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APPLICATION OF ^{68}GA-FAPI PET/CT IN CLINICAL PRACTICE – PERSPECTIVES FOR MALIGNANT TUMOR IMAGING: A LITERATURE REVIEW

Zh.Zh. ZHOLDYBAY[1], Zh.K. ZHAKENOVA[1], A.S. AINAKULOVA[1,2], M.O. GABDULLINA[1], J.M. AMANKULOV[2], E.V. FILIPPENKO[1], B.K. ISAMATOV[1], A.S. ALAKOVA[1], YU.T. DAUTOVA[1]

[1]«Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan;
[2]«Kazakh Institute of Oncology and Radiology» JSC, Almaty, the Republic of Kazakhstan

ABSTRACT

Relevance: *The incidence of malignant neoplasms in various localizations is growing worldwide and in Kazakhstan. The mortality rate from oncological diseases is also alarmingly high. To facilitate early diagnosis and optimal therapy, scientists are exploring molecular diagnostics, including PET/CT, using various markers, like ^{18}F-fluorodeoxyglucose, widely used in oncology but lacking specificity for certain types of tumors. The finding of Fibroblast Activation Protein (FAP) has sparked interest in FAP-targeted radiolabeled inhibitors (FAPI), which could serve as a universal marker for diagnosing different types of cancer. Various FAP markers for PET/CT are being studied, with special attention given to 68Ga-FAPI.*

The study aimed to *analyze the potential value of FAPI PET/CT for detecting malignant tumors.*

Materials: *A literature review was conducted using the MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials databases for the past decade using the following keywords: "malignant lesions," "PET/CT," and "FAPI." This review analyzes 48 literature sources with A1-level evidence dedicated to the ^{68}Ga-FAPI PET/CT diagnostic accuracy in detecting and staging malignant tumors and assessing treatment efficacy.*

Results: *According to the analyzed sources, the ^{68}Ga-FAPI PET/CT sensitivity and specificity in diagnosing cancer are 95% to 100% and 62% to 100%, respectively. However, clear indications for use in clinical practice require further study of ^{68}Ga-FAPI PET/CT diagnostic capabilities on larger cohorts and more homogeneous datasets.*

Conclusion: *The available literature data on FAPI PET/CT diagnostic capacity shows this marker's potential in diagnosing oncological disorders. Information provided by ^{68}Ga-FAPI PET/CT supplements the existing methods and generally impacts the treatment strategy for each unique case.*

Keywords: *malignant lesions, PET/CT, FAPI.*

Introduction: To date, cancer of various localizations ranks high in the global morbidity structure. The number of cancer cases has been growing worldwide and in Kazakhstan in recent years. In 2020, GLOBOCAN reported 19,292,789 new cases and 9,958,133 deaths from cancer worldwide [1].

According to Kaidarova et al., in Kazakhstan, cancer ranked 7th in total morbidity in 2020 but with a very high mortality rate. Over 13 thousand deaths from cancer per year post it second in mortality structure after circulatory system diseases. More than 37,000 new cancer cases are registered annually in Kazakhstan, and the number of patients under dynamic follow-up exceeds 205,000 [2].

Early diagnostics improvement and timely initiation of optimal therapy are of particular importance to reduce cancer mortality. For that reason, scientists worldwide conduct relevant clinical studies to reinforce the mission for health, increase life expectancy, and reduce the burden of disease and disability.

Global medicine has focused on morphological characteristics when diagnosing tumors for a long time. Today, special attention is paid to molecular diagnostics, which seeks to identify physiological activity in tissues and allows for the assessment of tumor biological properties [3]. Molecular diagnostics enables visualizing the body's processes at the cell level. Positron emission tomography/computed tomography (PET/CT) is a hybrid method that provides additional information about the tumor's functionality and structure [4].

