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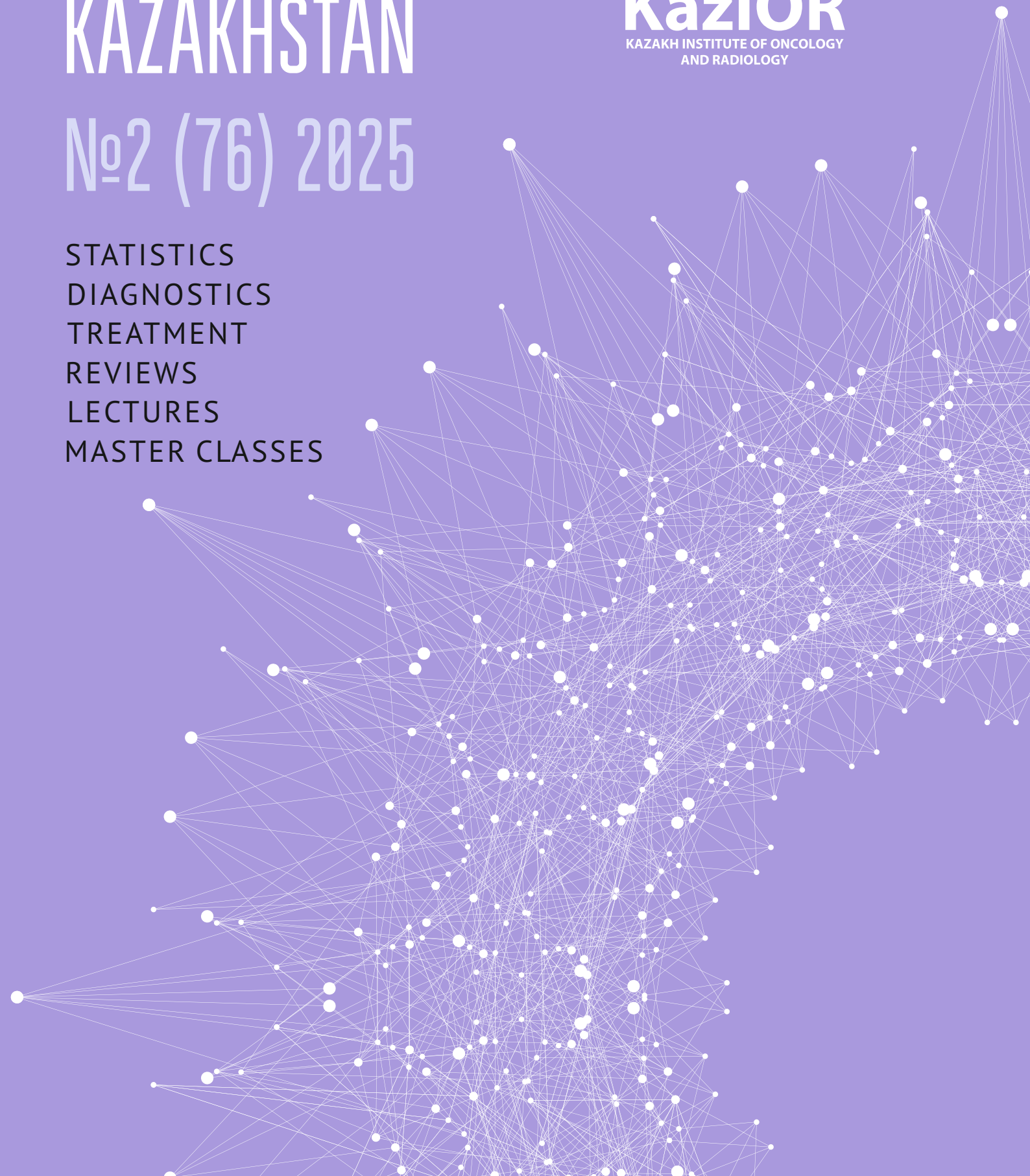

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Contents

Dear readers!

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

Oncology and radiology continue to offer us new opportunities, innovations, and updates. We are purposefully introducing new technologies and expanding our capabilities in this field.

We hope that this issue of the journal will be informative for specialists in oncology and radiology. The current issue offers a wide range of scientific research and practical recommendations for improving medical care. The authors study the role of extracellular neutrophil traps in the development of breast cancer; share the expereience of organ-preserving treatment of Wilms' tumor of the horseshoe kidney, discuss the surgical treatment and reconstruction of recurrent ameloblastoma of the mandible complicated by orostomy, and many other urging issues.

We wish you to reach new horizons, engage in interesting research, and find successful solutions to current problems!

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

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ANALYSIS OF PROVIDING HOSPITAL-REPLACING CARE IN SYSTEMIC TREATMENT OF CANCER PATIENTS AT ALMATY ONCOLOGY CENTER

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ABSTRACT

Relevance: *According to the statistics and reporting documentation, 23,732 cases of cancer were treated at Almaty Oncology Center (AOC) in 2024, with 69.8% of services provided by Day Patient Radiation Therapy and Chemotherapy Departments of the Center. The concept of AOC development envisions the expansion of patients' access to hospital-substituting forms of medical care. In this context, analyzing the activities of the day hospital for chemotherapy is an important area that contributes to the improvement of care organization for cancer patients in outpatient settings.*

The study aimed to *analyze the performance of the Almaty Oncology Center's Day Patient Chemotherapy Department from 2019 to 2024.*

Methods: *The Day Patient Chemotherapy Department performance analysis relied on primary reporting and documentation forms. Key indicators such as the number of hospitalized patients and recorded adverse events were extracted from the Damumed electronic medical record system. The study was part of the framework of the IRN BR24993051 project.*

Results: *During the study period, the number of patients admitted to the AOC Day Patient Chemotherapy Department increased by 124.17% due to the growth in the registration of new cancer cases in Almaty and the transition to hospital-replacing care. The average stay increased by 38% over five years, primarily due to the expansion of chemotherapy regimens in line with national diagnostic and treatment protocols for cancer patients in Kazakhstan. The number of adverse events has also increased from 602 to 18,202 cases, corresponding with the rise in the number of patients over the past 5 years (2019-2024).*

Conclusion: *The performance analysis of the Day Patient Chemotherapy Department highlights the need to enhance the department's staffing capacity, increase the number of available beds, and implement electronic queue systems. It is also necessary to enhance outpatient care for patients experiencing adverse events, which places a significant burden on the AOC Day Patient Chemotherapy Department personnel.*

Keywords: *inpatient replacement care, chemotherapy, cancer center.*

Introduction: According to the Order of the Minister of Health and Social Development of the Republic of Kazakhstan dated June 7, 2023 No. 106, under sub-item 95), item 1, Art. 7 of the Code of the Republic of Kazakhstan "On the health of the people and the health care system" dated September 18, 2009, the creation of organizational conditions for increasing the availability of modern medical care for cancer patients, taking into account the resource capabilities of the state, is the concept and key point in the development of healthcare in the field of oncology in Kazakhstan [1].

