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Lung cancer epidemiology in the Republic of Kazakhstan

Relevance: *Lung cancer (LC) was a rare disease in the early 20th century. However, the development of the tobacco industry, the increased environmental pollution, and increased longevity had contributed to the fact that LC became a world pandemic of the 20th and 21st centuries.*

The problem of LC epidemiology is relevant both in Kazakhstan and worldwide. The reasons for that are a significant LC prevalence, also among the working-age population, a rather high rate of late detection that complicates the efficient treatment, and high mortality.

Worldwide, LC is one of the most common cancers with a high mortality rate. According to WHO, lung, breast, and intestinal cancers make up the top three most common cancers. They are among the top five "killer cancers."

Purpose *of this study was to assess the dynamics of major indicators of the LC epidemiology in the regions of the Republic of Kazakhstan in 2014-2018 to detect the main trends in these indicators and develop measures to improve early detection of cancer, as well as to evaluate the effectiveness of regional oncology services.*

Results: *The trends in LC incidence, mortality, early detection, late detection, and 5-year survival in the regions of Kazakhstan were revealed, and an indirect assessment was made of the effectiveness of the regional oncological services to improve these indicators. According to the results of the evaluation of significant trends of indicators, it was decided to launch a pilot program for early detection of LC using low-dose computed lung tomography at the Kazakh Research Institute of Oncology and Radiology.*

Conclusion: *LC incidence and mortality in Kazakhstan remains an urgent problem. At that, in some regions, these indicators exceed the average republican values. Therefore, the early detection of LC is the principal organizational measure of public healthcare that can improve survival rates.*

Keywords: *lung cancer (LC), epidemiology, early detection.*

Introduction. The updated version of the world cancer database GLOBOCAN 2018 reports that the global cancer burden has increased up to 18.1 million cases and 9.6 million deaths from cancer [1].

