UDC: 616.24-007.63

*ZH.ZH. ZHOLDYBAY[1,2], Y.V. FILIPPENKO[2], ZH.K. ZHAKENOVA[2], G.S. AKHMETOVA[1], A. SCHULENBAEVA[2]*

[1]Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan
[2]Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan

# Association of chronic obstructive pulmonary disease and lung cancer on computer tomograms (literature review)

Relevance. *Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are an acute problem of modern medicine. COPD often accompanies LC. Computed tomography (CT) is a "gold standard" for lung examination. This paper provides an analysis of CT results at LC accompanied with COPD.*

Materials and methods. *The literature included sources from PubMed database for the period of 2000-2018 by keywords "COPD, lung cancer, CT". The literature review covers 65 literature sources meeting the selection criteria.*

Results. *The degree of airflow obstruction in COPD refers both to emphysema and to the thickening of the airway wall on CT sections. Emphysema visually identified on CT scans during screening for lung cancer was found to be a risk factor for lung cancer regardless of the degree of obstruction. A computerized analysis of emphysema severity of and airway diameter can help in determining the LC risk level.*

Conclusion. *Many researchers believe COPD to be a predictor of LC. Therefore, patients diagnosed with COPD shall periodically undergo CT to ensure early detection of LC.*

***Keywords:*** *chronic obstructive pulmonary disease, lung cancer, computed tomography (CT).*

***Relevance.*** Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are an acute problem of modern medicine. Thus, in 2013 mortality rates from respiratory diseases in the Republic of Kazakhstan (RK) amounted to 67,23‰ and increased by 10‰ (17.4%) compared to 2012 [1]. LC is leading in the structure of cancer morbidity in the RK. Computed tomography (CT) is a "gold standard" for lung examination [2]. COPD often accompanies LC. This paper provides an analysis of CT results with combined LC and COPD.

***Materials and methods.*** The literature review was based on the data of scientific research for 2000-2018 available in PubMed by keywords "COPD, lung cancer, CT". A total of 257 literary sources were found; 197 of the sources were not related to the topic of the review; practical cases, critical letters and commentary letters, as well as scientific studies without results of CT were excluded.

This literature review includes 60 literature sources meeting the selection criteria meaning that the selected studies are original scientific articles containing an analysis of CT results associated with LC and COPD.

***Results.*** COPD is a disease characterized by a restriction of air flow through the airways caused by a combination of abnormal inflammatory reactions in the small bronchi and lung parenchyma [3-5]. Over the past two decades, prevalence of COPD is higher in women than in men. At the same time, influence of the gender factor on COPD course has not yet been clearly explained [6]. COPD affects more than 200 million people worldwide and is expected to be the third leading cause of death in 2020 [7]. Cigarette smoking is the main cause of both COPD and LC [5]. The risk of LC development in patients with COPD is two to five times higher than in smokers without COPD [5, 8]. This observation suggests that chronic lung damage underlying smoking susceptibility is characteristic for both COPD and LC [5, 9]. Chronic inflammation in response to cigarette smoke is defined as a common etiologic factor, as it can lead to LC and to thickening of the airway wall and emphysema that often occur in COPD [10-12]. 85% of LC cases occur in smokers. In addition, smoking increases the risk of respiratory diseases including COPD and cardiovascular disease [13].

LC is the most common cause of cancer mortality [14]. LC is often diagnosed at a late stage already with distant metastases (in 40% of patients) and with a locally advanced process (30-35% of patients) [14]. LC is the main cause of death and hospitalization of patients with COPD. The degree of airway obstruction is a predictor of LC. There is a significant correlation between severity of emphysema and detectability of LC [15-17]. Several meta-analyzes also revealed a strong correlation between the degree of airway obstruction and LC presence. The risk of LC is associated with other clinical implications of COPD, such as acute inflammation of the respiratory tract that also require careful study [17-19].

