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Combined positron emission tomography and computed tomography to visualize lung cancer: false positive and false negative results (literature review)

Introduction. *Lung cancer is an acute problem in the world and in Kazakhstan, being the most common cause of cancer mortality. It is known that malignant tumor cells actively accumulate 18F-fluorodeoxyglucose during combined positron emission and computed tomography (PET CT).*

The purpose of this study *was to determine the role of combined PET CT in lung cancer diagnostics.*

Results. *Different authors report a varied diagnostic value of PET CT indicators in detecting malignant foci in the lungs. Meta-analysis of data of 12 studies conducted in 2012-2017 allowed deducing the average diagnostic values of PET CT in detecting malignant nodules in the lungs: the sensitivity was 0,819 (95% CI: 0,794-0,843), the specificity – 0,624 (95% CI: 0,582-0,665), positive predictive value - 0,802 (95% CI: 0,783-0,819), negative predictive value - 0,652 (95% CI: 0,618-0,684), and diagnostic accuracy – 0,649 (95% CI: 0,625-0,673).*

Conclusion. *PET CT has good diagnostic accuracy in assessing lung nodular formation, which is suspicious for malignancy. However, the estimated diagnostic value of PET CT indicators in detecting malignant focuses of the lungs varies. Therefore, PET CT is not a method of choice for primary lung cancer diagnostics. The researchers recommend using PET CT for patients with histologically verified lung cancer after.*

Keywords: *Positron emission computed tomography (PET CT), lung cancer.*

Relevance: Lung cancer (LC) dominates in total cancer morbidity and mortality in the Republic of Kazakhstan, ranking second and first, respectively [1-3]. Combined positron emission and computed tomography (PET CT) of the whole body using 18F-fluorodeoxyglucose (18F-FDG) is widely applied in cancer treatment practice [4]. PET CT utilizes higher metabolic activity of malignant cells that is manifested by a rapid and significant accumulation of 18F-FDG in the tumor. PET CT is widely used in differential diagnostics of lung nodules, for staging the process and evaluating the effectiveness of LC treatment. However, some authors note the low specificity of PET CT in LC diagnostics [5, 6].

The purpose of this study was to determine the role of combined PET CT in lung cancer diagnostics.

Materials and methods: The conducted literature review included the research data available in the Pubmed and e-Library databases for the period 2009-2018 by the keywords "Positron emission tomography (PET), computed tomography (CT), lung cancer, false positive, false negative, positron emission and computed tomography (PET CT), lung cancer." A total of 328 literary sources were found; 304 of them were excluded, as the described studies did not follow the selection criteria. Our literature review included 24 literary sources that met the selection criteria.

Results: G.E. Trufanov et al. [7] reported that PET CT results in patients with lung formations were false-positive in 3 (17.6%) out of 17 cases. The authors examined a group of patients (n=17) whose neoplasms were characterized by "low glucose uptake." Fourteen of them underwent a delayed PET CT scanning and demonstrated an increase in glucose uptake by the formation regarded as a malignant process. LC diagnosis was pathomorphologically confirmed in 11 patients, but in 3 patients, the histologic examination showed a benign lung process.

T.M. Babkina et al. [8] reported PET CT sensitivity of 96.5% at the specificity of 77.7% in LC.

According to A.M. Granov et al. [4], the PET sensitivity for LC was 91.8% at a specificity of 52.2% when using a generally accepted threshold criterion for a standardized level of radiopharmaceutical accumulation (SUV≥2.5) to differentiate between malignant and inflammatory processes in the lung. While trying to understand the reasons for the low PET specificity, the authors found the range of SUV values from 1.9 to 4.3 as hard to classify since SUV levels in patients with tuberculosis, Wegener's granulomatosis, and alveolitis fall within those limits. The metabolic activity values in focus did not exceed the generally accepted SUV value of ≥2.5 only in patients with pneumosclerosis. The researchers indicated the cut-off level (SUV≥2.5) to be efficient only in cases of distinguishing between LC and pneumosclerosis. Therefore, they proposed that threshold SUV values calculated depending on the scintigraphic sizes of foci should be used for LC detection.

In suspected LC, PET CT was false-positive in active inflammatory processes in the lung, including active pulmonary tuberculosis or fungal infection. False-negative results were observed in primary lung tumors presented by ground-glass opacity (GGO) and the presence of foci less than 7 mm [5, 9].