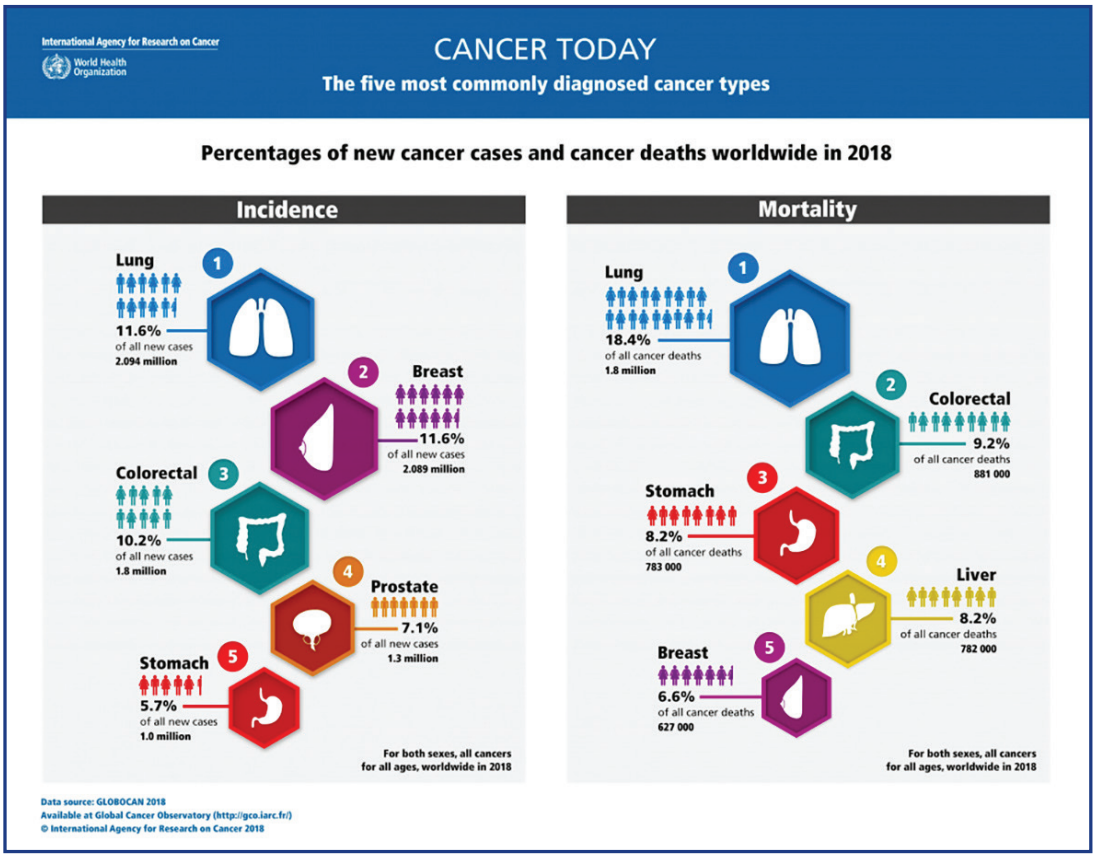

Figure 1 – Five cancer types most commonly diagnosed in the world in 2018

The International Agency for Cancer Research (IARC) informs that every fifth man and every sixth woman in the world are diagnosed with cancer during their lifetime. Probably, this is facilitated by a number of factors, in particular, the growing and aging population of the planet, and the increased exposure to socioeconomic risk factors for cancer. For growing economies, there is a treat of transition from cancer associated with poverty or infection to cancer, associated with a lifestyle more typical of industrialized countries.

In 2018, cancer incidence in the countries with a high Human Development Index (HDI) was 2-3 times higher than in the countries with low or medium HDI. The leading cancers have also changed all over the world in comparison with 2012 [1].

The World Health Organization (WHO) reports that LC ranks 1st both among the new cases of cancer, and the causes of death from cancer (Figure 1). In 2018, 2 094 million of LC cases were registered in the world amounting to 11.6% of all cancer cases (vs. 1.8 mln. (13%) in 2012).

Materials and Methods. The object of the study was information from the global cancer database GLOBOCAN 2018, information from statistical collections of Russia and the Republic of Kazakhstan (RK), as well as the articles by Russian and Kazakhstan authors. The data analysis for the RK took into account the administrative-territorial division into 16 regions and three cities of republican significance: Nur-Sultan, Almaty, and Shymkent. The traditional methods of statistical processing of the material were applied. The extensive, intensive, standardized, and age-specific incidence and mortality rates per 100 thousand population were calculated using methods recommended by the IARC. The standardized world population of WHO was used as a standard for calculating standardized indicators.

Results and Discussion.

LC incidence worldwide and in the Republic of Kazakhstan (per 100 000 population)

Lung cancer is considered the most common form of malignant neoplasms in most economically developed countries of the world. In many regions of the UK, especially in Scotland, lung cancer accounts for about one-third of all forms of cancer. At the same time, in Brazil in men it accounts for only 7%, in Iceland - 8%, in Sweden – 10% [2].

The survival rates differ depending on the type of cancer cells and the stage at detection. In average, only 12.6% of patients diagnosed with LC are still alive five years after the diagnosis [3].

In Russia, LC ranks 3rd after breast cancer and colon cancer in the overall incidence structure without gender. About 55 thousand new cases of LC are registered every year. In gender-specific incidence in Russia, LC ranks 1st in men and 6th in women.

High LC incidence (more than 30 cases per 100 000 population) is registered in the Baltic republics and Ukraine, the lowest incidence (less than 10.0) is in the Central Asian republics.

In Kazakhstan, LC today ranks 2nd after breast cancer in the overall cancer structure in both sexes. In gender-specific incidence in Kazakhstan, LC ranks 1st in men and 7th in women.

In the analyzed period (2014–2018), the LC incidence of lung cancer in both sexes in Kazakhstan was unstable. The decrease in incidence was followed by its growth the following year, but with a general slight decrease of -3.9% at the end of the observation period (Table 1).

