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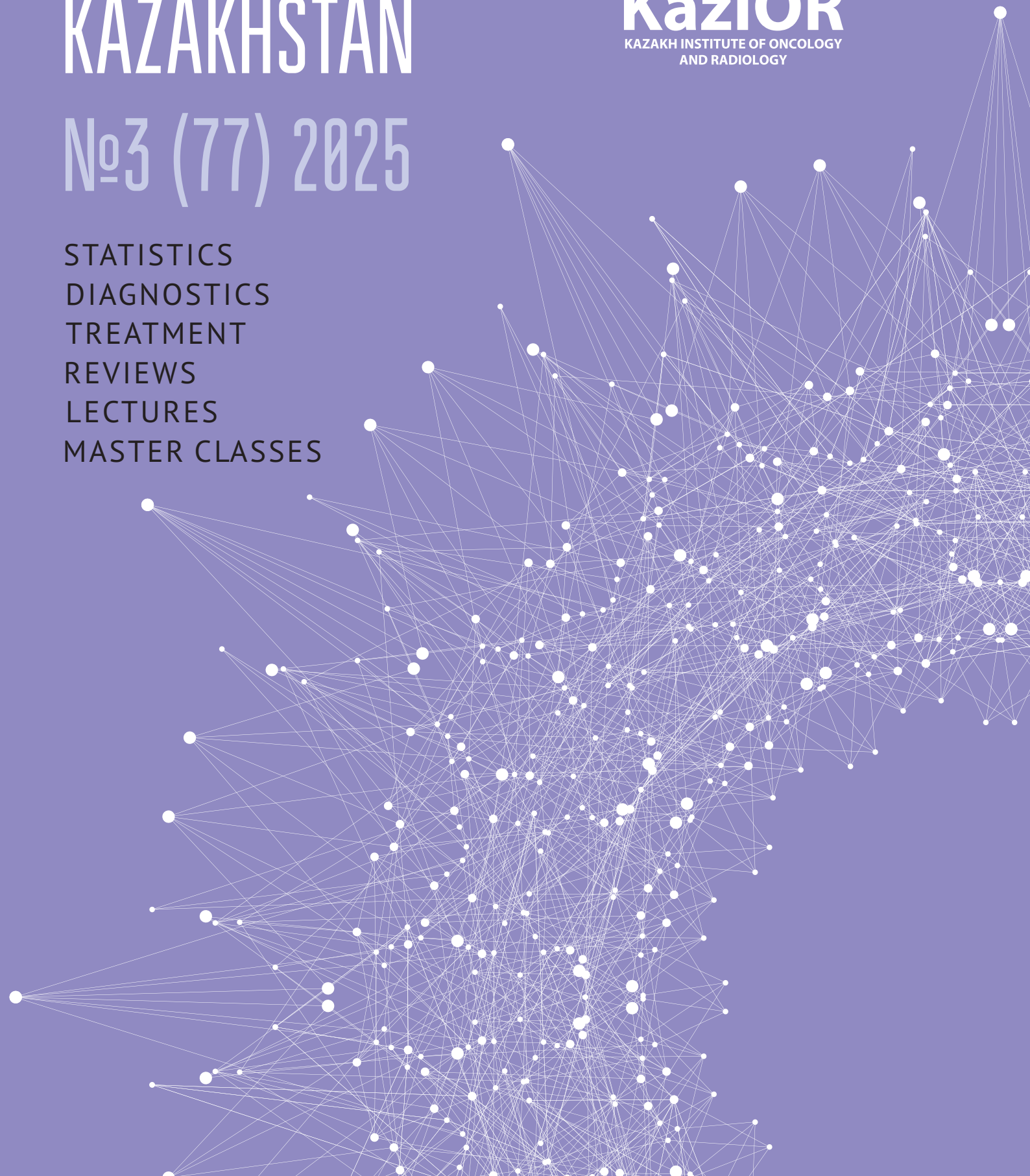

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Contents

Dear readers!

We are pleased to welcome you to the autumn issue of the journal "Oncology and Radiology of Kazakhstan"!

On behalf of the editorial team, I congratulate you on the arrival of the autumn season—a time for taking stock, new plans, and professional growth. Autumn brings not only changes in nature but also inspiration for the further development of medical science and practice.

2025 is a year of exciting events and advancements in oncology and radiology. We are witnessing the active implementation of modern diagnostic methods, the expansion of screening programs, and the strengthening of collaboration between specialists. This issue presents relevant and significant research, including:

• The role of the Oncological Alertness-3 program in the survival of patients with visually localized tumors in the Mangystau region

• Diagnostic capabilities of ^{68}Ga-FAPI PET/CT in gastric cancer

• Analysis of PDL-1 expression in T-cell lymphomas: correlation with clinicopathological prognostic factors

• Multigene testing in genetic screening of hereditary and sporadic colorectal cancer.

With each issue, our journal strives to advance knowledge and improve the quality of medical care. We continue to develop our content, emphasizing scientific validity, clinical significance, and the practical application of the data presented.

We are committed to further improving the publication, expanding our readership, and strengthening our professional community. May autumn inspire you with new ideas, give you strength, and bring you confidence in the future.

We wish you good health, professional success, and new achievements!

Respectfully Yours,
Dilyara Kaidarova,
Editor-in-Chief of the "Oncology and Radiology of Kazakhstan" journal

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ANALYSIS OF EPIDEMIOLOGICAL INDICATORS OF BREAST CANCER IN THE ALMATY REGION IN 2015-2024

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ABSTRACT

Relevance: *Breast cancer (BC) is the most common form of malignant neoplasm among women worldwide. In 2020, 2.3 million new cases and about 685,000 deaths were registered. More than 80% of the cases are women over 50. Developing countries have higher mortality rates. An increase in incidence to 3 million cases by 2040 is forecasted. This study is the first comprehensive 10-year regional analysis of breast cancer incidence, mortality, and stage at detection.*

The study aimed to *analyze the impact of measures implemented in the Almaty region (Kazakh-stan) for early detection and treatment of breast cancer on the dynamics of morbidity, mortality, and stage of detection in 2015-2024.*

Methods: *Assessment of trends and distribution of BC morbidity and mortality rates among the fe-male population of the Almaty region from 2015 to 2024. Statistical reporting forms No. 7, No. 090/U, and data from the regional cancer registry were used. Demographic data were obtained from the official public materials of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan (Committee on Statistics). The indicators were calculated using standard epidemiologi-cal formulas, direct standardization, and statistical software programs, including Microsoft Excel and SPSS Statistics 23.0.*

Results: *The incidence of BC increased from 34.8 to 42.5 per 100,000, and the standardized rate increased from 34.2 to 39.1. Mortality fluctuated, peaking at 11.6 in 2021, then decreased to 8.5 in 2024. The conditional mortality rate ranged from 20.1% to 35.1%. Early detection at stages I-II in-creased from 74.1% to 89.2% and decreased at stage III from 20.6% to 4.6%.*

Conclusion: *There is a positive trend in early diagnosis and survival in BC in the region. However, the continuing mortality rate and the stable proportion of stage IV indicate the need for further im-provement in the routing and availability of therapy.*

Keywords: *breast cancer (BC), epidemiology, morbidity, mortality, survival, Kazakhstan, Almaty region.*

Introduction: Breast cancer (BC) is the most common cancer among women worldwide. In 2020, approximately 2.3 million new cases were registered, accounting for 11.7% of all malignant tumors. More than 80% of cases are diagnosed in women over 50 years of age, highlighting age as a key risk factor. BC has become the leading cause of cancer death among women, claiming the lives of approximately 685,000 patients in 2020. Almost two-thirds of deaths occurred in low- and middle-income countries. While five-year survival rates in developed countries exceed 80%, in India, they are less than 70%, and in South Africa, they are less than 50% [1-3]. BC remains the most common form of malignant neoplasm (MN) among women in Southeast Asia. According to 2022 data, this type of cancer ranks first in incidence among women in all countries of the region. The highest standardized incidence rates (ASIRs) were recorded in Singapore, at 72.61 per 100,000 women, and in the Philippines, at 60.34 per 100,000. In addition, breast cancer is the leading cause of cancer death among women in several Southeast Asian countries. The highest standardized mortality rates (ASMR) from breast cancer were noted in the Philippines – 21.47 per 100,000, in Malaysia – 19.30, in Singapore – 17.82, in Vietnam – 14.67, in Indonesia – 14.35, and in Timor-Leste – 10.24 per 100,000 women [4]. In the United States of America, breast cancer ranks second among the causes of death from cancer in women, second only to lung cancer [5, 6]. In the United States, the highest incidence of breast cancer is observed in white women (130.8 per 100,000), and the highest mortality rate is in African American women (28.4 per 100,000), which is 40% higher than in white women. African American women are more often diagnosed with the aggressive triple-negative subtype of breast cancer, especially in women under 40 years of age. Mortality differences between black and white women are most pronounced in young women and decrease with age [7, 8].

Breast cancer remains the most common malignant disease among women in Kazakhstan. Between 2017 and 2021, 22,736 new cases were registered, representing a 14% increase over previous years. The highest number of cases was identified in 2019 and 2021 (4945 and 4939, respectively) [9]. According to forecasts, by 2040, the number of new cases of breast cancer will increase by more than 40% and reach approximately 3 million per year. The greatest increase in incidence and mortality is

predicted in countries with transition economies and a low development index, where the number of new cases and deaths may double. The share of these countries in the overall incidence structure will increase from 18.4% to 22.2%, and in the mortality structure, from 30.1% to 35.2%. Such changes are primarily due to population aging and growth, but the dynamics may intensify with changes in the incidence rate [10].

Among non-reproductive risk factors for breast cancer, obesity and alcohol consumption are particularly significant. Being overweight nearly doubles the risk of developing the disease in postmenopausal women. Approximately 4% of breast cancer cases in 2020 were associated with alcohol consumption [11].

Molecular diagnostics of breast cancer includes the determination of estrogen and progesterone receptors, HER2, and the proliferation marker Ki-67. These parameters allow us to determine the biological subtype of the tumor and select effective targeted or hormonal therapy. Breast cancer is a clinically and genetically heterogeneous disease. Mutations in the *BRCA1, BRCA2, TP53, PTEN, and other genes significantly increase the risk of its development, emphasizing the importance of genetic testing for early detec*tion and a personalized approach to treatment [12, 13].

A country-specific study covering 2015–2024 demonstrated an increase in breast cancer incidence, coupled with a decline in mortality and an increase in early detection to 88.7%. Five-year survival increased by 81%, demonstrating the effectiveness of preventive and diagnostic measures [14]. This study is the first to conduct a comprehensive regional analysis over 10 years, focusing on the dynamics of breast cancer incidence, mortality, and detection stages.

The study aimed to analyze the impact of measures implemented in the Almaty region (Kazakhstan) for early detection and treatment of breast cancer on the dynamics of morbidity, mortality, and stage of detection in 2015-2024.

Materials and methods: The trends and distribution of breast cancer incidence and mortality rates among the female population of the Almaty region were assessed for the period from 2015 to 2024. The study relied on data retrieved from annual medical reports, specifically Form No. 7, "Information on the Incidence of Malignant Neoplasms," and Form No. 090/U, "Statistical Card of Cancer Patients," as well as information from the regional cancer registry. Demographic data on the female population by age group for the corresponding years were obtained from official materials of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan (Statistics Committee).

An assessment of intensive and standardized incidence and mortality rates from breast cancer per 100,000 women was conducted, a conditional case fatality rate (mortality-to-incidence ratio, %) was calculated, the age structure of incidence was analyzed in comparison over two five-year periods (2015-2019 and 2020-2024), as well as the stage distribution at the time of primary diagnosis and the share of breast cancer in the structure of all malignant neoplasms in women.

Standardization was performed using the direct standardization method, based on the age structure of the World Health Organization standard population. Calculations were performed using standard epidemiological formulas and Microsoft Excel, as well as SPSS Statistics version 23.0. The evaluation included a comparison of absolute and relative values, an analysis of trends, and interperiod changes. Ethical approval was not required because the study utilized aggregated, anonymized data that did not contain identifiable patient information.

Results: Between 2015 and 2024, a 40.6% increase in the number of patients registered for malignant neoplasms was observed in the Almaty region, from 8,207 to 11,541. A similar trend is observed in relation to breast cancer: the number of women with this disease increased from 1,520 in 2015 to 2,494 in 2024, which amounted to an increase of 64.1%. The share of breast cancer in the overall structure of oncological morbidity in women also increased, from 18.5% in 2015 to 21.6% in 2024 (Figure 1).

Between 2015 and 2024, significant changes in breast cancer epidemiological indicators among the female population were observed in the Almaty region. During this period, the intensive incidence rates increased from 34.8 to 42.5 per 100,000 women, and the standardized rates grew from 34.2 to 39.1. The minimum values were recorded in 2019 (the intensive rate was 19.6, the standardized rate was 18.5). Since 2020, a steady upward trend in incidence has been observed, reaching a maximum of 43.7 (intensive rate) and 40.8 (standardized rate) per 100,000 women in 2022. Despite a slight decrease in rates in 2023-2024, the incidence rate remains stably high and significantly exceeds the values at the beginning of the period. This trend could be attributed to both an objective increase in the number of new cases and improved detection, including the expansion of access to diagnostics and the resumption of screening programs in the post-pandemic period (Figure 2).

Mortality rates in the Almaty region changed along a more complex trajectory. In 2015, the mortality rates were 7.0 (intensive) and 6.9 (standardized) per 100,000 women. Over the following years (2016-2020), those rates stabilized, ranging from 5.4 to 6.7. However, in 2021, the mortality rates spiked: the intensive rate reached 11.6, and the standardized rate reached 11.3. This trend could be attributed to delayed patient visits during the COVID-19 pandemic, late detection of malignant tumors, and temporary restrictions on scheduled medical care. The mortality began to decline between 2022 and 2024, reaching 8.5 (intensive) and 8.3 (standardized) in 2024, which was

still above the baseline. This trajectory highlights the partial restoration of oncology services and improvement in patient routing, although certain problems in the availability of timely therapy remain (Figure 3).

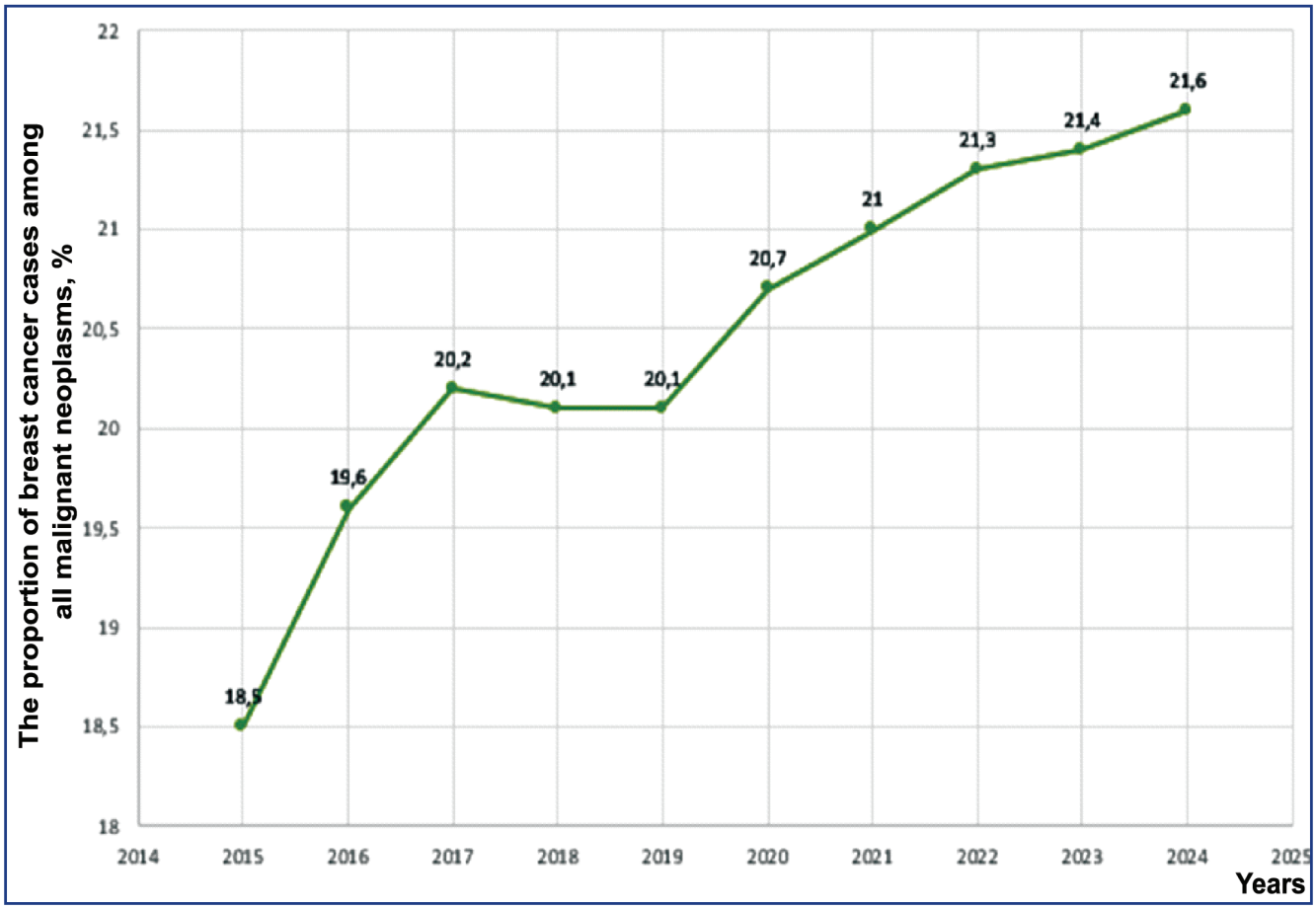

Figure 1 – Dynamics of the proportion of breast cancer in the structure of all newly diagnosed malignant neoplasms in the female population of the Almaty region for 2015-2024 (%)

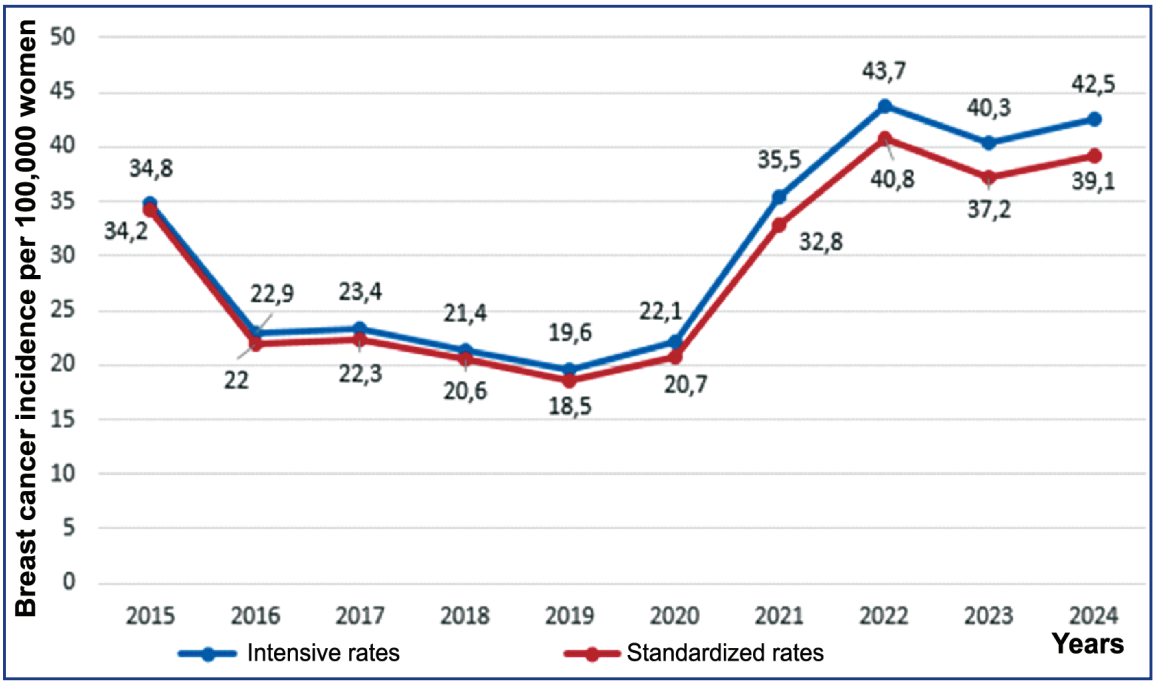

Figure 2 – Dynamics of intensive and standardized rates of breast cancer incidence among women in the Almaty region in 2015-2024 (per 100,000 female population)

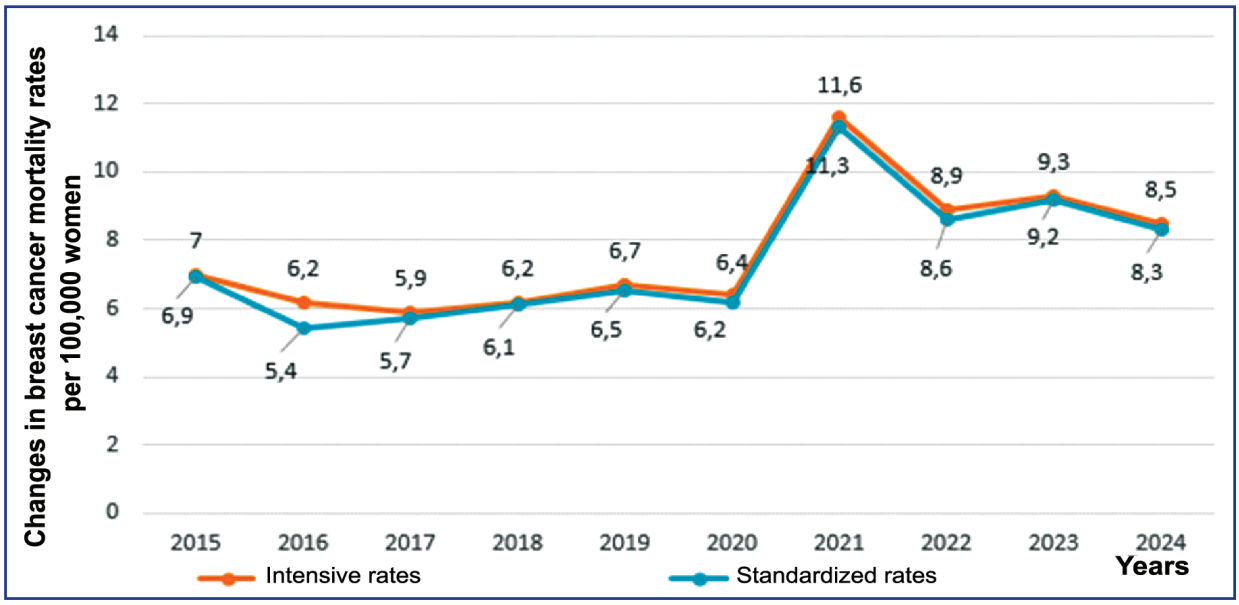

Figure 3 – Dynamics of intensive and standardized mortality rates from breast cancer among women in the Almaty region in 2015-2024 (per 100,000 female population)

Figure 4 shows the dynamics of intensive indicators of morbidity and mortality from breast cancer among women in the Almaty region for the period from 2015 to 2024 (per 100,000 women), as well as the conditional mortality rate, reflecting the mortality-to-incidence ratio as a percentage. Over the analyzed period, the intensive incidence rate increased from 34.8 to 42.5 per 100,000, with a minimum value of 19.6 in 2019. A steady increase was observed since 2020, reaching a maximum of 43.7 in 2022. The intensive mortality rate ranged from 6.2 to 11.6 per 100,000 women. The mortality rate peaked in 2021, after which it decreased to 8.5 in 2024.

The case fatality rate fluctuated from 20.1% in 2015 to a peak of 35.1% in 2019. The minimum value of 20.4% was recorded in 2022, amid the peak incidence rate. Over the last two years, the rate has increased to 28.2% and 27.2%, respectively (Figure 4).

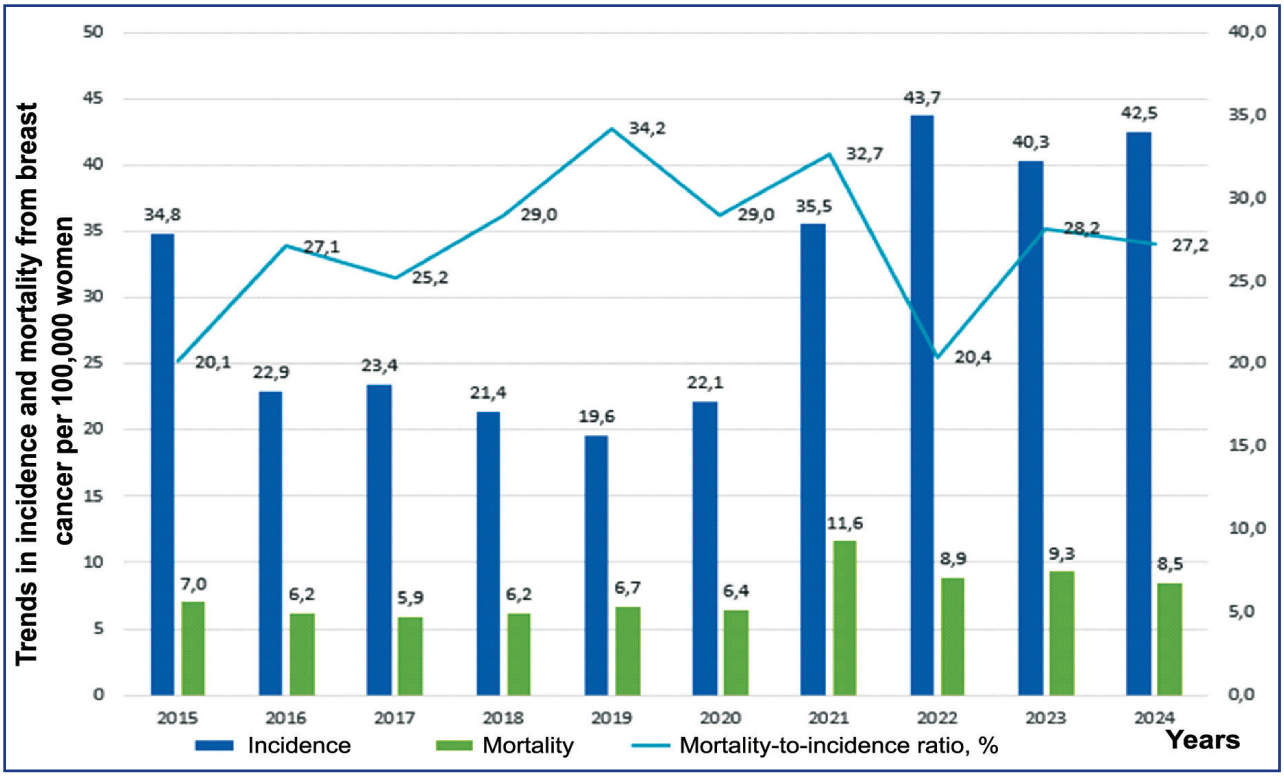

Figure 4 – Intensive indicators of morbidity and mortality from breast cancer and their ratio (conditional mortality rate) among the female population of the Almaty region in 2015-2024 (per 100,000 women)

A comparative analysis of standardized incidence and mortality rates from breast cancer among women in the Almaty region for 2015-2024 revealed clear changes in the epidemiological picture of the disease. Over this period, the incidence increased from 34.2 to 39.1 per 100,000 women, while mortality decreased from 6.9 to 8.3 per 100,000 women. Against this background, the conditional case fatality rate decreased from 20.2% to 21.2%, despite a short-term increase to 35.1% in 2019. The minimum case fatality rate was recorded in 2022 – 20.4%, which coincided with the peak incidence rates. The overall dynamics indicate improved early detection and treatment accessibility, despite the persistently high cancer burden in the region (Figure 5).

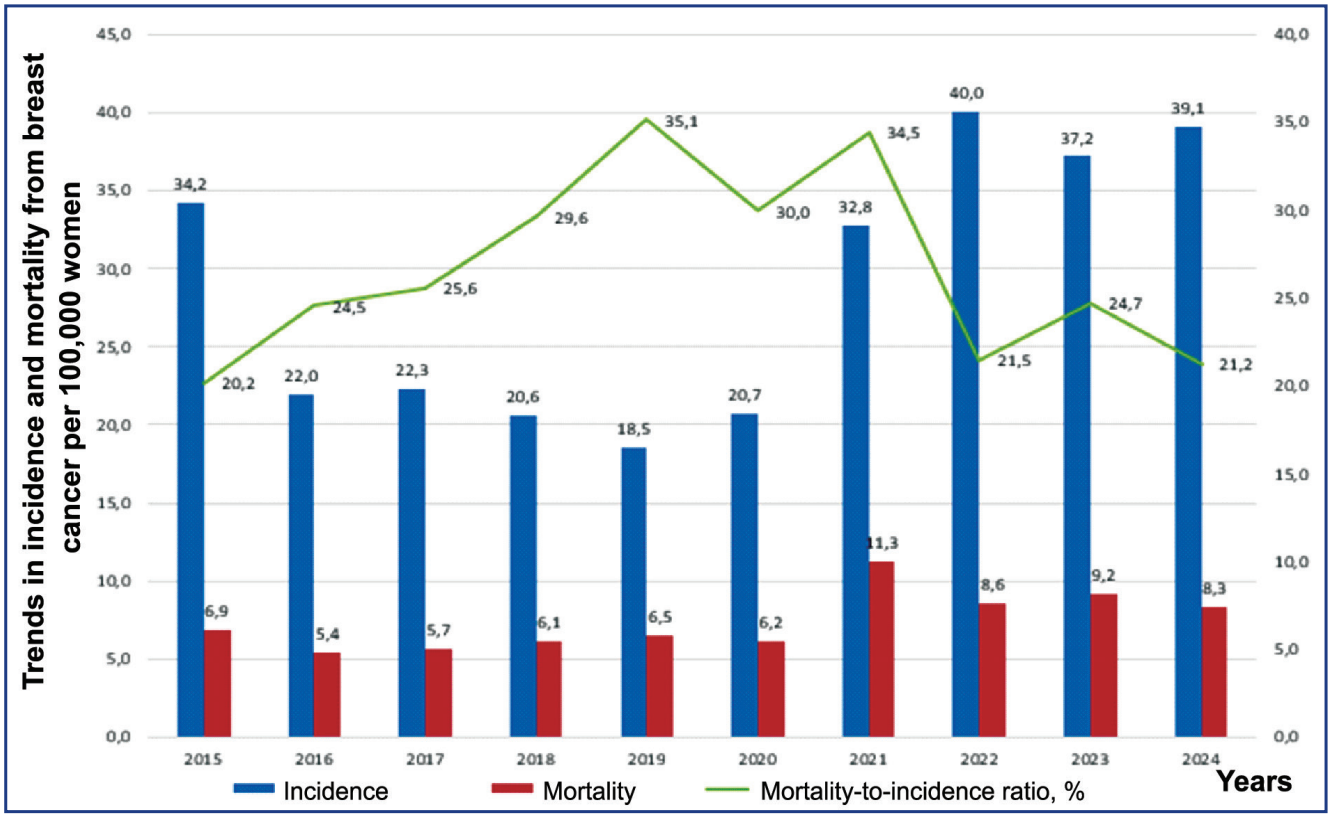

Figure 5 – Standardized incidence and mortality rates from breast cancer and their ratio (conditional case fatality rate) among the female population of the Almaty region in 2015-2024 (per 100,000 women)

The distribution of breast cancer cases by stages at initial detection demonstrated positive changes over the study period. In 2015, the proportion of patients with early-stage disease (I-II) was 74.1%, while by 2024, this figure had increased to 89.2%. This increase indicated a significant improvement in early diagnosis, likely due to expanded coverage by screening programs, increased awareness among healthcare professionals, and improved access to mammography. The proportion of stage III cancers decreased from 20.6% to 4.6%, also reflecting progress in reducing the incidence of advanced disease. A slight increase in stage IV cancers (from 5.3% to 6.2%) requires further investigation. However, given the overall increase in early detection, this indicator did not significantly impact the positive trend (Figure 6).

A comparative analysis of the age structure of identified breast cancer cases over two five-year periods (2015-2019 and 2020-2024) showed an increase in the number of cases in the age group of 60-64, from 31.8 to 52.6, and 65-69, from 24.4 to 41.2. The proportion of breast cancer among all malignant neoplasms in women in the Almaty region has also increased from 18.5% in 2015 to 21.6% in 2024. This increase could be due to both improved breast cancer diagnostics and a consistently high-risk level in this population (Figure 7).

Table 1 presents the epidemiological indicators for malignant neoplasms and breast cancer in the Almaty region for 2015-2024. During this period, the number of patients with oncopathology increased by 40.6% (from 8,207 to 11,541), as did the absolute number of patients registered for dispensary care with a diagnosis of breast cancer, which increased by 64.1% (from 1,520 to 2,494). The incidence of breast cancer continues to grow (intensive +22.1%; standardized +14.3%), while mortality rates from breast cancer are also increasing (intensive +21.4%; standardized +20.3%).

The staging structure reflects positive changes: the proportion of early stages (I-II) at detection increased by 20.4% (from 74.1% to 89.2%), the proportion of stage III decreased from 20.6% to 4.6% (-77.7%), while the pro-

portion of stage IV increased by 17% (from 5.3% to 6.2%). Overall, there has been an improvement in early breast cancer diagnosis rates, demonstrating the effectiveness of the interventions being implemented.

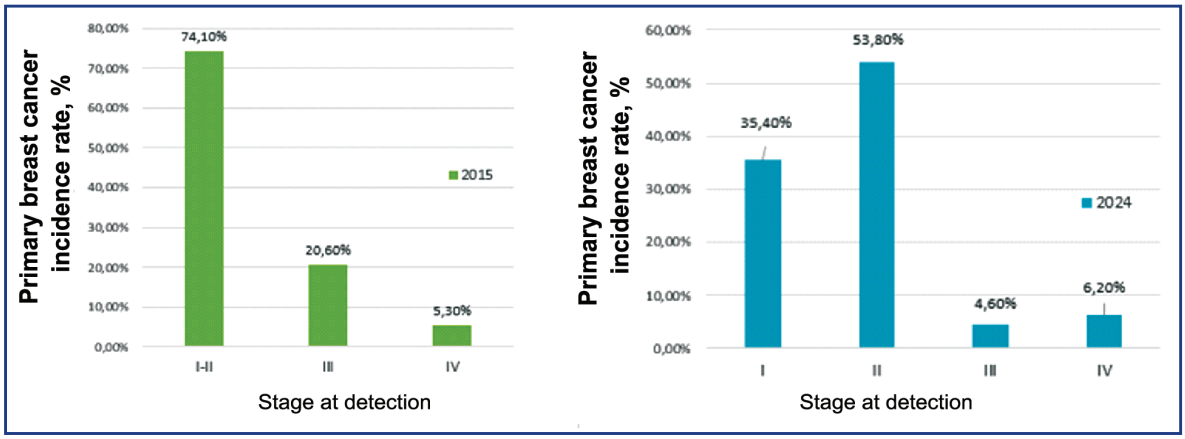

Figure 6 – Distribution of newly diagnosed cases of breast cancer by stage at the time of diagnosis among women in the Almaty region in 2015 and 2024 (%)

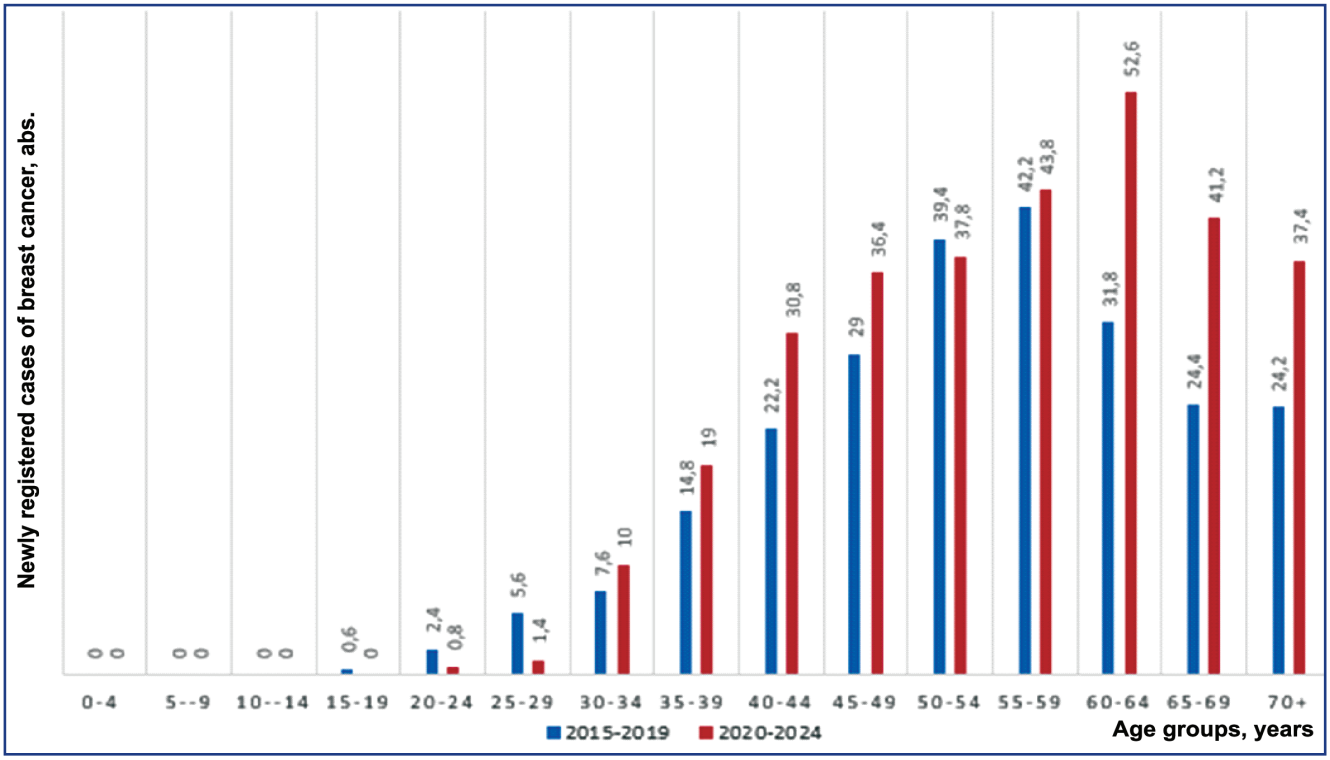

Figure 7 – Comparative distribution of newly registered cases of breast cancer by age group among women in the Almaty region in 2015-2019 and 2020-2024

Table 1 – Main epidemiological indicators of malignant neoplasms and breast cancer in the Almaty region, 2015 and 2024

Indicator	2015	2024
The number of patients with malignant neoplasms registered in the dispensa-ries	8207	11 541
The number of patients with breast cancer on the dispensary register	1520	2494
The proportion of breast cancer among all malignant neoplasms in women (%)	18.5%	21.6%
Breast cancer incidence (per 100,000)	34.8	42.5
Standardized incidence of breast cancer	34.2	39.1
Intensive mortality from breast cancer	7.0	8.5
Standardized mortality from breast cancer	6.9	8.3
The percentage of detection of stages I-II (%)	74.1%	89.2%
Proportion of stage III (%)	20.6%	4.6%
Proportion of stage IV (%)	5.3%	6.2%

Discussion: The study findings reveal significant changes in the epidemiological landscape of breast cancer in the Almaty region over a 10-year observation period. A distinct increase in incidence was established both by the intensive (from 34.8 to 42.5 per 100,000 women) and by the standardized indicator (from 34.2 to 39.1 per 100,000 women). The data are consistent with the results of a retrospective analysis covering large cities of Kazakhstan for 2009-2018. In the study by N. Igissinov et al., age-specific peaks in breast cancer incidence and mortality were identified, falling in the age groups 60-69 and 70 years and older, respectively, which confirms the observed shift in the oncological burden towards older age cohorts in the Almaty region. The authors also noted an increase in standardized morbidity rates, which was attributed to a decrease in mortality and was likely due to the expansion of screening programs and increased availability of specialized medical care [15].

The data obtained in this study on fluctuations in the breast cancer mortality rate, in particular the increase in the indicator in 2021 followed by a decrease, correlate with the findings of the aforementioned analysis, according to which the standardized mortality rate from breast cancer in the republic demonstrated a steady decline (APC = -4.0%, R^2 = 0.9218) during 2009-2018. The decrease in mortality is explained by increased coverage of mammography screening and improved treatment. The average age at death was 61.6 years, and the highest mortality was observed in the 70-84 age group, which is consistent with the age structure of mortality identified in this study. Additionally, pronounced interregional differences were observed, with the highest mortality rates noted in the Pavlodar and Almaty regions, as well as in Astana, and the lowest in the Mangistau and Turkestan regions. This highlights the need for further study of factors influencing the availability and quality of oncological care, including patient routing and the impact of environmental conditions [16]. Against the backdrop of an increase in the proportion of early detection of breast cancer in the Almaty region and an increase in incidence in the 40-49 age group, the international study by J. Rantala et al. (2025) deserves attention, as it established patterns of increasing breast cancer incidence in women under 50 years of age against the background of behavioral risk factors. In particular, the highest annual increase in incidence was recorded in women aged 40-49 who were overweight (AAPC = +4.0%), smokers (AAPC = +3.3%), and those leading a moderately active lifestyle (AAPC = +2.9%). These data partially explain the observed changes in the incidence structure in Kazakhstan and emphasize the importance of considering modifiable risk factors when developing preventive programs, especially for target age groups [17].

Conclusion: Between 2015 and 2024, the Almaty region saw a steady increase in breast cancer incidence, with a moderate decline in mortality rates and improved early diagnosis. The increase in detection rates at stages I and II, while simultaneously reducing the number of stage III cases, confirms the effectiveness of ongoing preventive and screening programs. The primary epidemiological focus is shifting toward older women, necessitating prioritization of this cohort in breast cancer control strategies.

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АҢДАТПА

2015-2024 ЖЫЛДАРЫ АЛМАТЫ ОБЛЫСЫНДА СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ЭПИДЕМИОЛОГИЯЛЫҚ КӨРСЕТКІШТЕРІН ТАЛДАУ

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Өзектілігі: *Сүт безінің қатерлі ісігі (СБҚІ) — бүкіл әлемдегі әйелдер арасында қатерлі ісіктің ең көп таралған түрі. 2020 жылы 2,3 миллион жаңа жағдай және шамамен 685 000 өлім тіркелді. Науқастардың 80% - дан астамы 50 жастан асқан әйелдер. Дамушы елдерде өлім-жітім деңгейі жоғары. 2040 жылға қарай болжам-сырқаттанушылықтың 3 млн жағдайға дейін өсуі күтілуде. Бұл зерттеу СБҚІ-нің аурушаңдық, өлім-жітім, сатысын анықтау, 10 жыл ішінде кешенді аймақтық талдау жүргізетін бірінші зерттеу болып табылады.*

Зерттеудің мақсаты *– 2015-2024 жылдарға арналған сүт безі обырын ерте анықтау және емдеу бойынша Қазақстанның Алматы облысында жүзеге асырылып жатқан шаралардың аурушаңдық, өлім-жітім, сатысын анықтау.*

Әдістері: *2015-2024 жылдар аралығындағы кезеңде Алматы облысының әйелдер халқы арасында СБҚІ сырқаттанушылық пен өлім-жітім көрсеткіштерін жіктеу және үрдістерді бағалау. №7, №090/Е статистикалық есептілік нысандары және өңірлік онкорегистрдің деректері пайдаланылды. Демографиялық деректер ҚР Стратегиялық жоспарлау және реформалар агенттігінің Ұлттық статистика бюросының ресми ашық материалдарынан алынды. Көрсеткіштерді есептеу тікелей стандарттауды қолдана отырып және Microsoft Excel және SPSS Statistics 23.0 бағдарламаларын қолдана отырып, стандартты эпидемиологиялық формулалар бойынша жүргізілді.*

Нәтижелері: *СБҚІ ауруы 100 000-ға шаққанда 34,8-ден 42,5-ке дейін, ал стандартталған көрсеткіш 34,2-ден 39,1-ге дейін өсті. Өлім-жітім 2021 жылы (11,6) шарықтау шегіне жетіп, 2024 жылы 8,5-ке дейін төмендеді. Өлім-жітімнің шартты коэффициенті 20,1%-дан 35,1%-ға дейін болды. I-II кезеңдерді анықтау үлесі 74,1%-дан 89,2%-ға дейін өсті, III кезең 20,6%-дан 4,6%-ға дейін төмендеді.*

Қорытынды: *Өңірде СБҚІ кезінде ерте диагностика мен өмір сүрудің оң динамикасы байқалады. Алайда, өлім-жітімнің тұрақты деңгейі және IV сатысының тұрақты үлесі терапияның бағытталуы мен қол жетімділігін одан әрі жетілдіру қажеттілігін көрсетеді.*

Түйінді сөздер: *сүт безі қатерлі ісігі (СБҚІ), эпидемиология, сырқаттанушылық, өлім-жітім, өмір сүру деңгейі, Қазақстан, Алматы облысы.*

АННОТАЦИЯ

АНАЛИЗ ЭПИДЕМИОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ В АЛМАТИНСКОЙ ОБЛАСТИ ЗА 2015-2024 гг.

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Актуальность: *Рак молочной железы (РМЖ) – наиболее частая форма злокачественных новообразований среди женщин во всём мире. В 2020 году зарегистрировано 2,3 млн новых случаев и около 685 000 смертей. Более 80% заболевших – женщины старше 50 лет. В развивающихся странах отмечаются более высокие показатели смертности. Прогноз к 2040 году – рост заболеваемости до 3 млн случаев. В настоящем исследовании проведен комплексный региональный анализ заболеваемости, смертности и стадии выявления РМЖ за 10 лет.*

Цель исследования *– проанализировать влияние мероприятий по раннему выявлению и лечению РМЖ, реализуемых в Алматинской области Республики Казахстан, на динамику заболеваемости, смертности и стадии выявления за 2015-2024 годы.*

Методы: *Оценка тенденций и распределения показатели заболеваемости и смертности от РМЖ среди женского населения Алматинской области за период с 2015 по 2024 годы. Использованы формы статистической отчётности №7, №090/У и данные регионального онкорегистра. Демографические данные были получены из официальных открытых материалов Бюро национальной статистики Агентства по стратегическому планированию и реформам Республики Казахстан. Расчёт показателей осуществлялся по стандартным эпидемиологическим формулам, с применением прямой стандартизации и использованием программ Microsoft Excel и SPSS Statistics 23.0.*

Результаты: *Заболеваемость РМЖ увеличилась с 34,8 до 42,5 на 100 000 женщин, а стандартизованный показатель – с 34,2 до 39,1. Смертность колебалась, достигнув пика в 2021 году (11,6), затем снизилась до 8,5 в 2024 году. Условный коэффициент летальности варьировал от 20,1% до 35,1%. Доля выявления I-II стадий увеличилась с 74,1% до 89,2%, при снижении III стадии с 20,6% до 4,6%.*

Заключение: *В регионе отмечается положительная динамика ранней диагностики РМЖ. Однако сохраняющийся уровень летальности и стабильная доля IV стадии указывают на необходимость дальнейшего совершенствования маршрутизации и доступности терапии.*

Ключевые слова: *рак молочной железы (РМЖ), эпидемиология, заболеваемость, смертность, Казахстан, Алматинская область.*

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EPIDEMIOLOGICAL ANALYSIS OF BREAST CANCER IN WOMEN OF CHILDBEARING AGE IN THE KARAGANDA REGION

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ABSTRACT

Relevance: *The article examines the epidemiological features of breast cancer among women of childbearing age (15-49 years). Over the past decade, the incidence of breast cancer in women of reproductive age has been steadily increasing. Awareness of prevention is the first and most important step in reducing mortality from breast cancer. Breast cancer, especially among women of childbearing age, is a major public health problem worldwide and is currently the most common cancer among women.*

The study aimed to *analyze the level and structure of breast cancer incidence among women of childbearing age in the Karaganda region (Kazakhstan) in 2013-2023.*

Methods: *A retrospective epidemiological analysis of the long-term dynamics of cardiovascular disease incidence among women of reproductive age in the Karaganda region for 2013-2023 was conducted. Statistical data on cardiovascular disease incidence in the Karaganda region for 2013-2023 are provided in terms of age, mortality and mortality rates. The data are taken from the statistical collections "Health of the population of the Republic of Kazakhstan and the activities of health care organizations for 2013-2023."*

Results: *Between 2013 and 2023, breast cancer incidence rates in the Karaganda region fluctuated, with ups and downs. Every year, breast cancer incidence among urban residents was higher than among rural residents. In recent years, the incidence of stage IV breast cancer has decreased signifi-cantly. The region's mortality rate decreased steadily between 2013 and 2023. The correlation coefficient ($r = 0.93$) indicates a very strong positive linear connection between the number of reported breast cancer cases and the patients' age.*

Conclusion: *The average annual rate increase in breast cancer incidence remains stable. In general, breast cancer incidence in urban areas is around 1.3-1.6 times higher than in rural areas. As the proportion of early diagnosis increases, the mortality from breast cancer decreases considerably. Early diagnosis is crucial for improving survival and reducing mortality from this disease, as evidenced by a significant decline in this indicator $t = 3.12$, $p < 0.01$.*

Keywords: *breast cancer, incidence, mortality, fertile age, screening.*

Introduction: Breast cancer (BC), including in women of reproductive age, is a pressing health problem worldwide and is currently the most common cancer among women [1]. Studies of the socioeconomic significance of BC have shown that it is not only one of the leading causes of mortality among women but also causes significant economic losses.

In 2023, the World Health Organization launched a global initiative aimed at reducing the incidence of breast cancer by 2.5% annually through prevention, timely diagnosis, and effective treatment [2]. In Kazakhstan, in 2023, breast cancer ranked first in the structure of oncological diseases and third in mortality. According to data for 2023, breast cancer accounts for 13.2% of all cancer cases in the country [3-4]. Increased awareness of breast cancer, increased public attention, and significant advances in breast research have had a positive impact on the detection and implementation of breast cancer screening [4].

As of 2024, approximately 5,000 patients are diagnosed with breast cancer in Kazakhstan annually, and up to 1,200 women die from it. Breast cancer is the second most common type of cancer among women. About 1,800 new cases are registered annually, and about 600 women die from it [3].

Despite the seriousness of the problem, it should be noted that there is a lack of systematic studies examining the prevalence of cancer among women of reproductive age. This is reflected in the limited available data, which hinders a full understanding of the problem's scale and the development of effective prevention and treatment strategies.

The study aimed to analyze the level and structure of breast cancer incidence among women of childbearing age in the Karaganda region (Kazakhstan) in 2013-2023.

Materials and methods: Statistical data on the incidence of breast cancer in women of childbearing age (ICD code C50.0-C50.9) in the Karaganda region for 2013-2023 were obtained from the Republican Statistical Digest No. 3 of the Karaganda City Multidisciplinary Hospital. The article "Kazakhstan and the Activities of Healthcare Organizations in 2013-2023" [5-15] was also used.

Statistical analysis of the data was performed using Statistica 13.3. Morbidity and mortality rates were calculated per 100,000 population. Student's t-test and Pearson's correlation coefficient (r) were used.

A descriptive epidemiological surveillance method was used. A retrospective epidemiological analysis (analysis of long-term incidence dynamics for 2013–2023) was conducted.

Results: A retrospective epidemiological analysis of newly diagnosed cancer incidence in the Karaganda region is presented in Figure 1. In the Karaganda region, an uneven incidence rate, with fluctuations, was recorded from 2013 to 2023. The highest rates were recorded between 2016 and 2018. In the Karaganda region, there were 280.3-290.3 cases per 100,000 population. In particular, in 2018, the highest incidence rate was recorded in the Karaganda region (290.3 cases) per 100,000 population. Between 2018 and 2022, a significant decrease was observed in the Karaganda region, from 278.5 cases per 100,000 population to 245.1. This phenomenon may be related to the reduction in the number of routine screenings and medical examinations during the COVID-19 pandemic.

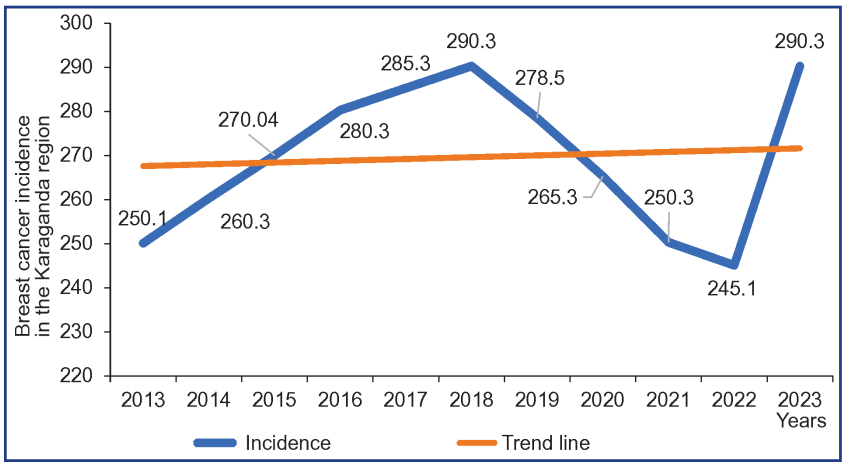

Figure 1 – Long-term dynamics of cancer incidence in the Karaganda region for the period 2013-2023 (per 100,000 population)

The lowest level was recorded in 2022, at 245. The average incidence rate in the analyzed years is 250.08. per 100,000 population. In 2023, a comparative analysis of incidence compared to 2013 revealed a 1.47-fold increase. In 2023, the highest incidence rate was reported in the Karaganda region, with 290 cases per 100,000 population. This figure is comparable to the peak in 2018. This increase could be due to the resumption of preventive examinations and timely diagnostic procedures in recent years.

Generally, the incidence rate in the Karaganda region remained consistently high throughout the review period. The average annual growth rate was stable at T^{sn}_{pr}=0.94%. The projected incidence rate in 2024 was 280.71 per 100,000 population. If the trend that developed in the previous period continued, the incidence rate could range from 278.9 to 281.86

An analysis of cancer incidence in urban and rural populations in 2013-2023 revealed that breast cancer was more common among urbanites (Figure 2). Figure 2 shows the annual breast cancer incidence in urban and rural populations of childbearing age in the Karaganda region for 2013-2023 (per 100,000 inhabitants). The average incidence in urban areas was 1.19 times higher than in rural areas, amounting to 260.6 and 219.3 cases per 100,000 inhabitants, respectively.

The incidence rate among urbanites was consistently higher every year compared to rural residents.

The lowest and highest rates were observed among urbanites, at 220 per 100,000 residents in 2013 and 275 in 2023, respectively. Among the rural population, the rates were 180 in 2013 and 210 in 2019 and 2023. The overall incidence in urban areas was about 1.3-1.6 times higher than in rural areas. A slight increase in breast cancer mortality was observed in both groups in 2018-2020, and screening and early detection efforts will likely be intensified during this period.

Table 1 presents an analysis of breast cancer incidence in the Karaganda region from 2013 to 2023, categorized by disease stage.

The incidence rates for stages I and II from 2013 to 2019 are presented separately. These stages have been combined since 2020. Notably, the incidence rates for stages I and II were higher per 100,000 population compared to stages III and IV. Between 2013 and 2023, there was an improvement in early detection of breast cancer (at stages I and II), likely due to screening programs and higher medical awareness among women. The decrease in the incidence of stages III and IV could indicate improved treatment efficacy.

A downward trend in long-term dynamics of mortality from breast cancer in the Karaganda region was revealed

(Figure 3), with a 2.9-fold decrease in mortality, from 15.7 to 5.4 per 100,000 population. The peak mortality rate of 15.7 was recorded in 2013. The projected mortality rate in 2024 was 4.94 cases per 100,000 population.

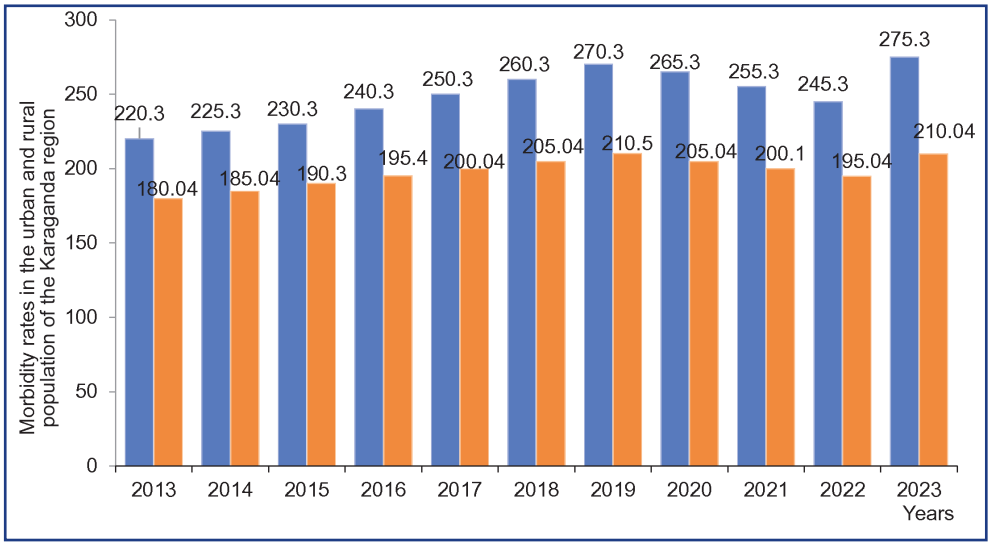

Figure 2 – Long-term dynamics of breast cancer incidence among the urban and rural population of childbearing age in the Karaganda region for the period 2013–2023 (per 100,000 inhabitants)

Table 1 – Prevalence of breast cancer by disease stage in the Karaganda region, 2013-2023

Year	Breast cancer (by stage)			
	Stage I	Stage II	Stage III	Stage IV
2013	38.7	41.2	12.8	7.4
2014	44.7	37.7	12.1	5.4
2015	40.7	40.5	12.3	6.3
2016	46.2	39.9	8.8	5.2
2017	46.9	38.8	6.7	4.7
2018	41.8	40.9	11.5	5.8
2019	31.8	45.4	15.2	7.4
2020	78.0		15.8	6.0
2021	78.8		14.0	7.1
2022	82.8		11.6	5.6
2023	73.3		21.8	4.7

A positive correlation with the total number of detections indicates improved diagnostic and screening coverage. However, a clear decline in early detections (7.2%) is observed, confirming the impact of the pandemic in 2020. The increase in the share of early detection is a positive sign, as it increases the chances of successful treatment and reduces mortality.

Statistical analysis revealed a very high correlation between the frequency of screening tests and the rate of early detection ($r = 0.98$). This provides important evidence of the direct link between early diagnosis and screening. Furthermore, a strong positive correlation was observed between the frequency of general preventive examinations and the rate of detected cases ($r = 0.993$). This confirms the high effectiveness of preventive examinations.

The study also included a statistical analysis of mortality rates. A significant reduction in mortality rates has been noted due to improved early diagnosis. The statistical significance of this reduction ($t = 3.12$, $p < 0.01$) indicates that early diagnosis is a key factor in improving survival and reducing mortality.

Discussion: Cancer remains one of the most significant health issues in modern medicine. Cancer diseases spread rapidly worldwide. According to the literature, breast cancer is more common in women living in urban areas than in rural areas. This is attributed to increased access to diagnostic capabilities, screening, and medical care. Late or inadequate diagnosis in rural areas, as well as low public awareness, can negatively impact early detection. Low registration rates in rural areas may be due not to a low true incidence but to limited diagnostic capabilities. This situation underscores the importance of developing targeted prevention programs in rural areas to reduce regional disparities among women of reproductive age [16-17].

Between 2013 and 2023, an improvement in the detection of early-stage breast cancer (stages I and II) was noted, which may be due to the availability of screening pro-

grams and increased medical awareness among women. An increase in the incidence of stage III and a decrease in stage IV cases during this period may indicate increased treatment effectiveness. In recent years, the integration of mass screening, mammography, ultrasound, and public education on self-examination methods into the medical examination of women over 40 years of age has provided a valuable opportunity for early disease detection [18-19].

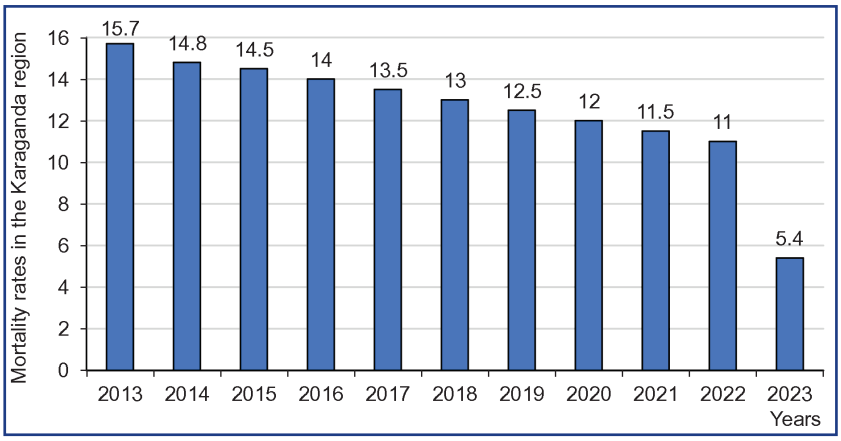

Figure 3 – Long-term dynamics of mortality from breast cancer in the Karaganda region for the period 2013-2023 (per 100,000 inhabitants)

Regular examinations and screening programs are the most effective tools for early detection of breast cancer, which in turn allows for timely initiation of treatment, prevention of disease complications, and reduction of mortality [20].

Several factors increase the risk of developing breast cancer [21-22]. Some risk factors are independent of a woman's lifestyle, such as age or genetic predisposition, but other factors, including reproductive behavior, hormonal use, and lifestyle, may also influence them. A systematic literature review [23] of 197 citations in PubMed, Web of Science, and Scopus summarized the influence of lifestyle factors on the risk of breast cancer; for example, smoking and alcohol consumption increase the odds ratio by 7% and 10%, respectively, while regular physical activity reduces the risk by 10%. The same study summarized the influence of reproductive behavioral factors (infertility, late pregnancy, breastfeeding, oral contraceptive use) and hormones (estrogen, progesterone, estrogen/progesterone, hormone therapy), as well as diet and radiation therapy. It is important to note that there are also secondary risk factors, such as night shift work, which influence the risk of developing cancer through changes in women's hormonal status [22, 24]. Furthermore, the influence of risk factors may vary depending on the genetic and ethnic characteristics of women [25-26].

The study demonstrates that the introduction of modern diagnostic and treatment methods has a significant impact on reducing cancer mortality. The findings confirm the importance of implementing innovative technologies and improving organizational processes in the healthcare system. Further research aimed at analyzing additional variables will help clarify the impact of various factors on mortality dynamics and facilitate the development of effective strategies to improve the quality of medical care.

Further research in this area includes conducting in-depth quantitative analysis using regression modeling and correlation analysis to identify key factors contributing to the development of the disease. This will not only enhance our understanding of epidemiological patterns but also enable the development of effective measures to reduce the incidence of the disease.

Conclusion: The incidence rate in the Karaganda region remains consistently high throughout the period under review. The average annual growth rate is estimated to be stable at T^{sn}_{pr} = 0.94%. The projected incidence rate in 2024 is 280.71 per 100,000 population, and if the trend established in the previous period continues, the incidence rate is expected to range from 278.9 to 281.86.

Generally, the incidence rate in urban areas is approximately 1.3 to 1.6 times higher than in rural areas. The incidence of diseases detected for the first time in life in the region and the city was 1.19 times higher than in rural areas, amounting to 260.6 and 219.3, respectively.

In the Karaganda region, a gradual decline in mortality was observed between 2013 and 2023. The mortality rate in the Karaganda region has decreased from 15.7 to 5.4 per 100,000 people. The number of registered cases has increased by 2.9 times. The maximum mortality rate was 15.7 in 2013. The projected mortality rate in 2024 is 4.94 cases per 100,000 population.

Between 2013 and 2023, an improvement in early detection of breast cancer (stages I and II) was noted, which may be due to the availability of screening programs and increased medical awareness among women. Furthermore, a decrease in the incidence of stage IV breast cancer has been observed in recent years. The relatively uniform incidence of cancer and the decrease in stage IV breast cancer incidence and mortality are due to several social, medical, and organizational factors. The increase in stage

III breast cancer cases and the decrease in stage IV breast cancer cases during this period may indicate improved treatment effectiveness.

Statistical analysis revealed a very high correlation between the frequency of screening tests and the rate of early detection (r=0.98). A strong positive correlation was also observed between the frequency of general preventive examinations and the number of cases detected (r=0.993). This confirms the high effectiveness of preventive examinations.

In conclusion, it should be noted that the increase in early breast cancer diagnosis rates over the past decade demonstrates the effectiveness of screening programs and awareness-raising activities in the healthcare system. These data are important from both a scientific and practical perspective, as early cancer detection is a crucial factor in improving treatment effectiveness and quality of life.

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АНДАТПА

ҚАРАҒАНДЫ ОБЛЫСЫ БОЙЫНША ФЕРТИЛЬДІ ЖАСТАҒЫ ӘЙЕЛДЕРДІҢ СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІН ЭПИДЕМИОЛОГИЯЛЫҚ ТАЛДАУ

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Өзектілігі: *Бұл мақалада фертильді жастағы (15-49 жас) әйелдер арасындағы сүт безі қатерлі ісігі (СБҚІ)-нің эпидемиологиялық ерекшеліктері зерттеледі. Соңғы онжылдықта репродуктивті жастағы әйелдер арасында СБҚІ-нің жиілігі біртіндеп өсіп келе жатқаны байқалды. Алдын алу туралы ақпараттандырылу – бұл СБҚІ-нен болатын өлімді азайтудың алғашқы және маңызды қадамы. СБҚІ, оның ішінде фертильді жастағы әйелдер арасында және бүкіл әлемде денсаулық сақтаудың өзекті мәселесін тудырады және қазіргі уақытта әйелдер арасында ең көп таралған ісік түрі болып табылады.*

Зерттеу мақсаты *– 2013-2023 жылдарға Қазақстан Республикасының Қарағанды облысында фертильді жастағы әйелдердің сүт безі қатерлі ісігінің аурушаңдығы мен құрылымын зерттеу.*

Әдістері: *Қарағанды облысы бойынша 2013-2023 жылдарға арналған репродуктивті жастағы әйелдердің жүрек-қан тамырлары ауруларының ұзақ мерзімді динамикасына ретроспективті эпидемиологиялық талдау жүргізілді. Қарағанды облысы бойынша 2013-2023 жылдарға арналған жүрек-қан тамырлары ауруларының статистикалық деректері жас, өлім және өлім-жітім көрсеткіштері бойынша берілген. Мәліметтер «Қазақстан Республикасы халқының денсаулығы және денсаулық сақтау ұйымдарының 2013-2023 жылдарға арналған қызметі» статистикалық жинақтарынан алынды.*

Нәтижелері: *Қарағанды облысында 2013-2023 жылдар аралығында СБҚІ-мен сырқаттанушылықтың біркелкі емес динамикасы көтеріліп, төмендеді. Қала тұрғындары арасында СБҚІ-мен сырқаттанушылық жыл сайын ауыл тұрғындарына қарағанда тұрақты түрде жоғары болды. Соңғы жылдары СБҚІ-нің IV сатысының төмендеуі байқалады. Қарағанды облысында 2013-2023 жылдары өлім-жітімнің тиісінше төмендеу үрдісі тіркелуде. Корреляция коэффициенті (r=0,93) пациенттердің орташа жасы мен сүт безі ісігінің тіркелген жағдайларының орташа саны арасындағы өте күшті оң сызықтық байланысты көрсетеді.*

Қорытынды: *Қарағанды облысында СБҚІ-мен сырқаттанушылықтың орташа жылдық өсу қарқыны тұрақты өсуде. Жалпы, қалалық жерлерде СБҚІ-нің аурушаңдығы ауылдық жерлерге қарағанда шамамен 1,3-1,6 есе жоғары. Ерте анықтау үлесінің ұлғаюымен СБҚІ-нен болатын өлім-жітім деңгейі айтарлықтай төмендейді. Бұл көрсеткіштің төмендеуі статистикалық маңызды болды (t=3,12, p<0,01), бұл ерте диагностика өмір сүруді арттыру және осы аурудан өлімді азайтудың шешуші факторы екенін көрсетеді.*

Түйінді сөздер: *сүт безі қатерлі ісігі (СБҚІ), сырқаттанушылық, өлім-жітім, фертильді жас, скрининг.*

АННОТАЦИЯ

ЭПИДЕМИОЛОГИЧЕСКИЙ АНАЛИЗ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН ФЕРТИЛЬНОГО ВОЗРАСТА В КАРАГАНДИНСКОЙ ОБЛАСТИ

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Актуальность: *РВ статье рассматриваются эпидемиологические особенности рака молочной железы среди женщин фертильного возраста (15-49 лет). За последнее десятилетие заболеваемость раком молочной железы (РМЖ) среди женщин репродуктивного возраста неуклонно растет. Информированность о профилактике является первым и самым важным шагом в снижениии смертности от рака груди. РМЖ, в том числе среди женщин фертильного возраста, представляет собой серьезную проблему общественного здравоохранения во всем мире и в настоящее время является наиболее распространенным видом рака среди женщин.*

Цель исследования *– изучить уровень и структуру заболеваемости раком молочной железы среди женщин фертильного возраста в Карагандинской области Республики Казахстан за период 2013-2023 годы.*

Методы: *Проведен ретроспективный эпидемиологический анализ многолетней динамики заболеваемости сердечно-сосудистыми заболеваниями среди женщин репродуктивного возраста Карагандинской области за 2013-2023 годы. Приведены статистические данные о заболеваемости сердечно-сосудистыми заболеваниями в Карагандинской области за 2013-2023 годы в разрезе возраста, смертности и показателей летальности. Данные взяты из статистических сборников «Здоровье населения Республики Казахстан и деятельность организаций здравоохранения за 2013-2023 годы».*

Результаты: *В течение 2013-2023 гг. в Карагандинской области отмечается неравномерный уровень заболеваемости РМЖ, с периодами подъемов и спадов. Уровень заболеваемости РМЖ среди городских жителей была ежегодно стабильно выше, чем среди сельских. В последние годы наблюдалось снижение уровня заболеваемости РМЖ IV стадии. В 2013-2023 годы в области отмечалась устойчивая тенденция снижения смертности. Коэффициент корреляции (r=0,93) показывает очень сильную положительную линейную связь между числом зарегистрированных случаев РМЖ и возрастом больных.*

Заключение: *Среднегодовой темп прироста заболеваемости РМЖ остается стабильным. В целом заболеваемость РМЖ в городской местности примерно в 1,3-1,6 раза выше, чем в сельской. С увеличением доли раннего выявления уровень смертности от РМЖ существенно снижается. Снижение данного показателя было статистически значимым (t=3,12, p<0,01), что означает, что ранняя диагностика является ключевым фактором повышения выживаемости и снижения смертности от данного заболевания.*

Ключевые слова: *рак молочной железы (РМЖ), заболеваемость, смертность, фертильный возраст, скрининг.*

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MODERN APPROACH TO THE TREATMENT OF T-CELL LYMPHOMA: A CLINICAL CASE OF USING HIGH-DOSE CHEMO- AND TARGETED THERAPY

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ABSTRACT

Relevance: *T-cell lymphomas are rare, aggressive non-Hodgkin lymphomas. Therapy for T-cell lymphomas remains a challenge for oncologists. In recent years, immunotherapy has developed greatly in the treatment of cancer. PD-L1 expression correlates with an unfavorable prognosis in many cancers; therefore, the prognostic value of PD-L1 levels in non-Hodgkin lymphomas is relevant.*

The study aimed to *determine the level of PDL-1 expression in T-cell lymphomas using TPS and CPS analyses, and to analyze the correlation between expression levels and clinical and pathological features, as well as patient treatment outcomes.*

Methods: *A retrospective study of pathomorphological material from primary patients with T-cell lymphomas was conducted from 2015 to 2020. PD-L1 expression was determined using a modified combined positive score (CPS) and tumor share index (TPS). Clinical, laboratory, and instrumental data, as well as the results of therapy for patients included in the study, were collected.*

Results: *The study included 40 patients; the average age was 48 years (range 18-76). 55% of patients were men, 45% were women. In 60% of cases, patients were under 60 years old. All patients received therapy according to the CHOP regimen (cyclophosphamide 750 mg/m² on Day 1, doxorubicin 50 mg/m² on Day 1, vincristine 1.3 mg/m² on Day 1, and prednisolone 60 mg/m2 on Days 1-5). Complete remission was achieved in 12 patients, disease progression was observed in 19 patients, and 6 patients died from disease progression. PDL-1 overexpression was detected in 37 patients. Statistical correla-tion of PDL-1 expression with late-stage disease ($p = 0.001$), high IPI index ($p = 0.001$), high relapse rate ($p = 0.001$), and high serum LDH level ($p = 0.001$) was observed. PD-L1 expression was a prognostic factor affecting therapy outcome and prognosis.*

Conclusion: *The significant increase in PDL-1 expression is a key prognostic factor and a predictor of poor response to standard therapy. The combination of two research types, CPS and TPS, more effectively detects PDL-1 expression, which is optimal given the biology of the tumor process. Immune therapy is a promising therapeutic option.*

Keywords: *epidemiology, T-cell lymphomas, immune therapy, PDL-1 expression.*

Introduction: Non-Hodgkin lymphomas (NHL) rank sixth among men and fifth among women worldwide among all oncological diseases, comprising both B-cell and T-cell variants of the condition [1]. T-cell lymphomas are a rare and aggressive type of NHL, with the most common forms being peripheral T-cell lymphomas (PTCL), ALK-positive and ALK-negative subtypes, Sézary syndrome, mycosis fungoides, nasal-type T/NK-cell lymphomas, and others [2]. For all types of T-cell lymphomas, except for Sézary syndrome and mycosis fungoides, disease staging is performed according to the Ann Arbor classification and the International Prognostic Index (IPI), which determines the disease prognosis [3, 4].