In the study by J. Kim et al. [10], 134 out of 188 GGO foci in the lungs detected by PET CT were pathological. Of them, 108 (80.6%) cases proved to be malignant after surgical treatment (bronchioloalveolar cancer (BAC) – 33, adenocarcinoma – 75), and 26 (19.4%) cases were benign (atypical adenomatous hyperplasia (AAH) – 22, focal fibrosis – 4). The authors suggested that PET-CT was not very informative in staging LC presented by GGO and queried the need for PET CT in differential diagnostics of LC presented by GGO.

According to L. Evangelista et al. [9], the PET CT sensitivity was 77% at a specificity of 89%. Out of 59 nodular formations in the lungs detected by PET CT, 3 results were false-positive and 5 false-negative after a biopsy. According to the figures provided by H. Chandarana et al. [12], PET CT showed an even lower sensitivity of only 61.6% in detecting small malignant nodules in the lung (<5 mm to ≥1.0 cm).

In the retrospective study by Li S. et al. [13], PET CT showed low diagnostic value for lung nodules (total patients – 298, sensitivity – 80.2%, specificity – 38%, positive predictive value – 86.5%, negative predictive value – 27.9%, the method accuracy – 73.1%). In the study of solitary lung foci in PET CT in 139 patients, the method sensitivity established by Zhao et al. was 88.8% at a specificity of 62.0% [14]. Cengiz A. et al. studied the PET CT capacity in detecting malignant lung tumors among 100 patients (malignant tumors – 62, benign neoplasms – 38). PET CT showed a significant variance in the differentiation of malignant and benign lung formations by SUVmax ($p<0.05$) criterion. The method sensitivity for malignant tumors was 82% at a specificity of 55% [15].

Liu Y. listed lung malignancies, which often produced false-negative results in PET CT in the form of absence or low 18F-FDG uptake by tumor node. The most common malignant processes with no or low 18F-FDG uptake were adenocarcinoma in situ and lung carcinoid. The tumor often showed no metabolic activity in the early LC stages what could be due to the small size of the formation. The malignant process in the form of a sub-solid lung nodule or a GGO syndrome could also produce a false-negative PET CT result [16]. The differentiation of a granulomatous inflammation from a malignant neoplasm using PET CT with 18F-FDG was challenging due to a large number of false-positive results. Ct turned out to be more informative for differential diagnostics of tuberculosis, sarcoidosis and lung cancer than quantitative assessment in PET CT [17]. Such processes as pneumoconiosis, organizing pneumonia, inflammation and infectious processes, as well as fibrotic changes in the lungs, could also actively uptake radiopharmaceuticals and thereby simulate a malignant process [18-20]. Given the presence of false-positive results in cases of suspected malignancy, the researchers recommended that patients without histologically verified diagnosis of lung cancer should not be exposed to PET CT due to the low specificity of this method in primary LC diagnostics [21].

Different authors provided varying assessments of PET CT diagnostic value in the detection of malignant foci in the lungs. Thus, the sensitivity varied from 80.2% to 95.1%, the specificity – from 34.7% to 88%, the positive predictive value – from 81.9% to 90.6%, the negative predictive value – from 27.9% to 94.8%, the method accuracy – from 73.1 to 87.5% [11, 12, 21-25].

According to the conducted meta-analysis of the database from 2012 to 2017 (12 studies included), the average PET CT value for the diagnostics of malignant nodules in the lungs was: the sensitivity – 0.819 (95% CI: 0.794-0.843), the specificity – 0.624 (95% CI: 0.582-0.665), positive predictive value – 0.802 (95% CI: 0.783-0.819), negative predictive value – 0.652 (95% CI: 0.618-0.684), diagnostic accuracy – 0.649 (95% CI: 0.625-0.673).

Based on the foregoing, the authors confirm that the 18F-FDG-PET-CT method has good diagnostic accuracy in assessing nodular formations in the lung suspicious for malignancy; however, it should not be considered as the method of choice for the lung disease diagnostics. It is better to include this method in the diagnostic algorithm along with other research methods in cases of suspected LC [26].

Conclusion: PET CT is a modern medical imaging method based on a quantitative assessment of radiopharmaceutical accumulation in tissues and organs of the human body vs. a standardized level. PET CT has good diagnostic accuracy in assessing lung nodular formation, which is suspicious for malignancy. Therefore, PET CT is not a method of choice for primary lung cancer diagnostics. The researchers recommend using PET CT for patients with histologically verified lung cancer. The interpretation of PET CT images of newly diagnosed lung cancer is underdeveloped; different researchers provide conflicting data. Therefore, further study is required to determine the role of this method in primary lung cancer diagnostics.

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