The degree of airflow obstruction in COPD refers both to emphysema and to the thickening of the airway wall on CT scans [10, 32-34]. Emphysema visually identified on CT scans during screening for LC was found to be a risk factor for LC regardless of the degree of airway patency [8, 10, 35]. Computed tomography (CT) is one of the main methods of instrumental diagnosis of pulmonary pathology [20, 21]. The quantification of emphysema with CT allows learning more about its prevalence and causes in patients with COPD [22-24]. In addition, CT allows to identify the risk factors associated with the emphysema development rate, evaluate the response to pharmacological therapy [22, 24, 25]. Clinical studies show that low-dose CT can be clinically acceptable and an appropriate diagnostic method for screening for LC [22, 26-30]. The introduction of multi-slice computed tomography allows obtaining very thin, submillimetre CT images [31].

A computerized analysis of emphysema severity and airway diameter can help determining the LC risk level among smokers who underwent CT in screening or diagnosis [10]. One of possible approaches to assess tumour aggressiveness is to determine the extensional time of doubling based on lung tumour measurements from CT images [31, 36, 37].

COPD is associated with a worsening of overall survival in non-small cell LC. Kinsey C. et al. suggested that emphysema in LC can lead to tumour growth and a lower overall survival [38].

LC is the most common cause of cancer mortality [14]. LC is often diagnosed at a late stage already with distant metastases (in 40% of patients) and with a locally advanced process (30-35% of patients) [14]. LC is the main cause of death and hospitalization of patients with COPD. The degree of airway obstruction is a predictor of LC. There is a significant correlation between severity of emphysema and detectability of LC [15-17]. Several meta-analyzes also revealed a strong correlation between the degree of airway obstruction and LC presence. The risk of LC is associated with other clinical implications of COPD, such as acute inflammation of the respiratory tract, that also require careful study [17-19].

The degree of airflow obstruction in COPD refers both to emphysema and to the thickening of the airway wall on CT scans [10, 32-34]. Emphysema visually identified on CT scans during screening for LC was found to be a risk factor for LC regardless of the degree of airway patency [8, 10, 35]. Computed tomography (CT) is one of the main methods of instrumental diagnosis of pulmonary pathology [20, 21]. The quantification of emphysema with CT allows learning more about its prevalence and causes in patients with COPD [22-24]. In addition, CT allows to identify the risk factors associated with the emphysema development rate, evaluate the response to pharmacological therapy [22, 24, 25]. Clinical studies show that low-dose CT can be clinically acceptable and an appropriate diagnostic method for screening for LC [22, 26-30]. The introduction of multi-slice computed tomography allows obtaining very thin, submillimetre CT images [31].

A computerized analysis of emphysema severity and airway diameter can help determining the LC risk level among smokers who underwent CT in screening or diagnosis [10]. One of possible approaches to assess tumour aggressiveness is to determine the extensional time of doubling based on lung tumour measurements from CT images [31, 36, 37].

COPD is associated with a worsening of overall survival in non-small cell LC. Kinsey C. et al. suggested that emphysema in LC can lead to tumour growth and a lower overall survival [38].

COPD is associated with a worse overall LC prognosis at an early stage [38, 39]. Emphysema of the lungs leads to tissue destruction, directly leading to airflow obstruction and COPD. These tissue changes can potentially affect growth or other characteristics of lung tumours in this area [38, 40]. Recently, it has been demonstrated that alveolar hypoxia promotes the lung tumour growth during experiment on mice [38, 41]. Emphysema is associated with a marked ventilation/perfusion mismatch and leads to worsening of alveolar hypoxia [38, 42].