According to international recommendations, global health care needs to be restructured to reduce the excess number of inpatient beds and simultaneously increase the number of less expensive day care beds [2].

According to the data from the National Cancer Registry, as of January 2025, 231,019 people were registered with malignant neoplasms (MN) in the Republic of Kazakhstan. In 2024, 40,148 people with cancer were registered for the first time in the country, with women accounting for 55.5% (23,406) of cases and men for 44.5% (17,887). In 2024, 12,703 fatal cases were registered [3].

In Almaty, according to the National Cancer Registry, 5,209 people were registered with newly diagnosed malignant neoplasms as of January 1, 2025, and 1,356 cases were fatal [4]. Almaty is among the regions with the highest incidence rates, above the national average.

According to the Almaty Oncology Center (AOC) Statistics Department and reporting documentation, 23,732 cases of malignant neoplasms were treated at the Center in 2024, with Day Patient Radiation Therapy and Chemotherapy Departments accounting for 69.8% of all cases of care.

The AOC development concept includes expanding patient care through inpatient replacement services [5, 6]. In this regard, studying the work of the Day Patient Chemotherapy Department is a crucial step in expanding care for cancer patients as an alternative to inpatient services.

The study aimed to analyze the performance of the Almaty Oncology Center's Day Patient Chemotherapy Department from 2019 to 2024.

Material and Methods: The analysis of the work of the Day Patient Chemotherapy Department was carried out

using the main accounting and reporting forms of documentation:

Updated information from official reports of regional oncology dispensaries - "Report on malignant neoplasms" (accounting form No. 7) for the city of Almaty for 2019 and 2024;

Card of a patient with a diagnosis of malignant neoplasm established for the first time in life (registration form 090/U);

030-6/y "Dispensary observation checklist";

Data from the National Cancer Registry (Electronic Registry of Cancer Patients) on malignant neoplasms;

International Classification of Diseases, 10th revision (ICD-10), on localizations.

Figures of the number of hospitalized patients and registered adverse events (AEs) were obtained from the "Damumed" electronic medical records database.

The study was conducted within the framework of the research scientific project BR24993051 on the topic "Development of an intelligent urban system based on IoT and data analysis" to assess the current situation of inpatient replacement care at the AOC.

Results: Over the analyzed period, the number of patients in the Day Patient Chemotherapy Department of the AOC increased by 124.17% due to the growth in the number of new cancer cases registered in Almaty, as well as the transition of AOC to inpatient replacement care (Table 1). The average stay of patients over the past 5 years has increased by 38% due to the expansion of chemotherapy options (the introduction of new drugs in Kazakhstan, expansion of the list of chemotargeted and immunotherapy drugs) used according to the protocol for cancer diagnostics and treatment in the Republic of Kazakhstan.

Table 1 – Number of patients with malignant neoplasms treated in the Day Patient Chemotherapy Department of the AOC for 2019, 2022, and 2024, abs.

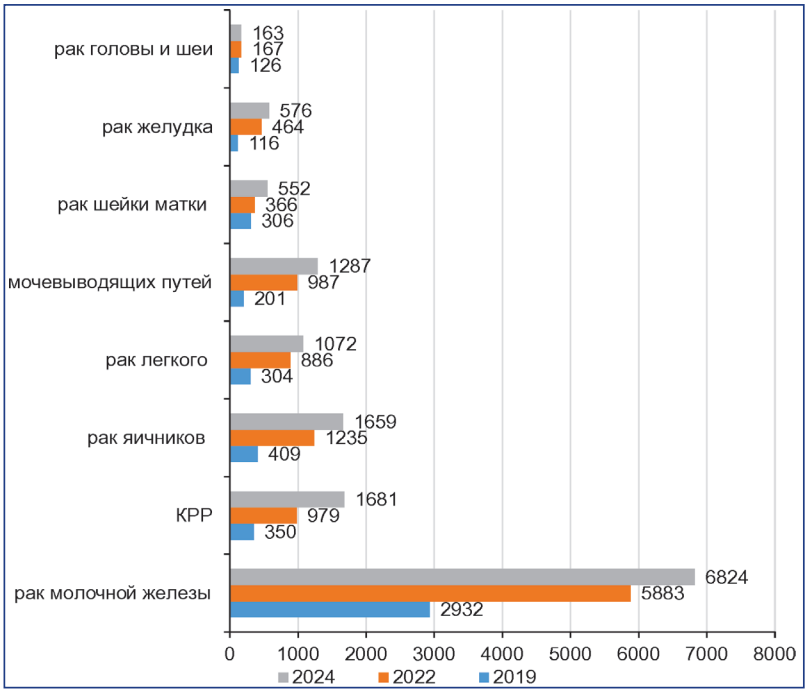
Indicator	Years				
	2019	Growth, %	2022	Growth, %	2024
Patients discharged	6857	78.2	12217	25.8	15 370
Bed days	42452	142.5	102947	48.9	153326
Average patient stays, days	6.2	35.5	8.4	19	10

The expansion of staffing in the Day Hospital Chemotherapy Department is worth noting (see Table 2). The need to expand the staffing of medical, nursing, and registration personnel (those who enter data into the electronic system) was justified.

In terms of treatment, the admission rate for main nosologies has increased significantly over the analyzed period, by more than 100% (Figure 1). Worth noting that patients with blood system diseases or advanced cases were referred for treatment to a 24-hour chemotherapy hospital.

