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№2 (52) 2019

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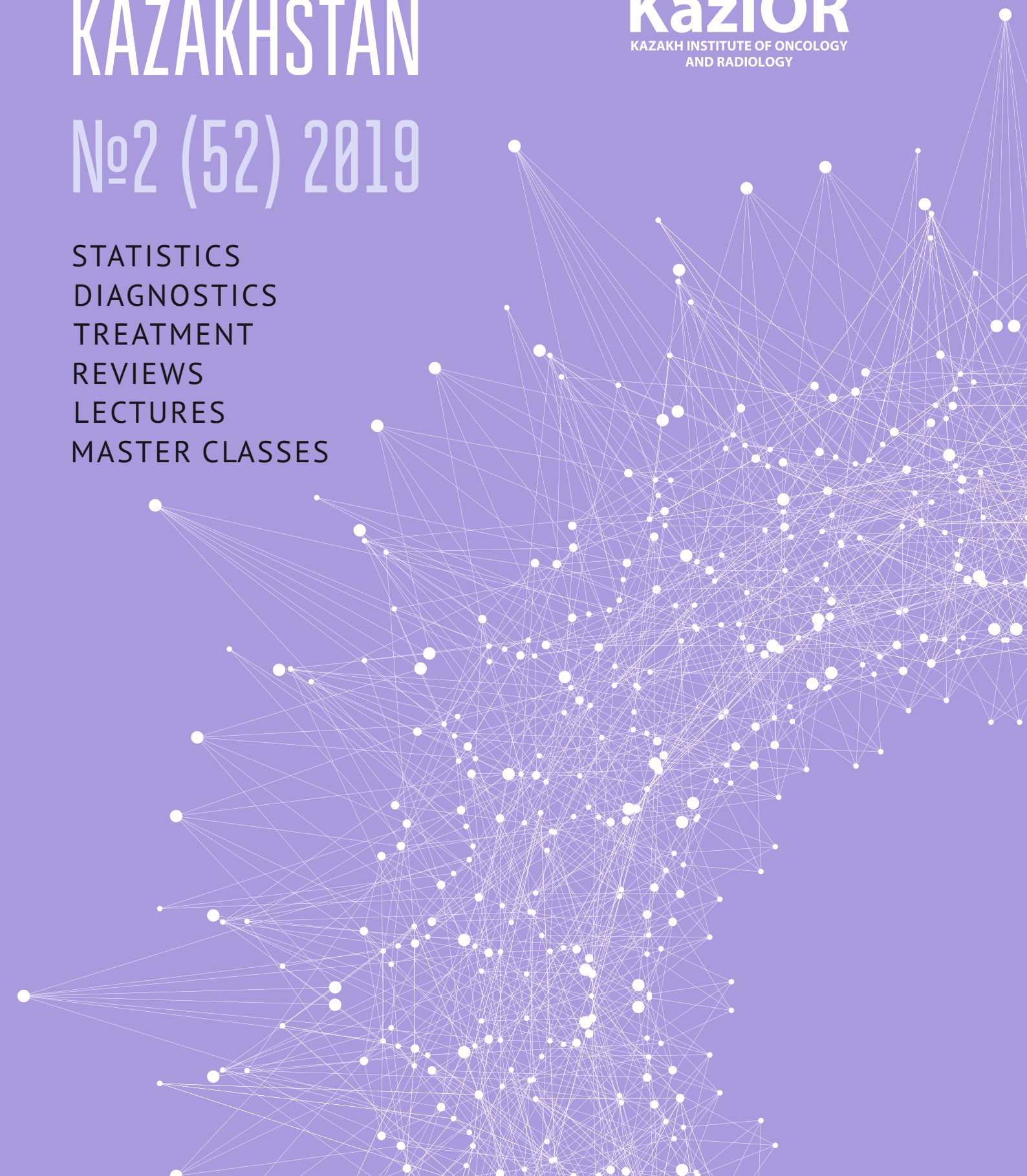

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LITERATURE REVIEW

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Hodgkin's lymphoma: epidemiological features, the current epidemiological situation in the regions of Kazakhstan

Relevance: *The diseases of the lymphoid and hematopoietic systems, including lymphomas, are among the top ten in the overall structure of oncopathologies. In Kazakhstan, they rank 4th accounting for about 5% of the total number of cancers; at that, hemoblastoses rank 8th in the structure of mortality.*

Hodgkin's lymphoma (HL) is one of the most common malignant lymphoid tumors. HL makes up no more than 0.5% of the total cancer burden worldwide; however, its unusual biology, epidemiology, and response to treatment attract close attention. The epidemiology of malignant lymphomas varies within and between geographic regions.

Purpose of the study: *to reflect the specifics of HL epidemiology in Kazakhstan.*

Results: *In 2018, 4611 patients were on file with malignant lymphoma. The absolute incidence of lymphoma was 794 cases per year (4.3‰), with an increase of 7.1% vs. 2017.*

The epidemiology of malignant lymphomas varied within and between geographic regions. The highest incidence of lymphoma was registered in Akmola, Karaganda, Qostanai, Pavlodar, East Kazakhstan, West Kazakhstan, and North Kazakhstan regions, and Nur-Sultan. It was partially associated with the ethnic structure of the population and might be associated with access to diagnostics.

The average national mortality rate was 1.8%000. The highest mortality rate from malignant lymphomas was registered in Pavlodar, East Kazakhstan, North Kazakhstan, Qostanai, and Karaganda regions.

Conclusion: *Certain regional dependence is traced both in incidence and, as a result, in mortality from lymphomas.*

Keywords: *Hodgkin's lymphoma, epidemiology, incidence, mortality, region, neoplasm.*

Introduction: Hodgkin's lymphoma (HL) is a malignant neoplasm from lymphoid tissue of B-cell origin. Its morphological substrate is composed of giant multinuclear Berezovsky-Reed-Sternberg cells and mononuclear Hodgkin cells. These types of cells are located in a kind of cell cluster – a "granuloma" formed by a mixture of tumor and non-tumor reactive cells such as lymphocytes, neutrophils, and plasma cells, sometimes surrounded by collagen fibers. The Berezovsky-Reed-Sternberg cells are derived from the B-cells of germinal centers of lymphatic tissue. They make up only about 1% of the entire tumor mass.

HL is a rare neoplasm. Its frequency varies greatly depending on age, gender, ethnicity, geographical location, and socio-economic status.

Although HLs make approximately 0.67% of the total cancer incidence, they account for about 30% of all lymphoma cases. It is important to note that every sixth oncologic diagnosis at the age of 15 to 24 is HL [1].

LH incidence is higher in more developed regions of the world, and lower in Asia; it is higher in men than in women. In the United States in 2013, about 9 300 new LH cases were registered; the annual incidence was 2.8 per 100,000 people [2].

A distinctive feature of HL epidemiology is its age variability at diagnosis. In industrialized countries, this is represented by a well-known bimodal curve having two peaks: the biggest one refers to young people (15–34 years old), and the second one observed at a later age (over 50 years old). These peaks represent mainly different subtypes of the disease: the nodular sclerosis variant is predominant at earlier peak age, and the mixed cell variant prevails at a later peak age [3].

Despite the relatively low incidence and low risk throughout life, HL accounts for 15% of all cancer cases in young people and has a significant impact on their quality of life.

Various epidemiological studies of HL conducted these days shall provide a better understanding of the nature of this disease and allow revealing the geographical, ethnic, socio-demographic, and economic factors influencing the development of this pathology.

Purpose of this work was to reflect the epidemiological features of HL in Kazakhstan.

Materials and methods: Global epidemiology of HL was analyzed based on data from the International Agency for Research on Cancer (IARC), GLOBOCAN 2012 [4], and the European Mediterranean Mediterranean Research Group [13]. Data on HL mortality and temporal trends for the covered Mediterranean countries were obtained from the World Health Organization (WHO) online mortality database [5]. The statistical data of the oncological service of the Republic of Kazakhstan for recent years was used to analyze the incidence, mortality, late detection, distribution by regions of Kazakhstan, and the dynamics of HL incidence. From now on we refer to the classic version of HL.

Results and Discussion

Hodgkin lymphoma epidemiology, global data

The WHO classification of lymphoid neoplasms is still evolving to account various variants of lymphoproliferative diseases which include not only HL, non-Hodgkin lymphomas (NHL) but also plasma cell neoplasms and lymphoid leukemias [6]. In 2012, nearly 566,000 new cases of lymphoma were registered worldwide, and about 305,000 deaths from this disease were reported [7]. Each variant of lymph-

oproliferative disease in principle does not matter much in the overall picture of the incidence of malignant neoplasms, but in the aggregate lymphomas rank 7th among oncopathologies detected all over the world [7].

According to GLOBOCAN, more than 385,000 new NHL cases and almost 66,000 HL cases were registered in 2012, and about 200,000 deaths from NHL and more than 25,000 deaths from HL [8]. New cases of NHL are equally often detected in regions with high, medium, and low incomes; however, the mortality rate was higher in middle-income and low-income countries (62%). In the same year, the vast majority of new cases and deaths from HL (56% and 75%, respectively) were registered in low-income regions. Projections show that both incidence and mortality rates for NHL and HL will increase by 2035, possibly due to improved diagnostic methods, industrialization, population aging, and an increase in HIV infection in some regions [8–9].

In 2012, HL cases accounted for no more than 0.5% of the total cancer burden worldwide; however, unusual biology and epidemiology and the response of HL to treatment attract close attention [8]. The overall frequency of HL varies considerably in the whole world. The pathogenesis of this geographical discrepancy is unknown; however, environmental and lifestyle factors were theorized as potential factors.

Unlike NHL, which shows an exponential increase in age-related incidence, age-related incidence indices of HL are bimodal, with the first peak in the European, American, Latin American and Australian populations occurring between the ages of 15 and 34, and the second after 60 years. In middle-income countries, the incidence of HL is high in early childhood and among the oldest age groups. A high incidence in childhood is associated with an increased risk of a young adult HL variant which indicates a delay in contact with the common infectious agent, whereas children living in less favorable conditions have a high incidence of lymphomas.

Progress in treatment, the improvement of diagnostic capabilities, and the access to medical care made HL largely curable in many parts of the world. Reported mortality has declined by more than 75% in North America, Western Europe, and Japan [9]. A noticeable decrease in HL mortality was also observed in most countries of Latin America, except for Cuba, Costa Rica, Mexico, and Venezuela.

In 1971, an international survey on HL showed that the distribution of bimodal age in the Western world correlated with the level of socio-economic development of the population. In developing countries, the HL incidence was relatively high in boys but low y young adult men, while in the developed regions, the incidence of HL was low in children, but high – in young people. Other evidence suggested that a mixed cell or lymphocyte subtype prevailed in developing regions, and a nodular sclerosis subtype dominated in developed regions. The ecological correlation between the socioeconomic level and the HL incidence has shown the opposite role of the child's environment in relation to the risk of HL in children and young people. One model suggested that HL was a rare consequence of a common infection, the risk of which increased when the age of infection was delayed, for example, through the improvement of living conditions.

Evidence confirming that the socioeconomic environment of childhood affects the risk of HL at a young age has been provided in several studies. For example, in a study that took into account such criteria as the level of socio-economic security in childhood, type of housing, mother's education and paternal social class, an association of an increased risk of HL incidence with a low level of socio-economic security was found, and this trend was traced more in young adults than in childhood [10].

Thus, these results confirm the multifactorial model of the pathogenesis of HL. This model accounts for both genetic factors and environmental risk factors [11].

The epidemiological situation on lymphomas in the Republic of Kazakhstan (RK)

The existing cancer registry of Kazakhstan provides information on the leading epidemiological indicators related to lymphoproliferative diseases. Unfortunately, it does not yet offer complete information on single variants of lymphoma but knowing that HL makes about 30% of all lymphomas, we can get an idea of the HL epidemiology in the Republic of Kazakhstan. In 2018, 4,611 patients were on file with malignant lymphomas. The annual incidence was 794 cases per year (4.3‰), with the growth rate of 7.1% to the previous year.

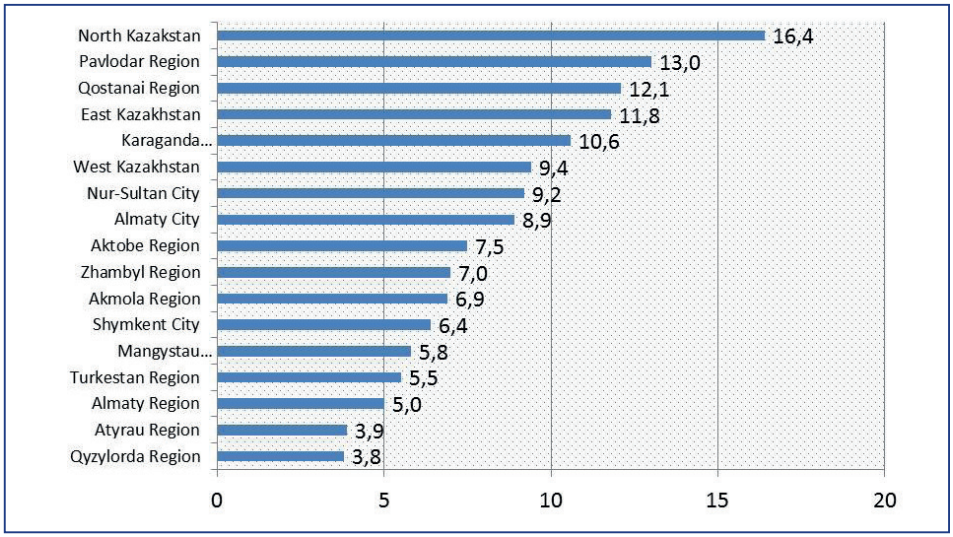

Figure 1 – Incidence of lymphomas in the regions of Kazakhstan, 2018 (‰)

The highest incidence (above the Republican average of 8.1 per 100 000 population) was registered in Akmola, Karaganda, Qostanai, Pavlodar, East Kazakhstan, West Kazakhstan, and North Kazakhstan regions and the city of Nur-Sultan. That might be partly due to the ethnic composition of the population; perhaps there was a connection with the access to diagnostics.

Some prevalence of men over women is observed in the structure of incidence, approximately 2.3 per 100 000 male population to 2.1 per 100 000 female population.

Of great importance is the possibility of morphological verification. Histological and immunological test methods have become a standard for diagnosing lymphoproliferative diseases in the past decade. According to the Diagnostic and Treatment Protocols of the Republic of Kazakhstan, these methods are mandatory for lymphoma verification. What is the situation with the morphological diagnostics of lymphomas in the Republic of Kazakhstan?

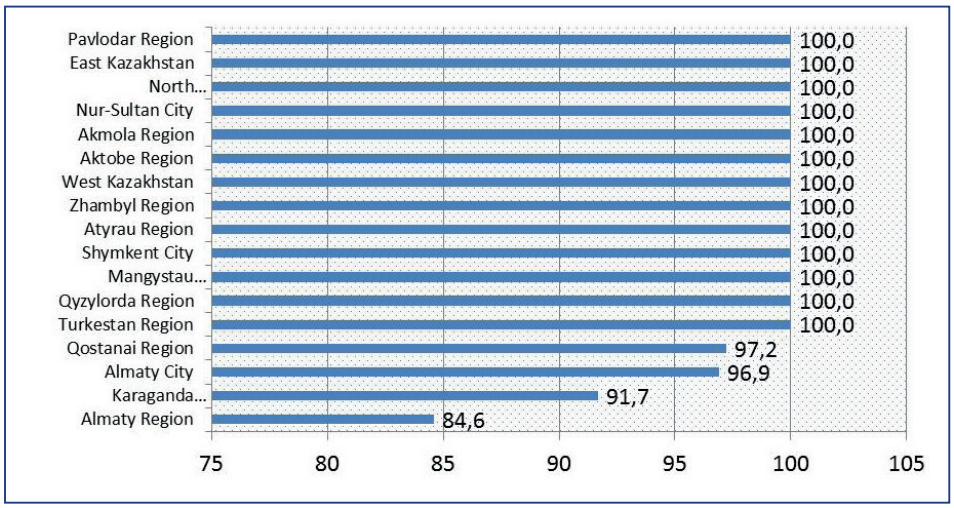

Figure 2 – Morphological verification of lymphomas in the regions of Kazakhstan, 2018 (%)

96% of all lymphomas pass morphological verification in Kazakhstan, with the lowest levels in Almaty and Karaganda regions.

The stage of the disease at detection is of great importance in terms of prognosis. What is the share of early detection in Kazakhstan?

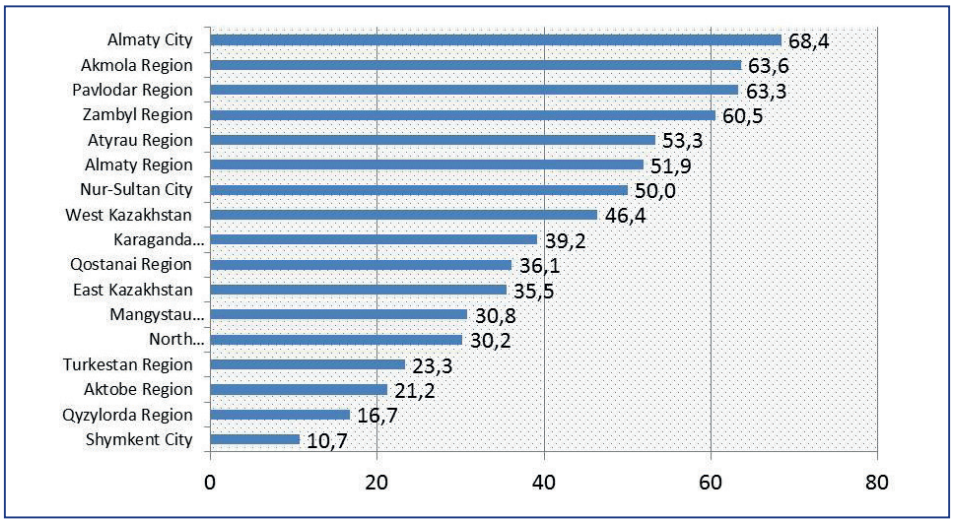

Figure 3 – The proportion of lymphoma stages 1 and 2 in the regions of Kazakhstan, 2018 (%)

On average, in the Republic of Kazakhstan in 2018, the percentage of early detection of lymphomas was 44.4%. The highest percentage of stages I and II at detection was recorded in Almaty, Akmola, Pavlodar, and Zhambyl regions, the lowest – in the city of Shymkent, as well as in Kyzylorda, Aktobe, and Turkestan regions.

As for the late detection (advanced stages of the disease), the average national detection rate for stage IV lymphomas in 2018 was 7.1%. At the same time, the highest percentage of late detection was noted in Karaganda, East Kazakhstan, Akmola and Turkestan regions, and the least high – in the cities of Almaty and Shymkent, and the Almaty region.

Currently, chemotherapy is the primary method of therapy for lymphoproliferative diseases. 85-88% of patients with newly diagnosed lymphoma receive specialized treatment, and in 65% of cases, they receive drug therapy (chemotherapy).

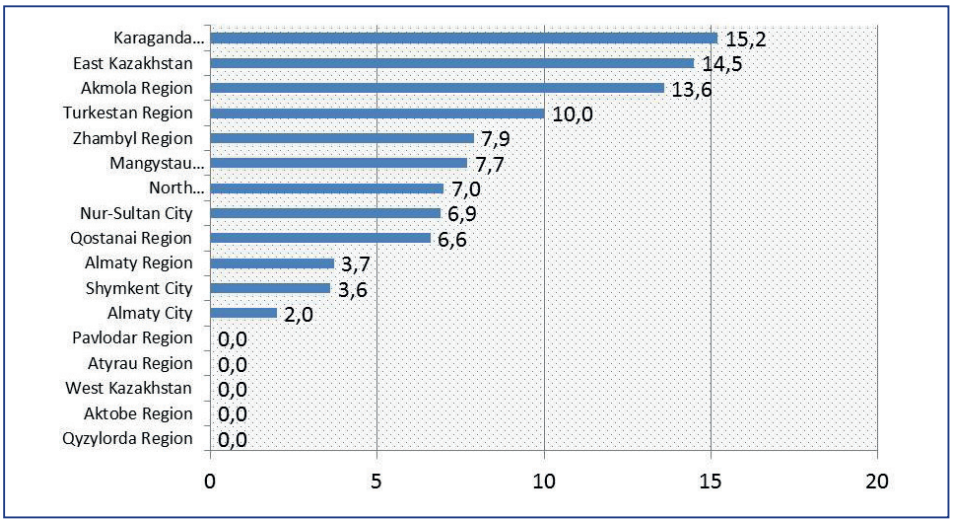

Figure 4 – The proportion of lymphoma stage IV in the regions of Kazakhstan, 2018 (%)

One-year mortality in patients with lymphoma is quite high – 22.4%, indicating a high aggressiveness of the tumor process. For reference, the annual mortality rate for breast cancer is 4.5%, for endometrial cancer – 7.5%, for prostate cancer – 8.1%.

The five-year survival of patients with lymphoma amounted to 54.8% in 2017, and 55.4% in 2018.

Mortality from lymphoma has amounted to 8.4% in 2017, and 7.0% in 2018 (322 people died of lymphomas in 2018). The mortality from lymphoma is reducing over time.