Table 1 – The incidence of lung cancer in the Republic of Kazakhstan, by region, 2014-2018, per 100 000 population*

Year	Regions of the Republic of Kazakhstan (RK)																	RK
	Akmola	Aktobe	Almaty	Atyrau	East Kazakhstan	Zhambyl	West Kazakhstan	Karaganda	Kyzylorda	Kostanay	Mangystau	Pavlodar	North Kazakhstan	Turkestan	Shymkent city	Almaty city	Nur-Sultan city	
2014	36.4	18.0	17.0	17.6	35.1	16.4	27.0	27.7	12.1	34.5	11.1	36.59	45.0	SKR -8.9		14.9	16.9	**21.3**
2015	37.4	18.6	18.6	19.4	37.0	17.1	28.7	26.8	15.3	32.2	14.4	36.2	43.3	SKR – 9.9		19.1	19.7	**22.5**
2016	33.0	19.3	14.2	16.8	34.6	13.8	25.5	29.3	12.7	31.9	12.3	34.7	41.5	SKR – 8.8		15.6	18.0	**20.4**
2017	33.8	23.5	14.3	20.1	35.6	17.4	27.1	28.5	15.0	30.9	10.9	31.0	43.7	SKR – 9.1		18.3	14.6	**21.0**
2018	34.9	21.2	14.1	19.6	30.2	16.2	22.8	29.1	16.0	34.9	13.5	36.6	38.8	6.9	11.3	18.5	13.7	**20.5**
Dynamics for 5 years, %	-4.1	17.6	-17	11.7	-14.1	-1	-15	5.07	32.6	1.1	21.8	-0.02	-13.7	-22	27	24	-18.9	**-3.9**

Note: *The color highlights the regions with the highest LC incidence

LC incidence rates greatly differed by regions of the country: from the maximum level in the North Kazakhstan region to the minimum in the South Kazakhstan region (since 2018 divided into the Turkestan region and the city of Shymkent).

In 2018, incidence rates above the average republican level (20.5 per 100 000 population) were reported in 8 regions. In table 1, a color highlights 5 regions with the highest rates: East Kazakhstan (30.2), Akmola (34.9), Kostanay (34.9), Pavlodar (36.6) and the North Kazakhstan region (38.8 – the highest rate). In previous years (2014-2017), the situation in those regions was almost the same.

Low LC incidence was reported in Atyrau (19.6), Zhambyl (16.2), Kyzylorda (16.0), Almaty (14.1), Mangystau (13.5), Turkestan (6.9 – the lowest rate) regions, and the cities of Almaty (18.5), Nur-Sultan (13.7), and Shymkent (11.3).

The dynamics of LC incidence in the analyzed period (2014-2018) has varied by region (Figure 2). A decrease in incidence in 2018 relative to the level of 2014 was reported in 9 regions, an increase - in 8 regions. Thus, the LC incidence has significantly decreased in Nur-Sultan (-18.9%) and Turkestan region (-22% – the biggest decrease vs. 2014 figures in the South Kazakhstan region), Almaty region (-17%), West Kazakhstan (-15%), East Kazakhstan (-14.1%), and North Kazakhstan (-13.7%) regions. In three regions (Akmola, Zhambyl, and Pavlodar), a slight decrease was reported, in the remaining 8 an increase was reported, the most significant in Kyzylorda region (+ 32.6%), cities of Shymkent (+ 27%) and Almaty (+ 24%), as well as in Mangystau (+ 21.8%), Aktyubinsk (+ 17.6%), and Atyrau (+ 11.7%) regions.