In contrast to B-cell lymphomas, for which various treatment options are available, the treatment of T-cell lymphomas remains a challenge for oncologists [5, 6]. Despite the availability of similar therapeutic options and treatment strategies, the prognosis of T-cell lymphomas varies depending on histological subtype, molecular variants, and the patient's clinical condition. Therefore, identifying new biomarkers may expand therapeutic options and help determine disease prognosis.

In recent years, immune therapy with immune checkpoint inhibitors (ICIs) has made significant advances in the treatment of many cancers [7]. Tumor immune regulation occurs through PD-1, PD-L1, and PD-L2 ligands in three stages: immune surveillance, immune homeostasis, and immune evasion [8].

PD-L1 is a ligand that is highly expressed not only on malignant cells in various solid tumors, but also on T-lymphocytes, B-lymphocytes, and antigen-presenting cells (APCs), and becomes further activated upon immune cell

stimulation [9]. PD-L2 is expressed by comparatively fewer cell types than PD-L1, primarily on APCs [10-11].

According to some researchers, PD-L1 expression correlates with poor prognosis, underscoring the importance of studying its prognostic significance in NHL [12]. Currently, there is no standardized interpretation of PD-L1 expression in NHL, which significantly complicates its analysis [13].

In this study, we evaluated the level of PD-L1 expression in T-cell lymphomas using a modified approach based on two methods of expression analysis: the Combined Proportional Score (CPS), which measures PD-L1 expression on both tumor cells and immune cells within the tumor microenvironment, and the Tumor Proportional Score (TPS), which measures PD-L1 expression on tumor cells only. We also compared the results of immunohistochemical PD-L1 expression analysis with other clinicopathological characteristics and patient treatment outcomes.

The study aimed to determine the level of PD-L1 expression in T-cell lymphomas using TPS and CPS analyses, and to analyze the correlation between expression levels and clinical and pathological features, as well as patient treatment outcomes.

Materials and Methods: A retrospective study was conducted using histological material from patients diagnosed with T-cell lymphoma during 2015-2020. A total of 40 patients were included in the study. All patients had a confirmed diagnosis of a T-cell lymphoma variant and underwent excisional biopsy. Medical records were analyzed for clinical and laboratory data and treatment outcomes. Treatment outcomes were categorized according to the Lugano classification [14].

Cases were classified based on the variant of T-cell lymphoma in accordance with the 2022 WHO classification of hematopoietic and lymphoid tumors [15]. Immunohistochemical staining for PD-L1 was performed using polyclonal PD-L1 antibodies (Biospes) according to the manufacturer's instructions, with appropriate positive and negative controls.

PD-L1 analysis in T-cell lymphomas is complex, as PD-L1 expression is also present in the tumor microenvironment. PD-L1 expression was evaluated using two assessment methods: a modified Combined Positive Score (CPS) and the Tumor Proportion Score (TPS) [16].

Figure 1 shows the ratio of the total number of PD-L1-positive tumor cells to lymphocytes and macrophages, as well as the total number of viable tumor cells.

TPS analysis calculates the ratio of PD-L1-positive tumor cells to the total number of tumor cells in the sample (Figure 1).

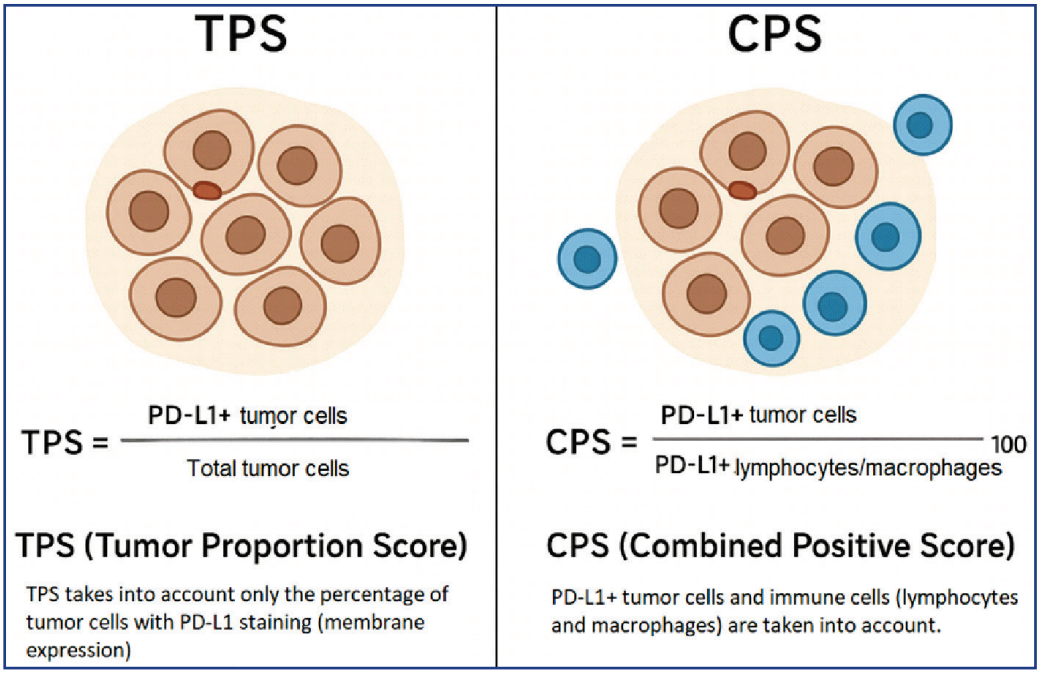

Figure 1 – Comparison of PD-L1 scoring systems.
Source: ChatGPT. Generated illustration [On-line resource]. Available at: https://chatgpt.com/c/68ad47b6-7ee0-8325-941c-6e8dbc30fe41 (accessed: 26.08.2025)

The threshold for CPS analysis was set at 5% of cells expressing cytoplasmic and/or membranous PD-L1. Cases were considered positive with either low expression (≥5% to <50% of cells) or high expression (≥50% of cells) [17, 18].

For TPS, the result – expressed as a percentage (0-100%) – indicated the level of expression: low expression was defined as <1% or ≥1%, and high expression as ≥50% [19].

Statistical Analysis: Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp.). Qualitative data were expressed as absolute numbers and percentages. Quantitative data were expressed

as mean ± standard deviation for parametric data after testing for normality using the Shapiro-Wilk test (n < 50).

The chi-squared test or Fisher's exact test was used to compare qualitative variables across two or more groups. Fisher's exact test value was 0.906.

Relapse-free survival (RFS) was measured in months from the date of complete response to the date of death, relapse, or last follow-up visit.

Overall survival (OS) was measured in months from the date of diagnosis to the date of death or last follow-up visit. Survival data were analyzed using the Kaplan-Meier method.

Cox regression analysis was used to identify independent factors that could jointly affect survival. The p-value was considered significant if it was less than 0.05 at the 95% confidence interval.

The Local Ethics Committee of Asfendiyarov Kazakh National Medical University reviewed and approved this study (Protocol No. 5(82) dated 24.04.2019). The authors declare adherence to the World Medical Association's Declaration of Helsinki.

Results: The study included 40 patients with T-cell lymphomas (Table 1). The median age of the patients was 48 years (ranging from 18 to 76 years). Men accounted for 55% of the patients, and women 45%. In 60% of the cases, patients were under 60 years of age. Serum lactate dehydrogenase (LDH) levels were elevated in 67.5% of patients, and extranodal involvement was observed in 70% of cases. 85% of cases were at an advanced stage (stage III or IV according to the Ann Arbor classification). 57% of cases had a high-intermediate or high IPI score.

Among the 40 patients included in the study, 19 were diagnosed with PTCL, 6 with anaplastic large-cell lymphoma (ALK-negative), 5 with anaplastic large-cell lymphoma (ALK-positive), 8 with mycosis fungoides, and 2 with Sézary syndrome.

Table 1 – Characteristics of the Study Patients (n=40)

Indicator	Absolute number, n	Relative quantity, %
Sex		
Male	22	55
Female	18	45
Age		
≤60	28	70
>60	12	30
Lactate dehydrogenase Level (normal: 135-214 U/L)		
Normal	16	33
Elevated	27	67
Disease Spread		
Nodal	12	30
Extranodal	28	70
Ann Arbor Stage		
I, II	13	32
III, IV	27	68
IPI Risk Group		
Low	5	13
Low-intermediate	12	30
High-intermediate	15	37
High	8	20
PD-L1 Expression		
Low	6	15
High	34	25
Response to Therapy		
Complete remission	12	30
Partial remission	7	17.5
Stable disease	2	5
Disease progression	19	47.5
Relapse after 1st-line therapy		
Yes	4	33.3
No	8	66.6

All patients included in the study received therapy according to the CHOP regimen (cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.3 mg/m^2 on day 1, and prednisone 60 mg/m^2 on days 1-5). Regarding treatment response, 12 patients achieved complete remission, 19 experienced disease progression, and 6 died of disease progression.

PD-L1 expression was detected in the majority of cases in the study. In 4 patients, expression was below 5% and

was classified as negative. One patient showed low expression (Figure 2).

High PD-L1 expression was observed in 35 patients (Figure 3). Lack of PD-L1 expression in 2 cases may be due to low-quality material.

PD-L1 Expression and Clinicopathological Features: According to the statistical analysis, high PD-L1 expression was significantly associated with: advanced disease stage (p=0.001), high IPI score (p=0.001), high relapse rate (p=0.001), and elevated serum LDH level (p=0.001).

No statistically significant association was found between PD-L1 expression and sex (p=0.73) or age (p=0.152) (Table 2).

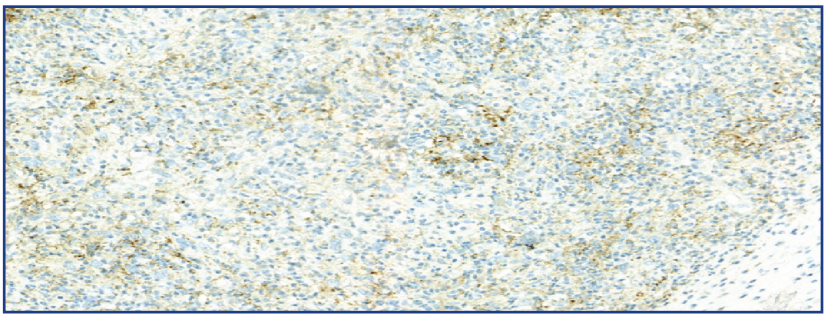

Figure 2 – Low PD-L1 Expression in T-cell Lymphomas

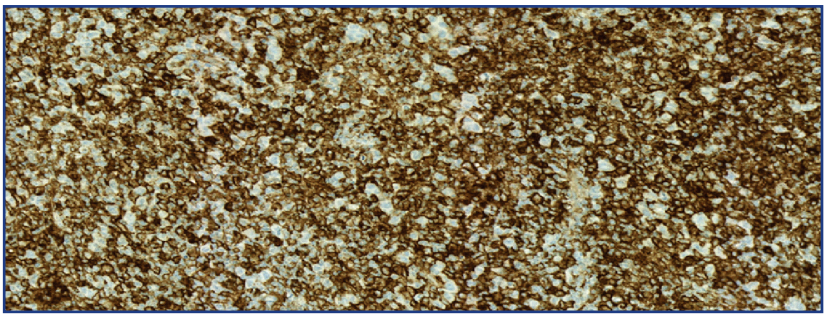

Figure 3 – High PD-L1 Expression in T-cell Lymphomas

Table 2 – Association of PD-L1 Expression with Clinical Features

Indicator	Low/Absent PD-L1 Expression (n=6)	High PD-L1 Expres-sion (n=34)	P-value
Sex			
Male	3	19	p<0.73
Female	3	15	
Age			
≤60	3	25	p<0.152
>60	3	9	
LDH level			
Normal	4	12	p<0.001
Elevated	2	25	
Ann Arbor Stage			
I, II	3	10	p<0.001
III, IV	3	24	
IPI Risk Group			
Low, low-intermediate	5	12	p<0.001
High-intermediate, high	1	22	
Relapse after 1st-line therapy			
Yes	0	4	p<0.001
No	6	2	

The estimated 1-year and 5-year progression-free survival (PFS) rates for the study cohort were 92.2% and 58.5%, respectively.

PD-L1 expression was found to be a prognostic factor: 5-year overall survival (OS) was 29% in patients with high PD-L1 expression and 84.8% in patients with low PD-L1 expression (p=0.001) (Figure 4).

Discussion: T-cell lymphomas are rare malignant neoplasms characterized by aggressive progression and the development of resistance to standard chemotherapy protocols [20]. Currently, novel agents such as brentuximab ve-

dotin, romidepsin, and pralatrexate are being used in the treatment of T-cell lymphomas [21]. Autologous bone marrow transplantation is performed at the consolidation stage [22]. The effectiveness of T-cell lymphoma therapy remains low, necessitating the search for new markers to accurately predict disease prognosis and treatment outcomes [23].

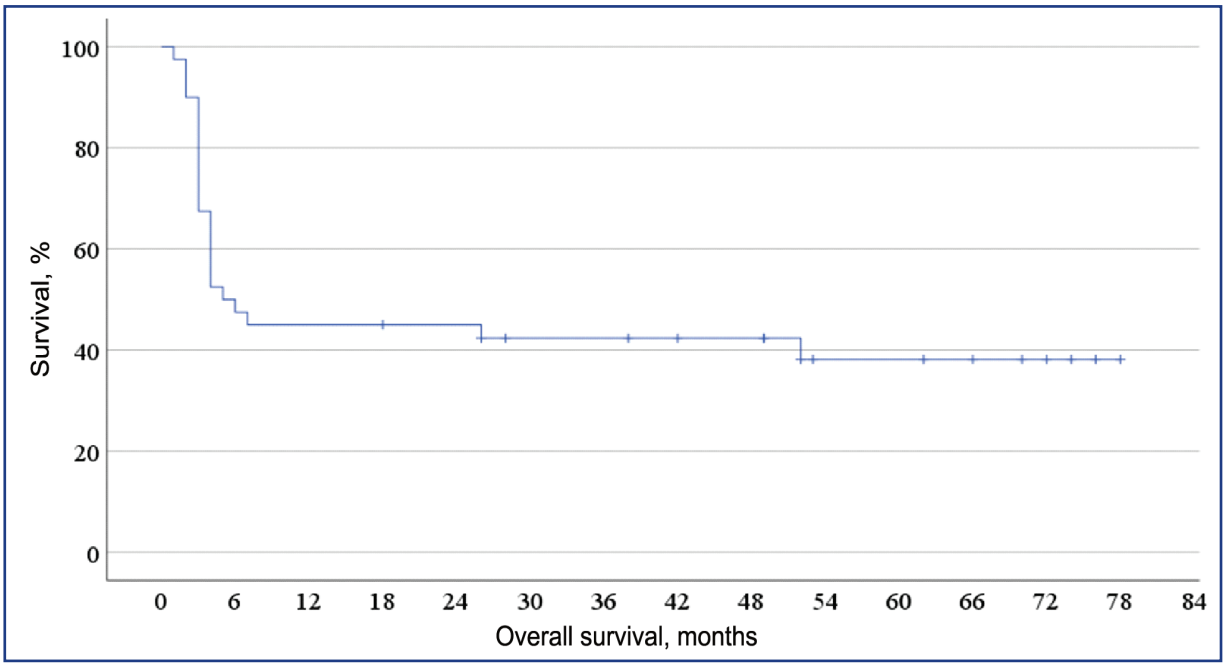

Figure 4 – Association Between Overall Survival and PD-L1 Expression Level

PD-L1 is expressed on the majority of hematopoietic cells at various stages of maturation and is constitutively expressed on T cells, B cells, macrophages, and dendritic cells. This ligand is additionally activated and induced by mitogenic stimulation and IFN-γ, resembling the expression pattern of the PD-1 receptor. High expression of this ligand has been identified in most hematologic malignancies, including primary mediastinal large B-cell lymphoma, Epstein-Barr virus (EBV)-associated lymphomas, T-cell/histiocyte-rich large B-cell lymphoma, plasmablastic lymphoma, extranodal NK/T-cell lymphoma, and Burkitt lymphoma [24]. This may be due to genomic aberrations at the 9p24.1 locus or to EBV proteins, which can upregulate PD-L1 expression [25-27].

To date, ICI drugs have been approved for the treatment of relapsed and refractory classical Hodgkin lymphoma (cHL), primary mediastinal large B-cell lymphoma, and the nasal-type T/NK-cell lymphoma variant [28-29].

M. Xie et al. (2019) believe that increased infiltration by PD-1+ tumor-infiltrating lymphocytes (TILs) is a favorable prognostic factor in diffuse large B-cell lymphoma, but not in HL. In follicular lymphoma, PD-1+ expression is higher than in other B-cell lymphoma subtypes; however, its prognostic significance remains controversial [30]. PD-L1 expression is highly heterogeneous across peripheral T-cell lymphoma subtypes.

P.K. Panjwani et al. (2018) evaluated PD-L1 expression in 702 patients with lymphoma and identified PD-L1-positive cells in 80% of both ALK-positive and ALK-negative anaplastic large-cell lymphomas (ALCL) [32].

In 2021, Y. Shi et al. assessed PD-L1 expression levels. PD-L1 expression ≥50% was identified in 78.9% of nasal-type T/NK-cell lymphomas, 71.4% of ALK+ ALCL, 38.5% of ALK-negative ALCL, and 35.7% of PTCL cases [33].

There are complexities in analyzing PD-L1 expression, including assessing PD-L1 levels in tumor tissue and the microenvironment, evaluating the specificity of different PD-L1 antibody clones for immunohistochemistry (IHC) analysis, and technical aspects such as tissue fixation, processing, and antigen retrieval [34]. Various commercially available companion/complementary diagnostic tests are available for PD-L1 IHC analysis. A companion diagnostic test can determine a patient's eligibility for anti-PD-L1 therapy. Validity, threshold values, and data registration methods vary across platforms [13]. As for PD-L1 cellular localization, complex measurement systems are used. The Tumor Proportion Score (TPS) measures the proportion of tumor cells expressing PD-L1 among all tumor cells. The modified Combined Positive Score (CPS) correlates the number of positive tumor and immune cells with the total cell count.

There is no clear consensus on which threshold level is relevant for distinguishing positive and negative results. The threshold for positive PD-L1 expression across studies ranged from 1% to 50% [35].

Conclusion: Increased PD-L1 expression correlates with prognostically unfavorable clinical variants and a low response to standard therapy. The combination of two assessment methods demonstrated an effective approach for determining PD-L1 expression, which is considered

an optimal option given the biology of the tumor process and the abundance of PD-L1 in microenvironmental cells. The detection of PD-L1 expression not only on cancer cells but also in their microenvironment confirms that ICIs are a promising treatment approach. However, to standardize PD-L1 assessment methods in NHL and the evaluation criteria for expression, more prospective multicenter studies with larger sample sizes are required.

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АҢДАТПА

МАҚАЛА ТАҚЫРЫБЫ Т-ЖАСУШАЛЫҚ ЛИМФОМАЛАРДАҒЫ PDL-1 ЭКСПРЕССИЯСЫН ТАЛДАУ: КЛИНИКОПАТОЛОГИЯЛЫҚ БОЛЖАМДЫҚ ФАКТОРЛАРМЕН КОРРЕЛЯЦИЯ

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Өзектілігі: *Т-жасушалық лимфомалар Ходжкиндік емес лимфоманың сирек кездесетін агрессивті түрі болып табылады. Т-жасушалық лимфомалардың терапиясы онкологтар үшін күрделі мәселе болып қала береді. Соңғы жылдары иммундық терапия ісік ауруын емдеуде айтарлықтай дамыды. PD-L1 экспрессиясы көптеген қатерлі ісіктердегі қолайсыз болжаммен корреляцияланады, сондықтан Ходжкиндік емес лимфомалардағы PD-L1 деңгейлерінің болжамдық мәнін зерттеу өзекті болып табылады.*

Зерттеудің мақсаты: *TPS және CPS талдауына негізделген Т-жасушалық лимфомалардағы PDL-1 экспрессиясының деңгейін анықтау, экспрессия деңгейінің клиникалық және патологиялық белгілермен және пациенттерді емдеу нәтижелерімен корреляциясын талдау.*

Әдістері: *Т-жасушалық лимфомасы бар бастапқы пациенттердің патоморфологиялық материалын ретроспективті зерттеу 2015 жылдан 2020 жылға дейін жүргізілді. PD-L1 экспрессиясы модификацияланған біріктірілген оң балл (CPS) және ісік үлесінің индексі (TPS) арқылы анықталды. Зерттеуге енгізілген науқастардың клиникалық, зертханалық және аспаптық деректері, терапия нәтижелері жиналды.*

Нәтижелері: *Зерттеуге 40 пациент қатысты, науқастардың орташа жасы 48 жасты (18-ден 76 жасқа дейін) құрады. Науқастардың 55%-ы ерлер, 45%-ы әйелдер. 60% жағдайда науқастар 60 жасқа толмаған. Барлық емделушілер CHOP режиміне сәйкес терапия алды (циклофосфамид 750 мг/м^2 1 күн, доксорубицин 50 мг/м^2 1 күн, винкристин 1,3 мг/м^2 1 күн және преднизолон 60 мг/м^2 1-5 күн). 12 науқаста толық ремиссияға қол жеткізілді, 19 науқаста аурудың өршуі байқалды, 6 науқас аурудың өршуінен қайтыс болды. 37 науқаста PDL-1 жоғары экспрессиясы анықталды. PDL-1 экспрессиясының аурудың кеш сатысымен (p=0,001), жоғары IPI индексімен (p=0,001), жоғары қайталану жылдамдығымен (p=0,001) және сарысудағы ЛДГ деңгейінің жоғары деңгейімен (p=0,001) статистикалық корреляция анықталды. PD-L1 экспрессиясы терапия мен болжамның нәтижесіне әсер ететін болжамдық фактор болды.*

Қорытынды: *PDL-1 экспрессиясының анық жоғарылауы аурудың болжамында маңызды және стандартты терапияға төмен жауап береді. CPS және TPS зерттеулерінің екі түрін біріктіру PDL-1 өрнектерін тиімдірек анықтайды, бұл ісік процесінің биологиясын ескере отырып, оңтайлы. Иммундық терапия перспективалы терапиялық нұсқа болып табылады.*

Түйінді сөздер: *эпидемиология, Т-жасушалық лимфомалар, иммундық терапия, PDL-1 экспрессиясы.*

АННОТАЦИЯ

АНАЛИЗ ЭКСПРЕССИИ PDL-1 ПРИ Т-КЛЕТОЧНЫХ ЛИМФОМАХ: КОРРЕЛЯЦИЯ С КЛИНИКО-ПАТОЛОГИЧЕСКИМИ ПРОГНОСТИЧЕСКИМИ ФАКТОРАМИ

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Актуальность: *Т-клеточные лимфомы являются редким, агрессивным видом неходжкинских лимфом. Терапия Т-клеточных лимфом остается вызовом для онкологов. В последние годы в лечении онкологических заболеваний большое развитие получила*

иммунная терапия. Экспрессия PD-L1 коррелирует с неблагоприятным прогнозом при многих онкологических заболеваниях, в связи с этим, исследование прогностического значения уровня PD-L1 при неходжкинских лимфомах является актуальным.

***Цель исследования** – определить уровень экспрессии PDL-1 при Т-клеточных лимфомах, на основании анализа TPS и CPS, провести анализ корреляции уровня экспрессии с клинико-патологическими признаками и исходами лечения пациентов.*

***Методы:** Было проведено ретроспективное исследование патоморфологического материала первичных пациентов с Т-клеточными лимфомами, в период с 2015 по 2020 год. Экспрессия PD-L1 определялась с помощью модифицированного комбинированного положительного балла (CPS) и индекса доли опухоли (TPS). Был проведен сбор клинических, лабораторно-инструментальных данных, результата терапии пациентов, включенных в исследование.*

***Результаты:** В исследование было включено 40 пациентов, средний возраст пациентов составил 48 лет (от 18 до 76 лет). 55% пациентов мужчины, женщин составило 45%. В 60% случаев пациенты были младше 60 лет. Все пациенты получали терапию по схеме CHOP (циклофосфамид 750 мг/м^2 1 день, доксорубицин 50 мг/м^2 1день, винкристин 1.3 мг/м^2 1день, и преднизолон 60 мг/м^2 1-5 дни). У 12 пациентов была достигнута полная ремиссия, у 19 пациентов – прогрессирование заболевания, 6 пациентов умерли от прогрессирования заболевания. Гиперэкспрессия PDL-1 была обнаружена у 37 пациентов. Определена статистическая корреляция экспрессии PDL-1 с поздней стадией заболевания ($p = 0,001$), высоким индексом IPI ($p = 0,001$), высокой частотой рецидивов ($p = 0,001$), и высоким уровнем сывороточной ЛДГ ($p = 0,001$). Экспрессия PD-L1 являлась прогностическим фактором влияющим на исход терапии и прогноз.*

***Заключение:** Определенно повышенная экспрессия PDL-1 значима в прогнозе заболевания и низким ответом на стандартную терапию. Комбинация двух видов исследования CPS и TPS эффективнее выявляет экспрессию PDL-1, что является более оптимальным с учетом биологии опухолевого процесса. Иммунная терапия является многообещающей терапевтической опцией.*

***Ключевые слова:** эпидемиология, Т-клеточные лимфомы, иммунная терапия, экспрессия PDL-1.*

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THE INFLUENCE OF SOCIO-ECONOMIC AND PSYCHOLOGICAL FACTORS ON THE QUALITY OF LIFE OF WOMEN WITH OVARIAN CANCER (ON THE EXAMPLE OF THE ABAY REGION, KAZAKHSTAN)

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ABSTRACT

Relevance: *This study analyzes the health status of women diagnosed with ovarian cancer, with a particular focus on identifying factors that influence their quality of life and evaluating their access to healthcare services and the level of disease-related awareness. Ovarian cancer remains one of the most prevalent oncological conditions affecting women, and its frequent late-stage diagnosis significantly contributes to poor prognostic outcomes. It is important to understand how different aspects of a patient's life affect their emotional and physical well-being.*

The study aimed to *investigate the impact of socio-economic and psychological factors on the quality of life of women diagnosed with ovarian cancer in the Abay Region, and to evaluate the existing relationships between factors within the framework of a multicenter study.*

Methods: *The study included 35 women with a verified ovarian cancer. Data was collected using a questionnaire comprising items related to travel time to healthcare facilities, educational attainment, marital status, financial circumstances, caregiving responsibilities, and the range of symptoms experienced by participants. Both quantitative and qualitative analytical methods were applied to interpret the collected data.*

Results: *A total of 68.6% of participants reported a travel time of 30 to 60 minutes to reach a healthcare facility, a factor that may negatively influence their overall well-being. Regarding educational attainment, 54.3% of the women had completed secondary vocational education. Similarly, 54.3% of respondents were married, suggesting the presence of a potential source of social support. In terms of economic status, 48.6% rated their income as average, which may have implications for their ability to access timely and comprehensive treatment. Additionally, 68.6% of participants reported having no caregiving responsibilities, potentially reducing their emotional burden. The most frequently reported symptoms were general weakness (48.6%) and abdominal enlargement (57.1%). Notably, the majority of respondents (42.9%) sought care from gynecologic oncologists.*

Conclusion: *The study found that socio-economic factors such as education level and financial status have a significant impact on the quality of life of women with ovarian cancer. A considerable proportion of participants reported reasonable travel times to healthcare facilities and access to medical specialists, underscoring the critical role of timely diagnosis and appropriate treatment in managing the disease. However, there is a need to increase awareness of the disease and access to psychological support.*

Keywords: *ovarian cancer, quality of life, anxiety and depression, oncopsychology, emotional well-being, family support.*

Introduction: Ovarian cancer (OC) is one of the most dangerous gynecological malignancies. According to Globocan, in 2024, OC was the eighth most common cancer among women, with 324,603 new cases reported worldwide. The highest incidence was recorded in Europe and the CIS countries, including Latvia and Russia. Forecasts indicate a significant increase: up to 503,448 new cases are expected annually by 2050, an increase of more than 55% [1]. Five-year survival rates for OC in developed countries are 36-46%, while in low- and middle-income countries (LMICs) they are significantly lower [2].

In China, OC is the second most common gynecological cancer in women and has one of the highest mortality rates (21.6%) [3]. In the United States, 21,179 new cases of OC and 13,230 deaths are expected in 2022. According to data for 2024, 19,680 new cases and 12,740 deaths are expected, with a five-year survival rate of about 50.8% [4].

In Kazakhstan, ovarian cancer ranks 8th among all oncological diseases in women and is the third most common gynecological cancer. In 2023, 1,251 new cases were registered, and the mortality rate was 5.3 per 100,000 women [5]. The highest number of cases was detected in Almaty

(228) and the Karaganda region (98), while the lowest rates were observed in the Ulytau region (8 cases). In most regions of Kazakhstan, an increase in the incidence rate is recorded, which may be due to improved diagnostics and increased public awareness [6].

Ovarian cancer is asymptomatic in its early stages, making early diagnosis difficult. Most diagnoses are made at stages III-IV of the disease, when the five-year survival rate is less than 20% [7].

In addition to clinical and statistical aspects, it is essential to consider the disease's impact on patients' quality of life. Treatment of ovarian cancer – primarily surgery and chemotherapy – is associated with physical and psychological stress: pain, fatigue, fear of relapse, depression, sleep disturbance, and social adaptation [8]. Long-term side effects, lifestyle changes, and fear of disease progression significantly worsen the general condition of patients [9].

Results of international studies show that socio-economic status, level of education, marital status, mental health, caregiving responsibilities, financial difficulties, and level of awareness all have a significant impact on the quality of life of women with ovarian cancer [10]. It has also been shown that lack of support, especially emotional and social, worsens the subjective perception of the disease and reduces treatment adherence [11].

In the context of Kazakhstan, research on the quality of life of women with ovarian cancer remains extremely limited, especially at the regional level. The Abay region is one of the country's new regions, characterized by a predominantly rural population and limited access to specialized oncological care. This is why studying this population within the framework of a multicenter study is justified and relevant [12].

Studying the relationship between socio-economic and psychological factors and quality of life will help identify vulnerable patient groups and develop more targeted support measures, both at the clinical practice level and at the regional healthcare program level [13].

The study aimed to investigate the impact of socio-economic and psychological factors on the quality of life of women diagnosed with ovarian cancer in the Abay region, and to evaluate the existing relationships between factors within the framework of a multicenter study.

Materials and methods: This study is part of the international *Every Woman Study™ project* organized by the World Ovarian Cancer Coalition (WOCC) and the International Gynecologic Oncology Society (IGCS), and aimed at assessing the epidemiological and clinical characteristics of ovarian cancer in LMICs [14]. The project includes more than 2000 women from 22 countries, with up to 10 centers in each country. For several countries, this was the first experience of participating in national or international studies. During the data collection process, the researchers encountered several organizational and logistical challenges, including the need to account for language barriers, literacy levels, and access to the Internet (surveys were conducted in both paper and electronic formats), as well as ensuring fair access to publications and funding.

The objectives of the Every Woman Study™ that are relevant to our research are:

– To estimate the prevalence and incidence of ovarian cancer in LMIC countries, taking into account age and ethnic characteristics;

– Determination of risk factors and prognosis of the disease;

– Analysis of the availability and quality of medical care (diagnostics, surgery, chemotherapy, palliative care);

– Identification of social, economic, cultural, and geographic barriers to accessing health care;

– Evaluation of the need and effectiveness of palliative and psychosocial support.

Methodology of the local study: As part of the Kazakhstani part of the Every Woman Study, 35 women with a confirmed diagnosis of ovarian cancer living in the Abay region took part in the study. A structured questionnaire adapted from the main toolkit of the Every Woman Study [14] was used to collect data. The questionnaire included sections on:

– socio-economic characteristics;

– access to health care;

– psychological aspects;

– symptoms and types of treatment;

– quality of life.

The analysis was conducted using quantitative methods, including correlation analysis and multiple regression, to identify relationships between socio-economic and psychological variables and quality of life indicators of patients.

Study cohort: A total of 35 women were surveyed, all of whom live in Semey, Republic of Kazakhstan, and are registered with the D-registration. They are observed and undergo treatment at the Center for Nuclear Medicine and Oncology of the Abay Region Health Administration (CNMO, Kazakhstan). All women included in the study were also diagnosed at the CNMO.

Inclusion criteria:

– women aged 18 to 99 years;

– availability of informed consent to participate in the study;

– The patient had been diagnosed with ovarian cancer within the previous five years (at the time of inclusion in the study).

Exclusion criteria:

– The patient was at the diagnostic stage, and the diagnosis had not been established;

– The patient was unable (physically or emotionally) to answer the questionnaire questions;

– The patient had been diagnosed with mental health problems (dementia, delirium, psychosis) and/or has learning difficulties.

Results:

Demographic characteristics and anamnesis. When selecting patients for the survey, in 6 cases (17.1%), women were invited who had been observed in our center for the past 5 years. Those who had recently visited an oncogynecologist or had undergone special treatment (in particular, chemotherapy courses) made up the majority of the surveyed women, 23 (65.8%). Another 6 (17.1%) women who were surveyed had already received special treatment at the beginning of the study.

Table 1 presents the age at diagnosis of ovarian cancer. The lowest ages were 25, 33, 35, and 44 years, and the highest were 67, 68, and 69 years.

Figure 1 shows the distribution of histological types of ovarian cancer among the surveyed women.

The data in Figure 1 show that epithelial forms of ovarian cancer, in particular without specifying the subtype, are the most common among the women surveyed. This is important information for understanding the epidemiology and clinical features of ovarian cancer in this group of patients.

Table 1 – Age at diagnosis, years (n = 35)

Unique values	Minimum age	Maximum age	Middle age	Standard deviation	Percentile of patient age at diagnosis (years)						
					0.05	0.10	0.25	0,50 Median	0.75	0.9	0.95
0.0%	23	69	56.63	10.59	34.40	44	53	58	64.50	67.60	69

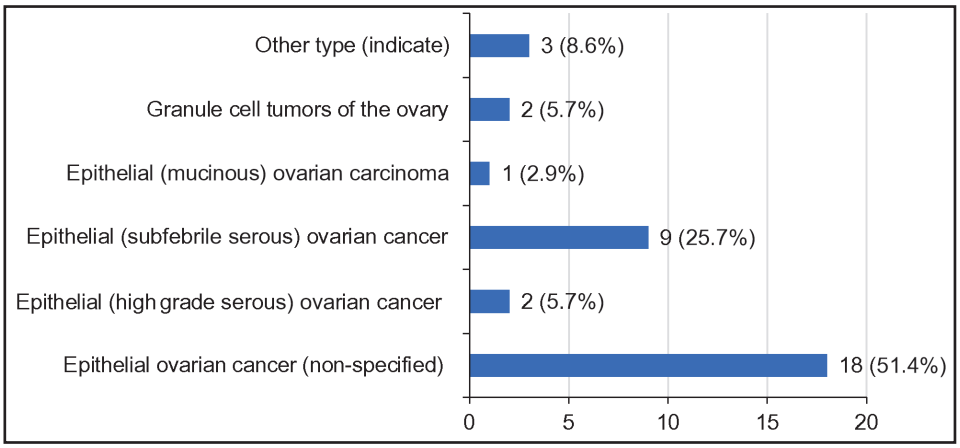

Figure 1 – Histological types of ovarian cancer among the surveyed patients (n=35)

Staging of ovarian cancer in women included in the study was performed mainly after surgical intervention – 32 (91.4%). Only three (8.6%) of the surveyed women had their stage diagnosed based on examination and biopsy data.

At the first stage of the survey, it was also analyzed at what stage, according to the FIGO (International Federation of Gynecology and Obstetrics) classification, the disease was diagnosed (Figure 2).

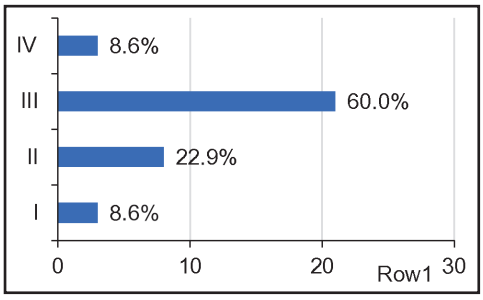

Figure 2 – Distribution of disease stages according to the FIGO classification among the surveyed women (n=35)

Among the women surveyed, only 1 (2.9%) did not undergo surgical intervention, while 8 (22.9%) patients had radical surgery, and the rest – 26 (74.3%) – did not undergo full surgical intervention.

Results of the survey. The average time spent by patients on the way to the hospital was analyzed (Figure 3).

Time spent to travel to the Center for Nuclear Medicine and Oncology of the Abay Region Health Department – less than 15 minutes for 4 (11.8%) and 15 to 30 minutes for 8 (22.9%) women – significantly affected their well-being. Most women spent 30-60 minutes on the road, with 10 (28.6%) doing so, while 4 of them (11.4%) – mainly city res-

idents – had to travel for 1-2 hours. Out-of-town women spent 2 to 5 hours on the road – 1 (5.7%), over 5 hours – 4 (11.4%), and more than 24 hours – 3 (8.6%).

Among the surveyed patients, one woman (2.9%) had a basic education; most had secondary education – 10 (28.6%), secondary specialized or technical education – 19 (54.3%). Five (14.3%) of the surveyed women had higher education.

The women surveyed indicated their marital status at the time of diagnosis (Figure 4).

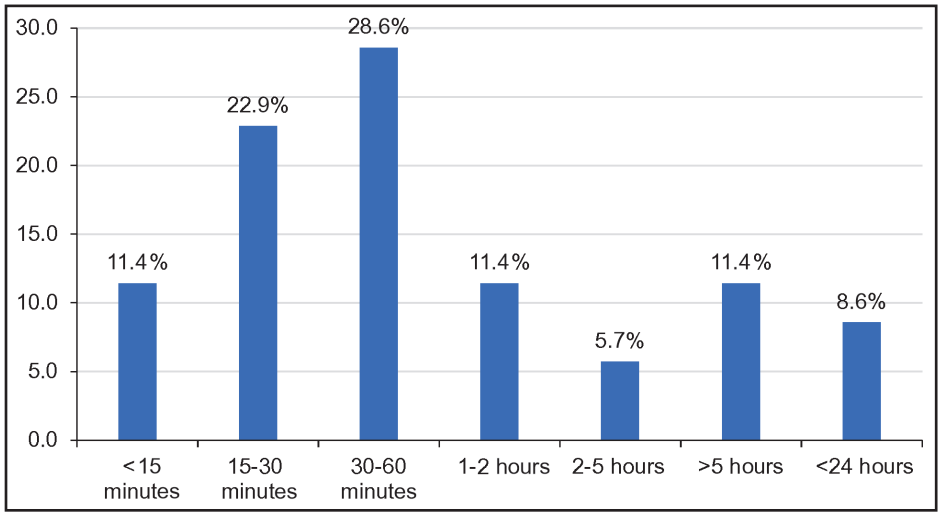

Figure 3 – Average travel time among women surveyed (n = 35)

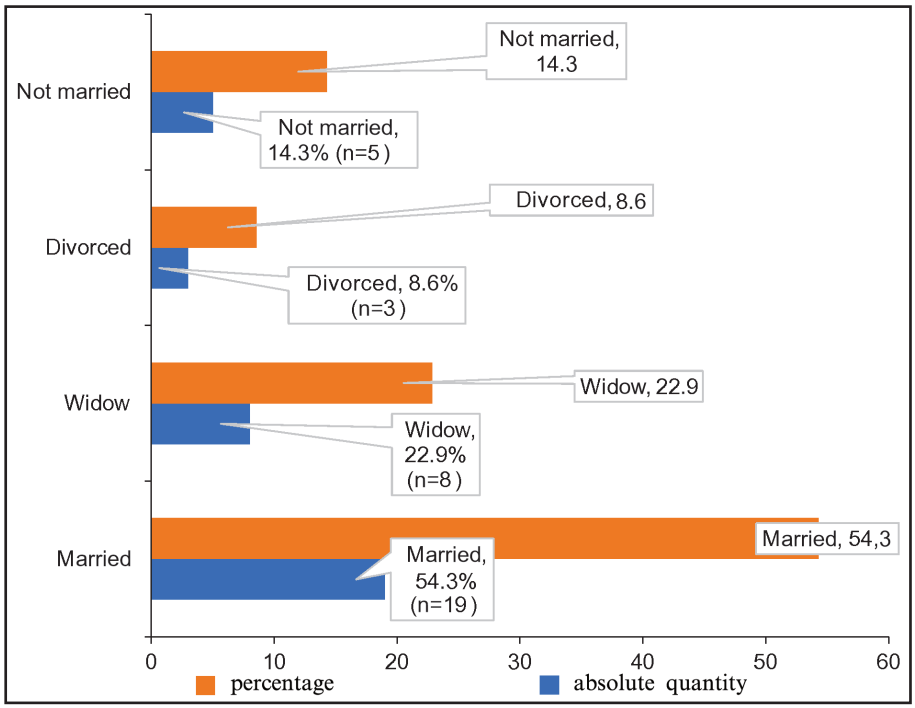

Figure 4 – Marital status of the women surveyed (n = 35)

The financial situation at the time of ovarian cancer diagnosis was also specified. Eight (25.7%) women assessed their financial situation as "below average", 16 (48.6%) patients reported the average income level, and 4 (12.5%) women assessed their financial situation as "above average". At the same time, 4 (12.5%) women surveyed preferred not to answer this question.

The quality of life, as well as emotional and physical well-being, is also affected by caring for loved ones and managing household responsibilities. The patients answered the question about the presence or absence of responsibilities for caring for other family members (Figure 5).

At the time of diagnosis, most women had the status of "employed" (n = 15) or were retired (n = 14), which reflects the mixed social profile of the patients (Figure 6).

At the time of diagnosis, women had the following gynecological status (there could be several answers to the question, as this affected the prognosis and identification

of the presence of risk factors for the development of ovarian cancer among respondents):

– menopause occurred - 11 (31.4%),
– absence of childbirth – 5 (14.3%),
– one birth – 5 (14.3%),
– birth twice – 6 (17.1%),
– three or more births – 13 (37.1%),
– breastfeeding – 13 (37.1%),
– taking oral contraceptives before 5 years – 1 (2.9%),
– taking oral contraceptives from 5 to 10 years – 1 (2.9%),
– infertility treatment – 1 (2.9%).

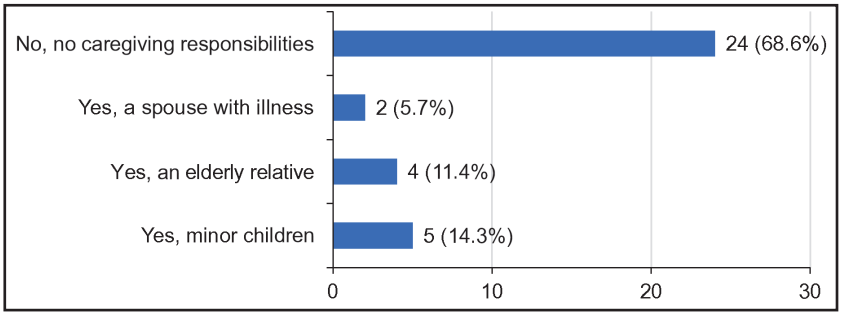

Figure 5 – Presence or absence of care responsibilities in the family among the women surveyed (n=35)

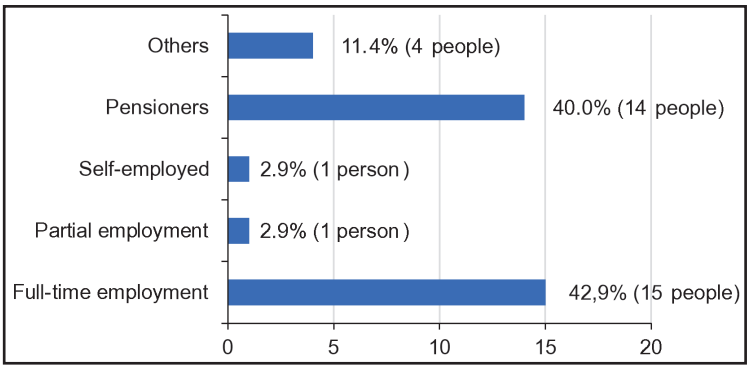

Figure 6 – Employment status of the women surveyed (n=35)

Taking into account the high risk of heredity in the development of ovarian cancer, the oncologic history of the women surveyed was assessed. At the same time, 16 (45.7%) women indicated the presence of oncologic disease in relatives, 15 (42.9%) noted the absence of an aggravated oncologic history, and some women – 4 (11.4%) – experienced difficulty in answering this question.

Among the women surveyed, only 4 (11.4%) participants knew enough information about the diagnosis of ovarian cancer, 17 (48.6%) had heard about it, but did not know full information, and 14 (40.0%) did not know anything about the disease.

The symptoms that bothered the women before the diagnosis were also assessed. The survey results are presented in Figure 7.

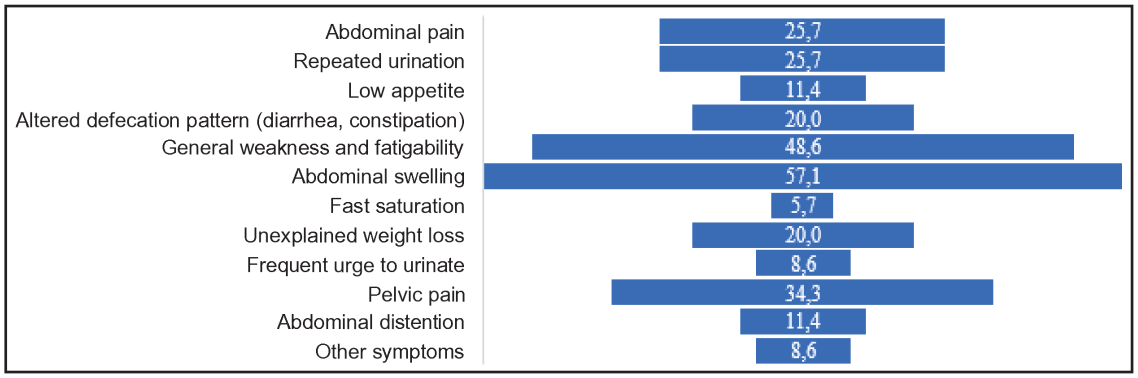

Figure 7 – Symptoms present before the diagnosis of ovarian cancer was established in the surveyed women (n=35)

Among the most common symptoms, women noted general weakness and fatigue - 17 (48.6%), an increase in abdominal size - 20 (57.1%), pain in the pelvis bothered 12 (34.3%) patients, while abdominal pain and frequent uri-

nation were noted in 9 (25.7%) cases, respectively. The remaining symptoms bothered patients less often.

Upon discovering alarming symptoms, most women turned to specialized specialists: to a gynecologist in 13 (37.1%) cases and directly to an oncogynecologist in 15 (42.9%) cases. Only in 7 (20.0%) cases did patients turn to other specialists (probably emergency doctors, general practitioners, healers, gastroenterologists in connection with non-specific complaints, an endocrinologist, etc.).

Significant delay in diagnosis is one of the main problems in ovarian cancer. In most cases, the diagnosis was established only 2-6 months after the first visit to the doctor. The main reasons included long waits for follow-up examinations and surgery, infrequent visits to the doctor, and territorial remoteness from medical institutions, which is especially relevant for rural areas.

According to the survey, the time from diagnosis to treatment was less than three months. At the same time, patient satisfaction with the doctors' actions during the examination, diagnosis, and treatment period was more than 70%.

When undergoing special treatment, all patients experience a wide range of side effects. When answering the questionnaire, patients most often indicated the following effects (Figure 8):

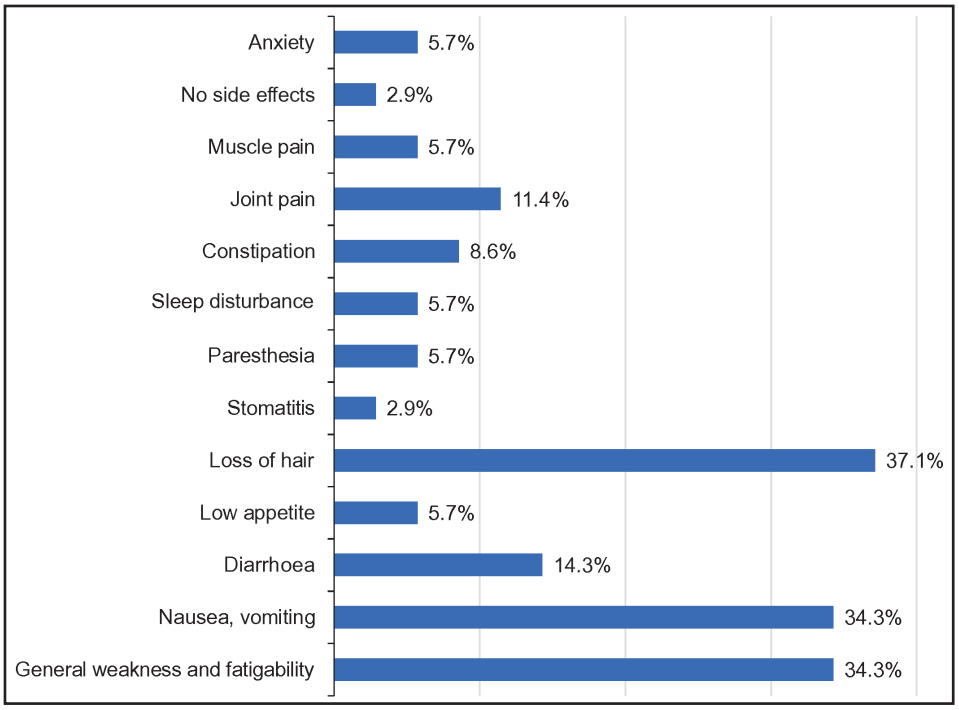

Figure 8 – Side effects during special treatment for ovarian cancer (n=35)

The questionnaire also inquired about the participation of medical workers in addressing side effects and the effectiveness of their actions. The results were distributed as follows: "yes, very" - 13 (37.1%); "yes, to some extent" - 19 (54.3%). The remaining respondents answered negatively or refrained from answering.

The questionnaire also included a question about the use of alternative means (alternative medicine, dietary supplements, etc.). The answers were "yes, all the time" – 3 (8.6%), "yes, at some point" – 6 (17.1%), "no, but I thought about it" – 5 (14.3%), and "no" – 18 (51.4%).

When asked about periods and moments of need for emotional support, respondents answered as follows (Figure 9):

The questionnaire also included a multiple-choice question: "Are there any particular problems you encountered?" Figure 1 shows the most common responses.

Patients, namely, did not select some answer options: fear of death, difficulties returning to "normal life" after treatment, partner or spouse leaving, feeling isolated, feeling unable to connect with other people, loss of fertility, regaining sexual intimacy with a partner, or overcoming menopause.

There was also a question about whether the women met and talked with other women or groups of women with ovarian cancer after diagnosis. The answers were as follows: "yes, we talked in person" – 10 (28.6%), "yes, we talked as part of an oncology group" – 6 (17.1%), "yes, we talked online (social networks, chat, forum)" – 1 (2.9%), "yes, we talked on the phone" – 2 (5.7%), and "no" – 16 (45.7%).

Other questions concerned the practical support that patients needed in connection with the established disease of ovarian cancer (it was possible to choose several answers) (Figure 12).

It was also specified who exactly provided the necessary practical support. The answers were as follows: family members – 23 (65.7%), friends – 5 (14.3%), someone else – 1 (2.9%), no one and/or herself – 0 (0.0%).

The questions also concerned financial problems. Figure 13 shows how the respondents' answers to the question "Did the diagnosis of ovarian cancer affect the financial situation?" were distributed.

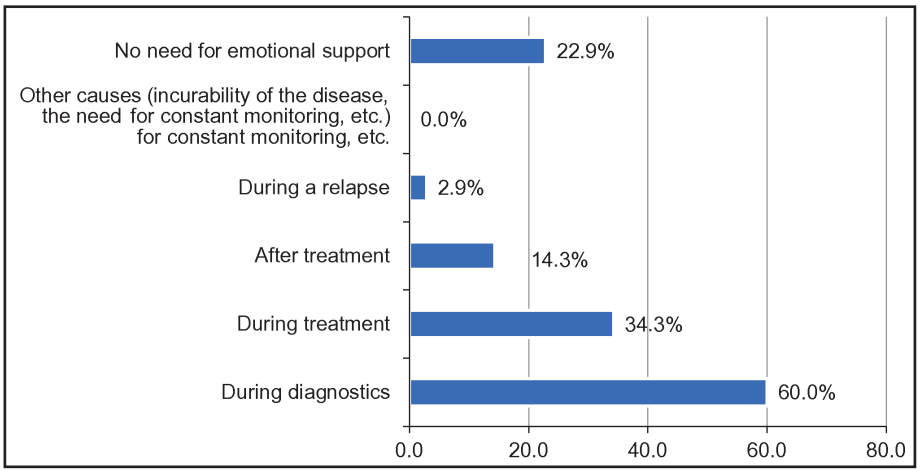

Figure 9 – Periods and moments, when the respondents need emotional support (n=35)

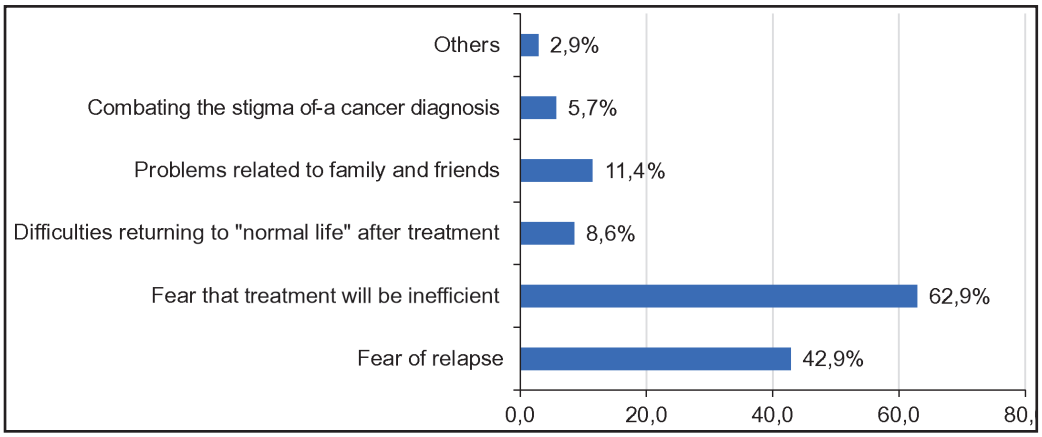

Figure 10 – Specific problems encountered by surveyed women with ovarian cancer (n=35)

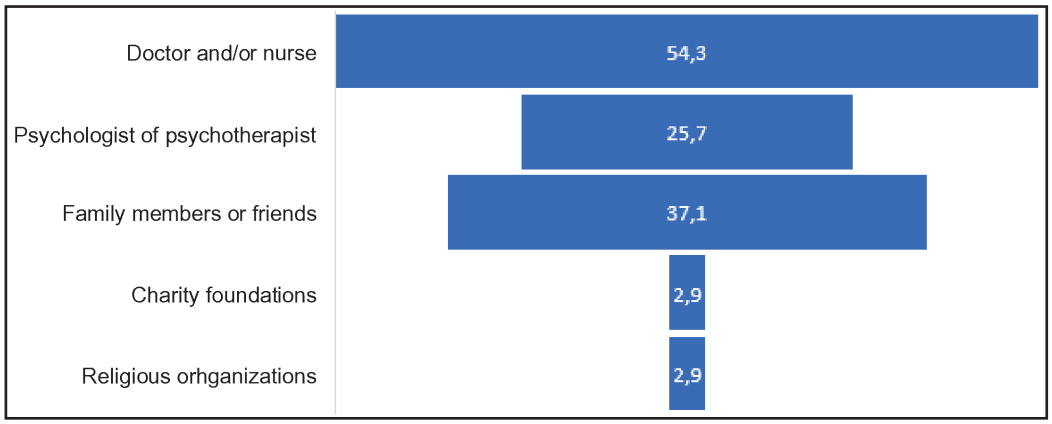

Figure 11 – The parties women with ovarian cancer apply to when they need emotional support, in % (n=35)

The questionnaire included a question regarding information and its necessary sources when identifying ovarian cancer in patients. Most often, respondents indicated doctors as a source of information – 26 (74.3%) or nurses – 3 (8.6%). One patient (2.9%) indicated that she contacted charitable organizations. Some respondents answered that they did not need help – 6 (17.1%).

Considering the relevance of digitalization of healthcare, the questionnaire included a question regarding the information space: did patients search for information about their diagnosis on the Internet, and several answer options could be given. The patients answered: “yes, and I found useful information in Kazakh” – 24 (68.6%), “yes, but I did not find any useful information in Kazakh” – 7 (20.0%), “I do not have easy access to the Internet” – 1 (2.9%) and “no, I did not use the Internet to search for information” – 1 (2.9%).

There was also a question about how willing patients were to participate in clinical research (multiple answer options) (Figure 14).

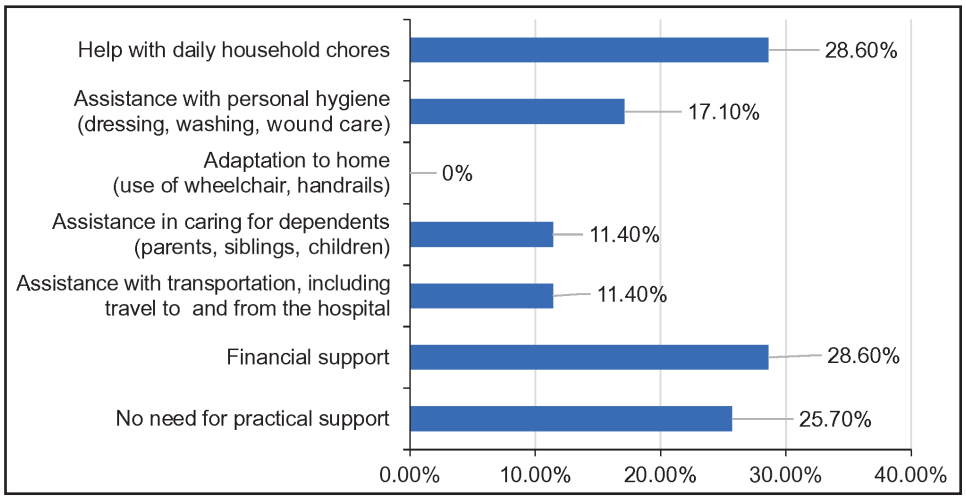

Figure 12 – Practical support required for women with ovarian cancer (n=35)

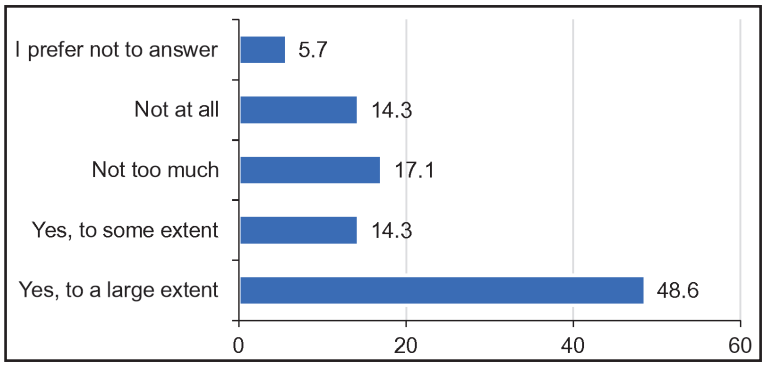

Figure 13 – Impact of ovarian cancer diagnosis on women's financial situation (n=35)

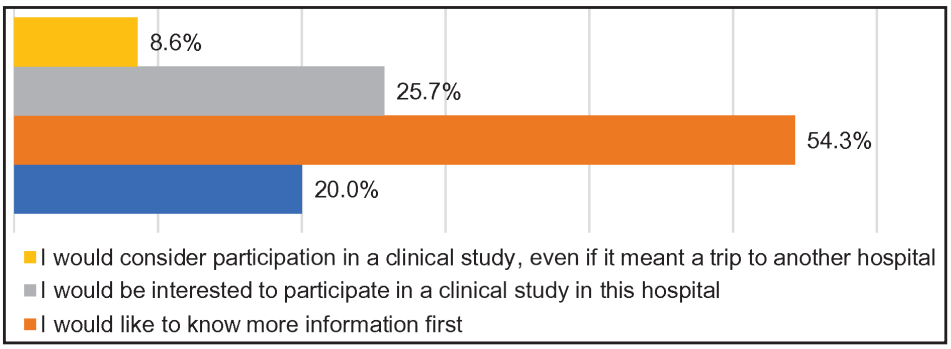

Figure 14 – Readiness of women with ovarian cancer to participate in clinical research (n=35)

In the final part of the questionnaire, answer options were offered for improving the diagnosis and treatment of women with ovarian cancer: what, in the opinion of women who have encountered this problem, requires development and investment (from 1 to 3 answer options).

Participants were also asked to select the areas that they believed were most important for improving ovarian cancer care (multiple answer options) (Figure 15).

Discussion: The obtained results confirm the main conclusions of the international study: social and psychological factors play a key role in the prognosis and quality of life of patients with ovarian cancer. Detailed information on global methodologies and conclusions is presented in the article, "The World Ovarian Cancer Coalition Every Woman Study: Identifying challenges and opportunities to improve survival and quality of life," and on the WOCC website [15].

A detailed analysis of the study and comparison with the results of other authors allows for a deeper understanding of the factors affecting the quality of life of patients with ovarian cancer. The study emphasizes the importance of timely access to treatment and diagnosis. One of the key problems for women from remote areas is the long time they spend on the road to a medical facility, which has a negative impact on their physical and emotional state. These results are confirmed by studies, such as one showing that long travel times and distance from specialized medical centers reduce patient compliance

and negatively affect survival [16]. This study also emphasizes the need to create local oncology centers, which will facilitate access to treatment, reduce waiting times, and improve the effectiveness of diagnosis and therapy, especially for women with limited financial means for transportation [17].

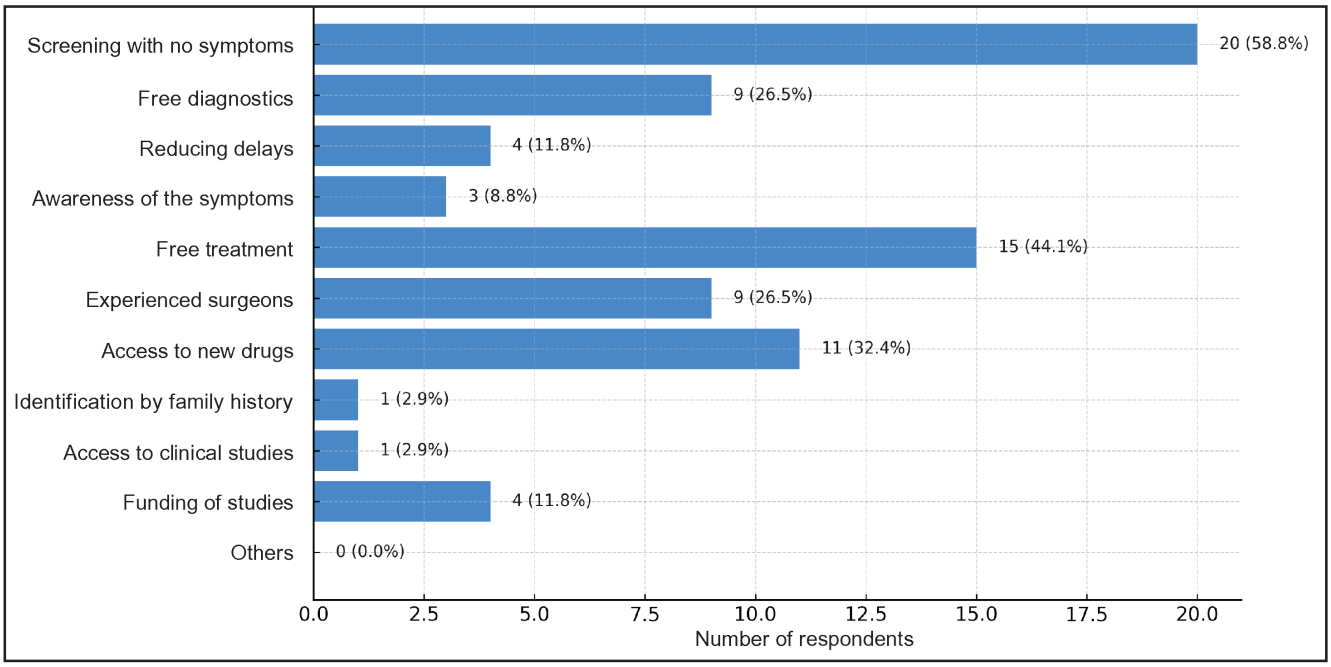

Figure 15 – Respondents' suggestions for improving care for ovarian cancer (n=35)

Social and family responsibilities have a significant impact on the psycho-emotional state of women with cancer. For example, a study (2021) showed that caring for children or elderly relatives significantly increases stress levels among patients and negatively affects their quality of life. Similar to this study, the authors' work emphasizes the importance of psycho-emotional support for women who face additional burdens associated with family responsibilities and financial difficulties. The study also highlighted the need for comprehensive support, including the assistance of specialists such as psychologists and social workers, as well as the involvement of relatives to provide care [18].

The distance from a healthcare facility has a significant impact on the physical and emotional well-being of patients. Our study found that 40% of women spend more than 30 minutes on the road, and 25.7% of out-of-towners spend more than two hours. These data confirm the findings of a systematic review [19], according to which a long distance to a healthcare facility is associated with increased stress, decreased adherence to treatment, and later stages of diagnosis, especially in patients from rural areas.

Socio-economic difficulties also play a key role. In our study, 25.7% of patients rated their financial situation as below average, which limited their ability to seek medical care on time. Comparable data are presented in a review [19], which emphasizes that economic vulnerability limits access to specialized treatment, especially in conditions of lack of insurance coverage or transportation accessibility.

Family responsibilities increase the burden on patients; in our study, 31.4% of women reported having to care for children, elderly relatives, or a spouse with a health issue. Such additional responsibilities may interfere with regular therapy and impact recovery. Other studies [19] also show that the role of primary caregiver negatively impacts treatment adherence.

Low awareness of the disease remains a problem. In the study, almost half (40%) of patients were previously unaware of their ovarian cancer diagnosis, despite the majority having typical symptoms. These findings are consistent with a study from Palestine [20], which also found low awareness, particularly among women under 50 and those living in rural areas, leading to delays in diagnosis.

Finally, the problem of insufficient support from medical personnel is also confirmed, as only 37.1% of our respondents reported receiving a high level of professional attention. This emphasizes the need to improve the system of psychological and informational support during the treatment process, which is also reflected in the systematic review [21], which emphasizes the importance of a patient navigation program and empathy from doctors to improve overall well-being and quality of life during therapy.

The data of the present study are also supported by the results presented in a systematic review [22], which examined the impact of distance to cancer centers on the stage of diagnosis, stress, and adherence to treatment. The results of our study coincide with the key findings of this review: patients from remote areas are more likely to experience delays, emotional instability, and low engagement in therapy. In addition, a study [23] conducted in Palestine noted insufficient awareness of women about the symp-

toms of ovarian cancer, which is also similar to our data. There was a clear link between low awareness and late seeking of medical care. Comparison of these results with our data allows us to state that the described barriers are cross-country in nature and require adaptation of communication and infrastructure solutions.

The results of this study are consistent with the data of the international Every Woman Study project, which also noted significant delays in diagnosis, low awareness of disease symptoms among women, and limited access to specialized care [10]. For example, in Canada, as part of the Every Woman Study™: Canadian Edition study, 557 women diagnosed with ovarian cancer from 11 Canadian provinces were surveyed. The study showed that only 46% of patients sought medical care within the first month after the onset of symptoms, despite a high level of awareness and the availability of genetic testing in 75% of women. Access issues were especially acute for women living in remote regions, who reported significant logistical, financial, and emotional difficulties [24]. These findings are consistent with the results of our study, which also identified problems of geographic remoteness, delays in diagnosis, and insufficient systemic support. The similarity in the results highlights the universality of the barriers identified and the need for integrated approaches to addressing access and awareness issues at both national and global levels.

Conclusion: The results of this study confirm the significant impact of various factors on the quality of life of patients with ovarian cancer. Thus, the data analysis revealed that long travel times to the medical center are a significant obstacle for women, especially those residing in remote areas. This creates a need to create local oncology centers, which will improve access to timely treatment and reduce waiting time.

Patient awareness of ovarian cancer symptoms also leaves much to be desired: a significant proportion of women do not have sufficient information about the disease. This delays seeking medical care and highlights the importance of educational programs aimed at increasing cancer awareness, especially among women with low levels of education and income.

Support from healthcare professionals and loved ones is also crucial for patients' psychological well-being. Although many women experience side effects from treatment, the level of support from healthcare professionals is often insufficient. This urges the need for improved communication between doctors and patients, which can contribute to increased patient satisfaction and overall well-being.