Table 2 – Staffing of the Day Patient Chemotherapy Department for 2019 and 2024, abs.

Indicator	Years	
	2019	2024
Doctors	11	15
Nursing staff	9	14
Paramedical personnel	4	3
Registrars	2	3
Total	26	35



Cancer nozologies (top to bottom): Head and Neck; Stomach; Cervix; Urinary Tract; Lung; Ovary; CRC; Mammary Gland

Figure 1 – Comparison of the number of patients by nosology, 2019, 2022, and 2024

In 2024, 18,202 AEs were registered in patients receiving chemotherapy at the Day Patient Chemotherapy Department. Most (92%) were grade I AEs, which is a 37.7% increase compared to 2019.

The trend analysis revealed several factors contributing to the increase in AE registration. Firstly, the introduction of digital recording and monitoring systems provided a more comprehensive and detailed registration of side effects, including mild clinical manifestations that could previously remain undocumented or underestimated, resulting in a significant impact. Strengthening pharmacovigilance, increasing alertness of medical personnel, and improving the quality of outpatient monitoring also contributed to the increase in the detection of AEs.

Additionally, in 2024, there was a wider use of high-intensity and heavy chemotherapy regimens with significant toxicity. This was reflected in an increase in the number of grades II–IV AEs, particularly neutropenia (2,745 cases), nausea and vomiting (7,868 cases), and diarrhea (6,695 cases). It should be taken into account that one patient could experience several different AEs during treatment, which also increases the total number of AEs recorded. For example, one patient could simultaneously experience neutropenia, nausea, and toxic hepatitis, each of which was recorded as a separate AE.

In 2024, 113 grade IV AEs were registered. This fact requires special attention in the context of individual risk assessment when prescribing toxic treatment regimens and the need for timely correction of therapy.

Thus, the increase in the total number of AEs in 2024 was most likely associated with an objective increase in the toxic burden on patients resulting from the use of more aggressive chemotherapy regimens, as well as an improvement in the AE recording system due to the digitalization of clinical practice (Tables 3, 4).

Table 3 – Adverse events in patients after chemotherapy in the Day Patient Chemotherapy Department in 2019, abs.

Side effects	Grade 0	Grade I	Grade II	Grade III	Grade IV
Leukopenia Anemia	-	176	159	13	-
Thrombocytope-nia	-	-	-	35	-
Diarrhea	-	42	25	-	-
Nausea	-	92	31		-
Vomit	-	18	11	-	-
Cardiotoxicity	-	-	-	-	-
Toxic hepatitis	-	-	-	-	-
Total	-	328	226	48	-

Table 4 – Adverse events in patients after chemotherapy in the Day Patient Chemotherapy Department in 2024, abs.

Side effects	Grade I	Grade II	Grade III	Grade IV
Neutropenia	-	2488	211	46
Anemia	-	104	25	1
Thrombocytopenia	-	119	21	8
Nausea, vomiting	-	7023	845	-
Diarrhea	-	6580	103	12
Neurotoxicity and phlebitis	-	18	19	-
Allergic	-	28	3	-
Cardiotoxicity	-	-	3	-
Toxic hepatitis	-	388	111	46
Total	-	16748	1341	113

Discussion: The obtained results indicate a significant change in the indicators of chemotherapy care in the day hospital of the AOC over the analyzed period. The 124.17% increase in hospitalizations of patients diagnosed with malignant neoplasms is primarily due to the growth in the registration of new cases of malignant neoplasms in Almaty, as well as the gradual transition to a hospital-substituting model of care. This trend corresponds to the global trend of increasing the availability of antitumor therapy in outpatient settings while maintaining the quality of medical care [7].

The analysis of the average inpatient stay showed a 38% increase, from 6.2 to 10 days. This was due to the expansion of the range of antitumor drugs used, including chemotargeted agents and immunotherapy, within the framework of updated clinical protocols. Such growth also indicates an increase in the complexity and duration of treatment courses, requiring more time under the supervision of specialists.

The dynamics of the department's staff deserve special attention. The increase in the number of doctors, mid-level and junior medical personnel, as well as residents, by 34.6% (from 26 to 35 people) confirms the institutional strengthening of the department and its readiness to handle an increased patient flow. The expansion of the staff is especially relevant due to the need for prompt data entry into electronic systems and monitoring of patients' conditions.

The analysis of the nosological structure of cases, presented in Figure 1, also revealed a significant increase in

the number of hospitalizations in key areas of oncology, likely due to improved patient routing and earlier disease detection.

Notably, the number of AEs following chemotherapy has also increased along with the increase in the number of hospitalized patients. Thus, compared to 602 AEs registered in 2019, by 2024 their number increased to 18,202, i.e., by almost 2924%. The increase in the proportion of grade I AEs from 54.4% to 92% may indicate improved monitoring, early detection, and possibly the use of less aggressive treatment regimens to control the severity of reactions. At the same time, the occurrence of 113 grade IV AEs in 2024 requires special attention and further analysis to minimize risks and optimize treatment regimens. The noted changes reflect both quantitative and qualitative gains in the provision of specialized oncological care, confirming the effectiveness of the selected model of the Day Patient Chemotherapy Department in the context of increasing cancer incidence.

Conclusion: Consequently, the number of cases treated at the AOC Day Patient Chemotherapy Department has increased due to a growing number of patients being admitted for all localizations, the registration of new cancer cases, and the transition to inpatient replacement care at the Day Department. The AE indicators (fewer grade 2-3 AEs and more grade 1 AEs) suggest an improvement in the selection of patients for day treatment, as well as an improvement in the criteria for admission to a 24-hour hospital. However, despite the increase in staff numbers, the workload on medical personnel remains high. The staff of the day hospital chemotherapy department provides treatment to patients in 3 shifts. This situation dictates the need not only to increase the number of personnel and beds in the department and create electronic queues, but also to expand the possibilities of outpatient treatment of patients with AE, which are a burden for the staff of the Day Patient Chemotherapy Department.