^{18}F-fluorodeoxyglucose (^{18}F-FDG), originally developed in the late 1970s to study brain metabolism, today is the most widely used PET marker with numerous applications in oncology and other fields [4, 5]. Despite its undeniable clinical value, the capture of ^{18}F-FDG is a sign of glucose transport and metabolism and is not specific to tumors. Further studies led to the development of more specific markers, such as radiolabeled agents targeting the somatostatin receptors and ligands of prostate-specific membrane antigen, which have been successfully implemented in modern methods of diagnosis and treatment of neuroendocrine tumors and prostate cancer [6]. The search for cellular

targets has led to the discovery of the fibroblast activation protein (FAP). This transmembrane glycoprotein has been expressed on activated fibroblasts, including cancer-associated fibroblasts (CAFs) [7]. Preliminary data have sparked interest in FAP as a promising marker for diagnosing various types of cancer in nuclear medicine [8]. Several radiolabeled fibroblast activation protein inhibitors (FAPIs) are currently being investigated as markers for PET/CT.

The study aimed to analyze the potential value of FAPI PET/CT for detecting malignant tumors.

Material and methods: A literature review was conducted using the MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials databases for the past decade using the following keywords: "malignant lesions," "PET/CT," and "FAPI."

A total of 253 articles on the search topic were found, of which 48 literature sources with an A1 level of evidence were included in this literature review.

Results: FAP is a transmembrane protein actively synthesized in the tumor stroma and inflamed tissues during the wound healing. FAP is actively synthesized on the surface of cancer-associated fibroblasts, which play an important role in tumor cell growth, aggressiveness, and migration. The elevation of the CAFs and FAPs expression was most commonly recorded in developing epithelial cancers [9]. In addition, FAP is synthesized on the tumor tissue stromal cells surface. In this microenvironment, tumor cells grow, proliferate, and spread, and drug resistance develops [9, 10].

The molecules that can be selectively connected with specific markers are required to create imaging techniques. Of all FAP markers developed up-to-date, ^{68}Ga-FAPI has the most promising characteristics that largely meet the specified requirements, supported by a growing number of clinical evidence.

It should be noted that FAP expression is practically absent in healthy tissues, except for stromal cells in the tissues of the uterus and placenta, alpha cells of the pancreas, as well as some dermal fibroblasts [10]. Due to the low FAP expression in normal tissues, it acts as a promising marker for diagnosing and treating cancer using radiopharmaceuticals [9, 10].

In 2018, Loktev et al. conducted a study of the FAPI PET/CT concept, in which, for the first time, they demonstrated a high level of marker capture in tumors in three patients with breast cancer (BC), lung cancer and pancreatic cancer [11]. Subsequently, Kratocwill et al., from the same group of researchers, presented the results of ^{68}Ga-FAPI-04 PET/CT in 80 patients with 28 different types of tumors. The accumulation values varied significantly depending on the tumor type and the patient's individual characteristics. The highest accumulation of ^{68}Ga-FAPI (SUVmax >12) was found in patients with sarcoma, esophageal cancer, breast cancer, cholangiocarcinoma, and lung cancer. In contrast, pheochromocytoma, renal cell carcinoma, differentiated thyroid cancer (TC), and gastric cancer (GC) had the lowest accumulation (SUVmax <6). Despite the intratumoral and interindividual variability, low background activity provided excellent contrast in the images, even with low tumor activity [12].

In the published literature sources, there are data on the sensitivity of PET/CT using ^{68}GaFAPI in diagnosing cancer of various localizations, which vary from 95% to 100%, and specificity indices range from 62% to 100% [12-39]. However, the study sample was small – from 12 to 80 patients.