Overall, the study highlights the importance of a comprehensive approach to treating ovarian cancer that includes not only medical aspects but also social, educational, and psychological factors. Investing in these areas can significantly improve the quality of life of women affected by the disease.

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АҢДАТПА

АНАЛЫҚ БЕЗ ОБЫРЫ БАР ӘЙЕЛДЕРДІҢ ӨМІР СҮРУ САПАСЫНА ӘЛЕУМЕТТІК-ЭКОНОМИКАЛЫҚ ЖӘНЕ ПСИХОЛОГИЯЛЫҚ ФАКТОРЛАРДЫҢ ӘСЕРІ (ҚАЗАҚСТАН, АБАЙ ОБЛЫСЫ МЫСАЛЫНДА)

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Өзектілігі: *Зерттеу аналық без ісігі диагнозы қойылған әйелдердің денсаулық жағдайын талдауға, олардың өмір сүру сапасына әсер ететін факторларды анықтауға, сондай-ақ медициналық қызметтерге қолжетімділік пен ақпараттандыру деңгейін бағалауға арналған. Аналық без ісігі әйелдер арасында кең таралған онкологиялық аурулардың бірі болып табылады, оны кеш анықтау көбінесе жағымсыз нәтижелерге әкеледі. Науқас өмірінің әртүрлі аспектілері оның эмоционалдық және физикалық әл-ауқатына қалай әсер ететінін түсіну маңызды.*

Зерттеудің мақсаты *– Абай ауданындағы (Қазақстан Республикасы) аналық без обырынан зардап шегетін әйелдердің өмір сүру сапасына әлеуметтік-экономикалық және психологиялық факторлардың әсерін анықтау және көп орталықты зерттеу шеңберінде факторлар арасындағы қалыптасқан байланыстарды бағалау.*

Әдістері: *Зерттеуге аналық без ісігі диагнозы қойылған 35 әйел қатысты. Деректерге дейінгі жол уақыты, білім деңгейі, отбасылық жағдайы, қаржылық жағдайы, жақындарына күтім көрсету міндеттерінің болуы және науқастарды мазалайтын симптомдар туралы сұрақтарды қамтитын сауалнама арқылы жиналды. Алынған деректерді интерпретациялау үшін сандық және сапалық талдау әдістері қолданылды.*

Нәтижелері: *Әйелдердің 68,6%-і медициналық мекемеге 30-60 минут ішінде жететінін, бұл олардың жалпы жағдайына әсер ететінін көрсетті. Әйелдердің 54,3%-і орта кәсіптік білімге ие болды. Респонденттердің 54,3%-і үйленген, бұл әлеуметтік қолдау бар екенін білдіреді. Әйелдердің 48,6%-і табыстарын орташа деп бағалаған, бұл емдеуге қолжетімділікке әсер етуі мүмкін. Респонденттердің 68,6%-інде күтім көрсету міндеттері болмаған, бұл эмоционалдық жүктемені азайтуы мүмкін. Ең көп алаңдатқан мәселелердің қатарында жалпы әлсіздік (48,6%) және іштің үлкеюі (57,1%) болды. Көптеген әйелдер онкогинекологтарға жүгінген (42,9%).*

Қорытынды: *Зерттеу көрсеткендей, білім деңгейі және қаржылық жағдай сияқты әлеуметтік-экономикалық факторлар аналық без ісігімен ауыратын әйелдердің өмір сүру сапасына айтарлықтай әсер етеді. Әйелдердің айтарлықтай пайызы медициналық мекемеге уақытында жете алған және медициналық мамандарға қол жеткізген, бұл уақытылы диагноз қою мен емдеуді қамтамасыз етудің маңыздылығын көрсетеді. Алайда, ауру туралы ақпараттандыру деңгейін және психологиялық қолдауға қолжетімділікті арттыру қажет.*

Түйінді сөздер: *Аналық без қатерлі ісігі, өмір сапасы, мазасыздық және депрессия, онкопсихология, отбасылық қолдау, эмоционалды әл-ауқат.*

АННОТАЦИЯ

ВЛИЯНИЕ СОЦИАЛЬНО-ЭКОНОМИЧЕСКИХ И ПСИХОЛОГИЧЕСКИХ ФАКТОРОВ НА КАЧЕСТВО ЖИЗНИ ЖЕНЩИН С РАКОМ ЯИЧНИКОВ (НА ПРИМЕРЕ ОБЛАСТИ АБАЙ, КАЗАХСТАН)

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Актуальность: *Исследование посвящено анализу состояния здоровья женщин с диагнозом рака яичников, выявлению факторов, влияющих на их качество жизни, а также оценке доступа к медицинским услугам и уровню информированности. Рак яичников является одним из самых распространенных онкозаболеваний среди женщин, его позднее выявление часто приводит к неблагоприятным исходам. Важно понимать, как различные аспекты жизни пациенток влияют на их эмоциональное и физическое состояние.*

Цель исследования *– выявить влияние социально-экономических и психологических факторов на качество жизни женщин, страдающих от рака яичников, в области Абай (Республика Казахстан), а также оценить существующие взаимосвязи между факторами в рамках мультицентрового исследования.*

Методы: *В исследовании приняли участие 35 женщин с установленным диагнозом рака яичников. Данные были собраны методом анкетирования. Анкета включала вопросы о времени в пути до больницы, уровне образования, семейном положении, финансовом состоянии, наличию обязанностей по уходу за близкими, а также симптомах, беспокоящих пациенток. Использовались количественные и качественные методы анализа для интерпретации полученных данных.*

Результаты: *68,6% женщин добирались до лечебного учреждения в течение 30-60 минут, что влияло на их общее самочувствие. 54,3% женщин имели средне-специальное образование. 54,3% респондентов были замужем, что свидетельствует о социальной поддержке. 48,6% женщин оценили свои доходы как средние, что может влиять на доступ к лечению. 68,6% респондентов не имели обязанностей по уходу, что может снизить эмоциональную нагрузку. Наибольшее беспокойство вызывали общая слабость (48,6%) и увеличение размеров живота (57,1%). Большинство женщин обращались к онкогинекологам (42,9%).*

Заключение: *Исследование показало, что социально-экономические факторы, такие как уровень образования и финансовое положение, оказывают значительное влияние на качество жизни женщин с раком яичников. Высокий процент женщин, добирающихся до больницы в разумные сроки и имеющих доступ к медицинским специалистам, свидетельствует о важности обеспечения своевременной диагностики и лечения. Однако необходимо повышать уровень информированности о заболевании и доступ к психологической поддержке.*

Ключевые слова: *рак яичников (РЯ), качество жизни, тревога и депрессия, онкопсихология, эмоциональное благополучие, семейная поддержка.*

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IDENTIFICATION OF FACTORS AFFECTING THE QOL OF WOMEN AFTER BREAST CANCER TREATMENT

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ABSTRACT

Relevance: *Breast cancer (BC) is one of the most common oncological diseases among women, and its physical, psychoemotional, social, and sexual consequences negatively affect pa-tients' quality of life (QoL). A decrease in QoL in the post-treatment period may hinder full rehabilitation. Therefore, studying the sociodemographic and clinical factors affecting QoL in women with BC remains relevant.*

The study aimed to *identify the impact of sociodemographic and clinical factors on the quality of life of women after breast cancer treatment.*

Methods: *The study was conducted at the West Kazakhstan Marat Ospanov Medical University Medical Center. Participants completed the EORTC QLQ-BR23 standardized questionnaire. A total of 103 women took part in the study. In addition to the questionnaire, sociodemographic and clinical data were collected. Data analysis was carried out using IBM SPSS Statistics 25.0. Multivariate logistic regression was used for statistical analysis.*

Results: *Single women ($p = 0.022$) and those who detected the disease independently ($p = 0.030$) reported significantly lower QoL. Employed women ($p = 0.040$) and those who underwent breast-conserving extended sectoral resection (BCESR) ($p = 0.013$) rated their body image and confidence in the future higher ($p = 0.041$). Unemployed and moderately educated women had signifi-cantly lower scores in sexual function and future outlook ($p < 0.05$). Pensioners more frequently experienced arm symptoms ($p = 0.003$), while increased hair loss was noted after BCESR ($p = 0.030$).*

Conclusion: *The findings reveal that multiple factors influence the QoL of women with BC. Socioeconomic status, type of surgery, and psycho-emotional support are key determinants of QoL. These results may provide a scientific basis for enhancing rehabilitation programs.*

Keywords: *woman, breast cancer (BC), quality of life (QoL), EORTC QLQ-BR23, sociodemographic factors, clinical factors.*

Introduction: Breast cancer (BC) is the most common malignant disease in women worldwide [1]. It is a unique disease because it can significantly affect women's appearance, which in turn directly or indirectly affects their quality of life (QoL). In addition, the cancer itself, the fear of its recurrence, or death, also complicates the psycho-emotional state of women [2]. In recent decades, the number of studies devoted to the QoL of patients with BC has increased. Assessment of QoL is particularly important, given that this is a common chronic disease with a favorable prognosis when diagnosed early and adequately treated [3]. QoL encompasses a person's perceptions of their physical and mental health, as well as various factors that affect it. Many theories of QoL are based on the World Health Organization's definition of health, which generally considers health to be physical, psychological, and social well-being [4]. The prognosis for the etiology and course of cancer emphasizes the importance of studying the interaction of various biological, psychological, and social factors [5]. This may be a prognostic factor for cancer patients and also an important factor influencing survival after recurrence of squamous cell carcinoma [6].

Overall survival of women diagnosed with BC is closely related to their socioeconomic status as well as the stage of the disease. In the context of universal health coverage, the impact of sociodemographic characteristics on overall survival components becomes more pronounced after the active treatment period. Gender roles in the family and society are also important factors that affect women's overall survival. Family obligations, the burden of household chores, or difficulties in balancing work and personal life may negatively affect overall survival in women. In addition, in women with BC, late diagnosis, aggressive disease relapse, and/or complexity of treatment methods may negatively affect overall survival [1].

In oncology, the concept of OS is particularly important due to the specific nature of the pathology and the radical nature of the treatment methods (surgery, radiation, and chemotherapy) [7]. Removal of the mammary gland, an aesthetically important organ, causes significant harm to women's physical, psychological, and emotional well-being [8]. Sexual function, sexual satisfaction, and body image were rated higher by women who underwent organ-preserving surgery, while they were rated lower by respondents who underwent radical mastectomy (RME). Decreased libido was often observed in the group of women who underwent RME, which led to a decrease in their OS. In these studies, although 80% of patients were satis-

fied with their appearance, only 54% of them were able to accept their naked body [9].

A meta-analysis showed a significant correlation between age and overall survival in patients with BC (p = 0.03), with each additional year of age associated with a 0.19 increase in overall survival. This result is consistent with other studies showing that breast conservation improves body image, social and emotional well-being, and, in turn, increases overall survival [10]. Some studies have shown that older patients are more psychologically prepared for treatment, despite the presence of comorbidities [11].

High levels of anxiety are observed in women who are married or in relationships. This may be due to a feeling of insecurity about their partners' acceptance of the disease, as well as a fear that the disease may cause the partner to break off the relationship or leave for another woman [12].

This was a great challenge, and some mothers preferred to hide their condition from their children. During the mother's illness, some children had difficulty with their studies. Patients felt that they had lost their social identity and were labeled as "cancer patients," which was so depressing and debilitating that they did not want anyone except their family to know about it. Other women tended to hide their emotional experiences from relatives and children [13]. Several studies have shown that women with minor children have higher levels of anxiety and depression. This may be explained by the increased responsibility for their children and the psychological burden associated with it [14].

Most of the factors identified in many studies are related to monthly income, medical expenses, and level of education. Level of education also influences OD [12]. Women with university education have higher OD rates, which may be related to a higher cultural level and education, as well as a better-paid job. Compared with those whose income is lower than their expenses, women with incomes equal to or higher than their expenses showed significantly higher scores on the quality of sexual life (mean scores 33.35±26.05 and 52.50±29.74, respectively; p=0.003), as well as on the level of dyadic adaptation (88.90±30.55 and 107.43±26.61; p=0.004) [15]. This enables them to access information and utilize more tools, resources, and strategies to manage the disease. Likewise, increased economic resources allow them to meet the needs arising from this new health situation [1, 2]. A better understanding of the QoL and body image of women with BC can contribute to the development and improvement of therapeutic and curative measures, as well as modern service and care models [16]. In addition, the study of QoL allows for individualization of rehabilitation programs for women who have undergone radical breast surgery [17]. Reconstructive surgery is an advanced method of surgical rehabilitation. The main goal of this method is to ensure a high level of psychosexual well-being and satisfaction with the QoL of patients while maintaining oncological safety [18].

This study is one of the first to comprehensively analyze sociodemographic and clinical factors affecting the QoL of women with BC undergoing treatment in Kazakhstan, including the Aktobe region. In addition, the study demonstrated the validity of using international questionnaires, the EORTC QLQ-BR23 and QLQ-C30, in Kazakhstan. An analysis of factors influencing the QoL of women with IBD demonstrates the multifaceted nature of this problem and the close relationship between physical, social, psycho-emotional, and sexual aspects.

This work is a continuation of the author's previous work on this topic. While the previous publications conducted a literature review based on international and domestic scientific sources to collect data on the impact of BC on women's QoL [12], and the QoL was assessed at a general descriptive level [19], then the present study, based on empirical data conducted in a specific region (Aktobe region), significantly deepens this topic and includes a comprehensive analytical study aimed at identifying the relationships between QoL and specific sociodemographic and clinical factors. The study employed multivariate logistic regression analysis, and statistically significant relationships were identified between patient characteristics and QoL scales.

The study aimed to determine the influence of sociodemographic and clinical factors on the quality of life of women undergoing treatment for breast cancer.

Materials and methods:

Data collection. The EORTC QLQ-BR23 questionnaire was administered to patients of the Medical Centre of the West Kazakhstan Marat Ospanov Medical University (letter of permission No. 13/8-21-77). The widely recognised standardised *EORTC QLQ-BR23 questionnaire* was used to determine the influence of sociodemographic and clinical factors on patients' QoL. This instrument was developed in 1996 by the Quality of Life Task Force of the European Organisation for Research and Treatment of Cancer (EORTC). The questionnaire consisted of 23 questions and was divided into 4 functional (body image, sexual function, sexual satisfaction, outlook on the future) and 4 symptomatic scales (side effects of systemic therapy, arm and breast symptoms, hair loss). Each question was rated on a scale from 1 (none) to 4 (very strong). In addition, to obtain comprehensive information on patients' QoL in line with the EORTC measurement guidelines, two questions from the EORTC QLQ-C30 health status/QoL scale were used. In these two questions, patients rated their health and overall QoL on a scale of 1-7 (1 = very poor, 7 = excellent). The assessment was scored on a 0–100 scale by linearly transforming each scale's raw scores, as recommended in the EORTC assessment guidelines. For the functional scales, a higher score corresponded to a higher QoL. In contrast, the

opposite was true for the symptom scales: higher scores indicated greater negative symptoms. Unanswered questions were handled according to the guidelines: if a scale consisted of a single item and was left unanswered, it was scored as "not available" [20].

During data collection, in addition to the questionnaire questions, respondents' sociodemographic and clinical data were collected, including age, marital status, number of children, level of education, employment status, place of residence, diagnostic method, and type of surgical intervention.

Sample. When planning the study, the sample size was calculated using Cohen's f^2 calculator for regression analysis with an effect size of $f^2 = 0.35$, power of 0.8, and significance level (α) of 0.05. As a result, the required sample size was 82 people. Taking into account possible losses (non-responses, etc.), a 20% margin was added, and a total of 98 people were planned to participate. Of the 210 patients who sought treatment at WKSU Medical Center between January 15, 2024, and January 1, 2025, 103 met the inclusion criteria and provided consent to participate in the study.

Inclusion criteria:

– all women first hospitalized for BC at Marat Ospanov West Kazakhstan State University Medical Center after surgery (in the volume of RME or breast-conserving extended sectoral resection (BCESR) of the mammary gland);

– those who have given consent to fill out the questionnaire.

Exclusion criteria:

– women with newly diagnosed BC not eligible for surgical treatment;

– patients who have undergone surgery for benign tumors;

– patients who have undergone breast-conserving sectoral resection of the mammary gland;

– those who did not give consent to complete the questionnaire.

Ethical aspects: Before the study, the local bioethics committee of the West Kazakhstan State Medical University, named after Marat Ospanov, approved the research work in strict compliance with all necessary ethical standards and rules (Protocol No. 9, dated 02.10.2023). Participants were informed about the study's goals and objectives, its significance, their right to refuse participation at any time, the confidentiality of the data, and the measures taken to maintain their anonymity. All respondents signed informed consent to participate in the study.

Statistical analysis: The data were processed using IBM SPSS Statistics (version 25.0, Armonk, NY: IBM Corp.). The distribution of numerical variables was assessed using the Shapiro-Wilk test. The mean (M) and standard deviation (SD) were calculated for numerical data, while the frequency (N) and percentage (%) were calculated for qualitative variables. Survey results from the EORTC measurement were presented to management, with values ranging from 0 to 100, which showed a linear relationship on the transformed scales [20]. These scales were then dichotomized (good/bad) based on their mean values. For the functional and health/QoL scales, scores from 0 to 50 were interpreted as "bad", from 51 to 100 as "good"; for the symptomatic scales, scores from 0 to 50 were interpreted as "good", from 51 to 100 as "bad". To determine the influence of sociodemographic and clinical factors on QoL, a multivariate logistic regression analysis was employed. This method enabled the estimation of the influence of several independent variables (e.g., age, socioeconomic status, treatment type) on the dependent variable, specifically the QoL level (good or poor). $p<0.05$ was taken as statistical significance, and the Exp(B) values characterize the direction and strength of the effect.

Results: The sociodemographic and clinical characteristics of the women participating in the study were as follows (Fig. 1). The average age of the respondents was 58.4 years (SD=10.89). By the age structure, most women were 56 to 65 years – 39.8% (CI: 30.4-49.3), the least of them were 25 to 35 years – 2.9% (CI: -0.3 to 6.2) (Fig. 1A). Most of the respondents were urban residents (81.6%; CI: 74.1-89.0), with 18.4% of rural residents (CI: 11.0-25.9) (Fig. 1B). By level of education, 70.9% of respondents (CI: 62.1-79.6) had secondary education, and 29.1% (CI: 20.4-37.9) had higher education (Fig. 1C). By employment status, the largest proportion was made up of employed women – 43.7% (CI: 34.1-53.3) and pensioners – 39.8% (CI: 30.4-49.3), while the unemployed accounted for 16.5% (CI: 9.3-23.7) (Fig. 1D). By marital status, 54.4% (CI: 44.7-64.0) of respondents were married, and 45.6% (CI: 36.0-55.3) were single (Fig. 1E). By the number of children, 65.0% of women (CI: 55.8-74.3) were mothers of 2-3 children, 18.4% (CI: 11.0-25.9) had 0 to 1 child, and 16.5% (CI: 9.3-23.7) had 4 or more children (Fig. 1F). By diagnostic method, 52.4% (CI: 42.8-62.1) were diagnosed with cancer through screening, and 47.6% (CI: 37.9-57.2) sought medical care by self-referral (Fig. 1G). Regarding treatment methods, most patients (70.9%; CI: 62.1-79.6) underwent RME, and 29.1% (CI: 20.4-37.9) underwent BCESR (Fig. 1H).

In our study, we identified and statistically analyzed the sociodemographic and clinical factors influencing sexual dysfunction (Fig. 2). However, the sexual satisfaction scale was not included in the calculations due to an insufficient number of responses (15). Take-aways:

1. Age, place of residence, or number of children did not have a significant effect on the health status/QoL scale of women who had undergone treatment for BC ($p > 0.05$), taking into account sociodemographic and clinical factors (Table 1). Compared with married women, single women (Exp(B) = 0.312; p = 0.022) and women examined and diagnosed independently, rather than through screening (Exp(B) = 0.339; p = 0.030), reported significantly lower health status/QoL.

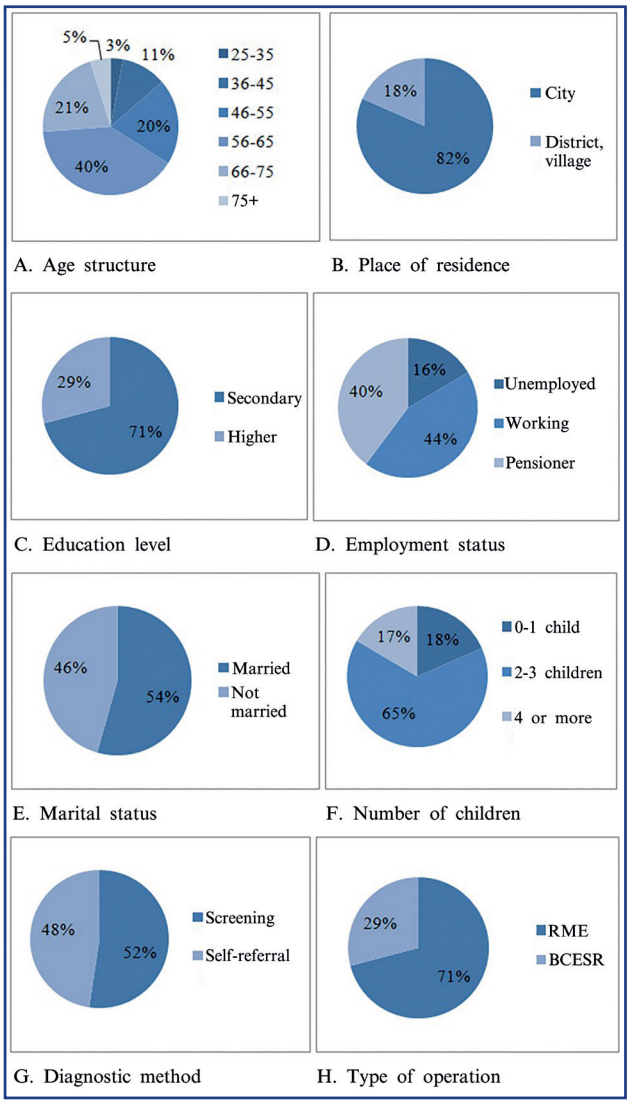

Figure 1 – Socio-demographic and clinical characteristics of respondents who took part in the study (A, B, C, D, E, F, G, H).

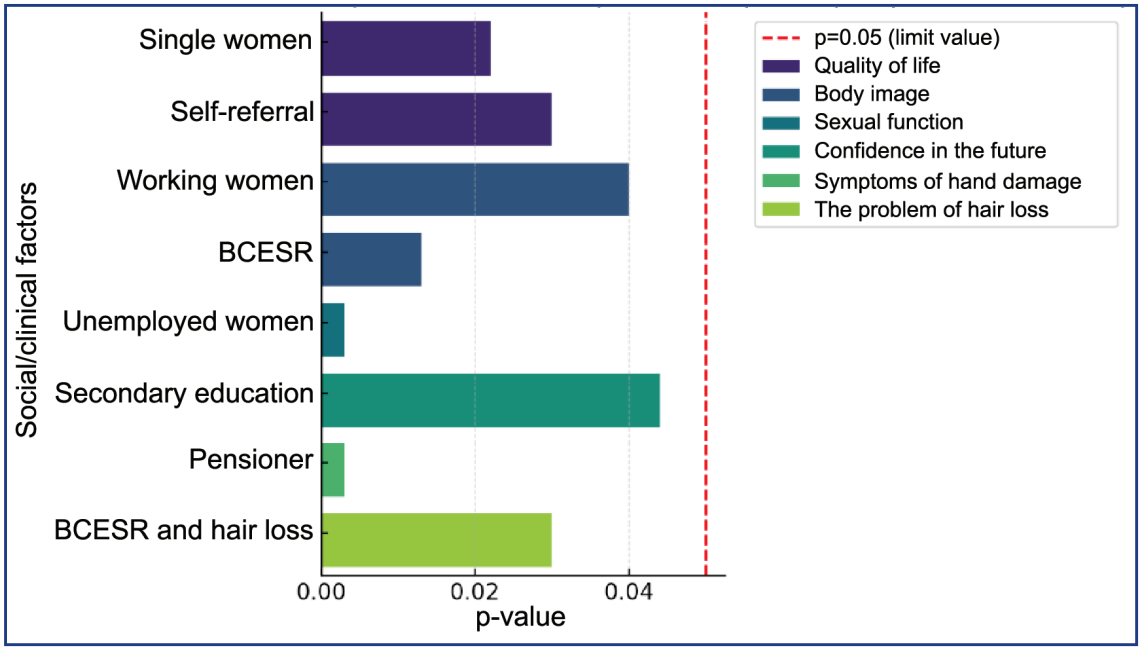

Figure 2 – Results of multivariate logistic regression of factors influencing the quality of life of respondents who participated in the study

Table 1 – Determination of the relationship between socio-demographic and clinical factors with health status/quality of life, functional scales of quality of life in women undergoing treatment for breast cancer

Functional parameters	Body image			Sexual function			Confidence in the Future			Health status/Quality of life		
	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m
Age												
25-35	3	1		3	1		3	1		3	1	
36-45	11	0.0	0.9	11	0.0	0.9	11	0.1 (0.0-4)	0.2	11	0.0	0.99
46-55	21	0.0	0.9	21	0.0	0.9	21	2.3 (0.1-45.8)	0.5	21	1.3 (0.1-18.9)	0.81
56-65	41	0.0	0.9	41	0.0	0.9	41	1.8 (0.1-30.1)	0.6	41	2.8 (0.2-34.2)	0.41
66-75	22	0.0	0.9	22	0.0	0.9	22	5.5 (0.4-71.1)	0.2	22	1.2 (0.1-10.6)	0.9
75+	5	0.0	0.9	5	0.0	1	5	2.9 (0.2-43.1)	0.4	5	0.6 (0.0-6.5)	0.64
Place of residence												
City	84			84			84	1		84	1	
District center, village	19	3.7 (0.7-18.6)	0.1	19	0.6 (0.1-5.6)	0.7	19	3.2 (0.8-12.6)	0.1	19	0.4 (0.1-1.6)	0.22
Level of education												
Secondary education	73			73			73			73		
Higher education	30	2.0 (0.5-7.6)	0.3	30	5.8 (1.0-32.3)	0.0*	30	0.1 (0.0-0.5)	0.0*	30	1.0 (0.3-3.4)	0.96
Employment status												
Unemployed	17	1		17	1		17	1		17	1	
Working	45	7.7 (1.1-54.6)	0.0*	45	0.0 (0.0-0.2)	0.0*	45	7.6 (1.1-53.7)	0.0*	45	0.8 (0.1-5.4)	0.85
Pensioner	41	4.6 (0.7-26.8)	0.1	41	0.2 (0.0-2.4)	0.2	41	5.7 (1.2-25.4)	0.0*	41	1.4 (0.3-5.7)	0.63
Marital status												
Married	56	1		56	1		56	1	1	56	1	
Single	47	3.0 (0.9-9.2)	0.0*	47	0.3 (0.0-2.2)	0.2	47	2.7 (0.9-7.8)	0.06	47	0.3 (0.1-0.8)	0.02*
Number of children												
0-1	19	1		19	1		19	1		19	1	
2-3	67	1.7 (0.2-13.6)	0.6	67	0.0	0.9	67	0.5 (0.1-3.2)	0.4	67	3.7 (0.5-24.2)	0.16
4 or more	17	2.6 (0.4-14.8)	0.2	17	0.0	0.9	17	0.6 (0.1-2.8)	0.6	17	0.8 (0.1-4.0)	0.83
Type of operation												
RME	73	1		73	1		73	1		73	1	
BCESR	30	5.9 (1.4-24.5)	0.0*	30	1.4 (0.2-9.1)	0.6	30	2.7 (0.8-9.1)	0.1	30	0.6 (0.2-2.1)	0.49
Diagnostic method												
Screening	54	1		54	1		54	1		54	1	
Self-referral	49	1.5 (0.5-4.6)	0.4	49	0.7 (0.1-3.9)	0.7	49	1.1 (0.4-3.3)	0.7	49	0.3 (0.1-0.9)	0.03*

* - Statistically significant p - value for the interaction between scales and factors, established in multivariate logistic regression (p<0.05)

2. Age, place of residence, or number of children did not have a significant effect on the functional scores of patients (p>0.05) (Table 1). Statistically significant factors influencing the functional scores ($p < 0.05$) included: Working patients (Exp(B) = 7.742; p = 0.040) who underwent organ-preserving BCESR (Exp(B) = 5.988; p = 0.013) demonstrated a better perception of body image and higher confidence in the future (Exp(B) = 7.652; p = 0.041) than unemployed patients who underwent radical surgery. Unemployed women had significantly lower sexual function scores (Exp(B) = 0.023; p = 0.003). In addition, women with secondary education rated sexual function (Exp(B) = 5.828; p = 0.044) and confidence in the future (Exp(B) = 0.123; p = 0.004) lower than women with higher education. Retired women, in contrast, had a higher confidence in the future (Exp(B) = 5.741; p = 0.022).

3. Marital status and employment status, diagnostic method, and type of surgical intervention did not have a significant effect on symptomatic indices ($p > 0.05$) (Table 2). Statistically significant factors influencing symptomatic scales ($p < 0.05$) included: Symptoms of hand damage are more common among pensioners (Exp(B) = 4.386; p = 0.003). Hair loss was more common among patients who underwent organ-preserving BCESR for squamous cell carcinoma (Exp(B) = 3.565; p = 0.030).

According to the study results, factors influencing the QoL of women undergoing treatment for BC are complex and multifaceted. Lower assessment of the QoL of single women (p = 0.022) and women who were diagnosed independently (p = 0.030) compared to married women may be associated with a lack of social support, a feeling of loneliness, and late seeking of medical care. These factors make it difficult for the patient to accept the disease, increase psychological distress, and negatively affect the overall QoL. According to the functional scale, better body image perception (p = 0.040) and greater confidence in the future (p = 0.041) among working women are likely due to their active engagement with society and a sense of social significance. Organ-preserving BCESR was also associated with a positive effect (p = 0.013 for body image; p = 0.041 for confidence in the future), as women perceived themselves more positively because their appearance was preserved without compromising body image.

In contrast, unemployed women showed a significant decrease in sexual function (p = 0.003). This situation may be associated with a decrease in social status, psycho-emotional stress, lack of income, and decreased self-confidence. Low assessment of sexual function (p = 0.044) and confidence in the future (p = 0.004) in women with secondary education is explained by their inability to fully comprehend information about the disease, lack of access to necessary resources, and limited adaptation strategies. High confidence in the future of pensioners (p = 0.022) may be associated with a shift in their expected life goals due to aging and a greater ability to adapt psychologically, resulting from life experience. Regarding symptom score, the higher incidence of symptoms of hand damage among retirees (p = 0.003) may be due to a slower recovery process associated with aging and impaired lymphatic circulation. In addition, patients who underwent organ-preserving BCESR for squamous cell carcinoma had a higher incidence of hair loss (p = 0.030), probably due to the side effects of chemotherapy that continue after surgery.

Thus, the results of the study indicate that many factors influence the outcome of the disease after traumatic brain injury, and it is necessary to pay attention not only to clinical treatment but also to the social and psycho-emotional state of the patient.

Discussion: The study's results showed that the factors influencing the QoL of women with BC receiving treatment are multifaceted and complex. This result is consistent with data from several studies demonstrating the major role of psychosocial and economic factors in shaping QoL [10]. However, some authors do not deny the importance of age. For example, a meta-analysis [11] found a statistically significant correlation between the patient age and QoL (p = 0.03), with each additional year of age associated with a 0.19-point increase in the QoL index. These contradictory results could be attributed to differences in age-related adaptation strategies and the level of social support available to patients.

The study's results showed that employment and educational level play significant roles in QoL perception. Patients with secondary education rated their sexual function (p = 0.044) and confidence in the future (p = 0.004) lower. It was found that employed women have a better perception of their body image (p = 0.040) and higher confidence in the future (p = 0.041). This finding is consistent with the literature. In particular, it was demonstrated that women with a university education have a higher ES, and women whose income exceeds their expenses also exhibit higher sexual function (p = 0.003) and dyadic adaptation (p = 0.004) [16]. Additionally, patients who underwent organ-preserving surgery reported a more positive body image (p = 0.013) and greater confidence in their future (p = 0.041). Other studies confirm these data: patients after organ-preserving operations better assessed their QoL in terms of physical (p = 0.001) and sexual (p = 0.007) indicators [10], and also showed that this was associated with higher functional indicators, increased confidence in the future (p = 0.005), and a higher level of sexual satisfaction (p = 0.001) [11].

The above data suggest that the main factors influencing the survival of women with BC are social support, economic stability, educational level, and type of surgery. The results of this study provide a comprehensive understanding of the factors that affect patients' QoL and can serve as a basis for guiding post-oncological support. In particular, it is demonstrated that during the post-treatment period, it is necessary to consider not only medical but also psycho-emotional, social, and aesthetic aspects. This study is considered a crucial scientific and practical foundation for planning programs and interventions in this area.

Table 2 – Determination of the relationship between socio-demographic and clinical factors on the symptom scale in women with breast cancer who have undergone treatment

Age	Side effects of systemic thera-py			Symptoms of hand damage			Symptoms of breast diseases			The problem of hair loss		
	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m	n (%)	Exp (B) (95% CI)	song p- m
Age												
25-35	3	1		3			3	1		2	1	
36-45	11	1.6 (0.0-68.7)	0.8	11	0.0	0.9	11	0.0	1	8	0.2 (0.0-20.3)	0.49
46-55	21	2.2 (0.1-37.6)	0.5	21	0.0	0.9	21	0.0	0.9	15	2.1 (0.0-107.2)	0.71
56-65	41	3.3 (0.2-49.3)	0.3	41	0.0	0.9	41	0.0	0.9	27	0.1 (0.0-3.2)	0.19
66-75	22	1.2 (0.1-15.2)	0.8	22	0.0	0.9	22	0.0	0.9	15	0.8 (0.0-16)	0.89
75+	5	0.7 (0.0-10.3)	0.7	5	0.0	0.9	5	0.0	0.9	3	3.7 (0.1-91.9)	0.42
Place of residence												
City	84	1		84	1		84	1		55	1	
District center, village	19	0.8 (0.2-3.2)	0.8	19	2.4 (0.6-8.5)	0.1	19	7.4 (0.4-120.5)	0.1	15	1.0 (0.2-4.9)	0.99
Level of education												
Secondary education	73	1		73	1		73	1		51	1	
Higher education	30	0.5 (0.1-1.6)	0.2	30	1.3 (0.4-4.1)	0.5	30	1.8 (0.3-8.9)	0.4	19	1.1 (0.2-4.7)	0.94
Employment status												
Unemployed	17	1		17			17	1		14	1	
Working	45	2.1 (0.3-12.1)	0.3	45	2.2 (0.7-7.2)	0.1	45	0.0	0.9	28	3.5 (0.3-33.1)	0.27
Pensioner	41	1.5 (0.3-6.7)	0.5	41	4.3 (1.6-11.7)	0.0*	41	1.1 (0.1-15.5)	0.9	28	4.7 (0.7-30.6)	0.10
Marital status												
Married	56	1		56	1		56	1		42	1	
Single	47	0.5 (0.1-1.5)	0.2	47	1.1 (0.4-2.6)	0.9	47	1.1 (0.2-4.7)	0.8	28	0.7 (0.2-2.5)	0.60
Number of children												
0-1	19	1		19	1		19	1		13	1	
2-3	67	1.9 (0.2-15.5)	0.5	67	2.1 (0.3-12.4)	0.4	67	3.6 (0.2-50.8)	0.3	45	4.3 (0.4-40.8)	0.19
4 or more	17	2.3 (0.3-14.2)	0.3	17	2.6 (0.6-10.9)	0.2	17	2.2 (0.2-18.3)	0.4	12	2.9 (0.4-18.6)	0.25
Type of operation												
RME	73	1		73	1		73	1		53	1	
BCESR	30	1.1 (0.4-3.8)	0.7	30	2.4 (0.8-6.4)	0.1	30	3.5 (0.5-23.8)	0.2	17	3.5 (1.1-11.2)	0.03*
Diagnostic method												
Screening	54	1		54	1		54	1		35	1	
Self-referral	49	2.8 (0.8-9.7)	0.1	49	0.5 (0.2-1.3)	0.2	49	1.2 (0.2-5.7)	0.7	35	0.7 (0.1-2.6)	0.63

* - Statistically significant p-value of the effect between scales and factors using the multivariate logistic regression method($p<0.05$)

Conclusion: A complex combination of sociodemographic and clinical factors influenced overall survival in patients with BC. The study's results showed that the levels of social support, employment status, education level, and type of surgery significantly influenced overall survival. In particular, women who were employed, had higher education, and underwent organ-preserving surgery had higher levels of body image satisfaction and future confidence ($p < 0.05$). In contrast, single, unemployed, and moderately educated patients had lower overall survival scores. In addition, specific symptomatic problems, such as symptoms of hand damage ($p = 0.003$) and hair loss after BCESR ($p = 0.030$), were reported by retired women.

The obtained results indicate the need to strengthen psychosocial support and rehabilitation in the fight against BC, not limited to drug treatment alone. An integrated approach that comprehensively considers the factors influencing BC development will enhance the effectiveness of oncological care and facilitate patients' successful adaptation to everyday life. The study can serve as a valuable scientific and practical foundation for developing measures of preventive, psychosocial, and informational support for cancer patients.

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АНДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІ БАР ЕМДЕУДЕН ӨТКЕН ӘЙЕЛДЕРДІҢ ӨМІР САПАСЫНА ӘСЕР ЕТЕТІН ФАКТОРЛАРДЫ АНЫҚТАУ

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Өзектілігі: *Сүт безі қатерлі ісігі (СБҚІ) – әйелдер арасында жиі кездесетін онкологиялық аурулардың бірі және оның физикалық, психоэмоционалдық, әлеуметтік және сексуалдық салдарлары әйелдердің өмір сапасына (ӨС) теріс әсер етеді. Емнен кейінгі кезеңде ӨС төмендеуі пациенттердің толыққанды оңалуына кедергі келтіруі мүмкін. Сондықтан СБҚІ бар әйелдердің ӨС әсер ететін әлеуметтік-демографиялық және клиникалық факторларды зерттеу өзекті мәселе болып табылады.*

Зерттеу мақсаты *– сүт безі қатерлі ісігі бар емдеуден өткен әйелдердің өмір сапасына әлеуметтік-демографиялық және клиникалық факторлардың әсерін анықтау.*

Әдістері: *Зерттеу М.Оспанов атындағы БҚМУ Медициналық орталығында жүргізілді. Қатысушылар EORTC QLQ-BR23 стандартына сәйкес сауалнама толтырды. Қатысушылар саны – 103 әйел. Деректерді жинау барысында сауалнама сұрақтарымен қоса респонденттердің әлеуметтік-демографиялық және клиникалық деректері анықталды. Деректер IBM SPSS Statistics 25.0 бағдарламасында өңделді. Статистикалық талдау көпөлшемді логистикалық регрессия әдісі арқылы жүргізілді.*

Нәтижелері: *Зерттеу нәтижелері бойынша, некеде тұрмайтын (p = 0,022) және ауруды өздігінен анықтаған әйелдер (p = 0,030) ӨС төмен бағалады. Жұмысы бар (p = 0,040) және ағза сақтайтын сүт безінің кеңейтілген секторалды резекция (СБКСР) операциясынан өткен әйелдер (p = 0,013) дене бейнесін жоғары бағалады және болашаққа сенімі жоғары болды (p = 0,041). Жұмыссыз және орта білімді әйелдерде сексуалдық функция мен болашаққа сенім көрсеткіштері едәуір төмен болды (p < 0,05). Зейнеткерлерде қол симптомдары жиірек (p = 0,003), ал СБКСР операциясынан кейін шаш түсу жиілігі артқаны байқалды (p = 0,030).*

Қорытынды: *Алынған зерттеу нәтижелері көрсеткендей СБҚІ бар әйелдердің ӨС әсер ететін факторлар көпқырлы. Әлеуметтік-экономикалық жағдай, операция түрі және психоэмоционалдық қолдау ӨС айқындайтын негізгі көрсеткіштер болып табылады. Бұл нәтижелер реабилитациялық бағдарламаларды жетілдіруде ғылыми негіз ретінде қызмет ете алады.*

Түйінді сөздер: *әйел, сүт безі қатерлі ісігі (СБҚІ), өмір сапасы (ӨС), EORTC QLQ-BR23, әлеуметтік-демографиялық факторлар, клиникалық факторлар.*

АННОТАЦИЯ

ОПРЕДЕЛЕНИЕ ФАКТОРОВ, ВЛИЯЮЩИХ НА КАЧЕСТВО ЖИЗНИ ЖЕНЩИН, ПРОШЕДШИХ ЛЕЧЕНИЕ ОТ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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Актуальность: *Рак молочной железы (РМЖ) является одним из наиболее распространённых онкологических заболеваний среди женщин, и его физические, психоэмоциональные, социальные и сексуальные последствия негативно влияют на качество жизни (КЖ) пациенток. Снижение КЖ в постлечебный период может затруднить полноценную реабилитацию. Поэтому исследование социально-демографических и клинических факторов, влияющих на КЖ женщин с РМЖ, является актуальной.*

Цель исследования *– определить влияние социально-демографических и клинических факторов на качество жизни женщин, прошедших лечение от рака молочной железы.*

Методы: *Исследование было проведено в Медицинском центре ЗКМУ имени М. Оспанова. Участницы заполнили анкету согласно стандарту EORTC QLQ-BR23. Общее количество участниц составило 103 женщины. В ходе сбора данных, наряду с анкетированием, были получены социально-демографические и клинические характеристики респондентов. Обработка*

данных проводилась в программе IBM SPSS Statistics 25.0. Статистический анализ выполнен с использованием метода многомерной логистической регрессии.

Результаты: *Согласно результатам исследования, незамужние женщины (p = 0,022) и женщины, самостоятельно выявившие заболевание (p = 0,030), оценили своё КЖ ниже. Трудоустроенные пациентки (p = 0,040) и женщины, перенёсшие органосохраняющую расширенную секторальную резекцию молочной железы (РСРМЖ) (p = 0,013), выше оценили образ тела и проявляли большую уверенность в будущем (p = 0,041). У безработных и женщин со средним образованием показатели сексуальной функции и уверенности в будущем были значительно ниже (p < 0,05). У пенсионерок чаще отмечались симптомы со стороны руки (p = 0,003), а после РСРМЖ чаще наблюдалось выпадение волос (p = 0,030).*

Заключение: *Полученные результаты показывают, что на КЖ женщин с РМЖ влияет множество факторов. Социально-экономическое положение, тип операции и уровень психоэмоциональной поддержки являются основными определяющими показателями КЖ. Эти данные могут служить научной основой для совершенствования реабилитационных программ.*

Ключевые слова: *женщина, рак молочной железы (РМЖ), качество жизни (КЖ), EORTC QLQ-BR23, социально-демографические факторы, клинические факторы.*

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SUCCESSFUL EXPERIENCE WITH FAECAL MICROBIOTA TRANSPLANTATION IN A PATIENT WITH MYELODYSPLASTIC SYNDROME AND GRAFT-VERSUS-HOST REACTION WITH INTESTINAL LESIONS COMBINED WITH ENTEROCOLITIS CAUSED BY CLOSTRIDIUM DIFFICILE INFECTION: A CLINICAL CASE

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ABSTRACT

Relevance: *Faecal microbiota transplantation (FMT) is the transfer of intestinal contents from a healthy donor to a patient to restore normal microflora. The material contains beneficial bacteria, fungi, antibodies, prebiotics, and other biologically active components. FMT is most effectively used for recurrent Clostridium difficile infection, showing better results compared to traditional treat-ment, such as vancomycin. Studies also suggest the potential of FMT in treating inflammatory bowel diseases, obesity, metabolic syndrome, and gastrointestinal tract functional disorders. In recent years, the method has gained widespread recognition and is now considered a potential first-line therapy for Clostridium difficile.*

The study aimed to *present the first successful clinical experience of faecal microbiota transplanta-tion in a patient with myelodysplastic syndrome and graft-versus-host disease, characterized by in-testinal lesions.*

Methods: *A clinical case of a 46-year-old patient who underwent allogeneic bone marrow trans-plantation for myelodysplastic syndrome is described. In the early post-transplantation period, the patient developed severe manifestations of Graft-versus-host disease (GvHD) with predominant in-volvement of the gastrointestinal tract: severe diarrhoea, abdominal pain, weight loss, signs of dysbiosis, and nutritional deficiency. After ineffective therapy with steroids and supportive care, a decision was made to perform FMT using carefully selected donor material.*

Results: *The FMT procedure was clinically successful, with improvements in general condition, a decrease in the severity of diarrhea, stabilization of body weight, and restoration of appetite noted within several days. Endoscopic and histological examinations of the intestinal mucosa confirmed a reduction in inflammatory changes. No side effects, complications, or signs of systemic infection were recorded after FMT.*

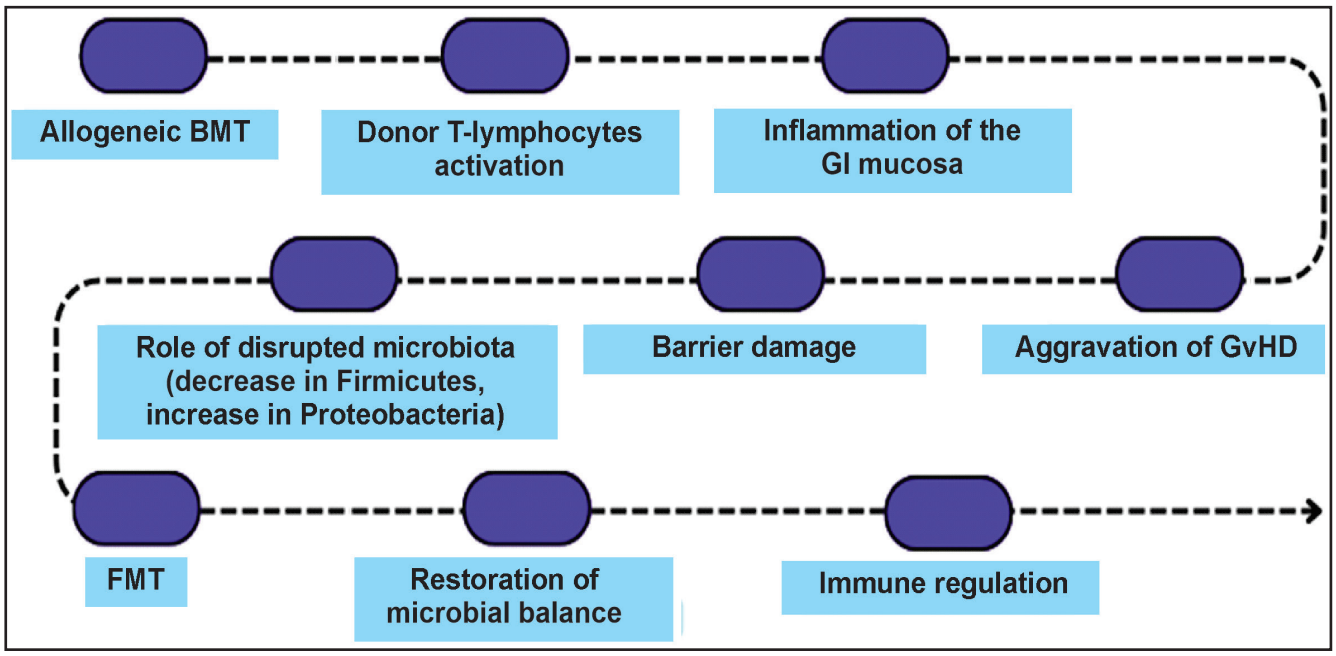
Conclusions: *The successful application of FMT in this case demonstrates the potential of the meth-od as an additional therapeutic tool in (GvHD) with intestinal involvement, particularly in steroid-resistant forms of the disease.*

Keywords: *Faecal microbiota transplantation (FMT), gut microbiota, myelodysplastic syndrome, graft-versus-host reaction (GvHD), dysbiosis.*

Relevance: Graft-versus-host disease (GvHD) is a severe complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), including transplantation for myelodysplastic syndrome (MDS). In GvHD, donor immune cells attack the recipient's tissues, recognizing them as foreign. GvHD can occur in acute or chronic forms, affecting various organs and systems of the body. Acute GvHD typically develops within the first 100 days post-transplantation and may manifest as skin rash, diarrhea, and liver damage. Chronic GvHD develops later and may present with skin changes, damage to the lungs, gastrointestinal (GI) tract, and other organs. Both forms of GvHD can be severe and pose a life-threatening risk to the patient. The pathogenesis scheme of GvHD is presented in Figure 1.

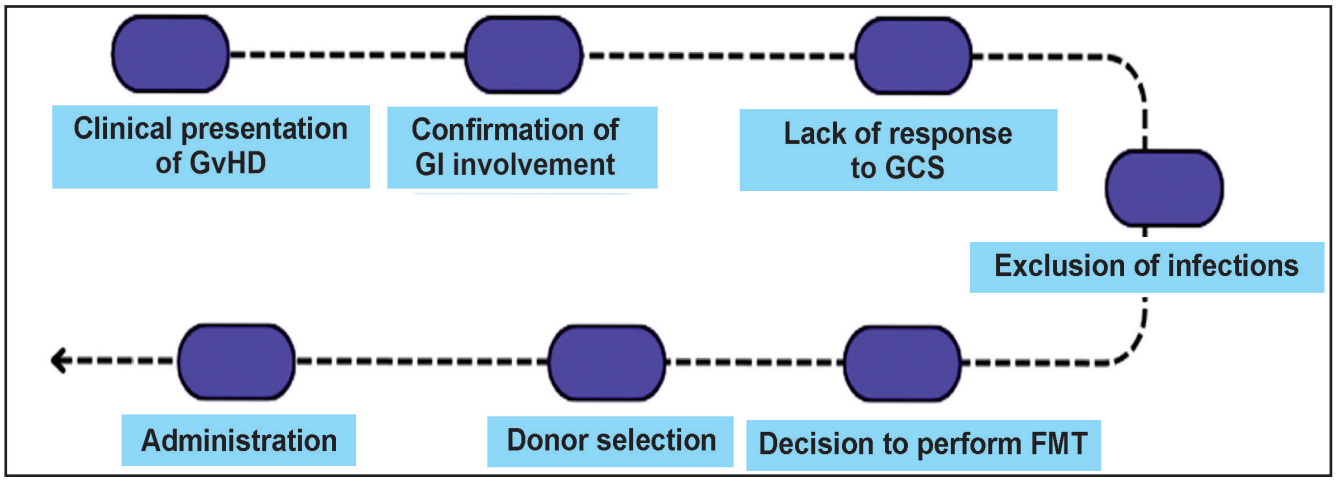
Faecal microbiota transplantation (FMT) is a medical procedure that involves transferring intestinal contents from a healthy individual into the patient's intestine. This is not merely the transfer of stool, but of an entire ecosystem that includes billions of bacteria, fungi, viruses (bacteriophages), prebiotics, natural antibiotics, secretory immunoglobulins (mainly IgA), mucin proteins, bile acids, and other biologically active components. This method gained widespread recognition due to its high efficacy in treating recurrent Clostridium difficile infection (CDI). Moreover,

preliminary data suggest the potential of FMT in treating inflammatory bowel diseases, obesity, metabolic syndrome, and functional GI disorders. Over the past decade, the method has been actively studied, and some experts now recommend FMT as first-line therapy for CDI, including recurrent and treatment-resistant forms. Randomized controlled trials have confirmed that the effectiveness of FMT exceeds that of traditional vancomycin therapy for recurrent CDI [1]. The decision-making algorithm for FMT is presented in Figure 2.



Legend: BMT – bone marrow transplantation, GI – gastrointestinal; GvHD – graft-versus-host disease, FMT – faecal microbiota transplantation

Figure 1 – Pathogenesis scheme of graft-versus-host disease with intestinal involvement and microbiota disruption



Legend: GCS – glucocorticosteroid, GI – gastrointestinal, GvHD – graft-versus-host disease, FMT – faecal microbiota transplantation.

Figure 2 – Algorithm for decision-making regarding faecal microbiota transplantation in intestinal graft-versus-host disease

Aim of the study: To present the first successful clinical case in Kazakhstan of faecal microbiota transplantation in a patient with myelodysplastic syndrome and graft-versus-host disease with intestinal involvement, complicated by Clostridium difficile infection.

Materials and Methods: A retrospective analysis was conducted of a clinical case involving a patient with MDS who developed intestinal GvHD following allogeneic bone marrow transplantation (BMT), complicated by severe dysbiosis and clinically significant symptoms. FMT was performed using donor material prepared in accordance with international safety protocols [2].

Clinical case:

Patient information: Patient T., 43 years old, upon admission complained of general weakness, periodic muscle pain in the legs, decreased appetite, and lack of weight gain. According to the medical history, the disease onset occurred in 2012, when intermittent bruises began to appear on the body.

Clinical data: In July 2018, in the hematology department of City Hospital No.1 in Astana (Kazakhstan), based on histological, cytological, flow cytometric, and FISH studies of the bone marrow, the diagnosis was confirmed: Myelodysplastic syndrome, hypoplastic variant with a paroxysmal nocturnal hemoglobinuria (PNH) clone, without signs of hemolysis.

Bone marrow histology from 05.07.2018: A morphological pattern consistent with hypoplasia of the megakaryocytic lineage is observed.

Bone marrow histology from 16.07.2018: Morphological features in the bone marrow are suspicious for MDS substrate.

Flow cytometry of peripheral blood for PNH from 27.06.2018: PNH clone on monocytes – 2.81%; granulocytes – 1.95%; erythrocytes type II – 0.23%; type III – 1.2% (total – 1.43%).

FISH from 02.08.2018: EGR1/D5S23, D5S721 -5;5q: not detected

FISH -7/7q- from 12.10.2022:

Karyotype: nucish (KMT2E, EZH2, CEP7) x2[200].

Conclusion: Deletion of 7q22/7q36 loci and monosomy of chromosome 7 were not identified in the analyzed interphase nuclei.

The patient received immunosuppressive therapy with Cyclosporin and blood component transfusions, but no positive effect was achieved.

After identifying a partially matched donor, the patient was referred to the National Research Oncology Center for HSCT.

On 17.05.2023, the patient was admitted to the National Research Oncology Center (NROC, Astana, Kazakhstan) for further evaluation. Bone marrow aspiration on May 18, 2023, showed no excess blasts or transformation; hypoplasia with signs of dysplasia persisted.

Myelogram from 18.05.2023: blasts – 2.4%. The bone marrow smear was cellular and polymorphic. Differential count performed on 500 myelokaryocytes. Erythropoiesis was of the normoblastic type with signs of megaloblastoid changes. The erythroid lineage was expanded to 30.6%, with preserved maturation and signs of dyserythropoiesis. The granulocytic lineage was preserved and represented evenly at all stages of maturation.

On May 22, 2023, Rituximab was administered at 375 mg/m^2/day in monotherapy, two weeks prior to the planned conditioning regimen and three weeks prior to the haplo-HSCT transfusion.

The patient underwent all necessary pre-transplant examinations and was evaluated by a team of specialists. No absolute contraindications for haplo-BMT from her son were found.

On 14.06.2023, following conditioning (Bu 8 mg/kg + Flu 30 mg/m^2) and premedication, the patient received a hematopoietic stem cell suspension transfusion: 330 mL, CD34 – 6.1 million/kg recipient's body weight, CD3 – 21.3 million/kg. The procedure was well tolerated.

On 13.06.2023 (day -1), prophylactic therapy for GvHD was initiated using the calcineurin inhibitor tacrolimus at 0.03 mg/kg/day, with serum level monitoring. Engraftment occurred on day 21 post-HSCT.

Diagnostics: On 31.08.2023, the patient was urgently hospitalized at the NROC due to a severe condition (ECOG score 3), caused by acute antral gastric ulcer pain syndrome, diarrhea (possible intestinal GvHD), and transfusion dependence. On 28.08.2023, the patient experienced a gastric ulcer exacerbation with bleeding. Esophagogastroduodenoscopy (EGD) showed an acute gastric ulcer with confirmed bleeding. On 05.09.2023, prednisolone was added to the immunosuppressive therapy at a minimal dose of 0.5 mg/kg due to increased stool volume (up to 750 ml), elevated calprotectin (448), and dyspeptic symptoms (nausea, vomiting). The condition was assessed as acute intestinal GVHD, with upper GI tract involvement. Gastrointestinal bleeding was noted.

On 11.09.2023, due to persistent GvHD symptoms and ulcer healing signs on EGD, methylprednisolone was prescribed at 1 mg/kg.

On 18.09.2023, methylprednisolone was discontinued due to a lack of clinical effect and the risk of profound immunosuppression. Tacrolimus IV was continued as immunosuppressive therapy. Colonoscopy under IV anesthesia revealed: Ulcerative terminal ileitis. Ulcerative colitis with total involvement.

On 19.09.2023, the patient was evaluated by a gastroenterologist. Diagnosis: Gastrointestinal GvHD? Pseudomembranous colitis? CMV colitis? Metronidazole therapy was initiated. A positive result for Clostridium difficile toxins was obtained.

On 25.09.2023, histological examination of the intestinal tissue showed: Colonic mucosa with ulceration, increased apoptosis, crypt distortion, and loss. This morphological pattern, taking into account the clinical and anamnestic data, most closely corresponds to GvHD with intestinal involvement (Grade IV according to Lerner).

Thus, based on endoscopic findings, Clostridium difficile toxin positivity, and intestinal biopsy, two concurrent intestinal pathologies were identified: enterocolitis caused by Clostridium difficile infection and severe intestinal GvHD. Clinical manifestations: Diarrhea up to 10 times per day, dark green mucous, mucous stool up to 1,100 mL, nausea, multiple episodes of vomiting, and abdominal pain requiring analgesia. Immunosuppressive therapy: IV tacrolimus under serum level monitoring. Frequent tramadol analgesia, symptomatic and syndrome-targeted therapy, and rectal mesalazine.

Treatment: On September 27, 2023, both EGD and colonoscopy were performed under IV anesthesia. Through the gastroscope, 50 mL of faecal microbiota

was administered into the descending part of the duodenum; during colonoscopy, 150 mL was introduced into the ileum. Starting from 20.10.2023, gradual clinical improvement was noted: Decrease in diarrhea frequency to 1 - 2 times/day, stool became pasty and brown. Pain resolved. Oral medication was resumed, and the patient began self-feeding. Intermittent dyspeptic symptoms persisted.

On 13.12.2023, the patient was hospitalized at the Hematology Center in Karaganda. An assessment of chronic GvHD activity was performed according to the criteria of the U.S. National Institutes of Health (NIH, Consensus Conference, 2014) [2]: ECOG – 2 points.

Skin: focal hyperkeratosis, peeling, dry skin syndrome – not included in score – 0 points.

Eyes: occasional dryness without visual impairment; uses drops as needed (Natural Tears/Dexatobrom) – 1 point.

GI tract: nausea, vomiting once daily, stool twice daily, pasty without pathological impurities – 2 points.

Results: Patient T., 43 years old, diagnosed with myelodysplastic syndrome, underwent allogeneic BMT. Post-transplantation, her condition worsened: febrile fever, diarrhea, hypotension, and severe neutropenia. Sepsis caused by *Staphylococcus epidermidis* was diagnosed, followed by severe diarrhea due to *Clostridium difficile* and subtotal pseudomembranous colitis. Intestinal GvHD developed, confirmed endoscopically and histologically (Grade IV).

Due to worsening condition, pronounced dysbiosis, and failure of conventional therapy, FMT was performed. The procedure was conducted on 27.09.2023, using a combination of: 50 mL via EGD and 150 mL via colonoscopy (Figures 3 and 4).

In the following days, marked positive dynamics were observed, including normalization of temperature, a progressive reduction in stool frequency, full normalization of stool characteristics, and laboratory improvements (leukocyte recovery, decreased C-reactive protein, and platelet stabilization). Detailed dynamics of clinical and laboratory parameters are presented in Table 1.

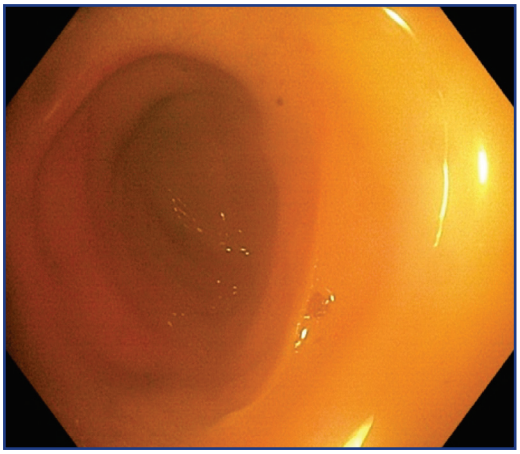


Figure 3 – Faecal microbiota transplantation into the duodenum lumen

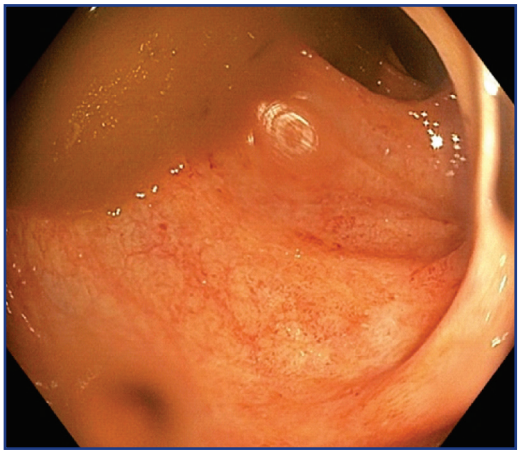


Figure 4 – Faecal microbiota transplantation into the colon lumen

Table 1 – Dynamics of Clinical and Laboratory Parameters

Date	Event / Condition	Temperature, °C	Leukocytes ($\times 10^9$/L)	Neutrophils (%)	Platelets ($\times 10^9$/L)	CRP (mg/L)	Diarrhea	Notes
31.08.2023	Hospitalization	37.5	1.2	38	12	102	+++	Anemia, hepatosplenomegaly
14.09.2023	Sepsis (Staph. epidermidis)	39.2	0.8	25	8	250	+++	Hypotension
24.09.2023	Clostridium difficile infection (CDI)	38.7	1.1	40	10	198	++++	Pseudomembranous enterocolitis
25.09.2023	Diagnosis: Intes-tinal GvHD, Grade IV	38.4	1.3	42	9	175	++++	Enteritis, ulcers, GIT involvement
27.09.2023	FMT (IV and endoscopic administration)	37.8	1.7	48	20	132	++	FMT via EGD and colonoscopy was administered
30.09.2023	Improvement after FMT	37.1	2.4	55	45	84	+	Improved appetite and general condition
10.10.2023	Reactivation of CMV infection	37.9	2.1	50	60	98	–	CMV: 6.5 × 10^2 IU/mL

Note: CMV – cytomegalovirus; EGD – esophagogastroduodenoscopy; CRP – C-reactive protein; GIT – gastrointestinal tract; GvHD – graft-versus-host disease; FMT – faecal microbiota transplantation

The timeline of disease progression is presented in Table 2.

Table 2 – Timeline of faecal microbiota transplantation in a patient with myelodysplastic syndrome and graft-versus-host disease with intestinal involvement and Clostridium difficile infection

Дата	Event	Note / Diagnosis
2012	Disease onset	Appearance of bruises
27.06.2018	Immunophenotyping	PNH clone detected: monocytes 2.81%, granulocytes 1.95%, total 1.43%
05.07.2018	Bone marrow histology	Hypoplasia of the megakaryocytic line-age
16.07.2018	Bone marrow histology	Suspected myelodysplastic syndrome
02.08.2018	FISH (5q)	Negative result
July 2018	Diagnosis confirmed: “Myelodysplastic syndrome, hypoplastic variant with PNH clone, without hemolysis”	
12.10.2022	FISH (7q)	No 7q deletion or monosomy 7 detected
17.05.2023	Hospitalization at NROC	Pre-transplant evaluation, planned ritux-imab therapy
18.05.2023	Bone marrow aspiration and myelogram	Hypoplasia, dysplasia, blasts – 2.4%
22.05.2023	Rituximab administration	375 mg/m², two weeks before condition-ing
13.06.2023	Tacrolimus initiated	GvHD prophylaxis
14.06.2023	Haplo-BMT after conditioning	Donor – son, Bu+Flu, CD34 – 6.1 mil-lion/kg
31.08.2023	Emergency hospitalization at NROC	Diarrhea, gastric ulcer, suspected GIT GvHD
05.09.2023	Prednisolone started	0.5 mg/kg. Diarrhea up to 750 mL, dys-pepsia
11.09.2023	Methylprednisolone started	1 mg/kg. GIT GvHD – clinical symptoms persist
18.09.2023	Methylprednisolone discontinued, tacrolimus continued; colonoscopy performed	Ulcerative ileitis, ulcerative colitis (total involvement)
19.09.2023	Diagnosis clarification, Metronidazole therapy started	Clostridium difficile confirmed
25.09.2023	Intestinal histology	Grade IV intestinal GvHD per Lerner
27.09.2023	Faecal microbiota transplantation performed	50 mL – duodenum, 150 mL – ileum
20.10.2023	Clinical improvement noted	Diarrhea reduced to 1 - 2 times/day, mushy stool, pain syndrome resolved
13.12.2023	Hospitalization at Hematology Center, Kara-ganda; evaluation of chronic GvHD	NIH criteria: ECOG 2; eyes – 1 point; GIT – 2 points; skin – 0 points
26.11.2024	Hospitalization at NROC, general condition evaluation	NIH criteria: ECOG 1; eyes – 1 point; GIT – 0 points; skin – 0 points
29.11.2024	Patient discharged with improvement for outpatient follow-up at the place of residence.	

Note: GIT – gastrointestinal tract; BM – bone marrow; NROC – National Research Oncology Center (Astana, Kazakhstan); PNH – paroxysmal nocturnal hemoglobinuria; GvHD – graft-versus-host disease; BMT – bone marrow transplantation; FMT – faecal microbiota transplantation; CMV – cytomegalovirus; EGD – esophagogastroduodenoscopy; NIH – U.S. National Institutes of Health

Discussion: Graft-versus-host disease (GvHD) remains one of the leading causes of adverse outcomes following allo-HSCT. When the gastrointestinal tract is affected – especially in steroid-resistant cases – the risk of fatal outcomes increases significantly, necessitating the search for new therapeutic approaches.

Faecal microbiota plays an important role in regulating the immune response and maintaining the barrier function of the mucosal lining. In patients with GvHD, particularly in the context of immunosuppression and antibiotic therapy, severe dysbiosis develops, characterized by the loss of beneficial commensal bacteria, which worsens the disease course and reduces treatment effectiveness [3, 4].

FMT helps restore microbial diversity, reduces pro-inflammatory cytokines, enhances the production of short-chain fatty acids, and contributes to the restoration of intestinal epithelial integrity. Although data on the use of FMT in GvHD remain limited in the literature, a Chinese pilot study (Qi et al., Suzhou, 2018) on steroid-refractory acute intestinal GvHD included eight patients who received FMT. All patients showed significant improvement, including reduced stool frequency, pain resolution, and restoration of microbial flora, with none of the procedures causing serious side effects [5]. Additionally, a review published in Biology of Blood and Marrow Transplantation (2019) described several cases in which FMT “cured” steroid-refractory intestinal GvHD [6].

Thus, accumulated clinical observations, including the presented case, confirm the safety and potential efficacy of this method in this patient population.

It is essential to emphasize the importance of strict adherence to safety protocols when selecting a donor, performing infection screening, and preparing biological material, particularly in immunosuppressed patients. Multidisciplinary management is essential for such patients, involving gastroenterologists, infectious disease specialists, and hematologists.

Conclusion: This clinical case demonstrates the successful application of FMT in treating severe post-transplant dysbiosis. The observed clinical improvement supports the theoretical rationale for using FMT as adjunctive therapy in immune-mediated gastrointestinal diseases, including GvHD. The described case highlights the importance of an individualized approach and opens new perspectives to introduce FMT into clinical practice in oncohematology, particularly in intestinal GvHD. However, randomized controlled trials are necessary to determine the efficacy, optimal regimen, frequency of procedures, and long-term safety of FMT in immunocompromised patients.

The successful experience of using FMT in a patient with GvHD and MDS demonstrates the potential of the method to expand its indications beyond CDI. Further studies involving a larger number of patients are required to assess the efficacy and safety of FMT under conditions of immunosuppression.

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АҢДАТПА

МИЕЛОДИСПЛАСТИКАЛЫҚ СИНДРОММЕН ЖӘНЕ ІШЕК ЗАҚЫМДАНУЫМЕН ЖҮРЕТІН «ТРАНСПЛАНТАТТЫҢ ИЕСІНЕ ҚАРСЫ РЕАКЦИЯСЫ» БАР, КЛОСТРИДИЯЛЫҚ ИНФЕКЦИЯМЕН ШАҚЫРЫЛҒАН ЭНТЕРОКОЛИТПЕН ҚАТАР ЖҮРЕТІН НАУҚАСҚА ФЕКАЛЬДЫ МИКРОБИОТА ТРАНСПЛАНТАЦИЯСЫН ЖҮРГІЗУДІҢ СӘТТІ ТӘЖІРИБЕСІ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Нәжіс микробиотаны трансплантациялау (НМТ) — бұл қалыпты микрофлораны қалпына келтіру үшін сау донордан пациентке ішек мазмұнын беру. Материалда пайдалы бактериялар, саңырауқұлақтар, антиденелер, пребиотиктер және басқа биологиялық белсенді компоненттер бар. Ең тиімді НМТ қайталанатын Clostridium difficile инфекциясында қолданылады, бұл Ванкомицин сияқты дәстүрлі еммен салыстырғанда жақсы нәтиже көрсетеді. Зерттеулер сонымен қатар ішектің қабыну ауруларын, семіздікті, метаболикалық синдромды және асқазан-ішек жолдарының функционалдық бұзылыстарын емдеудегі НМТ әлеуетін көрсетеді. Соңғы жылдары бұл әдіс кеңінен қабылданды және Clostridium difficile-де мүмкін болатын бірінші қатардағы терапия ретінде қарастырылды.*

Зерттеу мақсаты *– Миелодиспластикалық синдромы бар және ішек зақымдануы бар трансплантаттың иесіне қарсы реакциясы (ТИҚР) бар науқаста нәжіс микробиотасын трансплантациялаудың алғашқы сәтті клиникалық тәжірибесін ұсыну.*

Әдістері: *Миелодиспластикалық синдром үшін сүйек кемігін аллогенді трансплантациялаудан өткен 46 жастағы науқастың клиникалық жағдайы сипатталған. Трансплантациядан кейінгі ерте кезеңде науқаста асқазан-ішек жолдарының қатысуымен ТИҚР ауыр көріністері пайда болды: ауыр диарея, іштің ауыруы, салмақ жоғалту, дисбиоз белгілері және қоректік заттардың жетіспеушілігі. Стероидтермен тиімсіз терапиядан және демеуші күтімнен кейін мұқият таңдалған донорлық материалды пайдалана отырып, НМТ жүргізу туралы шешім қабылданды.*

Нәтижелері: *НМТ процедурасы клиникалық тұрғыдан сәтті өтті: бірнеше күн ішінде жалпы жағдайдың жақсаруы, диареяның ауырлығының төмендеуі, дене салмағының тұрақтануы және тәбеттің қалпына келуі байқалды. Ішектің шырышты қабығын эндоскопиялық және гистологиялық зерттеу қабыну өзгерістерінің төмендеуін растады. НМТ-ден кейін ешқандай жанама әсерлер, асқынулар немесе жүйелік инфекция белгілері тіркелген жоқ.*

Қорытынды: *Бұл жағдайда НМТ-ны сәтті қолдану ішектің қатысуымен, әсіресе аурудың стероидтерге төзімді түрлерінде трансплантаттың иесіне қарсы реакциясында қосымша емдік құрал ретінде әдістің әлеуетін көрсетеді.*

Түйінді сөздер: *Нәжіс микробиотаны трансплантациялау (НМТ), ішек микробиотасы, миелодиспластикалық синдром, трансплантаттың иесіне қарсы реакциясы (ТИҚР), дисбиоз.*

АННОТАЦИЯ

УСПЕШНЫЙ ОПЫТ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ ПАЦИЕНТУ С МИЕЛОДИСПЛАСТИЧЕСКИМ СИНДРОМОМ И РЕАКЦИЕЙ «ТРАНСПЛАНТАТ ПРОТИВ ХОЗЯИНА» С ПОРАЖЕНИЕМ КИШЕЧНИКА В СОЧЕТАНИИ С ЭНТЕРОКОЛИТОМ, ВЫЗВАННЫМ КЛОСТРИДИАЛЬНОЙ ИНФЕКЦИЕЙ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Трансплантация фекальной микробиоты (ТФМ) — это перенос кишечного содержимого от здорового донора пациенту для восстановления нормальной микрофлоры. Материал содержит полезные бактерии, грибки, антитела,*

пребиотики и другие биологически активные компоненты. Наиболее эффективно ТФМ применяется при рецидивирующей инфекции Clostridium difficile, показывая лучшие результаты по сравнению с традиционным лечением, например ванкомицином. Исследования также указывают на потенциал ТФМ в терапии воспалительных заболеваний кишечника, ожирения, метаболического синдрома и функциональных нарушений ЖКТ. В последние годы метод получил широкое признание и рассматривается как возможная терапия первой линии при Clostridium difficile.

