ANNOTATION

on PhD thesis of Panina Alexandra Sergeyevna entitled "Low-dose computed tomography in early diagnosis of lung cancer" presented as an application for the PhD degree on the specialty "6D110100" Medicine

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The relevance of research

Lung cancer is a serious medical and social problem both worldwide and in Kazakhstan. The relevance of the problem is associated with high morbidity and mortality rates. According to global statistics GLOBOCAN (2022), lung cancer is the most common oncological disease (12.4% of the total number of cases) and the main cause of death in the structure of oncopathology (18.7% of the total number of cases) (Bray F., 2024).

According to statistics from the oncology service of the Republic of Kazakhstan for 2022, lung cancer ranks second in the morbidity structure and first in the mortality structure. Despite the downward trend in morbidity and mortality rates, the percentage of lung cancer detection in the late stages remains high (74,2%) (Kaidarova D.R., 2022).

Chest X-ray and sputum cytology have been used for early diagnosis of lung cancer. However, international studies have not proven the effectiveness of these methods in early detection of lung cancer. (Adams J., 2023, Marshall H., 2013). According to the results of the conducted studies, high-resolution multispiral computed tomography is an informative method for diagnosing lung cancer (Sun K., 2021, Zhu L., 2023). However, the limitation is the radiation exposure to the patient during the study.

Currently, a search is underway for highly informative accessible methods of lung cancer diagnostics that allow minimizing the negative impact on the patient. Thus, for early diagnostics of lung cancer, the use of low-dose computed tomography (LDCT) is proposed, allowing diagnostic examination of a conditionally healthy population, with a dose of ionizing radiation of no more than 3 mSv (Kim L., 2018).

The large randomized trials The National Lung Screening Trial (NLST) and the Nederlands-Leuvens Longkanker Screenings Onderzoek Study (NELSON) showed that the use of LDCT in high-risk groups, including smokers with a smoking history of at least 30 and 25 pack-years, leads to a reduction in mortality from lung cancer by 20% and 44%, and the detection rate at the first stage was 63% and 40% (respectively) (Aberle D., 2012 старый источник, de Koning H., 2020).

However, despite the convincing results of NLST and NELSON, studies on LDCT in the early diagnosis of lung cancer continue in many countries around the world with the aim of optimizing selection criteria and increasing efficiency (Anuradha R., 2022).

According to a meta-analysis, the sensitivity of LDCT in lung cancer screening ranged from 68.5% to 93.8%, and the specificity from 73.4% to 99.2%. (Reck M., 2023). The variability in these values is due to differences in the populations studied, scanning parameters, image interpretation criteria and the number of studies, which highlights the need for further improvement of the methodology.

In improving the early diagnosis of lung cancer using LDCT, the possibilities of using modern artificial intelligence algorithms are being explored. Currently, there are a number of publications proving that the use of deep learning-based computer diagnostics for pulmonary nodule detection (DL-CAD) systems improves the diagnosis of lung cancer and reduces the time of interpretation of LDCT results. (Ardila D., 2019, Zhang Y., 2022). However, according to published data, the sensitivity of various DL-CAD systems ranges from 61.61% to 98.10%, and the false positive rate ranges from 0.125 to 32 per scan (Gu Yu., 2023), which is a limiting factor for the unanimous implementation of artificial intelligence elements in the interpretation of LDCT images. Factors affecting the variability of the above data include different deep learning models, image quality, and labeling. (Mastouri R., 2020, Park S., 2021, Cui X., 2021, Cellina M., 2023).

In connection with the above, the study of the possibilities of LDCT in the early diagnosis of lung cancer is a pressing issue and requires further improvement of the methodology with the development of more accurate data analysis algorithms, including the use of artificial intelligence (DL-CAD).

The aim of the study: improve early diagnosis of lung cancer using low-dose computed tomography.

The research objectives are:

1. To study the incidence and mortality rates of lung cancer in the Republic of Kazakhstan for 2009-2018 with the identification of risk factors.
2. To conduct low-dose computed tomography of the lungs of the conditionally healthy population in selected regions with high incidence and mortality from lung cancer and radon pollution.
3. To determine the diagnostic information content of low-dose computed tomography in the early diagnosis of lung cancer with the study of the radiation semiotics of pathological changes in the lungs.
4. To optimize the early diagnosis of lung cancer using LDCT and artificial intelligence based on deep learning (DL-CAD).