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АҢДАТПА

АЛМАТЫ ОНКОЛОГИЯЛЫҚ ОРТАЛЫҒЫНДАҒЫ ОНКОЛОГИЯЛЫҚ НАУҚАСТАРДЫ ЖҮЙЕЛІ ЕМДЕУДЕ СТАЦИОНАРЛЫҚ КӨМЕК КӨРСЕТУДІ ТАЛДАУ

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Өзектілігі: *Статистикалық және есеп беру құжаттарына сәйкес, 2024 жылы Алматы онкологиялық диспансерінде (АОО) 23 732 онкологиялық ауру емделді, оның ішінде орталықтың күндізгі стационарының сәулелік терапия және химиотерапия бөлімшелері қызметтің 69,8 пайызын көрсетті. АОО дамыту тұжырымдамасы пациенттердің медициналық көмектің стационарды алмастыратын түрлеріне қолжетімділігін кеңейтуді көздейді. Осы тұрғыда химиотерапия бойынша күндізгі стационар қызметін талдау амбулаториялық жағдайда онкологиялық науқастарға көмек көрсетуді ұйымдастыруды жетілдіруге ықпал ететін маңызды бағыт болып табылады.*

Зерттеу мақсаты *– Алматы онкологиялық орталығының күндізгі химиотерапиялық стационарының 2019-2024 жылдардағы жұмысын талдау.*

Әдістері: *Химиотерапия бойынша күндізгі стационардың жұмысын талдау құжаттаманың негізгі есеп және есеп беру нысандарын пайдалана отырып жүргізілді. Ауруханаға жатқызылған науқастар мен тіркелген жағымсыз құбылыстар санының көрсеткіштері Damumed деректер базасының электронды медициналық картасынан алынады. Зерттеу BR24993051 жобасы аясында жүргізілді.*

Нәтижелері: *Талданған кезеңде күндізгі стационарда қатерлі ісіктері бар науқастарды химиотерапияға жатқызу 124,17%-ға артты. Зерттеу нәтижелері бастапқы жағдайларды тіркеудің ұлғаюына байланысты, сондай-ақ стационарлық алмастыратын көмекке көшу есебінен науқастарды госпитализациялаудың артқанын көрсетті. Сонымен қатар, соңғы 5 жылда (2019 жылдан 2024 жылға дейін) пациенттердің ауруханаға жатқызу санының өсуімен жағымсыз құбылыстарды тіркеу 602-ден 18 202 жағдайға дейін өсті.*

Қорытынды: *Күндізгі стационар жұмысын талдау бөлімнің кадрлық әлеуетін кеңейту, бөлімшедегі төсек-орын санын көбейту, электронды кезек құру, сондай-ақ күндізгі стационар қызметкерлеріне химиотерапия үшін ауыртпалық түсіретін келеңсіз жағдайлары бар науқастарға амбулаторлық көмек көрсету мүмкіндіктерін кеңейту қажеттілігін көрсетеді.*

Түйінді сөздер: *стационарды алмастыратын көмек, химиотерапия, онкологиялық орталық.*

АННОТАЦИЯ

АНАЛИЗ ОКАЗАНИЯ СТАЦИОНАР-ЗАМЕЩАЮЩЕЙ ПОМОЩИ В СИСТЕМНОМ ЛЕЧЕНИИ ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ В АЛМАТИНСКОМ ОНКОЛОГИЧЕСКОМ ЦЕНТРЕ

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Актуальность: *По данным статистики и отчетно-учетной формы документации в Алматинском онкологическом центре (АОЦ) за 2024 г. пролечено 23 732 случаев ЗНО, причём на долю дневных стационаров лучевой терапии и химиотерапии пришлось 69,8% всех случаев оказания помощи. В рамках концепции развития АОЦ предусмотрено расширение доступа пациентов к стационар-замещающим формам медицинской помощи. В этом контексте анализ деятельности дневного стационара химиотерапии является важным направлением, способствующим совершенствованию организации помощи онкологическим пациентам в амбулаторных условиях.*

Цель исследования *– проанализировать работу дневного стационара химиотерапии Алматинского онкологического центра за 2019-2024 гг.*

Методы: *Анализ работы дневного стационара химиотерапии был проведен с использованием основных учетно-отчетных форм документации. Показатели числа госпитализированных пациентов, зарегистрированных нежелательных явлений (НЯ) взяты из электронных историй болезней базы Datumed. Исследование проведено в рамках проекта ИРН BR24993051.*

Результаты: *За анализируемый период количество пациентов дневного стационара химиотерапии АОЦ увеличилось на 124,17% за счет роста регистрации первичных случаев, а также перехода на стационар-замещающую помощь. При этом, с увеличением числа госпитализации пациентов за последние 5 лет (с 2019 по 2024 гг.) отмечается рост регистрации НЯ с 602 до 18 202 случаев.*

Заключение. *Анализ работы дневного стационара актуализирует необходимость расширения кадрового потенциала отделения, увеличения койко-мест в отделении, создания электронных очередей. Также требуется расширить возможности амбулаторной помощи пациентам с НЯ, которые ложатся бременем на персонал дневного стационара химиотерапии.*

Ключевые слова: *стационар-замещающая помощь, химиотерапия, онкоцентр.*

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EPIDEMIOLOGY OF BREAST CANCER IN KAZAKHSTAN: THE ANALYSIS OF MORBIDITY, MORTALITY, AND DISEASE STAGING IN 2015-2024

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АННОТАЦИЯ

Relevance: *Breast cancer (BC) ranks first in terms of prevalence among all malignant neoplasms in women in the Republic of Kazakhstan. Over the period 2015-2024, there has been a steady increase in the incidence, with the disease increasingly being detected in older women. Despite ongoing screening programs, breast cancer remains a significant cause of cancer mortality. For the first time, a comprehensive 10-year analysis of national breast cancer data was conducted with an assessment of the dynamics of morbidity, mortality, stage, and five-year survival.*

The study aimed to *analyze changes in the incidence, mortality, survival, and stage of BC in women in the RK from 2015 to 2024 to assess the effectiveness of measures for early detection and treatment of the disease.*

Methods: *The BC incidence and mortality analysis for 2015-2024 was based on official statistical reports (forms No. 7 and No. 090/U) and data from the national cancer registry. Demographic indicators were obtained from open sources of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan. Statistical processing was performed using SPSS software (version 23.0) with descriptive statistical methods, including calculating the means, confidence intervals, and trend rates.*

Results: *During the study period, the incidence rate of BC increased from 45.7 to 47.6 per 100,000 women, while mortality decreased from 14.2 to 7.8. Five-year survival rose by 81%, from 16,740 to 30,267 patients. The proportion of early-stage diagnoses (I-II) increased from 81.5% to 88.7%, and stage III cases nearly halved. The highest incidence was recorded in the 65-69 age group.*

A link has been established between screening coverage and mortality reduction. The results obtained refine and expand the previously presented regional data, providing a basis for improving preventive programs and enhancing the effectiveness of cancer care.