***Цель исследования** – представить первый в Казахстане успешный клинический опыт трансплантации фекальной микробиоты у пациента с миелодиспластическим синдромом и реакцией «трансплантат против хозяина» с поражением кишечника и клостридиальной инфекцией.*

***Методы:** Описан клинический случай 43-летнего пациента, перенесшего гаплоидентичную трансплантацию костного мозга по поводу миелодиспластического синдрома. В раннем посттрансплантационном периоде у пациента развились тяжёлые проявления реакции «трансплантат против хозяина» с преимущественным поражением желудочно-кишечного тракта: выраженная диарея, боль в животе, потеря массы тела, признаки дисбиоза и нутритивной недостаточности. После неэффективной терапии стероидами и поддерживающими средствами было принято решение о проведении ТФМ с использованием тщательно отобранного донорского материала.*

***Результаты:** Проведенная процедура ТФМ оказалась клинически успешной: в течение нескольких дней отмечено улучшение общего состояния, снижение выраженности диареи, стабилизация массы тела, восстановление аппетита. Эндоскопическое и гистологическое исследование слизистой кишечника подтвердило снижение воспалительных изменений. Никаких побочных эффектов, осложнений или признаков системной инфекции после ТФМ не зафиксировано.*

***Заключение:** Успешное применение ТФМ в данном случае демонстрирует потенциал данного метода как дополнительного терапевтического инструмента при наличии реакции «трансплантат против хозяина» с поражением кишечника, особенно при стероид-резистентных формах заболевания.*

***Ключевые слова:** трансплантация фекальной микробиоты (ТФМ), кишечная микробиота, миелодиспластический синдром (МДС), реакция «трансплантат против хозяина» (РТПХ), дисбиоз.*

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DIAGNOSTIC CAPABILITIES OF ^{68}GA-FAPI PET/CT IN GASTRIC CANCER

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ABSTRACT

Relevance: *Gastric cancer remains a significant medical issue due to its high incidence and mortality rates. Hybrid imaging techniques, including positron emission tomography/computed tomography (PET/CT), play an important role in the diagnosis of malignant tumors, including gastric cancer. The development and clinical evaluation of radiopharmaceuticals used in oncology continues to advance.*

The study aimed to *evaluate the diagnostic capabilities of PET/CT using fibroblast activation protein inhibitor labeled with gallium-68 ([^{68}Ga]FAPI-PET/CT) in gastric cancer.*

Methods: *This review includes data from 8 clinical studies (both prospective and retrospective) comparing the diagnostic performance of [^{68}Ga]FAPI-PET/CT and fluorodeoxyglucose labeled with fluorine-18 ([^{18}F]FDG) in patients with histologically confirmed gastric cancer. The number of patients in the studies ranged from 13 to 112, totaling 379 patients. The parameters analyzed included maximum standardized uptake value (SUVmax), tumor-to-background ratio (TBR), and the sensi-tivity in detecting primary gastric tumors, as well as lymph node and peritoneal metastases.*

Results: *According to multiple clinical studies, [^{68}Ga]FAPI demonstrated higher SUVmax and TBR values compared to [^{18}F]FDG, especially in the visualization of diffuse, mucinous, and signetring cell histological subtypes of gastric cancer. This is associated with strong expression of FAP in the tumor stroma, enabling effective tracer accumulation in affected areas. Furthermore, [^{68}Ga]FAPI-PET/CT showed higher sensitivity in detecting primary gastric lesions (100% vs. 53%), lymph node metastases (79% vs. 54%), and peritoneal metastases (96% vs. 55%) compared to [^{18}F]FDG-PET/CT. In 11-67% of patients, the use of [^{68}Ga]FAPI-PET/CT led to a change in tumor staging and influenced the formulation of an individualized treatment plan.*

Conclusion: *[^{68}Ga]FAPI-PET/CT demonstrated greater diagnostic performance compared to [^{18}F]FDG-PET/CT in staging gastric malignancies, particularly in histological subtypes with low glycolytic activity. The method offers superior sensitivity and visualization of peritoneal, visceral, and lymphatic metastases, playing a crucial role in determining treatment strategies.*

Keywords: *gallium-68 labeled fibroblast activation protein inhibitor ([^{68}Ga]FAPI), gastric cancer (GC), positron emission tomography/computed tomography (PET/CT), cancer staging, fibroblast activation protein (FAP).*

Introduction: According to GLOBOCAN 2022, gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, ranking fifth in terms of the number of new cases and deaths among all malignant neoplasms (MNs). It is estimated that in 2022, 968,784 new cases and 660,175 deaths related to this pathology were recorded, indicating that gastric cancer is one of the most prevalent types of oncological diseases [1]. Gastric MNs have risk factors, most of which are immutable characteristics [2].

The diagnostics of gastrointestinal MNs is conducted using standard imaging methods, such as radiographic examination, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) [3]. Each method has its advantages and limitations, including in assessing the extent of the malignant process [4].

Modern approaches to the diagnostics and staging of GC require high sensitivity, specificity, and reproducibility [5]. An important aspect of the diagnostic process remains hybrid imaging methods, particularly positron emission tomography/computed tomography (PET/CT) with the radiopharmaceutical (RPh) 18-fluorodeoxyglucose ([^{18}F]FDG). However, the informativeness of this method is significantly reduced in cases of mucinous, poorly differentiated, and undifferentiated tumors [6]. One of the reasons for this is the low glucose metabolism in some histological subtypes of gastric tumors, which results in insufficient accumulation of [^{18}F]FDG for their detection [7]. Fibroblast activation protein (FAP), expressed in cancer-associated fibroblasts (CAF), plays a key role in remodeling the tumor microenvironment, invasion, and metastasis [8, 9]. FAP belongs to the family of dipeptidyl peptidases and has enzymatic activity involved in the remodeling of the extracellular matrix, contributing to the progression and invasion of epithelial tumors [10]. In 90% of all epithelial-origin tumors, increased FAP expression is observed [11]. Given that the tumor stroma can predominate in the structure of the neoplasm, targeted imaging of its components, such as activated fibroblasts, represents a more sensitive alternative compared to the visualization of tumor cells alone [12]. The RPh fibroblast ac-

tivation protein inhibitor labeled with gallium-68 ([^{68}Ga]FAPI), developed as a high-affinity ligand to FAP, demonstrates a high degree of accumulation in most MNs, including gastric MNs. It has high affinity to FAP, rapid clearance from the blood, and low nonspecific accumulation in normal tissues [13]. [^{68}Ga]FAPI has become widely used in oncological imaging following the demonstration of its high affinity to FAP and its potential for radiolabeling for PET diagnostics [14]. Experience with the use of [^{68}Ga]FAPI in patients with other solid tumors, including thyroid tumors, confirms its universality and high diagnostic effectiveness [15]. Studies have also shown widespread accumulation of FAPI in patients with various solid tumors, including gastrointestinal tumors [16]. [^{68}Ga]FAPI-PET/CT has demonstrated clinical significance in planning radiation therapy and delineating the radiation volume [17]. Aggregated data confirm the high safety of [^{68}Ga]FAPI and its high accuracy in visualizing gastrointestinal tumors [18]. It should also be noted that the accumulation of [^{68}Ga]FAPI is independent of the glycolytic activity of the tumor, making it particularly useful for signet-ring cell tumors of the stomach and other forms with low glucose metabolism [19]. Several studies have shown that [^{68}Ga]FAPI has advantages in detecting peritoneal metastases and metastatic lymph nodes, as well as in identifying early disease recurrence after treatment [20]. Peritoneal metastases are the most common form of spread in GC and are responsible for nearly half of the mortality cases, highlighting the need for accurate methods to detect them at early stages. Additionally, [^{68}Ga]FAPI has proven effective in diagnosing tumors with low glucose metabolism and in cases with negative [^{18}F]FDG-PET/CT results [21]. Thus, [^{68}Ga]FAPI is a versatile tool for imaging the tumor microenvironment and staging the tumor [22].

The study aimed to evaluate the diagnostic capabilities of PET/CT using fibroblast activation protein inhibitor labeled with gallium-68 ([^{68}Ga]FAPI-PET/CT) in gastric cancer.

Materials and Methods: This study includes the results of 8 prospective and retrospective clinical studies published between 2018 and 2024, focusing on the comparison of diagnostic efficacy between [^{68}Ga]FAPI-PET/CT and [^{18}F]FDG-PET/CT in patients with confirmed gastric cancer (GC). The search was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases using the following keywords: "68Ga-FAPI", "PET/CT", "gastric cancer", "fibroblast activation protein". Inclusion criteria for the publications were: histological confirmation of the diagnosis, performance of both [^{68}Ga]FAPI-PET/CT and [^{18}F]FDG-PET/CT, reporting of maximum standardized uptake value (SUVmax) and tumor-to-background ratio (TBR), indication of TNM stage, and data on the impact of the method on treatment strategies.

Standardized PET/CT protocols were used in all included studies: intravenous injection of RPh, a field of view from the head to the upper third of the thighs, and hybrid PET/CT imaging.

Effectiveness of imaging was assessed by comparing SUVmax and TBR between [^{68}Ga]FAPI and [^{18}F]FDG in primary lesions, lymph nodes, and metastatic sites.

Results: An analysis of the results from 8 prospective and retrospective clinical studies allowed for a comprehensive overview of the existing evidence. Table 1 presents the clinical and methodological parameters of studies on the use of [^{68}Ga]FAPI-PET/CT in gastric cancer.

Study Design. 5/8 sources included in the review describe prospective studies, which enhances the evidence strength of the presented results. 3/8 studies followed a retrospective design, which potentially increases the risk of systematic errors and biases related to data selection and the lack of control over variables. Sample size varied from 13 patients [19] to 112 patients [3].

Indications for [^{68}Ga]FAPI. The indications to perform [^{68}Ga]FAPI-PET/CT were staging, restaging, diagnostics of [^{18}F]FDG-PET/CT negative cases, visualization of specific histological subtypes, and peritoneal metastatic lesions. These indications highlight the expanding clinical use of [^{68}Ga]FAPI beyond standard diagnostics.

Patients (n). A total of 8 clinical studies with 379 patients were included. Larger samples (e.g., S. Zhang [3], Y. Sun [7]) allow for statistically significant conclusions, while smaller series focus on more specialized subtypes.

Activity. The RPh activity used in the studies ranged from 1.11 to 2.96 MBq/kg. In 2 out of 8 studies, the activity was between 1.11-1.85 MBq/kg, in 2 studies it was 1.85 MBq/kg, in 2 studies it ranged from 1.8 to 2.2 MBq/kg, and one study used [^{68}Ga]FAPI activity in the range of 2.0-2.5 MBq/kg and 1.85-2.96 MBq/kg. The standard activity dosage range is 1.8-3.7 MBq/kg.

Interval. This parameter indicates the period from the intravenous injection of the RPh to the PET/CT scan. In 7 out of 8 studies, this interval was 60 minutes, and in 1 out of 8 studies, the PET/CT scan was performed between 60 and 90 minutes after the RPh injection.

Stage Correction. The highest frequency of stage modification was noted in the study by A. Selçuk [18], 2025, which was 67%, potentially related to the selection of patients with [^{18}F]FDG-negative tumors. Similarly, a high percentage of stage progression was observed in the studies by J. Kuten [19], 2022 (38.5%), and Z. Shumao [20], 2022 (27.9%). The lowest frequency of stage correction, 5.8%, was observed in the study by Y. Sun [7], 2024, which can be attributed to the prevalence of signet-ring cell and mucinous subtypes of gastric MNs with high FAPI accumulation, but without significant revision of the TNM stage.

Treatment Adjustment. The performance of [^{68}Ga]FAPI-PET/CT also impacted treatment strategies. In 4 out of 8 studies where this parameter was specifically tracked, changes in therapy ranged from 12.9% [4] to 67% [18]. In the study by S. Zhang, the proportion of therapy adjust-

ments was 17.9%, confirmed by the decision of a multidisciplinary team [3].

Table 2 presents a comparative analysis of [^{68}Ga]FAPI and [^{18}F]FDG in the visualization of gastric cancer (GC) based on the data from 8 studies.

Table 2 provides a comparative analysis of the diagnostic characteristics of [^{68}Ga]FAPI and [^{18}F]FDG based on data from 8 clinical studies. All studies included patients with confirmed GC, including difficult-to-visualize histological types such as signet-ring cell carcinoma (SRCC), mucinous carcinoma (MAC), and diffuse adenocarcinoma types. In some studies, the TBR value was not provided. In such cases, the contrast between the tumor and background tissues was calculated using the formula

$$\mathrm{TBR} = \frac{\mathrm{SUVmax\ \ опухоли.}}{\mathrm{SUVmean\ \ фона}} \quad (1)$$

The average SUVmean value of the ascending aorta (SUVmean≈2.5) was used as the standard for background accumulation in evaluating the effectiveness of [^{68}Ga]FAPI-PET/CT. Given the repeatability of these values in several publications (e.g., [4, 6, 7]), the adopted value can be considered a reasonably acceptable benchmark for comparative analysis.

The comparative analysis of the studies presented in the table confirms a consistent advantage of [^{68}Ga]FAPI-PET/CT over [^{18}F]FDG in terms of SUVmax and TBR in patients with GC, including aggressive histological subtypes and cases with low glucose metabolism.

J. Kuten et al. demonstrated that the SUVmax for [^{68}Ga]FAPI was 16.6, while for [^{18}F]FDG it was 11.6. The median TBR value for [^{68}Ga]FAPI was 11.9, compared to 3.2 for [^{18}F]FDG. These data were accompanied by 100% detection of primary tumors using [^{68}Ga]FAPI, while [^{18}F]FDG showed only 50% sensitivity [17].

In the study by Y. Pang et al., the SUVmax for [^{68}Ga]FAPI was 12.7, while for [^{18}F]FDG it was 3.7. The TBR was also significantly higher for [^{68}Ga]FAPI, with [^{18}F]FDG showing values of 7.6 versus 2.2. All tumors (n=20) were visualized with [^{68}Ga]FAPI, while [^{18}F]FDG detected only 53%, emphasizing the limitations of [^{18}F]FDG in non-intestinal tumor types [8].

A. Selçuk et al. reported a primary tumor SUVmax of 14.8 for [^{68}Ga]FAPI and 6.8 for [^{18}F]FDG. For peritoneal metastases, the values were 6.9 and 3.3, respectively. The calculated TBR for [^{68}Ga]FAPI was 5.92, while for [^{18}F]FDG it was 2.72. [^{68}Ga]FAPI enabled stage modification in 30% of patients [18].

In the study by S. Zhang et al., the average SUVmax for primary tumors with [^{68}Ga]FAPI was 10.28 versus 3.20 for [^{18}F]FDG. For metastatic lesions, the values were also higher for [^{68}Ga]FAPI: in lymph nodes, 9.20 versus 3.15, and in distant metastases, 8.00 versus 4.20, respectively. Based on our calculations, the TBR for [^{68}Ga]FAPI was 4.11, while for [^{18}F]FDG it was 1.28. This allowed for stage modification in 7 out of 25 patients [20].

D. Jiang et al. presented the most detailed comparison of SUVmax based on tumor size and T-stage: Overall SUVmax: 7.4 ([^{68}Ga]FAPI) vs. 6.5 ([^{18}F]FDG); Tumors >4 cm: 11.0±4.5 ([^{68}Ga]FAPI) vs. 6.3±1.8 ([^{18}F]FDG); T2–T4: 9.7±4.4 ([^{68}Ga]FAPI) vs. 5.6±1.9 ([^{18}F]FDG); T1: 3.1±1.5 ([^{68}Ga]FAPI) vs. 2.7±0.9 ([^{18}F]FDG); TBR: 9.2±5.9 ([^{68}Ga]FAPI) vs. 5.9±4.2 ([^{18}F]FDG) [6].

Y. Miao et al. demonstrated the highest absolute SUVmax among all studies: 18.81 for [^{68}Ga]FAPI compared to 10.44 for [^{18}F]FDG, also confirming the superiority of [^{68}Ga]FAPI across all stages and histological subtypes. The TBR for [^{68}Ga]FAPI was 12.9 and 4.5 for [^{18}F]FDG, respectively [4]

Y. Sun et al. studied [^{68}Ga]FAPI in patients with mucinous and signet-ring cell carcinoma (MAC/SRCC), showing a primary tumor SUVmax of 9.3 for [^{68}Ga]FAPI compared to 3.1 for [^{18}F]FDG. For peritoneal metastases, the values were 6.9 and 3.3, respectively. The TBR calculation indicated that [^{68}Ga]FAPI (3.7) outperformed [^{18}F]FDG (1.2). In the study by Y. Sun et al., FAPI outperformed [^{18}F]FDG in sensitivity for peritoneal and intestinal metastases. For peritoneal metastases, SUVmax was: 5.66±1.97 for [^{68}Ga]FAPI versus 4.28±2.70 for [^{18}F]FDG, and TBR was: 4.22±1.47 for [^{68}Ga]FAPI versus 1.41±0.89 for [^{18}F]FDG. For tumor implantation into the intestinal wall, SUVmax for FAPI was 6.70±0.25, and for [^{18}F]FDG it was 7.58±1.66, but the TBR was still higher for [^{68}Ga]FAPI (5.63 vs. 2.20) [7].

S. Zhang et al. provided the following values for [^{68}Ga]FAPI: SUVmax=13.6, TBR=5.44. For [^{18}F]FDG in this study, SUVmax and TBR values were not provided [3].

Advantages. Table 2 reflects the qualitative parameters highlighted by the authors of the original studies, and the comparative analysis of these allows the assessment not only of numerical parameters such as SUVmax and TBR but also the practical significance of each method. In 5 out of 8 of the analyzed sources, a clear advantage of detecting metastatic lesions was identified. The remaining studies emphasize that [^{68}Ga]FAPI-PET/CT provides a clear visualization of primary gastric MNs, histological subtypes like MAC and SRCC, and lymph nodes.

Discussion: FAP is expressed in the tumor microenvironment, particularly in activated fibroblasts, making it a valuable target for stromal imaging [22, 23]. FAP expression in the microenvironment of gastrointestinal tumors opens new opportunities for targeted visualization of stromal components, particularly in clinical scenarios where the effectiveness of conventional imaging modalities, such as CT, MRI, and [^{18}F]FDG PET/CT, is limited due to cirrhotic changes or high background activity in normal tissues [24]. Despite its high specificity, it is known that FAPI can accumulate in areas of inflammation, trauma, and IgG4-related diseases, which must be taken into account when interpreting imaging results [25]. [^{68}Ga]FAPI PET/CT demonstrates superior contrast and faster clearance kinetics, making it more suitable for use in frail patients [26]. The

increased sensitivity of [^{68}Ga]FAPI in detecting peritoneal metastatic lesions is a critically important factor in surgical decision-making, particularly concerning the need for laparoscopy and the extent of surgical intervention [27]. FAP, expressed by activated fibroblasts in the tumor microenvironment, has been identified as a key factor in tumor progression and has emerged as a promising target for the development of next-generation RPhs [28].

In contrast to [^{18}F]FDG, which reflects glucose metabolism, [^{68}Ga]FAPI accumulates more uniformly within the tumor background and is effective in tumors with low glycolytic activity, such as mucinous adenocarcinoma and signet ring cell carcinoma. Consequently, it can detect lesions that are poorly visualized by [^{18}F]FDG PET/CT [29]. Due to the low metabolic activity of [^{18}F]FDG and potential physiological confounders, the method has certain limitations in imaging specific subtypes of gastrointestinal tumors, including MAC and SRCC [30].

In recent years, [^{68}Ga]FAPI PET/CT has demonstrated expanding clinical utility in the diagnosis and staging of GC [31]. Several studies emphasize its superiority over traditional imaging methods, including [^{18}F]FDG PET/CT and CT, particularly in identifying peritoneal metastases, regional lymphatic spread, and tumors with low glucose metabolism [32, 33]. The high reproducibility across different histological tumor types, consistent uptake parameters, and high selectivity of [^{68}Ga]FAPI for tumor stroma underscore its diagnostic value [34]. Systematic reviews and meta-analyses confirm the superiority of [^{68}Ga]FAPI not only in terms of imaging performance but also in clinical relevance, from more accurate staging to direct influence on treatment strategies [35]. Furthermore, the use of [^{68}Ga]FAPI is actively discussed in contemporary clinical guidelines, including national protocols in China, where it is considered a potential alternative to [^{18}F]FDG PET/CT [36]. Its integration into preoperative diagnostics remains a promising direction, including the detection of [^{18}F]FDG-negative metastatic lesions, helping to avoid unnecessary surgical procedures and improve therapy personalization. The two tables presented in this study summarize both methodological and clinical parameters as well as the comparative diagnostic advantages of [^{68}Ga]FAPI relative to conventional [^{18}F]FDG.

Aggregated data from eight studies demonstrated that [^{68}Ga]FAPI PET/CT was used for initial staging and evaluation of disease extent, including signet ring cell carcinoma, mucinous adenocarcinoma, and other diffuse forms of GC. These histological tumor types are traditionally characterized by low glucose metabolism, limiting the sensitivity of [^{18}F]FDG PET/CT. In this context, FAPI shows an advantage by accumulating in the tumor stroma regardless of the glycolytic activity of tumor cells. Notably, all studies employed standardized protocols (60-minute interval post-injection, scan coverage from head to upper/mid-thigh, PET/CT acquisition), ensuring data comparability. Particular attention is given to "Treatment Correction." In 7 out of 8 studies, the impact was quantified numerically (ranging from 12.9% to 67.0%), where FAPI PET/CT findings led to changes in treatment strategy, including the choice between surgical and pharmacological approaches. In the remaining cases, the impact was reflected in improved staging, detection of peritoneal metastases, or clarification of tumor resectability. These data indicate that [^{68}Ga]FAPI PET/CT functions not only as a diagnostic tool but also as a patient management aid.

The second analytical section focuses on the comparison between [^{68}Ga]FAPI and [^{18}F]FDG. In all included studies, [^{68}Ga]FAPI outperformed [^{18}F]FDG in terms of SUVmax and tumor-to-background ratio (TBR), primarily due to lower physiological background in abdominal organs when using [^{68}Ga]FAPI. This is especially significant for visualizing: SRCC and MAC, which often yield false-negative results on [^{18}F]FDG PET/CT; Peritoneal metastases, where FAPI imaging enabled detection of lesions not visible with conventional PET or CT; Metastatic and small-volume lesions, including lymph nodes and subserosal spread. To date, [^{18}F]FDG PET/CT remains the imaging standard in oncology. However, in GC – particularly undifferentiated and mucinous forms – its effectiveness is limited. In the review by X. Liu et al., [^{68}Ga]FAPI PET/CT demonstrated 100% sensitivity in detecting primary gastric tumors and 96% sensitivity for peritoneal metastases, significantly surpassing [^{18}F]FDG, which showed 53% and 55%, respectively [37].

[^{68}Ga]FAPI also outperformed [^{18}F]FDG in detecting lymphatic metastases, with sensitivities of 79% and 54%, respectively [6, 38, 39]. [^{68}Ga]FAPI exhibited rapid and selective accumulation in the tumor microenvironment with minimal background uptake, enabling high-contrast visualization of peritoneal metastatic lesions [40]. These findings underscore the advantages of FAPI for imaging tumors with low glucose metabolism, particularly metastatic lesions. Several studies consistently confirm that [^{68}Ga]FAPI PET/CT improves the detection of malignant peritoneal involvement, which is often difficult to diagnose using conventional imaging methods [41, 42]. Additionally, the low background activity associated with [^{68}Ga]FAPI-04 provides a clearer contrast between tumor and surrounding tissues compared to [^{18}F]FDG, enhancing lesion visualization [43].

In all studies, [^{68}Ga]FAPI demonstrated superiority in SUVmax and TBR compared to [^{18}F]FDG. This was especially evident in difficult-to-visualize forms of gastric MNs and in cases where [^{18}F]FDG yielded negative results [44].

Thus, [^{68}Ga]FAPI is a more sensitive imaging tool for diffuse, mucinous, and metastatic disease forms. [^{68}Ga]FAPI PET/CT for GC staging demonstrates high effectiveness in detecting peritoneal metastases and histologically challenging tumor types [45, 46]. [^{68}Ga]FAPI has proven to be an effective component of a comprehensive therapeutic approach, facilitating optimized preoperative planning and objective assessment of tumor resectability [47, 48].

Table 1 – Clinical and methodological parameters of studies on the use of [^{68}Ga]FAPI-PET/CT in gastric cancer patients

Study	Year	Study Design	Indications	Patients (n)	Potency (MBq/kg)	Interval (min.)	Staging Correction (%)	Treatment Correction (%)
Kuten J. [19]	2022	P	Staging/restaging	13	1.8-2.2	60	38.5	30.8
Pang Y. [8]	2021	R	Staging	20	1.8-2.2	60	21.0	21.0
Selcuk A. [18]	2025	P	[^{18}F]FDG-negative/ peritoneal metastases	23	2.0-2.5	60	67	67
Shumao Z. [20]	2022	R	Staging/restaging	25	1.85	60	27.9	27.9
Jiang D. [6]	2021	P	Staging/peritoneal metastases	38	1,11-1.85	60	10.5	n/a
Miao Y. [4]	2023	P	Staging	62	1.85-2.96	60-90	12.9	12.9
Sun Y. [7]	2024	P	Histological subtype	86	1.85	60	5.8	30.0
Shunyu Z. [3]	2025	R	Restaging	112	1.11-1.85	60	18.8	17.9

Table 2 – Comparative analysis of the effectiveness of [^{68}Ga]FAPI and [^{18}F]FDG in gastric cancer imaging

Study	Radiopharmaceutical	SUVmax ([^{68}Ga]FAPI/ [^{18}F]FDG)	TBR ([^{68}Ga]FAPI/ [^{18}F]FDG)	Advantages [^{68}Ga]FAPI
Kuten J. [19]	[^{68}Ga]FAPI [^{18}F]FDG	16,6 / 11,6	11.9 / 3.2	Detection of peritoneal metastatic foci, [^{18}F]FDG-negative cases
Pang Y. [8]	[^{68}Ga]FAPI [^{18}F]FDG	12,7 / 3,7	7,6 / 2.2	Better visualization of tumors and lymph nodes in [^{18}F]FDG-negative cases
Selcuk A. [18]	[^{68}Ga]FAPI [^{18}F]FDG	14,8 / 6,8	5.92 / 2.72	Detection of peritoneal metastases in [^{18}F]FDG-negative cases
ShumaoZ. [20]	[^{68}Ga]FAPI [^{18}F]FDG	10,28 / 3,20	4.11 / 1.28	Effective in [^{18}F]FDG-negative cases, early detection of peritoneal metastatic foci
Jiang D. [6]	[^{68}Ga]FAPI [^{18}F]FDG	7,4 / 6,5	9.2 / 5.9	Clear visualization of primary tumors, early detection of metastases
Miao Y. [4]	[^{68}Ga]FAPI [^{18}F]FDG	18,81 / 10,44	12.9 / 4.5	High contrast of lymph nodes, submucosal lesions
Sun Y. [7]	[^{68}Ga]FAPI [^{18}F]FDG	9,3 / 3,1	3.7 / 1.2	Clear visualization of SRCC and MAC histological sub-types
Shunyu Z. [3]	[^{68}Ga]FAPI [^{18}F]FDG	13,60 / н. д.	5.44 / n/a	Early detection of peritoneal metastatic foci

Note: MAC – Mucinous adenocarcinoma, SRCC – Signet ring cell carcinoma, SUVmax – Maximum standardized uptake value, TBR – Tumor-to-background ratio

Its inclusion in clinical guidelines and research protocols confirms its practical value and clinical promise [49, 50]. Further research should aim to explore the prognostic significance of FAPI, its role in therapy monitoring, and the potential therapeutic use of FAPI-based RPhs.

Conclusion: [^{68}Ga]FAPI-PET/CT is a promising imaging method for GC staging, demonstrating high accuracy in detecting peritoneal metastases and difficult-to-diagnose tumor forms. This makes [^{68}Ga]FAPI a valuable tool in a multimodal approach to treatment. The potential of this method is confirmed by its integration into clinical guidelines and research protocols.

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АҢДАТПА

^{68}GA-FAPI ПЭТ/КТ-НЫҢ АСҚАЗАННЫҢ ҚАТЕРЛІ ІСІГІНІҢ ДИАГНОСТИКАСЫНДАҒЫ МҮМКІНДІКТЕРІ

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Өзектілігі: *Асқазанның қатерлі (АҚ) ісігі аурушаңдық пен өлім-жітімділік деңгейінің жоғары болуына байланысты медицинаның өзекті мәселесі болып табылады. Гибридті визуализация, соның ішінде ПЭТ/КТ қатерлі ісіктердің, сонымен қатар АҚ ісігінің диагностикасында маңызды орын алады. Онкологияда қолданылатын радиофармацевтикалық препараттарды әзірлеу және зерттеу жұмыстары жалғасуда.*

Зерттеудің мақсаты *– асқазанның қатерлі ісігінде [^{68}Ga]FAPI-ПЭТ/КТ диагностикалық мүмкіндіктерін зерттеу.*

Әдістері: *Зерттеуге гистологиялық түрде расталған АҚ ісігі бар науқастарға жүргізілген [^{68}Ga]FAPI-ПЭТ/КТ және [^{18}F]FDG-ПЭТ/КТ диагностикалық көрсеткіштері салыстырмалы аспектіде зерттелген 8 клиникалық зерттеудің (проспективті және ретроспективті) нәтижелері енгізілді. Зерттеулердегі науқастар саны 13-тен 112-ге дейін, жалпы саны – 379 пациентті құрады. SUVmax, TBR мәндері, асқазанның алғашқы ісігін, лимфа түйіндеріндегі және ішпердедегі метастатикалық зақымдануды анықтаудағы сезімталдық талданды.*

Нәтижелері: *Бірқатар клиникалық зерттеулердің мәліметтері бойынша, [^{68}Ga]FAPI визуализация кезінде [^{18}F]FDG-мен салыстырғанда жоғары SUVmax және TBR көрсеткіштерін көрсетті, әсіресе диффузды, муцинозды және шырышты жасушалы АҚ жағдайларында. Бұл FAP ақуызының ісік стромасында жоғары экспрессиясымен түсіндіріледі, нәтижесінде препарат зақымданған ошақтарда тиімді жинақталады. Сонымен қатар, [^{68}Ga]FAPI-ПЭТ/КТ [^{18}F]FDG-ПЭТ/КТ-мен салыстырғанда асқазандағы алғашқы ісік ошақтарын (100% қарсы 53%), лимфа түйіндеріндегі метастаздарды (79% қарсы 54%) және ішперделік метастаздарды (96% қарсы 55%) визуализациялауда жоғары сезімталдық көрсетті. [^{68}Ga]FAPI-ПЭТ/КТ зерттеуінен кейін науқастардың 11-67%-ында ісік процесінің сатысы нақтыланып, ем жоспарын даралау мүмкін болды.*

Қорытынды: *[^{68}Ga]FAPI-ПЭТ/КТ әдісі [^{18}F]FDG-ПЭТ/КТ-мен салыстырғанда АҚ сатыландыруда анағұрлым ақпараттылығы жоғары болды, әсіресе гликолитикалық метаболизмі төмен ісік гистотиптері жағдайында. Бұл әдіс ішперделік, висцералдық және лимфогендік метастаздарды жоғары сезімталдықпен анықтауға мүмкіндік береді және емдеу тактикасын анықтауда маңызды рөл атқарады.*

Түйінді сөздер: *фибробласттардың белсендену ақуызының тежегіші, галлий-68-мен таңбаланған ([^{68}Ga]FAPI), асқазан обыры (АҚ), позитрон-эмиссиялық томография/компьютерлік томография (ПЭТ/КТ), қатерлі ісік сатысы, фибробласттардың белсендену ақуызы (FAP).*

АННОТАЦИЯ

ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ 68GA-FAPI ПЭТ/КТ ПРИ РАКЕ ЖЕЛУДКА

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Актуальность: *Рак желудка (РЖ) является актуальной проблемой медицины, в связи с высокими показателями заболеваемости и смертности. Гибридная визуализация, в том числе позитронно-эмиссионная томография/компьютерная томография (ПЭТ/КТ), имеет важное значение в диагностике злокачественных опухолей, включая РЖ. Разработка и изучение возможностей радиофармпрепаратов, применяемых в онкологии, продолжаются.*

Цель исследования *– изучить диагностические возможности ПЭТ-КТ с применением ингибитора белка активации фибробластов, меченного галлием-68 ([68Ga]FAPI-ПЭТ/КТ) при раке желудка.*

Методы: *Проведено сравнение результатов 8 клинических проспективных и ретроспективных исследований, в которых приведены диагностические показатели ПЭТ/КТ с применением ингибитора белка активации фибробластов, меченного галлием-68 ([68Ga]FAPI-ПЭТ/КТ) и фтордезоксиглюкозы, меченной фтором-18 ([18F]FDG-ПЭТ/КТ) при гистологически верифицированном РЖ. Количество пациентов в исследованиях было от 13 до 112 пациентов, общее количество составило – 379. Проанализированы значения максимального стандартизованного накопления (SUVmax), отношения опухоли к фону (TBR),*

чувствительность обнаружении первичного очага в желудке, а также метастатических изменений в лимфатических узлах и брюшине.

Результаты: *Согласно данным проанализированных клинических исследований, [68Ga]FAPI продемонстрировал более высокие значения SUVmax и TBR по сравнению с [18F]FDG, особенно при визуализации диффузных, муцинозных и перстневидноклеточных форм РЖ. Это связано с выраженной экспрессией FAP в опухолевом строме, что обеспечивает эффективное накопление препарата в поражённых участках. Кроме того, [68Ga]FAPI-ПЭТ/КТ характеризуется более высокой чувствительностью при визуализации первичных очагов РЖ (100% против 53% для [18F]FDG-ПЭТ/КТ), метастатического поражения лимфатических узлов (79% против 54%), перитонеальных метастатических очагов (96% против 55%). У 11-67% пациентов проведение [68Ga]FAPI-ПЭТ/КТ позволило уточнить стадию опухолевого процесса и повлияло на формирование индивидуального плана лечения.*

Заключение: *Применение [68Ga]FAPI-ПЭТ/КТ показало более высокую информативность по сравнению с [18F]FDG-ПЭТ/КТ при стадировании злокачественных опухолей желудка, особенно при гистологических подтипах с низким гликолитическим метаболизмом. [68Ga]FAPI-ПЭТ/КТ обеспечивает более высокую чувствительность и более качественную визуализацию перитонеальных, висцеральных и лимфогенных метастатических очагов, что играет важную роль в определении тактики лечения.*

Ключевые слова: *ингибитор белка активации фибробластов, меченный галлием-68 ([68Ga]FAPI), рак желудка (РЖ), позитронно-эмиссионная томография/компьютерная томография (ПЭТ/КТ), стадирование рака, белок активации фибробластов (FAP).*

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THE ROLE OF THE MOLECULAR-BIOLOGICAL MARKER *CDKN2A* IN EARLY DETECTION OF COLORECTAL CANCER

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ABSTRACT

Relevance: *Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide, largely due to late diagnosis. In recent years, particular importance has been given to the search for accessible and sensitive molecular markers for the early detection of precancerous changes, especially in resource-limited countries, including Uzbekistan, where national screening programs are absent and access to colonoscopy remains limited. One of the most extensively studied markers is the hypermethylation of the tumor suppressor gene CDKN2A, which plays a crucial role in cell cycle regulation.*

The study aimed to *investigate the frequency of CDKN2A promoter hypermethylation in patients with colonic and rectal polyps and polyposis, and its association with morphological features of dysplasia.*

Methods: *The study included 31 patients with precancerous intestinal lesions. Mucosal biopsies and blood plasma samples were analyzed using methylation-specific PCR (MSP-PCR).*

Results: *CDKN2A hypermethylation was detected in 17 patients (54.8%). The methylation frequency was 65% in patients with polyps and 36.4% in those with polyposis (p=0.043). A direct association with morphological changes was established: patients with hypermethylation more frequently exhibited moderate dysplasia (70.6%), whereas in marker-negative cases, mild dysplasia or its absence predominated.*

Conclusion: *The findings confirm that CDKN2A hypermethylation is an early marker of CRC pathogenesis, closely associated with the progression of precancerous lesions. The MSP-PCR method demonstrated high sensitivity and accessibility, making it a promising tool for implementation in the regional laboratories of Uzbekistan. CDKN2A may serve as a risk stratification criterion, a component of molecular screening, and a basis for personalized surveillance of patients with precancerous intestinal changes.*

Keywords: *colorectal cancer (CRC), polyps, CDKN2A, hypermethylation, epigenetic biomarkers, MSP-PCR, molecular screening.*

Introduction: Colorectal cancer (CRC) is one of the most significant oncological challenges of our time, both clinically and epidemiologically. According to the global statistics GLOBOCAN 2022, CRC ranks third in incidence and second in mortality among all malignancies worldwide: in 2022, 1.93 million new cases and 935,000 deaths were recorded [1]. Although in high-income countries mortality has tended to decline in recent years thanks to screening programs and early treatment, in middle- and low-income countries, including Uzbekistan, the figures remain alarming. In particular, in the Republic of Uzbekistan in 2022, 2,125 new CRC cases were registered, and more than 50% of patients were first diagnosed at stages III-IV [2].

The principal cause of high CRC mortality is late diagnosis, driven by the absence of a national screening program, insufficient public awareness, limited access to colonoscopy, and deficiencies in the routing of patients within the primary care network. Therefore, the search for new, more sensitive, accessible, and reproducible markers of early diagnosis becomes especially urgent [3]. One of the priority directions in this regard is the introduction of molecular-genetic and epigenetic methods capable of detecting tumor transformation at a preclinical stage, well before morphological changes appear [4].

Despite clear advances in understanding the molecular bases of carcinogenesis, CRC continues to develop inconspicuously over a long period, often beginning with subtle precancerous changes – such as solitary adenomatous polyps or diffuse polyposis. These conditions may remain asymptomatic for years until key molecular alterations accumulate, triggering invasion and metastasis [5]. Modern colonoscopy with histological verification remains the diagnostic gold standard; however, it has several limitations – its invasiveness, high cost, shortages of personnel and equipment in primary health care, and limited coverage of target populations [6].

These circumstances amplify interest in finding alternative or adjunctive diagnostic methods that are highly sensitive and specific and applicable in outpatient settings. Epigenetic biomarkers, such as promoter methylation of tumor suppressors, exhibit all of these characteristics and are being actively adopted in clinical oncology in leading countries worldwide [7].

Hypermethylation of CDKN2A is among the most studied and reproducible alterations involved in early tumor transformation. Beyond the $p16^{INK4a}$ and $p14^{ARF}$ roles in critical antiproliferative mechanisms, studies have shown that methylation of their promoter regions can be detect-

ed long before clinical and histological signs of malignancy appear [8]. Moreover, these changes may be detectable not only in tumor tissues but also in circulating DNA, opening the possibility of so-called "liquid biopsy" [9].

In this context, in recent years there has been growing interest in incorporating molecular diagnostic methods, including CDKN2A methylation assessment, into standard protocols for early CRC detection. This is especially relevant for countries such as Uzbekistan, where both population-level screening and high-risk group screening require adapted, low-cost, and reproducible solutions. Given the lack of overt clinical symptoms in most patients and the limited availability of invasive diagnostic methods, plasma DNA-based molecular tests may become a vital component of a regional strategy against CRC [7].

The *CDKN2A* (cyclin-dependent kinase inhibitor 2A) gene, located at 9p21.3, is one of the most studied tumor suppressors in oncology [8, 10]. It encodes two independent proteins: $p16^{INK4a,}$ which inhibits *CDK4/6* and thereby controls the G1 phase of the cell cycle, and $p14^{ARF}$, which stabilizes p53 by inhibiting MDM2. Disruption of the expression of these proteins leads to deregulation of proliferation, suppression of apoptosis, and activation of the carcinogenic process. Promoter hypermethylation is a key mechanism of CDKN2A inactivation, making this gene particularly interesting for molecular diagnostics in oncology, including CRC.

Among the earliest foundational studies of *CDKN2A* hypermethylation were the papers by M. Toyota et al. (1999), which demonstrated CDKN2A hypermethylation in intestinal adenomatous polyps, long before the development of an invasive carcinoma. This allowed methylation to be considered an early event in the adenoma-carcinoma cascade [11]. These conclusions were confirmed in subsequent large meta-analyses, including those by M. Esteller et al. (2001), which detected p16 hypermethylation in more than 40% of patients with early-stage CRC [12].

The methods used to study *CDKN2A* methylation are varied. In addition to classical methylation-specific PCR (MSP-PCR), bisulfite sequencing, quantitative methylation-specific PCR, and, in recent years, DNA methylation arrays (Illumina 450K and EPIC) and methylated DNA immunoprecipitation sequencing (MeDIP-seq) are widely used [13].

In addition to tumor tissue and plasma, *CDKN2A* is being actively studied in stool samples, which is particularly relevant for non-invasive CRC screening. Studies conducted in China, South Korea, and Finland have shown that CDKN2A methylation in fecal DNA is highly sensitive compared with conventional immunochemical fecal occult blood tests [14].

Thus, *CDKN2A* hypermethylation is not merely a biochemical phenomenon but an important component of the molecular profile of CRC. Its measurement allows identification of patients in risk zones, prediction of disease course, assessment of therapy sensitivity, and, most importantly, enables early, non-invasive diagnostics of precancerous changes. Considering the simplicity and accessibility of the methodology, as well as its high reproducibility, the inclusion of *CDKN2A* methylation analysis in regional screening and diagnostic strategies – especially in resource-limited settings – appears justified and relevant.

In view of the foregoing, the authors sought in this study to evaluate the diagnostic value of this marker for early detection of tumor transformation, its association with morphological signs of dysplasia, and its potential for inclusion in national approaches to molecular screening for CRC in Uzbekistan.

The study aimed to investigate the frequency of *CDKN2A* promoter hypermethylation in patients with colonic and rectal polyps and polyposis, and its association with morphological features of dysplasia.

Materials and Methods: The study was conducted as part of an initiative to develop molecular methods for early diagnosis of colorectal cancer (CRC) in the Republic of Uzbekistan. The work was performed at the Department of Coloproctology and the Molecular Diagnostics Laboratory of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology (RSSPMCOR, Tashkent, Uzbekistan), and in cooperation with the High Technology Center of the Academy of Sciences of the Republic of Uzbekistan. The study protocol was approved by the local ethics committee, and all patients provided written informed consent.

Study design and sample selection. The study included 31 patients (n=31) with a confirmed diagnosis of polyps or polyposis of the colon and/or rectum, without signs of invasive cancer at the time of inclusion. Inclusion criteria: (1) age from 18 to 75 years; (2) presence of endoscopically confirmed intestinal neoplasms (single or multiple polyps); (3) no history of malignancies; (4) written consent to participate. Exclusion criteria: inflammatory bowel disease, prior radiotherapy or chemotherapy, and severe somatic comorbidities.

Clinical characteristics. The mean age was 49.2±3.3 years. The sample included 18 men (58%) and 13 women (42%). Among the patients, 20 had a single or multiple polyp(s) (64.5%), while 11 had polyposis (35.5%). All patients underwent colonoscopy with biopsy.

Collection and transport of biomaterials. Two types of biomaterials were used for molecular analysis: (1) intestinal mucosa biopsy tissue samples (weighing at least 50 mg), obtained endoscopically; and (2) venous blood (5 ml) collected into EDTA tubes. Tissue samples were placed into sterile tubes containing isotonic NaCl solution and transported at +4°C. Blood was centrifuged (1,600 g, 10 minutes), plasma was separated and re-centrifuged (16,000 g, 10 minutes) to remove cells.

DNA extraction. DNA from tissue and plasma was extracted using the QIAamp DNA Mini Kit (QIAGEN, Germany) according to standard protocol. The concentration and purity of DNA were assessed spectrophotometrically using a Nanodrop 2000 (Thermo Fisher Scientific, Massachusetts, USA) at 260/280 nm.

Bisulfite modification and MSP-PCR. The extracted DNA was subjected to bisulfite conversion with the EpiTect Bisulfite Kit (QIAGEN), which enables differentiation between methylated and unmethylated cytosines. Methylation-specific PCR (MSP-PCR) was used to detect methylation in the CDKN2A promoter region. Two pairs of primers were used: one for amplifying the methylated sequence and the other for the unmethylated sequence. Amplification conditions: 95 °C for 5 min, followed by 40 cycles (95 °C for 30 sec, 58 °C for 30 sec, 72 °C for 30 sec), with a final extension of 72 °C for 7 min. The amplicons were analyzed by electrophoresis in 2% agarose gel stained with ethidium bromide and visualized under UV light. The results were documented and stored digitally.

Histological verification. All biopsy samples underwent standard morphological processing and hematoxylin-eosin staining. Assessment of dysplasia grade (none, mild, moderate, severe) was performed by two independent pathomorphologists according to the WHO (2019) classification [15].

Statistical analysis. Data processing was conducted using SPSS v. 26. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Correlation analysis between methylation status and clinico-morphological features was performed using the φ (phi) coefficient.

Results: Hypermethylation of the *CDKN2A* promoter region was observed in 17 of 31 patients (54.8% of the sample). Significant differences in methylation frequency were observed when stratified by morphological lesion type: in patients with polyps, methylation was detected in 13 cases (65.0%), while in polyposis it was found in only 4 patients (36.4%). Statistical analysis showed a significant difference between the groups ($\chi^2 = 4.09$; $p = 0.043$), suggesting differences in the molecular pathogenesis of localized versus diffuse forms of pre-neoplastic intestinal processes (Table 1).

Table 1 – Frequency of *CDKN2A* promoter region hypermethylation

Type of lesion	Number of patients	*CDKN2A (+)*	Frequency (%)
Polyps	20	13	65,0
Polyposis	11	4	36,4
Total	31	17	54,8

Histological assessment of dysplasia severity showed moderate dysplasia in 10 patients (32.3%), mild in 12 (38.7%), and no dysplasia in 9 cases (29%). It was established that, among patients with positive CDKN2A status, moderate dysplasia predominated – 12 of 17 cases (70.6%) – when methylation data were compared with morphological findings. In contrast, in patients without methylation, mild dysplasia or its absence was more common (Table 2). Thus, a direct correlation was found between the extent of epigenetic changes and the degree of proliferative epithelial alteration, suggesting molecular-level progression toward morphologically overt cancer.

Table 2 – Histological assessment of dysplasia severity in patients with positive and negative *CDKN2A* status

Level of dysplasia	*CDKN2A (+)*	*CDKN2A (–)*
Moderate	12	1
Mild	4	8
Absent	1	5

The mean age of patients with hypermethylation was 50.6 ± 2.8 years, whereas among patients without methylation it was slightly lower – 47.3 ± 3.5 years. Although a statistically significant difference between these indicators was not observed ($p = 0.18$), there is a trend toward increasing methylation frequency with age, consistent with the literature.

Thus, the results of the present study demonstrated a high frequency of *CDKN2A* gene hypermethylation in patients with intestinal polyps and polyposis, with the most pronounced epigenetic changes observed in polyps accompanied by moderate dysplasia. These findings support the potential use of *CDKN2A* as an early molecular biomarker of malignancy, particularly in high-risk populations. The presence of a significant association between methylation and morphological features of proliferative activity allows *CDKN2A* to be considered a risk stratification criterion and a basis for enhanced clinical surveillance.

Discussion: In the present study, it was established that *CDKN2A* gene hypermethylation is a frequent molecular event in patients with precancerous lesions of the colon and rectum. Its frequency was 54.8%, consistent with international studies reporting rates of 40% to 70% among patients with adenomatous polyps. These data confirm that *CDKN2A* is involved in the earliest stages of colorectal carcinogenesis. Of particular importance is the finding that hypermethylation frequency was significantly higher in patients with localized polyps (65%) than in those with polyposis (36.4%). This difference may be related to the distinct nature of the pathologies: in sporadic polyps, acquired epigenetic alterations play a leading role, while in polyposis (including hereditary forms), mutational mechanisms involving genes such as *APC*, *MUTYH*, *SMAD4*, and others often predominate. The observed pattern may indicate that *CDKN2A* hypermethylation is a typical marker of

the sporadic pathway of tumor transformation, rather than the hereditary one.

An important clinicopathological conclusion concerns the association between *CDKN2A* hypermethylation and the severity of dysplasia. Among patients with hypermethylation, moderate dysplasia was identified in 70.6% of cases – significantly more frequent than in the unmethylated group. This may indicate that *CDKN2A* gene hypermethylation precedes and accompanies dysplasia progression. Thus, methylation may be considered not only a marker of a precancerous process, but also an indicator of its molecular aggressiveness.

The obtained results are also consistent with the epigenetic model of carcinogenesis, which posits that methylation of tumor suppressor genes, including *CDKN2A*, represents the first "epigenetic hit" in the multistep process of malignant transformation. In their classic 1999 study on adenomatous polyps, M. Toyota et al. first demonstrated that *CDKN2A* methylation can be detected long before the onset of invasion [11].

Our data confirm that *CDKN2A* hypermethylation can be used not only for diagnostics, but also for risk stratification. For example, a patient with moderate dysplasia and *CDKN2A* methylation may require more frequent monitoring than a patient with the same morphological diagnosis but without methylation. This aligns with the current principles of personalized medicine and biomarker-based surveillance.

From a technical standpoint, the MSP-PCR method used in our study demonstrated high sensitivity and reproducibility, making it especially attractive for resource-limited countries. Its application is feasible not only in large reference centers but also in regional laboratories, provided that basic molecular biology infrastructure is available.

It is also important to highlight CDKN2A's potential as a component of multigene panels for early CRC detection. Our results support the inclusion of *CDKN2A* in such panels as part of local adaptation and national screening strategy development.

Nonetheless, the study has limitations: a small sample size, lack of a control group with diagnosed CRC, and absence of case follow-up, which would allow assessment of the prognostic value of hypermethylation. Future studies should include expanded cohorts, evaluation of the sensitivity and specificity of *CDKN2A* methylation in cfDNA, and monitoring of clinical outcomes.

Conclusion:

CDKN2A gene hypermethylation is a common epigenetic event in patients with precancerous lesions of the colon and rectum: it was detected in 54.8% of the examined individuals, confirming its involvement in the early stages of colorectal carcinogenesis.

A significantly higher methylation frequency in patients with polyps (65%) than in those with polyposis (36.4%) suggests differences in epigenetic alterations between sporadic and diffuse precancerous intestinal processes.

CDKN2A hypermethylation is reliably associated with moderate dysplasia, highlighting its significance as a marker of early malignant transformation and the potential progression of benign neoplasms to cancer.

The MSP-PCR method is accessible, sensitive, and technologically reproducible, making it a promising tool for molecular diagnostics, especially in resource-limited settings. It can be implemented in the practice of regional and national laboratories.

CDKN2A is a potential clinically significant biomarker for risk stratification in patients with precancerous intestinal changes to decide on follow-up strategies and the need for intervention.

Further research should include a control group of patients with confirmed CRC, expand the sample size, and ensure case follow-up of clinical outcomes. Particular attention should be paid to the analysis of circulating DNA (cfDNA) as a non-invasive diagnostic modality.

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АҢДАТПА

CDKN2A МОЛЕКУЛАЛЫҚ-БИОЛОГИЯЛЫҚ МАРКЕРІНІҢ ТОҚ ІШЕК ОБЫРЫН ЕРТЕ ДИАГНОСТИКАЛАУДАҒЫ РӨЛІ

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Өзектілігі: *Колоректалды обыр (КРО) әлем бойынша қатерлі ісіктерден болатын өлім-жітімнің жетекші себептерінің бірі болып қала береді, бұл көбіне кеш диагностикалауға байланысты. Соңғы жылдары алдын ала ісік алдындағы өзгерістерді ерте анықтауға арналған қолжетімді әрі сезімтал молекулалық маркерлерді іздеу ерекше өзектілікке ие болды. Бұл, әсіресе ұлттық скринингтік бағдарламалары жоқ және колоноскопияның қолжетімділігі төмен мемлекеттер үшін маңызды, соның ішінде Өзбекстанда. Ең көп зерттелген маркерлердің бірі – жасуша циклін реттеуде негізгі рөл атқаратын ісік супрессоры CDKN2A генінің гиперметилденуі.*

Зерттеудің мақсаты *– тоқ және тік ішектің полиптері мен полипозы бар науқастарда CDKN2A промотор аймағының гиперметилдену жиілігін және оның дисплазияның морфологиялық белгілерімен байланысын зерттеу.*

Әдістері: *Зерттеуге ішектің ісік алды түзілімдері бар 31 науқас енгізілді. Шырышты қабық биоптаттары мен қан плазмасы метилге-спецификалық ПТР әдісімен талданды.*

Нәтижелері: *CDKN2A гиперметилденуі 17 науқаста (54,8%) анықталды. Полиптері бар науқастарда метилдену жиілігі 65%, ал полипозы бар науқастарда – 36,4% құрады (p=0,043). Морфологиялық өзгерістермен тікелей байланыс орнатылды: гиперметилденуі бар науқастарда орташа дисплазия жиі байқалды (70,6%), ал маркер теріс науқастарда жеңіл дисплазия немесе оның болмауы басым болды.*

Қорытынды: *Алынған деректер CDKN2A гиперметилденуі КРО патогенезіндегі ерте маркер болып табылатынын және ісік алды процестің үдеуімен тығыз байланысты екенін растайды. MSP-ПТР әдісі жоғары сезімталдық пен қолжетімділікті көрсетті, бұл оны Өзбекстанның өңірлік зертханаларына енгізу үшін перспективалы етеді. CDKN2A тәуекелді стратификациялау критерийі, молекулалық скринингтің компоненті және ішектің ісік алды өзгерістері бар науқастарды жекелендірілген бақылаудың негізі ретінде қолданылуы мүмкін.*

Түйінді сөздер: *колоректалды обыр (КРО), полиптер, CDKN2A, гиперметилдену, эпигенетикалық биомаркерлер, MSP-ПТР, молекулалық скрининг.*

АННОТАЦИЯ

РОЛЬ МОЛЕКУЛЯРНО-БИОЛОГИЧЕСКОГО МАРКЕРА *CDKN2A* В РАННЕЙ ДИАГНОСТИКЕ РАКА ТОЛСТОЙ КИШКИ

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Актуальность: *Колоректальный рак (КРР) остаётся одной из ведущих причин смертности от злокачественных новообразований во всём мире, что во многом обусловлено поздней диагностикой. Особую актуальность в последние годы приобретает поиск доступных и чувствительных молекулярных маркеров раннего выявления предопухолевых изменений, в том числе в странах с ограниченными ресурсами, включая Узбекистан, где отсутствуют национальные скрининговые*

программы, а доступность колоноскопии остаётся низкой. Одним из наиболее изученных является гиперметилирование гена-супрессора опухолей CDKN2A, играющего ключевую роль в регуляции клеточного цикла.

***Цель исследования** – изучение частоты гиперметилирования промоторной области CDKN2A у пациентов с полипами и полипозом толстой и прямой кишки, а также его ассоциации с морфологическими признаками дисплазии.*

***Методы:** В исследование включён 31 пациент с предопухолевыми образованиями кишечника. Биоптаты слизистой и плазма крови были проанализированы методом метил-специфической ПЦР.*

***Результаты:** Гиперметилирование CDKN2A выявлено у 17 пациентов (54,8%). При полипах частота метилирования составила 65%, при полипозе – 36,4% (p=0,043). Установлена прямая связь с морфологическими изменениями: у пациентов с гиперметилированием чаще наблюдалась умеренная дисплазия (70,6%), тогда как при отрицательном статусе по маркеру преобладали лёгкая дисплазия или её отсутствие.*

***Заключение:** Полученные данные подтверждают, что гиперметилирование CDKN2A является ранним маркером в патогенезе КРР, тесно связанным с прогрессией предопухолевого процесса. Метод MSP-PCR показал высокую чувствительность и доступность, что делает его перспективным для внедрения в региональные лаборатории Узбекистана. CDKN2A может быть использован как критерий стратификации риска, компонент молекулярного скрининга и основа для персонализированного наблюдения за пациентами с предопухолевыми изменениями кишечника.*

***Ключевые слова:** колоректальный рак (КРР), полипы, CDKN2A, гиперметилирование, эпигенетические биомаркеры, MSP-PCR, молекулярный скрининг.*

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EFFICIENCY OF TOMOTHERAPY IN THE TREATMENT OF LUNG CANCER IN MALES WITH CONCOMITANT CARDIOVASCULAR PATHOLOGY (EXPERIENCE OF THE "UMIT" INTERNATIONAL ONCOLOGY CENTER OF TOMOTHERAPY)

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ABSTRACT

Relevance: *Non-small cell lung cancer (NSCLC) is frequently diagnosed in men with associated myocardial pathologies. Radiation therapy is one of the treatment methods for NSCLC; however, in Kazakhstan, there are virtually no studies on the efficacy and safety of tomotherapy in cancer patients with cardiac pathologies.*

The study aimed to *evaluate the clinical results of mono-tomotherapy in patients with NSCLC and concomitant cardiac pathologies at the International Oncology Center for Tomotherapy "UMIT" (Astana, Kazakhstan).*

Methods: *The study included 201 men with NSCLC who underwent spiral mono-tomotherapy at UMIT between 2020 and 2024. Patients were divided into Group 1 (n=139) – patients without cardiac pathologies- and Group 2 (n=62) – patients with severe associated cardiac pathologies. The average course duration was 32 days, the average treatment duration was 15 minutes, OD, 5 days a week. Treatment efficacy was assessed 8-12 weeks after completion of the course using PET-CT and CT data.*

Results: *Complete regression was more common in patients in Group 1, while disease progression was more common in patients in Group 2. Partial responses were more common in Group 1, and stabilization of the oncological process was more common in Group 2. In Group 2, the proportion of patients with positive dynamics was 49%; after accounting for the identified stabilization of the process, it was 84%. In Group 1, the one-year overall survival rate was 84%, and 74% for stages III and IV, respectively, with a median progression-free survival of 10.3 months. The two-year survival rate for stage III disease was 65%. In Group 2, the one-year overall survival rate was 76% and 63% for stages III and IV, respectively, with a median progression-free survival of 8.1 months and a two-year survival rate of 54% for stage III. No device malfunctions were observed in Group 2. Two patients undergoing coronary artery bypass grafting experienced decompensated heart failure requiring temporary hospitalization.*

Conclusion: *Tomotherapy demonstrates high clinical efficacy in the treatment of NSCLC with severe comorbid cardiac disease, although overall survival and treatment efficacy were lower than in patients without cardiac disease. Our experience confirms the feasibility of a relatively safe treatment in such patients when a personalized approach, strict dosimetric control, and multidisciplinary monitoring are employed.*

Keywords: *lung cancer, tomotherapy, cardiopathology, pacemaker, hypofractionation, high-precision radiation therapy.*

Introduction: Malignant neoplasms of the lung remain one of the leading causes of cancer death worldwide. According to the Global Cancer Observatory international initiative, in 2022, lung cancer was the most common cancer diagnosed [1]. According to US cancer registries for 2020-2021, it ranked second (11% on average in men) in the number of diagnosed cases and first (20% in men) in estimated cancer deaths [2]. Globally, in 2022, the incidence of lung cancer reached 15.3% among other cancers (including unidentified ones), which amounted to more than 1,570,000 new cases per year. Moreover, the share of lung cancer in total cancer mortality, regardless of gender, was 22.7% or more than 1,233,000 deaths [1]. Lung cancer is usually diagnosed more often in men than in women, and the first detection in a significant number of cases occurs at late stages (III-IV), limiting the possibilities of radical treatment [1, 3-6].

Lung cancer occupies a leading position in the structure of oncological morbidity in the Republic of Kazakhstan. In 2010-2019, 36,916 cases of lung cancer were detected in the Republic of Kazakhstan, of which 80.5% were in men [4]. In a later study, covering the period from 2014 to 2022, the proportion of men in the total number of deaths from lung and respiratory tract cancer was more than 75% [5]. When using low-dose computed tomography, stage II and III lung cancer is detected in men on average 2 times more often than in women [6]. Despite a trend towards a slight decrease in the proportion of lung cancer (including trachea and bronchial cancer) in the total pool of oncological diseases in Kazakhstan from 2014 to 2022, it still constitutes about 16% of all types of cancer [5]. Moreover, according to recent national studies, the detection rate of asymptomatic patients with previously undiagnosed can-

cer may reach 2% among the population of regions with high background radiation levels, with more than half of them being diagnosed with lung cancer at stage III [6]. Similarly, regions with high levels of heavy metals (lead, cobalt, copper) also show a higher incidence of lung cancer [7]. As a result, lung cancer, along with other common cancers, makes a significant contribution to the total number of lost person-years, which negatively impacts the economy and social spectrum of the population of Kazakhstan [8]. This determines the relevance of assessing the effectiveness of new lung cancer treatments, including in men, as a significantly more vulnerable category of patients.

For patients with non-small cell lung cancer (NSCLC), when surgical intervention is not possible, conservative treatment, including chemotherapy, immunotherapy, and radiation therapy, becomes the priority. One of the modern approaches to radiation therapy is spiral tomotherapy with intensity-modulated tumor irradiation modes (Intensity-Modulated). Radiation Therapy (IMRT) with daily imaging during radiotherapy (Image-Guided Radiation Therapy (IGRT), which provides increased precision in planning and conducting sessions [9, 10]. As a result, it becomes possible to reduce the dose load on healthy tissues and organs surrounding the tumor (especially organs at risk) and to ensure a high level of control over tumor dynamics [11, 12].

Radiation therapy requires an individualized approach for all cancer patients. This is especially important for cancer patients with a complicated somatic background, particularly in the presence of severe cardiovascular diseases. Cardiovascular pathologies account for a significant part of the structure of comorbidities in cancer patients, occurring in approximately 22.6% of the total number of patients diagnosed with cancer of any type [13]. Concomitant congestive heart failure is detected in 16.5% of patients with lung cancer [14]. In patients with NSCLC, severe forms of cardiovascular pathology occur in 31.1% of cases, among which the most common are heart failure (47.7%), myocardial infarction (33.0%), and chronic arrhythmias (30.4%) [15]. These patients may also have implanted pacemakers (PMPs), cardioverter-defibrillators (ICDs), or may have a history of coronary artery bypass grafting (CABG). The presence of severe concomitant cardiovascular diseases significantly influences the choice of treatment strategy, increases the risk of cardiotoxic complications during radiation therapy, and requires the use of both high-precision and gentle radiotherapy methods, such as tomotherapy. Furthermore, antitumor therapy itself can provoke the manifestation or exacerbation of cardiac pathology and/or malfunction of implanted devices. In such patients, there is a clear need to strictly limit the dose to critical structures, including the heart, coronary vessels, and the pulmonary artery trunk [12].

Kazakhstan has accumulated limited but promising experience using high-precision tomotherapy in this patient population. However, the domestic literature is virtually devoid of studies evaluating the efficacy and safety of this method in cancer patients with significant underlying cardiac pathology.

The study aimed to evaluate the clinical results of mono-tomotherapy in patients with NSCLC and concomitant cardiac pathologies at the International Oncology Center for Tomotherapy "UMIT" (Astana, Kazakhstan).

Materials and Methods: This retrospective study included 201 male patients diagnosed with non-small cell lung cancer (NSCLC). All patients underwent a course of mono-tomotherapy at the UMIT Tomotherapy Center between January 2020 and December 2024. The patients were divided into two groups: patients in Group 1 (n = 139) had no significant cardiovascular diseases, while patients in Group 2 (n = 62) were diagnosed with severe comorbid cardiovascular conditions prior to the start of tomotherapy, including ischemic heart disease, the presence of implanted pacemakers, and a history of coronary artery bypass grafting (Table 1).

Inclusion criteria for Group 2 were: reduced left ventricular ejection fraction (EF) ≤50%, history of coronary artery bypass grafting (CABG), presence of pacemakers (PM) or implantable cardioverter-defibrillators (ICD), post-infarction cardiosclerosis, and angina pectoris of functional class III–IV.

Exclusion criteria for Group 2 included: unstable angina, acute coronary syndrome, or inability to complete a full course of tomotherapy.

Table 1 – Distribution of types of cardiovascular diseases and disorders in Group 2 patients

Category of cardiovascular pathology	Absolute number of cases (n)	Share in Group 2 (%)
Post-coronary artery bypass grafting	24	38.7
Ejection fraction <40%	19	30.6
Ejection fraction between 40-50%	28	45.2
Implanted pacemakers	12	19.4
Implanted cardioverter-defibrillators	6	9.7
Post-infarction cardiosclerosis	16	25.8
Angina pectoris (class III-IV)	21	33.9

The mean age was 62.3 years in Group 1 and 68.5 years in Group 2.

The distribution of patients by cancer stage is presented in Figure 1: the relative distribution across different stages was approximately equal in both groups, with a predominance of patients with stage III and IV NSCLC.

Spiral tomotherapy (Radixact X9, Accuray, Madison, WI, USA) was used in the study, combining the capabili-

ties of a computed tomography scanner and a linear accelerator. Adjustable parameters of the tomotherapy system were used, with an automatic correction system that adjusts patient positioning and irradiation parameters, reducing the likelihood of erroneous dose delivery (Table 2).

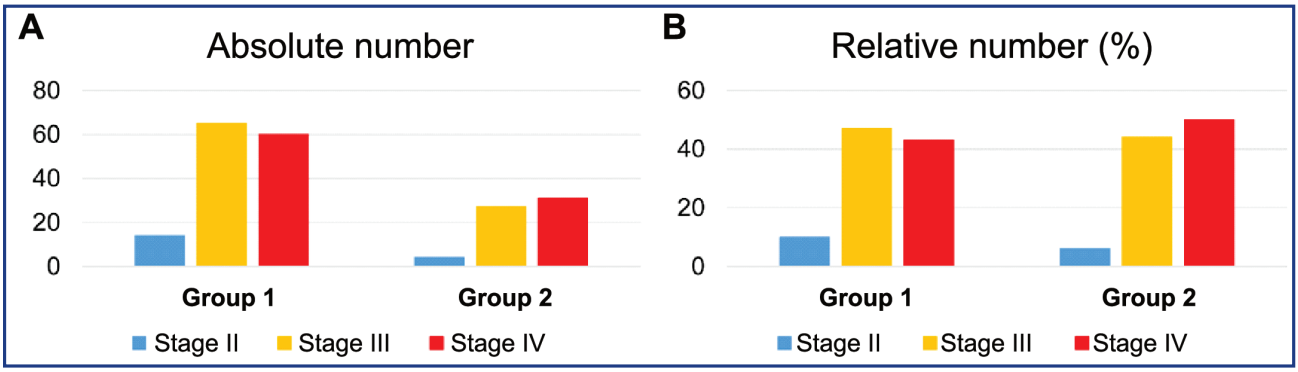


Figure 1 – Distribution of study participants by cancer stage: A – absolute number (n), B – relative number (%)

Table 2 – Technical parameters of the computed tomography system used in the study

Parameter	Description of the parameter
Accelerator power	6 MV (megavoltage) X-ray photons
Beam width (fan beam width)	Varies from 1 to 5 cm to adapt the treatment mode to individual anatomical features
Gantry rotation speed	Approximately 1 rotation every 15-30 seconds, depending on the selected mode
Dose intensity modu-lation	Achieved through real-time changes in the shape and intensity of the radiation beam
Tumor doses	Range from 50 to 60 Gy, distributed over 20-30 fractions, with daily monitoring and plan adaptation if needed
Exposure time	On average, 15-25 minutes per fraction

In some cases, multifocal irradiation modes were applied, in which several anatomical zones were irradiated simultaneously – both the primary tumor and regional lymph nodes – while providing maximal sparing of surrounding healthy tissues (average dosimetric exposure parameters are shown in Table 3, "Results" section).

The tomotherapy protocol included mandatory CT-based planning with a 2-3 mm slice thickness at the preliminary stage, with the patient in the supine position and fixed. The scan duration was 15 minutes. Irradiation was performed daily (5 times a week, on working days) with one session per day; in exceptional cases (<2% of patients), alternate-day regimens were used based on clinical indications, such as decompensation of chronic somatic pathology. The course duration ranged from 20 to 40 days, depending on the protocol (normo- or hypofractionation, radiation volume, individual tolerability, and treatment regimens). Hypofractionated regimens were used in 22% of cases (n = 44); however, the distribution across the groups was uneven: in Group 2, hypofractionated irradiation was used in 59.7% of cases (37 out of 62) vs. only 5% of cases in Group 1 (7 out of 139).

CT data were processed using MIM Maestro software and the TomoTherapy Precision® planning system. Statistical data analysis was performed using SPSS v.26 and Microsoft Excel. Student's t-test was used for normally distributed data and the Mann-Whitney U test for non-normally distributed data to compare quantitative variables between groups. Differences were considered statistically significant at $p < 0.05$.

Overall survival was defined as the time from the start date of the tomotherapy course to death from any cause or the date of the last follow-up. Progression-free survival was defined as the time from the start of treatment to the first documented disease progression (according to RECIST 1.1) or death. Comparison of survival values between groups was performed using the log-rank test. Median overall and progression-free survival were calculated for the entire cohort and for each study group, with 95% confidence intervals (95% CI) reported.

Results: Table 3 presents the recommended and actual average dose parameters to critical organs in the patients included in the study, used to assess the quality of treatment planning and radiation safety. In Group 2 patients (with cardiopathology), the mean heart dose was significantly higher than in Group 1 patients (without cardiopathology), whereas no significant differences were observed in other organs. At the same time, the mean dose in Group 2 did not exceed the recommended threshold, and the mean doses differed by no more than 1.4 Gy between the groups. Based on this, we assume that the observed statistically significant difference in myocardial dose between the study groups did not influence the effectiveness of the tomotherapy course.