Research methods

Radiological method: low-dose computed tomography of the chest organs was used for early detection of lung cancer. The study was performed with an ionizing radiation dose of no more than 1 mSv, according to the order of the Minister of Health of the Republic of Kazakhstan dated August 25, 2022 No. ҚР ДСМ-90 on approval of the Sanitary Rules "Sanitary and Epidemiological Requirements for Radiation Hazardous Facilities". Scanning was performed on a high-resolution multispiral computed tomography scanner with a slice thickness of no more than 1 mm and image reconstruction in the axial, coronal and sagittal planes. The resulting images were interpreted according to the Lung-RADS classification.

Epidemiological method: a prospective cohort study was performed among the conditionally healthy population in the regions of Kazakhstan with high lung cancer morbidity and mortality, as well as with elevated levels of radon pollution. The study included men and women from regions with high lung cancer morbidity and mortality rates, aged 50 to 75 years, regardless of smoking status. Exclusion criteria: history of

cancer, severe concomitant diseases limiting LDCT, patient weight over 140 kg. Study participants filled out specially designed questionnaires with information on demographic data, risk factors and medical history.

Morphological method: histological examination. When pulmonary nodes suspicious for malignancy were detected, morphological verification was performed (surgical treatment, transthoracic biopsy, fibrobronchoscopy). The obtained material was sent for histological examination to confirm or exclude a malignant process.

Statistical method. Statistical methods with specialized software (SPSS, Excel) were used for data processing and analysis. Sensitivity, specificity, positive and negative predictive value of LDCT in detecting lung cancer were calculated. To assess the significance of differences between groups, χ^2 (chi-square) criteria were used for categorical variables and t-test for independent samples with normal distribution of quantitative data. With non-normal distribution, non-parametric methods (Mann-Whitney test) were used. Differences were considered statistically significant at $p<0.05$.

Object of study:

Data of 36,744 registered cases of lung cancer from the electronic registry of cancer patients 2009-2018.

Data of low-dose computed tomography of the lungs of 3,671 residents of the regions of the Republic of Kazakhstan with high incidence and mortality from lung cancer.

Data of a low-dose tomographic study of patients with 614 nodules in the lungs.

Subject of research: to determine target groups and improve the efficiency of early diagnosis of lung cancer in the Republic of Kazakhstan, it is necessary to study the incidence and mortality rates, risk factors, methods of diagnosing lung cancer, radiological semiotics of lung cancer in comparison with the results of pathomorphological examination.

The main claims submitted for defense:

High rates of lung cancer morbidity and mortality in the Republic of Kazakhstan are predominant in the Northern and Eastern regions with a direct dependence on radon pollution, prevalence in the male population, in the age group of 70-75 years.

1. Low-dose computed tomography is a highly sensitive and specific method for diagnosing lung cancer, allowing for increased detection of early stages.

2. Application of deep learning-based artificial intelligence (DL-CAD) in parallel reading improves sensitivity for pulmonary nodule diagnosis and reduces interpretation time.

Scientific novelty

For the first time, a prospective cohort study was conducted on the conditionally healthy population of regions with high morbidity, mortality and radon pollution, regardless of smoking status, using the method of low-dose computed tomography with the detection of early stages of lung cancer (article in the journal Web of Science Core Collection and Scopus Q2).

For the first time, a low-dose computed tomography (DL-CAD) interpretation protocol using artificial intelligence has been optimized to improve lung cancer diagnosis (author's certificate No. 49608).

Practical significance

The use of low-dose computed tomography improves early diagnosis of lung cancer.

The use of the DL-CAD system improves LDCT diagnostics of lung cancer by increasing diagnostic information and reducing interpretation time.

Personal contribution of the doctoral candidate: All results presented in the dissertation and having scientific novelty were obtained by the author personally. The author personally performed the low-dose computed tomography technique, as well as a complete statistical analysis of the data. The low-dose computed tomography method was introduced in the radiation diagnostics department of the Multidisciplinary Center for Oncology and Surgery of the East Kazakhstan region (implementation act No. 31-2019), Pavlodar Regional Oncology Dispensary (implementation act No. 26-2021) and Kostanay City Oncology Multidisciplinary Hospital (implementation act No. 9-2022). The author developed methodological recommendations "Low-dose computed tomography in the early diagnosis of lung cancer", which were introduced in the regions of the Republic of Kazakhstan (implementation acts). The author received the copyright certificate No. 49608: Optimized protocol for interpretation of low-dose computed tomographic images using artificial intelligence based on deep learning (DL-CAD).