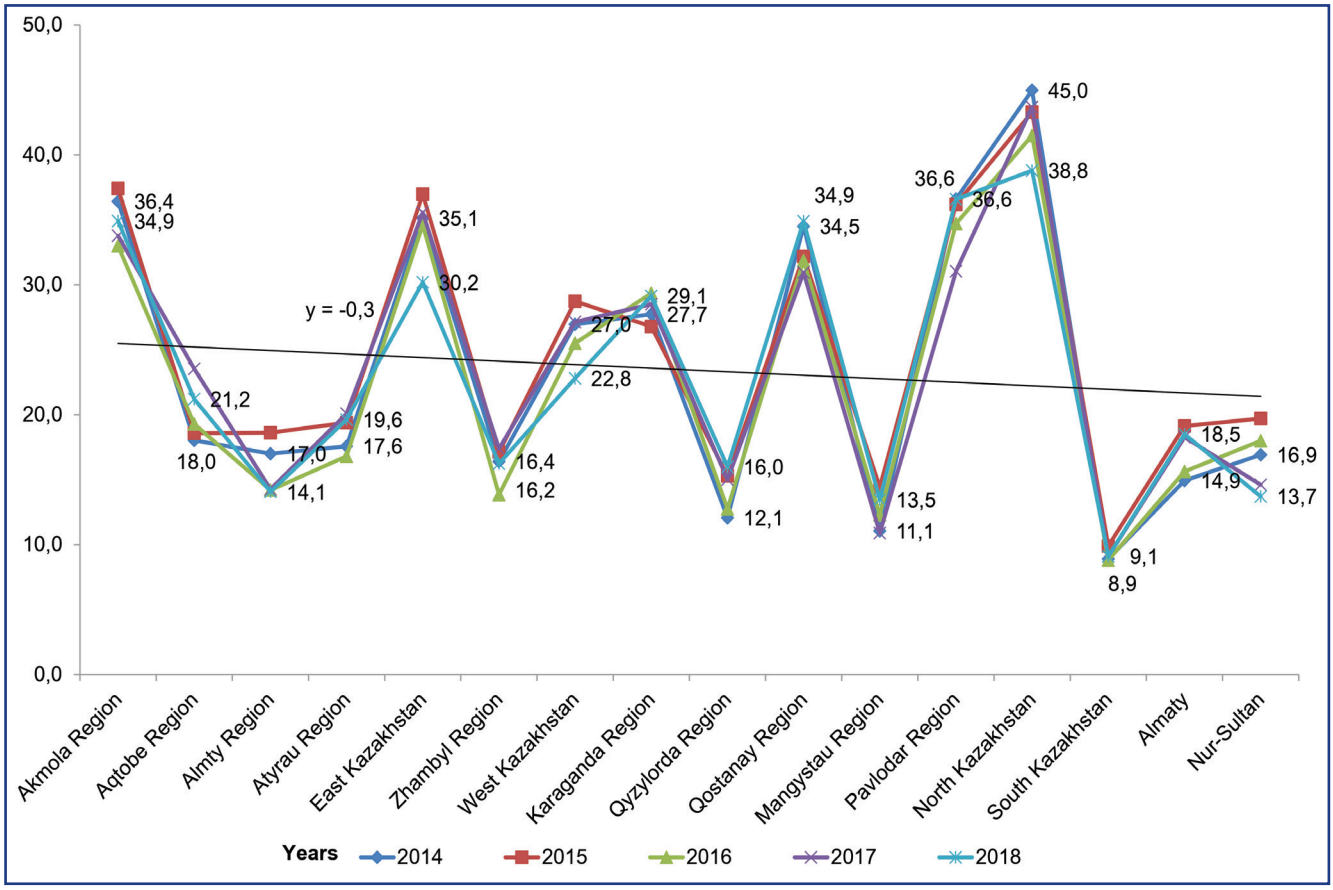

Figure 2 – Lung cancer incidence in the Republic of Kazakhstan, by regions, 2014-2018, per 100 000 population

LC incidence rate depends on many factors and is usually higher in industrialized than in rural areas. This indicator is also affected by age and gender, the prevalence of smoking, and the level of social well-being. Also, the incidence rate to a certain extent depends on the availability and quality of diagnostic assistance, the organization of cancer screening. The incidence is higher in the regions with better conditions for detecting the disease, proper formation of risk groups for periodic health examination, and high coverage of the population by medical examinations.