The positive results from previous studies on various cancers have led to follow-up studies using ^{68}Ga-FAPI PET/CT in certain types of cancer, including head and neck cancer. In a cohort of 45 patients with nasopharyngeal cancer, ^{68}Ga-FAPI-04 PET/CT showed its efficacy, surpassing ^{18}F-FDG PET/CT in detecting primary tumors, metastatically affected lymph nodes, and distant metastases, resulting in treatment change in 18% of patients [13]. Another study included 14 patients with head and neck cancer, including a comparison of ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT to distinguish between healthy and tumor tissues [40]. As a result, it was demonstrated that ^{68}Ga-FAPI-04 PET/CT increased the staging accuracy in a cohort of 12 patients with adenocystic cancer [41]. Besides, the possibility of using ^{68}Ga-FAPI-04 PET/CT was studied in 10 patients with oral squamous cell carcinoma, while the authors did not come up with conclusions [14].

The Serfing et al. study demonstrated the excellent efficacy of 68Ga-FAPI and 18F-FDG PET/CT for detecting primary pharyngeal lymphoid ring tumors [15]. However, ^{18}F-FDG was more effective in staging lymph nodes than ^{68}Ga-FAPI.

It was established that ^{18}F-FDG PET/CT had limited importance in diagnosing malignant brain tumors and was most useful for differential diagnosis of tumor recurrence and radiation necrosis. On the other hand, studies with FAPI PET/CT show high image contrast due to the absence of background activity, and this advantage over ^{18}F-FDG PET/CT has been highlighted in various publications, especially in the context of brain metastases. Concerning primary brain tumors, two studies focused on using FAPI PET/CT for glioblastoma. In the research of Windisch with co-authors, a group of 14 patients with glioblastoma was studied within the frames of the radiation therapy planning [16]. The diagnostic study of Rohrich M. et al., conducted on 18 patients with glioma, highlighted the prospects of applying FAPI PET/CT as a new tool for identifying differences between poorly differentiated and highly differentiated tumors [17].

CAFs in tumor tissues are positively associated with loss of differentiation and aggressive course of thyroid cancer [18]. Fu and co-authors were the first to describe the case of differentiated thyroid cancer with elevated thyroglobulin levels and negative iodine scintigraphy results, in which ^{68}Ga-FAPI-04 PET/CT revealed an intensive accumulation in the foci of local recurrence and

distant metastases [19]. In a follow-up study, the same group reported the additional metastatic foci that were detected by ^{68}Ga-FAPI-04 PET/CT but not by ^{18}F-FAPI PET/CT in a patient with differentiated thyroid cancer, which was explained by a better ratio between the focus and background on ^{68}Ga-FAPI PET/CT [20].

Breast cancer and other gynecological malignancies are characterized by a high degree of genetic and molecular diversity. The receptor expression plays an important role in the biological behavior of various breast cancer subtypes, directly affecting the diagnostic and treatment strategies [21].

In a study of patients with various gynecological tumors by Dendl et al., 14 women with breast cancer had a strong and moderate accumulation of the marker in the stroma of the mammary gland formations [22].

In a pilot study by Komek et al., where ^{68}Ga-FAPI PET/CT and ^{18}F-FAPI PET/CT were prospectively compared in 20 women with breast cancer, ^{68}Ga-FAPI showed a higher sensitivity (100% vs. 78.2%), compared to ^{18}F-FDG PET/CT, while maintaining a comparable specificity (96.5% vs. 100%) in detecting primary breast tumors. ^{68}Ga-FAPI showed a significantly higher accumulation in primary tumors of the breast, lymph nodes, and pulmonary and bone metastases compared to ^{18}F-FDG ($p<0.05$) [23].

In a retrospective study, Elboga et al. found that ^{68}Ga-FAPI PET/CT had a higher ability to detect foci and exhibited higher marker activity than ^{18}F-FDG PET/CT in 48 patients with invasive breast cancer [24].

The accumulation properties of ^{18}F-FDG in primary liver tumors, especially for hepatocellular carcinoma (HCC), are complex due to factors such as low metabolism and physiological activity of the liver [25]. A study involving 17 patients showed that ^{68}Ga-FAPI-04 accumulated more in liver malignancies than benign tumors [26].