Conclusion: *Kazakhstan demonstrates a steady rise in BC incidence alongside a reduction in mortality and improvements in early diagnosis. These trends affirm the effectiveness of screening programs and oncologic care, although the stable rate of stage IV diagnoses highlights the need to eliminate barriers to timely medical consultation.*

Keywords: *epidemiology, breast cancer, Kazakhstan, incidence, mortality, survival, screening.*

Introduction: Breast cancer (BC) occupies a leading place in global oncological statistics. In 2020, 2.3 million new cases were registered, which is 11.7% of all malignant neoplasms (MN), and 685 thousand deaths, making it the fifth leading cause of cancer death. In women, it accounts for about 25% of all MN and 16% of cancer deaths, ranking first in incidence in 159 countries and mortality in 110 [1]. In 2022, the annual incidence remained at 2.3 million, and the mortality rate was about 670 thousand. BC occurs in women of all ages after puberty, but the risk increases with age. In countries with a high development index, the probability of getting sick is 1 in 12, and dying is 1 in 71; in countries with a low Human Development Index (HDI), 1 in 27 and 1 in 48, respectively [2]. High incidence rates (>80 per 100,000) are recorded in developed countries – Western Europe, Australia, and the USA. The lowest rates are in Central America, Africa, and South Asia. However, the mortality rate is higher in countries with transition economies, which is associated with limited access to early diagnosis and treatment. The main factors of growth are reproductive, hormonal, and behavioral (alcohol, obesity, physical inactivity), as well as the expansion of mammographic screening in developed countries [1].

According to the World Health Organization (WHO), mammography screening every 2 years is recommended in resource-rich countries for women aged 50–69 years without high risk [3]. The American Cancer Society recommends annual screening beginning at age 45, with the option to begin at age 40 and continue as long as general health and life expectancy ≥10 years allow [4].

In Kazakhstan, breast cancer remains the most common malignant disease in women. According to the national epidemiological study, 22 cases were registered in the period 2017-2021. 736 new cases, which is 14% more than in previous years. The largest number of diagnoses occurred in 2019 and 2021 (4945 and 4939, respectively). The most vulnerable age category is women aged 65-74. In 44.6% of cases, the tumor was localized in the upper outer quadrant of the mammary gland (C50.4). At early stages (I-II), the disease was detected in 67.2% of cases, while stage IV

was diagnosed in only 4.6% of patients. Ethnic distribution showed a predominance of women of Kazakh nationality (48.1%), followed by Russians (33.1%) [5, 6]. An in-depth analysis within the ethnic group of Kazakh women showed that breast cancer accounts for 26.3% of all registered cases of malignant neoplasms and is the cause of 8.7% of all cancer deaths in this population [7]. Risk factors are divided into modifiable (obesity, physical inactivity, alcohol, hormones, radiation) and non-modifiable (age, BRCA1/2, TP53, PALB2 mutations, early menarche, late menopause, no childbirth). Physical activity, breastfeeding, and abstinence from alcohol have a protective effect [8].

In women with BRCA1/2 mutations, the risk of breast cancer reaches 69-72%, and ovarian cancer amounts to 17-44% by the age of 80 [9]. Molecular biological diagnostics of breast cancer includes assessment of expression of hormonal receptors (estrogen and progesterone), HER2 receptor, and level of proliferative activity by the Ki-67 marker. This approach allows identifying the subtype of HR-positive tumors for which targeted and hormonal therapy regimens have been developed and successfully used [10]. Breast cancer is a heterogeneous disease with a pronounced genetic component. It has been established that mutations in *the BRCA1/2*, *TP53*, *PTEN,* and other genes significantly increase the risk of breast cancer, which emphasizes the importance of introducing genetic screening and personalized preventive strategies [11].

The study aimed to analyze changes in the incidence, mortality, survival, and stage of BC in women in the RK from 2015 to 2024 to assess the effectiveness of measures for early detection and treatment of the disease.

Materials and methods: The analysis of the dynamics and structure of breast cancer morbidity and mortality among the female population of the Republic of Kazakhstan for the period 2015-2024 was conducted based on official statistical reporting data provided by health authorities. The incidence and mortality rates per 100,000 female population, five-year survival, and distribution of cases by disease stage at the time of primary diagnosis were estimated. Descriptive statistics were used as research methods, including calculation of mean values, confidence intervals, and average annual growth or decline rates. Official statistical and registration sources were used to conduct the epidemiological analysis. Information on malignant neoplasms was selected by localization codes under the International Classification of Diseases, 10th revision (ICD-10). The sample was based on data from the Electronic Registry of Cancer Patients (National Cancer Registry), as well as annual forms of state statistical reporting, including form No. 7 "Report on Malignant Neoplasms" for the period 2015-2024 and individual cards of primary cancer patients (form No. 090/U). To calculate the demographic coefficients, the materials of the Statistics Agency of the Republic of Kazakhstan were used, reflecting the number, age, and sex structure of the population of the Republic of Kazakhstan for the period under review.

Results: In 2015-2024, the total number of patients registered with malignant neoplasms increased from 156,280 to 231,019. The number of those who survived more than 5 years after diagnosis increased from 79,387 to 125,858. The indicators for breast cancer also show growth: the number of patients increased from 31,352 to 51,484, and the five-year survival rate increased from 16,740 to 30,267. The proportion of breast cancer among all malignant neoplasms increased from 20.1% in 2015 to 22.3% in 2024 (Fig. 1).

Dynamics of intensive and standardized rates of breast cancer incidence (2015-2024). Over the analyzed period, there has been a steady upward trend in both intensive and standardized rates of breast cancer incidence among the female population. The incidence rate increased from 48.8 per 100,000 women in 2015 to 55.1 in 2024, reaching its maximum for the entire analyzed period. The standardized rate also increased – from 45.7 to 47.6 per 100,000. There is a general upward trend, with a significant decline in 2020 and a subsequent rise, which may be due to fluctuations in screening coverage and the influence of external factors (e.g., the COVID-19 pandemic) (Fig. 2).

