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**A.G. DYO¹, G.R. AKHMETOVA¹, ZH.ZH. ZHOLDYBAY², J.M. AMANKULOV^{1,3},
G.T. ALISHEROV¹, A.D. AKYZHANOVA¹, M. TOKTASSYNKYZY³**¹Orhun Medical PET/CT center, Almaty, the Republic of Kazakhstan;²S.D. Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan;³Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan

Clinical application of 18F-FDG PET/CT in oncology: Rare gastrointestinal malignant tumors (literature review)

Relevance: PET/CT is now becoming an integral part of cancer management protocols. 18F-fluorodeoxyglucose (18F-FDG) is the most common radiopharmaceutical for PET. However, the 18F-FDG PET/CT sensitivity and specificity vary widely in tumors of different histological structures and cell atypia degrees.

The role of PET/CT in complex diagnostics of lymphomas is known. However, the specific use of this method in gastrointestinal neoplasms, especially at the initial stage of examination and in differential diagnostics, is not clearly defined since lymphomas account for only 1-5% of GI tumors.

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that arise from the diffuse neuroendocrine system enterochromaffin cells. NETs account for 0.5% of all neoplasms but become more common recently due to the advances in diagnostics. However, the significant achievements in the study of biological and molecular mechanisms of NETs' behavior have not yet resulted in a common algorithm for their diagnostics and treatment.

The purpose of this study was to review the experience of using 18F-FDG PET/CT in diagnostics of lymphomas and gastrointestinal neuroendocrine tumors as rare tumors to improve the criteria for the rational use of the 18F-FDG PET/CT method in their diagnostics and monitoring.

Results: The use of 18F-FDG PET/CT is advisable at any stage of non-Hodgkin lymphomas, which are most common in the gastrointestinal tract, and for differential diagnostics, primary staging, and treatment efficiency monitoring in gastrointestinal lymphomas. 18F-FDG PET CT is also most valuable in aggressive non-Hodgkin lymphomas.

Despite the importance of functional imaging in NETs, 18F-FDG PET/CT plays a supporting role in monitoring gastrointestinal NETs. 18F-FDG PET/CT is known to be efficient in prognosing the outcome of radionuclide therapy with peptide receptors in low-grade and progressive metastatic NETs.

Conclusion: In lymphomas, 18F-FDG PET/CT is useful for primary staging, assessing early response to treatment, and re-staging. 18F-FDG PET/CT has a diagnostic value in undifferentiated gastrointestinal NETs, while its usefulness in well-differentiated gastrointestinal NETs is limited.

Keywords: positron emission computed tomography (PET/CT), 18F-FDG, gastrointestinal lymphoma, neuroendocrine tumors (NETs).

Introduction: PET/CT is both a functional and structural research method. Its use in complex diagnostics of oncological diseases of various origins for primary diagnosis and assessment of the effectiveness of therapy is becoming an integral part of the protocols of managing patients with malignant tumors [1, 2]. 18F-fluorodeoxyglucose (18F-FDG) is the most commonly used radiopharmaceutical (RP) for PET, the use of which is based on the high glycolytic activity of tumor cells. This advantage of PET/CT with 18F-FDG over traditional radiation diagnostics methods in many cases makes it possible to detect pathological changes in the absence of signs of organ and tissue structural disorders according to CT and/or MRI data. Also, PET/CT can be used to assess the metabolic activity of the tumor in the morphologically unchanged tumor tissue already at the early stages of chemotherapeutic treatment [3-5].

However, the sensitivity and specificity of PET/CT with 18F-FDG vary widely in tumors of various histo-

logical structures and degrees of cell atypia. The role of PET/CT in complex diagnostics lymphomas, but specificity application I method at neoplasms of the gastrointestinal tract (GIT) uniquely not defined and, as lymphoma comprises only 1-5% of the tumors of this localization.

Neuroendocrine tumors (NEO) compose a heterogeneous group of tumors that develop from enterochromaffin cells of the diffuse neuroendocrine system. NEO account for 0.5% of all tumors. Over the past years, there has been a significant increase in the NET incidence due to improved diagnostic methods. However, despite significant advances in the study of the biological and molecular mechanisms of the behavior of this group of tumors, the formation of a unified algorithm for the diagnosis and treatment of NETs remains difficult to this day.

The purpose of this study was to review the experience of using 18F-FDG PET/CT in diagnostics of lym-

phomas and gastrointestinal neuroendocrine tumors as rare tumors to improve the criteria for the rational use of the 18F-FDG PET/CT method in their diagnostics and monitoring.

