-FDG PET/CT has become widely used to assess the extent of BC in cases where standard examination methods are ambiguous [60]. One of the limitations of this method is false negative results in some types of tumors and false positive results in some benign processes. Few studies to date demonstrate the potential of nuclear medicine methods with PSMA-targeted radiopharmaceuticals for imaging malignant BC [61–65], but most of them are represented by isolated clinical cases.

In the studies by A.G.Wernicke et al. [66], PSMA expression was assessed in the tumor-associated vasculature related with invasive breast carcinomas in 106 patients – 92 cases were primary BC, 14 patients had tumor metastases to the brain. Analysis of the obtained results showed that the tumor-associated vasculature was PSMA-positive in 68/92 (74%) cases of primary BC and in 14/14 (100%) cases of metastatic BC. PSMA receptors were not detected in healthy breast tissue or carcinoma cells and in almost all cases (98%) in healthy breast tissue vasculature. The authors found a statistically significant correlation between increased PSMA expression in the tumor-associated vasculature and tumor size, Ki-67 proliferation index, receptor status, and overall survival.

Several studies have also noted marked vascular PSMA expression in higher grade, Her2-positive, and triple-negative tumors [67, 68]. Thus, in the study by Y. Tolkach et al. [67], a negative correlation was shown between vascular PSMA expression and tumor hormone receptor expression. There was no correlation between pN stage, locoregional progression status, development of distant metastases, tumor size, and PSMA expression.

The study by N. Andryszak et al. [68] compared findings of PET/CT with [^{18}F]F-PSMA-1007 and [^{18}F]F-FDG in patients with triple-negative BC (n = 10). The detection rate of triple-negative tumors with [^{18}F]F-PSMA-1007 was comparable to [^{18}F]F-FDG in most patients. However, in patients with distant metastases, a higher number of metastatic lesions were detected using [^{18}F]F-PSMA-1007 due to more intense accumulation (higher SUVmax values) compared to [^{18}F]F-FDG. In addition, [^{18}F]F-PSMA-1007 demonstrated higher diagnostic efficiency in detecting metastatic lesions in areas with high physiological accumulation of [^{18}F]F-FDG, such as the brain and adjacent bones of the skull.

The literature also described a case of detecting metastatic BC following SPECT/CT with [^{99m}Tc]Tc-EDDA/HYNIC-PSMA, which was performed on a patient with suspected bone metastases from prostate cancer. Radiopharmaceutical accumulations were visualized in the projection of bone structures and the left mammary gland, where hormone-positive infiltrating ductal carcinoma was confirmed by biopsy results [69]. Our clinical experience also indicates the possibility of using SPECT/CT with [^{99m}Tc]Tc-HYNIC-PSMA for visualization of the primary tumor and metastases in this pathology (Fig. 2). A case of radionuclide PSMA therapy in a patient with metastatic BC with disease progression after 2 courses of [^{177}Lu]Lu-PSMA-617 is described [64].

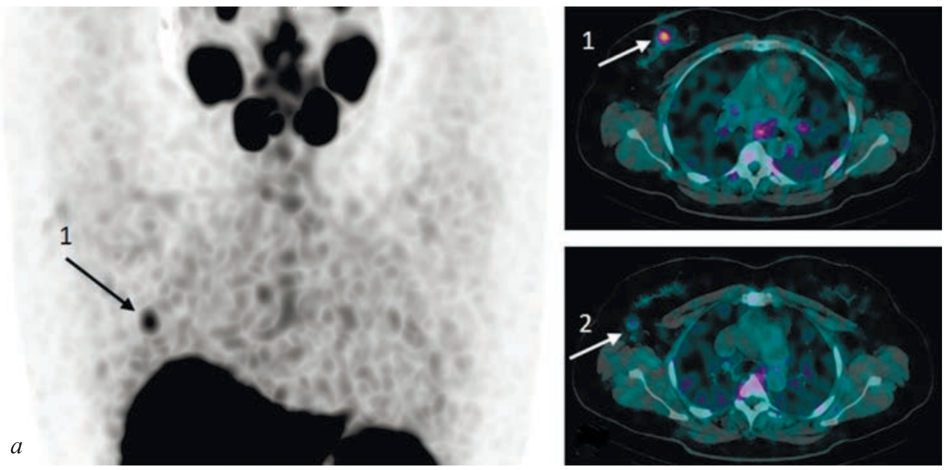


Fig. 2. MIP- reconstruction (*a*) and combined SPECT/CT images (*b*) at 2 h after administration of [^{99m}Tc]Tc-HYNIC-PSMA in a patient with BC, metastasis to the axillary lymph node: 1 – breast tumor, SUVmax 5.1; 2 – enlarged lymph node, SUVmax 1.93 (self-reported)