Main results of the study

Analysis of epidemiological data for the period under study showed a moderate downward trend in morbidity (-9.4%) and a significant reduction in mortality from lung cancer (-32.5%), with a predominance of diagnosis at late (III-IV) stages. The percentage of detection of early stages (I-II) did not exceed 30.4%, which was observed in 2017.

High levels of morbidity and mortality, exceeding the national average, have been registered in seven regions: North Kazakhstan, Pavlodar, East Kazakhstan, Akmola, Kostanay, Karaganda and West Kazakhstan regions.

A statistically significant relationship was found between radon pollution and morbidity and mortality rates. A direct correlation was observed between lung cancer morbidity and mortality rates with radon pollution of indoor air (R=0.8 and 0.7, respectively) and water sources (R=0.6 and 0.6, respectively).

Analysis of risk factors showed that the odds ratio of lung cancer detection in men is 2.8 times higher than in women (OR=2.808, 95% CI: 1.718-4.589, $p<0.05$); the odds ratio of lung cancer detection in smokers is higher than in non-smokers (OR=2.448, 95% CI: 1.526-4.056, $p<0.05$) and in former smokers (OR=2.325, 95% CI: 1.068-5.060, $p<0.05$). Statistically significant data were obtained when comparing the age groups of 60-69 years versus 70-75 years and 50-59 years versus 70-75 years. The risk of lung cancer among participants in the 70-75 age category is higher than in the 50-59 and 60-69 age groups (OR=0.452, 95% CI: 0.251-0.815 and OR=0.327, 95% CI: 0.168-0.636, respectively, $p<0.05$).

The Cancer Detection Rate (CDR) was 3.5% among smokers and 1.4% among non-smokers.

Characteristic pathognomonic LDCT signs of lung cancer: subsolid type of structure, irregular shape, unclear, uneven and spiculated contours, dimensions greater than 31 mm, density values of 10-35 HU, presence of reaction of adjacent pleura and perifocal infiltration ($p<0.001$).

The sensitivity of low-dose computed tomography of the lungs in detecting lung cancer was 94.1%, specificity was 85.2%, the positive predictive value was 55.7%, the negative predictive value was 98.6%, and the accuracy was 86.7%.

The number of false-positive results was higher when DL-CAD was used as the first reading 698/1018 (68.5%) compared to the other three options and was statistically significant when using the McNemar test, $p<0.001$.

The use of DL-CAD as a parallel reading showed the most effective result with a sensitivity rate of 94.8%, with a false-positive rate of 22/443 (5.2%).

Conclusions:

1. The incidence and mortality rates from lung cancer in the Republic of Kazakhstan over a 10-year period have decreased moderately and unevenly by 9.4% and 32.5%, respectively, with a prevalence of late stages (the average rate over 10 years was 74.2%), prevalence in the Northern and Eastern regions with a high correlation coefficient (0.6-0.8) depending on radon pollution, prevalence of 4 times among the male population and in the age group of 70-75 years ($p<0.001$).

2. Low-dose computed tomography in selected regions with high rates of morbidity, mortality and radon contamination allowed to detect early stages of lung cancer in 39.2% of cases (31/79), which improved early diagnosis by 28.8%.

3. Low-dose computed tomography demonstrates high sensitivity of 94.1%, specificity of 85.2% and accuracy of 86.7% in diagnosing lung cancer. Statistically significant LDCT patterns of lung cancer are: subsolid type of nodule structure, irregular shape, unclear/uneven and spiculated contours, size more than 31 mm, density of 10-35HU, presence of adjacent pleural reaction and perifocal infiltration ($p<0.001$).

4. The application of deep learning-based artificial intelligence (DL-CAD) in parallel reading has high sensitivity for diagnosing pulmonary nodules (94.8%) and reduces interpretation time by 21.1%. ($p<0,001$).

Approbation of the research:

The main provisions and results of the dissertation were reported at:

1.XXV European Congress of Radiology, Veinna, Austria, 2019, oral presentation;

2.International Congress of Radiology "Multimodal approaches in diagnostic imaging", Bishkek, Kyrgyzstan, 2019, oral presentation;

3.VIII Eurasian Radiological Forum, July, Nur-Sultan, Kazakhstan, 2019, oral presentation;

4.76th Korean Congress of Radiology, Seul, Korea, 2020, poster presentation;

5.International Conference "Oncology of Kazakhstan. Yesterday, Today, Tomorrow", Almaty, Kazakhstan, 2021, oral presentation;