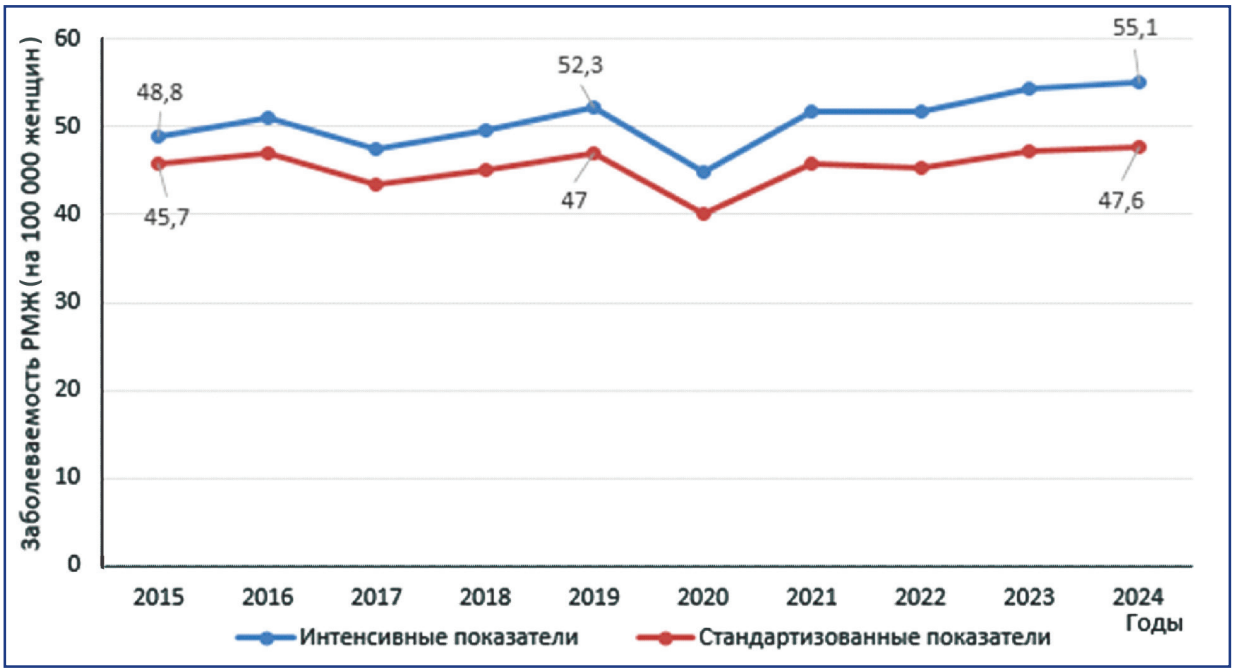
From 2015 to 2024, Kazakhstan has seen a steady downward trend in both intensive and standardized breast cancer mortality rates. The intensive rate decreased from 15.4 to 10.1 per 100,000 women, and the standardized rate decreased from 14.2 to 7.8. A particularly pronounced decrease was noted after 2021, which may reflect increased diagnostic and treatment efficiency (Fig. 3).

Comparison of incidence, mortality, and the ratio between them by intensive indicators (2015-2024). Figures 2-4 reflect the dynamics of intensive (crude) indicators of incidence and mortality from breast cancer per 100,000 women in Kazakhstan, as well as the ratio between them (%). Over the analyzed period, incidence increased from 48.8 to 55.1, while mortality decreased from 15.4 to 10.1. This led to a decrease in the relative case-fatality rate from 31.6% to 25.9%.

The most pronounced decrease in mortality was observed in 2022 (up to 20.5%), after which the indicator increased slightly. Such dynamics indicate an improvement in diagnostics and treatment, with a simultaneous increase in detection (Fig. 4).

Comparison of standardized incidence, mortality rates, and their ratio (2015-2024). Figures 2-4 also present standardized (by age) incidence and mortality rates from breast cancer in Kazakhstan and their ratio in percentage. Over the period from 2015 to 2024, incidence increased from 45.7 to 47.6 per 100,000 women, while mortality decreased from 14.2 to 7.8, which reflects an almost twofold decrease. The mortality-to-incidence ratio (CFR) decreased from 31.1% in 2015 to 16.4% in 2024, with the lowest value in the last two years (Fig. 5).

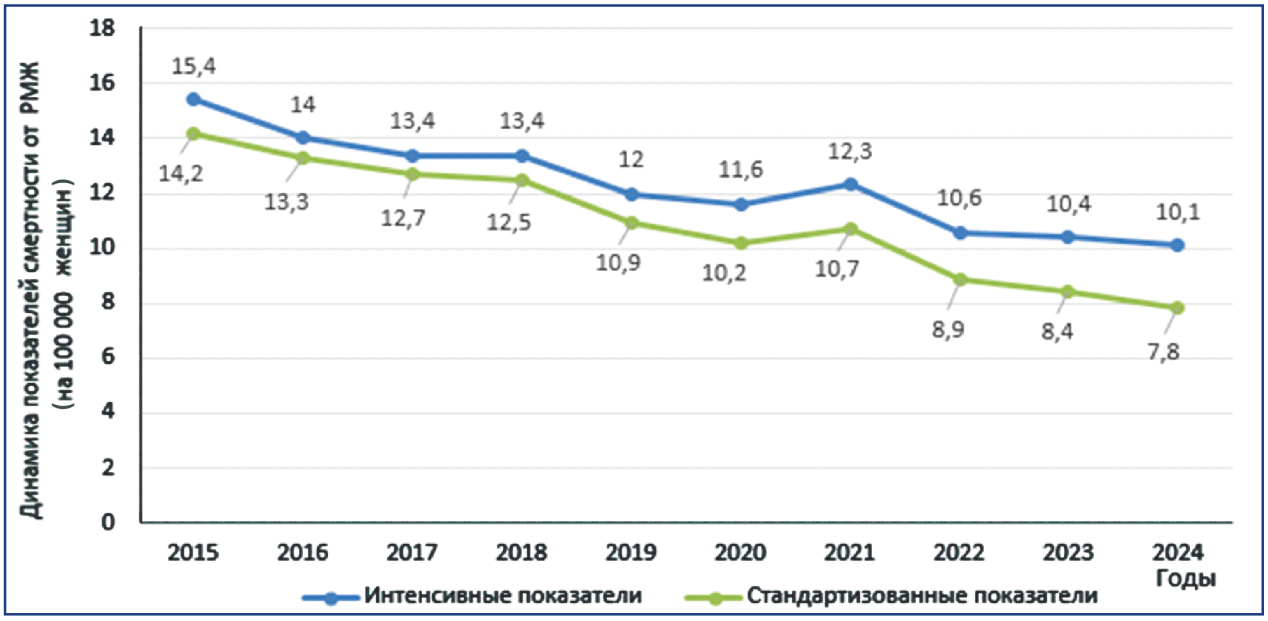
Legend: Y axis – Share of breast cancer cases among all MNOs (%), X axis – Breast cancer shares curve (years)
Figure 1 – The share of breast cancer in the total number of malignant neoplasms in Kazakhstan, 2015-2024 (%)