In the general structure of cancer pathologies in the Republic of Kazakhstan, the diseases of the lymphoid and hematopoietic systems, including lymphomas, ranked 8th in 2016, 6th in 2017, and 4th in 2018 making up to 5% of the total number of cancer diseases. In the structure of mortality, hematological cancer ranked 6th in 2017, and 8th in 2018 [12].

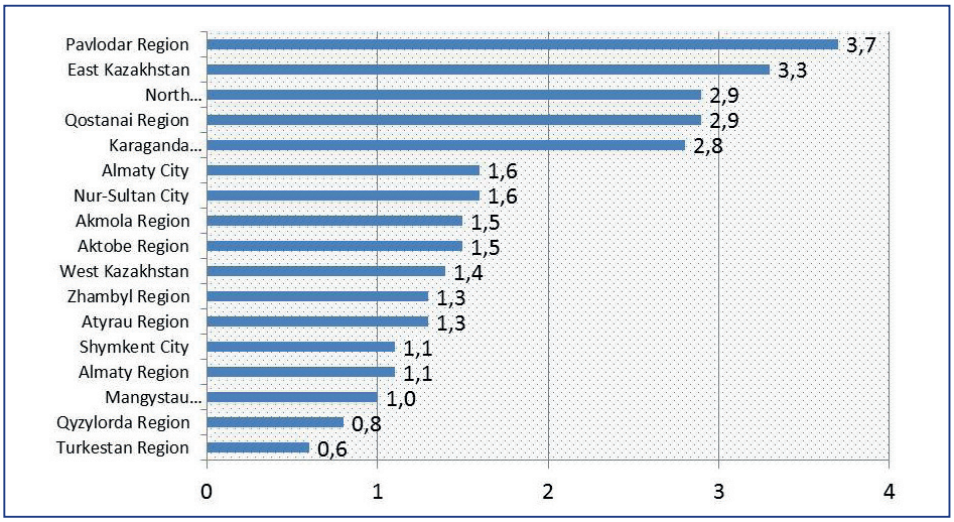

Figure 5 – Mortality from lymphomas in the regions of Kazakhstan, 2018 (‰)

The average national mortality rate is 1.8 per 100 000 population. The highest mortality rate from malignant lymphomas is noted in Pavlodar, East Kazakhstan, North Kazakhstan, Qostanai, and Karaganda regions.

Conclusions

The epidemiology of malignant lymphomas varies within and between geographic regions. Several studies show that the characteristics, incidence, and survival rates of different lymphoma subtypes for some racial groups differ from others. A better understanding of these factors will be required to identify the changing treatment barriers and improve outcomes for all patients. The incidence of lymphomas has a bimodal distribution with an increase in rates in young people, as well as in patients 55 years and older.

In the general structure of cancer pathologies, the diseases of the lymphoid and hematopoietic systems, including lymphomas, are among the Top 10. In Kazakhstan, they occupy the 4th rank position making up about 5% of the total number of cancer diseases, while in the structure of mortality, they hold the 8th place. The highest incidence of lymphoma is noted in Akmola, Karaganda, Qostanai, Pavlodar, East Kazakhstan, West Kazakhstan, and North Kazakhstan regions, and the city of Nur-Sultan. This might be partly due to the ethnic composition of the population;

perhaps there is a connection with the availability of diagnostics. The highest mortality rates from malignant lymphomas are recorded in Pavlodar, East Kazakhstan, North Kazakhstan, Qostanai, and Karaganda regions.

References:

1. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute, 2013;

2. Kaverzneva M.M., Kremenetskaya A.M., Moiseyeva T.N., Vorob'yev A.I. Limfogranulematoz // V kn: Rukovodstvo po gematologii / pod red. A.I. Vorob'yova [Hodgkin disease // In: Hematology manual / ed. A.I. Vorob'yev]. – Moscow: Newdiamed, 2007. – Vol. 2. – P. 389. Russian;

3. Cozen W, Katz J, Mack TM. Dependence of the risk of Hodgkin's disease from the cell type in Los-Angeles // Cancer Epidemiol Biomark Prev. – 1992. – Vol. 1(4). – P. 261–268;

4. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0. IARC CancerBase No. 11 [database online] / ed. by Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. // publications.iarc.fr/Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012. 17.06.2019;

5. WHO Mortality Database [online database]. www.who.int/healthinfo/mortality_data/en/.17.06.2019;

6. Swerdlow SH, Campo E, Pileri SA and other. Revision of lymphoid neoplasm classificathioon WHO in 2016 // Blood. – 2016. – Vol. 127. – P. 2375-2390;

7. Jaffe E, Swerdlow S, Вардиман J. Hematopoietic and lymphoid malignancies // In: World cancer report 2014 / eds. Stewart B, Wild C. – Lyon, France: International cancer research agency, WHO, 2014. – P. 482-494;

8. Muller A.M, Igorst H, Mertelsman R. et al. Epidemiology of Non Hodgkin lymphoma: geographic distribution and etiology trends // Ann Hematology. – 2005. – Vol. 84. – P. 1-12;

9. Phillips AA, Smith DA. Health Disparities and the Global Landscape of Lymphoma Care Today // In: American Society of Clinical Oncology Educational Book. – 37. – P. 526-534;

10. Link NJ, Maurer E, Largent J, Kent E, Morris RA, Sender LS, Anton-Culver H. Kids, Adolescents, and Young Adult Cancer Study—A Methodologic Approach in Cancer Epidemiology Research // J Cancer Epidemiol. – 2009;1687-8558:354257;

11. Salati M, Cesaretti M, Macchia M, El Mistiri M, Federico M. Epidemiological Overview of Hodgkin Lymphoma across the Mediterranean Basin // Mediterr J Hematol Infect Dis. – 2014. – Vol. 6;

12. Indicators of the Oncological Service of the Republic of Kazakhstan for 2017-2018, statistical materials. Russian.

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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].

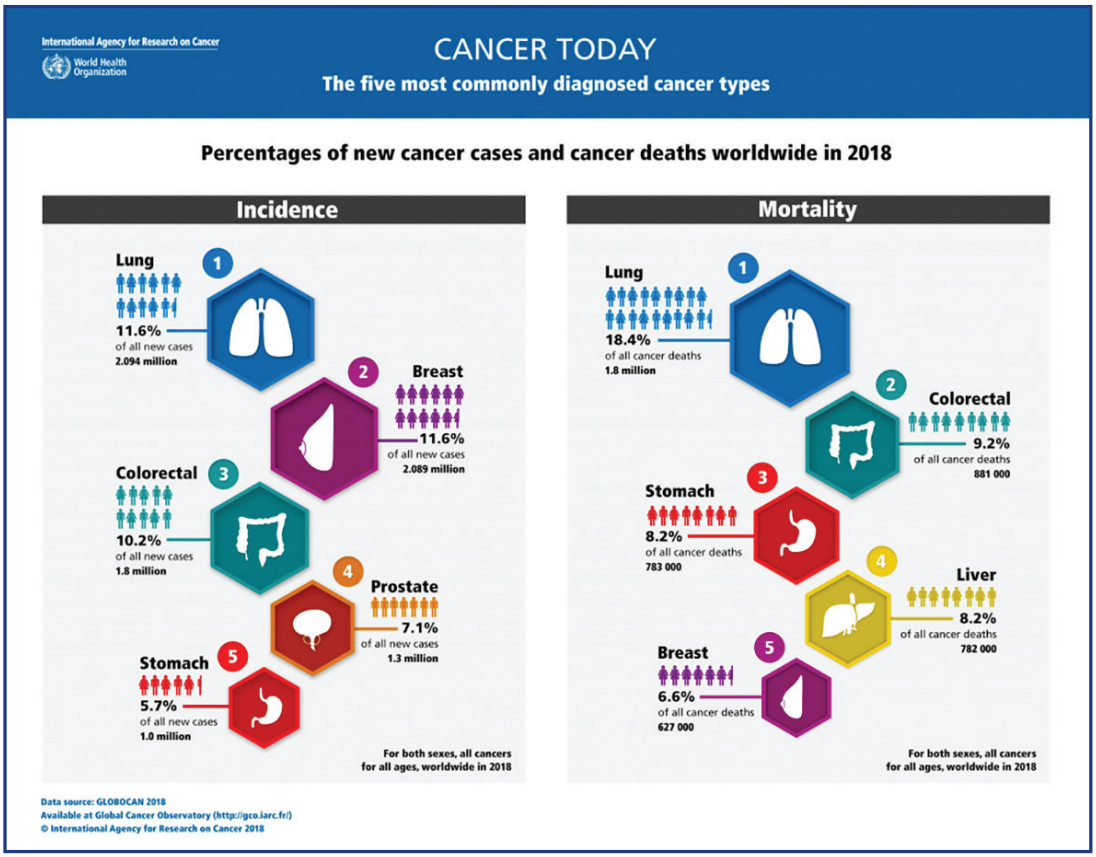

Figure 1 – Five cancer types most commonly diagnosed in the world in 2018

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.

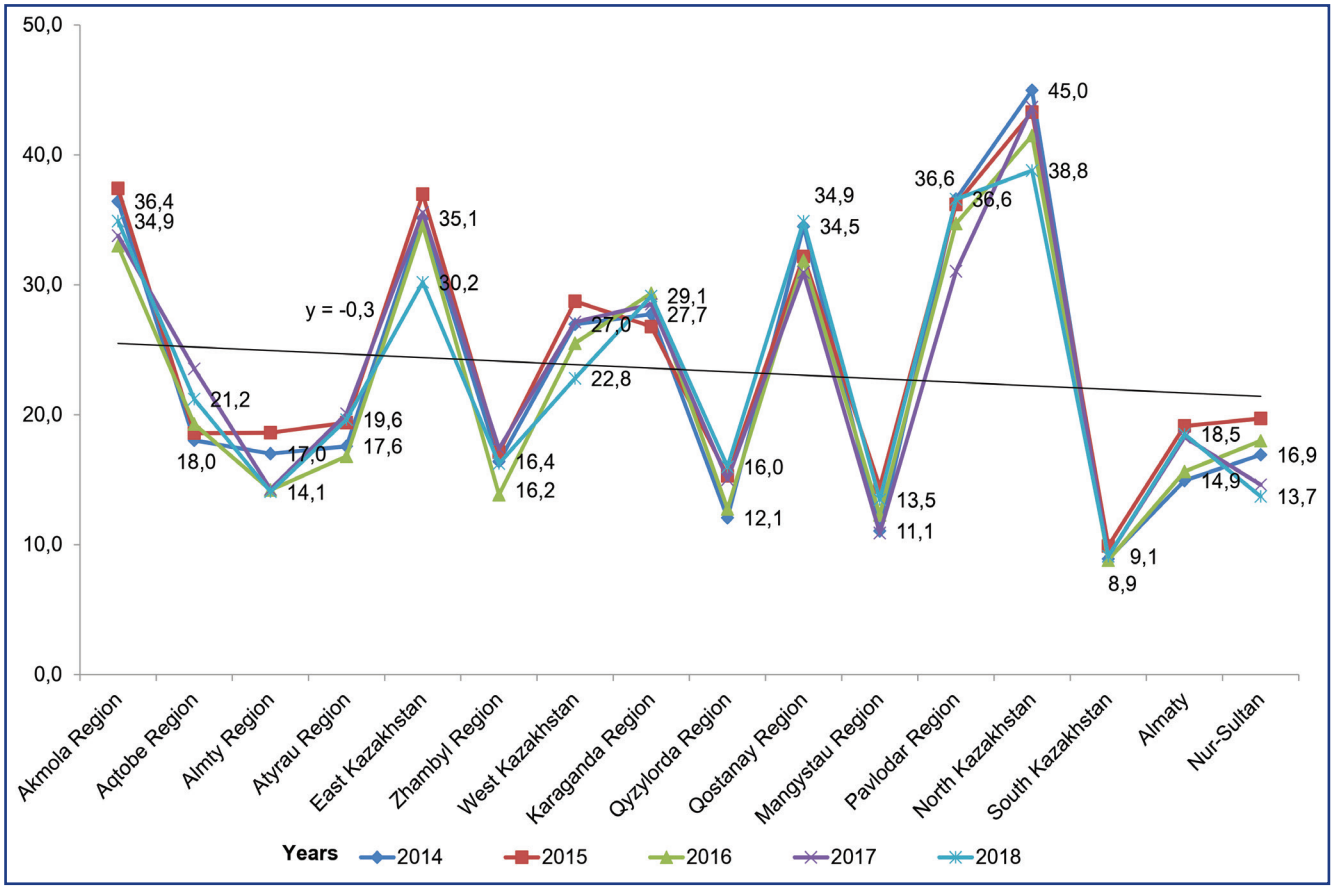

Figure 2 – Lung cancer incidence in the Republic of Kazakhstan, by regions, 2014-2018, per 100 000 population

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.

References:

1. New Global Cancer Data: GLOBOCAN 2018 // www.uicc.org/new-global-cancer-data-globocan-2018. 19.06.2019;

2. Spiro S., Hardavella G. Lung Cancer, European Lung White Book, 2013 // www.erswhitebook.org. 22.06.2019;

3. Pokazateli onkologicheskoy sluzhby Respubliki Kazakhstan za 2013-2018 gody (statisticheskiye materialy);

4. Kaprin A.D., Starinsky V.V., Petrova G.V. Sostoyaniye onkologicheskoy pomoshchi naseleniyu Rossii v 2017 godu. [The state of cancer care for the population of Russia in 2017] – Moscow: P.A. Herzen Moscow Scientific and Research Oncology Institute – branch of the FSBI «Scientific Medical Research Center of Radiology» of the Ministry of Health of the Russian Federation, 2018. – P. 5-6, 18. Russian;

5. Ismailova G.N., Rakhimzhanova R. Skrining rannego raka logkogo metodom nizkodoznoy komp'yuternoy tomografii. Screening for early lung cancer with low-dose computed tomography] // Klinicheskaya meditsina Kazakhstana [Clinical Medicine of Kazakhstan]. – 2014. – Vol. 32 (2). – P. 21–25. Russian;

6. Merabishvili V.M., Dyatchenko O.T. Statistika raka legkogo (zabolevayemost', smertnost', vyzhivayemost') [Lung cancer statistics (incidence, mortality, survival)] // Prakticheskaya onkologiya [Practical oncology]. – 2000. – №3. – P. 3–6. Russian;

7. Kaidarova D.R., Sagidullina G.G., Zholdybay Zh.ZH., Panina A.S., Ainakulova A.S., Toktosykykyzy M. Nizkodoznaya komp'yuternaya tomografiya v ranney diagnostike raka legkikh: pilotnyy proyekt [Low-dose computed tomography in the early diagnosis of lung cancer: a pilot project] // Onkologiya i Radiologiya Kazakhstana [Oncology and Radiology of Kazakhstan]. – 2019. – Vol. 51(1). – P. 18–19. Russian.

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The role of catheter jejunostomy in the esophageal-intestinal anastomosis failure: clinical case

Relevance: *The total incidence of stomach cancer (SC) is decreasing; however, the incidence of cancer of the proximal section of the stomach and cardioesophageal cancer (CEC) is increasing. Together, these two cancers make 37% of all SC localizations. At that, most of the patients with CEC are admitted to hospital at advanced stages of cancer. Some researchers report that 80-85% of CEC cases are diagnosed at stages III-IV of the tumor process. Proximal stomach cancers are the 6th most common cause of death from cancer and the 9th most common cause of death worldwide. Modern literature does not cover enough the conservative treatment in case of failure of esophageal-intestinal anastomosis in CEC and SC involving the esophagus.*

Despite improvements in the surgical method of treating cancer of the stomach and esophagus, postoperative complications are still quite frequent due to the high complexity and trauma of these operations. The failure of the esophageal-intestinal anastomosis remains the most dangerous complication. According to the literature, it develops in 2-14% of patients. In a retrospective multicenter study, the anastomosis failure was the cause of death within 30 days after surgery in 30% of cases. Aurello reports the overall mortality of 26.32%. Complete healing of the anastomosis can be achieved within 7-28 days in the group receiving conservative treatment. A conservative approach should always be considered as a method of choice.

Purpose of the study *is to assess the effectiveness of catheter jejunostomy as a method of conservative treatment of esophageal-intestinal anastomosis failure during operations for stomach cancer.*

Results: *The provided clinical case demonstrates that, in case of esophageal-intestinal anastomosis failure, the conservative treatment, including adequate drainage of the abdominal cavity, control of the total blood protein, maintaining stable homeostasis against adequate nutritional support via a catheter jejunostomy, allows achieving complete healing of the esophageal-intestinal anastomosis.*

Conclusion: *The implemented catheter jejunostomy technique allows limiting the use of surgical treatment as a method of choice in the failure of esophageal- intestinal anastomosis. Adequate nutritional support of patients allows maintaining the homeostasis indicators within normal limits what ultimately leads to a healing of the occurring complication.*

Keywords: *stomach cancer, failure of esophageal-intestinal anastomosis, catheter jejunostomy.*

Introduction. Recently, the total incidence of stomach cancer (SC) is decreasing; however, the incidence of cancer of the proximal section of the stomach and cardioesophageal cancer (CEC) is increasing. Together, these two cancers make 37% of all SC localizations. At that, most of the patients with CEC are admitted to hospital at advanced stages of cancer. Some researchers report that 80-85% of CEC cases are diagnosed at stages III-IV of the tumor process. In the UK, 50% of patients have unresectable tumors or distant metastases at primary diagnosis [2]. Proximal stomach cancers are the 6th most common cause of death from cancer, and the 9th most common cause of death worldwide [3].

Despite improvements in the surgical method of treating stomach cancer and esophagus cancer, postoperative complications are still quite frequent due to the high complexity and trauma of these operations. The failure of the esophageal-intestinal anastomosis remains the most dangerous complication. According to the literature, it develops in 2-14% of patients [1].

In a retrospective multicenter study, the anastomosis failure was the cause of death within 30 days after surgery in 30% of cases [4]. The overall mortality reaches 26.32% [5]. Complete healing of the anastomosis can be achieved within 7-28 days in the group receiving conservative treatment. A conservative approach should always be considered as a method of choice [5].

Modern literature does not cover enough the conservative treatment in case of failure of esophageal-intestinal anastomosis in CEC and SC involving the esophagus.

This category of patients is of undoubted scientific and practical interest.

The article presents a case of successful conservative therapy with catheter jejunostomy after the failure of the esophageal-intestinal anastomosis.

Patient information. Patient B., 67 years old, was admitted to the Center of Thoracic Oncology of the Kazakh Institute of Oncology and Radiology, JSC (KAZIOR) with the diagnosis: "Cancer of the proximal stomach with the abdominal esophagus spreading. Grade III. T3NxM0. Dysphagia grade III."

Disease history: The patient reported general weakness and pain in the epigastrium since January 2017. He noted problems with gastric transit of rough and thick food, loss of weight (7-8 kg in 3 months). Esophagogastroduodenoscopy: "Cancer of the gastric cardia with the transition to the lower third of the esophagus? Stenosis. Histology – Gastric adenocarcinoma, G-II". The patient was

admitted to the Center of Thoracic Oncology of KAZIOR for surgical treatment.

General state at admission: General state – relatively satisfactory, stable. Consciousness – clear, adequacy – preserved. Arterial Tension: 120/80 mm Hg. Pulse: 80 bpm. Temperature: 36.4°C. C. Breathing – vesicular, respiration rate – 15/min, no rales. Heart tones – clear, the rhythm – correct. The tongue – wet. The abdomen – soft, symmetrical, not swollen. The abdomen – soft, painless on palpation. No peritoneal signs. Urination – natural. Peristalsis – active. Defecation – independent.

Examination at admission:

Radiographic contrast study of the esophagus and stomach: The esophagus is unobstructed till the epiphrenic segment, where "stop contrast" is reported. The entry of contrast in the underlying sections is not registered during the delayed examination after 30 minutes, 60 minutes, 180 minutes, persistent filamentous narrowing of the esophagus is expressed. It is not possible to assess the extent of the lesion, due to the lack of contrast in the lower segments.

Conclusion decision: X-ray image of organic decompensated esophageal stenosis, more characteristic for blastoma (Figure 1).

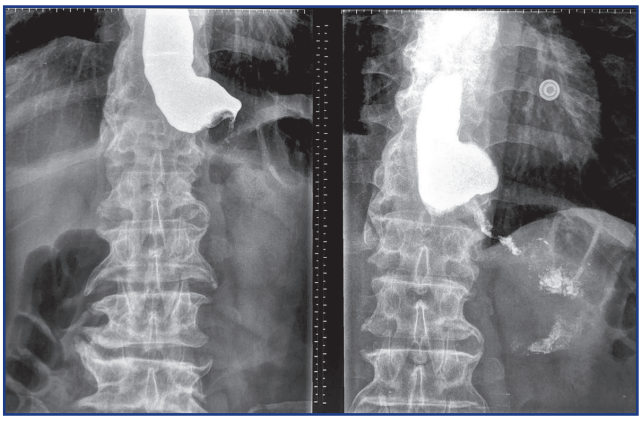

Figure 1 – Initial image, cardioesophageal blastoma

Computed tomography at admission: CT-picture of organic lesions of the abdominal esophagus and gastric cardia. Involvement of the pancreas tail in the process is not excluded. Lymphadenopathy of perigastric, intra-aortic, and para-aortic lymph nodes. Metastases?