The mortality from LC in the world and the Republic of Kazakhstan (per 100 000 population)

The mortality from LC is dependent on its incidence, the timeliness of detection, and the quality of dynamic monitoring and treatment. LC mortality is continuously growing all over the world. WHO reports that in 2018, LC has occupied the first place among the other causes of death from cancer, with 2.1 million deaths per year. The highest LC mortality is registered in England, Finland, Austria, the Netherlands, and Belgium - 40-70 cases per 100 000 population. In CIS, LC mortality follows up the mortality from stomach cancer in men and the mortality from uterine cancer in women.

In the Republic of Kazakhstan, the national LC mortality has decreased by 17% since 2014, from 15.8 to 13.1 per 100 000 population. This rate was steadily decreasing year by year, which evidenced the systemic approach and effectiveness of the measures taken (Table 2).

In 2018, the highest mortality was registered in 5 regions highlighted in table 2: Karaganda (16.9), Akmola (19.6), Pavlodar (22.0) and North Kazakhstan (20.6), and East Kazakhstan (24.9 – the highest level) regions. These regions also had a high LC incidence rate. The mortality level above the Republican average was also noted in West Kazakhstan (14.7) and Kostanay (15.3) regions.

In 10 regions, the mortality rate was reported below the national average, with the lowest rate (5.4 per 100 000 population) in Turkestan region.

A positive dynamics was reported in 16 regions, with the only increase in the city of Shymkent (+ 41.4% vs. the rate in South Kazakhstan region in 2014).

Table 2 – The lung cancer mortality in the Republic of Kazakhstan, by region, 2014-2018, per 100 000 population*

Year	Regions of the Republic of Kazakhstan (RK)																	RK
	Akmola	Aktobe	Almaty	Atyrau	East Kazakhstan	Zhambyl	West Kazakhstan	Karaganda	Kyzylorda	Kostanay	Mangystau	Pavlodar	North Kazakhstan	Turkestan	Shymkent city	Almaty city	Nur-Sultan city	
2014	27.3	11.4	13.5	13.6	29.8	12.9	15.3	20.9	12.6	15.4	6.9	27.8	30.0	SKR – 6.2			13.0	**15.8**
2015	27.1	12.1	11.2	15.1	27.2	13.8	15.5	16.6	13.6	15.4	9.7	27.1	27.3	SKR – 7.6			11.3	**15.1**
2016	23.9	11.3	8.2	16.1	26.2	14.0	16.1	18.0	9.5	15.5	8.2	23.8	23.8	SKR – 6.3			11.6	**14.0**
2017	21.1	11.7	9.2	16.1	25.5	12.5	15.9	17.4	7.5	16.3	6.1	22.3	22.9	SKR – 7.2			12.0	**13.7**
2018	19.6	11.0	8.6	11.1	24.9	12.4	14.7	16.9	9.4	15.3	6.1	22.0	20.6	5.4	8.8	13.0	12.8	**20.5**
Dynamics for 5 years, %	-28	-3.9	-37	-18	-16.5	-4.4	-4.1	-19	-25	-0.9	-12	-21	-31.3	-13	41.4	-20.3	-17	**-3.9**

Note: *The color highlights the regions with the highest LC mortality

Early and late detection of lung cancer in Russia and the Republic of Kazakhstan

The early detection of cancer has a positive impact on cancer mortality rate. It also characterizes the effectiveness of the national primary health care service and is achieved by means of preventive examinations of population, mainly the risk groups, the propaganda of the obligation to seek medical help early in the presence of the first symptoms of the disease, as well as the quality of cancer diagnostics.

According to the latest data published by the P.A. Herzen Moscow Scientific and Research Oncology Institute, in 2017 in Russia, about 40% of newly diagnosed malignant neoplasms were detected at stage III-IV of cancer. Late detection decreases the likelihood of positive treatment outcome and is associated with quite high one-year mortality (22.5%; according to alternative estimates, it exceeds 26%). Almost 2 million patients (1,958,223), or 53.9% of all patients with malignant neoplasms registered at oncological institutions, have been registered for 5 years or more (for comparison, in 2016 this rate was 53.3%) [4].