Legend: Y axis – Breast cancer incidence (per 100,000 female population), X axis – Years; Blue line – Intencive rates; Red liine – Standardized rates
Figure 2 – Dynamics of intensive and standardized incidence of breast cancer in Kazakhstan, 2015-2024 (per 100,000 women)

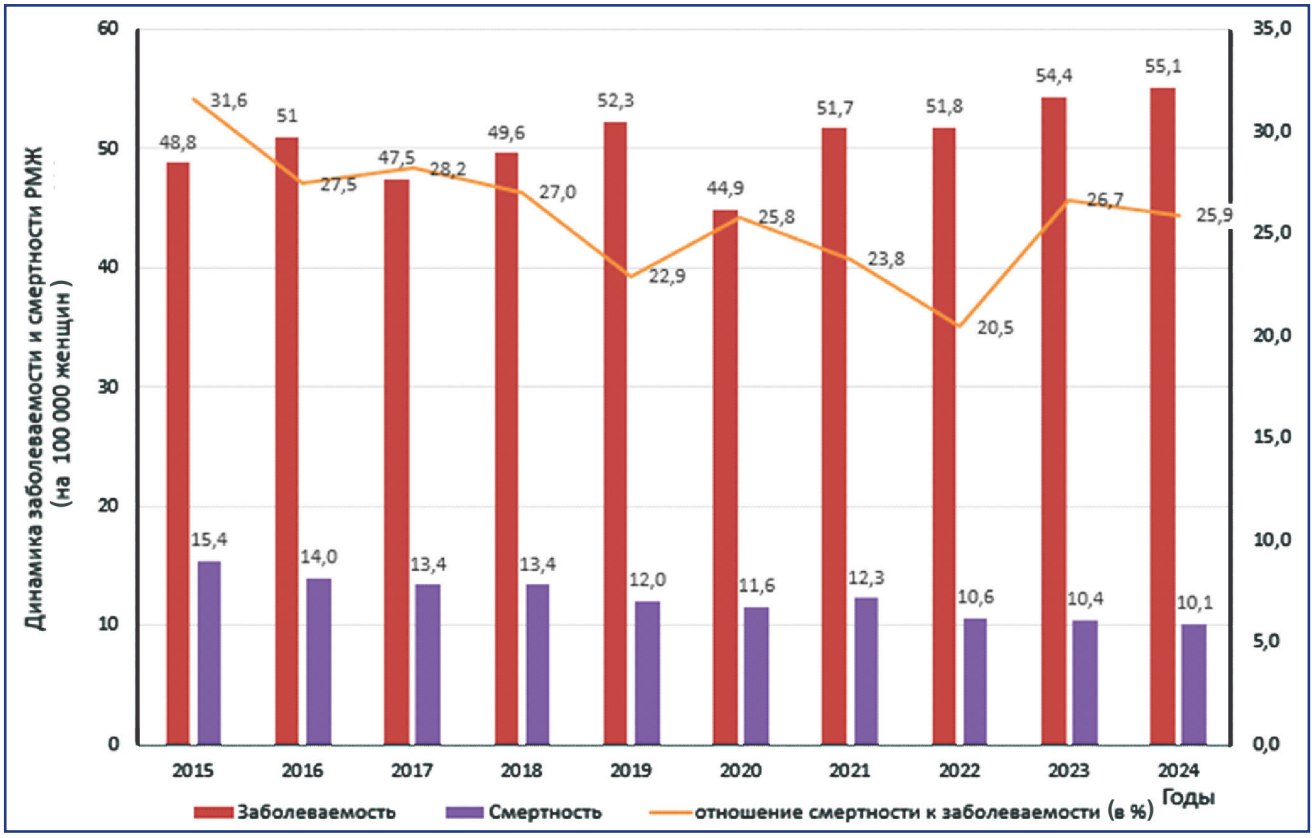
A comparative analysis of the structure of stages at the time of primary diagnosis of breast cancer in 2015 and 2024 demonstrates a clear positive trend towards earlier detection of the disease. In 2015, the bulk of cases were at stages I-II, which together accounted for 81.5% of all registered diagnoses. At the same time, stage III accounted for 13.8% of cases, and stage IV, 4.7%, which indicated a relatively high level of early diagnosis even at the initial stage of the period under review. By 2024, the structure of detection was clarified by dividing stages I and II. The first stage was diagnosed in 37.4% of cases, the second in 51.3%, which in total amounted to 88.7% of early detection. The proportion of patients with stage III decreased almost twofold, to 7.1%, while stage IV remained at a comparable level of 4.2%. Thus, over the decade, there has been a steady improvement in the rates of timely treatment and diagno-

sis. The increase in the proportion of early stages with a simultaneous reduction in later forms of the disease indicates the effectiveness of the mammographic screening programs implemented in the country, increased public awareness, and improvements in the work of primary health care. At the same time, maintaining the proportion of stage IV at the same level requires additional attention, taking into account both regional differences in the availability of diagnostics and the characteristics of the course of the disease in certain groups of patients (Fig. 6).