Surgical treatment: Combined extended gastrectomy with resection of the abdominal esophagus, LD-D2. Catheter jejunostomy.

Laboratory tests, Day 3 after surgery: Total protein – 57.4 g/l, WBC – 11.61;

Laboratory tests, Day 18 after surgery: Total protein – 69.6; WBC – 17.23;

Laboratory tests, Day 30 after surgery: Total protein – 62.2 g/L, WBC – 6.53;

Laboratory tests, Day 45 after surgery: Total protein – 65.8 g/L, WBC – 16.45;

Laboratory tests, Day 48 after surgery: WBC – 6.0.

Postoperative histology: Adenocarcinoma, GII of the stomach with invasion into all layers of the wall and omentum invasion, with foci of comedo necrosis.

In the lymph nodes No. 1, 3,6,7,8,9,12, tumor metastases were not detected.

In the lymph nodes No. 2, the lymph nodes of the lesser omentum the metastasis is determined. Greater omentum is of normal structure.

On Day 6 after surgery, after the removal of the drainage tube, the intestinal discharge flows from the wound of the abdominal cavity on the left. A radiographic contrast study of the esophageal-intestinal anastomosis has been recommended.

Radiographic contrast study of the esophageal-intestinal anastomosis: X-ray image of post-surgery status (gastrectomy), failure of the anastomosis, violation of the innervation of the small intestine (Figure 2).

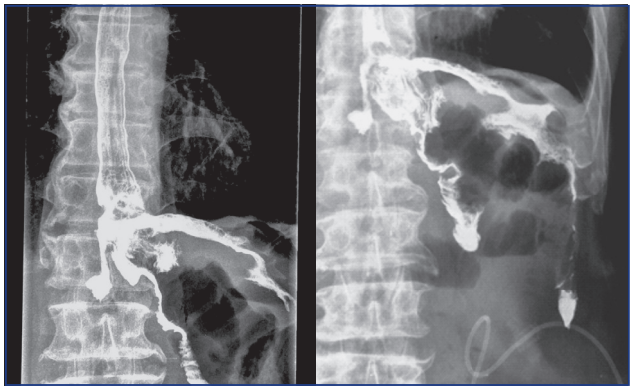

Figure 2 – Day 6 after gastrectomy

Considering the clinical and radiological data of the failure of the esophageal-intestinal anastomosis, per os nutrition was limited to the patient; nutritional support was provided exclusively through catheter jejunostomy. The drainage tube was washed with antiseptic solutions (Furacilin, betadine) and re-installed through the old passage at the left side of the abdominal cavity.

A control radiographic contrast study of the esophageal-intestinal anastomosis, Day 21 after surgery: X-ray image of post-surgery status (gastrectomy), failure of the anastomosis, a violation of the innervation of the small intestine. There is a stable picture over time (Figure 3).

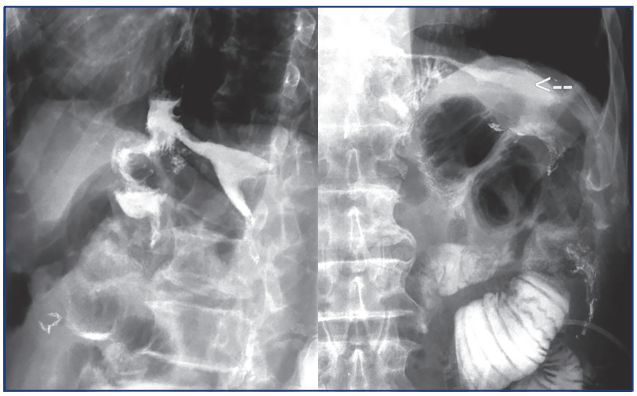

Figure 3 – Day 21 after gastrectomy

Control radiographic contrast study of the esophageal-intestinal anastomosis, Day 35 after surgery: X-ray image of post-surgery status (gastrectomy), anastomositis, the violation of innervation of the small intestine. There is lower lobe pneumonia at the right. The cessation of the flow of contrast beyond the anastomosis is registered over time.

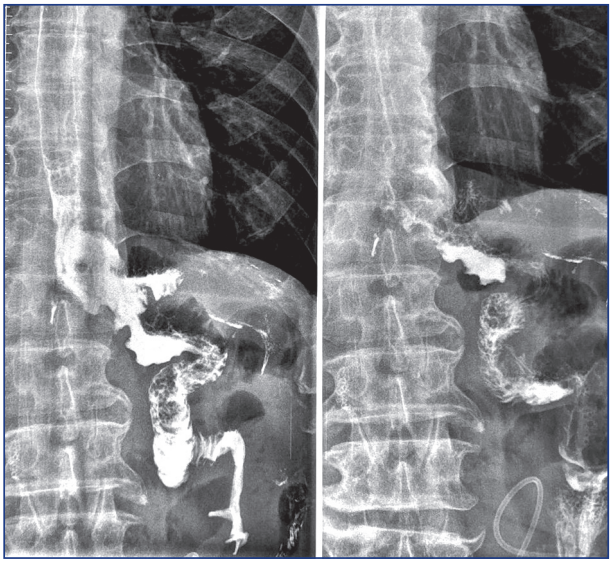

Figure 4 – Day 36 after gastrectomy

The discharge flow through the drainage tube was not noted over time; the drainage tube was removed on the 36th day after the operation. The patient's condition has improved; the patient was discharged in a relatively satisfactory condition for outpatient monitoring and treatment.

Conclusions: The implemented catheter jejunostomy technique allows limiting the use of surgical treatment as a method of choice in the failure of esophageal- intestinal anastomosis. Adequate nutritional support of patients allows maintaining the homeostasis indicators within normal limits what ultimately leads to a healing of the occurring complication.

References:

1. Chernousov A.F. et al. Nesostoyatel'nost' shvov pishchevodno-kishechnogo anastomoza u patsiyentov s kardioezofageal'nym rakom [The failure of the esophageal-intestinal anastomosis sutures in patients with cardio esophageal cancer] // Novosti khirurgii [Surgery News]. – 2011. – № 4. – C.16–23;

2. Volkov M.YU. Otsenka effektivnosti khirurgicheskogo lecheniya i kachestva zhizni bol'nykh kardioezofageal'nym rakom [Evaluation of the effectiveness of surgical treatment and the quality of life of patients with cardioesophageal cancer] // Synopsis of thesis ... Candidate of Medicine: 14.01.12. – Tomsk: Tomsk Research Institute of Oncology, 2014. – 180 p. Russian;

3. Vychuzhanin D.V. Khirurgicheskoye lecheniye kardioezofageal'nogo raka [Surgical treatment of cardioesophageal cancer] // Synopsis of thesis ... Candidate of Medicine: 14.00.27. – Moscow: I.M. Sechenov Moscow Medical Academy, 2010. – 133 p. Russian;

4. Robb W.B., Messager M., Goere D. et al. Predictive factors of postoperative mortality after junctional and gastric adenocarcinoma resection // JAMA Surg. – *2013. – №148. – P. 624–631;*

5. Aurello P. et al. Treatment of Esophagojejunal Anastomosis Leakage: A Systematic Review from the Last Two Decades // The American Surgeon. – 2015. –№ 5. – P.450–453.

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Pseudoangiomatous hyperplasia of mammary stroma: clinical cases

Relevance. *Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign breast pathology. Less than 300 cases of PASH are described in the literature; in most cases, the disease appears as a histological finding during a biopsy performed on a different diagnosis. PASH is often associated with other benign breast changes, and these changes may dominate in the clinical and radiological presentation. The BI-RADS scale classifies PASH as category 2 (benign changes). Differential diagnostics shall include fibroadenoma, phylloid tumor, and diabetic mastopathy. PASH is not a precancerous condition and does not require active surgical treatment or dynamic monitoring. After surgery, the risk of relapse occurs in 15-22% of cases.*

PASH diagnostics is challenging due to the variety of radiological patterns and the absence of pathognomonic radiological signs.

Purpose of this study *is to familiarize with this pathology and improve differential diagnosis.*

This article presents clinical cases of three patients with pseudoangiomatous stromal hyperplasia of mammal glands with different clinical and radiological patterns.

Conclusions. *In the case of questionable results of radiation examination, biopsy followed by histological examination is required to clarify the diagnosis.*

Keywords: *Pseudoangiomatous stromal hyperplasia, mammography, breast ultrasonography.*

Introduction. Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign breast pathology first described in 1986 by Vuitch and coauthors in 9 patients with palpable neoplasms in the mammary gland [1]. The scientific literature in English offers a range of publications devoted to this pathology and its diagnostics [2-5]. However, no publications on that topic could be found in Russian-language literature.

This article presents the results of a radiation examination of three patients to demonstrate the differences in clinical and radiological manifestations of histologically confirmed PASH.

The correct and timely PASH diagnostics at the preoperative stage allows for avoiding unnecessary invasive interventions. Despite the low prevalence of this pathology, practical radiologists should be aware of the disease, know its clinical symptoms, radiation semiotics, and tactics to ensure optimum management of patients.

Description of cases.

Case 1 (Figures 1-4).

A female patient, 47 years old, presented complaints on a neoplasm in her right breast, accidentally detected during the screening in 2012 and painfulness in the place of neoplasm. The neoplasm was not palpable; over the years, it slowly increased in size. Histological diagnosis of a core-needle biopsy has shown a mammary fibroadenoma.

The oval neoplasm of average density, precise contour, with dimensions 2.2x1.2 cm at a distance of 6 cm from the nipple was detected on a mammography study of the lower inner quadrant of the right mammary gland.

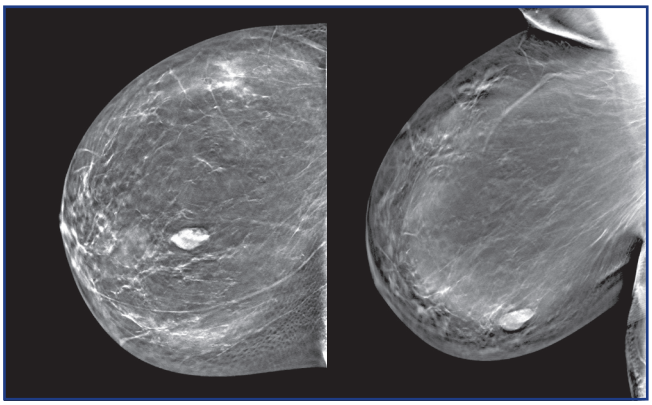


Figure 1 - Mammograms of the right mammary gland, frontal and oblique views. Neoplasm in the lower inner quadrant, with medium intensity, and precise contour.

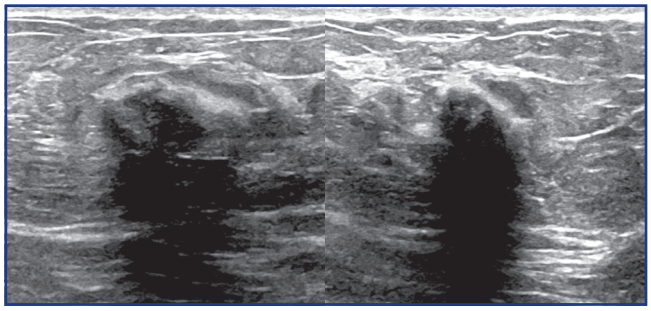


Figure 2 - Ultrasound examination of the right mammary gland. A hypoechoic mass with a fuzzy contour and heterogeneous structure.

Ultrasound examination: a hypoechoic neoplasm with a fuzzy contour, parallel to the skin, with a heterogeneous internal echo-structure and a marked distal acoustic shadow. The

patient was recommended surgery due to neoplasm growth.

Postoperative histology conclusion: PASH with foci of fibroadenomatous changes, without any signs of atypia.

Case 2 (Figures 3-5).

A female patient, 72 years old, without complaints. Screening mammography showed a locus of developing asymmetric tissue 4.5x2.0 cm in size, in the upper-outer quadrant of the mammary gland, 6.3 cm away from the nipple.

Ultrasound examination: an irregular shape neoplasm difficult to measure due to its ductal distribution. BI-RADS 4.Histological diagnosis after of core-needle biopsy: PASH with a simple ductal hyperplasia.

The patient was recommended to continue the routine mammography screening.

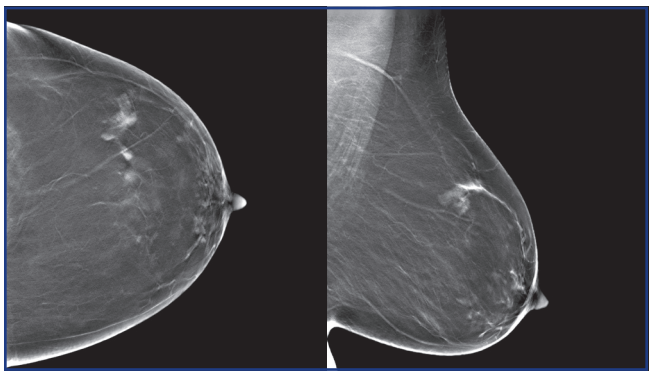
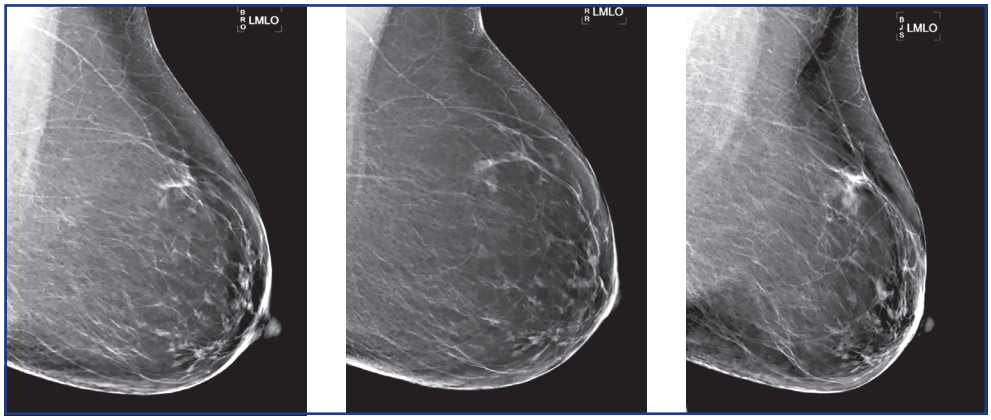


Figure 3 - Tomosynthesis (performed in 2019). In the upper-outer quadrant of the right mammary gland - the locus of focal asymmetry



Picture of 2016. Picture of 2017. Picture of 2019.

Figure 4 - Mammograms of the right mammary gland taken in 2016, 2017 and 2019: the developing asymmetry locus in the upper-outer quadrant

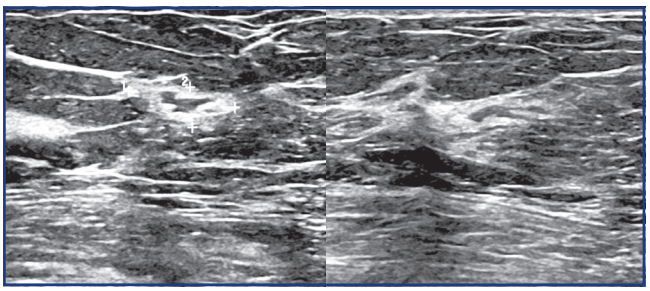


Figure 5 - Ultrasound examination of the right mammary gland: a neoplasm, irregular shaped

Case 3 (Figures 6-7).

A female patient, 45 years old, presented complaints on a neoplasm in the left mammary gland, accidentally detected during the screening mammography about 3 years ago, with the slow growth of the neoplasm. The biopsy showed a fibroadenoma. No other complaints were recorded; the neoplasm was not clearly palpable.

The mammography of the upper-outer quadrant of the left breast showed an oval neoplasm with partially indistinct contours, and low density sized 4.0x3.1 cm.

Ultrasound examination: a hypoechoic mass with precise contours, parallel to the skin, heterogeneous internal echo-structure, size 4.1x4.1 cm.

The patient was recommended surgery due to neoplasm growth.

The postoperative conclusion of the histology examination was the following: PASH associated with fibroadenomatous changes, steatonecrosis, and apocrine metaplasia.

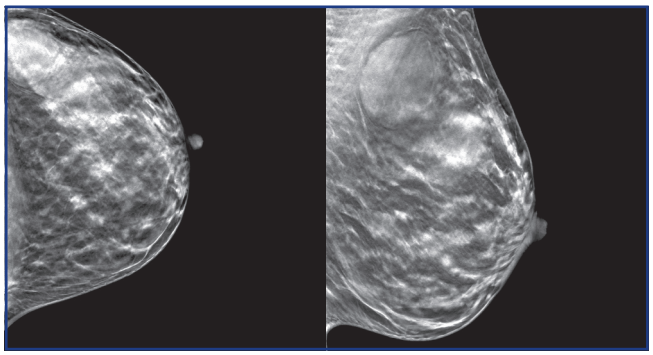


Figure 6 - Tomosynthesis: the neoplasm with partially indistinct contours in the upper-outer quadrant of the left mammary gland

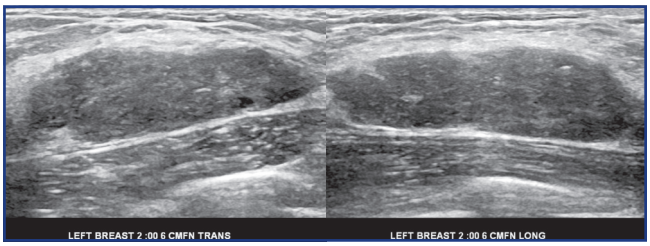


Figure 7 - Ultrasound examination of the left mammary gland: a hypoechoic neoplasm with precise contours and heterogeneous structure

Discussion

Pseudoangiomatous stromal hyperplasia is a benign condition of the mammary gland associated with a collagen proliferation. In most cases, that disease is an incidental histological finding during a biopsy performed because of a different diagnosis.

Less than 300 cases of PASH were described in English-language scientific literature; the most extensive series of cases included 79 patients [6]. In one of the studies, PASH was detected in histological samples of 23% of patients after sectoral resection for another reason [7].

That pathology is observed in both women and men; in men, it is often associated with gynecomastia. In a study, PASH as a comorbidity was detected in 24-47% of men with gynecomastia [8].

The etiology and pathogenesis of PASH are not thoroughly studied; however, hormonal factors are known to play a significant role in PASH development. PASH is more common in women in the premenopausal and perimenopausal period [9].

PASH affects patient of different ages and has been reported in women of 14 to 67 years, with the highest prevalence at the age of 30-50 years [10, 11]. This pathology is rare in patients after 50 years in the postmenopausal period without a hormone replacement therapy. This fact confirms the hormonal etiology of PASH.

Several studies reported the change in the size of neoplasms depending on the phase of the menstrual cycle phase what reconfirmed its hormonal genesis [12]. Histological findings showed a positive sensitivity of stromal cells to progesterone receptors and moderate stromal nuclear sensitivity to estrogen receptors, while the nuclei of the stromal cells in control cases without PASH stained none of the receptors [9].

Clinical and radiological manifestations

Clinically, PASH is usually manifested as moving palpable neoplasm in a mammary gland with a tendency to growth [13].

PASH is often detected during a histological examination with no clinical symptoms [14].

On a mammogram, PASH may look like a round or oval neoplasm which resembles a fibroadenoma, with a precise contour of high X-Ray density, more often with no signs of microcalcifications [15].

During a mammary gland ultrasound examination, PASH commonly manifests itself as a hypoechoic, oval, or round neoplasm, with slightly heterogeneous internal echo-structure [15].

The dimensions of the neoplasm may range from 1 to 23 cm [16].

On MRI study of the mammary glands, the PASH pattern is not specific and varies from a neoplasm accumulating the contrast to a focal accumulation of contrast no developing a neoplasm, usually with benign parameters on kinetic tests [17].

PASH is often associated with other benign breast changes, and these changes may dominate in clinical and radiological patterns.

Histology

The proliferation of stromal cells, more precisely, the proliferation of collagen, forms slit-like channels which are lined by myofibroblasts (spindle cells) and resemble vascular channels [18]. It should be taking into account that this is not a true angiomatous proliferation, and these channels are not the blood vessels. In this regard, PASH may be wrongly viewed as a vascular neoplasm.

A spindle tumor cells are positive to Vimentin, CD34, BCL2, CD99, and α-smooth muscle actin, but negative to CD31 and Factor VIII (endothelium-specific marker). Also, the cells exhibit a hormonal sensitivity and often express the progesterone and estrogen receptors [19].

Differential diagnosis

The clinical and radiological methods should be applied to differentiate PASH from other benign breast diseases such as fibroadenoma, phylloid tumor, and diabetic mastopathy [20].

Morphologically, PASH should be differentiated from low-differentiated angiosarcoma and tumors containing spindle cells such as phylloid tumors and desmoid [21].

Tactics

PASH is a benign breast disease. It is not a pre-cancerous condition or not the risk factor for breast cancer development [13]. The literature does not describe any cases of synchronous PASH and breast cancer; however, it is theoretically possible.

The literature also does not describe malignant PASH variants, except two cases of PASH with marked cytological atypia, multinucleated cells and high mitotic activity in adolescent girls finally diagnosed with myofibroblastic sarcoma. These cases were described by Rosen in his "Breast Pathology" [22].