Since emphysema is considered to be the main component of COPD and not a separate disease, the influence of emphysema on LC development has not attracted much attention of scientists. However, several studies have reported that the visual identification of emphysema studies and severity of the emphysema course on CT scans estimated by quantification method are associated with an increased risk of LC [35, 43, 44]. A recent study on a large population within the National Lung Screening in the USA showed a correlation between quantitative CT measurements of emphysema and the LC development risk [43, 45]. In addition to detection of potentially malignant lung formations, the detection of emphysema also increases because CT allows visualizing areas of lung lesions [43, 46]. Because of the common pathogenetic process of the two diseases and the heterogeneous distribution of emphysema in the lungs, the local, more pronounced pulmonary tissue lesions caused by emphysema were found to indicate the location of cancer in the lungs [43, 47, 48].

Emphysema was associated with a marked ventilation/perfusion mismatch and lead to worsening of alveolar hypoxia [38, 42].

Since emphysema is considered to be the main component of COPD and not a separate disease, the influence of emphysema on LC development has not attracted much attention of scientists. However, several studies have reported that the visual identification of emphysema studies and severity of the emphysema course on CT scans estimated by quantification method are associated with an increased risk of LC [35,43,44]. A recent study on a large population within the National Lung Screening in the USA showed a correlation between quantitative CT measurements of emphysema and the LC development risk [43, 45]. In addition to detection of potentially malignant lung formations, the detection of emphysema also increases because CT allows visualizing areas of lung lesions [43, 46]. Because of the common pathogenetic process of the two diseases and the heterogeneous distribution of emphysema in the lungs, the local, more pronounced pulmonary tissue lesions caused by emphysema were found to indicate the location of cancer in the lungs [43, 47, 48].

Lim J. et al. suggested that LC localization might be associated with severity of emphysema clinical course in COPD, that is, central LC tends to occur in patients with minimal emphysema, whereas peripheral LC occurs in persons with pronounced emphysema. The researchers also evaluated the relationship between cancer localization (peripheral and central) and demographic and clinical characteristics including smoking and spirometry results to determine the factors for the central location of LC in patients with COPD and without it. Recently, new phenotypes of COPD have been recognized based on the severity of emphysema course. Thus, the lighter severity of emphysema and the reduced forced expiratory volume proved to be independent predictors of the central location of LC in COPD. Therefore, it might be necessary to consider additional screening tools along with high-resolution CT scans to detect central LC in patients with COPD with severe emphysema and predominant airway disease [49]. Gierada D. et al. established a relationship between LC and CT quantitative measurement of emphysema which showed that in the upper pulmonary fields it was most pronounced [45]. Bae K. et al hold the same opinion. According to their data, more pronounced emphysema was visualized in the upper parts of the lungs, as well as higher incidence of cancer was also observed in the upper parts of the lungs [43]. Kinsey C. et al. found that patients with a tumour arising on a background of more pronounced emphysema had a worse prognosis for overall survival than patients with a tumour arising on a background of less pronounced emphysema.

The National Lung Screening in the US showed that low-dose CT reduced LC mortality by 20% in comparison to chest radiography. The authors proposed to evaluate emphysema based on low-dose CT used in the screening for LC [50, 51]. Zurawska J.H. et al. suggested that spirometry and emphysema measurements based on CT data could be used to stratify the risk of LC for smokers, and that future screening for LC based on CT might involve a stratification risk to limit the cost of screening [52].

Based on lung screening studies in Pittsburgh, the authors identified radiation symptoms of emphysema on CT that had prognostic significance for LC, regardless of the severity of airway obstruction. Evaluation of COPD-LC screening has confirmed the emphysema presence as an independent variable for the risk of LC development [17, 35, 53, 54].