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for approximately 90% of cases [70, 71]. The diagnosis of HCC is complicated by the latent course of the disease, fluctuations in serum alpha-fetoprotein levels, and inconclusive radiological results [72]. The most studied nuclear medicine methods for HCC are PET/CT with [^{18}F]F-FDG and labeled choline (with ^{18}F or ^{11}C). Both methods demonstrate a potential role in identifying extrahepatic lesions in HCC, however, their use is limited by the broader capabilities of CT and magnetic resonance imaging (MRI). In addition, [^{18}F]F-FDG PET/CT is known to have limitations for staging and restaging of HCC [73]. Since the enzymes of well-differentiated HCC are similar to those observed in a healthy liver, [^{18}F]F-FDG-6-phosphate formed after phosphorylation of [^{18}F]F-FDG may be dephosphorylated and released from the cells, which explains low uptake of [^{18}F]F-FDG and, consequently, low sensitivity of the assay.

The possibilities of PSMA-guided radionuclide diagnosis of HCC are currently presented in a few literary sources. In all the presented sources, [^{68}Ga]Ga-PSMA-11 was used as the radiopharmaceutical, which is undoubtedly justified, since the biodistribution feature of [^{18}F]F-PSMA-1007, due to its lipophilicity, is the dominant hepatic clearance, which, in theory, makes it less suitable for visualizing HCC [74–79]. On the whole, the results of the studies demonstrate the advantages of using PSMA ligands over [^{18}F]F-FDG both in terms of the number of detected lesions and the intensity of accumulation in the detected tumor foci [74, 75, 77].

In the study by M. Kesler et al. [74], [^{68}Ga]Ga-PSMA-11 uptake was shown to correlate with tumor vascularization, and HCC lesions are most often hypervascular. Radiopharmaceutical uptake was observed in 36 of 37 liver tumors, and only ten of these lesions were FDG-positive. Besides, the method allowed the authors to differentiate tumor formations and regenerative nodes in the context of cirrhotic changes and this fact may have high practical significance, since the cirrhotic liver has a nodular architecture with altered vascularization, which complicates the differentiation of regenerative nodes and HCC using traditional visualization methods.

Additionally, PSMA PET/CT showed slightly higher efficiency in detecting hepatic and extrahepatic HCC lesions compared to CT and MRI [74,76–78]. When comparing semi-quantitative parameters of PET with PSMA ligands (SUVmax) with the results of laboratory studies, in particular the level of alpha-fetoprotein and CA 19-9, no statistically significant correlation was found [76, 77]. Generally, the results of the studies demonstrate fairly variable absorption of PSMA ligands: according to different authors, the average SUVmax values vary from 8.3 to 16.7, while the average tumor-to-background values have a smaller spread – from 2 to 3.6 [74–79].

The rich blood supply of HCC plays a crucial role in tumor growth and metastasis. First-line therapy for locally advanced and metastatic HCC consists of a combination of immunotherapy and anti-neoangiogenic therapy [70]. In this situation, PET/CT with PSMA radioligands may become a valuable tool for predicting therapy outcomes and assessing a treatment response. It should also be noted that HCC is often diagnosed at late stages of the disease, which limits the possibilities of standard treatment for these patients. In this regard, the concept of a theranostic approach targeting PSMA receptors may become a relevant direction in the treatment of this disease. The study by N. Hirmas et al. [78] presented the results of [^{177}Lu]Lu-PSMA-617 administration to two patients who were diagnosed with liver lesions with high uptake of [^{68}Ga]Ga-PSMA-11 (SUVmax more than 10). However, in both cases, intratherapeutic dosimetry based on SPECT/CT showed that the radiation dose to the tumor was 10 times lower than that typically achieved in a single cycle of external beam radiotherapy for HCC. In this regard, radionuclide therapy with [^{177}Lu]Lu-PSMA-617 was suspended after one administration. Considering that nearly 95% of HCCs exhibit high levels of endothelial PSMA expression, it may be used as a therapeutic target for radioligand therapy [79–81]. The study of this issue may become quite relevant.