Another study evaluated patients with HCC (n=14) and cholangiocarcinoma CGC (n=3) and found the predominance of ^{68}Ga-FAPI-04 PET/CT over ^{18}F-FDG PET/CT in the detection of primary liver tumors. The efficacy of ^{68}Ga-FAPI-04 PET/CT was confirmed in 20 patients with HCC and 12 patients with CGC; the results were equivalent to contrast-enhanced CT and MRI. There were also two cases of benign liver tumors in which ^{68}Ga-FAPI was negative, emphasizing its potential to distinguish between benign and malignant liver tumors [27].

Röhrich et al. compared the diagnostic efficacy of ^{68}Ga-FAPI PET/CT and contrast-enhanced CT in patients with primary and recurrent pancreatic tumors. Application of ^{68}Ga-FAPI PET/CT led to stage reversal in 10 out of 19 patients [28].

Of particular interest is the study of the effectiveness of ^{68}GaFAPI PET/CT in the visualization of esophageal and breast cancer. According to the results of several studies, it was noted that GC was characterized by a high accumulation of ^{68}Ga-FAPI [29, 30]. Quin et al., in a study involving 20 patients with GC, also demonstrated high efficacy of PET/CT using ^{68}Ga-FAPI for imaging both primary and metastatic lesions [31]. Similar results were obtained by Pang et al. on a sample of 20 patients with GC. The study also included two patients with duodenal cancer and 13 with colon carcinoma. ^{68}Ga-FAPI PET/CT revealed all foci and was characterized by high image contrast due to high SUVmax values in pathological foci and low SUVmax values of background accumulation, contributing to more precise tumor differentiation [32]. Lin et al. reported an additional benefit of ^{68}Ga-FAPI-04 PET/CT as the control of therapy efficacy in patients with GC [33].

S. Koerber et al. studied the efficacy of ^{68}Ga-FAPI PET/CT in patients with colon, sigmoid colon, rectal, and anal cancer. They confirmed this marker's high efficacy in detecting primary and metastatic foci, which affects the determination of the process stage and treatment tactics [34].

Several studies evaluated the ^{68}Ga-FAPI PET/CT sensitivity and specificity in patients with abdominal carcinomatosis. One study enrolled 46 patients, the other – 35. Both groups of researchers obtained a high sensitivity and specificity of the method in detecting peritoneal metastases regardless of the type of carcinomatosis [35, 36].

Visual diagnostics of colorectal cancer by applying nuclear medicine technologies is difficult due to the peculiarities of the histological structure of cancer of these localizations and frequent physiological conditions leading to increased radiopharmaceutical capture and follow-up increase of the number of false-positive results. It has been revealed that the degree of FAP expression was directly proportional to the high aggressiveness and poor prognosis for colorectal cancer [37].

Numerous studies confirm that ^{68}Ga-FAPI PET/CT improves the detection of malignant lesions in the abdominal cavity, which are often difficult to detect using standard imaging methods [38, 39].

Almost simultaneously, studies have been conducted in several countries to assess the accumulation of ^{68}Ga-FAPI in patients with ovarian, cervical, endometrial, and fallopian tube cancer.

Depending on the age and hormonal status of the woman, there is a physiologically increased accumulation of FAPI in the endometrium [22]. However, in the presence of the tumor, the high image contrast is maintained due to the high accumulation of the marker in the tumor tissue [22]. Dendl et al. investigated the degree of marker accumulation in tumor foci in a diverse group of 31 patients with various gynecological tumors [22]. The ratio of standardized assimilation of tumor foci to background assimilation for distant metastases remained significantly high, contributing to the detection of metastatic foci. Some studies have demonstrated that FAP was highly expressed in the majority (>90%) of ovarian malignancies but had little expression in normal ovarian tissues, as well as in benign and borderline ovarian tumors [42, 43].

Based on the results of their work, K.Kessel and co-authors proved that ^{68}Ga-FAPI PET/CT was not inferior in effectiveness to other markers and could be used as an additional method for imaging of prostate cancer in assessing the prevalence of the process and searching for distant metastases [44].