The BI-RADS scale classifies PASH as category 2 (benign changes).

In the case of questionable results of radiation examination, biopsy followed by histological examination is required to clarify the diagnosis.

No active surgical tactics or dynamic observation is required for PASH management. The surgical resection may be indicated in the following cases: the neoplasm growth, the diffuse PASH with the mammary gland growth, and in case of non-conformity between the histological diagnosis and the radiation pattern. After surgery, the relapse occurs in 15-22% of cases [15].

There are no generally accepted recommendations for PASH conservative treatment. This disease is sensitive to tamoxifen; however, the treatment outcome is supported only within the long-term anti-estrogen therapy [23]. The long-term intake of tamoxifen has many side effects and cannot be recommended for young women in the pre-menopausal period.

Conclusion. The analysis of available literature has revealed no pathognomonic radiation signs of PASH, this rare benign breast pathology. The most frequent radiological manifestation is a round neoplasm of a precise contour with sonographic heterogeneous internal content. In a majority of cases, the solid nature of the neoplasm requires a histological verification using core-needle biopsy. The detection of PASH in pathological specimens can verify the benign nature of the neoplasm that requires no further dynamic observation.

References:

1. Vuitch M.F., Rosen P.P., Erlandson R.A. Pseudoangiomatous hyperplasia of mammary stroma // Hum Pathol. – 1986. – Vol.17. – P. 185–191;

2. Celliers L., Wong D., Bourke A. Psuedoangiomatous stromal hyperplasia: A study of the mammographic and sonographic features // Clin Rad. – 2010. – Vol. 65(2). – P. 145–149;

3. Vo Q.D., Koch G., Girard J.M. et al. A case report: pseudoangiomatous stromal hypetrplasia tumor presenting as a palpable mass // Frontiers in Surgery. – 2016. – Vol. 2. – P. 1–4;

4. Holloway T.L., Jatoi I. Tumorous PASH presenting as rapid unilateral breast enlargement // Mayo Clin Proc. – 2013. – Vol. 88(7). – P. e75;

5. Bowman E., Oprea G., Okoli J. et al. Pseudoangiomatous stromal hyperplasia of the breast: a series of 24 patients // Breast J. – 2012. – Vol. 18. – P. 242–247;

6. Drinka E.K., Bargaje A., Ersahin C. et al. Pseudoangiomatous stromal hyperplasia of the breast: a clinicopathological study of 79 cases // International journal of surgical pathology. – 2011. – Vol. 20(1). – P. 54–58;

7. Ibrahim R.E., Sciotto C.G., Weidner N. Pseudoangiomatous stromal hyperplasia of mammary stroma: Some observations regarding its clinicopathologic spectrum // Cancer. – 1989. – Vol. 63(6). – P. 1154–1160;

8. Milanezi M.F., Saggioro F.P., Zanati S.G., Bazan R., Schmitt F.C. Pseudoangiomatous hyperplasia of mammary stroma associated with gynaecomastia // J Clin Pathol. – 1998. – Vol. 51. – P. 204–206;

9. Anderson C., Ricci A., Pederson C. et al. Immunocytochemical analysis of oestrogen and progesterone receptors in benign stromal lesions of the breast: Evidence for hormonal aetiology in psuedoangiomatous hyperplasia of mammary stroma // Radiographics. –1999. –Vol. 19. – P. 1086–1088;

10. Okoshi K., Ogawa H., Suwa H., Saiga T., Kobayashi H. A case of nodular pseudoangiomatous stromal hyperplasia (PASH) // Breast Cancer. – 2006. – Vol. 13 (4). – P. 349–353;

11. Castro C., Whitman G., Sahin A. Pseudoangiomatous hyperplasia of the breast // Am J Clin Oncol. – 2002. – Vol. 25(2). – P. 213–216;

12. Powell C.M., Cranor M.L., Rosen P.P. Pseudoangiomatous stromal hyperplasia (PASH) // Am J Surg Pathol. – 1995. – Vol.19. – P. 270–277;

13. Jaunoo S.S., Thrush S., Dunn P. Pseudoangimatous stromal hyperplasia (PASH): A brief review // International journal of surgery. – 2011. – Vol. 9 (1). – P. 20–22;

14. Mercado C., Naidrich S., Hamele-Bena D. Pseudoangiomatous stromal hyperplasia of the breast: Sonographic features with histopathological correlation // Breast J. – 2004. – Vol. 10. – P. 427–432;

15. Polger M.R., Denison C.M., Lester S., Meyer J.E. Pseudoangiomatous stromal hyperplasia: Mammographic and sonographic appearances // Am J Roentgenol. –1996. – Vol.166. – P. 349–352;

16. Cohen M.A., Morris E.A., Rosen P.P. et al. Pseudoangiomatous stromal hyperplasia: Mammographic, sonographic, and clinical patterns // Radiology. – 1996. – Vol. 198(1). – P. 117–120;

17. Johnson K S, Bentley R C, Kelly Marcom P et al. Pseudoangiomatous stromal hyperplasia (PASH) causing massive breast enlargement: MRI findings // Breast J. – 2012. – Vol. 18(6). – P. 600–601;

18. Raj S.D., Sahani V.G., Adrada B.E. et al. Pseudoangiomatous stromal hyperplasia of the breast: multimodality review with pathologic correlation // Current problems in diagnostic radiology. – 2017. – Vol. 46. – P. 130–135;

19. Salvador R., Lirola J.L., Domínguez R. et al. Pseudoangiomatous stromal hyperplasia presenting as a breast mass: Imaging findings in three patients // Breast. – 2004. – Vol. 13. – P. 431–435;

20. Jones K., Glazebrook K., Reynolds C. Pseudoangiomatous stromal hyperplasia: Imaging findings with pathologic and clinical correlation // Am J Roentgenol. – 2010. – Vol. 195. – P. 1036–1042;

21. Ryu E.M., Whang I.Y., Chang E.D. Rapidly growing bilateral pseudoangiomatous stromal hyperplasia of the breast // Korean J Radiol. – 2010. – Vol. 11(3). – P. 355–358;

22. Rosen P.P. Breast Pathology. – Lippincott Williams & Wilkins, 2001. – P. 7;

23. Pruthi S., Reynolds C., Johnson R.E., Gisvold J.J. Tamoxifen in the management of pseudoangiomatous stromal hyperplasia // Breast J. – 2001. – Vol. 7(6). – P. 434–439.

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Results of surgical treatment and immunochemotherapy of primary non-Hodgkin's lymphomas of the orbit

Relevance: *Treatment of non-Hodgkin's lymphomas (NHL) of the orbit is an acute problem in oncophthalmology. In recent years, much importance in developing the tactics of treating lymphomas of the orbit is given to prognostic factors that influence the effectiveness of treatment and total survival of patients.*

Purpose of the study *was to assess the effectiveness of surgical treatment in combination with immune chemotherapy in patients with lymphoma of the orbit depending on prognostic factors and to achieve a better quality of life of patients.*

Results: *The results of histological and IHC verification of diagnosis and combination treatment of 17 patients with malignant lymphomas of the orbit were analyzed. The treatment outcome was compared by stage of the disease and the methods of treatment (surgery, immune chemotherapy). Surgery and immune chemotherapy of advanced stages of primary lymphomas of the orbit proved to be more effective; the remission amounted to 80%. The quality of life by ECOG scale has improved from 3-4 before treatment to 1 after treatment. Also, the predictors influencing the treatment effectiveness were identified. The total 3-years survival of patients after combination treatment amounted to 98.6%.*

Conclusion: *All studied tumors had a high proliferative index (above 80%) what dictated the use of adjuvant immunochemotherapy in all cases of B-cell lymphoma. In all patients with advanced stages, the use of combination therapy (surgery + immune PCT) allowed achieving a better effect compared with surgery alone, what has proven the adequacy of the chosen treatment tactics.*

Keywords: *primary malignant lymphoma of the orbit, surgical treatment, chemotherapy, and therapy prognosis.*

Introduction. Non-Hodgkin lymphomas (NHL) of the eye orbit make up from 8 to 12% of all primary extranodal NHLs [1]. According to other authors, primary NHL of the orbit account for 2 to 4% [2], 5 to 14% [3] of all extranodal lymphomas and 37.3% of all malignant orbit tumors [4]. The share of lymphomas in primary tumors of the orbit is also controversial. Academician A.F. Brovkina et al. report that they constitute more than half of primary orbit tumors [4], the other sources – no more than 10% [5].

NHLs of the orbit belong to extranodal lymphomas. They most often have a B-cell origin with a predominantly indolent course [1]. In the literature, extranodal NHLs range from 24% to 40.7% of all NHLs [6]. Poddubnaya et al. [7] report that extranodal NHLs account for 24-48% of all NHLs, while NHL of the orbit, the eye, and its sinus make 4.1 to 8% of all extranodal lymphomas [6]. In all disseminated forms, the involvement of orbit and conjunctive tissues is limited to 5.3% of patients [2]. Lymphomas make 37.3-40 % of all malignant neoplasms of the orbit [4].

WHO has classified a new variant of lymphomas, including B-cell lymphomas from MALT-type marginal cells, i.e., tumors developing from lymphoid tissue associated with mucous membranes. Among primary NHL of visual organs, the most frequent are indolent MALT lymphomas that make up to 54.4% [2, 8] and tumors from the cells of the mantle zone - up to 23.5% [7, 9, 10]. Diffuse large B-cell lymphoma (DLBCL) of the orbit ranks third in incidence among other lymphomas.

Lately, prognostic factors affecting treatment efficacy and patient survival are of particular importance when developing tactics for treating lymphomas of the orbit. The disease prognosis for NHL of the orbit was estimated by International Prognostic Index (IPI), which considers the patient's age (over 60 years old), general status by ECOG, LDH in serum (over 450 IU / l), Ki 67 proliferative index, IHC data, and Ann Arbor classification stage.

Purpose of the study was to assess the efficacy of combination therapy of patients with orbital lymphoma depending on prognostic factors.

Materials and Methods: We have analyzed the literature data and the results of our own study when conducting combination treatment in patients with lymphoma of the orbit.

The inclusion criteria: primary patients above 18 years with B-cell lymphoma, verified by histology and IHC tests, regardless of proliferative activity (Ki 67) and tumor stage; ECOG performance status – NMT 3. Other inclusion criteria included: ANC ≥1,000/μL, PLT CNT ≥50,000/μL, serum creatinine and urea levels ≤1.5x ULN, ALT and AST ≤2.5x ULN. Overall 3-year survival rate.

All surgery interventions were planned individually based on the findings of radiological examinations. Ultrasonography before the operation was performed using ex-

pert class "Logiq-7" ultrasonographer. We used multi-frequency transducers: linear with a frequency of 5-7.5 MHz and convex with a frequency of 3.5-5 MHz. Additionally, to assess the vascularization of the DDC, Power Doppler Mapping and SD in real-time, when the second tissue harmonic mode is activated.

All 17 patients received treatment and diagnostic orbitotomy with the removal of the orbit tumor and rapid histological examination of the surgical material. A rapid survey was conducted to exclude other morphological forms of neoplasms, which could affect surgical tactics.

Killian's transcutaneous orbitotomy was performed in 11 (64.7%) patients, transpalpebral orbitotomy – in 3 (17.6%), external orbitotomy by bone-temporal access – in 2 (11.7%), and by Smith access – in 1 (5.8%) patient.

After surgery, the patients received polychemotherapy (PCT) in different regimens depending on the prognostic factors (stage of the process, IHC data, proliferative index, etc.). The patients with B-cell lymphomas and CD 20 (+) antigene expression received PCT in the R-CHOP regimen (6 to 8 courses): Rituximab 375 mg/m^2 on Day 1, IV, Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2, all i / v on Day 2, prednisolone 40 mg/m^2 on Days 1-5. The patients with T-cell NHL received PCT in the CHOEP regimen (Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2 - all i / v on Day 2, Etoposide 100 mg/m^2 on Days 1-3 i.v., and Prednisone 40 mg/m^2 i.v. on Days 1-5), 6 courses in total. Five patients with stage IV of the process underwent an orbitotomy and partial removal of the tumor and subsequent immune PCT in the R-CHOP scheme up to 3-4 courses.

The effectiveness of treatment was assessed by the results of clinical, laboratory and instrumental studies (full blood count (FBC), lactate dehydrogenase (LDH), alkaline phosphates (ALP), radiation methods).

The primary points of assessment included: size and localization of the primary tumor according to radiology examination, FBC, blood chemistry (LDH and ALP), tumor biopsy IHC, myelogram, cytogenetic test results, immunological studies and the patient's activity by ECOG scale. The primary points were assessed by ophthalmoscopy, FBC, blood chemistry (LDH and ALP), tumor needle biopsy, orbitotomy with subsequent histological examination of the tumor, IHC-test to determine the CD 20 antigene expression.

The secondary endpoints of assessment included: tumor regression rate (complete, partial regression) based on the tumor size reduction data, intoxication symptoms relief, the improvement of results of radiology examination, blood biochemistry (LDH and ALP), the myelogram data after 4-6 PCT courses, as well as the EGOC performance status and 3-year total survival of the patients.

Results and Discussion: We analyzed the results of a combination treatment of 17 patients with NHL of the orbit, of them, 8 men and 9 women. The patients were aged 23 to 92, average age – 57 years. Distribution of disease stage: stage III – 12 (70.5%), stage IV – 5 (29.4%). Unilateral damage to the orbit – in 15 (88.2%) patients, bilateral – in 2 (11.7%) patients. In 12 (70.5%) patients, the process was localized in the anterior parts of the orbit, in 5 (29.4%) – in the middle and deep parts of the orbit with distribution to the maxillary sinus. All patients had the EGOC performance status 3-4 before the treatment.

The clinical picture of the NHL of the orbit was characterized by different degrees of exophthalmos, the difficulty of reposition, ptosis of the upper eyelid, diplopia, displacement of the eyeball, restriction of its mobility.

Radiation examination (figure 1) showed the process localization in the orbit, namely, nodular form of NHL and allowed to determine the damage to the lacrimal gland. Twelve patients (70.5%) with frontal localization of the process in the orbit underwent cytological verification of the process. The cytological sign of lymphoma was the detection of the proliferation of abnormal lymphoid elements in the resulting biopsy. Five (29.4%) patients with deep localization of the tumor underwent orbitotomy with subsequent histological and IHC examination.

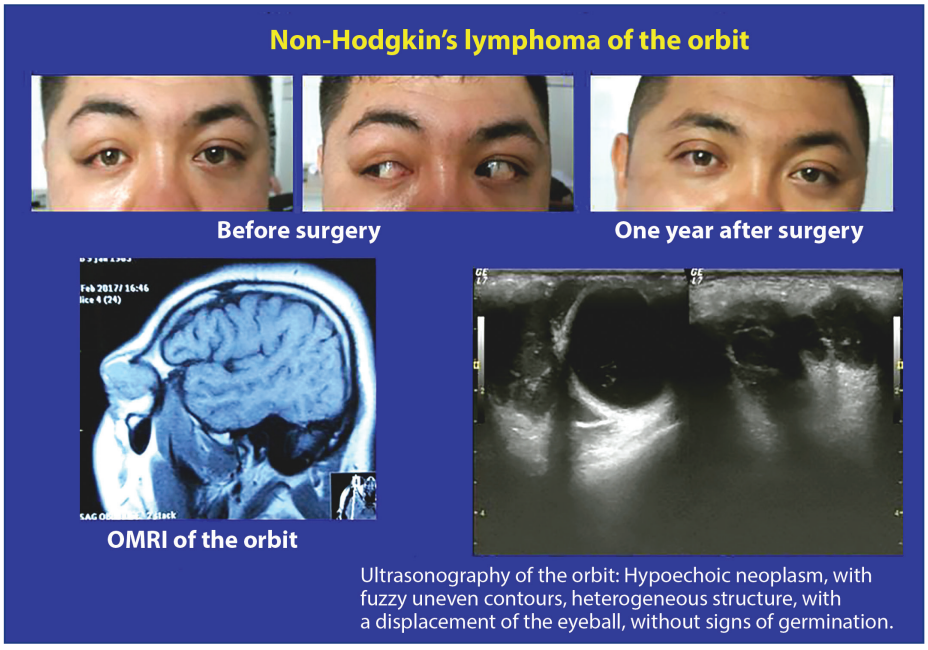

Figure 1 – Patient A., 45 years (episodes before and after treatment)

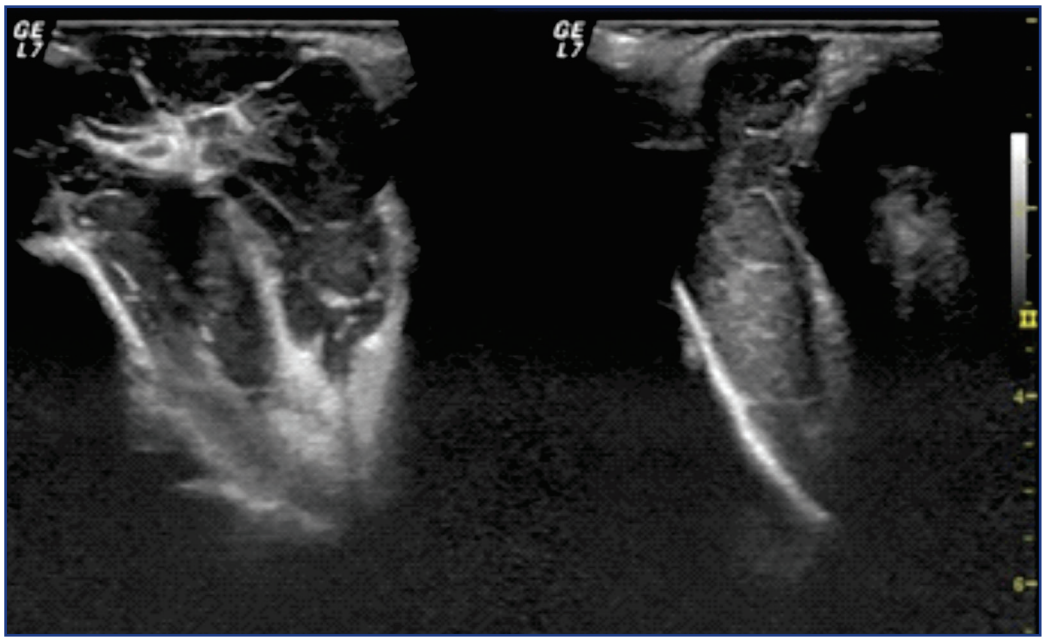

Figure 2 – Ultrasonography, Patient A., 67 years. Lymphoma of the orbit

The study of the incidence of morpho-immunological variants of primary NHL has shown the prevalence of DLBCL (8 cases, 47.0%) and MALT lymphoma (4 cases, 23.5%). Other cases included lymphomas from the mantle zone (2 cases, 11.7%), follicular lymphoma (2 cases, 11.7%), and T-cell lymphoma (1 case, 5.8%).

Saakyan et al. [10] reported the number of primary B-cell lymphomas of the orbit not to exceed 50% what is fully consistent with our data.

In most cases (16 out of 17), the tumor had high proliferative activity: Ki 67 varied from 56 to 80%. Besides, IHC examination has shown the CD20 antigene expression in all but one patient.

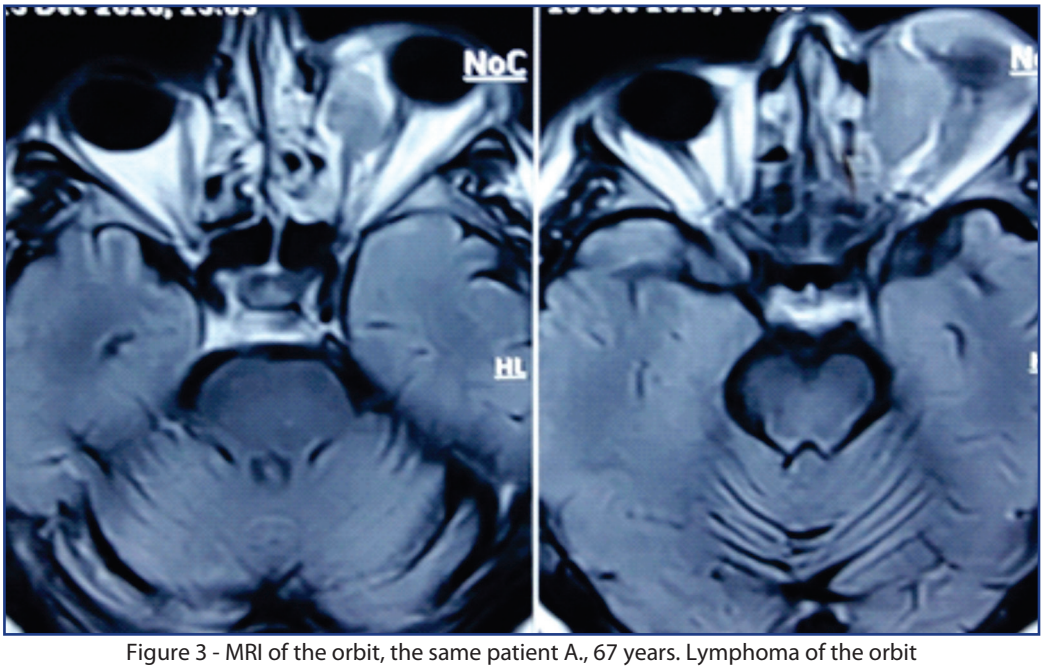

Figure 3 - MRI of the orbit, the same patient A., 67 years. Lymphoma of the orbit

Lymphoproliferative diseases of the orbit suggest conservative surgery. It is essential not only to preserve the vision but to avoid, as much as possible, such violations of the organ of vision, as squint, ptosis, coarse postoperative scars. Individual planning of operations and use of microsurgical equipment, careful hemostasis when performing orbital operations allowed to reduce the percentage of postoperative complications in this category of patients by 2-2.5 times compared to the results without individual planning of operations.