While cigarette smoking was a major risk factor for LC, other factors such as a family history of LC, preliminary diagnosis of a malignant tumour, occupational exposure of asbestos and a previous pulmonary disease such as COPD, might have also increased the risk of LC development [45, 55, 56]. CT of male smokers showed that carcinoma and COPD were often combine, with more often diagnosed squamous cell LC (51.7%). When COPD and LC were combined, the most frequent histological type of tumour in men was squamous cell cancer (60.7%), in women – adenocarcinoma (69.0%). The authors proposed mandatory periodic CT for early diagnosis of LC in patients with COPD [57]. Chubachi S. et al. offered two independent factors predicting LC in patients with COPD: the presence of emphysema or interstitial lung lesions or their combination on CT. According to their data, LC often developed on unchanged (places without emphysema) areas of the lung or in interstitial lung changes [58]. The study of biological pathways that put the grounds for the increased susceptibility to LC in patients with COPD would be important for screening, prevention, diagnosis and treatment of those two destructive pulmonary diseases [7].

Modern knowledge about the predictive value of quantitative CT measurements of emphysema and wall thickness in LC is limited. According to the authors, thickness of the airway wall is not an independent prognostic factor for LC onset, whereas emphysema is a reliable independent predictor of its occurrence [59].

Shin B. et al. have revealed that peripheral cancer was more often represented by adenocarcinoma. According to CT, adenocarcinoma more often developed around the periphery of pulmonary fields in the lungs without emphysema presence (58%), while squamous cell carcinoma often developed with underlying emphysema (61%) [60]. The researchers agree that LC is more often in patients with COPD than without this disease. Patients with COPD need screening for early detection of LC [61, 62].

***Conclusion.*** Thus, many researchers believe COPD to be a predictor of LC. Therefore, scientists include patients with COPD in a risk group for LC development and recommend them to undergo periodically CT for LC identification at an early stage of its development.

***References:***

*1. Zholdybay Zh.Zh., Zhakenova Zh.K., Akhmuldinova A.N. et al. Luchevaya semiotika i klinicheskoe techenie vnebol'nichnyh pnevmonij [Radiation semiotics and clinical course of community-acquired pneumonia ]// Bulletin of Kazakh National Medical University. – 2016. – №4. – P. 223-229*

*2. Zholdybay Zh.Zh., Zhakenova Zh.K. et al. Vozmozhnosti komp'yuternoj tomografii v rannej diagnostike raka legkih [Computed tomography capacity in lung cancer early diagnosis]// Onkologiya i radiologiya Kazahstana [Oncology and radiology of Kazakhstan]. – 2016. – №4 (42). – P. 51-53*

*3. Mizuho N. et al. Emphysema Quantification Using Ul- tralow-Dose CT With Iterative Reconstruction and Filtered Back Projection. // AJR. – 2016. – P. 1184-1192.*

*4. Rabe K.F., Hurd S., Anzueto A., et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.// Am J Respir Crit Care Med. – 2007. – Vol. 176. – P. 532–555.*

*5. Lim J. et al. Relationship Between Emphysema Severity and the Location of Lung Cancer in Patients With Chronic Obstructive Lung Disease. // AJR. – 2015. – Vol. 205. – P. 540–545.*

*6. Grabicki M. et al. COPD Course and Comorbidities: Are There Gender Differences? // Advances in Experimental Medicine and Biology. – 2018 Feb 28. – P. 1-9.*

*7. Vermaelen K., Brusselle G. Exposing a deadly alliance: nov- el insights into the biological links between COPD and lung can- cer. Pulmonary Pharmacology & Therapeutics. - 2013 Oct. – Vol. 26 (5). – P. 544-554.*

*8. De Torres J.P., Bastarrika G., Wisnivesky J.P. et al. Assessing the relationship between lung cancer risk and emphysema detect- ed on low-dose CT of the chest. // Chest. – 2007. – Vol. 132. – P. 1932-1938.*

*9. Schwartz A.G., Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease // Am J Respir Crit Care Med. – 2006. – Vol. 173. – P. 16-22.*

*10. Gierada DS. et al. Quantitative CT Assessment of Emphysema and Airways in Relation to Lung Cancer Risk // Radiology. – 2011. – Vol. 261, No. 3. – P. 950-959.*