^{68}Ga-FAPI PET/CT is a technique with high potential for visualization of various subtypes of sarcomas. For example, Koerber et al. conducted ^{68}Ga-FAPI PET/CT in 15 patients and noted the qualitative signal-background ratio in primary tumors and metastases. A special feature was the preservation of high image contrast when visualizing poorly differentiated sarcomas. The researchers also found that the degree of accumulation of the marker was directly proportional to the degree of malignancy and severity of the clinical course of the disease [45].

L. Kessler et al. analyzed the relationship between marker accumulation and the degree of FAP expression in 47 patients with bone and soft tissue sarcomas. ^{68}Ga-FAPI PET/CT demonstrated a high sensitivity due to the detection of additional foci in 8 patients, which accounted for 13% of the total number of participants [46].

There is no consensus on the effectiveness of ^{68}Ga-FAPI-04 PET/CT in diagnosing lymphomas. X.Jin et al. found a high accumulation of ^{68}Ga-FAPI in Hodgkin's lymphoma (n=11) and moderate accumulation in non-Hodgkin's lymphoma (n=62) [47].

Discussion: ^{68}Ga-FAPI PET/CT opens a new chapter in nuclear medicine, having a high potential for identifying, staging, and evaluating the effectiveness of treatment of malignant tumors. However, its clinical role and application in practice are not fully determined.

Based on the results of that review, it can be concluded that most of the studies focused on oncological disorders that have difficulties in diagnostics by use of other markers. Besides, most studies have limitations in the methodology due to a small sample of patients, heterogeneity of the sample, and imperfect study design, which does not permit the final conclusions.

FAP expression by inflamed tissues and further increased accumulation of the marker in chronic diseases allow the use of ^{68}Ga-FAPI PET/CT in the diagnostics of non-oncological diseases. Most studies in this area are devoted to cardiovascular and rheumatological diseases [48].

In any case, the diagnostic capacities of ^{68}Ga-FAPI PET/CT still require further research to form clear indications in practical use.

Conclusion: The increase in cancer morbidity and mortality worldwide encourages the creation and development of new diagnostic approaches that include nuclear medicine and molecular diagnostic capabilities.

The review of available literature data on FAPI PET/CT diagnostic capacity demonstrates this marker's potential in diagnosing oncological disorders. Information provided by ^{68}Ga-FAPI PET/CT supplements the existing nuclear medicine methods and generally impacts the treatment strategy for each unique case.

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АНДАТПА

КЛИНИКАЛЫҚ ТӘЖІРИБЕДЕ ^{68}GA-FAPI ПЭТ/КТ-НЫ ҚОЛДАНУ – ҚАТЕРЛІ ІСІКТЕРДІ ВИЗУАЛИЗАЦИЯЛАУ ПЕРСПЕКТИВАЛАРЫ: ӘДЕБИЕТКЕ ШОЛУ

Ж.Ж. Жолдыбай[1], Ж.К. Жакенова[1], А.С. Айнакулова[1,2], М.О. Габдуллина[1], Ж.М. Аманкулов[2], Е.В. Филиппенко[1], Б.К. Исаматов[1], А.С. Алакова[1], Ю.Т. Дауытова[1]

[1]«С.Д. Асфендияров атындағы Қазақ Ұлттық Медицина Университеті» КЕАҚ, Алматы, Қазақстан Республикасы;
[2]«Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ, Алматы, Қазақстан Республикасы