Lymphomas are among the most difficult malignant pathologies in terms of diagnosis and therapy. In addition, lymphomas are a fairly heterogeneous group of diseases in oncohematology. The incidence of this pathology is steadily increasing – the number of cases has increased by 22% over the past ten years [59]. Treatment of lymphomas is almost always associated with chemotherapy courses of varying degrees of toxicity and duration, which leads to the development of a number of complications, including delayed ones. With the advent of PET/CT with [^{18}F]F-FDG, the quality of lymphoma diagnosis has significantly improved, including monitoring during therapy, which has made it possible to optimize the therapeutic effect and, accordingly, reduce the number of complications

[82]. Thus, [^{18}F]F-FDG is currently the drug of choice for radionuclide diagnosis of Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL); however, some subtypes of indolent NHL are FDG-negative [83, 84].

In connection with the active introduction of PSMA theranostics into widespread clinical practice, reports of clinical cases of lymphoma visualization using diagnostic PSMA ligands have begun to appear in the literature. However, these were isolated publications involving a small number of subjects and, as a rule, these were incidental findings in patients with prostate cancer, which were subsequently confirmed by the results of the histological examination. In existing studies, increased accumulation of PSMA-targeted radiopharmaceuticals for PET diagnosis is described in various histologic variants of lymphomas – follicular lymphoma, Hodgkin's lymphoma, diffuse large B-cell lymphoma [85–90]. In the study by S.P.M. de Souza et al. [91], a direct comparative study of [^{18}F]F-FDG and [^{68}Ga]Ga-PSMA PET/CT was conducted in 10 patients with confirmed diagnosis of Hodgkin's lymphoma (n = 3) and NHL (n = 7). It was shown that [^{18}F]F-FDG accumulated in 59 of 59 abnormal sites, while [^{68}Ga]Ga-PSMA – in 47 of 59 sites. Overall, its accumulation was characterized by lower uptake in lesions, regardless of FDG uptake intensity. However, PET/CT with [^{68}Ga]Ga-PSMA demonstrated greater potential in detecting brain lesions compared to FDG, which is logical given the biodistribution characteristics of [^{18}F]F-FDG. Generally, it should be noted that regardless of the histologic variant of lymphomas included in the few studies, they, as a rule, demonstrated low intensity of PSMA ligand uptake.

Our research results also demonstrate the possibility of using SPECT/CT with PSMA-targeted radiopharmaceuticals for the diagnosis of lymphomas, including for the evaluation of therapy results (Fig. 3).

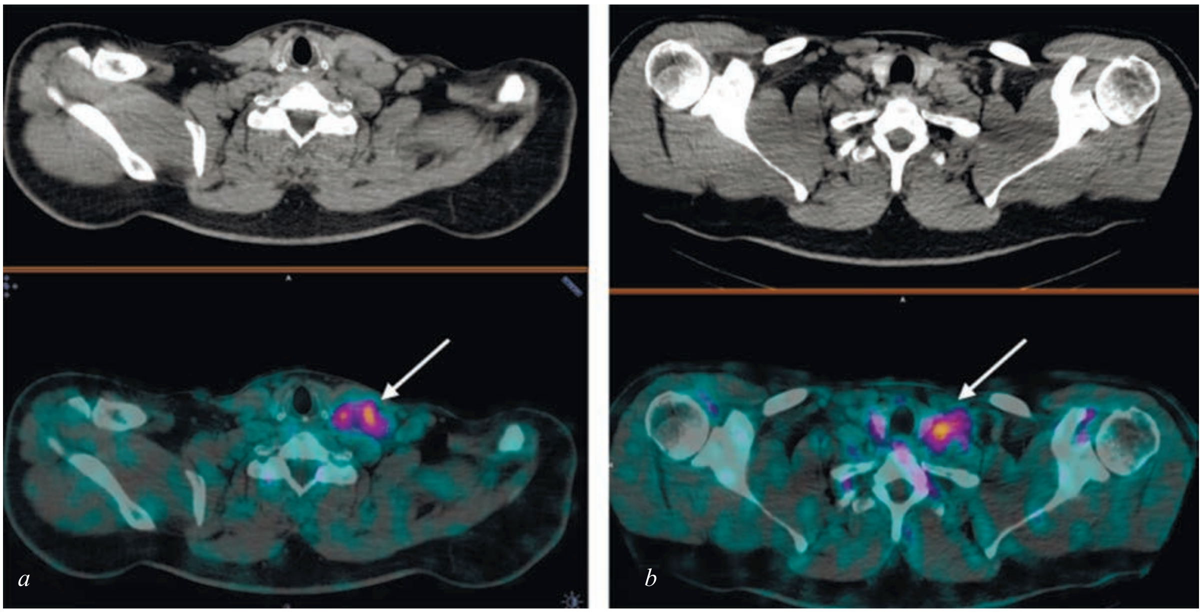


Fig. 3. CT and combined SPECT/CT images at 2 h after administration of [^{99m}Tc]Tc-HYNIC-PSMA in a patient with Hodgkin's lymphoma, with damage to the cervical and supraclavicular lymph nodes, the arrow indicates the tumor: *a* – before therapy, SUVmax 4.03; *b* – after 4 courses of polychemotherapy according to the BEACOPP protocol, SUVmax 1.46 (self-reported)