Table 3 – Recommended and actual mean dose parameters to critical organs in patients included in the study

Organ / Risk zone	Planning constraint (recommendation)	Actual mean dose		*p*-value
		Group 1	Group 2	
Lungs (V_{20})	≤30%	27.1±2.8%	28.4±3.1%	0.08
Heart (D_{mean})	<15 Гр	11.2±2.1 Gy	12.6±2.4 Gy	0.04*
Esophagus (D_{max})	≤50 Гр	41.5±5.3 Gy	43.1±4.8 Gy	0.21
Spinal cord (D_{max})	≤45 Гр	34.7±3.6 Gy	35.9±3.9 Gy	0.15

Note: The symbol "*" indicates a statistically significant difference between the study groups (at a significance level of $p < 0.05$).

Treatment efficacy was evaluated based on PET-CT and CT data obtained 8-12 weeks after completion of the course. The results on cancer disease dynamics are presented in Table 4. Complete regression was observed significantly more often in Group 1 patients, whereas disease progression was more frequent in Group 2. There was a trend toward a higher partial response rate in Group 1, whereas stabilization of the oncological process occurred more often in Group 2. A comparison of the relative frequency of complete regression, partial response, stabilization, or disease progression between the study groups indicates that tomotherapy was less effective in Group 2 than in Group 1. Nevertheless, in Group 2, positive dynamics were observed in nearly half of the participants (49%; complete regression + partial response), and, among patients with oncological process stabilization, in 84%. This suggests a fairly high effectiveness of mono-tomotherapy in patients with NSCLC and concomitant severe cardiopathology of various etiologies.

Table 4 – Outcomes in patients included in the study following tomotherapy

Outcome	Group 1	Group 2	*p*-value
Complete regression (%)	10% (14)	3% (2)	0.03*
Partial response (%)	58% (81)	46% (29)	0.10
Stable disease (%)	28% (39)	35% (22)	0.25
Oncological disease progression (%)	4% (5)	16% (9)	0.01*

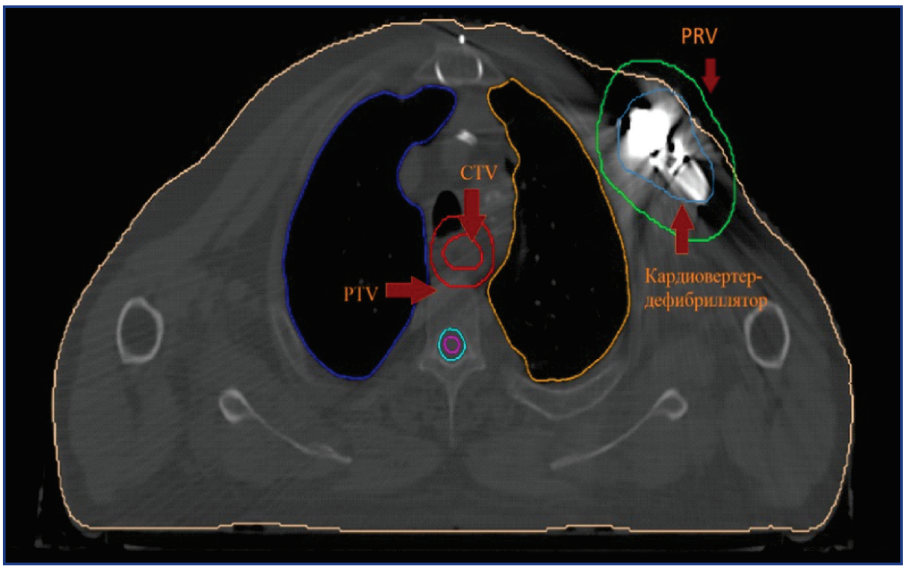
Note: The symbol "*" indicates a statistically significant difference between the study groups (at a significance level of $p < 0.05$).

The median overall survival in the entire patient cohort was 18.6 months (95% CI: 16.9-20.3); Group 1 – 19.8 months (95% CI: 18.2-21.4); Group 2 – 16.2 months (95% CI: 14.1-18.3) (significantly lower in Group 2; log-rank p=0.04). The median progression-free survival was 9.7 months (95% CI: 8.5-10.9); Group 1 – 10.3 months (95% CI: 9.2-11.4); Group 2 – 8.1 months (95% CI: 6.9-9.3) (log-rank p=0.03). The one-year overall survival rate was 82% for the entire cohort, 84% for Group 1, and 76% for Group 2. The two-year overall survival rate was 62% for the entire cohort (65% in Group 1 vs. 54% in Group 2). Depending on the stage of the disease, the median overall survival in the entire cohort was: Stage III – 20.4 months (95% CI: 18.5-22.3); Stage IV – 16.3 months (95% CI: 14.5-18.1). The median progression-free survival was 10.8 months (95% CI: 9.4-12.2) for stage III and 8.3 months (95% CI: 7.1-9.5) for stage IV. Both indicators showed a statistically significant difference between stages (log-rank p<0.01).

Comparative safety analysis showed that patients with significant cardiopathology had a higher risk of cardiovascular complications; however, the overall tolerability profile of tomotherapy remained acceptable. Other radiation-induced complications (esophagitis, pneumonitis) did not exceed grade II according to the Common Terminology Criteria for Adverse Events (CTCAE) and occurred in less than 10% of patients in both groups. Thus, helical tomotherapy demonstrated high efficacy and satisfactory tolerability in patients with cardiopathology. Key safety factors included contouring cardiac devices and bypass grafts as critical structures, strict dose control, IMRT, and daily IGRT.

Safety in patients with pacemakers (PMs) or implantable cardioverter-defibrillators (ICDs): In patients with implanted PMs or ICDs (n=18), irradiation was performed using adaptive planning, with the implanted devices contoured as critical organs (Figure 2). The mean distance from the tumor to the device was 4.3 cm. The maximum dose to the PM or ICD did not exceed 2 Gy. As a result of treatment, no cases of device malfunction or need for replacement were recorded (0/18 patients).

Treatment of patients after CABG and with low EF: In patients with prior CABG (n=24), the radiation dose to the graft region was limited to 15 Gy or less (Figure 3). Patients with EF<40% received standard irradiation regimens (2-2.5 Gy per fraction). In two patients, decompensated heart failure was observed, requiring temporary hospitalization, but the full course of tomotherapy was completed in both cases.



Legend: Кардиовертер-дефибриллятор – Implantable cardioverter-defibrillator

Figure 2 – Implanted devices (PM/ICD) were contoured as critical structures (the device is indicated by the arrow in the upper right corner). Average distance to the tumor: 4.3 cm; maximum dose to the device: ≤2 Gy. Notes: PRV (Planning Organ at Risk Volume) – region defined for an organ at risk; PTV (Planning Target Volume) – target irradiation area; CTV (Computed Tomography Venography) – region used for CT venography

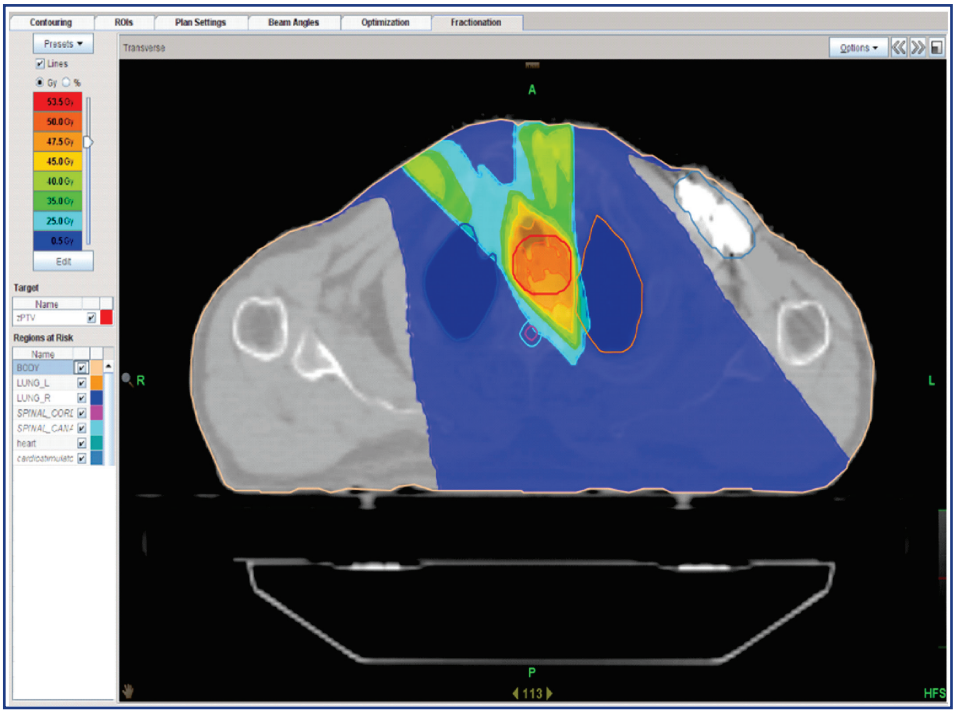


Figure 3 – Example of dose distribution to the target volume and critical organs in a patient with concomitant cardiopathology, demonstrating target coverage with minimal irradiation of adjacent structures. Color-coded regions represent different radiation dose levels, and different organs are delineated with predefined contour colors

Discussion: Tomotherapy continues to evolve as an approach to cancer treatment, including by reducing the risk of harmful radiation exposure [16]. This leads to a decrease in the incidence of radiation-induced toxic effects, as demonstrated in numerous studies on tomotherapy for prostate cancer [17], breast cancer [11, 18], metastatic liver cancer [19], grade II gliomas [20], craniospinal tumors [21], skin neoplasms [22], and other types of cancer. Advancements in particle accelerators across different tomotherapy systems have led to more effective spatial distribution of radiation doses, as demonstrated in a study involving patients with six cancer types, including lung cancer [23].

IGRT provides additional benefits by preventing or significantly reducing exposure to tissues and organs adjacent to the target, while simultaneously enhancing the irradiation efficacy of the target itself through respiratory motion management [24]. This approach is recommended by radiological associations for many types of cancer [9, 25].

Numerous publications have demonstrated the high efficacy and safety of helical tomotherapy in cancer treatment [16, 20-22], including head and neck cancers [26, 27], gastrointestinal malignancies [26], breast cancer (without regional lymph node metastasis) [18], inoperable stage III NSCLC [28], and localized prostate cancer in elderly patients [29, 30]. On the other hand, the presence of comorbidities increases the risk of developing toxic conditions during tomotherapy. For example, in patients with compromised immune status, the risk of pulmonary complications (e.g., pneumonia) increases during craniospinal irradiation with helical tomotherapy [31]. The same applies to the risk of complications in patients with comorbid cardiovascular conditions. Specifically, the risk of cardiotoxicity is directly related to the absorbed radiation dose delivered to the heart or its structures [32]. Helical tomotherapy, when combined with IMRT/IGRT, reduces this risk by minimizing the dose to the left ventricle and the left anterior descending artery compared with 3D-conformal radiation therapy [12, 33].

The role of computed tomography in the treatment and diagnostics of oncology patients (with or without cardiopathology) is evident. In particular, regarding myocardial pathophysiology, this method enables visualization and assessment of calcium accumulation, facilitating earlier detection of atherosclerotic lesions in cardiac vessels [34]. On the other hand, further clarification and continued data accumulation are required to conduct a more detailed analysis of the short- and long-term outcomes in patients with comorbidities. The results presented in this article are generally consistent with previously published data on the efficacy and safety of tomotherapy in oncology patients with cardiovascular disorders. Our quantitative assessments demonstrate that tomotherapy is an effective and safe treatment option for NSCLC, even in patients with significant cardiac pathology. However, to ensure the necessary level of safety and to reduce the risk of complications, at least three conditions must be met: 1) incorporation of PMs, ICDs, and bypass grafts into the treatment plan as risk structures, in order to minimize radiation exposure to these devices; 2) use of the IMRT mode to achieve the most uniform radiation dose distribution to the target, taking into account its anatomical and morphological features; 3) application of IGRT to ensure high precision in beam positioning and to monitor tumor and adjacent structure dynamics during each treatment session. In addition, the more frequent use of hypofractionated regimens in patients with cardiopathology may have contributed to the lower rates of complete tumor regression and higher incidence of oncological process progression observed in this group. Nevertheless, reduced radiation intensity is necessary in such patients to preserve the heart's functional characteristics and minimize the risk of interference with implanted cardiac devices.

Conclusion: Helical tomotherapy in patients with NSCLC and coexisting cardiopathology demonstrated a fairly high efficacy, albeit lower than in patients without cardiac conditions, in terms of complete regression and disease progression. One- and two-year overall survival rates were lower in patients with cardiopathology, although this may have been due to causes of death unrelated to cancer, such as complications arising from cardiovascular disease. Tomotherapy showed high safety and satisfactory tolerability, with infrequent side effects, in patients with cardiopathology. Key safety factors included contouring cardiac devices and bypass grafts as critical structures, strict dose control, IMRT, and daily IGRT. The experience of the UMIT International Tomotherapy Oncology Center confirms the feasibility of delivering relatively safe treatment in this patient population, provided that a personalized approach, rigorous dosimetric control, and interdisciplinary monitoring are implemented.

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АҢДАТПА

ЖҮРЕК-ҚАНТАМЫРЛАРЫНЫҢ ҚАТАРЛАС ПАТОЛОГИЯСЫ БАР ЕРЛЕРДЕ ӨКПЕ ОБЫРЫН ЕМДЕУДЕГІ ТОМОТЕРАПИЯНЫҢ ТИІМДІЛІГІ («UMIT» ХАЛЫҚАРАЛЫҚ ОНКОЛОГИЯЛЫҚ ТОМОТЕРАПИЯЛЫҚ ОРТАЛЫҒЫНЫҢ ТӘЖІРИБЕСІ)

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Өзектілігі: *Өкпенің ұсақ жасушалы емес қатерлі ісігі (NSCLC) көбінесе ер адамдарда миокард патологиясымен қатар диагноз қойылады. НМРЛ емдеу әдістерінің бірі сәулелік терапия болып табылады, алайда Қазақстанда кардиопатологиясы бар онкопациенттерде томотерапияның тиімділігі мен қауіпсіздігі бойынша зерттеулер іс жүзінде жүргізілген жайттар жоқ.*

Зерттеудің мақсаты: *Халықаралық онкологиялық Томотерапия «Umit» орталығында (Астана, Қазақстан) NSCLC және ілеспе кардиопатологиясы бар пациенттерде моно-томотерапияны қолданудың клиникалық нәтижелерін бағалау болып табылады.*

Әдістері: *Зерттеуге «UMIT» орталығында 2020-2024 жылдары спиральды моно-Томотерапия курсынан өткен NSCLC бар 201 ер адам кіреді. Пациенттер 1-топқа бөлінеді-кардиопатологиясыз (N=139) және 2 – топ-ауыр ілеспе кардиопатологиямен (N=62). Курстың орташа ұзақтығы - 32 күн, процедураның орташа ұзақтығы – 15 минут, күніне бір рет, аптасына 5 күн. Емдеу тиімділігі ПЭТ-КТ және КТ деректері бойынша курс аяқталғаннан кейін 8-12 аптадан кейін бағаланды.*

Нәтижелері: *Толық регрессия 1-топтағы пациенттерде, аурудың өршуі 2-топтағы пациенттерде жиі байқалды. Көбінесе жауап 1-топта, онкологиялық процестің тұрақтануы 2-топта жиі кездеседі. 2-топта оң динамикасы бар пациенттердің үлесі 49% – 8 құрады, процестің анықталған тұрақтануын ескере отырып-84% -. құрады. 1-топта жыл сайынғы жалпы өмір*

сүру деңгейі III және IV кезеңдерде 84% және 74% құрады, сәйкесінше прогрессиясыз орташа ұзақтығы – 10,3 ай, III кезеңдегі екі жылдық өмір сүру деңгейі – 65%. 2-топта жыл сайынғы жалпы өмір сүру деңгейі III және IV кезеңдерде 76% және 63% құрады, сәйкесінше прогресс 8,1 прогрессиясыз орташа ұзақтығы, III кезеңдегі екі жылдық өмір сүру деңгейі 54%. 2-топта имплантацияланған құрылғы функциясының бұзылу жағдайлары тіркелмеген, коронарлық артерияны айналып өтуі бар екі пациентте уақытша ауруханаға жатқызуды қажет ететін жүрек жеткіліксіздігінің декомпенсациясы болған.

Қорытынды: *Томотерапия ауыр қатар жүретін кардиопатологияда NSCLC емдеуде жоғары клиникалық тиімділікті көрсетеді, дегенмен жалпы өмір сүру және емдеу тиімділігі кардиопатологиясы жоқ науқастарға қарағанда төмен көрсеткіштер байқалды. Біздің тәжірибеміз жекелендірілген тәсіл, қатаң дозиметриялық бақылау және пәнаралық бақылау принциптерін сақтай отырып, мұндай пациенттерде салыстырмалы түрде қауіпсіз емдеу мүмкіндігі бар екенін растайды.*

Түйінді сөздер: *өкпе рагы, томотерапия, кардиопатология, кардиостимулятор, гипофракция, жоғары дәлдіктегі сәулелік терапия.*

АННОТАЦИЯ

ЭФФЕКТИВНОСТЬ ТОМОТЕРАПИИ В ЛЕЧЕНИИ РАКА ЛЁГКИХ У МУЖЧИН С СОПУТСТВУЮЩЕЙ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИЕЙ (ОПЫТ МЕЖДУНАРОДНОГО ОНКОЛОГИЧЕСКОГО ЦЕНТРА ТОМОТЕРАПИИ «UMIT»)

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Актуальность: *Немелкоклеточный рак лёгкого (НМРЛ) часто диагностируется у мужчин в сочетании с патологиями миокарда. Одним из методов лечения НМРЛ является лучевая терапия, однако в Казахстане практически отсутствуют исследования эффективности и безопасности томотерапии у онкопациентов с кардиопатологиями.*

Цель исследования *– оценить клинические результаты применения моно-томотерапии у пациентов с НМРЛ и сопутствующими кардиопатологиями в Международном онкологическом центре томотерапии «UMIT» (Астана, Казахстан).*

Методы: *В исследование включен 201 мужчина с НМРЛ, прошедший курс спиральной моно-томотерапии в 2020-2024 годах в центре «UMIT». Пациенты разделены на Группу 1 – без кардиопатологий (n=139) и Группу 2 – с тяжёлыми сопутствующими кардиопатологиями (n=62). Средняя длительность курса – 32 дня, средняя продолжительность процедуры – 15 минут, один раз в день, 5 дней в неделю. Эффективность лечения оценивали через 8-12 недель после завершения курса по данным ПЭТ-КТ и КТ.*

Результаты: *Полный регресс чаще отмечался у пациентов Группы 1, прогрессирование заболевания – чаще у пациентов Группы 2. Частичный ответ чаще встречался в Группе 1, стабилизация онкологического процесса – чаще в Группе 2. В Группе 2 доля пациентов с положительной динамикой составила 49%, с учетом выявленной стабилизацией процесса – 84%. В Группе 1 однолетняя общая выживаемость составила 84% и 74% при III и IV стадиях, соответственно, медианная продолжительность без прогрессирования – 10,3 месяцев, двухлетняя выживаемость при III стадии – 65%. В Группе 2 однолетняя общая выживаемость составила 76% и 63% при III и IV стадиях, соответственно, медианная продолжительность без прогрессирования – 8,1 месяца, двухлетняя выживаемость при III стадии – 54%. В Группе 2 не зафиксировано случаев нарушения функции имплантированного устройства, у двух пациентов с аортокоронарным шунтированием была декомпенсация сердечной недостаточности, потребовавшая временной госпитализации.*

Заключение: *Томотерапия демонстрирует высокую клиническую эффективность при лечении НМРЛ при тяжёлой сопутствующей кардиопатологии, хотя общая выживаемость и эффективность лечения были ниже, чем у пациентов без кардиопатологий. Наш опыт подтверждает возможность сравнительно безопасного лечения у таких пациентов при соблюдении принципов персонализированного подхода, строгого дозиметрического контроля и междисциплинарного наблюдения.*

Ключевые слова: *рак лёгкого, томотерапия, кардиопатология, кардиостимулятор, гипофракционирование, высокоточная лучевая терапия.*

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COMPARATIVE EFFECTIVENESS OF CHRONIC LYMPHOCYTIC LEUKEMIA THERAPY: THE EXPERIENCE OF THE ALMATY CLINIC

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ABSTRACT

Relevance: *Clinical and genetic heterogeneity of chronic lymphocytic leukemia (CLL) influences therapy choices and outcomes. Cytogenetic and biological markers are crucial for disease staging, therapeutic decision-making, and prognosis. Real-world data comparing chemo-, immunotherapy, and targeted regimens are essential for refining patient management strategies.*

The study aimed to *evaluate the comparative effectiveness of chemotherapy, immunotherapy, and targeted therapy in patients with chronic lymphocytic leukemia, taking into account cytogenetic parameters, age, and stage of the disease.*

Methods: *This retrospective cross-sectional study included 114 CLL patients treated at the City Clinical Hospital No. 7 (Almaty, Kazakhstan) between 2001 and 2024. Patients received either chemoimmunotherapy (FC, FCR, CR, COP, chlorambucil) or targeted regimens (BTK/PI3K inhibitors, anti-CD20 antibodies). Primary endpoints were progression-free survival (PFS) and overall response rate (ORR).*

Results: *Distribution of patients with CLL by disease stage: stage B – 59.6% (n = 68), stage A – 25.4% (n = 29), stage C – 9.6% (n = 11), stage not established – 5.4% of cases (n = 6). According to cytogenetic testing (n = 63), the most frequent abnormality was del(13q14) (33%, n = 21), either isolated or combined with other aberrations. Del(11q22.3) was detected in 17.5% (n = 11), trisomy 12 in 11% (n = 7), and TP53 mutations in 6.3% (n = 4). Among treatment regimens, the highest median PFS was observed with FC (46.6 months), CR (45 months), and ibrutinib (32.1 months). In patients receiving ibrutinib in later therapy lines (n=10), comparable complete response rates and disease stabilization were achieved.*

Conclusion: *In real clinical practice, targeted therapy demonstrates superior PFS and better tolerability in high-risk patients and in those pretreated with one or more prior lines of therapy, whereas chemotherapy remains a viable option for selected subgroups (younger patients, IGHV-mutated, favorable cytogenetics). Treatment personalization based on genetic profiling improves outcomes in CLL. Expanding access to comprehensive genetic testing is critical to further enhance prognosis and survival.*

Keywords: *chronic lymphocytic leukemia; comparative effectiveness; targeted therapy; chemoimmunotherapy; cytogenetics.*

Introduction: Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia in adults and represents a major public health problem [1]. The global age-standardized incidence rate (ASIR) is 4.7 cases per 100,000 people, resulting in more than 103,400 cases annually. By the end of 2025, 23,690 new cases of CLL are expected, with a projected increasing trend until 2030 [2, 3]. CLL incidence varies significantly by geographic location, gender, age, and ethnicity, with a higher prevalence in men and older adults. In East Asians, Asian Indians, and Native Americans, age-adjusted CLL incidence is 5-10 times lower than in people of predominantly European descent [4]. However, gender differences persist regardless of ethnicity [3]. Several studies have reported a growing incidence of CLL in developing countries. At that, overall survival (OS), treatment strategies, and effectiveness largely depend on socioeconomic conditions and access to quality medical care, including diagnostic methods and new medications [4].

The clinical course of CLL can be quite heterogeneous, ranging from an indolent disease requiring no treatment to an aggressive disease refractory to several lines of therapy. The vast majority of patients may be asymptomatic at the time of diagnosis [2, 3, 5]. However, in some patients, the disease progresses aggressively, with multiple relapses, and requires aggressive treatment.

The prognosis of CLL varies greatly depending on the stage of the disease, age, functional status of comorbidities, and many other factors, and remains serious for the majority of patients. Currently, risk group stratification is performed using the International Prognostic Index (CLL-IPI), which includes, in addition to age (>65 years), Rai staging (I-IV), determination of the level of ?-2 microglobulin (>3.5 mg/l), also genetic markers: the presence or absence of mutations in the genes of immunoglobulin heavy chains (*IGHV), TP53* and the del17p deletion determined by fluorescence in situ hybridization (FISH) [6]. These changes, independently of each other, can affect overall survival. Thus, patients with CLL and *TP53 dysfunction* or a complex karyotype belong to a very high-risk group and have a shorter survival [7]. Deletion of the short arm of chromosome 17 (del(17p)), which in-

cludes the *TP53* tumor suppressor gene locus, can often be mutated and is associated with both an unfavorable course of CLL and refractoriness to chemoimmunotherapy [8]. Based on the *IGHV mutation status,* a distinction is made between more mature, genetically stable CLL and more immature, genetically unstable CLL. Patients with unmutated *IGHV genes* have a more aggressive course of the disease and are more likely to develop adverse genetic events than patients with mutated *IGHV* [9].

Historically, CLL therapy has undergone significant changes. Beginning with the use of the alkylating agent chlorambucil or its combination with glucocorticoids in the 1970s, later combination regimens (CHOP, CVP), and the combined use of fludarabine and cyclophosphamide (FC regimen) in first-line therapy, to the recent use of targeted immunotherapy with the chimeric monoclonal antibody to CD20, rituximab, including in combination with fludarabine, cyclophosphamide (FCR), and other targeted and immunotherapeutic agents.

The introduction of new targeted and immune drugs into practice, such as Bruton kinase inhibitors, venetoclax (a selective inhibitor of the anti-apoptotic B-cell lymphoma (BCL-2) protein), ofatumumab, obinutuzumab, idelalisib, and duvelisib, among others, has significantly increased the survival of patients with CLL. However, in some cases, treatment remains ineffective, requiring multiple lines of therapy and a personalized approach with multiparametric risk assessment.

Due to the importance of molecular genetic markers of CLL in stratifying risk groups, and also considering the variability of data on disease course and the use of various treatment approaches and regimens, the authors assessed the effectiveness of CLL therapy in patients in Almaty.

The study aimed to evaluate the comparative effectiveness of chemotherapy, immunotherapy, and targeted therapy in patients with chronic lymphocytic leukemia, taking into account cytogenetic parameters, age, and the disease stage.

Materials and methods: A retrospective analysis of data from 114 patients diagnosed with CLL who received treatment at the City Clinical Hospital No. 7 (Almaty, Kazakhstan) from 2001 to 2023 inclusive was conducted.

Diagnosis and monitoring of CLL were performed in accordance with the recommendations of the 2018 International Workshop on Chronic Lymphocytic Leukemia (IWCLL).

The research methods for prognosis and monitoring of CLL included: complete blood count at the time of diagnosis and during the disease dynamics; morphological and cytological examination of bone marrow at diagnosis; immunophenotyping of atypical B cells of peripheral blood to confirm the diagnosis (n = 112 patients, normal B lymphocytes were not taken into account in the analysis, the panel included CD19, CD5, CD20, CD23, κ and λ to confirm the diagnosis); standard cytogenetic study and FISH on interphase nuclei of peripheral blood lymphocytes n = 63 (55.2%) using locus-specific probes for CLL from Abbot (Chicago, IL, USA).

Statistical processing of data was carried out using MS Excel tables.

The distribution of quantitative variables was analyzed using the Shapiro-Wilk test. After assessing compliance with the normal distribution law, the statistical analysis method was selected. In the normal distribution of quantitative variables, the central tendency and dispersion of features were described using the mean (M) and the standard deviation (SD). When the distribution of quantitative characteristics differed from normal, the description was carried out using the median (Me). Confidence intervals were calculated for a probability of p = 95%. Differences between compared parameters were considered statistically significant at $p < 0.005$.

When comparing patient groups by categorical characteristics, the $\chi 2$ test with Yates' correction was used. The statistical significance of differences between two related groups was calculated using Student's t-test. For two unrelated groups, the Student's t-test or the nonparametric Mann-Whitney test was used. At $p < 0.005$, the alternative hypothesis of group differences was accepted, and paired comparisons were performed using the Mann-Whitney test.

Results: The structure of a cohort of patients with CLL (the total number of those registered for dispensary care, newly diagnosed cases, and the number of deaths) was studied for the period from 2001 to 2023 in Almaty. The study included 114 patients with CLL; staging was established based on the 1981 Binet classification [10]. The age of patients ranged from 38 to 92 years, with a median of 68 years, which is consistent with the data from the world literature. The proportion of patients over 65 years was 62% (n = 71). Women predominated among the patients (57%, n = 65); men accounted for 43% (n = 49).

Distribution of patients by stages. Patients were divided according to CLL stages. as follows: stage B was the most frequently diagnosed stage in 59.6% (n = 68), stage A occurred in 25.4% (n = 29), stage C – in 9.6% of patients (n = 11), and some had no data on the stage of the disease (Table 1). It should be noted that most cases of CLL were asymptomatic at the time of diagnosis.

Cytogenetic testing was performed on 63 patients. Analysis of cytogenetic changes revealed that the most common alteration (33%, n = 21) was deletion of 13q14, either isolated or in combination with other abnormalities. Del 11q22.3 was detected in 18% of cases (n = 11), trisomy 12 in 11% (n = 7), and *TP53* mutations in 6.3% of cases (n = 4) (Figure 1).

The limitations of cytogenetic research data are primarily due to the lack of access to FISH research for adult patients in the Republic of Kazakhstan until 2017-2018.

Table 1 – Distribution of patients by CLL stages (Binet J, 1981) [10]

Stage	Number of patients, n	Percentage of patients, %
Stage A	29	25.4
Stage B	68	59.6
Stage C	11	9.6
No data	6	5.4

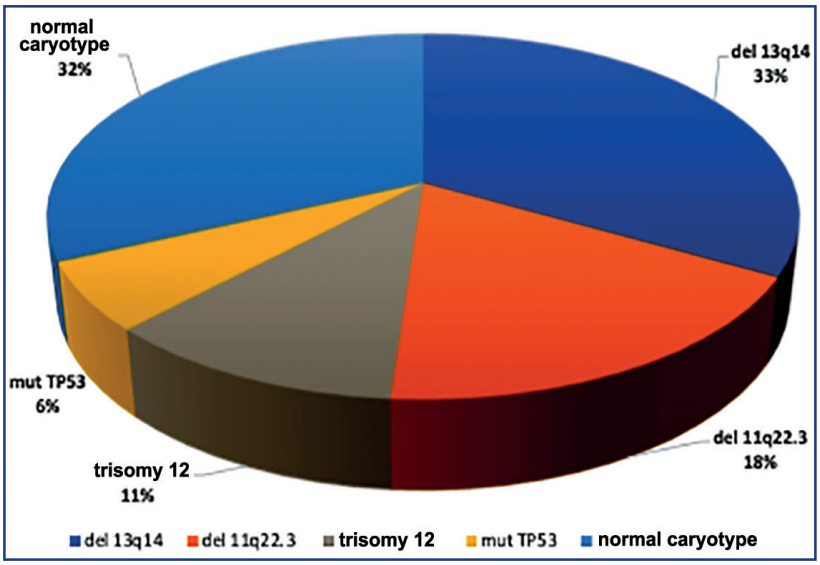

Figure 1 – Structure of cytogenetic aberrations in patients with CLL (n = 63)

Therapy. When choosing treatment tactics, in 32 cases (41.2%), patients did not receive initial active treatment due to a lack of indications for therapy initiation according to the protocols for managing patients with CLL. Chemo- and chemoimmunotherapy (FC, FCR, CR, COP, chlorambucil) was used in the majority of patients. Targeted therapy with the Bruton tyrosine kinase inhibitor ibrutinib was received by 14 patients (12.8%), including 4 patients with the *TP53* mutation. In 10 patients without the *TP53* mutation, ibrutinib was used after one or more previous lines of chemotherapy. As a previous therapy, patients received treatment in the form of combination regimens using fludarabine, chlorambucil, cyclophosphamide, and rituximab (FC, FCR, CR, COP) (Table 3).

Table 3 – Treatment of patients with CLL (n=114)

Treatment (with treatment regimen)	Number of patients, n	Percentage of patients, %
FC	17	14.9
Ibrutinib	14	12.8
With R	13	11.4
FCR	12	10,5
Chlorambucil	10	8.7
COP	2	1.75
No therapy at the time of diagnosis	47	41.2

Notes to Tables 3 and 4: FC – fludarabine, cyclophosphamide; CR – cyclophosphamide, rituximab; FCR – fludarabine, cyclophosphamide, rituximab; COP – cyclophosphamide, vincristine + prednisolone.

Response to therapy was recorded in all groups. Complete and partial response rates, as well as median progression-free survival (PFS), are presented in Table 4.

When comparing the treatment regimens, the highest median PFS was observed with the FC regimen (46.6 months), with sustained remission achieved in 55.5% of patients in this group. The CR rate was higher in the group of patients treated with the SOR regimen (the difference was not significant), with a PFS of 31.6 months. Patients receiving ibrutinib in subsequent lines of therapy achieved comparable rates of complete responses and disease stabilization.

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Table 4 – Response to therapy depending on the treatment regimen for CLL

Treatment regimen	Number of patients, n	Full answer, % patients	Partial response, % of patients	Disease progression, % of pa-tients	Medana progression-free survival (months)
FCR	12	78.2	15.1	14.4	31.4
FC	17	89.1	9	0.5	46.6
COP	2	91	6	0.0	31.6
CP	13	89	8	1.8	45.2
Ibrutinib	14	88	7	0.0	32.1

Discussion: The obtained results demonstrate that the structure of the Almaty cohort of patients with CLL is comparable with international data. The median age, stage distribution, and frequency of major cytogenetic changes are generally consistent with published epidemiological data [1-4].

The 13q14 deletion, being the most common anomaly, was associated with a favorable prognosis, consistent with the literature. Meanwhile, *TP53 mutations* and 17p deletion, not fully identified due to diagnostic limitations, remain key prognostic markers guiding treatment decisions.

Ibrutinib treatment has demonstrated efficacy even in patients with poor prognoses and multiple prior treatment lines. This confirms the high clinical value of targeted therapy in high-risk groups.

The use of traditional chemotherapy regimens has also shown an effect, especially in young people, which allows the use of traditional treatment regimens and careful stratification of patients.

Limitations of the study include its retrospective design, incomplete coverage of cytogenetic testing (due to limited availability of FISH and modern molecular technologies), and a small sample size of patients receiving targeted therapy.

Take-aways:

The structure of the cohort of patients with CLL in Almaty corresponds to international data on age and distribution of disease stages.

Cytogenetic alterations, especially del (13q14), del (11q22.3), TP53 mutations, and trisomy 12, play a key role in prognosticating the course of CLL.

Ibrutinib demonstrated efficacy in a cohort of patients with a poor prognosis and late lines of therapy, confirming its important role in modern CLL treatment strategies.

Expanded access to genetic research and the introduction of next-generation sequencing technologies are needed to stratify risk and optimally select treatments.

Further research in the field of CLL, including multicenter studies, particularly in asymptomatic, progressing, or relapsing patients as our own data accumulate, shall improve the quality of treatment and optimize approaches to patient management, including in conditions of limited access to modern treatment methods.

Conclusion: Modern tactics for managing patients with CLL involve a comprehensive assessment of the patient's condition and biological markers to stratify risk groups, determine treatment strategies, and assess prognosis. An important role is played by independent indicators, such as the patient's age, general physical condition, comorbidities, the presence of *TP53* and *IGHV* mutations, and the level of ?-2 microglobulin. Cytogenetic changes play a key role in prognosticating the course of CLL. Deletion of 13q14, the most common aberration, is associated with a relatively favorable prognosis. The presence of *TP53* mutations and the deletion of 17p (del17p) indicates an unfavorable prognosis and resistance to standard immune chemotherapy [7-9]. In these cases, the effectiveness of chemotherapy and CD20 monoclonal antibodies is reduced. The presence of isolated trisomy 12 is considered an "intermediate" prognosis, while the combination of trisomy 12 with deletion 11q22.3 is associated with a more aggressive course of the disease [7]. The data obtained by the authors correlate with data from the world literature regarding the age structure; discrepancies in the sex distribution may depend on the overall life expectancy in our country. The diagnostic capabilities, availability of necessary reagents, method resolution, and accessibility of genetic and biological diagnostics limit the spectrum of cytogenetic changes outlined in the study. Widespread implementation of genetic diagnostic methods is necessary for the purpose of stratification and the selection of treatment tactics, as well as the introduction of new drugs to expand therapeutic options, improve survival, and reduce the side effects of therapy.

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АҢДАТПА

СОЗЫЛМАЛЫ ЛИМФОЛЕЙКОЗДЫ ЕМДЕУДІҢ САЛЫСТЫРМАЛЫ ТИІМДІЛІГІ: АЛМАТЫ КЛИНИКАСЫНЫҢ ТӘЖІРИБЕСІ

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Өзектілігі: *Созылмалы лимфоцитарлық лейкоздың (CLL) клиникалық және генетикалық гетерогенділігі терапия таңдауы мен нәтижелеріне әсер етеді. Цитогенетикалық және биологиялық маркерлер аурудың сатылануында, емдеу тактикасын айқындауда және болжам жасауда маңызды рөл атқарады. Нақты клиникалық тәжірибе деректерін талдау, химио-, иммунотерапия және нысаналы терапия режимдерінің нәтижелерін салыстыру СЛЛ бар науқастарды емдеудің оңтайлы алгоритмдерін қалыптастыруға мүмкіндік береді.*

Зерттеудің мақсаты *– цитогенетикалық параметрлерді, аурудың жасын және сатысын ескере отырып, созылмалы лимфолейкозбен ауыратын науқастарда химиотерапияның, иммунотерапияның және мақсатты терапияның салыстырмалы тиімділігін бағалау болды.*

Әдістері: *Зерттеуге 2001-2024 жылдар аралығында №7 қалалық клиникалық ауруханада (Алматы, Қазақстан) емделген 114 CLL пациентінің медициналық деректеріне ретроспективті талдау енгізілді. Науқастар екі топқа бөлінді: химио-иммунотерапия тобы (FC, FCR, CR, COP, хлорамбуцил режимдері), нысаналы терапия тобы (BTK/PI3K тежегіштері, анти-CD20 препараттары). Негізгі нүктелер: удемесіз өмір сүру ұзақтығы (ҮӨҰ) және жалпы жауап жиілігі (ЖЖЖ).*

Нәтижелері: *СЛЛ-мен ауыратын науқастарды ауру сатысы бойынша бөлу: В сатысы – 59,6% (n=68), А сатысы – 25,4% (n=29), С сатысы – 9,6% (n=11), анықталмаған сатысы – 5,4% жағдайлар (n=6). Цитогенетикалық зерттеуге сәйкес (n=63), ең жиі аберрация del13q14 (33%, n=21), оқшауланған немесе басқа ауытқулармен біріктірілген. Del11q22.3 – 17,5% (n=11), 12-хромосоманың трисомиясы – 11% (n=7), TP53 мутациялары – 6,3% (n=4) науқастарда анықталды. Ем нәтижелері бойынша ең жоғары медианалық ҮӨҰ FC (46,6 ай), CR (45 ай) және ибрутиниб (32,1 ай) режимдерінде байқалды. Кейінгі емдеу желілерінде ибрутиниб қабылдаған науқастарда (n=10) толық жауап жиілігі мен аурудың тұрақтану көрсеткіштері салыстырмалы деңгейде болды.*

Қорытынды: *Нақты клиникалық тәжірибеде нысаналы терапия жоғары қауіп тобындағы науқастарда және бұрын бір немесе бірнеше ем желілерін алған топта ҮӨҰ бойынша артықшылық береді әрі жақсырақ көтерімділікпен ерекшеленеді. Ал химиотерапия жекелеген кіші топтарда (жас науқастар, IGHV-мутациясы бар, қолайлы цитогенетика) қолданылатын опция болып қала береді. Генетикалық профильге негізделген емді жекелендіру СЛЛ бар науқастардағы нәтижелерді жақсартады. Болжамды арттыру үшін генетикалық зерттеулердің қолжетімділігін және спектрін кеңейту қажет.*

Түйінді сөздер: *созылмалы лимфолейкоз; салыстырмалы тиімділік; нысаналы терапия; химиоиммунотерапия; цитогенетика.*

АННОТАЦИЯ

СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ТЕРАПИИ ХРОНИЧЕСКОГО ЛИМФОЛЕЙКОЗА: ОПЫТ КЛИНИКИ Г. АЛМАТЫ

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Актуальность: *Клинико-генетическая гетерогенность хронического лимфолейкоза (ХЛЛ) влияет на выбор терапии и исходы. Большое значение в стадировании, выборе тактики лечения и прогнозе заболевания имеют цитогенетические и биологические маркеры. Изучение данных реальных клинической практики, сравнение результатов химио-, иммунотерапии и таргетных режимов помогает определить алгоритмы ведения пациентов с ХЛЛ.*

Цель исследования *– оценить сравнительную эффективность химио, иммунотерапии и таргетной терапии у пациентов с хроническим лимфолейкозом с учётом данных цитогенетики, возраста и стадии.*

Методы: *Проведен ретроспективный анализ данных 114 пациентов с ХЛЛ, получавших лечение в ГКП на ПХВ «Городская клиническая больница №7» (Алматы, Казахстан) в 2001-2024 гг. Группы: химио-иммунотерапии (FC, FCR, CR, COP, хлорамбуцил) и таргетные режимы (ингибиторы BTK/PI3K, анти-CD20). Конечные точки: выживаемость без прогрессирования (ВБП), частота общего ответа (ЧО).*

Результаты: *Распределение пациентов с ХЛЛ по стадиям заболевания: стадия В – 59,6% (n=68), стадия А – 25,4% (n=29), стадия С – 9,6% (n=11), стадия не установлена – 5,4% случаев (n=6). Согласно цитогенетическому исследованию (n=63), наиболее распространённой аберрацией являлась del13q14 (33%, n=21), изолированная или в сочетании с другими нарушениями. Del11q22.3 выявлена у 17,5% (n=11), трисомия 12 хромосомы – у 11% (n=7), мутации TP53 – у 6,3% (n=4). По результатам лечения наибольшая медиана ВБП наблюдалась при применении схемы FC (46,6 мес), CR (45 мес), ибрутиниб (32,1). У пациентов, получавших ибрутиниб в последующих линиях терапии (n=10), удалось достичь сопоставимой частоты полных ответов и стабилизации заболевания.*

Заключение: *В реальной клинической практике таргетная терапия обеспечивает преимущество по ВБП и лучшую переносимость у пациентов высокого риска и в группе пациентов, получивших одну или несколько линий предшествующей терапии, тогда как химиотерапия остаётся опцией для выбранных подгрупп (молодые, IGHV-мутация, благоприятная цитогенетика). Персонализация лечения на основе генетического профиля улучшает исходы у пациентов с ХЛЛ. С целью улучшения прогноза, выживаемость необходимо расширение доступа и спектра генетических исследований.*

Ключевые слова: *хронический лимфолейкоз; сравнительная эффективность; таргетная терапия; химиоиммунотерапия; цитогенетика; TP53.*

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POTENTIAL OTOTOXIC EFFECTS OF DIFFERENT GENERATIONS OF *EGFR* TYROSINE KINASE INHIBITORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Lung cancer is one of the most frequent malignant tumors, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases. Mutations in the epidermal growth factor receptor (EGFR) gene contribute significantly to NSCLC development. EGFR is key for tumor occurrence and progression. The discovery of tyrosine kinase inhibitors (TKI) targeting EGFR has marked significant progress, offering a more rational and effective therapeutic approach. However, TKIs are not free of side effects. Evidence indicates a potential link between TKI therapy and ototoxicity. Given the chronic nature of the treatment of patients with advanced stages of the disease, even minor toxicity can significantly affect the quality of life. It is essential to inform patients about the potential risk of hearing impairment and to regularly monitor for early signs of ototoxicity, thereby optimizing long-term treatment outcomes for patients.*

The study aimed to *review the existing data on tyrosine kinase inhibitors and their potential ototoxicity, including the main mechanisms of pathogenesis.*

Methods: *The search utilized PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar, and ClinicalTrials.gov to identify scientific publications on ototoxicity caused by TKIs in NSCLC. The keywords "non-small cell lung cancer," "ototoxicity," "gefitinib," "erlotinib," "afatinib," "dacomitinib," and "osimertinib" were used for the search.*

Results: *EGFR plays an important role in developing, maintaining, and repairing sensory and non-sensory structures of the inner ear. In neonatal models, EGFR is expressed in cochlear cells, including the cortical organ, facilitating regeneration and repair. However, in mature systems, EGFR expression decreases, primarily localized in the spiral ganglion, limiting the regenerative ability of auditory cells. By inhibiting EGFR signaling, cellular proliferation and repair mechanisms are disrupted, damaging the cochlea's hair cells and supporting cells.*

Conclusion: *The prevalence and main molecular mechanisms of ototoxicity caused by TKI remain poorly understood. Further research is needed to clarify dose-dependent effects, genetic predisposition, and potential protective strategies. Knowledge of this adverse effect is necessary to monitor auditory health during EGFR-TKI therapy and to study interventions that mitigate its effects on patients undergoing long-term treatment.*

Keywords: *non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), tyrosine kinase inhibitor (TKI), ototoxicity.*

Introduction: Cancer remains one of the most prevalent and significant global health challenges. In 2022, the worldwide incidence of cancer reached 19,976,499 new cases, with an age-standardized incidence rate of 196.9 per 100,000 population. During the same period, the total number of cancer-related deaths was reported at 9,743,832. Lung cancer is one of the most frequently diagnosed malignancies among both men and women, which highlights its significant contribution to the global cancer burden [1]. Among these cases, non-small cell lung cancer (NSCLC) accounts for approximately 85% [2].

The treatment of NSCLC is based on a multimodal approach, including chemotherapy, radiation therapy, and targeted therapy, aimed at minimizing adverse effects and improving therapeutic efficacy. Mutations in the epidermal growth factor receptor *(EGFR)* gene contribute significantly to NSCLC development. *EGFR* is key for tumor occurrence and progression. The significance of this genetic alteration is supported by Melosky et al.'s (2022) [3] findings, which revealed a significantly higher prevalence of *EGFR* mutations among Asian populations compared to Western populations. This disparity underscores the necessity of developing population-specific therapeutic strategies. Consequently, given the higher prevalence of *EGFR* mutations in Asian countries, using tyrosine kinase inhibitors (TKIs) appears to be the most rational and effective treatment approach for this patient group.

TKI revolutionized the treatment of NSCLC by providing a highly selective mechanism of action, leading to improved clinical outcomes and reduced systemic toxicity compared to conventional chemotherapy [4]. These inhibitors specifically target aberrant signaling pathways driven by mutations in key oncogenes, including *EGFR* [5], *ALK*, and *ROS1*, essential for tumor proliferation and survival [6]. First-generation TKIs, such as gefitinib and erlo-

tinib, demonstrated substantial efficacy in patients harboring *EGFR* mutations; however, their clinical utility was limited by the emergence of acquired resistance, most notably the *T790M* mutation [7]. Second-generation inhibitors, including afatinib and dacomitinib, irreversibly bind to *EGFR*, overcoming some resistance mechanisms [8]. Third-generation TKIs, such as osimertinib, were specifically designed to target *T790M* mutations and have demonstrated improved central nervous system penetration, further enhancing treatment efficacy [9]. The introduction of TKIs into clinical practice has markedly improved the progression-free and overall survival among patients with NSCLC. This made TKIs the main component of personalized cancer therapy.

Although cancer therapy is essential for improving survival rates, it is often associated with significant adverse effects on various organ systems. One of the most severe complications is cardiotoxicity, which can result in heart failure and arrhythmias, particularly in patients receiving anthracyclines or targeted therapies affecting cardiovascular function [10]. Similarly, neurotoxicity is a prevalent adverse effect, manifesting as cognitive impairments and peripheral neuropathy, which may significantly impact patients' quality of life [11, 12]. In addition to cardiovascular and neurological complications, hepatotoxicity and nephrotoxicity are common consequences of chemotherapy and targeted therapies, potentially leading to liver and kidney dysfunction and further complicating treatment regimens [13, 14]. Moreover, ototoxicity represents another critical adverse effect, often causing irreversible damage to auditory and vestibular functions, communication, and balance [15].

Ototoxicity is a severe adverse effect of cancer therapy that significantly affects patients' quality of life [16]. This toxicity is particularly associated with certain chemotherapeutic agents, including platinum-based drugs such as cisplatin, as well as targeted therapies like TKI, both of which have been shown to cause irreversible damage to the auditory and vestibular systems [16, 17]. The underlying mechanisms of ototoxicity involve the accumulation of toxic metabolites within inner ear cells, increased oxidative stress, and the apoptosis of sensory cells, ultimately leading to progressive hearing loss and balance disorders. Given the increasing life expectancy of cancer patients and the need for prolonged treatment, the long-term impact of ototoxicity has become a critical concern in oncology. Further research is essential to understand this issue and formulate effective preventive strategies. Therefore, the current study evaluated and compared the ototoxic impacts linked to EGFR inhibitors across the first, second, and third generations.

The study aimed to review the existing data on TKIs and their potential ototoxicity, including the main mechanisms of pathogenesis.

Materials and Methods: The search was conducted across four electronic databases: PubMed, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov to identify scientific publications on TKI-induced ototoxicity in NSCLC. The search strategy utilized Medical Subject Headings (MeSH) terms, including «non-small cell lung cancer», «ototoxicity», «gefitinib», «erlotinib», «afatinib», «dacomitiniband», «osimertinib». These terms were combined using Boolean operators (AND, OR) to refine the search results.

Inclusion criteria:

– Type of study: Original research (clinical trials, randomized controlled trials, prospective and retrospective cohort studies, observational studies, descriptions of clinical cases). Systematic reviews and meta-analyses. Clinical trials submitted for registration on ClinicalTrials.gov.

– Language of publication: English and Russian.

– Publication time frame: 2014-2024.

– Publication type: Peer-reviewed articles published in journals indexed in the databases PubMed, Scopus, Web of Science, and Google Scholar; unregistered clinical trials, available on ClinicalTrials.gov.

Exclusion criteria:

– Type of research: Low-quality publications that have not passed the review procedure (for example, conference abstracts, letters to the editor, editorial comments, expert opinions, literature reviews without a systematic approach).

– Publication language: Publications in languages other than English and Russian.

– Publication type: Duplicate publications.

– Reviews, comments, unpublished materials, and gray publications (for example, dissertations, reports).

Thus, 47 out of 741 selected sources were included in this study.

Results: *Molecular Mechanisms of the EGFR Signaling Pathway in Oncogenesis. EGFR* is a critical regulator of cellular proliferation, angiogenesis, apoptosis, and metastasis, making it a key target in oncological research and treatment. *EGFR* is a member of the ErbB receptor family, which also includes HER1 (*EGFR*), HER2 (*ErbB2*), HER3 (*ErbB3*), and HER4 (*ErbB4*), so it shares structural similarities and activation mechanisms with these receptors, collectively influencing various cellular processes [18]. A crucial component of *EGFR*-mediated signaling is the *EREG* gene family on chromosome 4, which plays a significant role in cancer progression by activating proliferative and pro-angiogenic pathways [19]. Under normal physiological conditions, *EGFR* activation triggers a complex intracellular signaling cascade involving pathways such as Ras/Raf/MEK/ERK, PI3K/Akt, PLCγ, JAK/STAT, and Src, which regulate cell growth, survival, migration, and angiogenesis [20]. Dysregulation of these pathways due to aberrant *EGFR* activation is a major driver of tumorigenesis, further underscoring the receptor's role as a crucial therapeutic target in cancer treatment.

The Ras/Raf/mitogen-activated protein kinase (MAPK) signaling cascade is a key regulator of cell proliferation and survival. Upon *EGFR* phosphorylation, adaptor proteins such as Grb2 and Sos are recruited, facilitating the activation of Ras, which serves as a critical intermediary between receptor activation and downstream intracellular signaling pathways [21]. This activation initiates a cascade in which Ras stimulates Raf-1, ultimately leading to the phosphorylation and activation of MAPKs [22]. While MAPK signaling is essential for maintaining normal cellular

functions, its dysregulation can profoundly impact apoptotic regulation. Specifically, persistent activation of extracellular signal-regulated kinase (ERK) inhibits the pro-apoptotic c-Jun N-terminal kinase (JNK) and p38 pathways, thereby disrupting the balance between cell survival and programmed cell death [23]. As a result, excessive MAPK activation suppresses caspase activity, promoting uncontrolled cell survival and facilitating tumor progression. This dysregulation underscores the critical role of MAPK signaling in oncogenesis and highlights its potential as a therapeutic target in cancer treatment.

Another crucial signaling route is the phosphoinositide 3-kinase (PI3K)/Akt pathway, which governs cell growth, survival, and resistance to apoptosis. PI3K, a dimeric enzyme, produces signaling molecules that activate Akt, a key serine/threonine kinase in cellular protection mechanisms [24]. *EGFR*-dependent PI3K activation is primarily mediated through HER3 dimerization, as *EGFR* lacks direct binding sites for PI3K regulatory subunits. Additionally, phospholipase Cγ (PLCγ) interacts with activated *EGFR*, catalyzing the breakdown of phosphatidylinositol 4,5-bisphosphate into inositol triphosphate (IP3) and diacylglycerol (DAG) [25]. This reaction regulates intracellular calcium release and activates protein kinase C (PKC), subsequently influencing MAPK signaling [26]. Signal transducers and activators of transcription (STAT) proteins, particularly STAT3, play a pivotal role in *EGFR*-mediated signaling by regulating key oncogenic processes. Upon activation, STAT proteins form dimers and translocate to the nucleus, modulating gene expression in cell proliferation, survival, and metastasis, thereby contributing to cancer progression [27]. In parallel, the Src kinase pathway is another crucial regulator of *EGFR* signaling, influencing cellular processes such as proliferation, adhesion, migration, and immune responses [28]. Src enhances *EGFR* activation and contributes to resistance against targeted therapies by interacting with alternative receptor pathways, allowing tumor cells to circumvent *EGFR* inhibition [29]. The interplay between STAT, Src, and *EGFR* signaling underscores the intricate nature of oncogenic networks and highlights the need for therapeutic strategies that target multiple pathways to overcome resistance and improve treatment efficacy.

Mechanisms of Action of EGFR Inhibitors of Different Generations. EGFR TKIs are categorized into three generations, each targeting specific *EGFR* mutations and addressing resistance mechanisms. These inhibitors exert their therapeutic effects by competitively binding to the ATP-binding site of the EGF Rkinase domain, thereby preventing the activation of downstream signaling pathways involved in tumor proliferation, survival, and metastasis. First-generation *EGFR*-TKIs function as reversible inhibitors that selectively target tumors harboring activating *EGFR* mutations, particularly exon 19 deletions and the L858R substitution in exon 21 [30]. These inhibitors bind reversibly to the ATP-binding pocket of *EGFR*, effectively suppressing aberrant signaling. However, despite their initial efficacy, their clinical utility is significantly compromised by the emergence of acquired resistance, predominantly driven by the T790M mutation in exon 20. This mutation enhances ATP affinity, thereby reducing the binding efficiency of first-generation TKIs and ultimately leading to treatment failure [31]. The clinical significance of first-generation TKIs was underscored by the regulatory approval of gefitinib by the U.S. Food and Drug Administration (FDA) on July 13, 2015. This approval is specifically applied to patients with metastatic non–small cell lung cancer (NSCLC) whose tumors harbor *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, as confirmed by an FDA-approved diagnostic test [32].

Second-generation *EGFR*-TKIs function as irreversible inhibitors, offering a broader spectrum of inhibition than their first-generation counterparts. These inhibitors covalently bind to a cysteine residue within the ATP-binding domain of *EGFR*, leading to irreversible receptor inhibition. Unlike first-generation TKIs, second-generation inhibitors exhibit expanded activity by targeting multiple receptors within the ErbB family, including *EGFR*, HER2, and HER4, thereby reducing the likelihood of resistance development through alternative pathway activation [33]. However, despite their broader inhibition profile, second-generation TKIs remain ineffective against the T790M mutation, a major resistance mechanism limiting ATP-competitive kinase inhibitors' efficacy. The T790M mutation increases ATP affinity, thereby reducing the binding efficiency of these inhibitors and necessitating the development of third-generation TKIs. Although irreversible inhibitors address resistance by forming covalent bonds with *EGFR*, second-generation TKIs cannot selectively target T790M, making them insufficient in overcoming this specific mutation [34]. The clinical relevance of second-generation TKIs was demonstrated by the FDA approval of afatinib in 2018 for treating rare *EGFR* point mutations. Specifically, afatinib was approved for patients with tumors harboring the S768I, L861Q, and G719X mutations, underscoring the continued refinement of targeted therapies to address diverse *EGFR* mutation profiles [35].

Third-generation *EGFR*-TKIs, irreversible Mutant-Selective Inhibitors, include Osimertinib (AZD9291), Rociletinib (CO-1686), and WZ4002. These inhibitors selectively target both *EGFR*-activating mutations and the T790M resistance mutation, the most common mechanism of acquired resistance. They form an irreversible covalent bond with the ATP-binding site, inhibiting *EGFR* signaling even in resistant tumors. Unlike second-generation inhibitors, they spare wild-type *EGFR*, reducing off-target toxicities such as skin rash and diarrhea. Osimertinib was the first third-generation *EGFR*-TKI to receive regulatory approval from both the FDA and EMA (2015, 2016) for patients with metastatic *EGFR*-mutant NSCLC [36] harboring the T790M mutation [37].

Ototoxicity of EGFR Inhibitors. Mechanisms and Potential Consequences. Unlike traditional chemotherapy, targeted therapy offers a more selective mechanism of action by specifically inhibiting molecular markers, thereby reducing systemic toxicity and minimizing adverse effects [39]. However, despite its improved safety profile, *EGFR* TKIs are associated with various treatment-related toxicities.

Ding et al. (2017) evaluated the risk of adverse effects associated with *EGFR* TKIs, including gefitinib, erlo-

tinib, and afatinib. The study identified diarrhea (53.3%) and rash (66.5%) as the most frequently reported adverse events, affecting more than half of the patients. These toxicities represent the most common treatment-related adverse effects, underscoring the clinical burden of *EGFR*-targeted therapies [40]. The high incidence of cutaneous toxicities, particularly rash, is primarily attributed to the widespread expression of *EGFR* in the skin. Since *EGFR* plays a pivotal role in skin homeostasis and repair, its inhibition disrupts normal cellular processes, leading to dermatologic side effects such as rash and dryness (41). In addition to skin-related toxicities, *EGFR* TKIs have been associated with a range of systemic adverse effects, including fatigue, oral ulcers, constitutional symptoms, nausea, elevated alanine aminotransferase (ALT) levels, dyspnea, and pulmonary toxicity [41].

Table 1 – Mechanisms of Action and Selectivity of Epidermal Growth Factor Receptor *(EGFR)* Tyrosine Kinase Inhibitors (TKI) [38]

EGFR TKI		Selectivity	Mechanism
1 generation	Gefitinib Erlotinib	Reversible *EGFR* inhibitors	*EGFR*
2 generation	Afatinib Dacomitinib Lapatinib	Irreversible inhibitors of *EGFR*, HER2, and HER4	*EGFR*, HER2, HER4
2 generation	Osimertinib Rociletinib	Selective inhibition of mutant *EGFR* (T790M)	*EGFR* (T790M)

The ototoxic effects of *EGFR* inhibitors remain insufficiently studied in the scientific literature. However, several studies indicate a potential association between the use of TKI and the development of sensorineural hearing loss (SNHL), highlighting the need for further investigation. *EGFR* is a transmembrane receptor tyrosine kinase that regulates key cellular functions, including cell proliferation, survival, angiogenesis, and migration. It plays a crucial role in various tissues, including the inner ear, which is involved in auditory processing [42]. The organ of Corti, located within the cochlea, contains mechanosensory hair cells responsible for converting sound vibrations into electrical signals transmitted to the brain. These cells closely interact with sensory neurons, and any disruption in this connection may result in SNHL. Research suggests that *EGFR* signaling is essential for maintaining this interaction, and its dysfunction may contribute to hearing impairment [43].

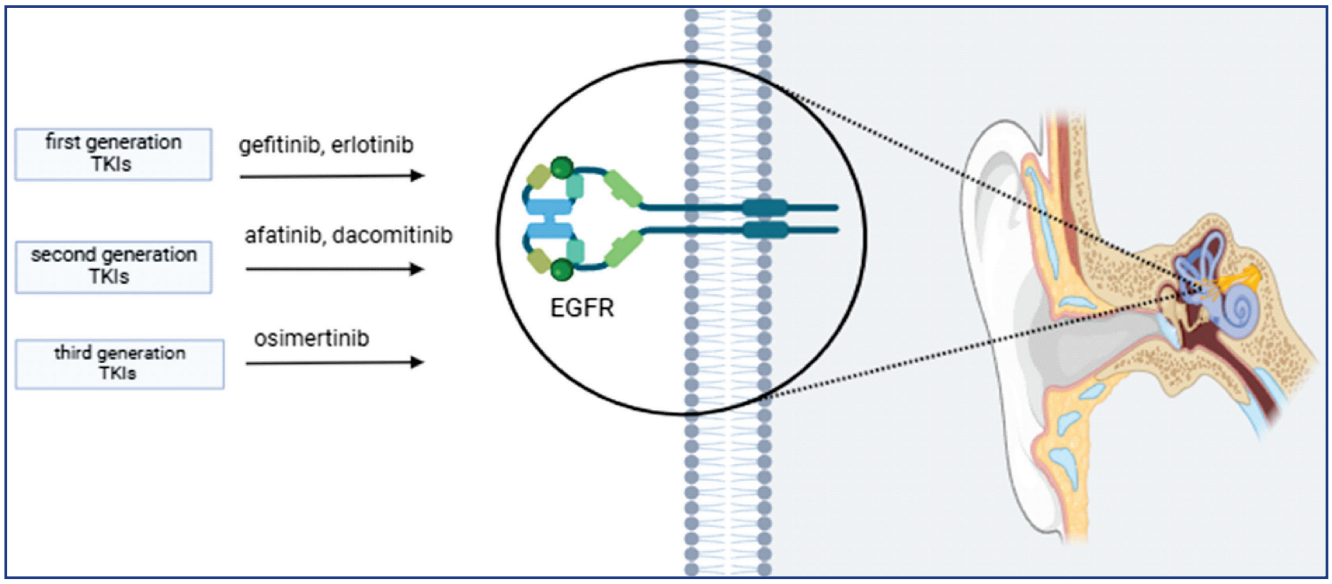

Figure 1 – Targeted Therapy Based on Types of Epidermal Growth Factor Receptor *(EGFR)* Tyrosine Kinase Inhibitors (TKIs)

One of the mechanisms explaining the role of *EGFR* in hearing is its involvement in the proliferation of cochlear-supporting cells. Normally, these cells possess a certain regenerative potential, but in the absence of *EGFR* signaling, they lose their ability to divide and repair damage, thereby limiting the regenerative capacity of the auditory system [44]. Various experimental studies support this hypothesis. For example, a study by Hume et al. (2003) conducted on Swiss Webster mice demonstrated that *EGFR* is expressed in sensory and non-sensory cochlear cells, including the organ of Corti, during early development. In the neonatal period, *EGFR* facilitates the repair of damaged cells; however, its expression declines with age and becomes predominantly restricted to the spiral ganglion. This reduction may explain the limited regenerative ability of the auditory system in adults [45]. Although these sources [44, 45] are over 10 years old, they represent foundational experimental work that has not been contradicted and is still cited in recent literature. These studies were among the first to describe the expression and function of *EGFR* in the cochlea and continue to provide essential mechanistic insight into the limited regenerative capaci-

ty of auditory cells – information that more recent studies often take as a basis for further investigation. These findings support the hypothesis that diminished *EGFR* signaling may contribute to progressive hearing loss. Additional evidence for this hypothesis has been obtained from experimental models. For instance, pharmacological inhibition of *EGFR* in Danio rerio (zebrafish) embryos has been shown to cause auditory dysfunction, underscoring the critical role of this receptor in auditory development and maintenance [46]. A potential link between TKI and hearing impairment has been observed in pharmacovigilance data. An analysis of reports from the FDA Adverse Event Reporting System identified a statistically significant association between the use of capmatinib, a MET TKI, and the development of adverse effects such as hearing loss and dysphagia [47].

Mechanisms of Ototoxicity: EGFR Inhibitors of Different Generations. As noted in the previous sections of this article, ototoxicity is a rare but noteworthy adverse effect associated with *EGFR* TKI. Although research on this phenomenon remains limited, existing studies provide evidence supporting the occurrence of ototoxicity in patients receiving these therapies. This section reviews documented cases and clinical studies investigating the ototoxic effects of *EGFR* TKIs. According to available data, several TKIs have been implicated in hearing impairment, including gefitinib, erlotinib, osimertinib, lapatinib, and canertinib.

First generation-Gefitinib. The ototoxic effects of first-generation *EGFR* TKIs are most commonly reported with gefitinib. For example, Zhu et al. (2023) documented a case of gefitinib-induced ototoxicity in a 51-year-old female patient diagnosed with right-sided bronchogenic adenocarcinoma (T4N3M1c, stage IVB, *EGFR*-mutation positive). The patient developed drug-induced bilateral SNHL and psychiatric disturbances after four months of gefitinib treatment. The patient had no prior history of hearing impairment or deafness before initiating gefitinib therapy. However, hearing loss occurred approximately four months after treatment initiation. Three months after starting treatment, she independently discontinued gefitinib, which resulted in a partial recovery of her auditory function. However, as her underlying malignancy progressed, she experienced worsening cough and wheezing, necessitating hospitalization. Following the deterioration of her condition, gefitinib therapy was resumed. After three days of reinitiation, the patient reported a recurrence and worsening of hearing loss, particularly in the right ear. Moderate to severe bilateral SNHL was confirmed through otoscopic evaluation, audiometric testing, and hearing assessment [43].

In another publication, Timuda et al. (2022) documented a case of a 51-year-old female patient diagnosed with right-sided bronchogenic adenocarcinoma (T4N3M1c, stage IVB, *EGFR* mutation-positive) who developed progressive visual impairment, severe bilateral SNHL, and psychiatric disturbances following 15 months of gefitinib therapy. Magnetic resonance imaging and computed tomography scans of the brain did not reveal evidence of metastatic involvement. Comprehensive audiological assessment, including otoacoustic [17].

In a case reported by Koutras et al. (2008), a 66-year-old female patient underwent surgical resection of pancreatic adenocarcinoma in December 2004 following endoscopic ultrasound-guided fine-needle aspiration. She subsequently received palliative chemotherapy with gemcitabine from November 2006 to May 2007. In August 2007, she initiated monotherapy with erlotinib (150 mg orally once daily). Notably, approximately 30 minutes after the first dose, the patient experienced the sudden onset of ear fullness, tinnitus, dizziness, and profound bilateral hearing loss, with greater severity in the right ear. While these symptoms partially subsided throughout the day, they recurred with increasing intensity following each subsequent dose of erlotinib. Despite the progressive worsening of auditory symptoms, the patient continued erlotinib therapy for 13 days, during which her hearing impairment significantly deteriorated, resulting in substantial communication difficulties. A physical examination revealed normal tympanic membranes with no evidence of nystagmus. The audiometric evaluation confirmed complete hearing loss in the right ear and severe SNHL in the left ear (80 dB at 1 kHz). Tympanometry results were within normal limits for both ears. Standard treatment protocols for drug-induced SNHL were administered; however, no significant improvement in auditory function was observed [42].

Second generation, Canertinib: J. Tang et al. (2015) investigated canertinib ototoxic effects using Danio rerio (zebrafish) and murine models. For an hour, free-swimming zebrafish larvae were exposed to canertinib (0-500 μM). Following exposure, the larvae were fixed, incubated with anti-parvalbumin primary antibodies, and stained with fluorescent secondary antibodies. The number of hair cells in neuromasts was assessed using a Zeiss Axioplan II microscope. In murine studies, two groups were used: a control group (receiving saline) and an experimental group (receiving canertinib at 30 mg/kg/day). Clinical trial dosages included 50, 150, and 450 mg/day, with the highest dose administered in a 14-day cycle followed by a 7-day break. The most common adverse effects in patients were rash and diarrhea. In murine studies, lethality was observed at 120 mg/kg/day doses, whereas 30-60 mg/kg/day doses were well tolerated without significant weight loss. Canertinib at concentrations up to 50 μM did not exhibit noticeable toxicity to zebrafish hair cells; however, at 100 μM ($p=0.28\times10^{-3}$) and 200 μM ($p=0.18\times10^{-10}$), significant hair cell loss was observed. In mice, ABR threshold shifts across five tested frequencies did not show a significant drug effect ($F=2.267$, $p=0.137$), but a significant impact was detected at 40 kHz ($F=5.392$, $p=0.024$). At the end of the experiment, cochlear histological analysis was performed to assess hair cell loss. Canertinib induced a dose-dependent loss of hair cells in the auditory system, confirming its potential ototoxicity [46].

Third generation – Osimertinib. Chee Chean Lim (2022) documented a case of a 72-year-old male diagnosed with stage IV lung adenocarcinoma harboring an exon 19 deletion in the *EGFR* gene [42]. The patient was prescribed oral osimertinib at a dosage of 80 mg once daily. However, six months into treatment, he developed progressive hearing impairment and bilateral tinnitus, prompting referral to an

otolaryngologist. Otoscopic examination revealed no abnormalities, while pure-tone audiometry (PTA) demonstrated moderate-to-severe bilateral SNHL.

Discussion: Our findings reaffirm that *EGFR* is a central regulator of cellular proliferation, apoptosis, migration, and angiogenesis, with its dysregulation playing a pivotal role in oncogenesis [18–20]. As a member of the ErbB receptor family, *EGFR* forms heterodimers with HER2-4, amplifying downstream signaling through MAPK and PI3K/Akt pathways, thus contributing to malignant transformation. These results align with recent literature emphasizing the multifaceted nature of *EGFR*-mediated signaling and the therapeutic challenges posed by pathway redundancy and acquired resistance mechanisms.

The *EREG* gene, located on chromosome 4, plays a particularly critical role, as it encodes an *EGFR* ligand and drives autocrine and paracrine stimulation of tumor proliferation and angiogenesis [19, 25]. Elevated expression of *EREG* has been associated with tumor aggressiveness and poor prognosis in various cancers, including NSCLC, colorectal cancer (CRC), and head and neck squamous cell carcinoma (HNSCC). Emerging evidence suggests that *EREG* contributes to resistance against *EGFR* TKIs, such as erlotinib and gefitinib, through sustained activation of PI3K/Akt and ERK pathways. This creates a state of oncogene addiction in tumor cells, making the *EREG-EGFR* axis a promising target for therapeutic intervention.

The MAPK pathway also plays a central role in *EGFR*-driven oncogenesis. *EGFR*-induced Ras/RAF/ERK signaling activation suppresses JNK/p38-mediated apoptotic responses, thereby enhancing tumor cell survival [21-23]. This is consistent with recent studies highlighting ERK1/2's regulatory influence on cell cycle progression via cyclin D and inhibition of pro-apoptotic cascades. Similarly, PI3K/Akt signaling, often initiated through HER3 dimerization with *EGFR*, supports cellular resistance to stress and apoptosis, underscoring its oncogenic significance [24].

Beyond these classical routes, our analysis underscores the importance of alternative signaling modules, including PLCγ/IP3/DAG–PKC, STAT3, and Src kinases. STAT3, upon activation by *EGFR*, modulates transcriptional programs related to proliferation, survival, and metastasis [27]. Src, in turn, enhances *EGFR* signaling and enables therapeutic escape by activating parallel oncogenic pathways [28, 29]. This complex interplay further illustrates the need for combinatorial therapeutic approaches.