*11. Brody J.S., Spira A. State of the art. Chronic obstructive pulmonary disease, infl ammation, and lung cancer // Proc Am Tho- rac Soc. – 2006. – Vol. 3(6). – P. 535-537 .*

*12. Lee G., Walser T.C., Dubinett S.M. Chronic inflammation, chronic obstructive pulmonary disease, and lung cancer // Curr Opin Pulm Med. – 2009. – Vol. 15(4). – P. 303-307 .*

*13. Sealock T., Sharma S. Smoking Cessation // Stat Pearls Publishing. – 2018, Jan 19. – P.10.*

*14. Constantinos T. Sofocleous et al. Ablation for the Management of Pulmonary Malignancies // AJR. – 2011, October. – Vol. 197. – P. 581-589.*

*15. F. Herth, M. Kirby, J. Sieren et al. The Modern Art of Read- ing Computed Tomography Images of the Lungs: Quantitative CT // Respiration. – 2018. – Vol. 95. – P. 8-17.*

*16. O.M. Mets, I. Isgum, Ch.P. Mol. Variation in quantitative CT air trapping in heavy smokers on repeat CT examinations // Eur Radiol. – 2012. – Vol. 22. – P. 2710-2717.*

*17. Carr L.L. et al. Features of Chronic Obstructive Pulmonary Disease as Predictors of Lung Cancer // CHEST. – 2018. – P. 1-44.*

*18. Fry J.S., Hamling J.S., Lee P.N. Systematic review with meta-analysis of the epidemiological evidence relating FEV1decline to lung cancer risk // BMC Cancer. – 2012. – Vol. 12(1). – P. 146.*

*19. Wasswa-Kintu S. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis // Thorax. – 2005. – Vol. 60(7). – P. 570-575.*

*20. Aziz Z.A. CT techniques for imaging the lung: recommen- dations for multislice and single slice computed tomography // Eur. J. Radiol. – 2004. – Vol. 52. – P.119-136.*

*21. Flohr T.G. Multi-detector row CT systems and imagereconstruction techniques // Radiology. – 2005. – Vol. 235. – P.756-773.*

*22. D. S. Gierada et al. Comparison of Standard- and Low-Ra- diation-Dose CT for Quantification of Emphysema. // AJR. – 2007, January. – Vol. 188. - P. 42-47.*

*23. Owsijewitsch M. et al. Quantitative Emphysema Distribution in Anatomic and Nonanatomic Lung Regions. // COPD: Journal of Chronic Obstructive Pulmonary Disease. – 2015. – P. 260-270.*

*24. Wang R. et al. Ultralow-Radiation-Dose Chest CT: Accura- cy for Lung Densitometry and Emphysema Detection // American Journal of Roentgenology. – 2015. – P. 743-749.*

*25. Saito Y. et al. Quantitative Assessment of Air Trapping Using Inspiratory and Expiratory Low-Dose Computed Tomography // Open Journal of Medical Imaging. – 2015. – P. 199-203.*

*26. Ji Y. Choo et al. Quantitative analysis of emphysema and airway measurements according to iterative reconstruction algorithms: comparison of filtered back projection, adaptive statistical iterative reconstruction and model-based iterative reconstruction // European Radiology. – 2014. – P. 799-806.*

*27. K. Joong Na et al. Quantification of emphysema with preoperative computed tomography has stronger association with pulmonary complications than pulmonary function test results after pulmonary lobectomy // The Journal of Thoracic and Car- diovascular Surgery. – 2014. – P. 915-920.*

*28. Ji Y. Choo et al. Quantitative Analysis of Lungs and Airways with CT in Subjects with the Chronic Obstructive Pulmonary Disease (COPD) Candidate FAM13A Gene // Journal of Computer Assisted Tomography. – 2014. – P. 597-603.*

*29. S. Soo Kim et al. Improved correlation between CT emphysema quantification and pulmonary function test by density correction of volumetric CT data based on air and aortic density // European Journal of Radiology. – 2014. – P. 57-63.*