6. International Conference "Lung Cancer, Advanced Solutions", Almaty, Kazakhstan, 2021, oral presentation;

7. I International Congress of Ultrasound Diagnostics, Almaty, Kazakhstan, 2021, oral presentation;

8. VIII Congress of Oncologists and Radiologists, Turkestan, Kazakhstan, 2021, oral presentation;

9. IX Congress of Oncologists and Radiologists, Almaty, Kazakhstan, 2023, oral presentation;

10. XIV Congress of Oncologists and Radiologists of the CIS and Eurasia, 2024, oral presentation

11. At the extended meeting of the Department of Visual Diagnostics, protocol No. 13 dated 10.06.2024.

Publications:

The author has published a total of 15 scientific papers, including 10 papers on the topic of the dissertation, 4 in the List of Publications, an international peer-reviewed scientific journal with an impact factor according to JCR (indexed in the Web of Science Core Collection database, Science Citation Index Expanded, CiteScore percentile indicator is 66, in the Scopus database is Q2) - 1, in the materials of international conferences - 2, methodological recommendations - 1, author's certificate - 1, in other scientific publications - 2.

1. Panina A.S., Zholdybay Zh.Zh. Multispiral low-dose computed tomography in the early diagnosis of lung cancer (literature review) // Bulletin of KazNMU. - 2019. - No. 4. - P. 98-101.

2. Kaidarova D.R., Shatkovskaya O.V., Zholdybay Zh.Zh., Zhylkaidarova A.Zh., Panina A.S. Lung cancer in the Republic of Kazakhstan: age and gender characteristics // Oncology and radiology of Kazakhstan. - 2020. - No. 1 (55). - P. 4-10.

3. Panina A.S., Zholdybay Zh.Zh., Turkinbayev E.K., Seisenbayev T.N., Tusupova A.U., Mukhamedzhan A.A. Characteristics of nodular formations of Lung-RADS 4a and 4b categories detected during lung cancer screening using low-dose computed tomography // Oncology and radiology of Kazakhstan. - 2022. - No. 2 (64). - P. 19-23.

4. Panina A., Kaidarova D., Zholdybay Zh. et al. Lung Cancer Screening With Low-dose Chest Computed Tomography: Experience From Radon-contaminated Regions in Kazakhstan. //J Prev Med Public Health. - No. 3 (55), 2022. – R. 273-279.

5. Panina A.S., Zholdybay Zh.Zh., Akhmetova G.S., Akhmetova G.R., Ainakulova A.S. Lung cancer screening with low dose computed tomography: the republic of Kazakhstan experience (thesis) Abstract book of the European Congress of Radiology is a supplement to Insight into Imaging, 2019. Vienna, Austria, P -403.

6. Panina A.S., Zholdybay Zh.Zh., Kaidarova D.R., Shatkovskaya O.V., Zhylkaidarova A.Zh., Toktassynkyzy M. Feasibility of implementing LDCT in lung cancer screening in the Republic of Kazakhstan (abstract). Abstract book of the 76th Korean Congress of Radiology and Annual Delegate Meeting of the Korean Society of Radiology, 2020, Seoul, Korea, P - 414.

7. Kaidarova D.R., Panina A.S., Zholdybay Zh.Zh. Guidelines. Low-dose computed tomography in the early diagnosis of lung cancer. Almaty. KazNIIOR, KazNMU named after S.D. Asfendiyarov, 2021. - 44 p.

8. Author's certificate No. 49608. Optimized protocol for interpretation of low-dose computed tomography images using deep learning-based artificial intelligence (DL-CAD) / Panina A.S., Kaidarova D.R., Zholdybay Zh.Zh. publ. 12.09.2024.

9. Kaidarova D.R., Sagidullina G.G., Zholdybay Zh.Zh., Panina A.S., Ainakulova A.S., Toktasynkyzy M. Low-dose computed tomography in the early diagnosis of lung cancer: a pilot project // Oncology and radiology of Kazakhstan. - 2019. - No. 1 (51). - P. 18-19.

10. Kaidarova D.R., Shatkovskaya O.V., Zholdybay Zh.Zh., Panina A.S. Lung cancer epidemiology in the Republic of Kazakhstan // Oncology and radiology of Kazakhstan. – 2019. – No. 2 (52). – P.10–16.

Structure and volume of the dissertation work:

The dissertation work is presented on 109 pages of computer text, consists of an introduction, literature review, description of the material and research methods, results of own research, discussion of the results, conclusion, list of references with 218 sources. The work is illustrated with 22 figures and 16 tables.