After immune PCT, all patients had remission of the disease, confirmed by radiation examination (more than 80%).

Only in one case, due to the residual tumor in the maxillary sinus, the patient had to undergo additional remote gamma therapy in the single boost dose 2 Gr to total boost dose 36 Gr after 4 PCT courses. One month after the radiation therapy radiation examination shows partial regression of the tumor in the maxillary sinuses. It is worth noting that before treatment all the patients, especially those with stage IV of the disease, had high LDH (560 to 645 U / L) and ALP (270 to 320 U / L) levels. After the conducted combination therapy, the LDH and ALP levels approached normal values: LDH varied in the range of 259 - 332 U / L and ALP – 132 to 143 U / L. FBC values were also normalized after their treatment.

After surgery and immune PCT, the ECOG performance status was equal to 1. All patients are currently in remission and under surveillance at the place of residence. Regardless of the effectiveness of treatment, 6-7 months later, they should pass PET-CT to evaluate the effectiveness of treatment and predict further therapy.

Analysis of data obtained in the limited cohort of patients with tumors of B-cell origin stages III-IV, leads to the following conclusion: the scope of surgery and the PCT regimens depended mainly on the stage and localization of the process, whereas the immune PCT was administered depending on the cell origin of the tumor and the proliferative index. Nearly all tumors had a high proliferative index, which dictated the use of adjuvant immune PCT in all cases of B-cell lymphoma. In all patients at terminal stages, the combination therapy (surgery + immune PCT) allowed to achieve a better effect compared with the surgical method, which indicates the adequacy of the choice of treatment tactics.

It should be noted that the effectiveness of treatment and the disease forecast did not significantly depend on the patient age. The liver enzymes (LDH and ALP) were back to normal levels after surgery and immune PCT what indicates their prognostic value.

The quality of life of patients has improved after treatment; the ECOG performance status was equal to 1.

Conclusions:

1. The orbit of the eye is most often affected by B-cell NHL. In our study, 16 out of 17 patients (94%) had B-cell lymphoma vs. 8 (47%) patients with DLBCL.

2. Combination therapy (surgery + immune PCT) has proven its high efficacy against advanced stages of the disease. Remission has exceeded 80%.

3. The proliferation index of tumors, the expression of CD 20 (+) antigen, as well as the LDH and ALP levels have a more significant effect on the prognosis of the disease compared with other prognostic signs.

References

1. Grishina E.E. Patogenez vnutriglaznoy limfomy [Pathogenesis of intraocular lymphoma] // Tumors and tumor-like diseases of the organs of vision: Collection of scientific works of the scientific and practical conference. – 2010. – P. 31–35. Russian;

2. Grishina E.E., Nechesnyuk S.YU. Nekhodzhkinskiye limfomy orbity: kliniko-morfologicheskiye paralleli [Non-Hodgkin lymphomas of the orbit: clinical and morphological parallels] // Diseases, tumors and traumatic injuries of the orbit: Collection of scientific works of international Symposium. – 2005. Russian;

3. Malek S.N. et.all. MALT Lymphomas // Curr. Treat. Options Oncol. – 2003. – Vol.4. –P. 269–279;

4. Grishina E.Ee. Zlokachestvennyye limfomy. Diagnostika i lecheniye s pozitsii oftal'mologa [Malignant lymphomas. Diagnosis and treatment from the perspective of an ophthalmologist] // Klinicheskaya oftal'mologiya [Clinical Ophthalmology]. – 2006. – Vol. 7, № 1. – P. 14–16. Russian;

5. Cahill-M et al. Ocular adnexal lymphoma – comparison of MALT lymphoma with other histological types // Br. J. Ophtalmol. – 1999. – Vol. 83. – P. 742–747;

6. Grishina E.Ee. Zlokachestvennyye limfomy. Diagnostika i lecheniye s pozitsii oftal'mologa [Malignant lymphomas. Diagnosis and treatment from the perspective of an ophthalmologist] // https://www.eurolab.ua/encyclopedia/565/47438. 07.06.2019. Russian;

7. Brovkina A.F. Bolezni orbity: rukovodstvo dlya vrachey [Diseases of the orbit: a guide for doctors]. – Medical Information Agency (MIA), 2008. Russian;

8. Bairey O. et al. Orbital and adnexal involvement in systemic non-Hodgkin's lymphoma // Cancer. – 1994. – Vol. 73. – P. 2395–2423;

9. Klinicheskaya onkogematologiya [Clinical oncohematology] / ed. M.A. Volkova – M.: Medicine, 2007. Russian;

10. Saakyan S.V. i dr. Zlokachestvennyye (Nekhodzhkinskiye) limfomy orbity po obrashchayemosti [Malignant (Non-Hodgkin) lymphomas of the orbit by negotiability] // Proceedings of the scientific conference dedicated to the 80th anniversary of the Academician N.N. Burdenko Neurosurgery Research Institute, RAMN. – M.: 2012. – P. 80–87. Russian.

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Risk assessment of metachronous peritoneal dissemination after radical surgery for gastric cancer

Relevance: *A high incidence of metachronous peritoneal dissemination (PD) and extremely unfavorable prognosis of gastric cancer (GC) in case of peritoneal carcinomatosis in comparison to the development of distant lymphohematogenous metastases [1] necessitate the prediction of metachronous PD in patients radically operated for GC to determine the high-risk cohort. The literature does not describe methods of evaluating the probability of PD in GC progression what justifies the feasibility of research in this direction.*

Purpose of the study *was to increase the efficiency of the prediction of metachronous PD.*

Results: *The results of 1065 radically operated patients (of them, men – 60%, women – 40%; aged 23-89, in average, 63±12 years) showed that a high-risk factors of GC progression with metachronous PD was associated with a metastatic damage of the regional lymphatic collector, with ulcerous-infiltrative and diffuse-infiltrative forms of GC progression, and with the spread of the primary tumor deeper submucosal layer. The proposed prognostic model based on multifactorial analysis (Fine-Gray model) can be used to evaluate the probability of metachronous MD development (concordance index – 0.81).*

Conclusion: *The proposed prognostic model using a nomogram or a formula ensures a differentiated approach to the choice of adjuvant treatment, taking into account the actual probability of metachronous PD development. The model can also be used in the planning of diagnostic and treatment measures aimed at maximum early detection and prevention of this type of GC progression.*

Keywords: *gastric cancer, peritoneal dissemination (PD).*

Introduction. A high incidence of metachronous peritoneal dissemination (PD) and extremely unfavorable prognosis of gastric cancer (GC) in case of peritoneal carcinomatosis in comparison to the development of distant lymphohematogenous metastases [1] necessitate the prediction of metachronous PD in patients radically operated for GC to determine the high-risk cohort. The latter will enable to introduce a differentiated approach in the planning of therapeutic and diagnostic measures aimed at the earliest possible detection and prevention of that GC progression form.

Materials and methods. The study includes 1065 patients, radically operated in N.N. Alexandrov National Cancer Center (Minsk, Republic of Belarus) in 2008–2016. Of them, the breakdown by sex was the following: men – 640 (60.1%), women – 425 (39.9%). The age of patients varied in an interval of 23-89 years old, on average, 63±12 years. The clinical and morphological patterns and the degree of the tumor process prevalence are presented in Table 1.

Table 1 – Degree of the tumor process prevalence pTN

The tumor invasion depth	Degree of metastatic lesion of the regional lymph collector pN				Total number of patients
	pN0	pN1	pN2	pN3	
pT1	204	22	5	0	231
pT2	146	44	12	4	206
pT3	78	44	30	13	165
pT4	153	95	86	129	463
Total patients	581	205	133	146	1065

By their histological structure, all distant tumors belonged to adenocarcinomas with various differentiation levels. 114 patients had highly differentiated adenocarcinoma GI, 352 had moderate differentiation GII, 518 had low differentiation GIII, and 81 had undifferentiated adenogenic cancer GIV. Diffuse-infiltrative and ulcerous-infiltrative were the most common forms for tumor growth (by Borrmann) - 55% of all patients, 253 and 329 cases, respectively. The saucer-like growth pattern was registered in 451 cases, and the polypus form was detected in 32 cases.

The analysis of competing risks [2] was applied to evaluate long-term treatment results. PD was the most common variant of GC progression. It differed from other options by both the development mechanism and approaches to its prevention and treatment [3]. That was the reason why we've chosen PD among the possible variants of distant metastasis in GC, that is, distant lymphohematogenous metastases (DLHM). The following events were considered to be competing: 1) GC progression with PD development; 2) GC progression with DLHM development.

The Fine and Gray model was used for multivariate analysis [4]. The confidence intervals (CI) of the relative

risk (RR) were calculated based on the corresponding CI regression coefficients. Among the possible risk factors were considered the following: sex, age, depth of invasion by the primary gastric stomach wall tumor (pT), degree of metastatic lesion of the regional lymph collector (pN), the volume of lymph node dissection (D1 or D2), and the nature of the performed surgery. The regression analysis was used to determine the effect of applied treatment and the tumor process characteristics in various variants of GC progression. The statistical data analysis was performed using the statistical package R v. 3.1.1 (GPL license) and the packages *survival* [5], and *cmprsk* [6].

Results and discussion. The observation median was 48 months, the median to progression with PD development – 10.1 months, DLHM – 13.4 months. The single-factor analysis has revealed the following factors which had a statistically significant effect on the both PD and DLHM progression: the macroscopic form of primary tumor growth (p <0.001), depth of the gastric wall invasion pT (p <0.001), number of metastases in the regional lymph nodes pN (p <0.001). The volume of performed LD (D1 or D2) and nature of the operation (standard or combined, gastrectomy or subtotal gastrectomy) statistically significantly affected only the PD development (p = 0.034 and p <0.001, respectively). The age of patients (in age groups of 23–55, 56–65, 66–75 and over 75 years old), as well as sex, did not affect the GC progression. The multifactor analysis using the competing risk model (Fine and Gray model) was conducted to determine the cumulative effect of these factors on GC progression with metachronous PD (Table 2).

In our study, as well as in the available literature, infiltrative forms of GC (infiltrative-ulcerative and diffuse-infiltrative) were associated with a high risk of PD development in remote terms after radical surgery [7]. A massive metastatic lesion of the regional lymph collector was another adverse prognostic factor for PD development. 1 or 2 metastases in regional lymph nodes indicated a tendency to an elevated risk of carcinoma development (p = 0.092), while 3 and more metastases in the regional lymph collector were associated with an elevated relative risk of carcinomatosis in remote terms after radical surgery. The statistical difference was significant: p = 0.030 at pN2, and p < 0.001 at pN3 (Table 2).

Table 2 – Relative risk of gastric cancer progression with peritoneal dissemination development

Factors associated with adverse outcome	Results of regression analysis				
	Preliminary model		Final model		
	β	p	β	RR (95% CI)	p
Age	0	0.15	–	–	–
Sex male *vs.* female	-0.11	0.48	–	–	–
Adenocarcinoma GII *vs.* GI	0.06	0.88	–	–	–
Adenocarcinoma GIII *vs.* GI	-0.02	0.32	–	–	–
Adenocarcinoma GIV *vs.* GI	0.52	0.96	–	–	–
Diffuse-infiltrative *vs.* saucer-like + polypus	0.75	0.001	0.90	2.4 (1,6–3,8)	< 0.001
Ulcerous-infiltrative *vs.* saucer-like + polypus	1.20	< 0.001	1.25	3.5 (2,4–5,1)	< 0.001
pN1 *vs.* pN0	0.38	0.08	0.35	1.4 (0,9–2,2)	0.092
pN2 *vs.* pN0	0.48	0.02	0.47	1.6 (1,0–2,4)	0.030
pN3 *vs.* pN0	0.94	< 0.001	0.96	2.6 (1.8–3.8)	< 0.001
pT2 *vs.* pT1	2.42	0.002	2.50	12.1 (1.6–93.4)	0.017
pT3 *vs.* pT1	3.49	< 0.001	3.56	35.2 (4.8–258.6)	< 0.001
pT4 *vs.* pT1	3.67	< 0.001	3.79	44.4 (6.1–321.5)	< 0.001
Lymphadenectomy D1 *vs.* lymph node dissection D2	-0.1	0.70	–	–	–
Combined operations *vs.* subtotal resection of stomach (distal and proximal)	0.53	0.01	–	–	–
Gastrectomy *vs.* subtotal gastrectomy (distal and proximal)	0.30	0.067	–	–	–

The obtained findings indicate the possibility for progression with PD development not only when the tumor invades the stomach serous membrane but also at less advanced tumor process corresponding to pT2-3, that is when the tumor overruns the submucosa membrane. At the same time, the concomitant metastatic lesion of the regional lymph collector elevates the risk for metachronous PD development. This highlights the feasibility and relevance of the development of methods for PD progression projection and prevention not only in patients with serous membrane invasion but also in less advanced tumor process – pT2-3.

Based on the multivariate analysis findings presented in Table 2, we have developed a model for prediction of risk for PD development. The following model variables were used for the mathematical description of the model:

$x1 = 1$, if the macroscopic form of primary tumor growth is diffuse-infiltrative, and $x1 = 0$, if the macroscopic growth form is ulcerous-infiltrative, polypus or saucer-like;

$x2 = 1$, if the macroscopic form of the primary tumor growth is ulcerous-infiltrative, and $x2 = 0$ in the other case;

$x3 = 1$, if there are one or two metastases in the regional lymph nodes (pN1), and $x3 = 0$ in the other case;

*x*4 = 1, if there are from three to six metastases in the regional lymph nodes (pN2), and *x*4 = 0 in the other case;

*x*5 = 1, if there are seven or more metastases in the regional lymph nodes (pN3), and *x*5 = 0 in the other case;

*x*6 = 1, if there is the tumor invasion of the muscular coat of the stomach (pT2), and *x*6 = 0 in the other case;

*x*7 = 1, if there is the tumor invasion of stomach wall sub-serous layer (pT3), and *x*7 = 0 in the other case;

*x*8 = 1, if there is the tumor invasion of stomach serous membrane (pT4a) or tumor invasion of neighboring structures (pT4b), and *x*8 = 0 in the other case.

The verification of assumption about the risks proportionality (presence or absence of correlation of ranked Schoenfeld' residues has been performed, which was not violated - p = 0.203. The model was subjected to internal validation [8] by bootstrapping with 1000 repetitions to assess its suitability for prognosis. The validation included calibration of the model to prevent re-training and error and the assessment of the model's discriminatory capacity.

Figure 1 shows the expected probability of progression with PD development, and calibration graphs for 12, 24, and 36 months with the calculation of the average absolute calibration error and the 90th quantile of absolute calibration error.

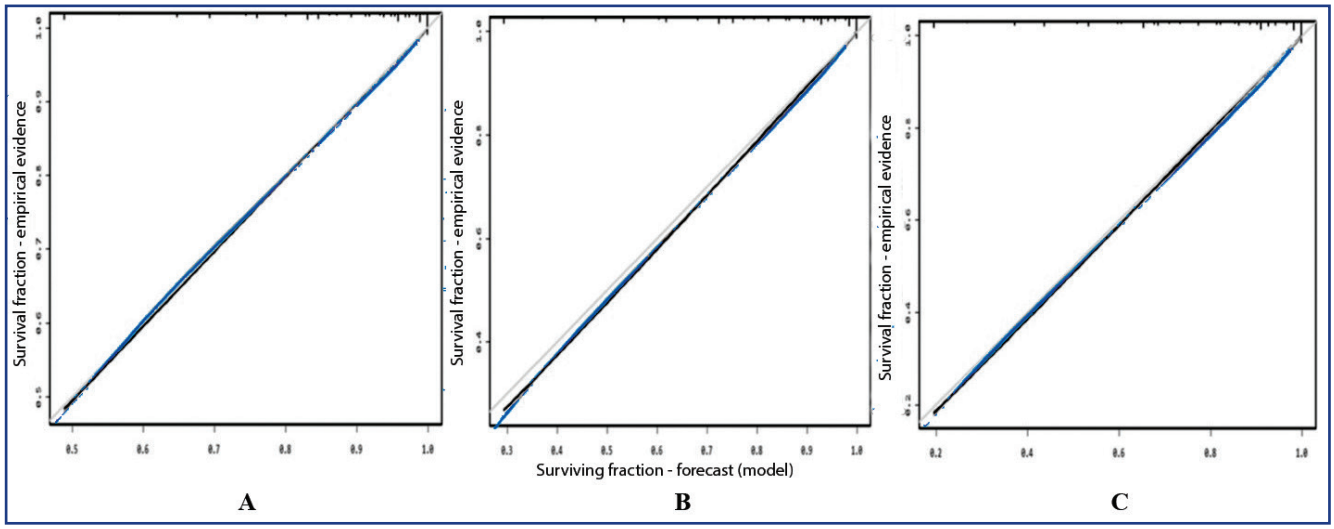

Figure 1 – Calibration graphs of the prognostic model for peritoneal dissemination in 12 (A), 24 (B), and 36 months (C) (gray – the ideal model, black – the follow-up data, blue – the corrected model)

According to Figure 1, the absolute calibration error did not exceed 5% in the 1-year, 2-years, and 3-years model prognosis, which means a high prognostic accuracy of the proposed model. The concordance index was 0.81. The choice of the follow-up period of 1 to 3 years for prediction of the dissemination probability was justified by the fact that the absolute number of cases of cancer progression after surgery was observed during the first 2 years after surgery, followed by a decline of death probability due to the tumor process progression [9].

Based on a linear combination of predictors, the formula was proposed for estimation of PD risk development after the GC radical surgical treatment.

$$PI = 0{,}8952 \times x1 + 1{,}2508 \times x2 + 0{,}3543 \times x3 + 0{,}4686 \times x4 + 0{,}9585 \times x5 + 2{,}4959 \times x6 + 3{,}5602 \times x7 + 3{,}7941 \times x8 \quad (1)$$

where PI – is a prognostic index (PI).

This formula reflects the relative risk logarithm change depending on the values of the variables x1–x8.

PIs were calculated for patients within the study cohort based on the formula above to assign them to risk groups. Concurrently, the 33rd and 67th quantiles of PI variable distribution were identified, based on which the following boundary intervals of three risk groups were determined: 1) standard with PI<3.4; 2) intermediate with 3.4≤PI≤4.75; 3) high with PI>4.75.

The probability values presented in Table 3 were used to estimate the probability of metachronous PD.

The data presented in Table 3 can be used in practice for rough risk estimation of peritoneal carcinomatosis development.

For a more precise estimation of the likelihood of metachronous PD development based on a linear combination of predictors, as the relative risk logarithm, the PD nomogram was developed (Figure 2).

Table 3 – Probability of peritoneal dissemination (PD) in 12, 24, 36 months of the follow-up period after radical surgery in risk groups

Risk groups for PD	Probability of PD, % / Follow-up period		
	12 months	24 months	36 months
Standard risk	0.7 ± 0.3	1.0 ± 0.5	1.2 ± 0.6
Intermediate risk	6.8 ± 1.2	10.2 ± 1.8	12.4 ± 2.1
High risk	24.1 ± 2.8	34.5 ± 3.7	40.6 ± 4.4

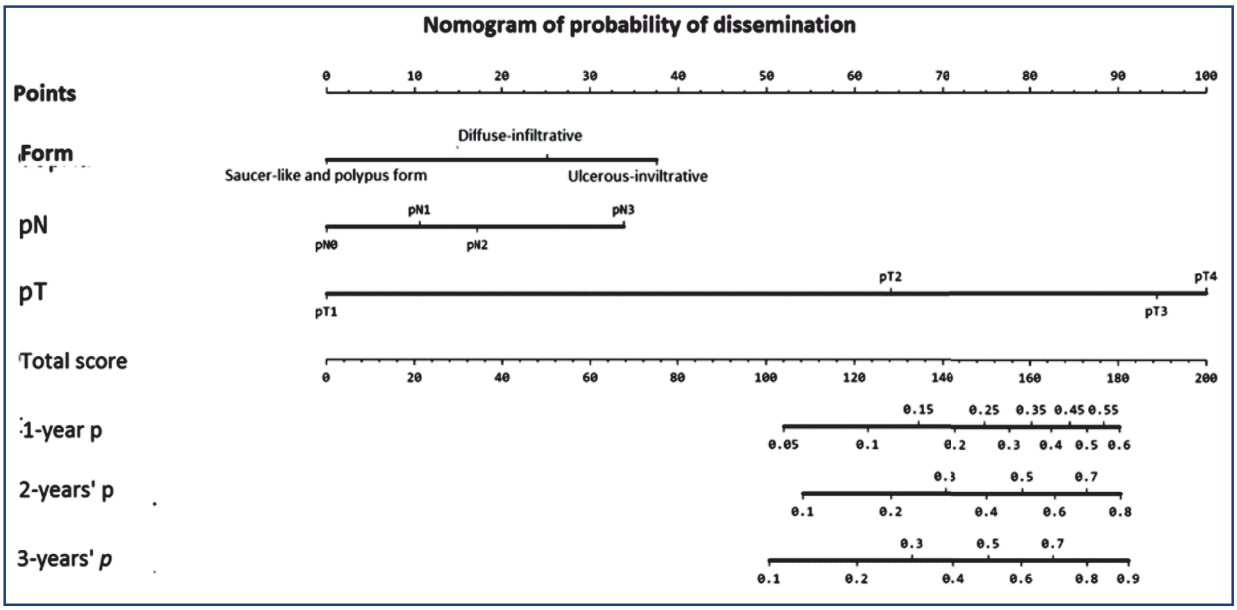

Figure 2 – Nomogram for prediction of the expected probability of the metachronous peritoneal dissemination development

The nomogram makes an account of independent prognostic factors established by the multivariate analysis (Table 2). Each factor in the nomogram is scored according to its regression coefficient, which is the logarithm of the relative risk. The total score defines the probability of the disease progression with PD development 1-3 years after radical surgery. The total score above 160 points indicates a high probability of PD development; the total score from 115 to 159 points indicates intermediate probability; the total score from 0 to 114 points indicates a low probability. The high or intermediate probability of PD development is the indication for intensive immunochemotherapy in one the regimens described in the literature to prevent GC progression with PD development.