*30. Wang X. et al. Trapping volumetric measurement by multidetector CT in chronic obstructive pulmonary disease: Effect of CT threshold // Medical Physics. – 2013. – P. 7.*

*31. Claudia I., Henschke et al. CT Screening for Lung Cancer: Part-Solid Nodules in Baseline and Annual Repeat Rounds // AJR. – 2016. – Vol. 207. – P. 1176-1184.*

*32. Kim W.J., Silverman E.K., Hoffman E. et al. CT metrics of airway disease and emphysema in severe COPD // Chest. – 2009. – Vol. 136 (2). – P. 396-404.*

*33. Nakano Y., Muro S. , Sakai H., et al . Computed tomograph- ic measurements of airway dimensions and emphysema in smok- ers. Correlation with lung function // Am J Respir Crit Care Med. – 2000. – Vol. 162 (3 pt 1). – P. 1102-1108.*

*34. Patel B.D., Coxson H.O., Pillai S.G., et al. Airway wall thick- ening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease // Am J Respir Crit Care Med. – 2008. – Vol. 178 (5). – P. 500-505.*

*35. Wilson D.O., Weissfeld J.L., Balkan A., et al. Association of radiographic emphysema and airflow obstruction with lung can- cer // Am J Respir Crit Care Med. – 2008. – Vol. 178(7). – P. 738-744.*

*36. Yankelevitz D.F. et al. Determination of malignancy in small pulmonary nodules based on volumetrically determined growth rates: preliminary results // Radiology. – 2000. – Vol. 217. – P. 251-256.*

*37. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening // Br J Radiol. – 2000. – Vol. 73. – P. 1252-1259.*

*38. Kinsey C. et al. Regional Emphysema of a Non–Small Cell Tumor Is Associated with Larger Tumours and Decreased Survival Rates. // Ann Am Thorac Soc. – 2015, Aug. – Vol. 12, No. 8. – P. 1197-1205.*

*39. Houghton A.M., Mouded M., Shapiro S.D. Common origins of lung cancer and COPD. // Nat Med. – 2008. – Vol. 14. – P. 1023-1024.*

*40. Zhai R. et al. The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection // Chest. – 2014. – Vol. 145. – P. 346-353.*

*41. Karoor V. et al. Alveolar hypoxia promotes murine lung tumor growth through a VEGFR-2/EGFRdependent mechanism // Cancer Prev Res (Phila). – 2012. – Vol. 5. – P. 1061-1071.*

*42. Kent B.D., Mitchell P.D., McNicholas W.T. Hypoxemia in patients with COPD: cause, effects, and disease progression. // Int J Chron Obstruct Pulmon Dis. – 2011. – Vol. 6. – P. 199-208.*

*43. Bae K. et al. Severity of pulmonary emphysema and lung cancer: analysis using quantitative lobar emphysema scoring // Medicine. – 2016. – Vol. 95:48(e5494). – P. 1-5.*

*44. De Torres J.P., Bastarrika G., Wisnivesky J.P., et al. Assess- ing the relationship between lung cancer risk and emphysema de- tected on low-dose CT of the chest // Chest. – 2007. – Vol. 132. – P.1932-1938.*

*45. Gierada D.S., Guniganti P, Newman BJ, et al. Quantitative CT assessment of emphysema and airways in relation to lung can- cer risk // Radiology. – 2011. – Vol. 261. – P. 950-959.*

*46. Omori H., Nakashima R., Otsuka N., et al. Emphysema detected by lung cancer screening with low-dose spiral CT: prevalence, and correlation with smoking habits and pulmonary function in Japanese male subjects // Respirology. - 2006. – Vol. 11. – P. 205-210.*