Of particular note are recent efforts to target *EREG* directly. Antibody-drug conjugates (ADCs) and neutralizing antibodies against *EREG* have demonstrated significant antitumor activity in preclinical models. In CRC, demethylation of the *EREG* promoter has been shown to restore sensitivity to cetuximab, suggesting that epigenetic modulation may augment *EGFR*-directed therapies. Additionally, the *EREG/EGFR* axis has been implicated in immune evasion. In HNSCC, glycosylated *EREG* upregulates PD-L1 expression, contributing to an immunosuppressive microenvironment. Inhibitors targeting STT3B-mediated glycosylation of *EREG* are currently under investigation as potential tools to enhance antitumor immunity.

Finally, while current *EGFR*-TKIs such as gefitinib and osimertinib provide clinical benefit in tumors harboring activating *EGFR* mutations, resistance inevitably develops through secondary mutations (T790M, C797S) or bypass signaling. Consequently, therapeutic strategies must evolve to include inhibitors of parallel and downstream effectors, including *EREG* and its associated cascades, to overcome resistance and achieve durable responses.

EGFR-TKIs have a more selective mechanism of action than traditional chemotherapy, allowing for reduced systemic toxicity. However, despite their improved safety profile, there have been reports of rare but clinically significant adverse effects, including ototoxicity. While cutaneous and gastrointestinal toxicities such as rash and diarrhea are well-documented, hearing impairment remains insufficiently studied. Nonetheless, both clinical observations and experimental data suggest a potential association between *EGFR*-TKI therapy and the development of SNHL.

EGFR plays a critical role in various tissues, including the inner ear. It is expressed in cochlear structures such as the organ of Corti, the spiral ganglion, and supporting cells, which are essential for transducing sound vibrations into neural signals. Disruption of *EGFR* signaling may impair the regenerative capacity of supporting cells, resulting in auditory dysfunction. Preclinical studies using zebrafish and murine models have demonstrated that pharmacological inhibition of *EGFR* leads to a dose-dependent loss of hair cells and elevated hearing thresholds. Age-related downregulation of *EGFR* expression in cochlear tissues may also explain the limited regenerative potential of the auditory system in adults.

Clinical case reports further support the ototoxic potential of *EGFR*-TKIs. For instance, a 51-year-old patient developed bilateral SNHL four months after initiating gefitinib therapy. Partial recovery was observed upon discontinuation, but symptoms recurred and worsened following the reintroduction of the drug [17]. In another case, a 72-year-old patient receiving osimertinib developed progressive bilateral hearing loss and tinnitus within six months of treatment, which deteriorated over the following year to severe SNHL [42]. Acute-onset hearing loss has also been reported following the initial dose of erlotinib.

Experimental evidence corroborates these findings. Canertinib exposure in zebrafish resulted in significant hair cell loss in neuromasts, while murine models showed hearing threshold shifts, particularly at high frequencies [46]. Similarly, lapatinib, especially in combination with trastuzumab, induced apoptotic changes in the organ of Corti and the spiral ganglion in rodent models [48].

Although many studies remain limited, existing data indicate that *EGFR*-TKIs may exert ototoxic effects. As patient survival improves with targeted therapies, the clinical relevance of such adverse events becomes increasingly important. Consequently, regular audiological monitoring should be considered, particularly when early symptoms such as tinnitus or aural fullness arise. There is also a pressing need for prospective studies to assess the true incidence of *EGFR*-TKI-induced ototoxicity, elucidate the underlying mechanisms of auditory damage, and explore potential protective strategies.

Conclusion: This study highlights the potential ototoxic effects of various TKIs, including erlotinib, canertinib, and osimertinib, as evidenced by clinical case reports and experimental research. While these targeted therapies are effective in oncology, they may contribute to SNHL through mechanisms that require further investigation. Preclinical studies using zebrafish and murine models demonstrate dose-dependent hair cell toxicity, raising concerns about auditory damage in human patients. Clinical cases further emphasize delayed-onset and progressive SNHL in individuals undergoing TKI therapy, underscoring the importance of early detection and monitoring.

Moreover, physicians should counsel patients receiving *EGFR* TKIs about the potential risk of hearing loss and monitor for early symptoms. Since these patients typically have advanced-stage disease and undergo long-term treatment, even mild toxicities must be managed to maintain their quality of life. Unaddressed hearing loss can lead to communication difficulties, social isolation, and reduced adherence to therapy. A multidisciplinary approach, including comprehensive supportive care, is essential to optimizing treatment tolerability and preserving auditory function in cancer patients.

Supportive care therapy aimed at reducing ototoxicity includes an integrated approach involving oncologists, otorhinolaryngologists, audiologists, pharmacologists, and nurses, covering the following areas. Hearing monitoring (audiological support): initial audiometry before starting tyrosine kinase inhibitor therapy. Regular audiological examinations (tonal audiometry, speech audiometry, otoacoustic emission, registration of auditory evoked potentials) during treatment. Early diagnosis and identification of the first signs of ototoxicity for timely intervention. Pharmacological prophylaxis: prescribing drugs with antioxidant action to reduce oxidative stress in the cochlea of the inner ear. The use of neuroprotective agents can reduce the risk of sensorineural damage.

Rational selection of the therapy regimen: individualization of the treatment regimen considering the risk factors of ototoxicity. Dose adjustment of drugs in case of early symptoms of ototoxicity. In case of severe ototoxicity, it is possible to switch to alternative drugs or adjust dosages.

Patient education and psychological support: informing the patient about possible symptoms of ototoxicity (tinnitus, congestion, dizziness, hearing loss) and the need to inform the doctor promptly. Psychological and social support for the adaptation of patients to possible hearing changes.

Hearing rehabilitation: the use of hearing aids and other technical means of hearing correction with a significant decrease in hearing function. Vestibular rehabilitation for balance disorders and dizziness.

Treatment of concomitant diseases (e.g., diabetes mellitus, cardiovascular diseases) that may increase the risk of ototoxicity.

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АҢДАТПА

EGFR ТИРОЗИНКИНАЗА ИНГИБИТОРЛАРЫНЫҢ ӘРТҮРЛІ БУЫНДАРЫНЫҢ ӘЛЕУЕТТІ ОТОТОКСИКАЛЫҒЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Контрасты Өзектілігі: Өкпенің қатерлі ісігі жиі диагноз қойылған қатерлі ісік. Барлық жағдайлардың ішінде өкпенің ұсақ жасушалы емес қатерлі ісігі (NSCLC) шамамен 85% құрайды. NSCLC дамуының негізгі факторы ісіктің пайда болуы мен дамуында шешуші рөл атқаратын эпидермиялық өсу факторы рецепторы (EGFR) генінің мутациясы болып табылады. EGFR-ге бағытталған тирозинкиназа ингибиторларының (TKI) пайда болуы негұрлым ұтымды және тиімді терапевтік тәсілді ұсына отырып, айтарлықтай прогреске қол жеткізді. Тирозинкиназа ингибиторларының жанама әсерлері жоқ емес. Тирозинкиназа ингибиторлары терапиясы мен отоуыттылық арасындағы ықтимал байланысты көрсететін деректер пайда болады. Аурудың асқынған сатысы бар науқастарды емдеудің созылмалы сипатын ескере отырып, тіпті шамалы уыттылық өмір сапасына айтарлықтай әсер етуі мүмкін. Пациенттерді есту қабілетінің нашарлау қаупі туралы хабардар ету, пациенттерді емдеудің ұзақ мерзімді нәтижелерін оңтайландыру үшін отоуыттылықтың ерте белгілеріне тұрақты мониторинг жүргізу маңызды.*

Зерттеудің мақсаты *– тирозинкиназа ингибиторлары, олардың ықтимал отоуыттылығы, соның ішінде патогенездің негізгі механизмдері туралы бар деректерді зерттеу.*

Әдістері: *NSCLC-де TKI индукцияланған отоуыттылық туралы ғылыми жарияланымдарды анықтау үшін PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar және Clinical Trials.gov дерекқорларында іздеу жүргізілді. Іздеу үшін «ұсақ жасушалы емес өкпе обыры», «отоуыттылық әсер», «гефитиниб», «эрлотиниб», «афатиниб», «дакомитиниб» және «осимертиниб» кілт сөздері қолданылды.*

Нәтижелері: *EGFR ішкі құлақтың сенсорлық және сенсорлық емес құрылымдарын дамытуда, сақтауда және қалпына келтіруде маңызды рөл атқарады. Неонатальды модельдерде EGFR кохлеарлы жасушаларда, соның ішінде Корти орган, онда ол регенерация мен қалпына келтіру процестерін жеңілдетеді. Алайда, жетілген жүйелерде EGFR экспрессиясы төмен-дейді, ең алдымен есту жасушаларының регенеративті қабілетін шектейтін спиральды ганглияда орналасады. EGFR дабылын тежеу арқылы жасуша пролиферациясы мен қалпына келтіру механизмдері бұзылады, бұл кохлеарлық шаш жасушалары мен тірек жасушаларына зақым келтіреді.*

Қорытынды: *TKI-индукцияланған отоуыттылықтың нақты таралуы мен негізгі молекулалық механизмдері аз зерттелген. Дозаға тәуелді әсерлерді, генетикалық бейімділікті және ықтимал қорғаныс стратегияларын анықтау үшін қосымша зерттеулер қажет. Бұл жағымсыз әсерді білу EGFR-TKI терапиясы кезінде есту денсаулығын бақылау және оның ұзақ емделетін науқастарға әсерін жеңілдететін араласуларды зерттеу үшін қажет.*

Түйінді сөздер: *өкпенің ұсақ жасушалы емес қатерлі ісігі, эпидермиялық өсу факторының рецепторы, тирозинкиназа ингибиторлары, отоуыттылық.*

АННОТАЦИЯ

ПОТЕНЦИАЛЬНАЯ ОТОТОКСИЧНОСТЬ РАЗНЫХ ПОКОЛЕНИЙ ИНГИБИТОРОВ ТИРОЗИНКИНАЗЫ *EGFR*: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак легкого – часто диагностируемое злокачественное новообразование. Немелкоклеточный рак легкого (НМРЛ) составляет примерно 85% случаев рака легкого. Ключевым фактором развития НМРЛ является мутация гена рецептора эпидермального фактора роста (EGFR), который играет ключевую роль в возникновении и прогрессировании опухоли. Появление ингибиторов тирозинкиназы (ИТК), нацеленных на EGFR, ознаменовало значительный прогресс,*

предложив более рациональный и эффективный терапевтический подход. Ингибиторы тирозинкиназы не лишены побочных эффектов. Появляются данные, указывающие на потенциальную связь между терапией ИТК и ототоксичностью. Учитывая хронический характер лечения пациентов с запущенной стадией заболевания, даже незначительная токсичность может существенно повлиять на качество жизни. Важно информировать пациентов о потенциальном риске ухудшения слуха, осуществлять регулярный мониторинг ранних признаков ототоксичности для оптимизации долгосрочных результатов лечения пациентов.

***Цель исследования** – изучение существующих данных об ингибиторах тирозинкиназы, их потенциальной ототоксичности, включая основные механизмы патогенеза.*

***Методы:** Поиск проводился по базам данных PubMed, Scopus, Embase, Cochrane Library, Web of Science, Google Scholar и Clinical Trials.gov для выявления научных публикаций об ототоксичности, вызванной приёмом ингибиторов тирозинкиназы при НМРЛ. Для поиска использовались ключевые слова «немелкоклеточный рак лёгкого», «ототоксичность», «гефитиниб», «эрлотиниб», «афатиниб», «дакомитиниб» и «осимертиниб».*

***Результаты:** EGFR играет важную роль в развитии, поддержании и восстановлении сенсорных и несенсорных структур внутреннего уха. В неонатальных моделях EGFR экспрессируется в кохлеарных клетках, включая кортиев орган, где он облегчает процессы регенерации и восстановления. Однако в зрелых системах экспрессия EGFR снижается, в первую очередь локализуясь в спиральном ганглии, ограничивая регенеративную способность слуховых клеток. Ингибируя сигнализацию EGFR, нарушается клеточная пролиферация и механизмы восстановления, что приводит к повреждению волосковых клеток улитки и поддерживающих клеток.*

***Заключение:** Точная распространенность и основные молекулярные механизмы ототоксичности, вызванной ИТК, остаются плохо изученными. Необходимы дальнейшие исследования для выяснения дозозависимых эффектов, генетической предрасположенности и потенциальных защитных стратегий. Знание этого неблагоприятного эффекта необходимо для мониторинга слухового здоровья во время терапии EGFR-TKI и для изучения вмешательств, которые смягчают его влияние на пациентов, проходящих длительное лечение.*

***Ключевые слова:** немелкоклеточный рак легкого (НМРЛ), рецептор эпидермального фактора роста, ингибиторы тирозинкиназы (ИТК), ототоксичность.*

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MULTIGENE TESTING IN GENETIC SCREENING OF HEREDITARY AND SPORADIC COLORECTAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Molecular genetic testing to determine the patient's genotype and tumor molecular profile is a key component of a personalized approach to treatment and follow-up. Current research in genetic screening focuses on transitioning from phenotypic diagnostic panels and PCR testing of predisposition genes to large panels that include many identified genes or whole-genome sequencing. Multigene testing is widely used across colorectal cancer (CRC) diagnostics and therapy, where genetic components make a significant contribution. Currently, practical oncology requires a review of high-throughput sequencing systems for the genetic screening of hereditary and sporadic CRC variants and for the optimization of early diagnosis in relatives of patients.*

The study aimed to *review the methodology and current results of next-generation sequencing (NGS) applications for genetic screening of hereditary and sporadic colorectal cancer.*

Methods: *This analytical review included 70 original research and review articles available in open-access databases, including Google Scholar, Web of Science, SpringerLink, Scopus, ScienceDirect, PubMed, and BMJ.*

Results: *NGS-based multigene testing enables the simultaneous analysis of multiple genes involved in carcinogenesis, the identification of germline pathogenic mutations associated with hereditary tumor syndromes, and the detection of genetic variants in less-studied regions of genes, such as introns and untranslated regions, which help identify previously unknown factors predisposing to colorectal cancer.*

Conclusion: *Molecular genetic diagnostics facilitate personalized treatment of patients and individualized clinical examination of relatives from risk groups. However, although approximately 25% of CRC cases are familial, fewer than 5% of families are studied genetically. The analyzed data confirm the need to transition from phenotypic panels to comprehensive panels, encompassing all identified genes involved in hereditary tumor syndromes or whole-genome sequencing. In addition, identifying new variants with moderate and low penetrance, as well as those with uncertain functional significance, expands the phenotypic spectrum of CRC and necessitates further studies to determine their inclusion in diagnostic sequencing panels.*

Keywords: *Colorectal cancer (CRC), pathogenic mutations, next-generation sequencing, hereditary variants, genetic screening.*

Introduction: It has been established that approximately 25% of colorectal cancer (CRC) cases are associated with a family history of cancer or colorectal adenomas, and up to 5% arise in the context of hereditary cancer syndromes (HCS) with a relatively clear clinical picture and known causative mutations [1]. However, in the majority of cases, the genetic etiology of the disease remains unidentified. Families with clustering of CRC cases are heterogeneous with respect to phenotype, inheritance patterns, and lifetime cancer risk [2]. At the same time, establishing an accurate genetic diagnosis and identifying mutations significantly improves the effectiveness of early diagnosis and personalized treatment for patients, as well as the monitoring of conditionally healthy relatives [3]. The diagnosis of HCS influences therapeutic approaches (total/subtotal colectomy vs. segmental resection; choice of chemotherapy regimen) and follow-up care (colonoscopy and CT scan frequency; detection of possible extracolonic manifestations and metachronous tumors) [4]. Multigene testing (MGT) for conditionally healthy blood relatives of patients with familial and hereditary CRC is relevant, as it enables early diagnosis optimization. In Kazakhstan, only isolated studies based on next-generation sequencing (NGS) have been published to date, focusing on the frequency and spectrum of pathogenic germline mutations (GM) in patients and their relatives. At the same time, as shown, the proportion of Kazakhstani patients with a hereditary burden (HB) accounts for approximately 15% [5]. This underscores the relevance of implementing NGS testing in genetic screening and early diagnosis of CRC, as well as the interest in published data on methodology and results across different age and ethnic groups of patients.

The study aimed to review the methodology and current results of next-generation sequencing (NGS) appli-

cations for genetic screening of hereditary and sporadic colorectal cancer.

Materials and Methods: Original studies and review articles available in open-access academic databases were analyzed, including Google Scholar, Web of Science, SpringerLink, Scopus, ScienceDirect, PubMed, and BMJ, to review the approaches and results of MGT in genetic screening for CRC. A total of 114 sources were identified, of which 70 were included in the review. The selection criteria for articles were: the use of NGS as the primary experimental method with "hybrid" gene panels; the description of novel, previously unannotated mutations; and study designs that included young patients, patients with familial and hereditary forms of CRC, and relatives of patients.

Results: NGS-based multigene testing (MGT) enables the simultaneous analysis of multiple genes involved in carcinogenesis, the identification of germline pathogenic mutations leading to tumors or HCS [6-8], as well as the detection of genetic variants in less studied regions of genes, such as intronic and untranslated regions, which contributes to the identification of new, previously unknown cancer predisposition factors [9-11]. The use of "hybrid" diagnostic panels makes it possible to identify various types of genomic instability – copy number variations (CNVs), gene fusions, loss of heterozygosity (including copy-neutral LOH), ploidy, breakpoint detection, mosaicism, clonal heterogeneity, chromothripsis – as well as to assess the methylation status of oncogenes, tumor mutational burden, and microsatellite instability (MSI). These approaches are actively implemented in the comprehensive molecular genetic analysis of sporadic and hereditary CRC [12, 13].

As shown by S.A. Schubert et al., although approximately 25% of CRC cases are "familial", about 95% of individuals with HB do not undergo molecular genetic testing [2]. According to N.J. Samadder et al., in the United States, approximately half of CRC patients with clinically significant genetic variants (mutations) are not identified when diagnostics are based solely on standard clinical guidelines and criteria [14, 15]. Currently, even for researchers from countries with well-characterized populations, it remains unclear how many CRC patients and their relatives could benefit from NGS testing using large gene panels [16].

The concept of a *loss-of-function* (LoF) *mutation* is not equivalent to that of a *pathogenic mutation* or *pathogenic genetic variant* that leads to the phenotypic manifestation of a disease. The effect of the latter and its correlation with carrier status must be confirmed by case-control studies or functional assays [17]. Similarly, a distinction is made between established *cancer predisposition genes*, whose roles in carcinogenesis are clearly defined, and candidate genes, whose associations with tumor development are yet to be determined. The convergence of somatic and germline mutation profiles is well established in CRC genetics. For example, universal testing for mismatch repair (MMR) deficiency is a widely accepted approach to identify patients with germline mutations or Lynch syndrome (LS). While targeted testing of germline mutations in known genes can confirm a diagnosis of LS (or another specific HCS), large-panel sequencing detects GMs whose clinical significance is ambiguous and difficult to interpret.

In a comparative study of a heterogeneous group of Russian patients, A. Bilyalov et al., using a 44-gene panel, identified pathogenic variants (PVs) and likely pathogenic variants (LPVs) in 21.6% of patients with CRC, gastric cancer (GC), pancreatic cancer (PC), breast cancer (BC), and ovarian cancer (OC), with a mean age of onset of 44.5 years. Most of the mutations (39.4%) were detected in the *BRCA1* and *BRCA2* genes. The second most frequent were variants in the *CHEK2* gene (9.8%), and the third most frequent were variants in the *ATM* gene (6.3%), which were found in cases of PC and BC. In patients with CRC, the highest number of PVs was identified in the *MLH1* and *APC* genes. A previously unknown PV, c.160_166del in the *MLH1* gene – a 7 bp deletion in exon 2 – leads to the formation of a premature stop codon. In the same study, patients with multiple primary tumors (MPTs) were found to carry previously unannotated LPVs in the *MSH2* gene (c.893del and c.1729del) in a heterozygous state, resulting in a frameshift and formation of a premature stop codon [18].

It is well known that cancer risk and survival outcomes correlate with mutations in specific genes associated with LS. Although P. Møller et al. previously estimated the cumulative risk of CRC by age 75 to be 46% for carriers of heterozygous MLH1 mutations and 43% for carriers of heterozygous MSH2 mutations, the mean age at diagnosis, according to most publications, is 44 years [19]. Germline defects in MMR genes – *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which form the molecular basis of LS – typically represent nucleotide-level changes within exonic sequences. These mutations induce generalized genomic instability, particularly at microsatellite loci. Loss of expression of *MLH1* and *MSH2* protein products, detected by immunohistochemistry (IHC), is used to identify patients with hereditary nonpolyposis colorectal cancer (HNPCRC) and germline mutations in the respective genes. It has been shown that the absence of known mutations or MSI in the tumor does not exclude a diagnosis of HNPCRC (so-called HNPCRC type X syndrome), and therefore necessitates sequencing to identify other germline mutations, as well as somatic mutations in the second allele or loss of heterozygosity [20].

Mutations in the *EPCAM* locus are associated with disruptions in cell migration, adhesion, proliferation, and signaling processes. It is known that 3'-deletions in *EPCAM* lead to hypermethylation of the MSH2 promoter, ultimately resulting in the phenotypic manifestation of LS. However, it remains unclear whether mutations in other re-

gions of *EPCAM*, including splicing regions, contribute to LS pathogenesis.

MLH genes are involved in maintaining genomic integrity during DNA replication and meiotic recombination. Studies on the association between germline MLH3 mutations and the development of HNPCRC have not established a clear link. Previously, H.X. Liu et al. demonstrated that *MLH3* is a low-penetrance gene. Furthermore, in a study of DNA isolated from tumor tissue, MLH3 mutations did not correlate with MSI levels, suggesting that this locus may not be involved in carcinogenesis by disrupting MMR mechanisms [21].

Recent publications report novel pathogenic variants in other MMR loci. M. Djursby et al., using a 32-gene panel, identified two variants in the *PMS2* gene in a cohort of young patients (under 40 years of age) [22]. The indel variant c.736_741delinsTGTGTGTGAAG/p.Pro246Cysfs*3 is annotated in the InSiGHT database as pathogenic and was previously identified in European patients [23]. The splice-site variant c.2275+1G>C, previously undescribed, was classified by the authors as an LPV based on results from long-range PCR, IHC, and *in silico* analysis. In the same study, a mutation in *MSH2* (c.2168C>T/p.Ser723Phe) was reported in a cohort of patients with familial forms of CRC. This variant had been previously identified in members of a family in Denmark and annotated in the InSiGHT database as a variant of uncertain functional significance. This variant was detected in a patient with MPTs – CRC (with loss of *MSH2* expression and unknown MSI status) and ampullary duodenal adenocarcinoma (with loss of *MLH1/PMS2* expression and *MLH1* promoter methylation). The HB pattern in this patient is of particular interest: early-onset CRC in the parents (44 years, non-carrier of the mutation in question) and extremely early-onset CRC in the offspring (25 years), who was a carrier of the mutation. Ser-723 is a highly conserved amino acid, and the c.2168C>T mutation is classified as pathogenic based on *in silico* analysis [22]. Previous studies using in vitro MMR models and human embryonic stem cells have demonstrated that this mutation disrupts MMR and is pathogenic [24, 25].

The *GALNT12* gene product participates in the catalysis of N-acetylgalactosamine (GalNAc) transfer from uridine diphosphate N-acetylgalactosamine (UDP-GalNAc) to a serine or threonine residue on a polypeptide acceptor. This reaction constitutes the first step of a type of post-translational modification known as O-linked protein glycosylation. K. Guda et al. suggested that germline loss-of-function mutations in *GALNT12* are associated with increased CRC risk [26]. The correlation between *GALNT12* PVs and CRC was further confirmed by D.R. Evans et al. [27].

Mutations in the tumor suppressor gene *APC* (nonsense or frameshift) lead to the formation of a premature stop codon and a functionally deficient protein. Loss of gene function may also result from hypermethylation. The *APC* gene, located on chromosome 5, encodes a protein that acts as a negative regulator of the evolutionarily conserved canonical Wnt signaling pathway. A key function of this protein is the cytoplasmic degradation of β-catenin: normally, this mechanism prevents its translocation into the nucleus, where it acts as a co-activator of transcription factors from the TCF/LEF family, thereby preventing uncontrolled cell division.

Several forms of familial adenomatous polyposis (FAP) are described, each characterized by different phenotypes. In Gardner-Turner syndrome, extracolonic manifestations are prominent (GI polyps, tooth anomalies, osteomas, cutaneous fibromas, and epidermoid cysts); in Turcot syndrome, brain tumors (e.g., medulloblastomas) occur. Correlations have been reported between mutation sites in the *APC* gene and corresponding clinical phenotypes. The classic form of FAP is caused by mutations in the central region of the gene, specifically between codons 168 and 1250, located closer to the 5' terminus. The diffuse form of FAP is observed in patients with mutations within codons 1285-1465. A missense variant, c.289G>A/p.Gly97Arg was described by M. Djursby et al. in siblings with the attenuated FAP (AFAP) phenotype, as well as in other family members [22]. This variant had previously been reported in AFAP patients in a study by D. Wang et al. [28]. The mutation leads to the formation of a cryptic splice acceptor site, disrupting normal splicing, and is annotated as an LPV.

Recently, a growing body of evidence has emerged regarding genetic alterations responsible for familial forms of CRC that are not related to HNPCRC or FAP. This category includes mutations in the *POLE*, *POLD1*, and *NTHL1* genes, identified through genome-wide association studies (GWAS) [29].

The *POLE* gene encodes the catalytic subunit of DNA polymerase epsilon, one of the four nuclear DNA polymerases involved in DNA repair. Homozygous pathogenic mutations in *POLE* cause autosomal recessive syndromes, such as FILS (OMIM #615139) and IMAGE-I (OMIM #618336) [18, 30-31]. According to P. Mur et al., germline PVs in *POLE* and *POLD1* are most frequently associated with CRC, endometrial cancer (EC), and OC [32]. Heterozygous variants in *POLE* that alter the structure of the exonuclease domain are associated with an increased risk of CRC. Further studies confirmed this association and identified numerous clinically significant pathogenic variants in *POLE* [33]. In the previously mentioned study, A. Bilyalov et al. described a novel LPV in *POLE* – c.802-2A>G – in a CRC patient. This variant represents a single-nucleotide substitution in the canonical splice site. According to the authors, the variant may lead to loss of function in the exonuclease domain or the entire protein [18]. M.F. Hansen et al. reported a PV in *POLE* c.1373A>T/p.Tyr458Phe was identified in three individuals from the same family. The inherited mutation c.824A>T/p.Asp275Val was

identified in a patient with OC and HB (CRC), and was initially considered a somatic alteration in EC, rather than a germline PV [34]. Previously, A. Rohlin et al. [35] and P. Vande Perre et al. [36] described the variant c.1089C>A/p.Asn363Lys in two large families with a phenotype including multiple tumors. The mutation affects the highly conserved amino acid Asn-363 in the exonuclease domain of POLE; however, to date, only missense variants in this domain have been considered pathogenic [37]. M. Djursby et al., who identified this same variant in a cohort of patients with very early-onset disease (under 40 years), reclassified it as a likely pathogenic variant based on *in silico* analysis and segregation data in families, as previously published by Rohlin and Vande Perre [22].

The serine/threonine kinase ATM is a member of the phosphoinositide 3-kinase-related protein kinase family and plays a critical role in the cellular response to DNA damage. Loss-of-function PVs in the *ATM* gene cause *ataxia-telangiectasia*, a rare autosomal recessive disorder characterized by neurodegeneration, increased radiation sensitivity, immunodeficiency, and cancer predisposition. Heterozygous carriers of germline PVs have an increased risk of developing various types of cancer, including BC [18, 38]. Hansen et al., using a 112-gene panel for sequencing, identified pathogenic germline mutations c.8494C>T/p.Arg2832Cys and c.8584+2T>C in patients with CRC – one of whom had a family history of BC, and the other had HB with synchronous tumors and polyposis. The same study also described patients with early-onset CRC and PVs in the *BRCA* genes. In carriers of BRCA1 c.4096+3A>G and BRCA2 c.2808_2811del/p.Ala938Profs*21, the family history included CRC, BC, and OC. Based on a segregation analysis within the family, the authors concluded that variant c.4096+3A>G in the patient and their first-degree relative is associated with CRC predisposition to a greater extent than with BC or OC [34].

In a cohort of Norwegian and Australian patients previously tested for LS, M.F. Hansen et al. described a PV in the *PTEN* gene in a patient with MPTs consistent with the Cowden syndrome spectrum [34]. The missense variant c.377C>T/p.Ala126Val is located in a highly conserved catalytic domain and, as shown by Costa et al., results in the formation of a completely inactive protein [39]. The *CHEK2* variant c.1100del/p.Thr367Metfs*15 was identified in a patient with early-onset CRC (age 37). This mutation has previously been described as being associated with BC, CRC, and prostate cancer.

In addition to variants in high-penetrance loci, NGS platforms are increasingly used to study mutations in moderate- and low-penetrance genes, such as *GALNT12* [23] and *EXO1* [40], as well as the effects of heterozygous PVs in autosomal recessive genes like *NTHL1* and *MSH3* [41, 42].

Discussion: NGS and GWAS are currently widely used to identify the etiology of familial CRC by detecting new candidate genes and PVs whose association with CRC has not yet been confirmed through case-control studies [43, 44]. In addition, whole-exome sequencing (WES) is applied to identify homozygous and polygenic mutations in cases of FAP, LS, or other familial forms of CRC [45, 46]. Polygenic variation has also been recognized as a potential cause of increased penetrance in LS [47]. The selection of candidate genes (panel design) for sequencing may be based on prioritization scores [48]; however, WES may also provide clinically significant information from non-coding regions of the genome. Using extended panels for WES, it is possible to expand the scope of analysis to include regions beyond exons, such as 5′ untranslated regions to capture transcription factor binding sites and reading frames, and 3′ untranslated regions to identify microRNA binding sites involved in gene regulation.

Mendelian inheritance syndromes account for approximately 5% of all CRC cases in which hereditary factors play an etiological role. These syndromes are caused by mutations and epimutations in well-studied predisposition genes, including MLH1, PMS2, MSH2, MSH6, EPCAM, APC, SMAD4, BMPR1A, STK11, MUTYH, PTEN, KLLN, PIK3CA, AKT1, POLE, POLD1, AXIN2, BUB1, and *BUB3*. It is not uncommon for a patient's personal or family history to require the simultaneous evaluation of multiple high-penetrance genes with known clinical impact – especially when clinical criteria for several syndromes are met within a single family (a phenomenon known as phenotypic overlap, often attributed to gene pleiotropy) [34], or when the patient presents with metachronous or synchronous tumors. When detailed family history is unavailable or when there is a high likelihood of a syndrome in individuals who do not meet standard diagnostic criteria, MGT is warranted. In clinical genetic counseling, patients with previous negative or inconclusive results from single-gene testing but with a clear familial predisposition to cancer should undergo NGS-based testing using multigene panels [49]. MGT is particularly clinically valuable in colorectal tumors with overlapping phenotypes, where differential diagnosis requires the analysis of multiple genes. For example, in Lynch syndrome, NGS may be more appropriate when IHC results are inconclusive.

In some families with FAP or LS-like features, no mutations are detected in *APC*, *MUTYH*, or MMR genes. Recently, mutations in *POLE*, *POLD1*, and other DNA repair genes have been identified in such families, leading to the diagnosis of "polymerase proofreading-associated polyposis" [37]. Considering the evidence of the functional significance of newly identified genes and the "phenotypic overlap" of the most common hereditary syndromes, as well as cases in which mutations in more than one gene may cause the condition, MGT represents a cost-effective approach to molecular genetic analysis and allows for the detection of mutations that are not identified through candidate gene testing [50]. Comprehensive genomic

profiling can be implemented in several formats: testing both tumor and normal tissue, testing tumor tissue only, or using circulating tumor DNA (the so-called "liquid biopsy"). For MGT performed using tumor-only DNA, the ESMO Precision Medicine Working Group (ESMO-PMWG) has proposed a PV filtering strategy to confirm germline origin. This strategy considers factors such as age at diagnosis, cancer type, the clinical significance of the gene, and the variant's allele frequency in tumor tissue [51]. The germline conversion rate for each gene is calculated as the ratio of germline PVs to the total number of PVs identified in the tumor.

In current molecular oncology practice, gene panels are used for targeted or broad NGS-based sequencing. Diagnostic panels allow for a more comprehensive assessment of syndromic conditions and the evaluation of CRC risk in patients' relatives. Panels routinely used in the U.S. (e.g., NCCN, Ambry Genetics®) include genes associated with: FAP (*APC*), MUTYH-associated polyposis (*MUTYH*), Peutz-Jeghers syndrome (*STK11*), juvenile polyposis (*BMPR1A*, *SMAD4*), Lynch syndrome (*MLH1, MSH2, MSH3, MSH6, PMS2, EPCAM*), polymerase proofreading-associated polyposis (*POLE, POLD1*), PTEN-related polyposis, and other genes whose association with familial or hereditary CRC has been confirmed in case-control studies (*AXIN2, ATM, GALNT12, CHEK2, GREM1, NTHL1*, and *TP53*). However, implementing such panels in Kazakhstan's oncology practice is limited, as the gene sets were designed for patient cohorts from the U.S., Europe, Southeast Asia, and China, whose ethnic-genetic backgrounds differ from those of the Kazakh population. It is known that some pathogenic variants exhibit ethnic and racial specificity in modulating CRC risk. Another limiting factor is the restricted scope of any diagnostic panel used for sequencing; in particular, the absence of clinically relevant genes such as *GSTM1, GSTT1, DCC*, and *RAS* in several commercial panels [50].

Conclusion: Over the past decade, multigene panels based on next-generation sequencing (NGS) have been introduced into both fundamental and practical oncology, enabling the analysis of multiple genes associated with specific HCS. This approach identifies variants in less well-studied gene regions and improves understanding of the mechanisms underlying predisposition to colorectal cancer (CRC), including early-onset disease. The NGS methodology enables the identification not only of pathogenic mutations but also of variants of uncertain functional significance, which may influence CRC predisposition. Variants in the *BRCA1, BRCA2, DICER1, FANCC, FANCM*, and *TSC2* genes, which alter protein function by disrupting critical cellular and tissue processes these genes regulate, expand the phenotypic spectrum of malignancies in CRC and help identify synchronous and metachronous neoplasms in other organs [50]. This personalizes treatment strategies for patients and enables early diagnosis and medical surveillance for their relatives.

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АҢДАТПА

ТҰҚЫМ ҚУАЛАЙТЫН ЖӘНЕ СПОРАДИКАЛЫҚ КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІКТІҢ ГЕНЕТИКАЛЫҚ СКРИНИНГІНДЕГІ МУЛЬТИГЕНДІК ТЕСТІЛЕУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Науқастың генотипін және ісіктің молекулалық профилін анықтауға арналған молекулалық-генетикалық тестілеу емдеуге және клиникалық тексеруге дербестендірілген тәсілдің негізгі құрамдас бөлігі болып табылады. Генетикалық скринингтегі қазіргі зерттеулер фенотиптік диагностикалық панельдерден және сезімталдық гендерін ПТР тестілеуден көптеген анықталған гендерді немесе тұтас геном секвенциясын қамтитын үлкен панельдерге өтуге бағытталған. Мультигендік тестілеу колоректальды қатерлі ісік (КҚІ) диагностикасы мен терапиясының әртүрлі салаларында кеңінен қолданылады, оның пайда болуына генетикалық компоненттер маңызды үлес қосады. Қазіргі уақытта практикалық онкология КҚІ тұқым қуалайтын және спорадикалық нұсқаларының генетикалық скринингі үшін жоғары өнімді секвенирлеу жүйелерін қайта қарауды және пациенттердің туыстарында оның ерте диагностикасын оңтайландыруды талап етеді.*

Зерттеудің мақсаты *– тұқым қуалайтын және спорадикалық колоректальды обырдың генетикалық скринингі үшін келесі буынды секвенирлеуді (NGS) қолданудың әдіснамасы мен ағымдағы нәтижелеріне шолу.*

Әдістері: *Google Scholar, Web of Science, Springer Link, Scopus, Science Direct, PubMed, BMJ сайттарында ашық қолжетімділікте қолжетімді түпнұсқалық зерттеулер мен шолу мақалаларын қоса алғанда, 70 ғылыми жарияланымға аналитикалық шолу жүргізілді.*

Нәтижелері: *NGS негізіндегі мультигенді тестілеу канцерогенезге қатысатын бірнеше гендерді бір уақытта талдауға мүмкіндік береді, тұқым қуалайтын қатерлі ісік синдромдарымен байланысты патогенді ұрық сызығының мутацияларын, сондай-ақ интрондық және трансляцияланбаған аймақтар сияқты гендердің нашар түсінілген аймақтарындағы генетикалық нұсқаларды анықтауға мүмкіндік береді, бұл КҚІ қоздыратын бұрын белгісіз факторларды анықтауға көмектеседі.*

Қорытынды: *Молекулярлық-генетикалық диагностика пациенттерді жеке емдеуге және тәуекел топтарындағы туыстарды жеке медициналық тексеруге мүмкіндік береді. Дегенмен, КҚІ жағдайларының шамамен 25% отбасылық болса да, отбасылардың шамамен 95% генетикалық сынақтан өтпеген. Талданған деректер тұқым қуалайтын ісік синдромдарына немесе тұтас геномды секвенирлеуге қатысатын барлық анықталған гендерді қоса алғанда, фенотиптік панельдерден үлкен*

панельдерге көшу қажеттілігін қолдайды. Сонымен қатар, орташа және төмен еніп кететін жаңа нұсқаларды немесе функционалдық мәні белгісіз нұсқаларды анықтау ККІ фенотиптік спектрін кеңейтеді және диагностикалық секвенирлеу панельдеріне қосу үшін осы нұсқаларды әрі қарай зерттеуді қажет етеді.

Түйінді сөздер: *Колоректальды қатерлі ісік (ККІ), патогендік мутациялар, келесі ұрпақ секвенирлеу, тұқым қуалайтын тұқым қуалайтын тоқ ішек қатерлі ісігі, генетикалық скрининг.*

АННОТАЦИЯ

МУЛЬТИГЕННОЕ ТЕСТИРОВАНИЕ В ГЕНЕТИЧЕСКОМ СКРИНИНГЕ НАСЛЕДСТВЕННОГО И СПОРАДИЧЕСКОГО КОЛОРЕКТАЛЬНОГО РАКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Молекулярно-генетическое тестирование для определения генотипа пациента и молекулярного профиля опухоли представляет собой ключевой компонент персонализированного подхода к лечению и диспансеризации. Современные исследования в области генетического скрининга фокусируются на переходе от диагностических панелей, основывающихся на фенотипе, и ПЦР-тестирования отдельных генов предрасположенности к большим панелям или полногеномному секвенированию. Мультигенное тестирование находит широкое применение в различных областях диагностики и терапии колоректального рака (КРР), в возникновении которого значителен вклад генетических компонентов. В настоящее время в практической онкологии необходим обзор систем высокопроизводительного секвенирования для генетического скрининга наследственных и спорадических вариантов КРР и оптимизации его ранней диагностики у родственников пациентов.*

Цель исследования *– обзор методологии и современных результатов применения секвенирования нового поколения (NGS) для генетического скрининга наследственного и спорадического колоректального рака.*

Методы: *Проведен аналитический обзор 114 научных публикаций, включая оригинальные исследования и обзорные статьи, находящихся в открытом доступе в Google Scholar, Web of Science, Springer Link, Scopus, Science Direct, PubMed, BMJ.*

Результаты: *Мультигенное тестирование на основе NGS позволяет проводить одновременный анализ множества генов, участвующих в канцерогенезе, идентифицировать герминальные патогенные мутации, ассоциированные с наследственными опухолевыми синдромами, а также генетические варианты в менее изученных областях генов, таких как интронные и нетранслируемые области, что способствует выявлению ранее неизвестных факторов предрасположенности к КРР и оценке их вклада в реализацию опухолевого процесса.*

Заключение: *Молекулярно-генетическая диагностика делает возможным персонализированное лечение пациентов и индивидуализированную диспансеризацию родственников из групп риска. Однако несмотря на то, что около 25% случаев КРР являются семейными, около 95% семей остаются генетически не исследованы. Проанализированные данные подтверждают необходимость перехода от панелей, основанных на фенотипе к большим панелям, включающим все идентифицированные гены, вовлеченные в наследственные опухолевые синдромы или секвенирование всего генома. Кроме того, идентификация новых вариантов с умеренной и низкой пенетрантностью или вариантов с неопределенным функциональным значением, обладающих патогенным эффектом по данным in silico анализа, расширяет фенотипический спектр КРР, и обусловливает необходимость дальнейших исследований этих вариантов для включения в диагностические панели.*

Ключевые слова: *колоректальный рак (КРР), патогенные мутации, секвенирование нового поколения (NGS), наследственный рак толстой кишки, генетический скрининг.*

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TRANSGENERATIONAL CARCINOGENESIS: RISK FACTORS AND EPIGENETIC MECHANISMS (A LITERATURE REVIEW)

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ABSTRACT

Introduction: *Traditional models of carcinogenesis based on genetic mutations and direct exposure to carcinogens cannot explain all cases of cancer. The increasing incidence of certain cancers does not always correlate with known genetic factors, suggesting a significant role for environmental and lifestyle factors in their development. The concept of transgenerational carcinogenesis offers a new explanation, linking these factors with an increased risk of cancer in future generations through epigenetic changes.*

This study aimed to *systematize and critically analyze scientific publications published between 2014 and 2024 that concern the factors contributing to transgenerational carcinogenesis and the underlying epigenetic mechanisms.*

Methods: *To identify relevant publications, extensive searches were conducted in electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science. Combinations of keywords were used: ("transgenerational" OR "intergenerational" OR "parental exposure") AND ("cancer" OR "carcinogenesis" OR "tumor" OR "oncogenesis") AND ("epigenetic" OR "DNA methylation" OR "histone modification" OR "miRNA" OR "non-coding RNA").*

Results: *The phenomenon of transgenerational carcinogenesis, which is the transmission of an increased risk of cancer from generation to generation, is a proven fact. Epigenetic changes that persist in the germline affect gene expression in subsequent generations, and they can be caused by various factors affecting the parents. Animal models provide convincing evidence of cause-and-effect relationships. Long-term cohort studies in humans consistently confirm this mechanism, despite methodological difficulties.*

Conclusion: *Epigenetic changes in the germline can be passed on to offspring, significantly increasing their risk of developing pathological neoplasms. The primary mediators are changes in DNA methylation, histone modifications, and modifications to non-coding RNA. The study of transgenerational carcinogenesis will allow for the prevention of malignant neoplasms in future generations. Cause-and-effect relationships are convincing in models; in human populations, evidence is limited by associations and requires multigenerational cohorts with admixture control.*

Keywords: *epigenetics, predisposition to cancer, DNA methylation, histone modification, miRNAs, and cancer prevention.*

Introduction: Carcinogenesis, the complex multi-step process of cancer development, has traditionally been viewed through the lens of genetic alterations. The classical model posits that cancer arises from the accumulation of somatic mutations in key tumor suppressor genes and proto-oncogenes, leading to uncontrolled cell proliferation. Concurrently, hereditary cancer is explained by the transmission of specific mutations in predisposition genes (e.g., BRCA1/2, TP53) from parents to offspring via germ cells [1]. However, despite significant advancements in understanding these mechanisms, they cannot explain all instances of cancer. For example, the increasing incidence of certain cancers does not always correlate with an increase in genetic mutations within the population, and environmental and lifestyle factors play an increasingly evident role in cancer etiology [2].

In recent years, scientists worldwide have been actively studying the role of epigenetic changes, which are hereditary modifications of gene expression unrelated to changes in the DNA sequence. Modifications include DNA methylation, histone modifications, and regulation by non-coding RNAs [3]. Initially, epigenetics was considered in the context of individual cell development and differentiation. Breakthroughs in research have led to the understanding that epigenetic marks can not only be stable throughout an organism's life but can also be transmitted across generations. This concept is known as *transgenerational inheritance* [4, 5].

Transgenerational carcinogenesis (or transgenerational cancer susceptibility) is a relatively new but rapidly evolving area of research that posits that exposure of one or both parents (even pre-conception) can lead to changes in the germline that, in turn, increase the risk of cancer in their offspring (F1, F2, and subsequent generations) without direct exposure of the offspring to the carcinogen [6, 7]. The key distinction from hereditary cancer lies in the fact that transmission occurs not through changes in the nucleotide sequence of DNA, but through *epigenetic patterns* that modulate the expression of genes associated with carcinogenesis.

Several factors determine the relevance of this topic. First, it offers a new explanation for the etiology of malignant neoplasms in the absence of obvious hereditary predisposition or direct exposure to carcinogens. Sec-

ond, the phenomenon of transgenerational carcinogenesis presents new opportunities for preventing malignant neoplasms, allowing special attention to be paid to individual behavior and factors that affect the health of parents and their great-grandparents [8]. Third, this area highlights the interplay between the environment, genetics, and epigenetics in shaping health and susceptibility to disease [9].

The study aimed to systematize and critically analyze scientific publications published from 2014 to 2024 concerning the factors contributing to transgenerational carcinogenesis and the underlying epigenetic mechanisms.

Materials and Methods: Extensive searches were conducted in electronic databases, including PubMed/Medline, Scopus, and Web of Science, to identify relevant publications. The search covered the period from 2014 to 2024. The following keywords were used: ("transgenerational", OR "intergenerational", OR "parental influence") And ("cancer", OR "carcinogenesis", OR "tumor", OR "oncogenesis") And ("epigenetic", OR "DNA methylation", OR "histone modification", OR "microRNA" OR "non-coding RNA").

For the preparation of the review, a multi-stage publication selection procedure following the PRISMA principles was performed.

• Identification: A search in scientific databases (2014-2024) identified 300 potentially relevant publications. After removing the duplicates, 250 unique records remain.

• Screening: at the annotation screening stage, 180 papers were excluded as not relevant to the topic (i.e., not related to epigenetics or cancer transgeneration, or not peer-reviewed studies). Seventy publications have been accepted for full-text analysis.

• Eligibility: A full-text analysis of 70 publications led to the exclusion of another 20 papers for reasons of non-compliance with the criteria (for example, lack of data on transgenerational effects, poor quality of methodology, duplication of results).

• Included: The final review includes 49 studies that fully meet the criteria (original experimental papers and reviews highlighting the epigenetic mechanisms of transgenerational carcinogenesis).

Results: Transgenerational carcinogenesis has been actively studied in recent years. Environmental influences can affect the risk of developing cancer not only in exposed individuals but also in their descendants in subsequent generations. Experiments on animal models show that such epigenetic transgenerational effects are possible. In rodents, it has been found that exposure to endocrine disruptors, a high-fat diet, or stressors can lead to epigenetic changes in the germ cells of parents and to an increased tendency to tumor diseases in offspring up to 2-3 generations. However, in general, this area remains controversial. Transgenerational epigenetic transmission is viewed with skepticism by many researchers, as it is extremely difficult to separate it from the influence of hereditary genetic factors, as well as environmental and cultural conditions common to generations.

The analysis of the publication for the period 2014-2024 reveals several contradictions. Several influential animal studies reported multifactorial epigenetic inheritance of cancer predisposition. On the other hand, a significant part of such results requires independent confirmation. Thus, some landmark studies on the transgenerational effects of endocrine chemicals or a high-fat diet on DNA methylation were subsequently questioned by other authors. Certain carcinogenic effects that are clearly traceable in generations of laboratory animals (for example, testicular tumors in rat offspring after exposure to antiandrogens, or breast cancer in mouse offspring after experimental overfeeding of fathers) are not always confirmed in epidemiological data in humans. In some cases, the data are contradictory or show an effect only under extremely strong influences. In general, a critical analysis shows that the concept of epigenetic transgenerational carcinogenesis has been developed and partially confirmed in animal experiments, but the degree of its manifestation in humans remains uncertain and the subject of active research.

Epigenetic mechanisms of transmission from generation to generation. The transmission of acquired traits from generation to generation is contrary to the fundamental laws of genetics. However, epigenetics explains this phenomenon. The study of transgenerational carcinogenesis has shown that epigenetic changes acquired by parents in response to external influences are not eliminated during gametogenesis and early embryonic development; they are transmitted to offspring, changing their predisposition to malignant neoplasms [4, 8].

DNA methylation is the most deeply studied epigenetic mechanism. It involves covalent attachment of a methyl group to cytosine residues (mainly CpG dinucleotides). In the promoter regions of genes, hypermethylation is associated with transcription repression, which leads to gene activation [10]. Disorders in DNA methylation can inactivate tumor suppressor genes (hypermethylation) or activate oncogenes (hypomethylation) [11]. Studies in animal models have shown that the effects of various factors on parents can lead to specific changes in DNA methylation in germ cells, which can subsequently be passed on to offspring [12, 4]. These changes can affect genes related to the cell cycle, apoptosis, DNA repair, and metabolism, thereby increasing the risk of developing malignancies in subsequent generations. For instance, research demonstrates that exposure of pregnant females to certain chemicals, such as vinclozolin, can induce aberrant methylation in the sperm of F1 generation males, predisposing the F2 generation to the development of diseases, including ovarian, prostate, and kidney cancers [7, 13, 14].

Histone Modifications. Chromatin, a complex of DNA and proteins (histones), forms the genome inside the

cell nucleus. Histone modification (acetylation, methylation, phosphorylation) alters the structure of chromatin and makes it accessible to transcriptional mechanisms [15]. These modifications are dynamic and regulate gene expression. Changes in these patterns in parental germ cells can also be transmitted to offspring. For example, abnormal patterns of histone methylation (e.g., H3K4me3, H3K27me3) or histone acetylation in sperm can serve as epigenetic markers that determine disease susceptibility in offspring [16]. Recent studies suggest that dietary or environmental interventions in parents can alter histone modification profiles in their gametes, which correlates with an increased risk of cancer in offspring [17, 18].

Non-coding RNAs (ncRNAs), particularly *microRNAs (miRNAs),* play a crucial role in post-transcriptional gene expression regulation [19]. It has been shown that miRNAs are present in germ cells and can be transmitted to offspring. Alterations in miRNA expression profiles in sperm or oocytes resulting from parental exposure to external factors can disrupt the regulation of tumor suppressor genes or oncogenes in the developing embryo, thereby increasing the risk of cancer [16, 20]. For example, studies have revealed that paternal exposure to high-fat diets or certain toxins can alter the spectrum of miRNAs in sperm, which is associated with metabolic disorders and an increased risk of cancer in offspring [21, 18]. Long non-coding RNAs are also gaining significance as potential mediators of transgenerational effects, influencing chromatin structure and gene regulation [22].

Germline Inheritance. A key factor in transgenerational carcinogenesis is the ability to bypass epigenetic "reprogramming" during gametogenesis and early embryonic development. Most epigenetic marks are erased and restored; however, some regions of the genome and specific epigenetic marks may be stable. This enables information to be transmitted from one generation to the next [23, 5]. The mechanisms of this "bypass" are not fully understood, but they include protection of specific chromatin regions, association with certain carrier proteins, or transmission via small RNAs encapsulated in sperm or oocytes [20, 24]. Understanding these mechanisms is critical to fully realizing the potential of transgenerational carcinogenesis as a new paradigm in cancer etiology.

Key Factors Inducing Transgenerational Carcinogenesis (Focus on the Last 10 Years of Research). Over the past decade, numerous studies, primarily using animal models, have identified a range of factors that can induce transgenerational carcinogenesis. These factors span a broad spectrum of exposures, from chemicals to diet and stress.

Environmental Exposures and Toxins. Exposure to various environmental chemicals poses a significant threat to human health, and increasing evidence points to their role in the transgenerational transmission of cancer susceptibility.

• **Endocrine Disrupting Chemicals (EDCs):** These compounds mimic or block the action of hormones, thereby disrupting the endocrine system. In the past decade, EDCs such as *bisphenol A (BPA)* and its analogs (BPS, BPF), as well as *phthalates*, have been shown to induce transgenerational effects. For instance, rodent studies have indicated that prenatal or perinatal BPA exposure of the mother can lead to an increased risk of mammary gland, ovarian, prostate, and kidney tumors in F1 and even F2 generations of offspring [7, 25]. Mechanisms involve changes in DNA methylation of genes related to hormonal signaling and cell growth [25]. Similarly, phthalate exposure has been linked to transgenerational increases in prostate cancer incidence in male offspring [26].

• **Pesticides and Herbicides:** Certain widely used agrochemicals have also been associated with transgenerational effects. For example, studies demonstrate that exposure of pregnant rats to *vinclozolin* (a fungicide) leads to an increased incidence of various tumors (kidney, prostate) in F1-F3 generations [6, 7]. This is linked to aberrant DNA methylation and alterations in non-coding RNAs in the germline [13, 14]. While direct evidence of carcinogenesis from *glyphosate* via transgenerational mechanisms in humans is still limited, animal studies raise concerns about its potential impact on epigenetic inheritance [27].

• **Heavy Metals:** Chronic exposure to heavy metals, such as arsenic and cadmium, is associated with carcinogenic effects. Recent research indicates that parental exposure to these metals can induce transgenerational epigenetic changes, leading to increased offspring susceptibility to carcinogens or direct tumor development [28]. For example, arsenic exposure in pregnant mice was associated with altered DNA methylation in F1 generation sperm and an increased risk of hepatocellular carcinoma in the F2 generation [29].

• **Air pollution:** Components of air pollution, such as particulate matter and polycyclic aromatic hydrocarbons, can induce epigenetic changes. Evidence of transgenerational carcinogenesis due to air pollution in humans is still being investigated. Animal studies suggest that parental exposure to polycyclic aromatic hydrocarbons can lead to changes in germline DNA methylation, potentially increasing the risk of malignancies in offspring [30].

Nutritional and metabolic factors. The diet and metabolic status of parents have a profound impact on the health of their offspring, and epigenetic mechanisms play an important role in this process.

Parental weight problems: a deficiency or excess of nutrients in parents may increase the risk of neoplasms in their offspring [31]. A *high-fat diet (HFD)* in mothers or fathers is associated with an increased risk of liver, breast, and colorectal cancer in offspring of F1 and F2 generations [17, 32] due to changes in DNA methylation, histone modification, and microRNA profiles in germ cells that affect genes related to metabolism, inflammation, and cell

growth [16]. Deficiency of trace elements, such as *folic acid* (a methyl group donor) in parents, can disrupt the DNA methylation patterns in the germline and increase the predisposition to cancer [33, 34].

• **Parental Obesity and Diabetes:** The epidemics of obesity and diabetes have long-term consequences not only for the health of affected individuals but also for their offspring. Studies indicate that parental obesity or diabetes can be associated with a transgenerational increase in cancer risk in offspring [35]. For example, paternal obesity in mouse models has been linked to an increased risk of colorectal cancer in offspring, mediated by changes in miRNA expression in sperm [21]. Maternal gestational diabetes can also alter fetal epigenetic marks, potentially increasing the risk of certain cancers later in life [36].

• **Stress and Psychological Factors.** Chronic parental stress and psychological trauma, particularly during critical periods of germ cell development or pregnancy, can have long-term consequences for offspring [37]. For example, prenatal stress in rodents is associated with DNA methylation changes in the offspring's brains and predisposes them to behavioral disorders [38]. Some studies suggest a link with increased sensitivity to carcinogens or risk of developing certain types of diseases. However, direct evidence for transgenerational carcinogenesis through psychological stress in humans is still lacking. The influence of glucocorticoids and neuroimmune pathways on germ cell epigenetics is an active area of research [39].

• **Pharmacological Agents and Medications.** The use of certain medications by parents can also induce transgenerational effects.

• **Chemotherapy and Radiotherapy:** Cancer therapy may also have long-term effects. Exposure to chemotherapeutic drugs (e.g., cyclophosphamide) or ionizing radiation can induce epigenetic changes in parental germ cells, leading to an increased risk of malignancy in offspring [40]. Mechanisms include changes in DNA methylation and microRNA profiles, which may disrupt genomic stability or cellular signaling pathways in offspring [41]. This is particularly important for young cancer survivors planning pregnancy.

• **Diethylstilbestrol (DES):** Although this is a historical example (used to prevent miscarriages from the 1940s to 1970s), the effect of DES is a classic illustration of transgenerational carcinogenesis. Women whose mothers took DES during pregnancy have an increased risk of developing a rare form of vaginal cancer (clear cell adenocarcinoma) and other reproductive abnormalities [42, 43]. Research continues to uncover the epigenetic mechanisms underlying these effects, highlighting the long-term consequences of drug exposure during early development [44].

Infectious Agents. Direct viral (HPV, HBV)-associated etiocarcinogenesis is well studied, and researchers are beginning to consider whether parental infections may cause transgenetic changes that predispose offspring to cancer [45]. Chronic inflammation caused by infections may influence the epigenetic landscape [5]. This area requires further study to identify specific transgenerational effects in the context of oncogenesis.

Research Models. Studying transgenerational carcinogenesis presents a complex challenge requiring specialized approaches. Over the past decade, significant progress has been made in developing and applying various research models.

Animal Models. Mice, rats, and zebrafish are primary models for studying transgenerational carcinogenesis. These models enable strict control over exposure (type, dose, timing, and duration), the study of multiple generations, and the analysis of molecular mechanisms in offspring tissues and parental germ cells [5, 44].

• **Maternal Exposure Models:** In these studies, pregnant females are exposed to the factor under investigation (e.g., an endocrine disruptor) during pregnancy. The cancer susceptibility of their offspring (F1) and subsequent generations (F2, F3+), born from unexposed F1 females, is then analyzed [6, 7]. This approach allows for the exclusion of direct exposure of the factor to subsequent generations.

• **Paternal Exposure Models:** In some studies, male founders are exposed before mating. Analysis of their sperm for epigenetic changes, as well as the cancer risk in their offspring, allows for the assessment of the paternal line's contribution to transgenerational effects [6, 21].

• **Advantages:** Strict control over experimental conditions, ability to establish cause-and-effect relationships, and accessibility of tissues for molecular analysis (DNA methylation, histone modifications, miRNAs) [44].

• **Limitations:** Differences in physiology and metabolism between animals and humans, as well as complexities in extrapolating results to the human population [5].

Human Epidemiological/Cohort Studies. Studying transgenerational carcinogenesis in humans is considerably more challenging due to uncontrolled exposure to numerous environmental and lifestyle factors. However, long-term cohort studies and the analysis of large databases are beginning to yield valuable information [46].

• **Advantages:** Direct relevance to human health.

• **Limitations:** Difficulty in establishing cause-and-effect relationships, the need for very large sample sizes and long-term follow-up across multiple generations, challenges in controlling for all potential confounding factors, and ethical restrictions on experimental exposures [5].

• **Examples:** Ongoing cohort studies where mothers were exposed to specific agents (e.g., DES) [43], as well as studies investigating the link between parental obesity, diabetes, or exposure to certain toxins and cancer risk in offspring. The use of biobanks and the analysis of epigenetic marks in cord blood or offspring tissues help to identify potential correlations [36, 41].

Clinical Significance and Future Perspectives. Understanding transgenerational carcinogenesis has profound clinical and public health implications, opening new horizons for cancer prevention and risk management.

Potential Impact on Cancer Prevention. Traditional cancer prevention strategies focus on individual lifestyle modifications (e.g., smoking cessation, adopting a healthy diet, and engaging in physical activity) and early detection. The concept of transgenerational carcinogenesis offers a fundamentally new approach, focusing on *pre-conception or prenatal interventions* [44].

• **Pre-conception Prevention:** Counseling prospective parents on the importance of healthy lifestyles (nutrition, avoidance of harmful habits), minimizing exposure to environmental toxins before conception can reduce the risk of transgenerational transmission of cancer susceptibility [5].

• **Environmental Protection:** Regulation and reduction of endocrine disruptors, pesticides, and other industrial pollutants become even more critical, given their potential transgenerational effects [6, 7].

• **Pharmacological Development:** Considering transgenerational risks during the development and safety assessment of new drugs, especially those that may be used by women of childbearing age or men [43].

• **Identification of At-Risk Groups.** The identification of epigenetic biomarkers in germ cells or at early stages of offspring development could enable the detection of individuals with an increased risk of cancer.

• **Biomarkers in Sperm/Oocytes:** In the future, analysis of specific epigenetic marks (e.g., DNA methylation patterns, miRNA profiles) in parental gametes could become part of screening for assessing transgenerational risk [16].

• **Biomarkers in umbilical cord blood**: The study of epigenetic markers in the umbilical cord blood of newborns can serve as an indicator of the environmental impact on the mother and a potential predisposition to cancer, allowing for earlier personalized monitoring and prevention [36, 41].

• **Molecular mechanisms:** It is necessary to study how epigenetic tags are transmitted along the germline, which of them are resistant to reprogramming, and how they affect gene expression during ontogenesis [8, 5].

• **Long-term studies:** Long-term cohort studies spanning several generations are crucial for a convincing demonstration of the transgenerational phenomenon in humans [46].

• **Combined effects:** Most studies focus on a single factor, whereas in real life, organisms are exposed to multifactorial effects. The study of the synergistic and/or antagonistic effects of combined factors is a promising direction [26].

• **Development of therapeutic strategies**: understanding the mechanisms of the "phenomenon" will lead to the development of approaches aimed at "erasing" unwanted epigenetic marks and/or protecting the germline from harmful effects.

• **The role of the paternal line:** Research often focuses on the impact on the mother, and there is a growing understanding of the important role of paternal material in transmission from generation to generation. It is necessary to study the mechanisms of epigenetic changes in spermatozoa that affect the development of offspring and the risk of developing malignant neoplasms [16, 21].

Table 1 summarizes the associations between the type of exposure, epigenetic mechanism, and type of cancer.

Table 1 – Main categories of ancestral influences, putative epigenetic mechanisms of inheritance, and related cancers in offspring (according to peer-reviewed publications 2014-2024) [4-6, 12, 23, 30, 45, 46-48]

Type of exposure	The epigenetic mechanism of inheritance	Associated types of cancer in offspring
Chemical toxicants (pesticides, endocrine disruptors – DDT, vinyl chloride, etc.)	– Persistent changes in DNA methylation in germinal cells, leading to epimutations in oncogenes/tumor suppressors that can avoid embryonic reprogramming. – Disruption of the chromatin structure: changes in repressive histone tags that affect the long-term shutdown of genes. – Imbalance of non-coding RNAs: changes in the profile of microRNAs and other small RNAs in sperm transmitted to the zygote.	There is often an increased risk of childhood tumors due to parental contact with pesticides: leukemia, lymphoma, CNS tumors, and neuroblastoma in children. In adult descendants, there is an increased incidence of hormone–dependent tumors: breast cancer is associated with exposure to DDT ancestors. Tumors of the reproductive system are possible (according to data from animal models).
Nutritional factors (parental diet, starvation)	– Epigenetic rearrangement of spermatozoa: changes in global DNA methylation and in the content of small non-coding RNAs. For example, a deficiency or excess of nutrients in males leads to differential expression of multiple sperm microRNAs and tRNA fragments, which restart gene expression after fertilization. – Modification of signaling pathways of development: changes in the expression of metabolic control genes are revealed in the offspring as an echo of the dietary factors of the ancestors.	An increase in the predisposition to breast cancer in offspring with obesity or protein starvation of the female parent has been shown in animals. In humans, there is evidence that extreme starvation of grandmothers is associated with an increased risk of breast cancer in granddaughters. Effects on other cancers are possible, but there is insufficient clear epidemiological evidence.
Psychological stress (severe traumatic events, chronic parental stress)	– Long-term dysregulation of neuroendocrine genes: extreme stress can lead to changes in the methylation of genes regulating the stress response. – Histone labeling disorder: presumably, chronic stress can affect posttranslational modifications of histones in germ cells, which affects the work of genes in the embryo.	In humans, extreme stressors are associated with a general deterioration in the health of the offspring, but a clearly increased risk of cancer has been confirmed mainly for the generation itself that has experienced stress. Data on the effect of parental stress on childhood cancer is contradictory; further research is needed to establish a cause-and-effect relationship.

Table 1 (continued)

Medications (pharmacological effects on pregnant women or before conception; for example, diethylstilbestrol)	– Hormonal and epigenetic effects: Exogenous hormones during critical periods of development can cause persistent epigenetic shifts. In the case of DES, an increased level of EZH2 expression was found in the mammary gland tissues of the offspring, which indicates an increase in the repressive histone modification H3K27me3 and the associated suppression of tumor suppressor genes. – Violation of genomic imprinting: Some drugs can probably disrupt the installation of methyl tags in imprinted genes during gametogenesis; this effect is probably inherited.	The "DES daughters" syndrome is well documented: women whose mothers took diethylstilbestrol during pregnancy had a sharply increased risk of clear-cell adenocarcinomas of the vagina and cervix. Experiments on mice and rabbits have shown that the effects of DES are transmitted to the next generation: the "granddaughters" have an increased development of tumors of the uterus and ovaries. In addition, there is evidence of a slightly increased risk of breast cancer and melanoma in daughters exposed to DES in utero. This example highlights the reality of the transgenerational effects of medications, although there are few such confirmed cases so far.

Notes: EDC – endocrine destructive chemicals (endocrine disruptors), DDT – dichlorodiphenyltrichloroethane, DES – diethylstilbestrol.

Discussion: The data are summarized, which convincingly show that the phenomenon of transgenerational carcinogenesis is an important and multifaceted aspect of the etiology of malignant neoplasms. Unlike traditional models focusing on direct genetic mutations or individual carcinogen exposure, the concept of transgenerational transmission emphasizes that parental exposures can "program" offspring's predisposition to cancer through epigenetic mechanisms. These mechanisms, including alterations in DNA methylation, histone modifications, and non-coding RNA profiles, act as a bridge between environmental factors and inherited disease risk.

The review identified a wide range of factors capable of inducing transgenerational effects that predispose individuals to carcinogenesis. Among these, particular attention is given to endocrine-disrupting chemicals (EDCs) (e.g., BPA, phthalates), which affect hormonal regulation and can cause persistent epigenetic changes in the germline [12, 18]. Results from animal models, such as vinclozolin exposure, convincingly show that chemical agents can lead to an increased risk of various cancers in subsequent generations [7, 14]. This underscores the urgent need to re-evaluate regulations regarding widely used chemicals and their long-term effects.

Nutritional and metabolic factors have also proven to be powerful modulators of transgenerational risk. Specifically, high-fat diets and parental obesity have been shown to alter the epigenetic landscape of germ cells, leading to an increased oncological predisposition in offspring [17, 32, 21]. These data expand the understanding of "intrauterine programming effects" and point to the critical role of parental metabolic health in shaping cancer risk in their children and grandchildren. While direct human evidence is limited, epidemiological studies are beginning to identify correlations that confirm the importance of these links [35, 36].

Stress and pharmacological agents, including chemotherapy, represent another category of factors that can induce transgenerational epigenetic modifications [39, 40]. This raises important ethical and clinical questions, especially concerning the treatment of young cancer patients who later wish to have children. A balance is needed between life-saving treatments and potential long-term risks to offspring. The example of diethylstilbestrol (DES) [43] serves as a stark historical warning that the consequences of medical interventions can manifest decades and generations later.

While animal models are the gold standard for studying cause-and-effect relationships in transgenerational carcinogenesis due to controlled conditions [4, 44], their results are not always directly extrapolatable to humans. Epidemiological studies in humans, though more complex to conduct, are indispensable for confirming these links in real populations [46]. Progress in high-throughput omics technologies allows for the identification of subtle epigenetic changes in human biomaterials (e.g., cord blood, sperm), opening new avenues for identifying risk biomarkers [16, 24].

However, significant knowledge gaps remain. A better understanding of the precise molecular mechanisms that ensure the resistance of certain epigenetic marks to reprogramming in the germline is needed. Most studies examine the effects of a single factor, whereas in real life, organisms are exposed to multiple combined influences, which require more complex research models. It is important to consider the contribution of the paternal line to transgenerational inheritance, since spermatozoa carry a unique epigenetic load that can influence the development of offspring [16, 21]. Data from the last decade indicate that transgenerational carcinogenesis is an emerging area of public health importance. Integration of the acquired knowledge into preventive programs and clinical recommendations will be the next logical step in preventing and controlling malignant diseases.

Data comparison: animal models vs human studies. The results of animal and human studies in this area show significant differences. There is convincing evidence in animal models that exposure to parents can increase the carcinogenic risk in offspring. When exposed to endocrine-disrupting pesticides (DDT) in rodents, there is an increase in the incidence of tumors in offspring up to the third generation. In classical experiments, it was shown that the synthetic estrogen diethylstilbestrol (DES), administered to pregnant female rodents, causes the development of tumors of the reproductive tract not only in their daughters (directly exposed in utero), but also in "granddaughters" – the third generation, who had no direct contact with the substance [47]. There was also evidence that parental nutrition affects oncogenesis in offspring. For example, obe-

sity or dietary deficiencies in male mice before mating led to epigenetic restructuring of their spermatozoa, resulting in changes in breast development and an increased incidence of breast tumors in their daughters. These animal models allow us to establish a causal relationship: exposure → epigenetic "tag" in germinal cells → phenotype change and tumor risk in the offspring. It is important that mechanisms can be directly identified in animals: for example, to find specific epigenetic changes in spermatozoa (DNA methylation of certain genes, disruption of the microRNA profile, changes in histone tags) that correlate with the occurrence of cancer in offspring [47, 49].

In human studies, the picture is less definite. Direct experimental data are naturally lacking, and scientists rely on retrospective or epidemiological observations. Some of them support the hypothesis of a transgenerational effect: for example, women conceived during starvation (such as the Holodomor in the Netherlands in 1944-1945) demonstrated an increased risk of breast cancer in adulthood. This indirectly indicates that the lack of nutrition in grandmothers could affect the cancer incidence in granddaughters through intergenerational epigenetic changes. Another example is the analysis of the offspring of war veterans exposed to certain chemical agents (for example, dibutyl phthalate, which is dangerous for the endocrine system). According to some data, the daughters of war veterans have a higher-than-average risk of developing breast cancer. There is a historical case with the DES drug: women whose mothers took diethylstilbestrol during pregnancy had a sharply increased risk of rare vaginal cancer (clear-cell carcinoma) [48, 49]. However, it is important to emphasize that such studies on humans have the character of associations. It is challenging to interpret them unambiguously, as the results may be influenced by genetic predisposition and related environmental factors. In addition, different studies often give contradictory conclusions: for example, some studies find a link between the diet of parents and cancer in children, while others do not find a statistically significant effect. Collectively, animal data provide more direct and reproducible evidence of transgenerational carcinogenesis, whereas in humans, such effects are unclear and require further study. Every phenomenon observed in human populations needs to be carefully evaluated and, if possible, confirmed by independent samples.

Limitations of human research. Research on transgenerational effects in humans faces several limitations:

• Confounding of factors: Descendants inherit not only epigenetic marks from their ancestors, but also genes, and often share a similar environment. For example, families that have experienced hunger or stress may have a similar lifestyle and diet in subsequent generations. This makes it difficult to isolate a purely epigenetic contribution to cancer risk. Genetic predisposition and cultural traditions can mimic the "inherited" effects of the environment.

• Long latency period: Transgenerational effects appear after one or more generations, i.e., decades. To establish a connection, very long-term observations are needed. During this time, the external conditions themselves, medicine, etc., may change, which makes interpretation difficult.

• Sample size and accessibility: for a convincing analysis, large cohort samples spanning several generations are needed, where ancestral impacts are known and outcomes in descendants are traced. Such data is extremely rare. Many studies rely on unique historical cohorts, and their results are still awaiting confirmation by independent experts.

• Retrospective nature of the data: Most of the available human data is retrospective. The accuracy of information about exposure doses and the state of ancestral health is limited. There may be systematic errors and biases.