Өзектілігі: *Әртүрлі локализациялардағы қатерлі ісіктермен сырқаттанушылық бүкіл әлемде де, Қазақстанда да өсуде. Онкологиялық аурулардан болатын өлім – жітім де жоғары. Ерте диагностика және оңтайлы терапия үшін ғалымдар молекулалық диагностиканы, соның ішінде әртүрлі маркерлерді қолданатын ПЭТ/КТ әдісін зерттейді. ^{18}F-фтородезоксиглюкоза онкологияда кеңінен қолданылады, бірақ кейбір ісіктердің түрлерін нақты ажырата алмайды. Белсендіретін фибробластикалық ақуыздың (FAP) анықталуы әртүрлі қатерлі ісіктерді диагностикалаудың әмбебап маркері бола алатын FAP-бағытталған радио таңбаланған ингибиторларға (FAPI) қызығушылық тудырды. Қазіргі уақытта ПЭТ/КТ үшін әртүрлі FAP маркерлері зерттелуде, олардың арасында ^{68}Ga-FAPI ерекше орын алады.*

Зерттеудің мақсаты *– қатерлі ісіктерді анықтаудағы FAPI ПЭТ/КТ-ның мүмкіндіктерін талдау.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed Cochrane Central Register of Controlled Trials дерекқоры бойынша келесі түйінді сөздермен: "қатерлі ісіктер", "ПЭТ/КТ" және "FAPI" шолу жүргізілді. Бұл шолуда әртүрлі локализациялардағы ісіктерді анықтау, сатылау, емдеу тиімділігін қарастыруда ^{68}Ga-FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктерін бағалауға арналған А1 дәлелдеу деңгейі бар 48 дерекқоздің нәтижелері сипатталған.*

Нәтижелері: *68Ga-FAPI PET/CT маркерінің сезімталдығы мен өзгешелігі туралы мәліметтерді жинайтын жұмыстарды талдау келесі көрсеткіштерді айқындайды: сәйкесінше 95%-дан 100%-ға дейін және 62%-дан 100%-ға дейін. Алайда, тәжірибеде қолдануға нақты көрсеткіштерді қалыптастыру үшін ^{68}Ga-FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктері әлі де қатысушылардың саны мен біртектілігін арттыра отырып қосымша зерттеулерді қажет етеді.*

Қорытынды: *FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктері туралы деректерге шолу маркердің қатерлі ісік диагностикасында қолданылу әлеуетін көрсетеді. 68Ga-FAPI ПЭТ/КТ-ның көмегімен алынатын ақпарат ядролық медицинаның өзге маркерлары арқылы алынған мағлұматты толықтырады және науқастардың әрбір нақты жағдайдағы емдеу тактикасына әсер етеді.*

Түйінді сөздер: *қатерлі ісіктер, ПЭТ/КТ, FAPI.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ 68GA-FAPI ПЭТ/КТ В КЛИНИЧЕСКОЙ ПРАКТИКЕ – ПЕРСПЕКТИВЫ ДЛЯ ВИЗУАЛИЗАЦИИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ: ОБЗОР ЛИТЕРАТУРЫ

Ж.Ж. Жолдыбай[1], Ж.К. Жакенова[1], А.С. Айнакулова[1,2], М.О. Габдуллина[1], Ж.М. Аманкулов[2], Е.В. Филиппенко[1], Б.К. Исаматов[1], А.С. Алакова[1], Ю.Т. Дауытова[1]

[1]НАО «Казахский Национальный Медицинский Университет имени С.Д. Асфендиярова», Алматы, Республика Казахстан;
[2]АО «Казахский научно-исследовательский институт онкологии и радиологии», Алматы, Республика Казахстан

Актуальность: *Заболеваемость злокачественными опухолями различных локализаций имеет тенденцию к росту, как во всем мире, так и в Казахстане. Смертность от онкологических заболеваний также имеет высокие показатели. Для ранней диагностики и оптимальной терапии ученые исследуют молекулярную диагностику, включая метод ПЭТ/КТ с использованием различных маркеров. ^{18}F-фтордезоксиглюкоза широко применяется в онкологии, но не является специфичным для некоторых опухолей. Открытие*

активирующего фибробластического белка (FAP) привело к интересу к FAP-ориентированным радиомеченым ингибиторам (FAPI), которые могут стать универсальным маркером для диагностики различных видов рака. На данный момент исследуются различные FAP маркеры для ПЭТ/КТ, среди которых особое место занимает ^{68}Ga-FAPI.