Table 3 – Early detection (stage I-II) of lung cancer in the Republic of Kazakhstan, by region, 2014-2018, %

Year	Regions of the Republic of Kazakhstan (RK)																	RK
	Akmola	Aktobe	Almaty	Atyrau	East Kazakhstan	Zhambyl	West Kazakhstan	Karaganda	Kyzylorda	Kostanay	Mangystau	Pavlodar	North Kazakhstan	Turkestan	Shymkent city	Almaty city	Nur-Sultan city	
2014	26.1	37.2	34.9	22.2	30.9	31.8	31.7	15.9	25.8	30.8	55.4	30.4	27.7	SKR – 12.6			21.1	**27.5**
2015	30.8	34.5	27.9	23.6	37.1	29.2	26.3	21.2	36.2	21.8	44.3	30.8	29.0	SKR – 18.9			22.5	**28.3**
2016	35.1	32.3	18.6	21.0	36.5	19.2	25.8	15.6	31.6	26.4	42.9	29.5	35.7	SKR – 14.8			17.9	**26.5**
2017	29.7	41.7	27.2	32.2	37.3	24.7	33.3	21.8	49.1	33.1	47.1	28.6	37.4	SKR – 9.3			29.4	**30.4**
2018	28.8	30.9	24.7	29.3	34.5	20.0	34.3	21.8	36.5	21.3	41.1	28.3	36.4	16.8	17.8	26.5	27.0	**27.5**
Dynamics for 5 years, %	10	-17	-29	32	12	-37	8	37	42	-31	-26	-7	32	33	41	26	2	**0**

Note: *The color highlights the regions with the highest rates of early detection of lung cancer

In Kazakhstan, the early detection rate (at stages I-II) was unstable. The growth alternated with a decrease, but in total, for the period, the change without dynamics was 27.5%.

In 2018, the highest early detection rate was reported in 6 regions: Aktobe (30.9%), West Kazakhstan (34.3%), East Kazakhstan (34.5%), North Kazakhstan (36.4%), Kyzylorda (36.5%), and Mangystau (41.1% – the best rate) regions. The rate above the Republican average (27.5%) was also noted in Pavlodar (28.3%), Akmola (28.8%), and Atyrau (29.3%) regions.

In the remaining 8 regions, early detection was lower than the national average, with the worst situation in the Turkestan region (16.8%).

In the analyzed period, the late detection of lung cancer (stage IV) across Kazakhstan was almost stable and ranged from 22.8% in 2015 to 23.7% in 2016. At the end of the period, it was equal to 23% (table 4).

The high rate of late detection of lung cancer in 2018 was reported in 5 regions: East Kazakhstan (26.7%), Karaganda (28.8%), Turkestan (31.4%) regions, the cities of Shymkent (26.2%), and Nur-Sultan (35.5% – the highest rate). The average Republican rate of late detection (23%) was exceeded in 4 more regions: Almaty (23.4%), Kostanay (23.6%), Akmola (24.7%), and Pavlodar (25.3%) regions. Lower rates of late detection were reported in 8 regions: the city of Almaty (21.1%), Aktobe (19.4%), North Kazakhstan (19.2 %), Mangystau (18.9%), Atyrau (12.2%), Kyzylorda (11.1%), and West Kazakhstan (10% – the best result) regions.