*47. Hohberger L.A., Schroeder D.R., Bartholmai B.J., et al. Correlation of regional emphysema and lung cancer: a lung tissue research consortiumbased study // J Thorac Oncol. – 2014. – Vol. 9. – P. 639-645.*

*48. Bishawi M., Moore W., Bilfinger T. Severity of emphysema predicts location of lung cancer and 5-y survival of patients with stage I non-small cell lung cancer // J Surg Res. – 2013. – Vol. 184. – P. 1-5.*

*49. Lim J.et al. Relationship Between Emphysema Severity and the Location of Lung Cancer in Patients With Chronic Obstructive Lung Disease // AJR. – 2015. – Vol. 205. – P. 540-545.*

*50. Nishio M. et al. Emphysema Quantification Using Ultralow-Dose CT With Iterative Reconstruction and Filtered Back Projection // American Journal of Roentgenology. - 2016. – Vol. 206:6. – P. 1184-1192.*

*51. National Lung Screening Trial Research Team, Aberle D.R., Adams A.M., et al. Reduced lung-cancer mortality with low-dose computed tomographic screening // N Engl J Med. – 2011. – Vol. 365. – P. 395-409.*

*52. Zurawska J.H., Jen R., Lam S. et al. What to do when a smoker's CT scan is "normal"? Implications for lung cancer screen- ing // Chest. – 2012. – Vol. 141. – P. 1147-1152.*

*53. Sanchez-Salcedo P., Wilson D.O., De-Torres J.P., et al. Improving selection criteria for lung cancer screening. The potential role of emphysema // American Journal of Respiratory and Critical Care Medicine. – 2015. – Vol. 191(8). – P. 924-931.*

*54. de-Torres J.P., Wilson D.O., Sanchez-Salcedo P., et al. Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD Lung Cancer Screening Score // American Journal of Respiratory and Critical Care Medi- cine. – 2015. – Vol. 191(3). – P. 285-291.*

*55. Marcus M.W., Raji O.Y., Field J.K. Lung cancer screen- ing: identifying the high risk cohort // J Thorac Dis. – 2015. – Vol. 7(Suppl 2). – P. S156-162.*

*56. Turner M.C., Chen Y., Krewski D., et al. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers // Am J Respir Crit Care Med 2007;176:285–90.*

*57. Zhao S., Nie X., Zhang L. et al. [Clinical Characteristics of 118 Cases of Chronic Obstructive Pulmonary Disease Complicat- ed with Primary Bronchopulmonary Carcinoma]. // Zhongguo Fei Ai Za Zhi. – 2017. – Vol. 20(8). – P. 538-542.*

*58. Chubachi S., Takahashi S., Tsutsumi A. et al. Radiologic features of precancerous areas of the lungs in chronic obstructive pulmonary disease // Int J Chron Obstruct Pulmon Dis. – 2017. – Vol. 12. – P. 1613-1624.*

*59. Aamli Gagnat A., Gjerdevik M., Gallefoss F. et al. Incidence of non-pulmonary cancer and lung cancer by amount of emphy- sema and airway wall thickness: a community-based cohort // Eur Respir J. – 2017, May 11. – Vol. 49(5).*

*60. Shin B., Shin S., Chung M.J. et al. Different histological subtypes of peripheral lung cancer based on emphysema distribution in patients with both airflow limitation and CT-determined em- physema // Lung Cancer. – 2017. – Vol. 104. – P. 106-110.*

*61. Ho C.H., Chen Y.C., Wang J.J. et al. Incidence and rela- tive risk for developing cancer among patients with COPD: a na- tionwide cohort study in Taiwan // BMJ. - 2017. – Vol. 7 (3). – P. e013195*

*62. Alaa M., Shibuya K., Fujiwara T. et al. Risk of lung cancer in patients with preinvasive bronchial lesions followed by autofluorescence bronchoscopy and chest computed tomography // Lung Cancer. – 2011, Jun. – Vol. 72(3). – P. 303-308.*