***Цель исследования** – проанализировать возможности FAPI ПЭТ/КТ в диагностике злокачественных опухолей.*

***Методы:** проведен литературный обзор по базе данных MEDLINE, Embase, Scopus, PubMed, Cochrane Central Register of Controlled Trials за последние 10 лет по следующим ключевым словам: «злокачественные новообразования", "ПЭТ/КТ" и "FAPI". В данном обзоре описаны результаты анализа 48 литературных источников с уровнем доказательности А1, посвященных оценке диагностических возможностей ^{68}Ga-FAPI ПЭТ/КТ в выявлении, стадировании, оценке эффективности лечения опухолей различных локализаций.*

***Результаты:** Чувствительность и специфичность ^{68}Ga-FAPI ПЭТ/КТ в диагностике рака различных локализаций составляют от 95% до 100% и от 62% до 100%, соответственно. Однако для формирования четких показаний к применению в практической деятельности, диагностические возможности ^{68}Ga-FAPI ПЭТ/КТ все еще требуют дальнейших исследований с большим количеством участников и более однородной выборкой.*

***Заключение:** Имеющиеся литературные данные о диагностических возможностях FAPI ПЭТ/КТ демонстрируют потенциал маркера для применения в диагностике онкологических заболеваний. Информация, полученная с помощью ^{68}Ga-FAPI ПЭТ/КТ, дополняет уже используемые методы ядерной медицины и в совокупности влияет на тактику лечения пациентов в каждом конкретном случае.*

***Ключевые слова:** злокачественные новообразования, fibroblast activation protein inhibitor (FAPI), ПЭТ/КТ.*

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Authors' data:
Zholdybai Zh.Zh. – Doctor of Medical Sciences, Prof. and Head of Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77772101612, e-mail: joldybay.j@gmail.com, ORCID ID: 0000-0003-0553-9016;
Zhakenova Zh.K. – Candidate of Medical Sciences, Professor of Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77754983950, e-mail: jja18@yandex.ru, ORCID ID: 0000-0002-6764-6821;
Ainakulova A.S. – PhD, Ass. Prof. at Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Doctor of radiation Diagnostics of «Kazakh Institute of Oncology and Radiology» JSC, Almaty, the Republic of Kazakhstan, tel. +77017242429, e-mail: ar89@list.ru, ORCID ID: 0000-0003-1773-5145;
Gabdullina M.O. (corresponding author) – Ph.D. student, Assistant at Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77064095432, e-mail: madina.orazaykyzy@gmail.ru, ORCID ID: 0000-0003-4993-4747;
Amankulov Zh.M. – PhD, Head of Radiology and Nuclear Medicine Department, «Kazakh Institute of Oncology and Radiology» JSC, Almaty, the Republic of Kazakhstan, tel. +77013514213, e-mail: zh.amankulov@kaznmu.kz, ORCID ID: 0000-0001-7389-3119;
Filippenko E.V. – Assistant at Visual Diagnostics Department, «Asfendiyarov Kazakh National Med-ical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77051916774, e-mail: eclips_90@mail.ru, ORCID ID: 0000-0002-7153-3002;
Isamatov B.K. – Ph.D. student, Assistant at Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77078288351, e-mail: b.isamatov@mail.ru, ORCID ID: 0000-0002-5515-8468;
Alakova S.A. – Resident of Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77780004158, e-mail: alakova_akerke@mail.ru, ORCID ID: 0009-0006-4047-6267;
Dauytova Yu.T. – Ph.D. student, Assistant at Visual Diagnostics Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77077474580, e-mail: juldiz.dauytova@mail.ru, ORCID ID: 0000-0002-9411-7589.

Address for correspondence: Gabdullina M.O., Satpayev St. 90/43, office 31, Almaty 050046, the Republic of Kazakhstan.