• Ethical limitations and verification of mechanisms: Naturally, it is impossible to purposefully experiment on humans, exposing one generation to exposure and observing grandchildren. Therefore, we cannot directly prove a causal relationship but rely on correlations. In addition, it is difficult to study the epigenetic changes themselves: the embryonic germ line is not available for analysis in humans, so direct confirmation of label transfer is difficult. These limitations necessitate caution in interpreting the results in humans and explain why transgenerational epigenetic transmission in humans remains a hypothesis, despite some indirect evidence [48].

Conclusion: The phenomenon of transgenerational carcinogenesis is changing the understanding of the etiology of malignant neoplasms, expanding beyond genetic mutations and individual exposure. Environmental factors can cause epigenetic changes in parental germ lines, which are then passed on to offspring, thereby increasing the risk of developing malignancies. DNA methylation, histone modifications, and non-coding RNAs are key mediators of these transgenerational effects. The study of transgenerational carcinogenesis opens new possibilities for the prevention of malignant neoplasms. A healthy lifestyle is important for expectant parents. Strengthening environmental protection and chemical regulation measures is necessary to minimize the impact on human reproductive health. The identification of epigenetic biomarkers that predict the risk of cancer in offspring is a promising area of future research that may lead to the development of personalized strategies for screening and preventing malignancies. The scientific community faces complex challenges, including conducting long-term human studies, exploring combined effects, and gaining a deeper understanding of molecular mechanisms. A full understanding and integration of the phenomenon of transgenerational carcinogenesis into clinical practice and public health policy will be crucial in the fight against cancer.

Cause-and-effect relationships are convincing in models; in human populations, evidence is limited by associations and requires multigenerational cohorts with admixture control.

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АҢДАТПА

ТРАНСГЕНЕРАЦИЯЛЫҚ КАНЦЕРОГЕНЕЗ: ҚАУІП ФАКТОРЛАРЫ ЖӘНЕ ЭПИГЕНЕТИКАЛЫҚ МЕХАНИЗМДЕР (ӘДЕБИЕТКЕ ШОЛУ)

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Өзектілігі: *Генетикалық мутацияларға және канцерогендердің тікелей әсеріне негізделген канцерогенездің дәстүрлі үлгілері қатерлі ісіктің барлық жағдайларын түсіндіре алмайды. Кейбір қатерлі ісік ауруларының көбеюі әрқашан белгілі генетикалық факторлармен байланысты бола бермейді, бұл олардың дамуындағы қоршаған орта мен өмір салтының маңызды рөлін көрсетеді. Трансгенерациялық канцерогенез тұжырымдамасы осы факторларды эпигенетикалық өзгерістер нәтижесінде болашақ ұрпақтарда қатерлі ісік қаупінің жоғарылауымен байланыстыратын жаңа түсініктеме ұсынады.*

Зерттеудің мақсаты *– трансгенерациялық канцерогенезге ықпал ететін факторларға және олардың негізінде жатқан эпигенетикалық механизмдерге қатысты 2014-2024 жылдар аралығында жарияланған ғылыми басылымдарды жүйелеу және сыни тұрғыдан талдау болды.*

Әдістері: *Тиісті басылымдарды анықтау үшін PubMed/MEDLINE, Scopus және Web of Science сияқты электронды мәліметтер базасында кең іздеу жүргізілді. Кілт сөздердің тіркесімдері қолданылды: (“трансгенерация” немесе “ата-ана тәжірибесі”), және (“қатерлі ісік “немесе” канцерогенез “немесе” ісік “немесе” онкогенез”) және (“эпигенетикалық “немесе” ДНҚ метилденуі “немесе” гистон модификациясы “немесе” микроРНҚ “немесе”кодталмаған РНҚ”).*

Нәтижелері: *Трансгенерациялық канцерогенез құбылысы дәлелденген факт болып табылады. Ұрық сызығында сақталатын эпигенетикалық өзгерістер кейінгі ұрпақтардағы гендердің экспрессиясына әсер етеді және олар ата-аналарға әсер ететін әртүрлі факторлардан туындауы мүмкін. Жануарларға арналған модельдер себеп-салдарлық байланыстардың нақты дәлелдерін береді. Адамдардағы ұзақ мерзімді когорттық зерттеулер әдістемелік қиындықтарға қарамастан бұл механизмді дәйекті түрде қолдайды.*

Қорытынды: *Жыныстағы эпигенетикалық өзгерістер ұрпаққа берілуі мүмкін, бұл патологиялық ісіктердің даму қаупін айтарлықтай арттырады. Негізгі медиаторлар ДНҚ метилденуіндегі өзгерістер, гистондық модификациялар және кодталмаған РНҚ модификациялары. Трансгенерациялық канцерогенезді зерттеу болашақ ұрпақтарда қатерлі ісіктердің алдын алуға мүмкіндік береді. Себеп-салдарлық байланыстар модельдерде сенімді, адам популяцияларында дәлелдер ассоциациялармен шектеледі және араласуды бақылайтын көп буынды когорттарды қажет етеді.*

Түйінді сөздер: *эпигенетика, қатерлі ісікке бейімділік, ДНҚ метилденуі, гистон модификациясы, микроРНҚ (miRNAs), қатерлі ісіктің алдын алу.*

АННОТАЦИЯ

ТРАНСГЕНЕРАЦИОННЫЙ КАНЦЕРОГЕНЕЗ: ФАКТОРЫ РИСКА И ЭПИГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ (ОБЗОР ЛИТЕРАТУРЫ)

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Актуальность: *Традиционные модели канцерогенеза, основанные на генетических мутациях и прямом воздействии канцерогенов, не могут объяснить все случаи рака. Рост заболеваемости некоторыми видами рака не всегда коррелирует*

с известными генетическими факторами, что указывает на значительную роль окружающей среды и образа жизни в их развитии. Концепция трансгенерационного канцерогенеза предлагает новое объяснение, связывая эти факторы с повышенным риском развития рака у будущих поколений в результате эпигенетических изменений.

***Цель исследования** – систематизировать и критически проанализировать научные публикации, опубликованные в период с 2014 по 2024 год, которые касаются факторов, способствующих трансгенерационному канцерогенезу, и лежащих в их основе эпигенетических механизмов.*

***Методы:** Для выявления соответствующих публикаций был проведен обширный поиск в электронных базах данных, включая PubMed/MEDLINE, Scopus и Web of Science. Использовались комбинации ключевых слов: (“трансгенерационный” ИЛИ “родительский опыт”), и (“рак” ИЛИ “канцерогенез” ИЛИ “опухоль” ИЛИ “онкогенез”) и (“эпигенетическое” ИЛИ “метилирование ДНК” ИЛИ “модификация гистонов” ИЛИ “микроРНК” ИЛИ “некодирующая РНК”).*

***Результаты:** Феномен трансгенерационного канцерогенеза является доказанным фактом. Эпигенетические изменения, которые сохраняются в зародышевой линии, влияют на экспрессию генов в последующих поколениях, и они могут быть вызваны различными факторами, влияющими на родителей. Модели на животных дают убедительные доказательства причинно-следственных связей. Долгосрочные когортные исследования на людях последовательно подтверждают этот механизм, несмотря на методологические трудности.*

***Заключение:** Эпигенетические изменения в зародышевой линии могут передаваться потомству, значительно увеличивая риск развития патологических новообразований. Основными медиаторами являются изменения метилирования ДНК, модификации гистонов и модификации некодирующей РНК. Изучение трансгенерационного канцерогенеза позволит предотвращать злокачественные новообразования у будущих поколений. Причинно следственные связи убедительны на моделях, однако в человеческих популяциях доказанность ограничена ассоциациями и требует многопоколенных когорт с контролем смешения.*

***Ключевые слова:** эпигенетика, предрасположенность к раку, метилирование ДНК, модификация гистонов, микроРНК (miRNAs), профилактика рака.*

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APPLICATION OF 3D PRINTING TECHNOLOGY OF BIO-EXCHANGE CARBON MATERIALS FOR LARYNGEAL IMPLANTS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *The high incidence of laryngeal cancer and the limitations of traditional implants (low biocompatibility and infectious complications) require the development of new materials. Carbon nanostructures and 3D printing are promising for the development of personalized laryngeal implants.*

The study aimed to *assess the potential of using carbon nanostructures, such as fullerenes, carbon nanotubes, and graphene, in 3D-printed laryngeal implants to promote cartilage regeneration and restore laryngeal function by enhancing their biocompatibility, mechanical properties, and anti-bacterial activity.*

Methods: *A literature search for the years 2015-2025 was conducted in PubMed, Scopus, Web of Science, and Google Scholar using the keywords "carbon nanostructures," "3D printing," and "laryngeal implants." A total of 50 references were included in the systematic analysis.*

Results: *Fullerenes, carbon nanotubes, and graphene enhance the biocompatibility, mechanical properties, and antibacterial properties of 3D-printed scaffolds, supporting cartilage regeneration and laryngeal functions (breathing, swallowing, and speech).*

Conclusion: *Carbon nanostructures and 3D printing hold promise for laryngeal implants; however, further research is needed on their biocompatibility and large-scale production.*

Keywords: *carbon nanostructures, 3D printing, laryngeal implants, biocompatibility, cartilage re-generation, antibacterial properties.*

Introduction: The larynx, a bony structure comprising the larynx, thyroid cartilage, and other cartilages, performs the basic functions of breathing, swallowing, and speech. Oncological diseases, injuries, congenital anomalies, or the consequences of surgical interventions, such as aphthous stomatitis, may necessitate implants to restore the anatomy and functionality of the organ [1]. According to global cancer statistics for 2022, laryngeal cancer is one of the most common cancers, with 188,960 new cases and 103,216 deaths recorded [2]. According to the GLOBOCAN 2022 update, the global incidence of laryngeal cancer was approximately 184,615 new cases, with an age-standardized incidence (ASR) of 2.0 per 100,000 population and a mortality rate of 99,840 (ASR 1.0), which is expected to increase to approximately 190,000 new cases by 2025 due to demographic changes. Furthermore, due to risk factors such as smoking and alcohol consumption, the main areas of treatment for laryngeal cancer in the field of oncology are organ-preserving strategies, including concurrent chemoradiotherapy (CRT), which allows preserving laryngeal function in 70-80% of patients with localized stages, while reducing the need for surgical reconstruction**.** For advanced or recurrent cases, immunotherapy (PD-1/PD-L1 inhibitors) and targeted therapy are being developed to improve outcomes at the metastatic stage, with an emphasis on personalized medicine and a multidisciplinary approach [3]. The five-year relative survival rate for laryngeal cancer ranges from 79% at localized stages to 34% at distant stages, with an overall rate of approximately 61%, highlighting the need for innovations in post-laryngectomy reconstruction, including 3D printing and nanomaterials, to improve patients' quality of life. Traditional silicone, titanium, or polymer-based implants have significant drawbacks, including poor biocompatibility, limited integration with underlying tissues, a high risk of infectious complications, and insufficient mechanical strength of cartilaginous structures [2, 4]. These limitations motivate the search for new materials and technologies to improve treatment outcomes.

Carbon nanostructures, such as fullerenes and carbon nanotubes (CNTs), have garnered attention in tissue engineering due to their unique physicochemical properties [5]. Fullerenes (C60, C70) possess radical-scavenging properties that reduce oxidative stress and inflammation, which are essential for preventing implant rejection [6]. Functional fullerenes such as C60(OH)n exhibit high

biocompatibility and the ability to stimulate tissue regeneration [7]. Carbon nanotubes provide high mechanical strength, electrical conductivity, and support cellular adhesion, which is important for laryngeal cartilage tissue [8]. Graphene and its derivatives, such as graphene oxide, enhance scaffold properties, improve biomechanical properties, and exhibit antibacterial activity [9]. These properties make carbon nanostructures promising for the development of bioreplacement materials.

3D printing (additive manufacturing) technology has revolutionized the fabrication of implants, enabling the complex anatomy of the larynx to be reproduced from computed tomography (CT) or magnetic resonance imaging (MRI) data [10]. Techniques such as fused deposition modeling (FDM) and bioprinting enable precise modeling of cartilage structures using polymers (e.g., polycaprolactone, polylactide) or hydrogels [11]. The integration of carbon nanostructures into these materials enhances their biocompatibility, mechanical strength, and antibacterial properties, as confirmed by research in otolaryngology [12, 13]. For example, composites based on CNTs and graphene have shown improved electrical conductivity, which has been shown to stimulate cartilage cells [14]. Fullerenes used in photodynamic therapy (PDT) generate reactive oxygen species, which reduces the risk of bacterial infections caused by *Staphylococcus aureus* [15]. However, the clinical application of such materials is limited by a lack of data on their use in laryngeal implants, although studies in bone and cartilage tissues have shown significant progress [16].

The study aimed to assess the potential of using carbon nanostructures, such as fullerenes, carbon nanotubes, and graphene, in 3D-printed laryngeal implants to promote cartilage regeneration and restore laryngeal function by enhancing their biocompatibility, mechanical properties, and antibacterial activity.

Materials and Methods: This review included studies on the use of carbon nanostructures, such as fullerenes, carbon nanotubes, and graphene, in tissue engineering, with a focus on cartilage regeneration, as well as studies on extrusion 3D printing and bioprinting technologies for the production of biosubstitute materials or implants. Articles with experimental data on the biocompatibility, mechanical properties, antibacterial activity, or clinical significance of carbon nanostructures for laryngeal implants were included. The review included original studies, reviews, or patents published in English, Russian, or Kazakh between 2005 and 2025. Papers without experimental data (e.g., editorial columns or letters to the editor) or not related to tissue engineering and implants were not included in the analysis. Articles in languages other than English, Russian, or Kazakh were also excluded if a translation was not available.

Results: A systematic literature review revealed that carbon nanostructures (fullerenes, carbon nanotubes (CNTs), and graphene) possess unique properties and are promising for the development of bioreplacement materials. Fullerenes, particularly functionalized forms such as C60(OH)n, reduce oxidative stress in tissues through their radical-scavenging properties and exhibit high biocompatibility. Carbon nanotubes exhibit very high mechanical strength and electrical conductivity, which improves cartilage cell adhesion and proliferation. Graphene and its derivatives (e.g., graphene oxide) enhance the mechanical properties of scaffolds and exhibit pronounced antibacterial activity. These properties are presented in Table 1, which compares the biocompatibility, mechanical properties, and antibacterial activity of carbon nanostructures.

Table 1 – Comparison of properties of carbon nanostructures

Material	Biocompatibility	Mechanical properties	Antibacterial activity
Fullerenes	High, reduces oxidative stress [6]	Low strength, radical scavenging[7]	High level of PDT (S. aureus, E. coli) [15]
Carbon nanotubes	Moderate, improved by functionalization [8]	High strength (up to 100 GPa), electrical conduc-tivity [8]	Moderately destroys bacterial membranes [5]
Graphene	Tall, supports cells [9]	High strength (up to 130 GPa), plasticity [9]	High, destroys mem-branes (S. aureus) [9]

Carbon nanostructures have demonstrated significant results in cartilage tissue engineering. Fullerenes increase chondrocyte proliferation by 4.5-fold over 7 days, as confirmed by *in vitro studies*. In those studies, type II collagen expression reached 85% compared with the control group. Carbon nanotubes embedded in polycaprolactone (PCL) increased the compressive strength of scaffolds to 8.4 MPa and Young's modulus to 146.2 MPa, providing optimal conditions for mesenchymal stem cell chondrogenesis. When added to graphene hydrogels (e.g., GelMA), they improve cell adhesion and increase their density by 60% compared to pure hydrogels over 14 days. These data demonstrate the ability of carbon nanostructures to support cartilage regeneration, which is necessary for the restoration of the cricoid and thyroid cartilages of the larynx.

3D printing technologies, such as fused deposition modeling (FDM) and bioprinting, enable the reconstruction of the complex larynx structure as anatomically accurate scaffolds from CT data. PCL-based composites with 0.013 wt% fullerene nanorods (FNRs) increase hydrophilicity and decrease the contact angle from 80° to 45°, which promotes improved cell adhesion. These scaffolds inhibit the growth of *Staphylococcus aureus* and *E. coli* by 90% within 24 hours. Similarly, GelMA hydrogels with

graphene promote chondrogenesis, providing a compressive strength of 7.8 MPa and increasing SOX9 expression by 70%. PLA composites with CNTs achieve a compressive strength of 9.2 MPa and become electrically conductive, stimulating cellular differentiation. The characteristics of the 3D-printed materials are presented in Table 2.

Table 2 – Characteristics of 3D printed frames

Material	Technology	Compressive strength, MPa	Biological effect
PCL + 0.013% FNR	FDM	8.4 [11]	Chondrocyte proliferation 4 times [7]
GelMA + Graphene	Bioprinting	7.8 [1 2]	Chondrogenesis, cell adhesion (SOX9 +70%) [9]
PLA + CNT	FDM	9.2 [1 3]	Electrical conductivity, cellular dif-ferentiation [14]
PLA + CNT	FDM	9.2 [1 3]	Electrical conductivity, cellular dif-ferentiation [14]

Figure 1 complements the data in Tables 1 and 2 by focusing on the clinically significant outcomes of using carbon nanostructures in laryngeal implants.

Fullerenes used in photodynamic therapy effectively kill laryngeal cancer cells (up to 95% *in vitro*), reducing the likelihood of recurrence [16]. Graphene in 3D-printed scaffolds slows tumor cell growth, promoting their destruction. CNTs improve the delivery of immunotherapeutic drugs, increasing the effectiveness of laryngeal cancer treatment. Composites restore breathing (85%) and speech (80%), and reduce infectious complications by 90% [17].

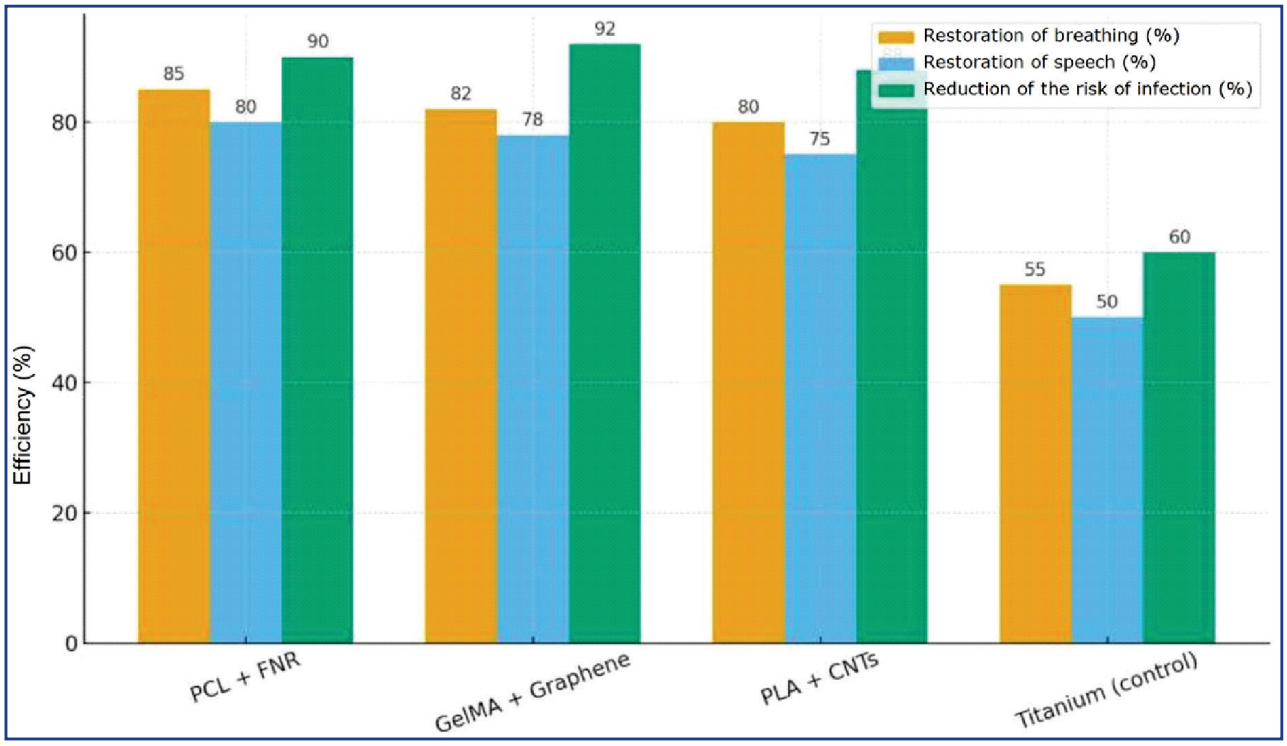

Figure 1 – Comparative clinical results [3, 7, 13-17]

Fullerenes increase chondrocyte proliferation by 4.5-fold over 7 days (collagen II expression: 85%). CNTs in PCL increase the scaffold strength to 8.4 MPa, and graphene in GelMA – up to 60% cell adhesion (Table 2). 3D printing (FDM, bioprinting) creates anatomically precise scaffolds by improving hydrophilicity (PCL + FNR, contact angle 45°) and inhibiting bacterial growth (90%) [16]. Tables (1, 2 - Table er) show chondrocyte growth (5.4×10^5 cells/cm^2 in 21 days) and antibacterial activity (*S. aureus* – survival rate 10%). Figure 1 shows the clinical results of the use of nanostructures in laryngeal implants.

Fullerene nanocore (FNR)-enhanced PCL composites provide 85% respiratory function recovery, 80% speech function recovery, and a 90% reduction in infectious complications, as confirmed by studies of 3D-printed scaffolds in otolaryngology [17]. Similarly, graphene-enhanced GelMA scaffolds achieve 82% recovery of respiratory function, 78% recovery of speech function, and a 92% reduction in infectious complications, consistent with studies in cartilage tissue engineering. Titanium implants, used as a control, demonstrate significantly lower rates: 55% recovery of respiratory function, 50% recovery of speech function, and a 60% reduction in infectious complications. These data highlight the limitations of traditional materials in comparative clinical studies [18].

Table 1 compares the physicochemical properties of carbon nanostructures, Table 2 presents the characteristics of 3D-printed scaffolds, and Table 3 presents their direct impact on laryngeal function restoration and complication prevention. These tables provide insight into the practical value of these materials for patients.

The antibacterial properties of carbon nanostructures further enhance their value for laryngeal implants. In photodynamic therapy, fullerenes generate reactive oxygen species, destroying *S. aureus* and *E. coli* with 95% efficiency for 12 hours. Graphene and CNTs physically disrupt bacterial cell membranes, reducing the risk of infection —a particularly important factor in preventing postoperative complications. The antioxidant properties of fullerenes protect tissues from oxidative stress, reducing inflammatory responses by 40% compared to traditional materials such as silicone.

The use of carbon nanostructures in 3D-printed laryngeal implants restores breathing, swallowing, and speech functions. Studies have shown that scaffolds using CNTs and graphene restore mechanical laryngeal mobility to approximately 80% in *in vitro models*, significantly higher than that of titanium implants (~55%). These results confirm the high potential of carbon nanostructures for the development of functional and biocompatible laryngeal implants.

Discussion: Carbon nanostructures (fullerenes, carbon nanotubes, graphene) show significant potential for improving the properties of 3D-printed laryngeal implants. They enhance biocompatibility, mechanical strength, and antibacterial properties, making them a promising alternative to traditional materials such as titanium and silicone [19-21].

Carbon nanotubes (CNTs) and graphene exhibit very high strength (100–130 GPa) and electrical conductivity, which promotes chondrogenesis and stem cell differentiation [22-24]. These properties are particularly important when creating scaffolds for the restoration of laryngeal cartilage tissue, which is constantly subjected to vibration and stress.

Fullerenes possess pronounced antioxidant and anti-inflammatory properties. Studies have shown that fullerenes reduce the production of proinflammatory cytokines (IL-6, TNF-α) by 35-40% compared to silicone and titanium implants [25, 26], which reduces the risk of postoperative fibrosis and infection.

Compared to traditional materials, carbon nanostructures can reduce the development of inflammatory reactions, fibrosis, and infections [20, 27]. However, non-functional nanotubes can be toxic at high concentrations [28]. Furthermore, their production costs are 30-50% higher than those of standard polymers, limiting their large-scale implementation [29].

Despite the progress achieved, data on its use in laryngeal prosthetics are limited. Targeted studies are needed that account for the characteristics of the limb: vibration loads, mechanical strength, and tissue elasticity [30].

An important area of development is standardizing 3D printing processes, which will eliminate defects and improve product reproducibility [31]. Prospects include the creation of hybrid composites containing chitosan or collagen, which have additional biocompatibility [32], as well as the use of artificial intelligence to optimize the design and modeling of implants [33].

Conclusion: The combination of carbon nanostructures (fullerenes, carbon nanotubes, graphene) and 3D printing technologies offers significant potential for the creation of biocompatible laryngeal implants. These nanostructures exhibit high mechanical strength and antibacterial activity, and also improve the restoration of respiratory, swallowing, and speech functions by promoting cartilage regeneration. Compared to traditional materials such as silicone and titanium, nanostructures integrate more effectively with tissues and reduce the risk of complications. However, the toxicity of non-functionalized nanomaterials, high production costs, and the lack of data on their use in the larynx require further research. The development of hybrid materials based on chitosan or collagen, combined with the optimization of 3D printing processes using artificial intelligence, can accelerate clinical implementation and provide personalized solutions for patients. In oncology, they reduce the rate of relapse and complications. Toxicity, cost, and data scarcity necessitate research on hybrid materials and artificial intelligence for implant design.

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АНДАТПА

КӨМЕЙ ИМПЛАНТТАРЫ ҮШІН БИОАЛМАСТЫРҒЫШ КӨМІРТЕКТІ МАТЕРИАЛДАРДЫ 3D БАСЫП ШЫҒАРУ ТЕХНОЛОГИЯСЫН ҚОЛДАНУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Көмей обырының жоғары аурушаңдығы және дәстүрлі импланттардың шектеулері (биосәйкестіктің төмендігі, инфекциялық асқынулар) жаңа материалдарды қажет етеді. Көміртекті наноқұрылымдар мен 3D басып шығару жекелендірілген көмей импланттары үшін перспективалы.*

Зерттеудің мақсаты *– фуллерендер, көміртекті нанотүтіктер және графен сияқты көміртекті наноқұрылымдарды шеміршек регенерациясын ынталандыру және көмей функциясын қалпына келтіру үшін биоүйлесімділігін, механикалық қасиеттерін және бактерияға қарсы белсенділігін жақсарту үшін 3D басып шығарылған көмей импланттарында пайдалану әлеуетін бағалау.*

Әдістері: *2005-2025 жылдардағы әдебиеттерді PubMed, Scopus, Web of Science, Google Scholar базаларында «carbon nanostructures», «3D printing», «laryngeal implants» кілт сөздерімен жүйелі талдау жүргізілді. 50 дереккөз талданды.*

Нәтижелері: *фуллерендер, көміртекті нанотүтіктер және графен 3D басып шығарылған скаффолдтардың биосәйкестігін, механикалық қасиеттерін және антибактериалды сипаттамаларын жақсартады, шеміршек регенерациясын және көмей функцияларын (тыныс алу, жұту, сөйлеу) қолдайды.*

Қорытынды: *Көміртекті наноқұрылымдар мен 3D басып шығару көмей импланттары үшін перспективалы, бірақ олардың биосәйкестігі мен ауқымды өндірісі бойынша қосымша зерттеулер қажет.*

Түйінді сөздер: *көміртекті наноқұрылымдар, 3D басып шығару, көмей импланттары, биосәйкестік, шеміршек регенерациясы, антибактериалды қасиеттер.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ ТЕХНОЛОГИИ 3D-ПЕЧАТИ БИООБМЕННЫХ УГЛЕРОДНЫХ МАТЕРИАЛОВ ДЛЯ ГОРТАННЫХ ИМПЛАНТАТОВ : ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Высокая заболеваемость раком гортани и ограничения традиционных имплантатов (низкая биосовместимость, инфекционные осложнения) требуют новых материалов. Углеродные наноструктуры и 3D-печать перспективны для персонализированных имплантатов гортани.*

Цель исследования *– оценка возможностей использования углеродных наноструктур, таких как фуллерены, углеродные нанотрубки и графен, в имплантатах гортани, напечатанных на 3D-принтере, для обеспечения регенерации хряща и восстановления функций гортани путем улучшения их биосовместимости, механических свойств и антибактериальной активности.*

Методы: *Проведен систематический анализ литературы 2015-2025 годов в базах PubMed, Scopus, Web of Science, Google Scholar по ключевым словам «carbon nanostructures», «3D printing», «laryngeal implants». Проанализировано 50 источников.*

Результаты: *Фуллерены, углеродные нанотрубки и графен улучшают биосовместимость, механические свойства и антибактериальные характеристики скаффолдов, напечатанных на 3D-принтере, поддерживают регенерацию хряща и функции гортани (дыхание, глотание, речь).*

Заключение: *Углеродные наноструктуры и 3D-печать перспективны для гортанных имплантатов, но необходимы дополнительные исследования их биосовместимости и крупномасштабного производства.*

Ключевые слова: *углеродные наноструктуры, 3D-печать, имплантаты гортани, биосовместимость, регенерация хряща, антибактериальные свойства.*

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PROSPECTS FOR DEVELOPING AN INTEGRATIVE CANCER PATIENT REHABILITATION MODEL: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Despite significant progress in diagnosing and treating oncological diseases, rehabilitation remains poorly integrated into comprehensive patient care. As the number of cancer survivors increases, the development of personalized and multidisciplinary rehabilitation models becomes especially important to ensure sustainable recovery and improved quality of life.*

The study aimed to *examine scientific studies analyzing modern approaches to cancer patient rehabilitation and to develop an integrative model that ensures a personalized and multidisciplinary approach to recovery.*

Methods: *A literature review was conducted using the Scopus, Web of Science, PubMed, Google Scholar, and ScienceDirect databases for publications from 2015 to 2024. Inclusion criteria: publications in Russian and English considering the physical, psychological, nutritional, social, and telemedicine rehabilitation of cancer patients. Exclusion criteria: case reports and clinical symptoms or complications not related to rehabilitation. A total of 94 publications were selected, of which 42 were included in the analysis.*

Results: *The State Strategy of Kazakhstan for 2023-2027 declares the introduction of an integrated approach to oncological rehabilitation; however, problems of standardization, staff shortages, and accessibility of services remain. The approaches of Germany, the United States, and Japan are described, and various models are illustrated. Six key components of the integrative model are identified: physical activity, psychological support, nursing support, pelvic and sexual rehabilitation, telemedicine, and nutritional support.*

Conclusion: *Integrating multidisciplinary cancer rehabilitation into the healthcare system is essential for improving quality of life, reducing disability, and enhancing the social adaptation of cancer patients. Adapting international practices to the national context will help improve the effectiveness of rehabilitation programs in Kazakhstan.*

Keywords: *cancer rehabilitation, multidisciplinary approach, quality of life, cancer survivors, telemedicine.*

Introduction: Cancer is the leading cause of death worldwide. According to WHO, more than 19 million new cases of malignant neoplasms are registered annually, and more than 10 million people die from cancer [1]. According to GLOBOCAN 2022, a significant increase in cancer incidence and mortality is projected worldwide in 2050 (Figure 1) [2].

In recent years, oncological diseases have remained a key health problem both in Kazakhstan and worldwide. Over the past 20 years, cancer incidence in Kazakhstan has increased by 25%, while mortality has decreased by 33%. Similar trends are observed in OECD countries, but 5-year survival rates in these countries remain significantly higher. Today, oncological diseases occupy the 7th place in the structure of all diseases in Kazakhstan, and mortality from them is second only to diseases of the circulatory system, occupying the 2nd place. More than 205 thousand patients with oncological diseases are under dynamic observation in the country, with more than 37 thousand new cases detected annually. In first place is breast cancer (13.2%); in second place is lung cancer (10.0%), in third place is colorectal cancer (9.3%), in fourth place is stomach cancer (7.4%) in terms of incidence, and women get sick more often than men, which is associated with the leading position of breast cancer. The 5-year survival rate continues to increase, amounting to 55.3% in 2022, but the target level (60%) has not been achieved. A decrease in the proportion of advanced stages (III–IV) and an increase in early detection rates (from 27.1% in 2019 to 29.0% in 2022) demonstrate success in the fight against cancer in Kazakhstan [3].

In recent decades, the number of patients successfully completing primary treatment has increased significantly due to improvements in early diagnosis and treatment of oncological diseases [4]. However, this progress is accompanied by new challenges: more than half of the patients are of working age (55.8%) [3], which leads to the need for their rehabilitation to return to a full life. Cancer is becoming not only a medical but also a socioeconomic problem: long-term rehabilitation and support for these patients is critical to reducing disability, improving their quality of life, and reducing the burden on the healthcare system [5].

Modern treatment methods allow achieving survival, but rehabilitation remains a poorly integrated component of oncological care [6]. Onco-rehabilitation is an active process aimed at restoring functions, reducing disability, and improving the quality of life of patients who have undergone oncological treatment. In developed countries (USA,

Germany, Sweden, Japan), rehabilitation is the standard of oncological care, while in Eastern Europe, Asia, and Africa, this component is often overlooked. In particular, low-resource countries face several barriers to providing cancer rehabilitation and care for survivors [7, 8]. Oncological patients encounter such problems as asthenia, lymphedema, pain syndrome, depression, cognitive impairment, and social isolation. Without systemic rehabilitation, patients often lose their ability to work and experience a deterioration in their psychoemotional state [6, 7]. International and regional studies confirm that multi-level rehabilitation significantly improves the quality of life and psychological state of patients, reduces the risk of relapse and hospitalization [5, 9].

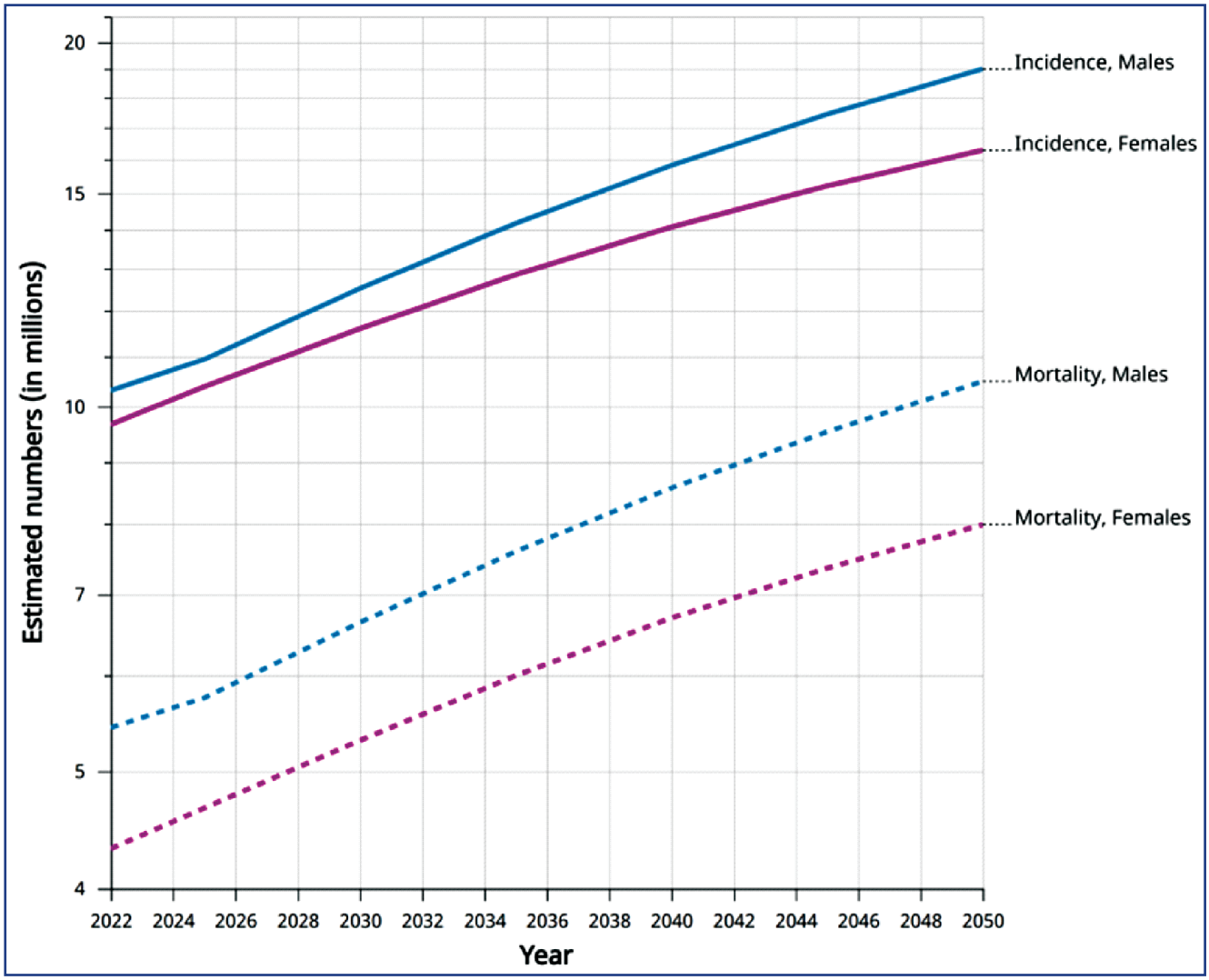

Figure 1 – Dynamics of growth in cancer incidence and mortality in the world from 2022 to 2050, men and women, age (0-85+) [2]

This indicates the need to introduce an integrated approach that includes medical, psychological, and social support, adapted to national realities [10]. In Kazakhstan, this area is given strategic importance. In the Comprehensive Plan to Combat Cancer for 2023–2027, rehabilitation is included as a mandatory element of the system. The implementation of the Comprehensive Plan of Measures to Combat Cancer contributed to a 15% reduction in mortality from malignant neoplasms: from 78.1 per 100 thousand population in 2018 to 66.8 per 100 thousand population in 2022. This trend is observed in all regions of Kazakhstan [3].

With the increasing number of surviving patients, the issues of assessing their rehabilitation needs and developing an effective rehabilitation model are becoming strategically important. Targeted study of these aspects will not only meet the current needs of patients, but also provide the national health care system with an effective tool for their rehabilitation [11].

The national significance of this problem is also due to the limited research on the rehabilitation needs of surviving patients. In the context of an increase in the number of survivors and a rejuvenation of the age composition of patients, it is necessary to develop a comprehensive approach to their rehabilitation, taking into account medical, psychological, and social aspects. This will improve the quality of life of patients, reduce disability, and return

them to an active life, which has both social and economic significance [12].

Regional characteristics such as access to health services, socioeconomic factors, and cultural differences can have a significant impact on the needs of cancer patients. It is necessary to study the unmet needs of cancer patients, as it is unclear how these issues are addressed [13].

Thus, the study aimed at identifying the needs of cancer patients and developing an integrated rehabilitation model is a timely and important step in strengthening the healthcare system of Kazakhstan [3].

The study aimed to examine scientific studies analyzing modern approaches to cancer patient rehabilitation and to develop an integrative model that ensures a personalized and multidisciplinary approach to recovery.

Materials and methods: The review included publications in Russian and English in the Scopus, Web of Science, PubMed, Science Direct, and Google Scholar databases. The search depth was 10 years, from 2015 to 2024. Published articles were classified according to their general topics and summarized. Literature sources contained reports on randomized and cohort studies, meta-analyses, and systematic reviews. Inclusion criteria: publications related to physical, psychological, nutritional, social, and telemedicine rehabilitation of cancer patients. The following were excluded: case reports, clinical symptoms, and complications not related to rehabilitation. A total of 94 publications were selected, of which 42 were included in the analysis. The data was structured according to rehabilitation components.

Results: Oncological diseases remain one of the leading causes of morbidity and mortality in the world, including the Republic of Kazakhstan. In response to these challenges, the Government of Kazakhstan approved a Comprehensive Plan to Combat Cancer for 2023-2027, aimed at improving the diagnosis, treatment, and rehabilitation of patients. Particular attention is paid to the implementation of a comprehensive approach to rehabilitation, which includes physical activity, psychological support, and nutritional therapy [3].

In the context of Kazakhstan, the adaptation of such models requires taking into account the infrastructural, personnel, and socio-cultural realities. Key problems hindering the development of oncological rehabilitation have been identified:

– lack of standards and protocols for rehabilitation components;

– limited access to rehabilitation services in the regions;

– lack of trained personnel, especially in the area of psychoemotional and nutritional support;

weak integration of telemedicine into practical healthcare.

A positive aspect is the existence of a state strategy that provides for the introduction of rehabilitation as a mandatory stage of oncology care. This creates a window of opportunity for the development of a national model based on an analysis of best practices [3].

Exercise is an effective strategy to improve the quality of life and physical fitness in breast cancer survivors. Study results further support the need to incorporate supervised clinical exercise programs into the treatment and care of patients with cancer [14]. Pulmonary rehabilitation performed after surgery significantly improved exercise capacity at 6 months in patients who underwent lung resection; it also significantly reduced the decline in exercise capacity observed at 1 month after surgery [15]. Pelvic floor rehabilitation has shown positive effects in patients with colorectal cancer, but there is a lack of uniform standards for pelvic floor rehabilitation interventions in patients with colorectal cancer [16]. International guidelines and cancer associations recommend a multidisciplinary approach to lung cancer care. A multidisciplinary team can significantly improve treatment decision making and patient coordination by placing different physicians and other health care professionals “in the same room” to jointly decide on the best possible treatment [17]. Those most in need of information support are young people, ethnic minorities, less educated people, and rural residents experiencing financial difficulties [18]. The need to improve the quality of life dictates the need to develop and systematically advance complex therapy for cancer patients [9].

International experience shows that effective oncological rehabilitation is based on the principles of multidisciplinarity, personalization, and a stage-by-stage approach. In Germany, a three-stage rehabilitation model is in place: early, specialized inpatient and outpatient support [19]. In Germany, oncological rehabilitation is an integral part of the healthcare system and part of modern cancer treatment, which immediately follows surgery, drug therapy, or radiotherapy [20]. The United States is actively developing telerehabilitation platforms and programs for the care of survivors, “Survivorship Care” [21, 22]. In Japan, the emphasis is on nutritional and psychoemotional rehabilitation of elderly patients; in Scandinavia, rehabilitation centers are organized based on oncology clinics and offer physiotherapy, art therapy, and support groups [7, 8].

Based on literary data, the following basic principles of the integrative model of rehabilitation of cancer patients are described :

1. Physical activity. Systematic reviews demonstrate significant improvements in fatigue, physical function, and quality of life in patients who have undergone physical rehabilitation [23, 24]. Exercise programs are effective even during chemotherapy or before surgery [4]. With increasing cancer survival rates, there has been an increased need to support people living with cancer to have a good quality of life, including physical activity [25]. Exercise training is safe during and after cancer treatment and results in improvements in physical functioning, quality of life, and cancer-related fatigue in cancer survivors [26]. Physi-

cal activity has also been shown to be effective in improving overall quality of life in breast cancer survivors, either through direct physiological effects or indirectly by reducing the side effects of cancer treatment [27].

2. Psychological support and the SOC approach. Both the CaSUN tool and programs based on the "sense of coherence" (SOC) have proven their effectiveness [28, 29]. Inclusion of psychotherapy and social support in the post-treatment period reduces anxiety levels and improves adaptation [12, 13]. Art therapy can help reduce symptoms of anxiety and depression, as well as improve the quality of life of adult cancer patients [30].

3. The role of nursing staff. An integrative review highlights the important coordinating role of nurses in the rehabilitation process, especially in outpatient and telemedicine environments. Patients report them as a stable point of support during long-term follow-up [31].

4. Pelvic and sexual rehabilitation. Pelvic floor muscle rehabilitation, especially in patients with colorectal cancer, has a significant impact on restoring quality of life [10, 16].

5. Telemedicine and digital platforms. Home-based programs based on a multidisciplinary approach can effectively support patients in settings with limited access to clinics [32, 33]. Case studies have shown that such approaches are comparable in effectiveness to face-to-face programs [34]. Advances in telemedicine have revolutionized the delivery of health services, which is particularly important for cancer rehabilitation. The integration of telemedicine into cancer rehabilitation services is being explored from diagnosis to survivorship, taking into account the unique challenges and opportunities at each stage [35].

6. The diet also improves quality of life in breast cancer survivors [27].

Discussion: The results of the review confirm that effective rehabilitation of cancer patients requires a comprehensive, multidisciplinary, and personalized approach. Physical activity has demonstrated a significant impact on improving physical condition, reducing fatigue, and increasing the quality of life of cancer patients [23-27]. Exercising is safe and beneficial even during periods of active treatment, including chemotherapy and radiotherapy [26]. This emphasizes the need to implement exercise programs not only during remission but also during treatment.

Psychological support also plays a key role in the successful adaptation of patients after treatment. Tools such as CaSUN, SOC programs, and art therapy have proven their effectiveness in reducing anxiety, depression, and improving the emotional state of patients [28-30]. These approaches are especially relevant for Kazakhstan, where the level of psychoemotional support for patients is still insufficient [12, 13].

One of the significant problems remains the availability of high-quality rehabilitation for rural residents and socially vulnerable groups, since these categories are more likely to need additional information and social support [18]. This requires the adaptation of international practices, taking into account regional and cultural characteristics, including digitalization and telerehabilitation.

Additional attention should be paid to the involvement of nursing staff in the coordinating and supporting role [31]. The importance of nutritional support, which contributes to improving quality of life, should also be emphasized [27].

International experience (Germany, USA, Japan, Scandinavian countries) demonstrates the successful implementation of models that include early and long-term rehabilitation, which may be useful for implementation in the healthcare system of Kazakhstan [19, 20]. The implementation of such a model requires not only organizational changes, but also personnel training, development of standards and protocols [36, 37].

Thus, the data presented in the article emphasize the need to revise approaches to the rehabilitation of cancer patients in the Republic of Kazakhstan, with a focus on international recommendations and local realities [38]. Reliance on the evidence base and successful practices of other countries will significantly improve the effectiveness of oncological care in general [39, 40].

Conclusion: Thus, the conducted literature review confirmed the need to introduce comprehensive, personalized, and interdisciplinary rehabilitation into the oncology care system. Effective rehabilitation not only helps restore the physical and psychoemotional state of patients but also improves their quality of life, reduces the risk of relapse, and facilitates social adaptation. International experience demonstrates the high effectiveness of systemic rehabilitation, including with the participation of multidisciplinary teams and the use of digital technologies [41-45]. For the Republic of Kazakhstan, it is important to adapt these approaches, taking into account local characteristics, increase the availability of rehabilitation, especially for socially vulnerable groups, and develop human resources. The results of the review emphasize the need to develop national standards and strategies in the field of oncology rehabilitation.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРДЫ РЕАБИЛИТАЦИЯЛАУДЫҢ ИНТЕГРАЦИЯЛЫҚ ҮЛГІСІН ӘЗІРЛЕУДІҢ БОЛАШАҒЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Онкологиялық ауруларды диагностикалау мен емдеуде елеулі ілгерілеулерге қарамастан, реабилитация кешенді көмектің толыққанды бөлігі ретінде жеткілікті деңгейде интеграцияланбаған. Онкологиялық емнен кейін тірі қалғандар санының өсуі жағдайында тұрақты қалпына келтіру мен өмір сапасын жақсартуды қамтамасыз ететін жеке және мультидисциплинарлық реабилитациялық үлгілерді әзірлеу ерекше маңызға ие.*

Зерттеу мақсаты *– онкологиялық науқастарды реабилитациялаудың қазіргі заманғы тәсілдерін талдау және қалпына келтіруге жекелендірілген және мультидисциплинарлық көзқарасты қамтамасыз ететін интеграциялық модельді әзірлеуге бағытталған ғылыми зерттеулерді зерделеу.*

Әдістері: *2015-2024 жылдар аралығында Scopus, Web of Science, PubMed, Google Scholar және ScienceDirect деректер базаларында әдебиеттерге шолу жүргізілді. Іріктеу критерийлері: онкологиялық науқастарды физикалық, психологиялық, нутритивтік, әлеуметтік және телемедицина арқылы оңалтуға байланысты. Зерттеуден шығарылғандар: оңалтумен байланысты емес клиникалық белгілер мен асқынулар сипатталған жағдайлық есептер (кейс-репорттар). 94 жарияланым таңдалып алынды, олардың 42-сі талдауға енгізілді.*

Нәтижелері: *Қазақстанның 2023–2027 жылдарға арналған мемлекеттік стратегиясы онкореабилитацияға кешенді тәсілді енгізуді көздейді. Алайда стандарттаудың болмауы, кадр тапшылығы және қызметтердің қолжетімділігі мәселелері сақталуда. Германия, АҚШ және Жапонияның онкореабилитация модельдерінің әртүрлілігін көрсетілді.*

Интегративті модельдің алты негізгі компоненті анықталды: физикалық белсенділік, психологиялық қолдау, мейірбикелік сүйемелдеу, жамбас және жыныстық функцияларды қалпына келтіру, телемедицина және нутритивтік қолдау.

Қорытынды: *Онкологиялық науқастардың өмір сапасын жақсарту, мүгедектік деңгейін төмендету және әлеуметтік бейімделуді арттыру үшін мультидисциплинарлық онкореабилитацияны денсаулық сақтау жүйесіне интеграциялау қажет. Халықаралық тәжірибелерді ұлттық ерекшеліктерді ескере отырып бейімдеу Қазақстандағы қалпына келтіру бағдарламаларының тиімділігін арттыруға мүмкіндік береді.*

Түйінді сөздер: *онкологиялық реабилитация, мультидисциплинарлық тәсіл, өмір сапасы, қатерлі ісіктен кейін аман қалғандар, телемедицина.*

АННОТАЦИЯ

ПЕРСПЕКТИВЫ РАЗРАБОТКИ ИНТЕГРАТИВНОЙ МОДЕЛИ РЕАБИЛИТАЦИИ ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Несмотря на значительный прогресс в диагностике и лечении онкологических заболеваний, реабилитация остаётся слабо интегрированной частью комплексной помощи пациентам. В условиях роста числа выживших после онкологического лечения особую важность приобретает разработка персонализированных и мультидисциплинарных реабилитационных моделей, обеспечивающих устойчивое восстановление и улучшение качества жизни.*

Цель исследования *– изучение современных подходов к реабилитации онкологических пациентов и разработке интегративной модели, обеспечивающей персонализированный и мультидисциплинарный подход к восстановлению.*

Методы: *Проведен обзор литературы в базах данных Scopus, Web of Science, PubMed, Science Direct и Google Scholar за 2015-2024 гг. Критерии включения: публикации, касающиеся физической, психологической, нутритивной, социальной, телемедицинской реабилитации онкопациентов. Исключались: кейс-репорты, клинические симптомы и осложнения, не связанные с реабилитацией. Было отобрано 94 публикации, из которых в анализ включено 42.*

Результаты: *Государственная стратегия Казахстана на 2023-2027 гг. декларирует внедрение комплексного подхода к онкореабилитации, при этом остаются проблемы стандартизации, кадрового дефицита и доступности услуг. Описаны подходы Германии, США и Японии, демонстрирующие разнообразие моделей. Выделены шесть ключевых компонентов интегративной модели: физическая активность, психологическая поддержка, сестринское сопровождение, тазовая и сексуальная реабилитация, телемедицина и нутритивная поддержка.*

Заключение: *Интеграция мультидисциплинарной онкореабилитации в систему здравоохранения необходима для улучшения качества жизни, снижения инвалидизации и повышения социальной адаптации онкологических пациентов. Адаптация международных практик с учетом национального контекста позволит повысить эффективность восстановительных программ в Казахстане.*

Ключевые слова: *онкологическая реабилитация, мультидисциплинарный подход, качество жизни, выжившие после рака, телемедицина.*

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THE ROLE OF ALPHA-FETOPROTEIN IN SUPPRESSING ANTITUMOR IMMUNE RESPONSE IN HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) is one of the most aggressive and deadly malignant tumors, characterized by treatment complexity and high resistance to immunotherapy. Alpha-fetoprotein (AFP) is traditionally used as a diagnostic marker for HCC. Recent studies reveal its key role in carcinogenesis and in forming a tolerogenic microenvironment that suppresses the anti-tumor immune response. Despite numerous publications, contradictions remain in assessing AFP's functions and prognostic value, necessitating an analytical review.*

This study aimed to *summarize current data on AFP's role in tumor immune evasion mechanisms and to evaluate its potential as a target for novel immunotherapeutic approaches for HCC treatment.*

Methods: *A systematic search and analysis of publications on AFP and HCC were conducted in PubMed and Google Scholar, and several specialized medical and scientific journals (including Cancer Research) from 2017 to 2025. Keywords included: "alpha-fetoprotein", "hepatocellular carcinoma", "immunosuppression", "tumor immune evasion", "AFP immunomodulation", "immune response in HCC". Selected articles met relevance and novelty criteria.*

Results: *The review revealed that AFP plays a central role in HCC progression through its immunosuppressive effects and activation of tumor immune evasion mechanisms. Contradictions in prognostic data reflect the complexity and multilayered biological functions of AFP.*

Conclusion: *AFP is not only a key diagnostic marker for HCC but also plays an active role in establishing immune tolerance. Its ability to suppress antitumor immune response makes AFP a promising therapeutic target, especially in combined immunotherapeutic approaches aiming to improve treatment efficacy.*

Keywords: *alpha-fetoprotein (AFP), hepatocellular carcinoma (HCC), immunosuppression, AFP-mediated immunomodulation, immune response.*

Introduction: Hepatocellular carcinoma (HCC) is one of the most common and aggressive malignant liver tumors, most often developing in the context of cirrhosis and chronic viral hepatitis. HCC is characterized by high mortality, late diagnosis, and limited treatment options, making this pathology one of the most significant medical and social problems.

According to the World Health Organization, as of 2020, HCC ranked seventh in prevalence and third in mortality among oncological diseases worldwide [1]. According to official data from the oncology service of the Republic of Kazakhstan for 2023 [2], mortality from liver malignancies accounted for 4.2% of overall oncological mortality, resulting in a shift in this pathology from 10th to 9th place. At the same time, significant regional variability is noted, with the highest mortality rate recorded in the East Kazakhstan region (7.0 per 100,000) and the lowest in the Zhetysu region (1.3 per 100,000). Figure 1 presents data on mortality from malignant neoplasms of the liver per 100 thousand of the population in the regions of the Republic of Kazakhstan for 2023. The data were compiled based on official statistics from the oncology service of the Republic of Kazakhstan for 2023. These data indicate significant differences in access to healthcare, the timeliness of diagnosis, and the prevalence of risk factors that warrant further investigation.

Despite numerous studies on HCC diagnostics and treatment, the effectiveness of existing approaches remains limited. Particular attention is paid to the search for molecular markers that can serve dual roles, both as diagnostic tools and as therapeutic targets. One of these factors is alpha-fetoprotein (AFP). Traditionally, AFP is used to diagnose and monitor HCC; however, accumulating data indicate that it not only reflects tumor progression but also actively participates in pathogenesis, including the suppression of antigen-presenting cells, inhibition of cytotoxic T lymphocytes, and stimulation of signaling pathways that promote tumor growth [3]. Al-

though the number of studies examining the role of AFP in immunomodulation in HCC is constantly increasing, the existing data remain controversial. While some studies emphasize the importance of AFP in creating an immunosuppressive microenvironment, others indicate that AFP has only a limited effect on tumor progression. This underscores the need for a systematic, critical review of the literature.

This study aimed to summarize current data on AFP's role in tumor immune evasion mechanisms and to evaluate its potential as a target for novel immunotherapeutic approaches for HCC treatment.

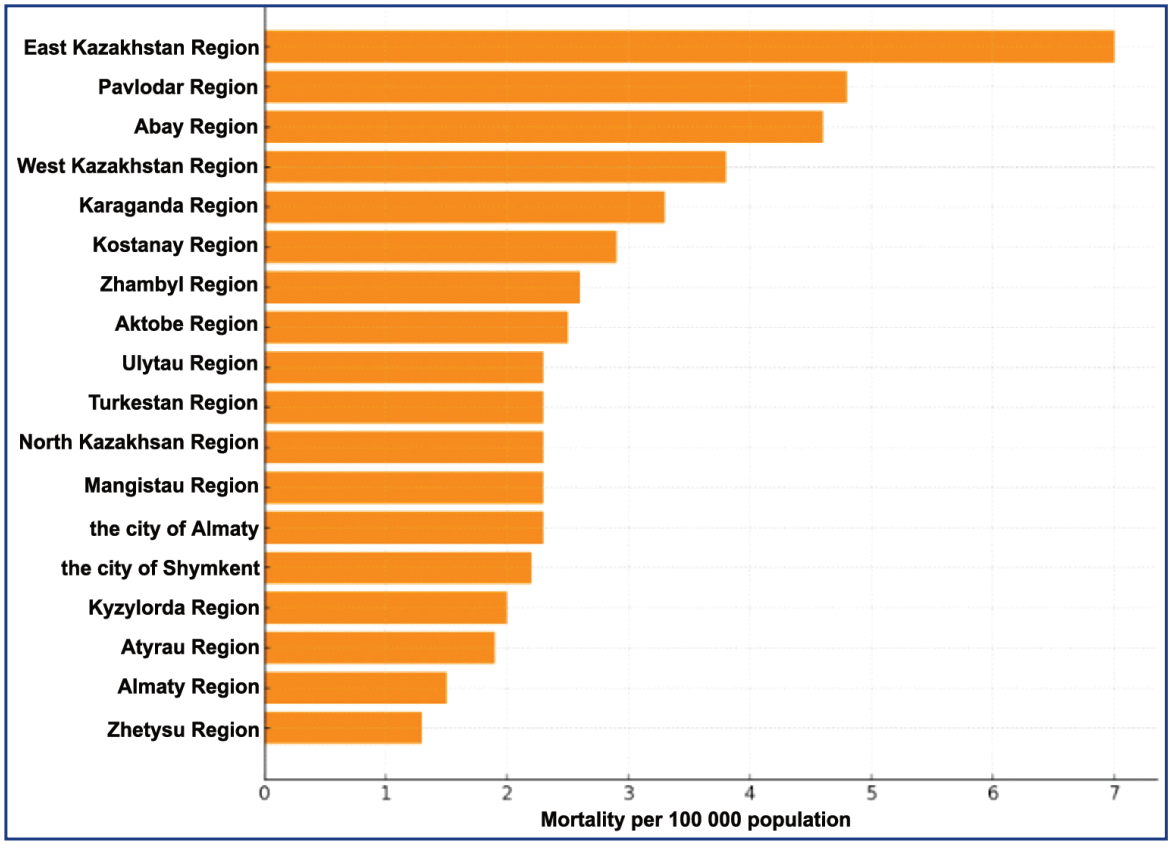

Figure 1 – Mortality from malignant neoplasms of the liver in Kazakhstan, 2023 [2]

Materials and Methods: Scientific papers from the Medline (PubMed) and Google Scholar databases were analyzed to identify available literature on the study topic. The following terms were used in the search: "alpha-fetoprotein" and/or "hepatocellular carcinoma" and/or "immunosuppression" and/or "tumor immune evasion" and/or "AFP immunomodulation" and/or "immune response in HCC". As a result, approximately 148 potentially relevant sources (articles and reviews) were identified. After removing duplicates and assessing the content, the most significant and informative works (including reviews and descriptions of original research) were selected. Selection criteria: novelty, completeness of the presented data, and the presence of unique information (works of low quality or those duplicating data from previously published studies were excluded). The final analysis comprised 50 sources, including those that provided detailed data on the mechanisms of the immune response, angiogenesis, and AFP-mediated signaling pathways, as well as two sources that contained statistical data on the disease prevalence in Kazakhstan. The search covered studies published up to and including April 2025 (Figure 2).

Results:

1. Alpha-fetoprotein (AFP)

AFP is a glycoprotein belonging to the albuminoid protein family, playing a key role in embryonic development [5]. Its structure includes three domains, each involved in the regulation of various signaling pathways [6]. Of particular significance is the interaction between domain III and PTEN, which activates the PI3K/AKT signaling cascade, thereby promoting the growth and progression of hepatocellular carcinoma (HCC). Normally, AFP levels drop sharply after birth; however, they rise again during malignant liver processes, especially in HCC [7]. To provide a broader understanding, the domain structure and functional characteristics of AFP are summarized in Table 1.

AFP is synthesized in the fetal liver and yolk sac, reaching peak levels between the 12th and 16th week of gestation [8]. In adults, its concentration is minimal. An increase in AFP levels is observed in both malignant conditions (primarily HCC and germ cell tumors) and several

benign conditions (pregnancy, chronic hepatitis, cirrhosis). In clinical practice, AFP is a key marker for early HCC diagnosis, evaluation of treatment efficacy, and monitoring for recurrence [9]. Table 2 describes the conditions associated with elevated AFP levels and their clinical significance.

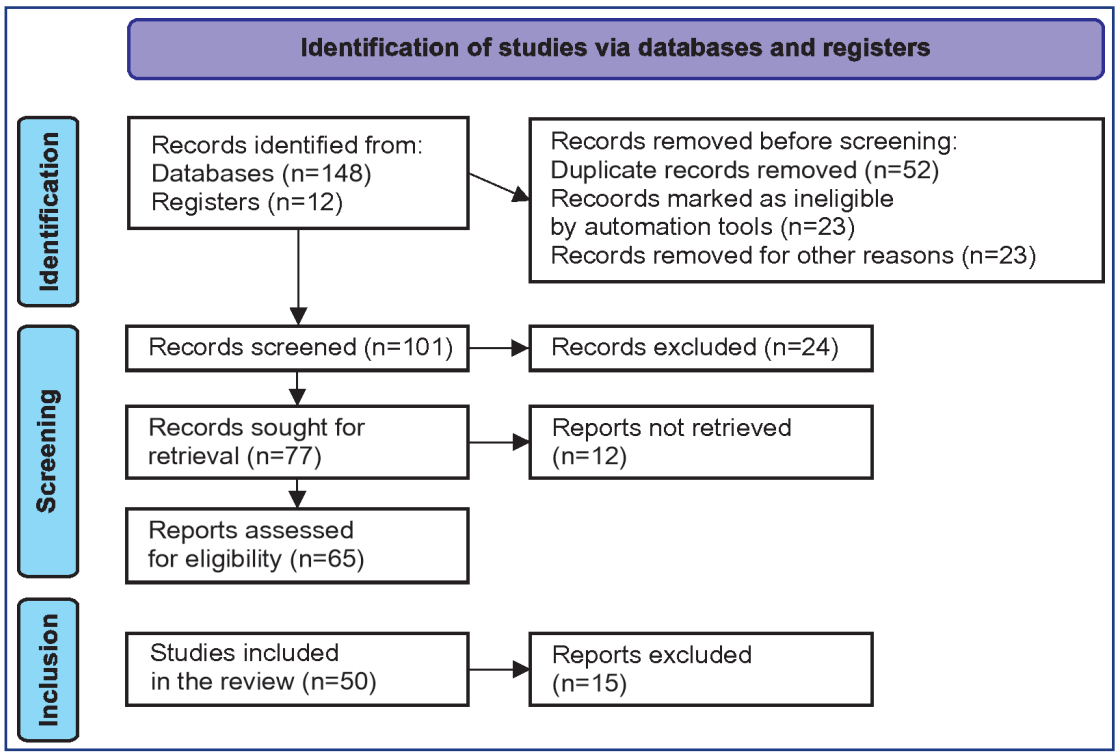

Figure 2 – PRISMA research source selection scheme [4]

Table 1 – Domain Structure and Functions of AFP

Domain	Characteristics	Primary Functions
I (N-terminal)	1-210 a.a.r.	Interaction with PTEN
II (central)	211-402 a.a.r.	Flexibility, protease-mediated cleavage
III (C-terminal)	403-609 a.a.r.	Stability, activation of PI3K/AKT

Note: a.a.r. – amino acid residues

Table 2 – Conditions Associated with Elevated AFP Levels and Their Diagnostic Significance

Condition / Disease	AFP Level (ng/mL)	Clinical Significance	Source
Normal in adults	< 10	Physiological level	Kachanov D.Yu. et al. [10]
Pregnancy (2nd trimester)	100 - 500 (may be higher)	Physiological elevation	Zakharov V.V. et al. [11]
Chronic hepatitis/cirrhosis	10 - 200	Moderate elevation requires differential diagnostics	Glowska-Ciemny J. et al. [12]
Hepatocellular carcinoma	> 400 (often > 1000)	Most specific, used for diagnostics and prognosis	Kong F. et al. [13]
Germ cell tumors (testes, ovaries)	100 - 10,000	Diagnostics, therapy monitoring	Sharma A. et al. [14]
Hepatoblastoma (in children)	> 1000	Highly diagnostic marker	Sharma A. et al. [14]
Metastatic liver tumors	50 - 500	Additional marker, less specific	Sharma A. et al. [14]

2. Mechanisms of Immune Response Suppression by Hepatocellular Carcinoma Cells.

HCC tumor cells utilize various mechanisms to evade the immune response [15]. The primary mechanisms include reduced expression of major histocompatibility complex class I (MHC-I) molecules, disruption of antigen presentation, and activation of non-classical immunosuppressive molecules [16]. Key signaling pathways involved in immune evasion in HCC are presented in Table 3 and Figure 3.

The Role of AFP in Liver Cancer Development.

Over the past decades, it has been demonstrated that AFP is not only a diagnostic marker but also actively participates in the progression of liver cancer. Elevated AFP levels (>400 ng/mL) are often associated with aggressive disease course and poorer prognosis. At the same time, changes in AFP levels during treatment allow for monitoring therapy effectiveness: a decrease in levels is associated with a positive response, while a renewed increase may indicate relapse even in the absence of signs on CT or MRI.

It is important to note that AFP affects not only prognosis but also the tumor's immune microenvironment. It suppresses the activity of key immune cells, including macrophages, dendritic cells, NK cells, and T lymphocytes. As a result, a so-called "immunosuppressive niche" forms, helping the tumor evade immune surveillance [29]. The effects of AFP on the immune microenvironment of HCC are summarized in Table 4.

Table 3 – Main Mechanisms of Impaired Antigen Presentation in HCC

Mechanism	Prevalence	Consequences for Immune Response	Source
Decreased MHC-I expression (HLA-A, HLA-B, HLA-C)	≈78% of cases	Reduced recognition by $CD8^+$ T cells	Kamilova T.A. et al. [17]
Hypermethylation of HLA promoters	Frequent	Suppression of MHC-I gene transcription	Liu H. et al. [18]
miRNA regulation (miR-148a, miR-152)	Reported in clinical samples	Inhibition of HLA translation	Bird T.G. et al. [19]
TAP1/TAP2 mutations	30-40%	Disruption of antigen transport to the ER	Bird T.G. et al. [19]
B2M mutations	25-30%	Instability of MHC-I on the membrane	Galle P.R. et al. [20]
Decreased PSMB8/PSMB9 (proteasome subunits)	–	Defective antigen processing	Yang Z. et al. [21]
Increased expression of HLA-E, HLA-G	Frequent	Suppression of NK and T cells via inhibitory receptors	Zhu M. et al. [22], Hong G.Q. et al. [23]

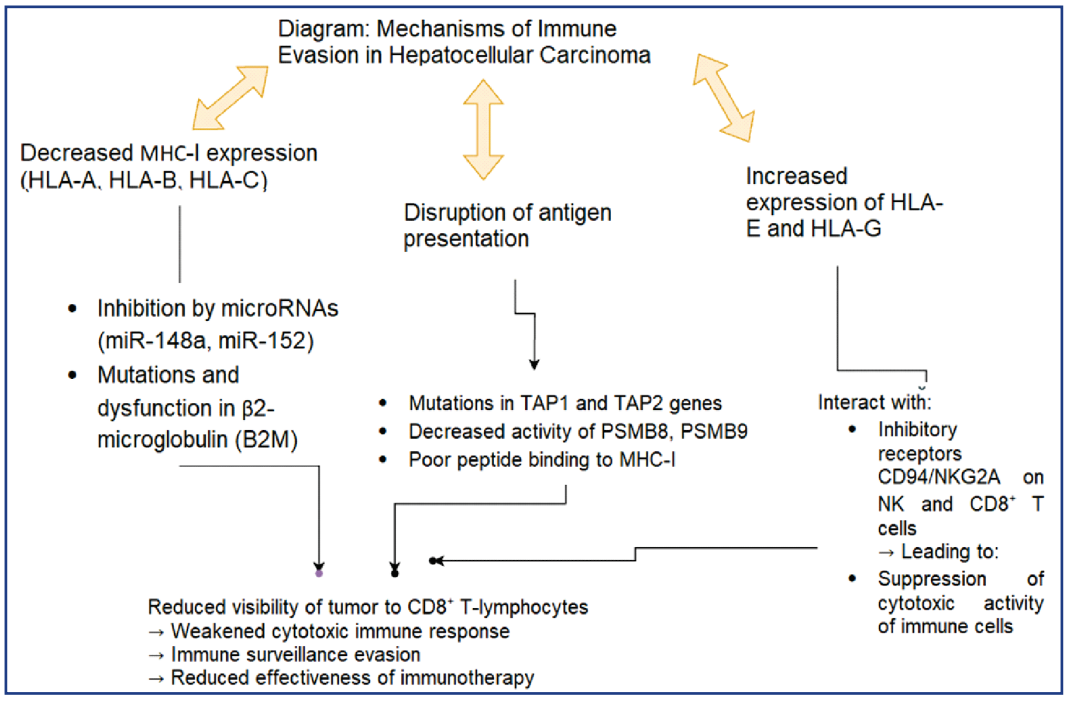

Figure 3 – Mechanisms of Immune Evasion in HCC [24-28]

Table 4 – Mechanisms of AFP Action on Target Cells

Target Cell	Mechanism of Action	Immune Consequences	Source
Macrophages	Stimulates transition to M2 phenotype via PI3K/Akt pathway	Suppression of antitumor response, support of tumor growth	Wu S. et al. [30]
Dendritic cells	Induces apoptosis, reduces CD80/CD86 expression	Impaired antigen presentation and T-lymphocyte activation	Palucka K. & Banchereau J. [31]
NK cells	Indirectly decreases activity via reduced IL-12	Reduced cytotoxic activity	Zhou Y. et al. [32]
$CD8^+$ T-lymphocytes	Inhibits the IL-2R signaling pathway	Loss of proliferation and cytotoxicity	Shang N. et al. [33]
$CD4^+$ T-lymphocytes	Reduces IL-2 and IFN-γ production	Weakened coordination of the immune response	Isyangulova A.Z. [34]
Regulatory T-cells	Stimulates differentiation via TGF-β/Smad3	Formation of a tolerogenic environment	Tian L.Y. et al. [35]
Myeloid-derived suppressor cells (MDSCs)	Enhances immunosuppressive activity	Suppression of NK and T-cell responses	Mishra R. et al. [36]
Tumor cells	Activation of NF-κB → ↑PD-L1 expression	Inhibition of T-cell activity	Ebrahimi N. et al. [37]

In addition to its impact on immunity, AFP contributes to the maintenance of liver cancer stem cells (LCSC) [38]. These cells possess self-renewal capability and are associated with recurrence and drug resistance. Studies have shown that AFP stimulates the expression of LCSC markers (CD44, CD133, EpCAM) and activates the PI3K/Akt signaling pathway, thereby enhancing tumor malignancy [39].

AFP is considered a potential therapeutic target given its active role in the development of immunosuppression in HCC. The main research directions can be divided into several categories. Thus, AFP has become a target for the development of new treatment strategies given its key role in HCC progression and immunosuppression. The main approaches are presented in Table 5.