Conclusion. High risk of gastric cancer progression with peritoneal dissemination occurs with any degree of the regional lymph collector metastatic lesion: pN1 – RR 1.4 (95% CI 0.9–2.2), p = 0.092; pN2 – RR 1.6 (95% CI 1.0–2.4), p = 0.030; pN3 – RR 2.6 (95% CI 1.8-3.8), p <0.001; in ulcerous-infiltrative – RR 3.5 (95% CI 2.4–5.1), p <0.001 and diffuse-infiltrative forms of GC growth – RR 2.4 (95% CI 1.6–3.8), p <0.001; in the primary tumor spread deeper than submucous membrane: pT2 – 12.1 (95% CI 1.6–93.4), p = 0.017; pT3 – 35.2 (95% CI 4.8–258.6), p <0.001; pT4 – 44.4 (95% CI 6.1–321.5), p<0.001.

The proposed prognostic model using the nomogram or the formula ensures a differentiated approach to the choice of adjuvant treatment, taking into account the actual probability of metachronous PD development. This model allows predicting the probability of metachronous peritoneal dissemination development in patients radically treated for gastric cancer immediately after morphological clarification of the tumor process stage. This model can also be used to plan adjuvant treatment on a case-by-case basis to prevent peritoneal carcinomatosis progression.

References:

1. Lee J.H., Son S.Y., Lee C.M., Ahn S.H. Park D.J., Kim H.H. Factors predicting peritoneal recurrence in advanced gastric cancer: implication for adjuvant intraperitoneal chemotherapy // Gastric Cancer. – 2014. – Vol. 17, № 3. – P. 529–536;

2. Kalbfleisch J.D., Prentice R.L. The Statistical Analysis of Failure Time Data. – New York: John Wiley and Sons; 1980. – 321p.

3. Revtovich M.YU., Kras'ko O.V., Sukonko O.G. Prognozirovaniye peritoneal'nogo kantsermatoza posle radikal'nogo khirurgicheskogo lecheniya raka zheludka [Prediction of peritoneal carcinomatosis after radical surgical treatment of gastric cancer] // Onkolog. zhurn. {Cancer J] – 2018. – Vol. 12, № 2. – P. 25–34. Russian;

4. Fine J.P., Gray R.J. A proportional hazards model for the subdistribution of a competing risk // J. Am. Stat. Assoc. – 1996. – Vol. 94. – P. 496–509;

5. R Core Team. R: A language and environment for statistical computing. – Vienna, Austria: R Foundation for Statistical Computing, 2014;

6. Gray B. cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-7. // CRAN.R-project.org/package=cmprsk. 17.06.2019;

7. Nered S.N., Klimenkov A.A. Khirurgicheskoye lecheniye raka zheludka s vysokim riskom implantatsionnogo metastazirovaniya [Surgical treatment of gastric cancer with a high risk of implantation metastasis] // Vopr. onkologii. [Issues of Oncology]. – 2005. – № 1. – P. 75–80. Russian;

8. Harrell F.E., Lee K.L., Mark D.B. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors // Stat. Med. – 1996. – Vol. 15, №. 4. – P. 361–387;

9. Dikken J.L., Baser R.E., Gonen M., Kattan M.W., Shah M.A., Verheij M., van de Velde C.J.H., Brennan M.F., Coit D.C. Conditional probability of survival nomogram for 1-, 2-, and 3-year survivors after an R0 resection for gastric cancer // Ann. Surg. Oncol. – 2013. – Vol. 20, № 5. – P. 1623–1630.

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Scientific and practical grounds for the model of mobile outpatient assistance to incurable cancer patients (short literature review)

Palliative care (PC) is active, comprehensive care for patients whose disease does not respond to therapy. Primary objectives of PC include management of pain and other symptoms, assistance to patients in solving their psychological, social, and spiritual problems. PC is aimed to ensure the highest possible quality of life for both the patient and his family.

PC involves relieving patient suffering throughout his disease (along with radical treatment) and medical care in the last months, days, and hours of life. It would be wrong to think that a dying patient needs only care. Many professional nuances that help alleviate suffering can only be applied by trained specialists.

Mobile palliative outpatient care is one of the modern, humanistic methods of assistance to dying cancer patients and their relatives.

Keywords: *terminal cancer patients, palliative care, mobile team, quality of life.*

The state social policy of Kazakhstan provides for health promotion, increased care, improving the quality of life of the population, and the availability of medical services.

The RK Code on Health of the Population of the Republic of Kazakhstan (of September 18, 2009) states the right of each RK citizen for palliative care (PC) [1].

PC is a complex of medical interventions aimed at relieving pain and alleviating other severe manifestations of the disease, as well as providing psychological, social and spiritual assistance to the patient and his family in order to improve the quality of life of the incurables [2, 3].

The World Health Organization (WHO) has been the sole initiator of the provision of palliative care to patients with incurable malignant tumors. In the 1970s, a small expert team under the aegis of WHO started to promote PC in more than 40 countries headed by Switzerland, United States, United Kingdom, Canada, Netherlands, Belgium, France, and Australia. PC has become a specialized discipline, with its rights, academic and clinical positions, specialized research and literature, and integrated development program [4, 5].

20.4 mln. people all over the world need PC. Of them, 94% are adults, 69% are above 60 years, 25% are aged 15 to 59, and 6% are children (WHO data). 34% of those who died from cancer needed PC at the end of life. 80% of people who need PC live in low-income countries [6].

WHO reports that malignant neoplasms have become one of the major causes of death. GLOBOCAN reports that in 2018, 18.1 mln. people were living with cancer vs. 9.6 million of deaths from cancers [7].

Today, many countries conduct large-scale scientific research, establish large cancer centers that offer diagnostics, prevention, treatment, and specialized services aimed at improving the quality of life of the incurables [8, 9].

According to many scientists, in developed and developing countries many people who suffer from incurable diseases that limit the life expectancy or are associated with acute conditions often dye in fear and loneliness, in anguish, without any actions taken to relieve pain and treat other pathological symptoms [10]. PC can prevent and reduce this suffering. Healthcare workers are ethically obliged to alleviate suffering.

Many foreign researchers have come to a single conclusion that about 90% of incurables would prefer to spend their last days at home [11-13].

A.V. Gnezdilov, Chief Physician of the first Russian hospice, says that the incurables and their family members can not always obtain the necessary attention and assistance of specialists [14]. Improving the quality of life of a suffering patient in his last days is always related to the accessibility of the relevant desensitization [15, 16]. There are several reasons for that:

- Proper characterization of the disease symptoms that is, the use of special scales that determine the symptoms of pain;
- Fear of side effects of drugs that remove the feeling of pain [17];
- Lack of access for many cancer patients to a comprehensive PC due to limited access to pain killers [18, 19].

Kazakhstan has just recently started recognizing PC as an essential part of sociomedical assistance to the population [20, 21]. Though the first hospices were opened in Kazakhstan in 1999, the legal framework for PC development was approved only ten years later, with the introduction into force of the RK Code "On Health of the Population of the Republic of Kazakhstan." Still, a lot is yet to be done today to make PC accessible for the patients who need it. The PC department re-opened at cancer dispensaries and the quality of training of specialized personnel do not meet generally accepted international standards.

The socio-economic conditions raise the importance of providing PC in outpatient settings. Many international studies evidence that providing PC in clinical conditions is too expensive for the state budget [9]. In Kazakhstan, most of the patients prefer to receive PC at home, being surrounded by their relatives and friends.

Mobile PC is one of the most humanistic modern methods of providing care to cancer patients and their relatives. Today, PC is provided all over the world, and providing PC at home by mobile teams takes leadership in this sphere of services.

Unfortunately, Kazakhstan still has no official register of people who need PC. According to an assessment by the international adviser on palliative care, Thomas Lynch, made in 2012, this figure for 2012 amounted to 94,000 to 98,000 people, and at least 15 500 of them needed PC. He also concludes that usually two and more family members are involved in taking care of each patient, so about 283 000 people need PC each year. This massive volume of PC requires rearrangement of medical workers in rural and urban areas, as well as training and retraining of about 6 675 medical workers including doctors, nurses, psychologists, social workers and volunteers, and the provision of 825 beds for PC services.

In his study, Thomas Lynch communicates other PC-related problems shared with him by the representatives of hospices:

- Lack of hospices and services providing PC;
- Lack of possibilities for training and retraining;
- Legal and political obstacles for the development of the discipline;
- Poor awareness of medical workers about PC, lack of public knowledge;
- Problems with access to or lack of opiates;
- Lack of interdepartmental cooperation/coordination (e.g., between the ministries of healthcare and social protection), the absence of the National PC Association;
- Lack of means for agitation and promotion of the introduction of PC in the Kazakhstan healthcare system [21].

In 2018, 179 000 people in Kazakhstan were suffering from various forms of malignancies. 37 000 new cases are registered each year, and more than 17 000 people die. The disease rates add 3-5% each year. The early detection of cancer is improving, but the share of late detection (stage III-IV) is still equal to 44.2% [22, 23].

The Comprehensive Plan to Combat Cancer Diseases for 2018-2022 and the actions under the Roadmap for Improving Palliative Care in the Republic of Kazakhstan assume that every city center, district center, and each city of Republican level shall arrange mobile/multidisciplinary teams to provide home care to incurable cancer patients, with planned training and retraining of specialists.

The analysis and assessment of the current situation, the lack of scientific research in this field in our country necessitate the development of scientifically based recommendations aimed at improving the quality of life of cancer patients.

The lack of real mobile teams providing home care in the settings of the growing demand for their services requires rationalization of PC in our country with the formation of mobile outpatient teams providing medical, social, and psychological assistance.

References

1. The RK Code "On Public Health and Healthcare System: approved on September 18, 2009, # 193-IV;

2. Baines M. Pioneering days of palliative care // European Journal of Palliative Care. – 2011. – Vol. 18(5). – P. 223–227;

3. Kleminson B. Vvedeniye v palliativnuyu pomoshch' [Introduction into palliative care] / trans. from Eng. By O. Tseytlina, Ye. Bakunina; eds. D.V. Nevrozovd. – Moscow, 2016. – 276 p. Russian;

4. Vazhenin A.B., Sharabura T.M. Organizatsiya palliativnoy pomoshchi v regional'nom uchrezhdenii onkologicheskogo profilya [Organization of palliative care in a regional institution of oncological profile] // Palliativnaya meditsina i reabilitatsiya [Palliative medicine and rehabilitation]. – 2004. – № 1. – P. 24-28. Russian;

5. Voronova Ye.A., Podluzhnaya M.YA., Zlobina G.M. Organizatsionno-metodicheskiye predposylki formirovaniya tsentra palliativnoy pomoshchi v usloviyakh krupnogo promyshlennogo goroda [Organizational and methodological prerequisites for the formation of a palliative care center in a large industrial city]. – Perm: State Autonomous Educational Institution of Additional Professional Education "Perm Regional Center for Retraining of Health Care Workers", 2012. – 136 p. Russian;

6. Global atlas of palliative care at the end of life / World Palliative Care Alliance; WHO // www.who.int/cancer/publications/palliative-care-atlas/en/. 22.06.2019;

7. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries // CA: A Cancer Journal for Clinicians. – 2018. – Vol. 68. – P. 394-424;

8. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report // www.thelancet.com/commissions/palliative-care. 22.06.2019;

9. Palliative care is an essential part of cancer control / World Health Organization, Cancer Control Programme Department of Chronic Diseases, Health Promotion (CHP). – Geneva: World Health Organization, 2015;

10. Palliativnaya pomoshch' onkologicheskim bol'nym [Palliative care for cancer patients] / eds. G.A. Novikov, V.I. Chisson. – Moscow: All-Russian Public Movement "Medicine for the quality of life", 2006. – 192 p. Russian;

11. Vvedenskaya E.S., Varenova L.E. Mesto smerti bol'nykh kak indikator dlya vybora organizatsionnoy formy palliativnoy pomoshchi v kontse zhizni [Place of death of patients as an indicator for choosing the organizational form of palliative care at the end of life] // Problemy standartizatsii v zdravookhranenii [Problems of standardization in health care]. - 2013. - № 7/8. – P. 32-36. Russian;

12. Vvedenskaya E.S., Varenova L.E. Smertnost' bol'nykh na domu i neobkhodimost' organizatsii palliativnoy pomoshchi v kontse zhizni [Mortality of patients at home and the need to organize palliative care at the end of life] // Medical Almanac. – 2013. – № 5. – P. 71-74. Russian;

13. Wright A.A., Keating N.L., Balboni T.A., et al. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health // J. Clin. Oncol. – 2010. – Vol. 28. – P. 4457-4464;

14. Gnezdilov A.V. Pyatiletniy opyt raboty Lakhtinskogo khospisa № 1 [Five-year experience of the Lakhta hospice #1] // In: Problemy palliativnoy pomoshchi v onkologii. Antologiya nauchnykh publikatsiy [Problems of palliative care in oncology. Anthology of scientific publications] / eds. G.A. Novikova, V.I. Chissova, N.A. Osipova. – M., 2002. – Vol. I-II. – 13 p. Russian;

15. Abuzarova G.R., Alekseeva G.S. Differentsirovannaya farmakoterapiya bolevykh sindromov u onkologicheskikh bol'nykh [Differentiated pharmacotherapy of pain syndromes in cancer patients] // Materials of the IX Congress of Oncologists and Radiologists of CIS countries. – Minsk, 2016. – 682 p. Russian;

16. Paice J.A., Fine P.G. Pain at the end of life // In: Textbook of palliative nursing / eds. B.R. Ferrel, N. Coyle. – 2nd ed. – New York, NY: Oxford Univ. Press, 2006. – P. 131-153;

17. Novikov G.A., Rudoy S.V., Vaysman M.A. et al. Strategiya razvitiya palliativnoy meditsinskoy pomoshchi v Rossiyskoy Federatsii. Nekotoryye itogi i perspektivy [The development strategy of palliative care in the Russian Federation. Some results and prospects] // Palliativnaya meditsina i reabilitatsiya [Palliative medicine and rehabilitation]. – 2015. – № 3. – P. 5-12. Russian;

18. Vlasov YA.V., Sineok E.V., Dronov N.P. Analiz osnovnykh problem dostupnosti okazaniya palliativnoy meditsinskoy pomoshchi onkobol'nym [Analysis of the main problems of the availability of palliative care for cancer patients] // Vestnik Roszdravnadzora [Bulletin of the Federal Service on Surveillance in Healthcare and Social Development of Russian Federation]. – 2015. – № 4. – P. 24-32. Russian;

19. Novikov G.A., Rudoy S.V., Vaysman M.A. et al. Sovremennoye sostoyaniye i perspektivy razvitiya palliativnoy pomoshchi v Rossiyskoy Federatsii [The current state and prospects for the development of palliative care in the Russian Federation] // Palliativnaya meditsina i reabilitatsiya [Palliative medicine and rehabilitation]. – 2008. – № 3. – P. 5-11. Russian;

20. Shakenova A. Kazakhstan: the approved National Standards of Palliative Care. – Almaty: Soros-Kazakhstan Foundation, February 28, 2014. Russian;

21. Kaidarova D.R., Kunirova G.ZH. Palliativnaya pomoshch' v Kazakhstane: Etapy razvitiya i tekushchiye vyzovy [Palliative care in Kazakhstan: Stages of development and current challenges] // Onkologiya i radiologiya Kazakhstana [Oncology and Radiology of Kazakhstan]. – 2016. – № 41(3). – P. 114-121. Russian;

22. Kaidarova D.R., Afonin G.A. Modern system of palliative care in oncology [Sovremennaya sistema palliativnoy pomoshchi v onkologii] / eds. A. Eggermont, M. Zilbermann, B.I. Dolgushin. - Almaty, 2017. – 512 p. Russian;

23. Kunirova G.Zh. Memorandum of Kazakh Association of Palliative Care as of October 2017. Russian.

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The role of epigenetic research in diagnostics and treatment of breast cancer

Relevance: *Genetic mutations play an essential role in the development of malignant tumors; still, the part of epigenetic processes can also be significant. Epigenetic changes are not inherited and do not violate the DNA nucleotide sequence. However, they can critically change their accessibility for the transcriptional apparatus of the cell by chemical modification of specific chromosomal loci and associated genes. Acetylation and methylation of histones or DNA are examples of epigenetic changes. Epigenetic activation/deactivation of genes is the basis for the differentiation of all types of somatic cells. A change in the specific "epigenetic labeling" of a cell of a particular type causes cell de-differentiation or results in changing its phenotype (transdifferentiation). Given the scale of epigenetic regulation, it is logical that any violations of this process can lead to pathologies, including cancer.*

This paper reviews the modern approaches and methods of study of the molecular genetic basis for the development of malignant tumors and epigenetic mechanisms, in particular, DNA methylation in breast cancer.

Purpose of the study *is to review and analyze the existing molecular genetic methods for studying DNA methylation in breast cancer.*

Results: *DNA methylation is a critical mechanism of epigenetic modification, which is involved in gene expression programming and can contribute to the development of cancer, including breast cancer. Methylation of CpG islands of DNA methyltransferase, which is usually reversible, modifies the transcriptional activity of main proliferation genes or transcription factors involved in cell growth suppression or stimulation.*

Many genes can serve as biomarkers for early detection of breast cancer. For example, the researchers have detected hypermethylation of the DOK7 gene promoter portion, which is one of the diagnostic specific epigenetic markers of breast cancer. The study results we have analyzed show that combined epigenetic therapy leads to a synergistic antitumor response in patients with breast cancer [1-9].

Conclusion: *The currently available diagnostic and treatment methods aimed at aberrant methylation with DNA methyltransferase inhibitors trigger the repeated expression of "silent" genes and make it possible to increase the effectiveness of treatment. Aberrant methylation found in gene promoters is a sign of oncological transformation that can serve as a non-invasive biomarker in body fluids (blood, plasma) for early detection of breast cancer. However, there is currently no unique biomarker that would have sufficient specificity and sensitivity for use in therapy.*

Therefore, for a particular therapeutic case, a panel of several genes is required.

Thus, the methods of epigenetics were found to have vast diagnostic and therapeutic potential.

Keywords: *molecular and genetic methods, epigenetics, DNA methylation, breast cancer, biomarker.*

Introduction. Breast cancer (BC) is leading in the structure of cancer diseases. WHO reports more than 1.38 million new cases of BC every year in the world, at the death rate, is about 460 thousand. In the Republic of Kazakhstan, BC also ranks first in incidence. 4653 cases of BC registered in 2016 made 26.1 per 100,000 populations of both sexes. 1-year mortality was 5.4%, and 5-year survival was 57.8% [1]. Despite developed screening programs and high awareness of BC, there are still a high proportion of female patients who are admitted with grade III-IV of the disease. Therefore the survival rates remain extremely low. It maintains the relevance of early diagnosis of primary cancer and its recurrence, as well as the selection of effective therapy.

There is a growing number of papers [2–17] devoted to the study of molecular biological factors that regulate the mechanisms controlling cell division and death, as well as the maintenance of genetic stability and study of epigenetic mechanisms of cancer.

Epigenetic changes are changes in gene expression which come without any disturbances in the DNA sequence. They are important critical factors in cancer development and disease prognosis caused by the development of genetic and phenotypic instability [2]. Modifications can occur at both the genetic and epigenetic levels.

For example, a mutation in the tumor suppressor gene (TSG) indicates the accumulated DNA damage. In the absence of DNA repair, such cell becomes more prone to cancer development. Epigenetic disorders in the expression of main genes, including TSG, were found to play an essential role in carcinogenesis in general, and especially in the development of BC [3-5]. The increase in epigenetic disorders makes cancer cells more aggressive and changes their behavior from invasion in surrounding tissues to dissemination in lymphatic and blood vessels. This ultimately leads to the death of the patient if untreated.