Materials and methods. A literature search was conducted in the PubMed database and the Cochrane library among original studies conducted from 2012 till January 2020. Keywords used for searching included "PET/CT," "18F-FDG," in conjunction with the terms "gastrointestinal lymphoma," "neuroendocrine tumor." Twenty-two most relevant articles out of 117 found that met the above selection criteria and discussed the role of 18F-FDG in these pathologies were manually selected and analyzed.

Results and discussion:

Gastrointestinal lymphoma. Up to 50% of primary lymphomas or gastrointestinal lymphomas affect the stomach. Lymphomas account for 3-5% of malignant gastric lesions. In most cases (up to 95%), they are histiocytic or lymphocytic NHL, including MALT-lymphomas (mucosa-associated lymphoid tissue lymphoma) [1, 4, 5]. Next in frequency are the small intestine lesions, mainly its distal parts: ileum is affected in 70% of cases, mainly by B-cell NHL; T-cell lymphomas that primarily affect the duodenum and jejunum make the rest 30% of cases. Colon lymphomas are rare (up to 1.5% of abdominal lymphomas); the blind and ascending colon lesions are more frequent. Esophageal lymphomas are extremely rare (less than 1% of all patients with lymphoma have esophageal involvement), while non-Hodgkin's lymphomas (NHL) and Hodgkin's lymphoma (HL) occur in this localization, more often in the form of secondary infiltration from adjacent lymph nodes [4, 5].

18F-FDG PET/CT is a standard imaging modality for HL and NHL staging. In NHL, which most often affects the gastrointestinal tract, the use of 18F-FDG PET/CT is advisable at any stage of the process, both for differential diagnosis and primary staging of gastrointestinal lymphomas and to monitor the treatment efficacy [4]. 18F-FDG PET/CT is especially valuable for aggressive NHL forms. The sensitivity and specificity of 18F-FDG PET/CT in the diagnosis of extranodal lymphoma forms is 88% and 100%, respectively, while for MSCT, these figures are 50% and 90%. The factor that reduces PET/CT's specificity is the physiologically high activity of the stomach and intestines that could mask the manifestations of low and medium avid lymphomas in 18F-FDG.

18F-FDG PET/CT allows a more accurate staging of gastric lymphomas. The disease stage was increased in 22% of cases and decreased in 14% of cases of extranodal lesions. SUV_{max} also correlated well with the aggressiveness of the course of the disease, and a higher uptake of the radiopharmaceutical (RP) is associated with a higher stage of the disease, according to Lugano [5, 6].

However, the intensity of RP absorption (the so-called degree of avidity) differs in lymphomas of different histological types. In general, high sensitivity of 18F-FDG PET/CT has been proven for three main groups of lymphomas – diffuse large B-cell lymphoma, follicular lymphomas, and HL. PET/CT sensitivity in poorly differentiated lymphomas is also dependent on histological subtype: high – in follicular lymphomas, moderate – in marginal zone lymphoma, and low – in small lymphocytic lymphomas. Highly differentiated lymphomas usually show high avidity to 18F-FDG, while a SUV_{max} absorption rate >10 indicates a high probability of an aggressive disease [4, 5].

In marginal zone lymphomas (mantle cell lymphomas), PET/CT's effectiveness remains a matter of debate. High sensitivity has been shown for nodular forms and low – for extranodal forms of this type of lymphoma [6-8]. This aggressive type of B-cell NHL is characterized by rapid growth and high relapse rates; and predominant extranodal lesions of the gastrointestinal tract and bone marrow. The existing publications mentioned high single specificity but suboptimal (60%) sensitivity of 18F-FDG PET/CT in diagnosing mantle-cell GIT lymphomas.

In the data presented in the literature, the avidity to 18F-FDG in MALT-lymphomas varied widely and correlated with the type of growth, the stage of the process, and the Ki index-67. The index of 18F-FDG- SUV_{max} accumulation was significantly correlated with the Ki index-67 [8, 9]. MALT-lymphomas of the GIT usually have low avidity to 18F-FDG, especially at the early stages of the process, but the sensitivity is much higher with common forms and MALT-lymphomas with a plasmacyte component [4, 10].

Early assessment of lymphoma therapy efficacy using PET/CT has a sensitivity and specificity of 79% and 92%, respectively, and is carried out after 1-2 courses of chemotherapy or in the middle of the course. It helps to predict the therapy efficacy, duration of remission, and overall survival [11].

In assessing the treatment efficacy after the end of the full course of therapy, 18F-FDG PET/CT's sensitivity and specificity for NHL are 72% and 100%, respectively.

Lack of response to the first courses of therapy is an indication for changing the line of chemotherapy. A complete or partial metabolic response after the first course of therapy in aggressive lymphomas predicts long-term remission better than a negative PET scan after completing the chemotherapy course [4, 11, 12].