Table 4 – Late detection (stage IV) of lung cancer in the Republic of Kazakhstan, by region, 2014-2018, %

Year	Regions of the Republic of Kazakhstan (RK)																	RK
	Akmola	Aktobe	Almaty	Atyrau	East Kazakhstan	Zhambyl	West Kazakhstan	Karaganda	Kyzylorda	Kostanay	Mangystau	Pavlodar	North Kazakhstan	Turkestan	Shymkent city	Almaty city	Nur-Sultan city	
2014	26.5	16.6	19.8	10.1	30.9	11.0	11.2	34.4	19.1	28.1	13.8	24.1	21.3	SKR – 24.7			14.7	**23.1**
2015	33.5	23.0	18.9	15.5	24.6	14.6	17.0	26.7	13.8	30.7	14.8	25.6	23.3	SKR – 22.6			19.0	**22.8**
2016	24.9	21.7	28.7	20.0	28.2	22.6	20.6	25.1	8.2	27.2	11.7	25.1	19.1	SKR – 24.7			17.1	**23.7**
2017	26.8	20.3	23.5	17.4	31.5	17.9	6.7	27.3	9.5	22.2	17.1	25.4	15.1	SKR – 27.4			23.6	**23.3**
2018	24.7	19.4	23.6	12.2	26.7	16.1	10.0	28.8	11.1	23.6	18.9	25.3	19.2	31.4	26.2	21.1	35.5	**23.0**
Dynamics for 5 years, %	-7	17	19	21	-13	46	-11	-16	-42	-16	37	5	-10	27	6	44	42	**-1**

Note: *The color highlights the regions with the highest rates of late detection of lung cancer

In the dynamics of over the five years under study, the late detection rate has decreased in 7 regions and increased in 10 regions.

5-year survival of LC patients

5-year survival of LC patients is an integrated indicator of the availability and quality of cancer care provided to the population, starting from the stage of primary health care, and depends on the timeliness of pathology detection, the quality of diagnosis and the given treatment.

The lack of clinical manifestations of early LC often leads to its late detection. Smoking worsens the course of the disease as it promotes cancer with severe KRAS mutation, which has a very poor prognosis when treated with standard chemotherapy. Effective treatments for this type of mutation are absent worldwide. The average life expectancy of such patients is 2-6 months from the start of clinical manifestations. The only way to increase life expectancy for such patients is to detect LC at an early stage, before clinical manifestations [5].

Table 5 presents the latest data on observed and relative survival in a European study conducted under the auspices of the IARC. In most countries, one-year survival was 20-30%; five-year survival was 6-15%. In Russia, survival rates were available only in the Population Cancer Register of St. Petersburg. Observed survival rates across countries varied significantly.

Table 5 – Observed (o) and relative (r) survival rate of lung cancer patients in European countries* [6]

Countries	Men						Women					
	1-year		3-year		5-year		1-year		3-year		5-year	
	o	r	o	r	o	r	o	r	o	r	o	r
Austria	34	35	14	15	9	11	32	33	18	19	14	15
England	21	22	7	9	5	7	21	22	8	9	6	7
Germany	30	32	10	12	8	10	33	34	16	17	13	15
Denmark	23	24	7	8	5	6	25	26	9	9	6	7
Iceland	35	37	16	18	10	12	38	39	15	17	11	13
Spain	30	31	13	14	11	13	31	31	16	17	13	15
Italy	32	33	11	13	8	10	30	31	13	14	9	11
Netherlands	38	40	14	16	10	12	42	43	18	19	13	14
Poland	27	28	9	10	6	7	27	28	10	11	8	10
Russia (Saint Petersburg**)	38	40					38	40				
Slovakia	32	33	12	14	10	12	32	34	19	21	16	19
Slovenia	30	31	10	11	6	8	26	27	10	11	6	7
Finland	39	40	13	15	9	11	39	41	15	17	10	12
France	40	41	15	17	11	13	42	43	24	25	18	20
Switzerland	38	40	15	17	10	12	38	39	16	17	10	12
Sweden	30	32	10	12	7	9	33	33	13	14	10	11
Scotland	21	23	7	8	5	6	22	22	8	9	12	14
Estonia	29	30	8	9	5	7	32	33	16	18	12	14

* Eurocare-II Study (1995-1989); ** Data from PCR for 1995.

In the Republic of Kazakhstan, the 5-year survival of patients, first registered for LC in 2012, was 6.9%. This rate varied by regions of the country, from 2.5% in West Kazakhstan to 11.5% in Kyzylorda (table 6).