DISCUSSION

To date, there are no large, well-designed studies investigating the role of PSMA-guided imaging techniques in non-prostate tumors. However, the limited available data, mostly retrospective in nature, demonstrate some correlation between PSMA ligand accumulation and PSMA receptor expression in different tumor types. It is logical that most of the tumors studied are those for which [^{18}F]F-FDG PET imaging has low sensitivity either due to high physiological uptake in surrounding healthy tissue, such as brain tumors, or due to low glucose metabolism or specific characteristics that limit the intensity of [^{18}F]F-FDG uptake, such as increased glucose-6-phosphatase activity in differentiated HCC.

A number of tumors show mixed evidence for the utility of PSMA imaging. For example, in urothelial carcinoma, according to research data, there is relatively poor expression of PSMA receptors, which, of course, limits the use of diagnostic PSMA ligands. Also, low information content of the method is observed in malignant neoplasms of the gastrointestinal tract and pancreas, which is associated with low expression of PSMA in tumor tissue and high physiological absorption of PSMA ligands in background organs [92]. In breast carcinoma, the method demonstrates significant variation in the expression of these receptors in both primary and metastatic tumors, as well as in different patients, which confirms the heterogeneity of this disease.

Preliminary results indicate fairly high diagnostic sensitivity and specificity of PSMA-guided imaging in clear cell renal carcinoma, glioma, and hepatocellular carcinoma, which has led to changes in treatment strategy in some clinical situations. However, the currently published results require confirmation by larger prospective studies that further evaluate the impact of the data obtained on patient treatment outcomes.

Numerous studies have already proven that the expression of PSMA receptors is associated with neovascular endothelial cells in many tumors [35]. This fact makes these receptors an interesting target for antiangiogenic therapy. For example, according to the hypothesis of R. Jain, treatment with antiangiogenic agents is supposed to improve the effectiveness of chemotherapy by improving the delivery conditions [93]. At the same time, preclinical studies show that when chemotherapy drugs are administered outside the so-called “normalization window” in the context of antiangiogenic therapy, it turns out to be ineffective [94]. It is suggested, that suboptimal clinical results obtained with the use of bevacizumab as an antiangiogenic agent in combination with chemotherapy may have resulted from improper sequencing of the chemotherapeutic agents. In this regard, PSMA-guided imaging could be a potential tool to identify the “window of normalization,” which in turn could potentially optimize the efficacy of VEGF-targeted therapy [95].

Radioligand therapy with [^{177}Lu]Lu-PSMA is currently actively used in many countries for the treatment of metastatic castrate-resistant PCa. Retrospective and prospective data show favorable safety and efficacy of this therapy, high response rates, and significant improvement in quality of life and survival [96–101]. Taking into account that in addition to PCa a number of tumor processes demonstrate high PSMA expression, it is considered relevant to study the issue of a PSMA-directed theranostic approach in relation to these nosologies. Despite the limited clinical examples of the use of radioligand therapy with [^{177}Lu]Lu-PSMA in various solid tumors with insufficient efficacy published to date, this area requires further, larger-scale studies.

CONCLUSION

Although the exact role of PSMA in neoplasia and neoangiogenesis remains unclear, it can be assumed that PSMA-guided imaging may be useful not only in relation to PCa, but also in other tumor nosologies. It is likely that the routine use of conventional imaging methods for many tumors will continue to be a priority, both in primary diagnosis and in staging the process and assessing therapy. However, PSMA-guided imaging methods may in the future provide useful prognostic information, assisting in patient selection for systemic therapy by providing data on PSMA expression associated with some tumors with aggressive behavior [49–52, 67, 68].

It should also be noted that one of the important modern strategies in cancer treatment is the selective inhibition of angiogenesis, either by interfering with angiogenic growth factors or by directly targeting tumor-associated blood vessels [102, 103, 104]. In this regard, the use of diagnostic PSMA ligands may become a valuable tool for planning personalized treatment, increasing the effectiveness and safety of antitumor treatment. Another rather relevant direction may be PSMA theranostics of various malignant tumors, and radionuclide diagnostics with PSMA ligands in this situation will become a necessary option for patient routing.

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Received on February 03, 2025;
approved after peer review on March 13, 2025;
accepted on March 20, 2025