Neuroendocrine tumors of the gastrointestinal tract (GIT NETs). NETs are found in all organs that possess neuroendocrine cells but are most frequent in GIT and pancreatic gland. Due to the small size of the lesion, varied anatomical sites, and low metabolic rate, routine visualization of these tumors is often difficult. There-

fore, functional imaging plays a crucial role in NET diagnostics.

NET is associated with marked overexpression of somatostatin receptors (SSTR), and SSTR-based PET imaging is now becoming a standard of medical diagnostics. Three major ⁶⁸Ga-DOTA peptides are currently available for PET/CT imaging of GI NETs – ⁶⁸Ga-DOTA-Phe1-Tyr3-octreotide (TOC), ⁶⁸Ga-DOTA-Nal 3-octreotide (NOC), SSTR-based ⁶⁸Ga-DOTA, and ⁶⁸Ga-DOTA-Tyr3-octreotide (TATE) [13]. However, according to available data, combined PET/CT imaging with two tracers in NET gives additional possibilities for monitoring patients with NETs.

In their study, Zhang et al. evaluated the clinical and prognostic value of PET/CT imaging with a combination of ⁶⁸Ga-DOTATATE and 18F-FDG in gastroentero-pancreatic neuroendocrine tumors in 83 patients [14]. The sensitivity of double tracers correlated with cell differentiation and the Ki-67 index. They recommended using ⁶⁸Ga-DOTATATE to diagnose highly differentiated NET and 18 F-FDG – for NET with a Ki-67 index of $\geq 10\%$.

Yu et al. evaluated the value of 18FDG and ⁶⁸Ga-DOTA-TATE PET/CT in patients with GIT NET and the correlation between glucose metabolism, SSTR expression, and the tumor differentiation degree. 18 F-SUV_{max} showed a positive correlation with Ki-67 ($r=0.693$, $P=0.000$). On the contrary, there was a negative correlation between ⁶⁸Ga-SUV_{max} G/F and Ki-67 ($r=0.544$, $p=0.002$; $r=0.679$, $p=0.001$). Thus, glucose metabolism and SSTR expression correlated with the GIT NET differentiation degree. Those two functional studies showed different biological characteristics suitable for clinical diagnosis and complementary to the Ki-67 value [15].

Zhang et al. evaluated 18F-FDG PET/CT's prognostic value in patients with advanced metastatic neuroendocrine tumors who received peptide receptor radionuclide therapy (PRRT). 495 patients were treated with ¹⁷⁷Lu- and/or ⁹⁰Y-DOTATOC/DOTATATE PRRT. All subjects received ⁶⁸Ga-DOTATOC/TATE/NOC and 18F-FDG PET/CT before treatment and were observed 3-18.9 months. High SSTR expression combined with 18F-FDG negative PET/CT imaging is associated with the most favorable long-term prognosis. 18F-FDG PET/CT was positive in 77.2% of patients and 22.8% were 18F-FDG negative before PRRT, while 100% were ⁶⁸Ga-DOTATOC/TATE/NOC positive [16].

Treatment regimens for GIT NET are based primarily on the histological assessment of biopsy; however, tumor heterogeneity cannot be fully assessed with biopsy [17]. Although the Ki-67 index has been shown to have prognostic value in GIT NET, the current laboratory diagnostic method, which counts 2000 cells, depends on the pathologist's qualifications and experience [18]. Also, a small amount of tissue on biopsy may, in some cases, prevent an accurate assessment of the Ki-67 index, given the potential for heterogeneity

in Ki-67 expression in tumors. Finally, the Ki-67 index can change over time in the same patient, with possible changes both in response to treatment [19] and as the disease progresses [20].

Kashyap et al. evaluated the therapy results with the ¹⁷⁷Lu-octreotide peptide receptor in patients with 18F-FDG - active NETs [20]. Increased glycolytic activity on 18F-FDG PET/CT has identified a subgroup of patients with metastatic HPNET with poor prognosis. On 18F-FDG PET/CT, 27% achieved a complete metabolic response during the follow-up period. The biochemical response (decrease in the level of chromogranin a-A $>25\%$) was observed in 45% [21-22].

Conclusion: Despite some limitations, computed tomography remains a standard method of assessing the response to treatment. 18F-FDG PET/CT is useful both for initial staging and the assessment of early response to treatment and re-staging in lymphomas. 18F-FDG PET/CT's sensitivity and specificity depend on lymphoma histological type. However, more prospective data are needed to determine the role of 18F-FDG PET/CT and the appropriate time intervals for therapy monitoring.

18F-FDG PET/CT plays a limited role in patients with well-differentiated GIT NET but is most informative in patients with undifferentiated GIT NET. 18F-FDG PET/CT can be used to diagnose undifferentiated tumors, monitor the treatment efficacy for radionuclide therapy with peptide receptors, and predict the disease course.

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