Table 5 – Potential Therapeutic Strategies Targeting AFP

Approach	Examples	Results	Limitations	Source
Restoration of antigen presentation	IFN-γ, decitabine	Increased HLA-I expression, enhanced tumor recognition	Preclinical stage only	Son C.H. et al. [40]
CAR-T cells against AFP	AFP-specific CAR-T	High efficacy in murine models	Risk of off-target toxicity, intratumoral immunosuppression	Yershov A.V. et al. [41], Gavrilina O.A. et al. [42]
Dendritic vaccines	DCs loaded with AFP	Phase I/II: safety confirmed, 20% objective response rate	The low immunogenicity of AFP requires combination with other antigens	Chekhonin I.V. et al. [43], Shardina K.Yu. et al. [44]
Signaling pathway inhibitors	Alpelisib (PI3Kα)	Tumor growth reduction in HepG2/Huh7 models	Preclinical data only; combination strategies need optimization	Semiglazov V.F. et al. [45]
Combination approaches	TACE + immunotherapy	Enhancement of local immune response	Limited clinical data	Phillips C. [46]

Discussion: Hepatocellular carcinoma (HCC) remains one of the most challenging oncological diseases due to its high mortality rate and the limited effectiveness of current therapeutic approaches [47]. The presented data confirm the key role of AFP not only as a diagnostic marker but also as an active participant in the pathogenesis of HCC. AFP creates an immunosuppressive microenvironment by modulating macrophages, dendritic cells, NK cells, and T lymphocytes. Such remodeling of the immune niche reduces the effectiveness of the antitumor immune response and promotes tumor progression. An important aspect is the influence of AFP on the population of liver cancer stem cells (LCSC), which are associated with recurrence and drug resistance. Thus, AFP plays a dual role: on the one hand, it suppresses immune surveillance; on the other, it supports LCSC and enhances tumor aggressiveness. Despite the accumulated data, certain contradictions remain: in some patients with low AFP levels, the disease still shows aggressive progression, and the mechanisms of AFP's influence on immune cells have not been fully confirmed in clinical studies. This highlights the need for further research to clarify the prognostic value of AFP and its therapeutic potential. From a therapeutic perspective, the most promising strategies are combined approaches, in which AFP is not considered a sole target but as part of a multi-antigen strategy. Current directions include AFP-targeted CAR-T cells, dendritic cell vaccines, and PI3K/Akt pathway inhibitors [48]. However, most of these methods remain limited to preclinical models or early-phase clinical trials, and their transition to widespread clinical use is hindered by the risks of off-target toxicity and the immunosuppressive tumor microenvironment. Overall, a promising direction appears to be integrating targeted and immunotherapeutic approaches with local methods (e.g., TACE), as well as monitoring AFP dynamics as a biomarker of therapeutic effectiveness.

Study Limitations: Given the retrospective design and lack of clinical outcomes data, several limitations should be considered when interpreting the results. Firstly, relapse-free survival and overall survival were not analyzed in this study, which prevents establishing a direct link between AFP, immunological changes, and actual clinical outcomes. Additionally, the effects of comorbidities and ongoing therapies (targeted and antiviral) were not accounted for, even though they may influence AFP levels and immune response parameters. Liver regeneration after surgical intervention can also affect AFP dynamics. Moreover, the limited sample size and heterogeneity in HCC stage, cirrhosis status, and viral load may reduce the analytical power and complicate the interpretation of these results.

To date, AFP retains its important clinical role as a diagnostic marker; however, it is not limited to that role alone. For example, AFP levels have prognostic significance, as elevated AFP is associated with more aggressive disease progression in most cases. Changes in AFP levels during treatment serve as a surrogate response indicator: a post-treatment decrease typically correlates with clinical response, whereas a renewed increase signals relapse. Current preclinical and clinical studies also suggest that AFP may act as an active immunomodulator within the tumor microenvironment, as evidenced by its effects on dendritic cell maturation and function, suppression of NK and $CD8^+$ T-lymphocyte activity, stimulation of regulatory T-cell differentiation, and enhancement of immune checkpoint molecule expression.

The conducted literature review is not limited to listing known associations between AFP and molecular phenomena in HCC. In the present study, existing data were synthesized into a single, functionally oriented model, in which AFP is considered an active immunomodulator that establishes a tolerogenic microenvironment and facilitates tumor immune evasion. Based on the comparison of preclinical and clinical studies, specific mechanisms were identified – such as its effects on dendritic cells, NK and T lymphocytes, stimulation of regulatory T lymphocytes (Tregs), activation of PI3K/AKT and NF-κB - mediated pathways, associated upregulation of PD-L1 expression, and the role of AFP in supporting the LCSC population – all presented not as isolated findings, but as an interconnected pathophysiological network contributing to HCC progression. This integrated data indicates that AFP is not just a marker of tumor burden but also a biologically active factor that alters the composition of immune cell populations and reduces the clinical efficacy of immunotherapies.

Conclusion: AFP plays a central role in the development and progression of HCC. Its ability to suppress antigen presentation, modulate immune cell activity, and maintain the stem-like properties of liver cancer stem cells (LCSC) makes AFP not only a biomarker but also an important therapeutic target [49]. Current research highlights the potential of approaches involving CAR-T cells, dendritic cell vaccines, and inhibition of the PI3K/Akt and NF-κB signaling pathways [50]. However, their clinical efficacy remains limited, underscoring the need for further preclinical and clinical studies. AFP continues to serve as an indicator for diagnostics, prognosis, and monitoring of treatment effectiveness. In the future, a comprehensive approach – combining immunotherapy, targeted agents, and local treatment methods with consideration of AFP dynamics – may become the foundation for personalized HCC therapy strategies.

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АҢДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫ КАРЦИНОМА КЕЗІНДЕ АЛЬФА-ФЕТОПРОТЕИННІҢ ІСІККЕ ҚАРСЫ ИММУНДЫҚ ЖАУАПТЫ БАСУДАҒЫ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Гепатоцелюлярлық карцинома (ГЦК) – емдеуде күрделі және иммунотерапияға жоғары төзімділігімен ерекшеленетін ең агрессивті әрі өлімге әкелетін қатерлі ісіктердің бірі. Альфа-фетопротеин (АФП) әдетте ГЦК диагнозында маркер ретінде қолданылады. Соңғы зерттеулер оның канцерогенезде және қарсы ісікке иммундық жауапты басатын төзімді микробейтарап ортаны қалыптастыруда маңызды рөл атқаратынын көрсетті. Көптеген жарияланымдарға қарамастан, АФП функциялары мен болжамдық мәнін бағалауда қайшылықтар сақталады, бұл аналитикалық шолу қажеттігін туындатады.*

Зерттеу мақсаты *– АФП-ның ісік иммундық жауаптан қашу механизміндегі ролін жинақтап, ГЦК-ны емдеуге арналған жаңа иммунотерапиялық тәсілдерді әзірлеуде АФП-ның әлеуетін бағалау.*

Әдістері: *PubMed және Google Scholar мәліметтер базаларында, сондай-ақ профильді медициналық және ғылыми журналдарда (оның ішінде Cancer Research) 2017-2025 жылдар аралығында АФП және ГЦК тақырыбындағы жарияланымдар жүйелі түрде ізделіп, талданды. Іздеу кілт сөздері: «альфа-фетопротеин», «гепатоцелюлярлық карцинома», «иммуносупрессия», «ісік иммундық жауаптан қашу», «АФП иммундық модуляциясы», «ГЦК иммундық жауабы». Таңдалған мақалалар өзектілік пен жаңалық талаптарына сай болды.*

Нәтижелері: *Шолу барысында АФП иммуносупрессивті әсерлері және ісіктің иммундық бақылаудан қашу механизмдерін белсендіріп, ГЦК прогрессиясында орталық рөл атқаратыны анықталды. Болжамдық мәліметтердегі қайшылықтар АФП-ның көпқырлы биологиялық қызметінің күрделілігін көрсетеді.*

Қорытынды: *АФП тек ГЦК-ның маңызды диагностикалық маркері ғана емес, сонымен қатар иммундық төзімділіктің қалыптасуында белсенді қатысушы. Оның қарсы ісік иммундық жауаптарын басу қабілеті емдеу тиімділігін арттыруға арналған кешенді иммунотерапиялық тәсілдерде перспективалы терапевтік мақсат болып табылады.*

Түйінді сөздер: *льфа-фетопротеин (АФП), гепатоцелюлярлық карцинома (ГЦК), иммуносупрессия, АФП-бақыланатын иммундық модуляция, иммундық жауап.*

АННОТАЦИЯ

РОЛЬ АЛЬФА-ФЕТОПРОТЕИНА В ПОДАВЛЕНИИ ПРОТИВООПУХОЛЕВОГО ИММУННОГО ОТВЕТА ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) – один из самых агрессивных и смертельно опасных типов злокачественных новообразований, который характеризуется сложностью в лечении и высокой устойчивостью к иммунотерапии. Альфа-фетопротеин (АФП) традиционно используется в качестве маркера для диагностики ГЦК. Кроме этого последние исследования показывают, что он также играет важную роль в канцерогенезе и в формировании толерогенного микроокружения, подавляющего противоопухолевый иммунный ответ. Несмотря на значительное число публикаций, остаются противоречия в оценке функций и прогностической ценности АФП, что обусловливает необходимость проведения аналитического обзора.*

Цель исследования *– обобщить современные данные о роли АФП в механизмах уклонения опухоли от иммунного ответа и оценить потенциал АФП как мишени для разработки новых иммунотерапевтических подходов лечения ГЦК.*

Методы: *Проведен систематический поиск и анализ публикаций по теме α-фетопротеина и ГЦК в базах данных PubMed и Google Scholar, а также в ряде профильных медицинских и научных журналов (в том числе Cancer Research) за период с 2017 по 2025 год. Для поиска использовались ключевые слова: «альфа-фетопротеин», «гепатоцеллюлярная карцинома», «иммуносупрессия», «иммунное уклонение опухоли», «иммуномодуляция АФП», «иммунный ответ при ГЦК». Отобранные статьи соответствовали критериям релевантности и новизны.*

Результаты: *Обзор показал, что АФП играет центральную роль в прогрессировании ГЦК за счёт иммуносупрессивных эффектов и активации механизмов уклонения опухоли от иммунного надзора. Кроме того, выявлены противоречия в данных о его прогностическом значении, что отражает сложность и многоуровневость биологических функций АФП.*

Заключение: *АФП является не только ключевым диагностическим маркером ГЦК, но и активным участником формирования иммунной толерантности. Его способность подавлять противоопухолевый иммунный ответ делает АФП перспективной терапевтической мишенью, особенно в контексте комбинированных иммунотерапевтических подходов, направленных на повышение эффективности лечения.*

Ключевые слова: *альфа-фетопротеин (АФП), гепатоцеллюлярная карцинома (ГЦК), иммуносупрессия, АФП-опосредованная иммуномодуляция, иммунный ответ.*

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POSSIBILITIES OF DUAL-ENERGY CONTRAST SPECTRAL MAMMOGRAPHY IN COMPLEX RADIATION DIAGNOSIS OF BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Contrast spectral mammography (CSM) is an innovative technology that combines the principles of traditional digital mammography with intravenous administration of an iodine-containing contrast agent. This makes it possible to obtain images reflecting angiogenesis and vascularization of pathological foci, which potentially increases the sensitivity and specificity of breast cancer (BC) diagnosis. BC occupies the first place in the structure of cancer morbidity and mortality from cancer among the female population worldwide and remains an urgent problem today. Despite promising research results, many aspects of the clinical application of CSM require further study. In particular, it is relevant to compare the diagnostic value of CSM with other radiation imaging meth-ods such as digital mammography (DM) and magnetic resonance imaging (MRI) of the mammary glands.*

The study aimed to *explore the diagnostic capacity of contrast spectral mammography in breast cancer detection compared to other radiation methods.*

Methods: *A search and selection of articles in the databases PubMed, Web of Science, Scopus, and Google Scholar from 2015 to 2025, devoted to the diagnosis of breast cancer. To write this review, 107 literary sources were found for all resources, of which 30 were included in the presented review.*

Results: *The results showed that CSM is easily performed and well tolerated by patients. The meth-od is superior to DM because it provides information about the presence of pathological neoangiogenesis of the tumor. Compared to MRI, CSM is similar in sensitivity and specificity. Therefore, CSM can be used as an alternative method of breast imaging due to its higher accessibility and usability in patients with contraindications for MRI.*

Conclusion: *CSM exceeds the capacity of conventional DM, regardless of breast density. As a result, this method can reduce the number of false positive results and limit the number of unwanted invasive interventions. Early detection of BC significantly increases the chances of successful treat-ment, reduces the risk of metastasis, and improves overall and disease-free survival.*

Keywords: *contrast spectral mammography (CSM), digital mammography (DM), magnetic resonance imaging (MRI), breast cancer.*

Introduction: Breast cancer (BC) is a malignant tumor that originates from the epithelial cells of the ducts and lobules of the mammary gland. BC is characterized by aggressive growth and variability of the clinical course, with invasion into the ducts and lobules. The main risk factors are stress, immunosuppression, heredity, late menopause, hormonal factors, obesity, smoking, and alcoholism [1]. Globally, BC leads both in the number of detected cases and the mortality rate among women and remains a pressing problem today. According to GLOBOCAN (2022), more than 2.3 million new cases of BC are registered worldwide among both sexes, taking the lives of 670,000 women per year. The disease ranks first among the causes of cancer both in countries with mature and transitional economies. In Kazakhstan, about 5,500 new cases and 1,600 deaths from BC are registered annually [2]. With such high morbidity and mortality rates, timely and early diagnosis is of particular importance, requiring the improvement of existing visualization methods [3].

The study aimed to explore the diagnostic capacity of contrast spectral mammography in breast cancer detection compared to other radiation methods.

Materials and Methods: This review included the search and analysis of literature sources from PubMed, Web of Science, Scopus, and Google Scholar databases that were published from 2015 to 2025. The main objective was to study the effectiveness and accuracy of various methods for diagnosing breast cancer. The search keywords included: contrast spectral mammography (CSM), digital mammography (DM), magnetic resonance imaging (MRI), and breast cancer.

The literature analysis was conducted taking into account formal criteria: type of publication, level of evidence (according to the GRADE scale), quality of methodology, and indexation of the source in international databases. The following criteria were applied:

Inclusion criteria: open access, full text, period, article type: clinical trial, systematic reviews, original articles, and meta-analyses.

Exclusion criteria: Articles without a description of the methodology or with incomplete data on the group of patients and the diagnostic methods used. Publications without access to the full text and duplicate publications. Literature in languages other than Russian and English.

During the search, 107 literature sources were identified from all sources; of them, 30 were included in the final review. The main steps of the search were performed according to the PRISMA guidelines, as shown in Figure 1.

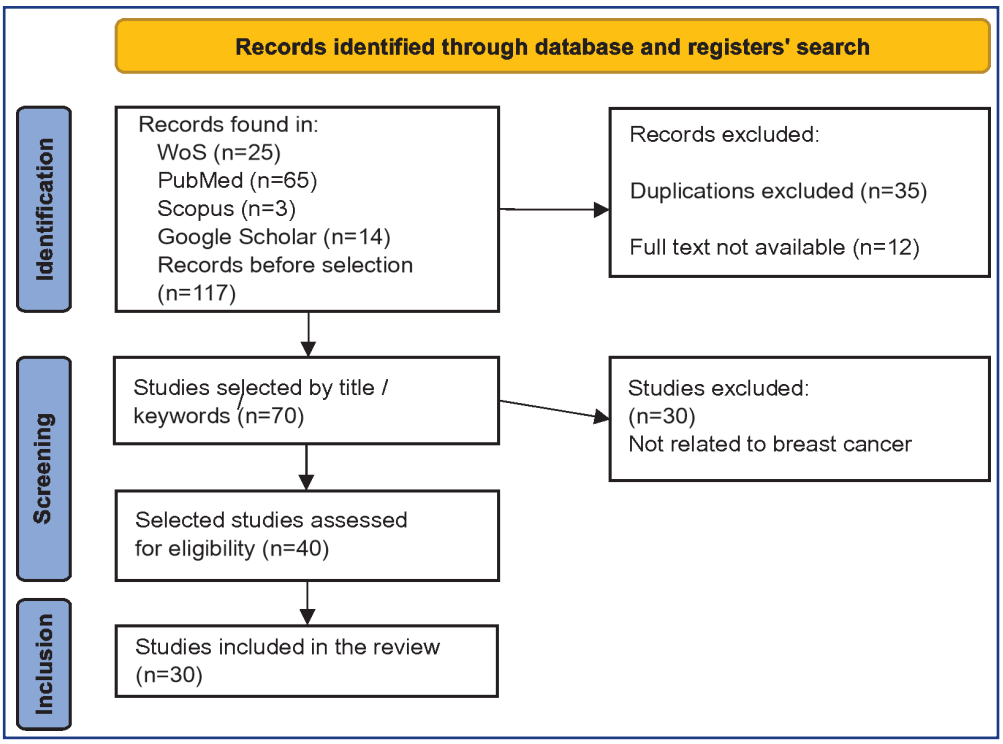

Figure 1 – PRISMA flow diagram

The quality of included publications was assessed using the Newcastle-Ottawa Scale (NOS), covering three domains: selection of participants, comparability of groups, and completeness of outcome reporting. The maximum score was 9 points. The GRADE approach was used to assess the certainty of evidence for key diagnostic indicators, taking into account study design, risk of bias, consistency, and precision of results [4].

In 2022, the Joint Commission for Quality Control of Medical Care of the Ministry of Health of the Republic of Kazakhstan approved clinical protocols for the diagnosis and treatment of breast cancer (Minutes No. 174) [5].

Digital mammography is a non-invasive radiological breast imaging method, considered the standard for breast cancer screening and diagnostics. The national screening program involves testing women aged 40 to 70 every two years. This approach has reduced mortality rates by 15-25% [3, 6]. However, this method's capacity is limited when visualizing mammary glands with high tissue density (dense breasts), which reduces the diagnostic sensitivity of digital mammography. The ratio of adipose and fibroglandular tissue determines the structure of the mammary gland. Dense breasts are assessed according to the classification of the American College of Radiology (ACR) [7]. BI-RADS system, in its latest edition (5th) applied since 2013, distinguishes the following categories: ACR A – predominantly adipose tissue (<25% fibroglandular); ACR B – moderately dense (25-50%); ACR C – heterogeneously dense (5-75%); ACR D – extremely dense (>75%). Digital mammography sensitivity is lower in detecting breast cancer in ACR C & D types' mammary glands.

CSM, as an innovative method of breast imaging, combines standard digital mammography with low (26-32 keV) and high (40-49 keV) energy modes with intravenous administration of iodine-containing contrast medium (ICCM). This makes it possible to visualize pathological changes accompanied by neovascularization, even with dense breasts [8]. CSM is gaining popularity since its introduction in 2003 [9]. Still, along with the benefits, it carries potential risks, including allergic reactions (0.2-0.7%) and nephrotoxicity, as described in the studies of K. Coffey et al.(2022) [10]. According to a meta-analysis, the frequency of side effects is comparable to CT – about 0.8%. In addition, the total radiation dose during CSM is 1.5-1.8 times higher than during digital mammography [11]. CSM technique involves bolus administration of ICCM at a dose of 1.5 ml/kg at a rate of 2.5 ml/s. Two minutes after the injection, a series of images of both mammary glands is taken in standard projections (CC and MLO). The use of low- and high-energy X-rays allows for constructing post-contrast maps reflecting zones of increased ICCM accumulation. MLO projection of the side of interest is performed last to estimate

the rate of contrast washout. If necessary, additional projections (lateral, enlarged) are possible [12]. L. Nicosia et al. demonstrated a higher sensitivity and specificity of CSM in diagnosing breast cancer, especially in women with dense breasts [13]. A systematic review by T. Tagliafico et al., covering retrospective and prospective studies, confirmed high diagnostic efficiency of the method: CSM sensitivity reaches 98% [14].

In addition to the above diagnostic methods, magnetic resonance imaging (MRI) is used for accurate diagnostics. The examination requires MRI machines with a power of 1.5 Tesla and higher, which provide higher spatial and temporal resolution. This increases diagnostic reliability in identifying pathological foci. MRI using gadolinium-enhanced ICCM can detect more aggressive and invasive types of breast cancer. MRI has a high sensitivity in detecting cancer compared to traditional diagnostic methods. Its high sensitivity is due to the fact that no cancerous tumor can grow larger than 2 mm without forming blood vessels, which provide large amounts of nutrients for tumor growth. Gadolinium-enhanced ICCMs have relatively large molecules that easily pass out of the vessels and quickly accumulate in the tumor stroma [15]. A standard MRI protocol includes T1 and T2 modes with signal suppression from fat tissue, dynamic contrast enhancement, diffusion-weighted images, and the construction of maps of the measured apparent diffusion coefficient [16]. High vascular permeability in cancer allows for rapid accumulation of ICCM in the tumor and leads to rapid leaching of ICCM from the lesion, which helps to better visualize pathological areas of enhancement and differentiate malignant and benign tumors [17]. According to the European Society of Breast Imaging (EUSOBI) recommendation [18], MRI is used when the results of standard imaging are inconclusive and it is necessary to exclude a malignant tumor, to determine preoperative staging, and to determine the exact tumor size. The tumor size of invasive carcinoma on MRI corresponds to the actual tumor size in the postoperative material. Besides, 25% of tumors are multifocal (one or more foci are located in one quadrant of the breast) and 20% are multicentric (one or more invasive foci are located at a distance of more than 4 cm from the primary tumor). Incorrect size assessment and failure to detect additional foci of spread may result in positive resection margins after surgery or early recurrence. Another MRI advantage is the detection of synchronous breast lesions, which occur in approximately 3% of all patients with breast cancer [19]. Digital mammography does not detect synchronous contralateral lesions, and they remain undetected in approximately 75% of cases. Main disadvantages of MRI include its high cost, the presence of contraindications in patients with metal implants in the body, pacemakers, allergy to gadolinium-enhanced ICCM, and claustrophobia, which limits the widespread use of MRI in breast imaging.

Results: CSM has a high sensitivity (90-95%) and specificity (85-90%), especially when cancer is detected in dense breasts. M. Mori et al. have compared CSM and digital mammography diagnostic effectiveness in dense breasts. In their study, CSM had a sensitivity of 86.2%, a specificity of 94.2%, and a diagnostic accuracy of 90.9%, while digital mammography had a low sensitivity of 53.4%, a specificity of 85.9%, and a diagnostic accuracy of 72.7% [20]. M. Helal et al. demonstrated the added benefit of CSM: their study showed that the method allows for effective differentiation of breast cancer recurrences after surgical intervention. The sensitivity of CSM in detecting breast cancer recurrence in the postoperative scar area was 91.2%, and the positive predictive value was 77.5%. Of all those examined, 48.6% had a postoperative relapse [21]. CSM allows detecting qualitative characteristics of breast cancer, such as the degree of ICCM accumulation (absent, weak, moderate, and pronounced). A type of accumulation in the pathological focus (lacunar, cloud-like, diffuse-spherical, point, mesh, cotton-like, ring-shaped, heterogeneous-ring-shaped) allows for differential diagnostics between benign and malignant neoplasms in the mammary gland [22].

S. Weigel et al. performed a systematic review of prospective studies to compare CSM and digital mammography in women with a varied degree of breast density. In their study, digital mammography sensitivity decreased with increasing breast density, from 100% with ACR A to 50% with ACR D. The sensitivity of digital mammography for the overall sample was 79.9%. The study included 438 patients, of whom 154 were confirmed to have malignant tumors, and 284 were confirmed to have benign tumors. Comparing the diagnostic characteristics of women with high-density breasts (ACR C & D), CSM demonstrated better results, with a sensitivity of 96.8%, specificity of 93.3%, and accuracy of 94.5%, compared to digital mammography, where the corresponding figures were 85.7%, 87.3%, and 86.8% [23].

Contrast-enhanced magnetic resonance imaging (MRI) can detect tumor formations inaccessible for visualization with digital mammography. A pilot study by M. Jochelson et al. (2023) assessed CSM and MRI diagnostic capacity under screening conditions in 307 women with moderate and high risk of developing breast cancer. All participants underwent both CSM and MRI and were monitored for two years. The first stage of screening revealed three cases of malignancies: two invasive cancers were detected by both CSM and MRI, while one duct carcinoma in situ was detected only by MRI. Neither of those cases was visible on low-energy CSM mammograms; also, no palpable interval tumors were found. Notably, the specificity indicators of CSM and MRI were comparable – 94.7% and 94.1%, respectively [24, 25]. Gadolinium-enhanced MRI allows differentiation between benign and malignant processes, assessment of

the anatomical localization and extent of tumor spread, and visualization of lymph nodes with signs of metastatic lesions. The method demonstrates high efficiency in detecting relapses of the disease after surgical intervention and remains a reliable diagnostic tool even in the presence of silicone implants. MRI is widely used to plan the volume of surgical treatment and monitor the treatment efficacy [26].

To improve the reliability and objectivity of the analysis of the observational and diagnostic studies included in the review, a quality assessment was performed using the NOS scale, which covers three domains: participant selection, group comparability, and outcome completeness. Most studies scored 7-9 points out of 9 possible, indicating their high methodological level.

In addition, the GRADE approach was used to assess the certainty of evidence for key diagnostic characteristics (sensitivity, specificity, accuracy), taking into account study design, risk of bias, indirect evidence, consistency, and precision. Thus, in the study by S. Weigel et al., the sensitivity of the CSM for dense tissue was 96.8% (for ACR density types C-D). This level of evidence is assessed as high, since the study was prospective, with a low risk of systematic errors and high consistency of indicators [23].

Table 1 presents the quality assessment of the included observational and diagnostic studies using the NOS scale.

Table 1 – Assessment of the quality of included studies using the NOS scale

Research / Year	Type of study	Selection (up to 4+)	Comparability (up to 2+)	Outcomes (up to 3+)	Σ NOS	Quality
Mori et al. (2016) [20]	Prospective study	++++	++	+++	9/9	High
Helal et al. (2019) [21]	Retrospective study	+++	++	++	7/9	Moderate - High
Weigel et al. (2022) [23]	Prospective study	+++	++	++	7/9	Moderate
Jochelson et al. (2023) [24]	Pilot cohort study	+++	++	++	7/9	Moderate
Hobbs et al. (2015) [29]	Small qualitative study	++	++	+	4/9	Low

CSM has become increasingly important in recent years not only as a diagnostic method, but as a tool for dynamic monitoring of patients with breast cancer under systemic therapy, including neoadjuvant chemotherapy (NACT). Studies show that CSM can detect changes in tumor vascularization, which can serve as an early marker of therapeutic response before the appearance of morphological signs of regression [27]. Comparative prospective studies demonstrated comparable performance of CSM and MRI in assessing residual tumor after NAC. At that, CSM advantages include lower cost, availability, and better tolerability of the procedure by patients [28]. CSM is also better perceived by patients. In a study by M. Hobbs et al., including 49 women, CSM was perceived as more comfortable than MRI. The patients reported lower anxiety, less noise, quicker examination, and better overall tolerability of the procedure. This makes the method particularly attractive for screening and repeat examinations, as well as for patients with contraindications to MRI [29]. Thus, CSM can be considered as an alternative to MRI in dynamic monitoring of treatment effectiveness in patients receiving NACT, especially in limited access or contraindications to MRI.

Discussion: Since its introduction into clinical practice, CSM has been actively spreading in some countries in Europe, Asia, and North America. CSM is most often used in France, Italy, Germany, Great Britain, the USA, China, and South Korea, where it serves as an addition or an alternative to MRI in breast cancer diagnosis and monitoring. In the UK, according to a 2017 study, CSM demonstrated comparable performance in screening women with dense breast tissue compared to MRI, with significantly lower cost of the examination [30]. Despite the high diagnostic efficacy of CSM, several factors limit its universal use and require critical thinking when interpreting results. Firstly, the method remains dependent on the quality of the examination and the experience of the radiologist. Interpretation of contrast enhancement may vary, especially in the presence of postoperative cicatricial changes, fibrosis, or benign proliferative processes, creating a risk of false positive results and overdiagnosis. CSM is a promising and clinically relevant imaging method, capable of increasing the accuracy of breast cancer diagnostics and improving the optimization of patient routing. Table 2 presents a comparison of modern visualization methods in the diagnosis of breast cancer.

Conclusion: The conducted analysis of domestic and foreign sources confirms that CSM has high diagnostic value and can serve as an effective addition to traditional methods of radiographic imaging in breast cancer. This method provides a simultaneous assessment of the morphological and functional characteristics of the tumor, including visualization of pathological neoangiogenesis, thus significantly expanding diagnostic capabilities, especially in women with dense breasts and a higher risk of developing breast cancer. A good tolerability, lower cost, and ease of implementation make CSM a practically significant tool for routine use in clinical practice. The use of CSM helps to increase oncological alertness, reduce the number of false positive results, and improve the effectiveness of treatment and diagnostic decisions.

Table 2 – Comparative characteristics of breast cancer imaging methods

Criterion	Digital mammography	Contrast-enhanced spectral mammography (CSM)	Magnetic resonance imaging (MRI)
Availability	Widely available, included in screening	Limited availability, being introduced into clinics	Limited, requires equipment ≥1.5 T
Sensitivity	53-80%, decreases with ACR C and D	86-98%, especially with highly dense breasts	90-100%, high even with thick fabric
Specificity	85-90%	85-95%	85-95%
The impact of breast density	The method's sensitivity and effec-tiveness are reduced	Less significant, works well with ACR C-D	Independent of tissue density
Invasiveness	Non-invasive	Invasive (ICCM administration)	Invasive (ICCM administration)
Radiation	Ionizing	Increased radiation exposure	No ionizing radiation
Contrast agent	Not required	Iodine containing	Gadolinium
Contraindications	Pregnancy	Allergy to iodine, renal failure	Metal implants, claustro-phobia, and allergy to ICCM
Detection of multifocality	Limited	Reliably identifies multifo-cal/ multicentric forms	Reliably identifies multifocal/ multicentric forms
Evaluation of recurrence after surgery	Low information content	High sensitivity	High sensitivity
Patient comfort	Good tolerance	Faster and more comforta-ble than MRI	Discomfort and anxiety may occur.
Cost	Relatively low	Average	High

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ КЕШЕНДІ СӘУЛЕЛІК ДИАГНОСТИКАСЫНДАҒЫ ЕКІ ЭНЕРГИЯЛЫ КОНТРАСТТЫ СПЕКТРЛЬДЫ МАММОГРАФИЯНЫҢ МҮМКІНДІКТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Контрасты спектральды маммография (КСМ) – бұл дәстүрлі маммография принциптерін йодты контрасты затты енгізумен біріктіретін инновациялық технология. Бұл патологиялық ошақтардың ангиогенезін және васкуляризациясын көрсететін суреттерді алуға мүмкіндік береді, бұл сүт безі қатерлі ісігін (СБҚІ) диагностикалаудың сезімталдығы мен спецификалығын потенциалды түрде арттырады. СБҚІ әлемдегі әйелдер арасында онкологиялық аурулар мен қатерлі ісіктер бойынша бірінші орында тұр және бүгінгі күнге дейін өзекті мәселе болып қала береді. Зерттеулердің көптеген нәтижелеріне қарамастан, КСМ клиникалық қолданысының аспектілері одан әрі зерттеуді қажет етеді. Атап айтқанда, цифрлық маммография (ЦМ) және сүт бездерінің магнитті-резонанстық томографиясы (МРТ) сияқты басқа да сәулелік әдістерімен салыстырғанда КСМ-ның диагностикалық құндылығын салыстырмалы бағалау өзекті болып табылады.*

Зерттеу мақсаты *– басқа сәулелік әдістермен салыстырғанда сүт безінің қатерлі ісігін диагностикалаудағы контрастты спектрльды маммографияның мүмкіндіктерін зерттеу.*

Әдістері: *СБҚІ диагностикасына арналған мақалаларды Pubmed, Web of Science, Scopus, Google scholar дерекқорларында 2015 жылдан 2025 жылға дейін іздеу және іріктеу жүргізілді. Осы шолуды жазу үшін барлық ресурстар бойынша 107 әдеби дереккөз табылды, оның 30-ы ұсынылған шолуға енгізілді.*

Нәтижелері: *Көптеген зерттеулердің нәтижелері бойынша КСМ-ның орындалуы оңай және пациенттер жақсы көтереді. Бұл әдіс ЦМ-дан артық, себебі ісіктің патологиялық неоангиогенезінің болуы туралы ақпарат береді. МРТ-мен салыстырғанда, КСМ сезімталдығы мен спецификалығы бойынша ұқсас. Демек, КСМ сүт бездерін визуализациялаудың балама әдісі ретінде қолданылуы мүмкін, бұл ретте КСМ қолжетімдірек және МРТ қарсы көрсеткіштері бар пациенттерге жасалуы мүмкін.*

Қорытынды: *КСМ әдісінің сезімталдығы, спецификалығы және дәлдігі сүт безінің тығыздығының түріне және пациенттердің жасына қарамастан, ЦМ көрсеткіштерінен асып түседі. Осының арқасында бұл әдіс жалған оң нәтижелердің санын азайтуға және қажетсіз инвазивті әдістердің санын шектеуге мүмкіндік береді. Қатерлі ісіктерді уақтылы анықтау сәтті емдеу мүмкіндігін едәуір арттырады және метастаздану қаупін төмендетеді.*

Түйінді сөздер: *контрасты спектральды маммография (КСМ), цифрлық маммография (ЦМ), магнитті-резонансты томография (МРТ), сүт безінің қатерлі ісігі (СБҚІ).*

АННОТАЦИЯ

ВОЗМОЖНОСТИ ДВУХЭНЕРГЕТИЧЕСКОЙ КОНТРАСТНОЙ СПЕКТРАЛЬНОЙ МАММОГРАФИИ ПРИ КОМПЛЕКСНОЙ ЛУЧЕВОЙ ДИАГНОСТИКЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Контрастная спектральная маммография (КСМ) представляет собой современную методику визуализации, сочетающую цифровую маммографию с внутривенным контрастированием на основе йода. Метод позволяет получать изображения, отражающие ангиогенез и васкуляризацию патологических очагов, тем самым потенциально повышая диагностическую точность при раке молочной железы (РМЖ). Заболеваемость и смертность от РМЖ среди женщин остаются на высоком уровне по всему миру, что определяет его актуальность. Несмотря на многообещающие результаты исследований, многие аспекты клинического применения КСМ требуют дальнейшего изучения. В частности, актуальным является сравнительная оценка диагностической ценности КСМ с другими лучевыми методами визуализации, как цифровой маммографии (ЦМ) и магнитно-резонансной томографии (МРТ).*

Цель исследования *– проанализировать диагностические возможности контрастной спектральной маммографии в сравнении с другими методами лучевой диагностики при раке молочной железы.*

Методы: *Произведен поиск и отбор статей, посвященных диагностике РМЖ, в базах данных PubMed, Web of Science, Scopus, Google Scholar за период с 2015 по 2025 года. Для написания данного обзора по всем ресурсам было найдено 107 литературных источника, из которых 30 были включены в представленный обзор.*

Результаты: *Исследования показывают, что КСМ является технически выполнимой процедурой и хорошо переносится пациентками. Метод позволяет визуализировать неоангиогенез опухоли, что делает его более информативным по сравнению с ЦМ. По чувствительности и специфичности КСМ сопоставима с МРТ, однако отличается большей доступностью и может применяться при наличии противопоказаний к МРТ.*

Заключение: *КСМ демонстрирует более высокую информативность по сравнению с традиционной ЦМ, особенно в случае высокой плотности тканей молочной железы. Благодаря которым, метод позволит уменьшить количество ложноположительных результатов и ограничить количество нежелательных инвазивных вмешательств. Своевременное выявление РМЖ на ранних стадиях существенно повышает шансы на успешное лечение, снизить риск метастазирования и улучшить показатели общей и безрецидивной выживаемости.*

Ключевые слова: *контрастная спектральная маммография (КСМ), цифровая маммография (ЦМ), магнитно-резонансная томография (МРТ), рак молочной железы (РМЖ).*

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THE IMPACT OF T-REGULATORY CELLS ON CANCER STEM CELLS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *One of the key challenges in modern oncology remains tumor resistance to therapy and the high risk of relapse, which are largely associated with cancer stem cells (CSCs). Regulatory T cells (Tregs) are considered one of the factors supporting the stem-like phenotype of tumor cells; however, the mechanisms of their interaction remain insufficiently studied. Despite the growing number of studies addressing the impact of Tregs on CSCs in breast cancer (BC), colorectal cancer (CRC), and glioblastoma (GBM), the fragmented and contradictory findings necessitated the con-duct of this analytical review.*

The study aimed to *systematize experimental, review, and clinical data on Treg-CSC interactions and to formulate hypotheses that define future research directions and therapeutic approaches.*

Methods: *This comprehensive literature search was conducted in Medline (PubMed), NCBI, and Google Scholar databases covering the years 2015 to 2025. The following terms were used: "T-regulatory cells" and/or "cancer stem cells" and/or "breast cancer stem cells" and/or "colorectal cancer stem cells" and/or "glioma stem cells."*

Results: *The literature review showed that Tregs, both directly and indirectly, activate key signaling cascades (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3) that maintain the stem-like phenotype of tu-mor cells and are associated with poor prognosis in BC, CRC, and GBM.*

Conclusion: *Tregs and the molecular mechanisms they mediate can be considered potential targets for anticancer therapy; however, their use in clinical practice requires further experimental and clinical research.*

Keywords: *Regulatory T cells (Treg), cancer stem cells (CSCs), breast cancer stem cells, colorectal cancer stem cells, glioblastoma (GBM), oncological diseases, oncoimmunology.*

Introduction: According to GLOBOCAN data for 2022, malignant tumors are the cause of more than 9.7 million deaths, of which 9.3% were due to colorectal cancer (CRC), 6.8% to breast cancer (BC), and 2.6% to tumors of the central nervous system, including glioblastoma [1]. In the Republic of Kazakhstan in 2022, more than 20 thousand deaths from oncological diseases were registered, of which 9.5% were due to CRC, 7.6% to breast cancer, and 2.8% to tumors of the central nervous system, including glioblastoma (GBM) [2].

The high recurrence rate and resistance to cancer therapy are largely explained by the presence of cancer stem cells (CSCs). CSCs are a subpopulation of cancer cells that possess the ability to self-renew and undergo multilineage differentiation, which enables them to stimulate tumor development and heterogeneity [3]. CSCs can reduce the effectiveness of antitumor therapy by activating treatment-resistant molecular mechanisms [4].

Within the tumor microenvironment, CSCs interact with multiple immunosuppressive cell populations. These include tumor-associated macrophages, myeloid-derived suppressor cells, cancer-associated fibroblasts, and regulatory T cells (Treg). The latter are recruited to the tumor microenvironment by the chemokines CCR4, CCR8, and CCR10, as well as CXCR3 [5]. Tregs are capable not only of suppressing the antitumor immune response but, as many review articles have shown, also of directly or indirectly supporting the stem cell phenotype of tumor cells [6-12].

Published studies on this topic have yielded disparate results to date, with most reviews focusing on specific tumor types or specific molecular mechanisms. Therefore, this review aims to systematize and critically examine the data regarding the role of Tregs in regulating CSCs in breast cancer, CRC, and GBM.

The study aimed to systematize experimental, review, and clinical data on Treg-CSC interactions and to formulate hypotheses that define future research directions and therapeutic approaches.

Materials and Methods: To search for available literature data on the research topic, scientific publications from 2015 to 2025 indexed in the Medline (PubMed), NCBI, and Google Scholar databases were analyzed. The following terms were used in the search: "T-regulatory cells" AND/OR "cancer stem cells" AND/OR "breast cancer

stem cells" AND/OR "colorectal cancer stem cells" AND/OR "leukemic stem cell" AND/OR "glioma stem cells." The search revealed 89 potentially relevant sources (articles and reviews) on the research topic. After removing duplicates and assessing their content, the most significant and informative works (including reviews and descriptions of original research) were selected. The selection criteria were novelty, completeness of the data presented, and the presence of unique information (works of low quality or those duplicating data from previously published studies were excluded). The final analysis included 48 sources.

The source selection process included several sequential stages. At the identification stage, 89 publications were identified from the Medline (PubMed), NCBI, and Google Scholar databases. After removing 9 duplicate records, 80 sources were included in the analysis. At the abstract screening stage, 15 articles that did not mention Tregs were excluded. A total of 65 publications were selected for full-text evaluation, of which 17 were excluded due to insufficient data (n=4), lack of reliable results (n=5), overlap with previously published materials (n= 4), and failure to meet language criteria (n=4). Thus, the final systematic analysis included 48 articles that most fully and reliably reflect the molecular mechanisms of interaction between Tregs and CSCs in various malignant tumors. Inclusion criteria were: original studies or reviews, a clear description of the interaction between Tregs and CSCs, and the presence of data on signaling mechanisms or clinical correlations. Publications were selected independently by two authors. The source selection process is presented in the PRISMA diagram (Figure 1).

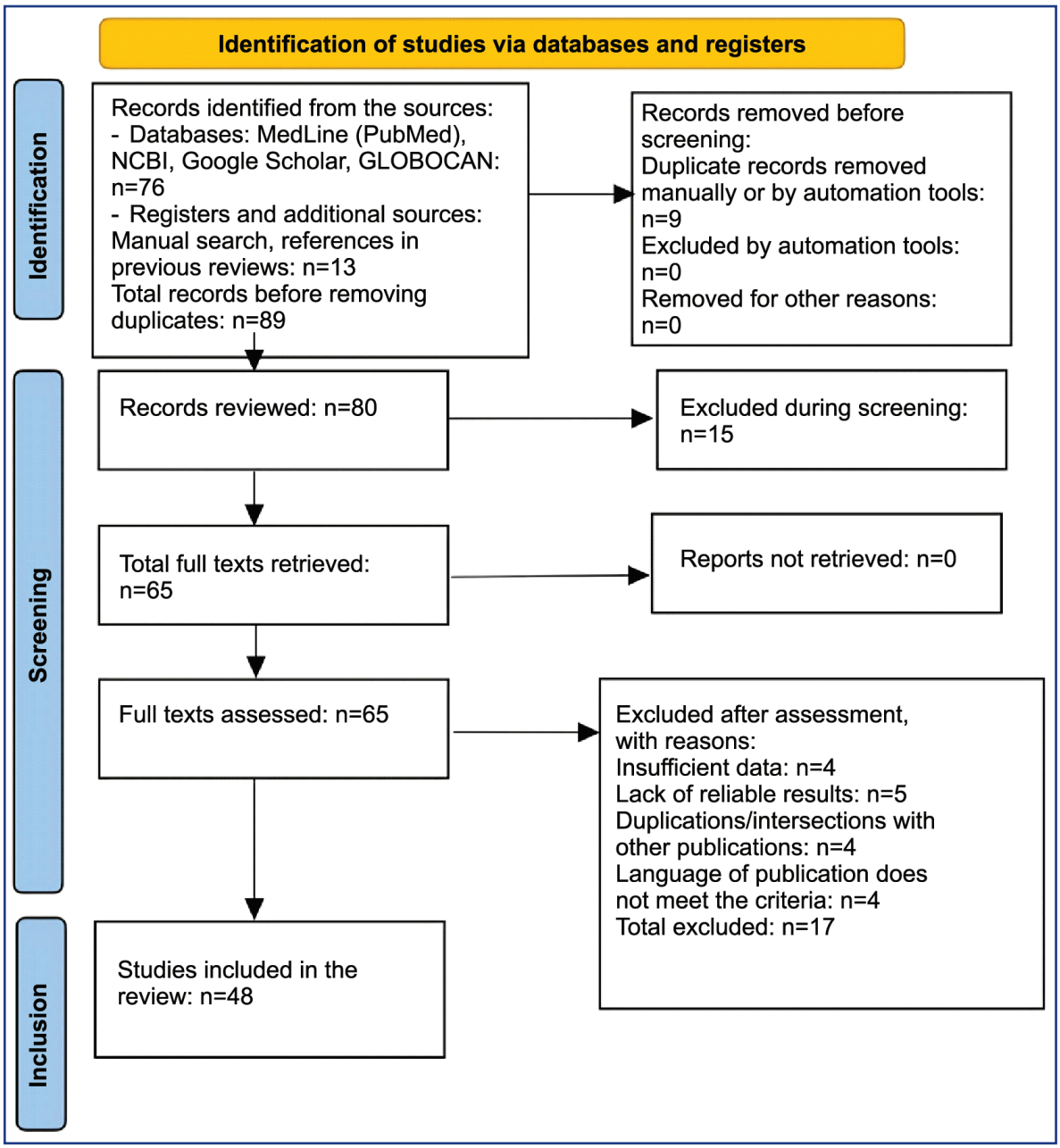


Figure 1 – PRISMA diagram reflecting the process of selecting sources for analysis

Results:

General characteristics of cancer stem cells. CSCs are a subpopulation of cancer cells that contribute to tumor development and heterogeneity. Seven common core intracellular signaling pathways are involved in both embryonic development and malignancy (Table 1).

Table 1 – Main intracellular signaling pathways of cancer stem cells (CSCs)

Signaling pathways	Key effects for CSCs	Source
JAK/STAT	Support of the stem cell phenotype promotes activa-tion of epithelial-mesenchymal transition (EMT), in-vasion, and metastasis	Huang B. et al. [13]
NOTCH	Regulation of differentiation, maintenance of the CSC population, and participation in drug resistance	Shi Q. et al. [14]
NF-κB	Activation of IL-6/IL-8 production, support of CSC survival, and development of drug resistance	Guo Q. et al. [15]
Wnt/β-catenin	Maintenance of self-renewal, activation of NANOG and c-MYC transcriptional programs, formation of therapeutic resistance	Song P. et al. [16]
TGF-β/SMAD	Initiation of EMP, enhancement of plasticity, and ex-pansion of the CSC pool	Allgayer H. et al. [17]
PI3K/AKT/mTOR	Metabolic adaptation of CSCs, maintenance of surviv-al, and resistance to therapy	Prabhu KS et al. [18]
MAPK/ERK	Stimulation of CSC proliferation and formation of tumor spheres	Chu X. et al. [19]

Even small numbers of isolated CSCs expressing characteristic stem cell markers can initiate tumor development in immunodeficient mice [20]. In some types of cancer, CSCs exhibit resistance to chemotherapeutic drugs such as docetaxel, doxorubicin, cyclophosphamide, and trastuzumab [21]. Therefore, this cell population is attracting increasing attention from researchers as a key target for the development of new cancer therapy strategies.

General characteristics of regulatory T cells. Tregs are a population of $CD4^+$ T-cells that regulate both innate and adaptive immune responses against the body's own cells, virulent agents, and tumors [22]. Tregs play a crucial role in maintaining immune system homeostasis by eliminating autoreactive T cells, promoting self-tolerance, and suppressing inflammatory processes [23].

FOXP3 is a specific marker of Tregs, which belongs to the family of regulatory transcription factors. In the absence of this protein expression, Tregs lose their ability to suppress the immune system [24].

The influence of regulatory T cells on breast cancer cancer stem cells. Breast cancer CSCs can differentiate into various tumor cell types, thereby maintaining tumor heterogeneity. Due to their self-renewal capacity, they provide a constant stem cell pool throughout breast cancer progression [25].

The NF-κB/CCL1 signaling cascade is a key molecular mechanism that recruits Tregs to tumor sites. Activation of the NF-κB transcription factor in CSCs leads to increased production of the chemokine CCL1, which promotes the recruitment of Tregs to the tumor microenvironment. Possessing pronounced immunosuppressive properties, Tregs not only suppress the antitumor response but also stimulate CSCs. They promote the increased expression of key stemness transcription factors—SOX2, OCT4, and NANOG [26–29].

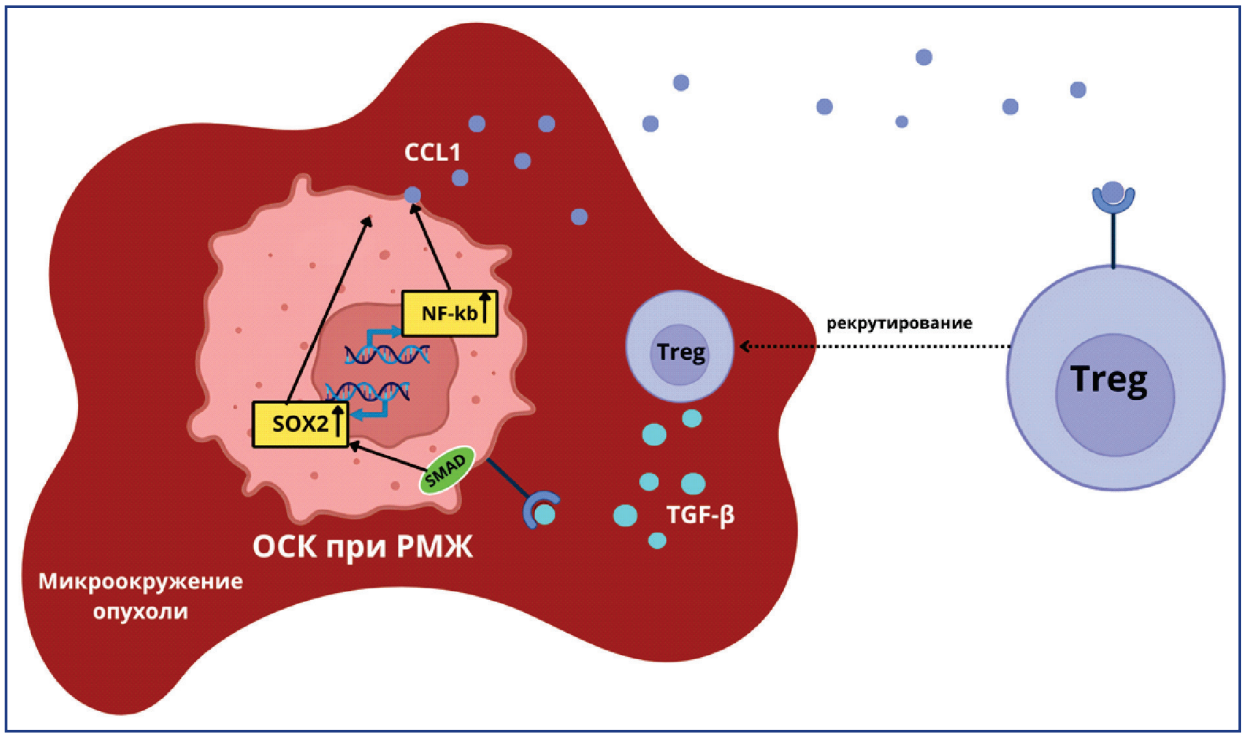
Interestingly, overexpression of SOX2 activates transcription of the chemokine CCL1, which, as previously reported, attracts Tregs to tumors [27]. Thus, a unique relationship emerges in which stem cell factor markers enhance tumor infiltration of Tregs, which in turn maintain a persistent CSC phenotype in breast cancer (Figure 2).

One of the primary mechanisms by which Tregs influence CSCs in breast cancer is the production of the cytokine TGF-β, which induces the expression of the aforementioned stem cell transcription factors, as well as the WNT3a and ESR1 *genes*. These genes, in turn, promote the formation of mammospheres – spherical structures consisting of a cluster of cells with stem cell properties [26, 28].

The influence of regulatory T cells on colorectal cancer cancer stem cells (CRC CSCs). One of the variants of direct interaction between CRC CSCs and Tregs is the RANKL/RANK molecular mechanism. The RANK receptor (TNFRSF11a), expressed on CRC CSCs, induces an increase in intracellular Ca^{2+} levels through the PLCγ-IP3-STIM1 signaling pathway. This leads to the dephosphorylation of NFATC1, which activates the transcription of the ACP5 gene, associated with an unfavorable prognosis in patients with cancer, particularly in those with CRC [30, 31].

Tregs, in turn, express RANKL (TNFRSF11), a ligand of the RANK receptor. It has been established that activation of the RANKL/RANK pathway leads to increased expression of CD44 and CD133, the main markers of CRC cells [32].

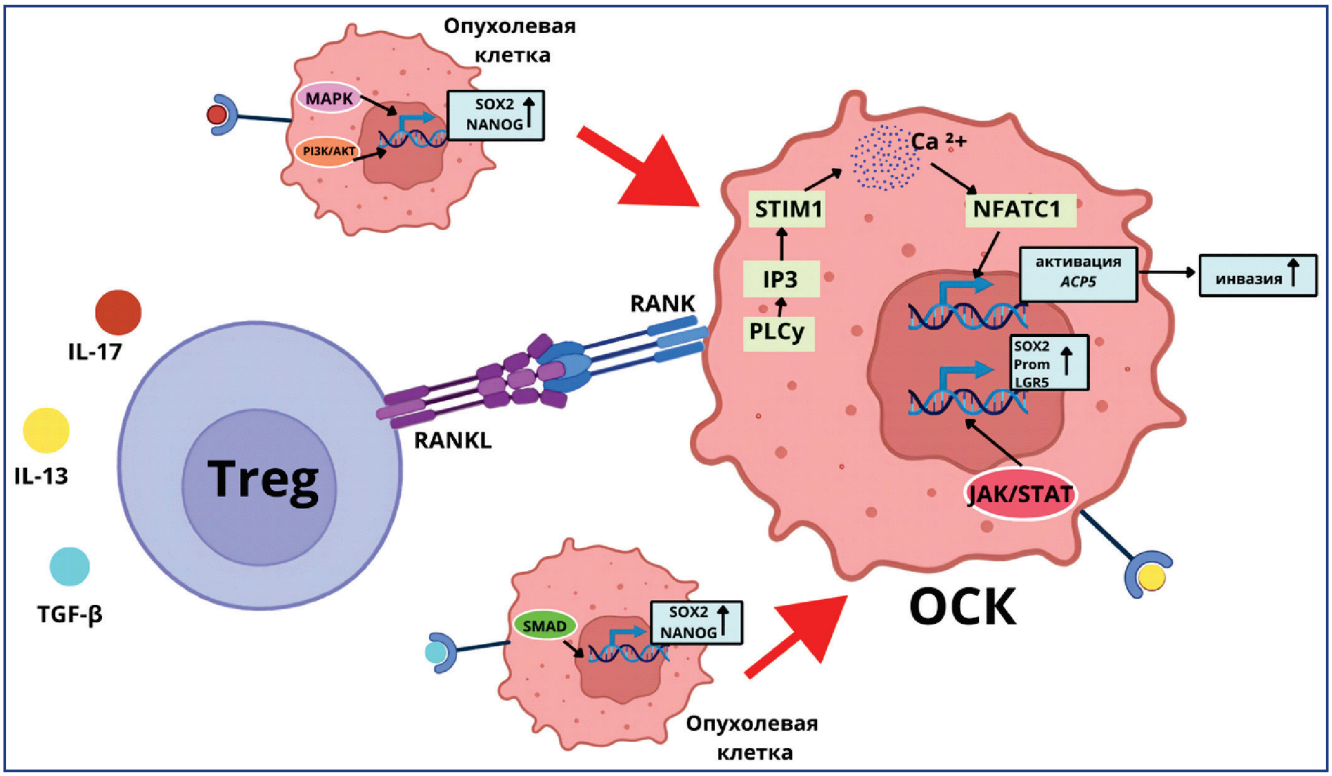
Cytokines such as TGF-β, IL-13, and IL-17 play a key role in stimulating the activity of CRC CSCs. TGF-β triggers epithelial-mesenchymal transition (EMT), thereby promoting the dedifferentiation of CRC cells into CRC CSCs. This leads to an expansion of the CRC CSCs' pool and increases tumor resistance to therapy [33, 34]. IL-13 activates the STAT3 signaling pathway, increasing the expression of *SOX2, LGR5, and Prom*1 genes, which are critical for tumor cell self-renewal and stemness maintenance [35, 36]. IL-17, through the activation of MAPK and AKT kinases, promotes the formation of CRC CSCs. It was also previously noted that IL-17 stimulates the expression of CD44, CD133, and CD166, which are markers of CRC cells [37] (Figure 3).



Legend: Микроокружение опухоли – Tumor microenvironment; ОСК при РМЖ – breast cancer CSCs; рекрутирование – recruiting

Figure 2 – The SOX2–CCL1–Treg loop supporting the CSC stemness in breast cancer

Note: The image was created by the author using the BioRender.com web resource.

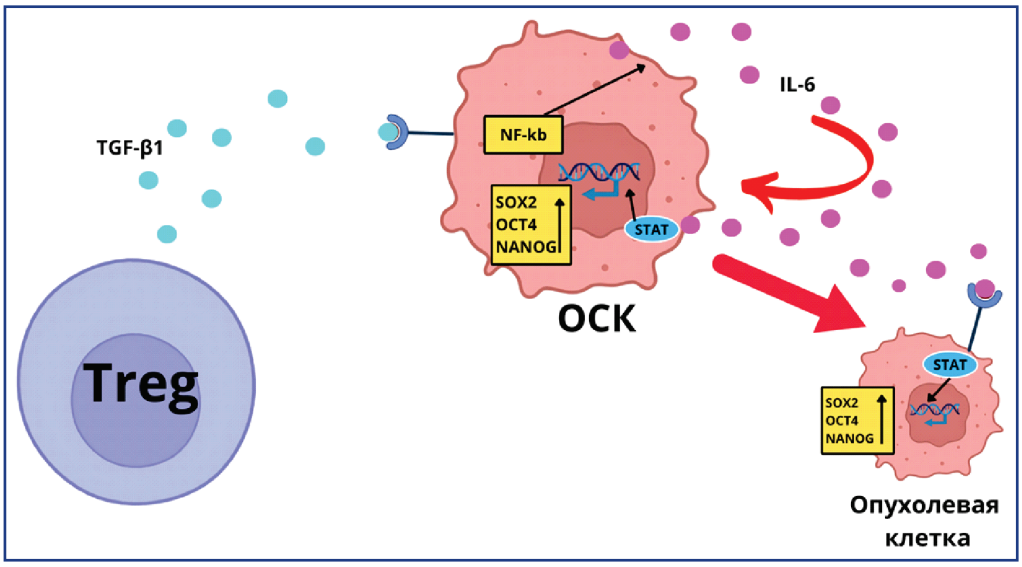


Legend: Опухолевая клетка – Cancer cell; Активация ACPS – ACPS activation; Инвазия – Invasion; ОСК – CSC

Figure 3 – Key molecular mechanisms of interaction between Tregs and colorectal cancer cells

Note: The image was created by the author using the BioRender.com web resource.

The influence of regulatory T cells on cancer stem cells in glioblastoma. One of the key mechanisms by which Tregs mediate their action on CSCs in glioblastoma is the secretion of TGF-β1, which stimulates the production of IL-6 by tumor cells. This cytokine activates the STAT signaling pathway in both autocrine and paracrine manners, inducing the expression of SOX2, OCT4, and NANOG (Figure 4). This leads to increased formation of neurospheres – spherical structures consisting of stem-like glioma cells that are associated with tumor aggressiveness [38].



Legend: Опухолевая клетка – Cancer cell; ОСК – CSC

Figure 4 – Indirect influence of Tregs on cancer stem cells in glioblastoma

Note: The image was created by the author using the BioRender.com web resource.

Discussion: The experimental preclinical studies and review articles reviewed above indicate the ability of Tregs to enhance the stem-like properties of tumor cells. Systematization of the available modern data enabled us to identify the best-studied molecular mechanisms by which Tregs influence CSCs in breast cancer, CRC, and GBM. The data presented in Table 2 demonstrate the similarity of the final effects of Tregs in the tumor types considered, despite the differences in their mechanisms of action. Tregs increase the activity of genes and transcription factors responsible for the stem-like properties of tumor cells, which ensures their survival, promotes the maintenance of CSC populations, and is associated with an unfavorable prognosis.

It is also worth noting that a common trend for all cancer types described in the article is the presence of a clinical correlation between a high level of Treg infiltration and unfavorable clinical outcomes, which is expressed in a reduction in overall survival (OS) and increased hazard ratio (HR) values for breast cancer, GBM, and CRC (Table 3).

Clinical cohort studies that simultaneously analyze CSCs and Tregs are currently limited in number. The most methodologically comprehensive example remains the study by TJ Miller et al., which found that Tregs modified the prognostic value of SOX2 in CRC [39]; however, comparable data are lacking for breast cancer and GBM. This highlights an unmet clinical need and provides direction for future research.

Based on the analysis of the presented material, we propose several hypotheses that could potentially form the basis for the development of new therapeutic strategies (Table 4).

However, the degree of clinical feasibility of these hypotheses varies. Thus, cytokine blockade has been preclinically confirmed [38, 47-48], while simultaneous blockade of Treg chemokine receptors and key CSC signaling pathways requires further experimental and clinical studies.

This review has several limitations that must be considered when interpreting the results. Most of the studies reviewed were conducted in preclinical settings (cell lines, animal models), which limits their direct extrapolation to clinical practice. The differences between individual Treg subtypes (FoxP3E2+, CCR8+, CD177+) and their impact on the CSC population were not examined in detail, leaving unclear which Treg subsets play a key role in maintaining the stem cell phenotype. The question of how modern therapies (immunotherapy, chemotherapy, targeted therapy) modify the balance between Treg and CSCs is also insufficiently addressed. Furthermore, the temporal aspects of Treg recruitment to tumors, the specifics of their direct contacts with CSCs in vivo, and the consequences of therapeutic Treg modification for tumor resistance and the effectiveness of immunotherapy remain poorly understood.

At the same time, this review is not limited to listing individual molecular mechanisms, but represents an attempt to synthesize disparate data into a holistic model of the role of Tregs in maintaining CSCs. It has been demonstrated that Tregs are involved not only in the formation of an immunosuppressive microenvironment but also directly support the stem phenotype through the activation of signaling pathways, such as TGF-β/SMAD, IL-10/STAT3, NF-κB/CCL1, and RANKL/RANK. These mechanisms are associated with the induction of transcription factors SOX2, OCT4, and NANOG, as well as increased expression of stemness markers (CD44, CD133), and are linked to the formation of mammospheres and neurospheres, which reflects the plasticity and therapeutic resistance of tumors.

The contribution of this review lies not only in its systematization of existing data but also in the formulation of its own hypotheses. The proposed approaches, based on a comparison of current data, allow us to identify specific directions for further preclinical and clinical validation.

Table 2 – Clinical data on the association of Treg infiltration with hazard ratio for overall survival in patients with breast cancer, colorectal cancer, and glioblastoma

Tumor type	Key mechanisms of Treg influence on CSCs		The involved CSC signaling pathway	Impact on SCS	Clinical significance	Sources
	Indirect	Direct				
Breast cancer	TGF-β (via activation of EMP)	-	TGF-β/SMAD	1. Increased expression of SOX2, OCT4 and NANOG. 2. Increased expression of *WNT3a* and *ESRG* genes, and an accordingly higher number of mammospheres.	It is associated with a severe clinical course: early relapses, metastasis, and poor prognosis.	[26, 27, 39]
Colorectal cancer	-	RANKL/RANK (via the PLCy-IP3-STIM1 signaling pathway)	Cross-activation of signaling pathways: Wnt/β-catenin NF – κB PI3K/AKT JAK/STAT	1. Activates transcription of the ACP5 gene 2. Enhance the expression of stemness markers CD44 and CD133.	Increased tumor size and metastasis; decreased overall and relapse-free patient survival.	[30-32]
	TGF-β (via EMF)	-	TGF-β/SMAD	Dedifferentiation of CRC cells into CRC CSCs.	Increased recurrence rate; Decreased overall survival; Reduced sensitivity to chemotherapy; High risk of metastatic spread	[33-37, 42, 43]
	IL-13 (via STAT3)	-	JAK/STAT	Increased expression of *SOX2, LGR5 genes*		
	IL-17	-	MAPK/ERK PI3K/AKT	Stimulation of expression of stemness markers CD44, CD133, and CD166.		
Glioblastoma	TGF-β1 (via stimulation of IL-6 production)	-	NF-κB JAK/STAT	1. Induction of expression of stem transcription factors: SOX2, OCT4, and NANOG. 2. Formation of neurospheres	Associated with tumor aggressiveness, as well as poor prognosis and resistance to therapy	[38, 41]

Table 3 – Clinical data on the association of Treg infiltration with hazard ratio to overall survival in patients with breast cancer, colorectal cancer, and glioblastoma

Tumor type	Study design	Cohort, n	Hazard ratio for overall survival	p-value	Confidence interval	Prognosis	Source
Breast cancer	Cohort study	990	1.8	p = 0.014	1.1-2.8	Adverse	[28]
Breast cancer	Meta-analysis	8666	1.60	p < 0.05	1.06-2.42	Adverse	[44]
Colorectal cancer	Retrospective cohort study	1720	1.35	p = 0.028	–	Adverse	[45]
Glioblasto-ma	Bioinformatic analysis	152	1.199	p < 0.001	1.101-1.305	Adverse	[46]

Table 4 Potential strategies for blocking Treg-mediated mechanisms and their impact on cancer stem cells (CSCs)

Гипотеза	Потенциальный механизм действия	Предполагаемый эффект
Simultaneous block-ade of Treg chemo-kine receptors (CCR4, CCR8) and key CSC signaling pathways in breast cancer	Blocking Treg chemokine receptors (CCR4, CCR8) with monoclonal antibodies can limit the re-cruitment and migration of Tregs into the tumor microenvironment. Suppression of key intracellular signaling pathways using small-molecule inhibitors or epigenetic inhibitors.	1. A decrease in the number of Tregs in the tumor microenvironment could potentially partially reduce immunosuppression, contributing to the normalization of the antitumor activity of $CD8^+$ T-cells. 2. Suppression of key CSC signaling pathways will reduce the expression of the CSC stem cell phenotype, re-sistance to therapy, and the likelihood of relapse.
Blockade of IL-6 cy-tokines in glioblas-toma	Inhibition of IL-6 prevents the activation of the JAK/STAT pathway, which in turn blocks the expression of SOX2, OCT4, and NANOG.	1. Reduced autocrine and paracrine support of CSC stem cell phenotype. 2. Reduced neurosphere formation associated with maintenance of CSC population. 3. Reduced CSC pool will weaken their ability to self-renew and recover after therapy.
TGF-β cytokine blockade for breast cancer, glioblastoma, and colorectal cancer	Neutralization of TGF-β pre-vents SMAD-dependent acti-vation of EMT.	1. Limited activation of stem transcription factors (SOX2, OCT4, NANOG). 2. Decreased formation of mammospheres and neurospheres. 3. Reduced CSC tumor cell dedifferentiation. 4. Reduced CSC pool.

Conclusion: The combined data presented indicate that Tregs may be involved not only in forming an immunosuppressive microenvironment but also in maintaining the properties of CSCs that determine the aggressiveness of the disease and resistance to therapy. Although this relationship has not yet been definitively confirmed clinically, a comparison of experimental and clinical observations suggests it as a promising avenue for further research.

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АҢДАТПА

Т-РЕГУЛЯТОРЛЫҚ ЖАСУШАЛАРДЫҢ ҚАТЕРЛІ ІСІК ДІҢ ЖАСУШАЛАРЫНА ТИГІЗЕТІН ЫҚПАЛЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Қазіргі онкологияның негізгі мәселелерінің бірі – ісіктердің терапияға төзімділігі және қайталану қаупінің жоғары болуы, бұл көбінесе ісік бағаналы жасушаларымен (ІБЖ) байланысты. Регуляторлы Т-жасушалар (Treg) ісік жасушаларының бағаналы фенотипін қолдайтын факторлардың бірі ретінде қарастырылады, алайда олардың өзара әрекеттесу механизмдері жеткілікті зерттелмеген. Сүт безі обыры (СБО), колоректалды обыр (КРО) және глиобластома*

(ГБМ) кезіндегі Treg пен ІБЖ әсеріне арналған зерттеулер санының артуына қарамастан, нәтижелер әлі де фрагментті және қарама-қайшы болып отыр. Бұл аналитикалық шолуды жүргізудің қажеттілігін айқындайды.

***Зерттеу мақсаты** – Treg пен ІБЖ өзара әрекеттесуіне қатысты эксперименттік, шолу және клиникалық деректерді жүйелеу және келешектегі зерттеулер мен терапевтік тәсілдерді айқындайтын гипотезаларды тұжырымдау.*

***Әдістері:** Medline (PubMed), NCBI, Google Scholar деректер базаларында 2015 жылдан 2025 жылға дейін кешенді әдебиет іздеуі жүргізілді. Іздеу кезінде мына терминдер қолданылды: «T-regulatory cells» және/немесе «cancer stem cells» және/немесе «breast cancer stem cells» және/немесе «colorectal cancer stem cells» және/немесе «glioma stem cells».*

***Нәтижелері:** Әдеби шолу Treg жасушаларының тікелей де, жанама түрде де негізгі сигналдық каскадтарды (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3) белсендіріп, ісік жасушаларының бағаналы фенотипін қолдайтынын және олардың СБО, КРО және ГБМ кезінде қолайсыз болжаммен байланысты екенін көрсетті.*

***Қорытынды:** Treg және олардың опосредиялайтын молекулалық механизмдері ісікке қарсы терапия үшін әлеуетті нысан ретінде қарастырылуы мүмкін, алайда клиникалық практикаға енгізу үшін қосымша эксперименттік және клиникалық зерттеулер қажет.*

***Түйінді сөздер:** Регуляторлы Т-жасушалар (Treg), ісік бағаналы жасушалары, сүт безі обырының бағаналы жасушалары, колоректалды обырдың бағаналы жасушалары, глиобластома, онкологиялық аурулар, онкоиммунология.*

АННОТАЦИЯ

ВЛИЯНИЕ РЕГУЛЯТОРНЫХ Т-КЛЕТОК НА ОПУХОЛЕВЫЕ СТВОЛОВЫЕ КЛЕТКИ: ОБЗОР ЛИТЕРАТУРЫ

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***Актуальность:** Одной из ключевых проблем современной онкологии остаётся устойчивость опухолей к терапии и высокий риск рецидивов, во многом связанных с опухолевыми стволовыми клетками (ОСК). Регуляторные Т-клетки (Treg) рассматриваются как один из факторов, поддерживающих стволовой фенотип опухолевых клеток, однако механизмы их взаимодействия остаются недостаточно изученными. Несмотря на возрастающее число исследований, посвящённых влиянию Treg на ОСК при раке молочной железы (РМЖ), колоректальном раке (КРР) и глиобластоме (ГБМ), результаты остаются фрагментарными и противоречивыми, что обусловило необходимость проведения данного аналитического обзора.*

***Цель исследования** – систематизация экспериментальных, обзорных и клинических данных о взаимодействии регуляторных Т-клеток и опухолевых стволовых клеток и формулировка гипотез, определяющих перспективные исследования и терапевтические подходы.*

***Методы:** Проведен комплексный поиск литературы в базах данных Medline (PubMed), NCBI, Google Scholar с 2015 по 2025 гг. При поиске использовались термины: «T-regulatory cells» и/или «cancer stem cells» и/или «breast cancer stem cells» и/или «colorectal cancer stem cells» и/или «glioma stem cells».*

***Результаты:** Обзор литературы показал, что Treg как непосредственно, так и опосредованно активируют ключевые сигнальные каскады (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3), которые способствуют поддержанию стволового фенотипа опухолевых клеток и ассоциированы с неблагоприятным прогнозом при РМЖ, КРР и ГБМ.*

***Заключение:** Treg и опосредуемые ими молекулярные механизмы могут рассматриваться как потенциальные мишени для противоопухолевой терапии, однако их применение в клинической практике требует дальнейших экспериментальных и клинических исследований.*

***Ключевые слова:** Регуляторные Т-клетки (Treg), опухолевые стволовые клетки, стволовые клетки рака молочной железы, стволовые клетки колоректального рака, глиобластома, онкологические заболевания, онкоиммунология.*

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Almaty Regional Branch of
Halyk Bank of Kazakhstan
BIC: HSBKKZKX
Beneficiary code – 18

Payment purpose code
for sponsorship transfers – 119

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