Such epigenetic change as aberrant DNA methylation does not include changes in the DNA sequence; however, this covalent chemical modification of DNA has a significant influence on the whole gene expression. This altered gene expression leads to many accumulated changes which promote oncogenesis [6]. The use of epigenetic

methods, at first glance, seems to be secondary in comparison with the determination of the patient's genetic profile. However, standard genetic analysis reveals only the DNA nucleotide sequence that may not be disrupted. However, if the gene that protects the cell from cancer is methylated incorrectly, the gene can become malfunction and fail to perform its protective function.

In this case, epigenetic analysis is the only way to detect potential cell violations. An important difference between genetic and epigenetic changes is that drugs are efficient against epigenetic changes but absolutely helpless against genetic mutations [2].

Understanding the role of epigenetic methods in diagnostic and treatment of malignant tumors, in particular, BC, will provide a better view on the processes occurring in the body during tumor development and allow finding efficient approaches to their early diagnostics and treatment.

The purpose of the study was to review and analyze the existing molecular genetic methods for studying DNA methylation in BC.

***Materials and methods*:** The published sources on the topic "DNA methylation methods for diagnosis and therapy, in particular, early diagnostics and therapy of BC" were analyzed, including fundamental works of scientists, articles in scientific periodicals, materials of conferences and symposiums. The search in electronic databases was done by the following keywords: "epigenetics," "DNA methylation," "epigenetics in breast cancer diagnosis."

Results and discussion:

The use of DNA methylation as a biomarker in the early detection of *И*C.

Currently, histological verification and determination of invasion grade and tumor phenotype make the gold standard of BC diagnostics. These diagnostic methods require a biopsy of tumor material. Biomarkers of high sensitivity and specificity can be found in tissues and fluids of the patient's body. Since changes in the DNA methylation pattern are one of the earliest modifications in cancer development, these changes can serve as a biomarker for early detection of BC [7–8] as they make testing more objective.

Various methods to assess DNA methylation include bisulfite conversion, which is performed using a panel of selected genes and primers for amplifying CpG islands specific for Real-time-PCR methylation [3]. The general genomic approach with high-throughput sequencing utilizes bisulfite-converted DNA obtained from various non-invasive biological sources such as whole blood, serum, and plasma [3].

Several promising epigenetic markers for early BC detection are based on peripheral blood genomic analysis. For example, Yan et al. have found that the CpG islands of hyaluronoglucosaminidase 2 (HYAL2) were significantly hypomethylated in the peripheral blood of BC patients compared with the control group.

The level of blood HYAL2 methylation also acts as an early predictor of BC compared with the control group, with 64% sensitivity and 90% specificity [8]. At that, HYLA2 locus is hypermethylated specifically in BC tissue but hypomethylated in the blood, which indicates the same risk of BC. Therefore, HYAL2 hypomethylation in the blood can also be an early non-invasive peripheral biomarker.

Another similar study on the plasma of patients with BC and healthy women has revealed hypermethylation of kinesin 1A family (KIF1A) promoter in BC. The researchers concluded that high KIF1A promoter methylation in plasma could also be an early biomarker of BC [3]. The analysis of DNA methylation in twins has shown that the dock protein 7 (DOK7) promoter was hypermethylated in the blood of patients compared to their twins. Such hypermethylation was present several years before the diagnosis.

Consequently, DOK7 promoter methylation level could potentially be a biomarker for early detection of BC [9]. The status of DNA methylation inside and outside the CpG islands of a certain number of genes has shown that some of them were associated with the risk of BC. Kloten et al. have evaluated the methylation status of the TSG group (secreted by SFRP1, SFRP2, SFRP5 associated with proteins), the heavy chain family of the alpha trypsin inhibitor, member 5 (ITIH5), a WNT inhibitory factor 1 (WIF1), Dickkopf inhibitor WNT signaling pathway 3 (DKK3), and RASSF1A) [10] in circulating tumor DNA. A particularly important finding was that the DKK3 and ITIH5 CpG islands were unmethylated in women with benign breast pathologies and significantly hypermethylated in women with BC. The researchers hypothesized that promoter methylation of DKK3 and ITIH5 in blood could be used as a biomarker, mainly in patients with dense breast tissue, while RASSF1A methylation of CpG islets was not a good biomarker taking into account its low rate in healthy women.

Brennan's et al. [11] have studied the DNA methylation status outside the CpG of island ATM serine/threonine kinase (ATM) clusters and the repetitive elements of a long interspersed nuclear element 1 (LINE1) in leukocytes in a large group of women with and without BC. They observed higher methylation of the ATMmvp2a locus in BC patients compared with the control group and concluded that the locus could be used as a biomarker for the risk of BC. They also found that the association of ATM methylation with the risk of BC was more reliable in young women and that the biomarker remained stable for at least six years [11].

Kuchiba et al. found that the global DNA methylation of peripheral blood leukocytes was below the norm in patients with BC and could be a potential biomarker for the risk of BC [12].

Data analysis has also revealed about 10,000 sites in T-cells that correlated with BC progression. The scientists compiled a list of 89 CG sites highly correlated ($p < 0.01$, $r > 0.7$, $r < -0.7$) with BC progression. The vast majority of those hypomethylated sites were directly related to the genes responsible for immune system function [13].

Thus, the assessment of tumor biomarkers could be used as an alternative minimally invasive objective method of early detection of BC.

Treatment of BC adjusted for the regulation of methylation. Detection and treatment of BC at an early stage (stages I and II) improves 5-years survival (> 93%) compared to the late detection of metastatic cancer (stage

IV – 22%) [14]. Numerous TSGs (for example, genes of DNA repair, apoptosis, hormone receptors, cell cycle and genes of transcription factors) were found to be differentially methylated in BC and, accordingly, could serve as good therapeutic targets [15]. Therefore, the treatment of BC by regulating proteins involved in methylation processes was found to be a promising method of treatment.

Candidate treatment methods of BC include regulation of methylation activity using DNA methyltransferase (DNMT) inhibitors. Lower DNMT activity inhibits tumor growth due to increased expression of "silent" genes, such as TSG, estrogen alpha receptor genes, E-cadherin, and SFRP. Cytidine analogs, such as decitabine (5-aza-2'-deoxycytidine) and 5-azacytidine, act as DNMT inhibitors and, thus, can reactivate the expression of main genes by depleting DNMT1 [16].

Both of these analogs have been approved by the US Food and Drug Administration (FDA) for the treatment of the myelodysplastic syndrome. These residues of the DNMT inhibitor are incorporated into the DNA during the S-phase of the replication process and establish irreversible bonds with DNA-methyltransferase enzymes to prevent their action [17]. Other studies [18] also reported an increase in the effectiveness of treating BC with a similar approach. Studies have been conducted in vivo to evaluate the effect of the above compounds on solid breast tumors. However, in addition to their poor stability and lack of specificity for cancer cells, these drugs are quickly inactivated by cytidine deaminase.

Consequently, these drugs have serious limitations for treating advanced solid tumors, including BC. In addition, these agents can activate a panel of prometastatic genes in addition to the activation of tumor suppressor genes, thus increasing metastasis. The question that has to be answered is how to target tumor suppressor genes and block the growth of cancer with DNA demethylation drugs while avoiding activation of prometastatic genes and preventing cancer metastasis [19].

These disadvantages have led to the development of new DNMT inhibitors, namely, zebularine, SGI-110, and NPEOC-DAC, which are more selective for cancer cells and demonstrate a higher resistance to deamination. Zebularine has a potent inhibitory effect on both DNMT and cytidine - deaminase.

Zebularine has a potent inhibitory effect on both DNMT and cytidine deaminase. It was shown in vitro that Zebularine in combination with decitabine has a significant inhibitory effect on cell proliferation and colony formation in the MDA-MB-231 breast cancer cell line by inducing the expression of mRNA estrogen receptor alpha and progesterone [20]. It has also been shown that this drug inhibits the growth of breast tumor cells in vivo, causing necrosis and apoptosis of tumor cells with early onset in transgenic mice that develop mammary tumors [21]. Although zebularine initially showed promising effects associated with its high selectivity against cancer cells, its toxicity makes this drug less attractive for the treatment of breast cancer patients. SGI-110 is a modified dinucleotide that exhibits increased resistance to cytidine-deaminase and an increased half-life period compared with decitabine and 5-azacytidine [22]. This short oligonucleotide may be provided to ensure efficient delivery of the nucleotide drug and protection against deamination. NPEOC-DAC is a metabolic precursor of the decitabine molecule and has a dose-dependent depressive effect on DNA methylation [23].

Some other natural compounds containing specific molecules, such as anthocyanins and polyphenols, were found to have anti-DNMT activity [24]. The DNMT1 knockdown, with the help of small interference RNA has also led to promising results in HCT116 colon cancer cells [25].

Since the side effects of DNMT inhibition include concomitant activation of both TSG and proto-oncogenes, some studies have evaluated the impact of a combination of cytidine analogs with chemotherapeutic agents, immunotherapy or specific genes knockdown, such as methyl-CpG (MBD2) protein 2 and lysine (K) -specific demethylase 1B (KDM1B/LSD2) [15]. Vijayaraghavalu et al. noted a significant increase in the effectiveness of doxorubicin treatment in MCF-7, MDA-MB-231, and BT-459 cells in combination with decitabine [26]. Such dual treatment caused a cessation of the cell cycle phase for more than 90% of the cells and resulted in the restoration of sensitivity to doxorubicin by increasing the expression of the p21 proto-oncogene. In turn, it allowed overcoming the drug resistance of the breast cells. In another study, Wrangle et al. have evaluated the sequential combination of 5-azacytidine and immunotherapy and shown that combined epigenetic therapy using a DNA methyltransferase inhibitor and a programmed death blockade led to a synergistic antitumor response, also in patients with non-small-cell lung cancer [27].

On the one hand, MBD2 suppresses methylated genes, but on the other, it is involved in the activation of gene expression due to its ability to interact with gene promoters. A recent study has shown that the introduction of a methyltransferase inhibitor (5-azacytidine) combined with suppressing MBD2 expression using RNA interference technology activates apoptosis and decreases cell growth, as well as inactivates the invasive and metastatic processes in BC cells. Simultaneous inhibition of depletion of MBD2 (methylated DNA binding protein 2) and DNA methyltransferase (DNMT) in BC cells leads to a combined in vitro and in vivo effect: it enhances the delay in tumor growth while inhibiting the invasiveness caused by 5-azaCdR. The combined treatment of MBD2 and 5-azaCdR depletion suppresses and strengthens various gene networks induced only by DNMT inhibition. This indicates the potentially new approach to targeting DNA methylation mechanism by a combination of MBD2 and DNMT inhibitors [28]. MBD2 depletion counteracts the proto-oncogenes activation as a result of hypomethylation therapy. The same strategy, including DNA methyltransferase inhibition and LSD2 knockdown, is also efficient in inhibiting MDA-MB-231 and MCF-7 BC cell growth. Such therapy enhances the expression of epigenetically silenced genes such as the genes encoding the progesterone receptor and the alpha-receptor estrogen [29].

Mahmood et al. have shown that treatment using SAM (universal methyl-S-Adenosyl methionine donor) significantly decreases proliferation, invasion, and migration de-

pendent on the dose and independent of growth fixation and increases apoptosis in vitro. The results have been reproduced in vivo: oral administration of SAM reduced tumor volume and metastasis in an MDA-MB-231 xenograft model labeled with a green fluorescent protein (GFP).

Gene expression analysis has confirmed the ability of SAM to reduce the expression of several main genes involved in cancer progression and metastasis, both in cell lines and in BC xenografts. The results of this study provide good evidence for evaluating the therapeutic potential of methylating agents, such as SAM, for reducing the morbidity and mortality from BC [31].

Conclusion: In the past decade, several gene expression signatures were established to characterize and subtype breast tumors. However, at present, methylation is considered the leading player which regulates gene expression. Unlike RNA transcription profiles, which illustrate the transcriptional activity at a specific moment, DNA methylation status is a more stable and long-lasting marker of the molecular state and susceptibility of cells to cancer.

Though many models of metastatic processes have been proposed, recent studies show the metastatic capacity of breast tumors to be an inherent feature of the host's genetic background. Epigenetic changes are assumed to occur at the early stages of breast carcinogenesis before the metastatic process, and, therefore, the methylation profile, to a certain extent, reflects the genetic background of individuals.

All these observations confirm the potential significance of the evaluation of the methylation profile in biological fluids for accurate risk determination in women prone to or affected by BC. Considering that circulating cell-free plasma DNA contains tumor-specific mutations and DNA methylation patterns associated with the disease, identification of new biomarkers being the precursors of potential susceptibility to cancer or aggressiveness in such DNA will be a huge achievement in predictive medicine for women at high risk of BC.

Minimally invasive testing, such as screening for epigenetic changes in the blood, is a fairly convenient and objective technique. However, mainly due to the limited number of affected and matched control DNA samples in the studied cohorts, no specific methylation biomarker has yet been confirmed for clinical use.

Combined studies of the entire epigenome could contribute to the creation of a whole group of BC biomarkers to improve the diagnostics and early detection of BC in women. Although some DNMT inhibitors are reported to increase the effectiveness of standard chemotherapy only for certain types of cancer, further studies of the effect of demethylation agents in vivo on various solid tumors are quite reasonable. It should not be forgotten that DNMT inhibitors increase the rate of cell division and proliferative activity. Therefore, repeated treatment is required to increase their antitumor efficacy [28]. Beyond that, such factors as toxicity, the lack of specificity, low stability, and the simultaneous activation of proto-oncogenes impede the development of new inhibitors. However, the combined use of these DNMT inhibitors with other types of agents, such as chemotherapeutic drugs and RNA interference, gives promising results.

Thus, epigenetic methods in combination with wider access to minimally invasive biological material (blood, plasma) are crucial for a deeper understanding of the biology of BC and the development of new methods for early diagnostics and personalized therapy to improve the prospects for patients with BC.

References

1. Kaidarova D.R., Auezova E.T., Chingisova ZH.K., Seysenbayeva G.T., Azhmagambetova A.Ye., Zhylkaydarova A.ZH. Pokazateli onkologicheskoy sluzhby za 2016 god (statisticheskiye pokazateli) [Cancer Service Indicators for 2016 (statistical indicators)]. – Almaty, 2017. – 89 p.;

2. Szyf M. DNA methylation signatures for breast cancerclassificationandprognosis // Genome Med. – 2012. –Vol. 4. – P. 26;

3. Guerrero-Preston R., Hadar T., Ostrow K.L., Soudry E., Echenique M., Ili-Gangas C., Pérez G., Perez J., Brebi-Mieville P., Deschamps J., Morales L., Bayona M., Sidransky D., Matta J. Differential promoter methylation of kinesin family member 1a in plasma is associated with breast cancer and DNA repair capacity // Oncol Rep. – 2014. – Vol. 32. – P. 505–512;

4. Kanwal R., Gupta S. Epigenetic modifications in cancer // Clin Genet. – 2012. – Vol. 81. – P. 303–311;

5. Cheishvili D., Christiansen S., Stochinsky R., Pepin A.S., Sapozhnikov D.M., Zhou R., Schmeltzer L., Dymov S., Szyf M. DNA methylation controls unmethylated transcription start sites in the genome in trans // Epigenomics. – 2017 May. – Vol. 9(5). – P. 611–633;

6. Santos-Rebouças C.B., Pimentel M.M.G. Implication of abnormal epigenetic patterns for human diseases // Eur J Hum Genet. – 2007. – Vol. 15. – P. 10–17;

7. Cheishvili D., Stefanska B., Yi C., Li C.C., Yu P., Arakelian A., Tanvir I., Khan H.A., Rabbani S., Szyf M. A common promoter hypomethylation signature in invasive breast, liver and prostate cancer cell lines reveals novel targets involved in cancer invasiveness // Oncotarget. – 2015. – Vol. 6(32). – P. 33253–33268;

8. Yang R., Pfütze K., Zucknick M., Sutter C., Wappenschmidt B., Marme F., Qu B., Cuk K., Engel C., Schott S., Schneeweiss A., Brenner H., Claus R., Plass C., Bugert P., Hoth M., Sohn C., Schmutzler R., Bartram C.R., Burwinkel B. DNA methylation array analyses identified breast cancer associated HYAL2 methylation in peripheral blood // Int J Cancer. – 2015. – Vol. 136. – P. 1845–1855;

9. Heyn H., Carmona F.J., Gomez A., Ferreira H.J., Bell J.T., Sayols S., Ward K., Stefansson O.A., Moran S., Sandoval J., Eyfjord J.E., Spector T.D., Esteller M. DNA methylation profiling in breast cancer discordant identical twins identifies DOK7 as novel epigenetic biomarker // Carcinogenesis. – 2013. – Vol. 34. – P. 102–108;

10. Kloten V., Schlensog M., Magnus L., Heide T., Eschenbruch J., Steib F., Tator M., Rose M., Noetzel E. Epigenetic loss of putative tumor suppressor SFRP3correlates with poor prognosis of lung adenocarcinoma patients // J Epigenetics. – 2018. – Vol. 13(3). – P. 217–227;

11. Brennan K., Flanagan M. Is There a Link Between Genome-Wide Hypomethylation in Blood and Cancer Risk? // Cancer Prev Res. – 2012. – Vol. 5(12). – P. 1345–1357;

12. Kuchiba A., Iwasaki M., Ono H., Kasuga Y., Yokoyama S., Onuma H., Nishimura H., Kusama R., Tsugane S., Yoshida T. Global methylation levels in peripheral blood leukocyte DNA by LUMA and breast cancer: a case–control study in Japanese women // Br J Cancer. – 2014 May 27. – Vol. 110(11). – P. 2765–2771;

13. Parashar S., Cheishvili D., Mahmood N., Arakelian A., Tanvir I., Khan H.A., Kremer R., Mihalcioiu C., Szyf M., Rabbani S.A. DNA methylation signatures of breast cancer in peripheral T-cells // BMC Cancer. – 2018 May 18. – Vol. 18(1). – P. 574;

14. Breast cancer survival rates by stage / American Cancer Society //www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage. 14.11.2014;

15. Pouliot M., Labrie Y., Diorio C., Durocher F. The Role of Methylation in Breast Cancer Susceptibility and Treatment //Anticancer Research. – 2015. – Vol. 35. – P. 4569–4574;

16. Santi D.V., Garrett C.E., Barr P.J. On the mechanism of inhibition of DNA-cytosine methyltransferases by cytosine analogs // Cell. – 1983. – Vol. 33. – P. 9–10;

17. Creusot F., Acs G., Christman J.K. Inhibition of DNA methyltransferase and induction of Friend erythroleukemia cell differentiation by 5-azacytidine and 5-aza-2'-deoxycytidine // J Biol Chem. – 1982. – Vol. 257. – P. 2041–2048;

18. Appleton K., Mackay H.J., Judson I., Plumb J.A., McCormick C., Strathdee G., Lee C., Barrett S., Reade S., Jadayel D., Tang A., Bellenger K., Mackay L., Setanoians A., Schätzlein A., Twelves C., Kaye S.B., Brown R. Phase I and pharmacodynamic trial of the DNA methyltransferase inhibitor decitabine and carboplatin in solid tumors // J Clin Oncol. – 2007. –Vol. 25. – P. 4603–4609;

19. Cheishvili D., Boureau L., Szyf M. DNA demethylation and invasive cancer: implications for therapeutics // Br J Pharmacol. – 2015 Jun. – Vol. 172(11). – P. 2705–2715;

20. Billam M., Sobolewski M.D., Davidson N.E. Effects of a novel DNA methyltransferase inhibitor zebularine on human breast cancer cells // Breast Cancer Res Treat. –2010. – Vol. 120. – P. 581–592;

21. Chen M., Shabashvili D., Nawab A., Yang S.X., Dyer L.M., Brown K.D., Hollingshead M., Hunter K.W., Kaye F.J., Hochwald S.N., Marquez V.E., Steeg P., Zajac-Kaye M. DNA methyltransferase inhibitor, zebularine, delays tumor growth and induces apoptosisin a genetically engineered mouse model of breast cancer // Mol Cancer Ther. – 2012. – Vol. 11. – P. 370–382;

22. Yoo C.B., Jeong S., Egger G., Liang G., Phiasivongsa P., Tang C., Redkar S., Jones P.A. Delivery of 5-aza-2'-deoxycytidine to cells using oligodeoxynucleotides // Cancer Res. – 2007. – Vol. 67. – P. 6400–6408;

23. Byun H.-M., Choi S.H., Laird P.W., Trinh B., Siddiqui M.A., Marquez V.E., Yang A.S. 2'-Deoxy-N4-[2-(4-nitrophenyl) ethoxycarbonyl]-5-azacytidine: A novel inhibitor of DNA methyltransferase that requires activation by human carboxylesterase 1// Cancer Lett. –2008. – Vol. 266. – P. 238–248;

24. Subramaniam D., Thombre R., Dhar A., Anant S. DNA methyltransferases: a novel target for prevention and therapy // Front Oncol. – 2014. – Vol. 4. – P. 80;

25. Morita R., Hirohashi Y., Suzuki H., Takahashi A., Tamura Y., Kanaseki T., Asanuma H., Inoda S., Kondo T., Hashino S., Hasegawa T., Tokino T., Toyota M., Asaka M., Torigoe T., Sato N. DNA methyltransferase 1 is essential for initiation of the colon cancers // Exp Mol Pathol. – 2013. – Vol. 94. – P. 322–329;

26. Vijayaraghavalu S., Dermawan J.K., Venugopalan C., Labhasetwar V. Highly synergistic effect of sequential treatment with epigenetic and anticancer drugs to overcome drug resistance in breast cancer cells is mediated via activation of p21 gene expression leading to G2/M cycle arrest // Mol Pharm.– 2013. – Vol. 10. – P. 337–352;

27. Wrangle J., Wang W., Koch A., Easwaran H., Mohammad H.P., Pan X., Vendetti F., Vancriekinge W., Demeyer T., Du Z., Parsana P., Rodgers K., Yen R.-W., Zahnow C.A., Taube J.M., Brahmer J.R., Tykodi S.S., Easton K., Carvajal R.D., Jones P.A., Laird P.W., Weisenberger D.J., Tsai S., Juergens R.A., Topalian S.L., Rudin C.M., Brock M.V., Pardoll D., Baylin S.B. Alterations of immuneresponse of non-small cell lung cancer with azacytidine // Oncotarget.– 2013. – Vol. 4. – P. 2067–2079;

28. Cheishvili D., Chik F., Li C.C., Bhattacharya B., Suderman M., Arakelian A., Hallett M., Rabbani S.A., Szyf M. Synergistic effects of combined DNA methyltransferase inhibition and MBD2 depletion on breast cancer cells; MBD2 depletion blocks 5-aza-2'-deoxycytidine triggered invasiveness // Carcinogenesis. – 2014. – Vol. 35. – P. 2436–2446;

29. Katz T.A., Vasilatos S.N., Harrington E., Oesterreich S., Davidson N.E., Huang Y. Inhibition of histone demethylase, LSD2 (KDM1B), attenuates DNA methylation and increases sensitivity to DNMT inhibitor-induced apoptosis in breast cancer cells // Breast Cancer Res Treat.– 2014. – Vol. 146. – P. 99–108;

30. Nie J., Liu L., Li X., Han W. Decitabine, a new star inepigenetic therapy: the clinical application and biologicalmechanism in solid tumors // Cancer Lett. – 2014. – Vol. 354. – P. 12–20;

31. Mahmood N., Cheishvili D., Arakelian A., Tanvir I., Khan H.A., Pépin A.S., Szyf M., Rabbani S.A. Methyl donor S-adenosylmethionine (SAM) supplementation attenuates breast cancer growth, invasion, and metastasis in vivo; therapeutic and chemopreventive applications // Oncotarget. – 2017 Dec 26. – Vol. 9(4). – P. 5169–5183.