Table 6 – 5-year survival rate of patients with lung cancer by Kaplan-Meier among the patients first registered in Kazakhstan in 2012

Name of regions	Total number of patients newly diagnosed in 2012	Number of deaths of newly diagnosed patients in 2012-2018	Absolute number of lung cancer patients living for 5 years or more	5-year survival rate,%
Akmola	226	214	12	5.3%
Aktobe	156	141	15	9.6%
Almaty	287	266	21	7.3%
Atyrau	89	84	5	5.6%
EKR	451	431	20	4.4%
Zhambyl	147	140	7	4.8%
WKR	158	154	4	2.5%
Karaganda	397	378	19	4.8%
Kyzylorda	131	116	15	11.5%
Kostanay	300	279	21	7.0%
Mangistau	59	53	6	10.2%
Pavlodar	298	276	22	7.4%
NKR	230	208	22	9.6%
SKR	230	212	18	7.8%
Nur-Sultan city	140	128	12	8.6%
Almaty city	249	222	27	10.8%
Republic of Kazakhstan	**3548**	**3302**	**246**	**6.9%**

The result was higher than the national average in 10 out of 16 regions (before the split of the South Kazakhstan region into the Turkestan region and the city of Shymkent): Kyzylorda (11.5% – the best result), Mangystau (10.2%), North Kazakhstan (9.6%), Aktobe (9.6%), South Kazakhstan (7.8%), Pavlodar (7.4%), Almaty (7.3%), and Kostanay (7%) regions, as well as in the cities of Nur-Sultan (10.8%) and Almaty (8.6%).

Low 5-year survival rate was reported in 6 regions: Atyrau (5.6%), Akmola (5.3%), Zhambyl (4.8), Karaganda (4.8%), East Kazakhstan (4.4%), and West Kazakhstan (2.5% – the worst result) regions.

At that, a high 5-year survival rate of lung cancer patients in Kyzylorda region was achieved against the background of high early detection and low late detection of cancer, which was completely logical.

Cancer control activities, including LC

In 2017, the World Health Assembly has adopted the resolution "Cancer prevention and control in an integrated approach" (WHA70.12), in which it called on governments and WHO to accelerate actions aimed at achieving the goals for reducing early cancer mortality set in the Global Plan of Action and the United Nations Sustainable Development Agenda until 2030.

Kazakhstan, in its actions to reduce cancer mortality, including LC, is guided by the Comprehensive Cancer Control Plan for 2018–2022 adopted by the statement of the Government of the Republic of Kazakhstan No.395 dated June 29, 2018. This Plan envisages a number of state-funded measures to improve and develop cancer services, revision of treatment standards, inter-institutional approach to the prevention of all types of cancer.

In 2018, Kazakh Institute of Oncology and Radiology has launched a pilot program for early diagnostics of lung cancer using low-dose computed tomography (LDCT). The institute has arranged a consultative "hub center" which interprets all LDCT images obtained under the pilot program. Suspected patients are further examined locally. The technique of digitalization of computed tomographic studies allows receiving a "second opinion" from the specialists of the "hub center" in a short time and without the patient's participation. The pilot program covers East Kazakhstan and Pavlodar regions, where the LC incidence exceeds the national average level. Today, the pilot program is being expanded to cover more regions.

This program provides for a comprehensive study including all the processes, from screening and verification to LC treatment. The exposure dose is comparable to the traditional chest X-ray and is less than 1 mSv.

In 2018, more than 1,000 patients were examined; 250 pathologies were found, of them, 15 were LC cases.

Conclusion: The LC incidence and mortality in Kazakhstan remain an acute problem; at that, in some regions, these indicators exceed the national average. Such regions require a wide use of modern methods of LC diagnosis and treatment.

LC can be successfully treated when detected at an early stage. Therefore, adequate early detection is the principal organizational measure of public healthcare that can improve survival rates. Timely sparing organ preservation treatment allows preserving working capacity and improving the social rehabilitation of patients.

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