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Hereditary breast cancer: the mutation spectrum and prevention measures (literature review)

Relevance. *Breast cancer (BC) is a heterogeneous pathology characterized by various clinical manifestations. BC ranks first in in the structure of cancer in Kazakhstan and around the world. Many factors influence the development of BC such as long menstrual period, lack of parturition, lack of breastfeeding, some benign changes like atypical hyperplasia, intraductal dysplasia, age over 50 years, and family history. Genetic predisposition is one of the main factors in the development of BC. This category of patients often has first or second-degree relatives with breast cancer on the maternal side of the family; they experience an early manifestation of the disease with a more aggressive clinical course, early metastasis, short relapse-free period, and a shortened overall survival against adequate combination therapy.*

The relevance of precision therapy that targets the cellular and genetic tumor structures is now growing as it has high efficiency and allows increasing the survival rate of patients with BC.

Many genes are associated with a predisposition for BC; of them, the BRCA1 and BRCA2 mutations are the most common and studied. The prevalence of this pathology has urged the study of genes associated with known hereditary syndromes, such as P53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6, and PMS2. The ATM, RAD51C, RAD51D, b BRIP1 genes are also actively studied.

Purpose of this study *is the study of the role of the mutation spectrum in the prevention and diagnosis of breast cancer.*

Results. *The emergence of a new generation of sequencing methods, the identification of new candidate genes predisposing to the development of breast cancer allow establishing a genome-verified diagnosis. Various preventive measures taken by women with hereditary mutations have yielded significant results concerning the risks of BC development.*

Conclusion. *Individuals with BRCA1 / 2 mutations should seek individual counseling and undergo screening and prevention, with a thorough study of the family history and, if possible, testing of other family members. Genetic studies conducted by the scientists of KazIOR and the Institute of Genetics and General Cytology will allow determining the ethnic characteristics of mutation spectra and introduce DNA diagnostics to identify groups at high risk of breast cancer in Kazakhstan.*

Keywords: *breast cancer, next-generation sequencing, genetic screening, prevention.*

Introduction. Breast cancer (BC) is a heterogeneous pathology characterized by various clinical manifestations. BC ranks first in cancer structure in Kazakhstan and worldwide. Many factors that influence the development of BC include long menstrual period, lack of parturition, lack of breastfeeding, some benign changes like atypical hyperplasia, intraductal dysplasia, age over 50 years, and family history. Often, cancer occurs at the site of injury or burns of the breast. Genetic predisposition is one of the main factors in the development of BC. This category of patients often has first or second-degree relatives with breast cancer on the maternal side of the family; they experience an early manifestation of the disease with a more aggressive clinical course, early metastasis, short relapse-free period, and a shortened overall survival against adequate combination therapy.

Many genes related to susceptibility to BC have been studied. Some countries have presented ethnicity-dependent recommendations on genetic screening and prevention of BC.

Materials and methods. The conducted literature review covered the data for the last ten years from PUBMED, SPRINGER, MEDLINE, and ELSEVIER databases, as well as the NCCN and ESMO national guidelines. The search was conducted by the following keywords: breast cancer, next-generation sequencing, reconstruction, genetic screening, and mutations.

Results. According to the literature, BRCA1 and BRCA2 are the most common and best studied BC susceptibility genes. Such genes as TP53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6, and PMS2 were found to be associated with the known hereditary syndromes. ATM, RAD51C, RAD51D, b BRIP1 genes are also under study. The NCCN (National Comprehensive Cancer Network) and NICE (National Institute for Health and Cancer Excellence) guidelines, as well as ESMO recommendations, are used for risk assessment and genetic counseling. The guidelines based on the opinions of international experts reflect the need to collect a database of newly identified mutations to optimize the screening, prevention, and monitoring recommendations for patients of different ethnic groups at remission [1-3]. See Table for the overview of screening and prevention tactics in these gene mutations.

Table 1 – Recommendations for breast cancer prevention and screening in mutations in various genes (ESMO, NCCN guidelines) [1-3]

Type of mutation	Screening activities	Prevention/risk reduction activities
Lee-Fraumeni Syndrome/P53	1) Clinical examination of mammary glands every 6–12 months starting from the age of 20–25 years. 2) Annual MRI / mammography at the age of 20–75 years. 3) Colonoscopy every 5 years starting from the age of 25. 4) Annual dermatological and neurological examination 5) Annual full body MRI	1) Avoid exposure to ionizing radiation 2) Consider the possibility of pre-implantation genetic diagnostics of the embryo before pregnancy. 3) Consider the option of prophylactic mastectomy.
PTEN/ Cowden Syndrome	1) Clinical examination of mammary glands every 6–12 months starting from the age of 20–25 years 2) MRI and/or mammography every year at the age of 30–75 years 3) Annual ultrasound examination of the endometrium ± biopsy at the age of 30–35 years	1) Consider the option of prophylactic mastectomy 2) Consider the option of prophylactic hysterectomy 3) Consider the possibility of pre-implantation genetic diagnosis of the embryo before pregnancy
ATM	1) Annual MRI of the mammary glands (no data on the onset age)	
Lynch syndrome MLH1, MSH2, MSH6, EPSAM, PMS2	1) Colonoscopy every year starting from the age of 20–25 years 2) Annual neurological examination for CNS tumors screening 3) Annual ultrasound examination of endometrium ± biopsy at the age of 30-35 years	Consider the option of prophylactic hysterectomy and salpingo-ovariectomy after the delivery
RAD51		Consider the option of salpingo-ovariectomy after the age of 45 years
BRIP1		Consider the option of salpingo-ovariectomy after the age of 45 years
PALB2	1) Clinical examination of mammary glands every 6–12 months starting the age of 20–25 years 2) MRI every year at the age 20-29 years 3) MRI and/or mammography every year at the age of 30–75 years	Consider the option of prophylactic mastectomy
CHEK2	1) Clinical examination of mammary glands every 6–12 months starting the age of 20–25 years 2) MRI every year at the age of 20-29 years 3) MRI and/or mammography every year at the age of 30–75 years	
STK11 / Peutz-Jeghers Syndrome	1) Clinical examination of mammary glands every 6–12 months starting from the age of 20–25 years 2) MRI every year at the age of 20-29 years 3) MRI and/or mammography per year at the age of 30–75 years 4) EGD and colonoscopy every 2–3 years at the age of late adolescence 5) MRI screening for pancreatic cancer starting from the age of 30 years 6) Annual examination of pelvic organs from the age of 25 years old 7) Regular annual check (observation) by a gynecologist 8) Counseling on lung cancer (?) risk reduction	Consider the option of prophylactic mastectomy
CDH1	1) Clinical examination of mammary glands every 6–12 months starting from the age of 20–25 years 2) MRI every year at the age of 20-29 years 3) MRI and/or mammography every year at the age of 30–75 years	Consider the option of prophylactic mastectomy

The development of next-generation sequencing (NGS) has promoted the global complete genome study in various cancer pathologies.

On request of the Ministry of Healthcare of the Republic of Kazakhstan, Kazakh Institute of Oncology and Radiology (KazIOR) together with the Institute of Genetics and General Cytology of the Ministry of Education and Science of the Republic of Kazakhstan are implementing an NGS-based project to study 94 genes. The project aims to create genetic diagnosticums for breast and colorectal cancer pre-symptom detection.

Incidence of hereditary breast cancer (hBC). The hereditary cancer syndromes occur as a result of germinal (germ line) mutations inherited from any of the parents and significantly increase the risk of cancer development compared to the general population. In particular, the BRCA1 or BRCA2 germinal mutation significantly increases the risk of BC and ovarian cancer (OC) (by 7 and 25 times, respectively) among the average risk population [4-6].

Over 90% of hereditary cases of BC and OC are the outcome of BRCA1/2 mutations [7]. The estimated prevalence depends on the population and may vary from 1 to 300 and 1 to 800 persons, respectively. The international database contains over 2,000 different BRCA1/2 mutations. However, despite this diversity, the so-called "founder effect" is observed in many countries. The founder effect means the predominance of specific BRCA1/2 mutations in a particular popu-

lation. Thus, BRCA1-185delAG, BRCA1-5382insC, and BRCA2-6174delT mutations prevail in Ashkenazi Jews — these three mutations account for 98–99% of all BRCA1 and BRCA2 mutations in that population group [8]. In the Republic of Kazakhstan, in 2014, the scientists of Nazarbayev University have conducted a study to identify BRCA1/BRCA2 mutations in 112 female patients and have found several non-significant (non-pathogenic) mutations and polymorphisms [9]. However, in the search for mutation spectrum in BC conducted by KazIOR, BRCA1/2 mutations with the founder effect prevail. The results of this NGS-based study will be published later.

Genetic counseling of BRCA mutation carriers. Fundamental recommendations for BRCA1/2-positive women form the basis of breast screening and risk reduction measures, including surgical and drug treatment, healthy lifestyle, and fertility issues in nulliparous women. Genetic counseling shall take into account the life quality aspects and the influence of psychosocial factors after preventive surgery. The recommendations on early detection, including annual visual diagnostic methods (ultrasound examination, mammography, magnetic resonance imaging (MRI) of mammary glands), shall be applied after the age of 25 years.

Recommendations on BC risk reduction.

1) Lifestyle change:

There is published evidence that breastfeeding reduces the risk of BC among BRCA1/2-positive women [10]. Regular exercise, healthy body mass maintenance, limitation of alcohol, and smoking consumption are as crucial as the rejection of hormone replacement therapy in the absence of indications.

2) Screening:

Women aged 25 and above, or aged 15 and above in the case of a family history of BC, should undergo clinical checkup and examination of mammary glands every 6-12 months. Women shall be aware of and trained in breast self-examination. A woman shall immediately visit a doctor in case of any changes in mammary glands or underarms area.

MRI of mammary glands is a widely used and the most sensitive screening tool in the high-risk population [11-14]. Annual MRI screening should start at the age of 25 years, with additional annual mammography after the age of 30 years. Retrospective data suggest a correlation between the elevated risk of BC and the exposure to diagnostic radiation before 30 years [15]. If MRI is unavailable, women before 30 years can do ultrasound examination of mammary glands instead. Ultrasound examination may be considered as an addition to mammography at any age and as an alternative option if MRI is unavailable.

Drug prevention of hBC. The data on the use of selective estrogen receptor modulators (tamoxifen, raloxifene) and aromatase inhibitors as the primary prevention in BRCA1/2-positive patients is limited. Several observational studies have shown that tamoxifen reduces the risk of contralateral BC development in BRCA1/2-associated patients with BC [16, 17]. Other studies have demonstrated the capacity of tamoxifen to reduce the risk of contralateral BC in patients with estrogen receptor negative tumors.

Surgical prevention of hBC. Bilateral simple mastectomy is the most effective method of reducing the risk of BC in BRCA1/2 mutation carriers. Complete removal of glandular tissue reduced the risk by 90% [18–25]. A large number of retrospective and prospective studies with an observation period of more than ten years have demonstrated the risk reduction advantages [26]. However, there is no related data on randomized studies and survival rates.

These types of surgical treatment include full mastectomy, skin-saving mastectomy, and skin-nipple-saving mastectomy. Mastectomy is often performed with simultaneous reconstruction with endoprostheses or autogenous tissues to improve the cosmetic outcome. In the case of proper performance, these methods have similar safety indices [27, 28]. Therefore, mastectomy with a reconstructive component is an alternative to total mastectomy. The advantages, limitations, risks related to the surgical intervention, as well as the complications, and psychosocial effects should be discussed with each patient and her close relatives. Complete mastectomy leads to a significant aesthetic defect and is conducted when the patient refuses to implant endoprostheses. BC in the dissected gland is detected in less than 5% of cases. Therefore, a routine biopsy of the sentinel lymph node or lymph node dissection is not prescribed. The mammology center of KazIOR conducts about 50 subcutaneous mastectomies a year with simultaneous reconstruction with endoprostheses in patients with BC. BRCA 1/2 gene mutation carriers are usually recommended a bilateral mastectomy with reconstructive plastics. This type of surgical intervention is also used at detection in situ of cancer, grouped micro calcifications in more than two quadrants, or mammary gland polycystosis with complex cysts.

Conclusion. Next-generation sequencing and the identification of new candidate genes of susceptibility for BC allow conducting genome-verified diagnostics. Various preventive measures in women with hereditary mutations yield significant results concerning BC development risks. Individuals with BRCA1/2 mutations should seek individual counseling and undergo screening and prevention, with a thorough study of the family history and, if possible, testing of other family members. The genetic studies conducted by the scientists of KazIOR and the Institute of Genetics and General Cytology will allow determining the ethnicity-related specifics of mutation spectra and introduce DNA diagnostics to identify BC high-risk groups in Kazakhstan.

References

1. NCCN Clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast & ovarian. – Ver. 2.2016, ed.2016 // www.nccn.org/professionals/physician_gls/pdg/genetics_screening.pdf. 05.08.2016;

2. National Institute for Health and Clinical Excellence. Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. – Cardiff (UK): National Collaborating Centre for Cancer (UK); 2013 Jun. www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf;

3. Paluch-Shimon S., Cardoso F., Sessa C. et al. ESMO Clinical Practice Guidelines for cancer prevention and screening in BRCA mutation carriers // Annals of Oncology. – 2016. – Vol. 27. – P. v103-110;

4. Paul A., Paul S. The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers // Front Biosci (Landmark Ed). – 2014. – Vol. 19. – P. 605–618;

5. Torres D.R., Bermejo J.L., Rashid M.M., Briceño I., Gil F., Beltran A., Ariza V.Z., Hamann U. Prevalence and Penetrance of BRCA1 and BRCA2 Germline Mutations in Colombian Breast Cancer Patients // Scientific Reports. – 2017;

6. Walsh T., Casadei S., Lee M.K. et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing // Proc Natl Acad Sci USA. – 2011. – Vol. 108. – P. 18032–18087;

7. Mersch J., Jackson M.A., Park M. et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian // Cancer. – 2015. – Vol. 121. – P. 2474–2475;

8. Nevin Karakuş, Nurten Kara, Serbülent Yiğit, İsmail Okan. Evaluation of BRCA1 and BRCA2 gene mutations in breast cancer patients, Cumhuriyet Medical Journal, March 2017, Volume: 39, Number: 1. – P. 374-379;

9. Roa B.B., Boyd A.A., Volcik K., Richards C.S. Ashkenazi Jewish population frequencies forcommon mutations in BRCA1 and BRCA2 // Nat Genet. – 1996. – Vol. 14. – P. 185–187.

10. Akilzhanova A.R., Nyshanbekkyzy B., Nurkina Z.M., Shtephanov I.I., Makishev A.K., Adylkhanov T.A., Rakhypbekov T.K., Ramankulov E.M., Momynaliev K.T. BRCA1 and BRCA2 Gene Mutations Screening In Sporadic Breast Cancer Patients In Kazakhstan // Cent Asian J Glob Health. – 2013. – Vol. 2(1). – P. 29;

11. Ellen Warner et al. Screening BRCA1 and BRCA2 Mutation Carriers for Breast Cancer, Published online 2018 Nov 30. doi: *10.3390/cancers10120477*

12. Antony Raikhlin, Belinda Curpen, Ellen Warner, Carrie Betel et al. *Breast MRI as an Adjunct to Mammography for Breast Cancer Screening in High-Risk Patients: Retrospective Review, American Journal of Roentgenology. 2015;204: 889-897.10.2214/AJR.13.12264*

13. Kuhl C[1], Weigel S, Schrading S, Arand B, Bieling H, König R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010 Mar 20;28(9):1450-7. doi: 10.1200/JCO.2009.23.0839.

14. Chiarelli A.M., Prummel M.V., Muradali D. et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario high risk breast screening program // J Clin Oncol. – 2014. – Vol. 32. – P. 2224–2230;

15. Pijpe A., Andrieu N., Easton D.F. et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK) // BMJ. – 2012. – Vol. 345. – P. e5660;

16. Phillips K.A., Milne R.L., Rookus MA et al. Tamoxifen and risk of contralateral breast cancer for BRCA1/2 mutation carriers // J Clin Oncol. – 2013. – Vol. 31. – P. 3091–3099;

17. Xu L, Zhao Y, Chen Z, Wang Y, Chen L, Wang S. Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in BRCA1 and BRCA2: a meta-analysis. Breast Cancer. 2015 Jul;22(4):327-34. doi: 10.1007/s12282-015-0619-6.

18. Valerie Lemaine *et al. Bilateral Prophylactic Mastectomy and Immediate Breast Reconstruction in High-Risk Women: The Importance of Health-Related Quality of Life in Decision Making.* Annals of Surgical Oncology, September 2017, Volume 24, *Issue 9,* pp 2434–2435

19. David M. Euhus *et al. Risk-Reducing Mastectomy for BRCA Gene Mutation Carriers //* Annals of Surgical Oncology, September 2015, Volume 22, *Issue 9,* pp 2807–2809

20. Anne Irene Hagen, Lovise Mæhle, Nina Veda, Hildegunn Hoberg Vetti, Astrid Stormorken, Trond Ludvigsen et al. Risk reducing mastectomy, breast reconstruction and patient satisfaction in Norwegian BRCA1/2 mutation carriers // the breast February 2014Volume 23, Issue 1, Pages 38–43

21. Judith Balmaña BRCA in breast cancer: ESMO Clinical Recommendations, Annals of Oncology, 2009, Vol. 22. – P. 1055–1062;

22. James C Cusack, Kevin S Hughes managing Patients at High Risk for Hereditary Breast Cancer: A Guide for the Practicing Physician. Annals of Surgical Oncology 19(6):1721-2 · March 2012

23. Domchek S.M., Friebel T.M., Singer C.F. et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality // JAMA. – 2010. – Vol. 304. – P. 967–973;

24. Evans D.G., Baildam A.D., Anderson E. et al. Risk reducing mastectomy: outcomes in 10 European centres // J Med Genet. – 2009. – Vol. 46. – P. 254–258;

25. Skytte A.B., Crüger D., Gerster M. et al. Breast cancer after bilateral risk-reducing mastectomy // Clin Genet. – 2011. – Vol. 79. – P. 431–437;

26. Mulligan A.M., Couch F.J., Barrowdale D. et al. Common breast cancer susceptibility alleles are associated with tumour subtypes in BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 // Breast Cancer Res. – 2011. Vol. 13. – P. R110;

27. Niemeyer M., Paepke S., Schmid R. et al. Extended indications for nipple-sparing mastectomy // Breast J. – 2011. – Vol. 17. – P. 296–299;

28. Chung A.P., Sacchini V. Nipple-sparing mastectomy: where are we now? // Surg Oncol. – 2008. – Vol. 17. – P. 261–266.

29. Harris Carmichael, Cindy Matsen, Phoebe Freer, Wendy Kohlmann, Matthew Stein, Saundra S. Buys, Sarah Colonna. Breast cancer screening of pregnant and breastfeeding women with BRCA mutations. Breast Cancer Research and Treatment. April 2017, Volume 162, *Issue 2,* pp 225–230.