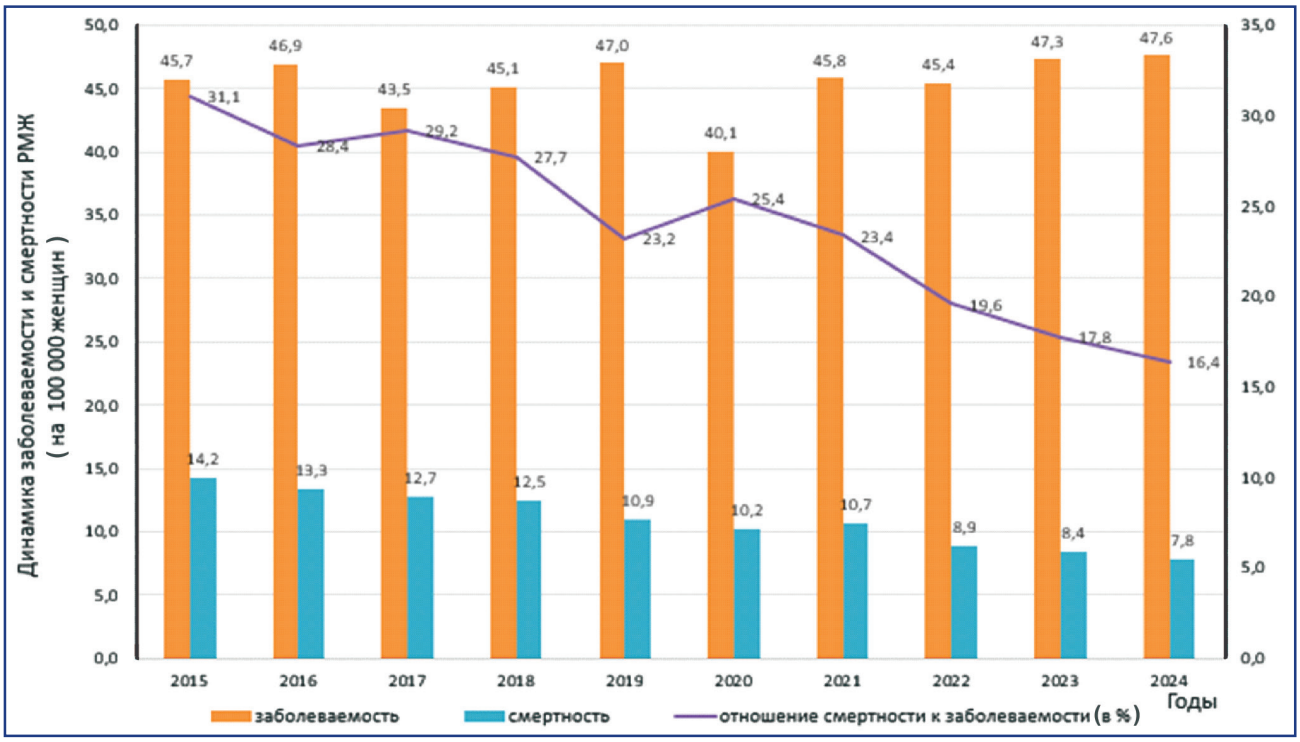
Legend: Y axis – Breast cancer mortality trends (per 100,000 female population), X axis – Years; Blue line – Intencive rates; Red liine – Standardized rates

Figure 3 – Dynamics of intensive and standardized mortality from breast cancer in Kazakhstan, 2015-2024 (per 100,000 women)



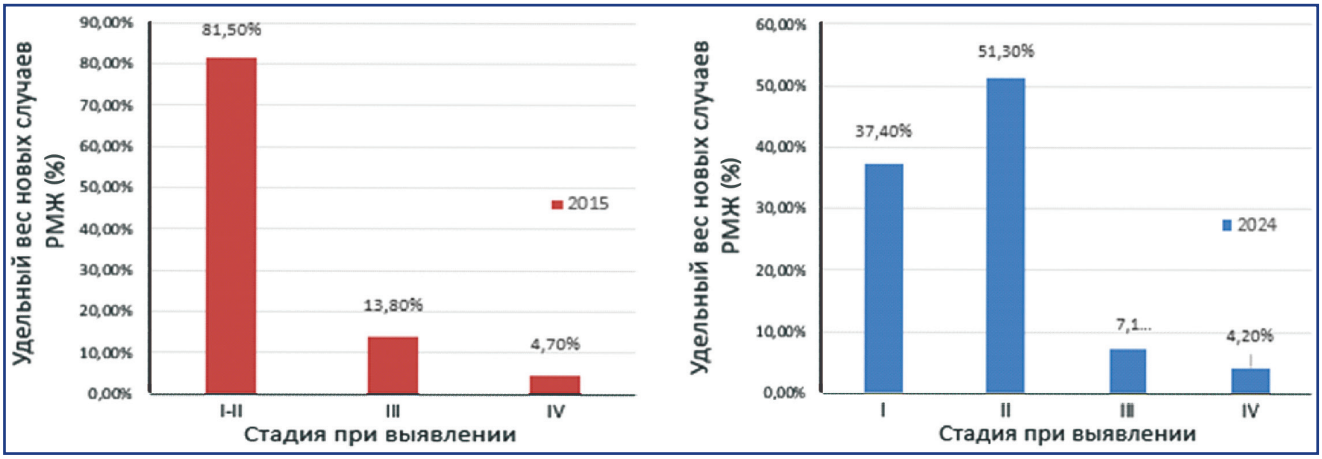
Legend: Y axis – Breast cancer incidence & mortality (per 100,000 female population), X axis – Years; Red bars – Incidence; Violet bars – Mortality; Yellow line – Incidence-to-Mortality ratio (%)

Figure 4 – Intensive incidence & mortality rates and their ratios in breast cancer in Kazakhstan, 2015-2024 (per 100,000 women)



Legend: Y axis – Breast cancer incidence & mortality (per 100,000 female population), X axis – Years; Red bars – Incidence; Violet bars – Mortality; Yellow line – Incidence-to-Mortality ratio (%)

Figure 5 – Standardized incidence & mortality rates and their ratios in breast cancer in Kazakhstan, 2015-2024 (per 100,000 women)



A B

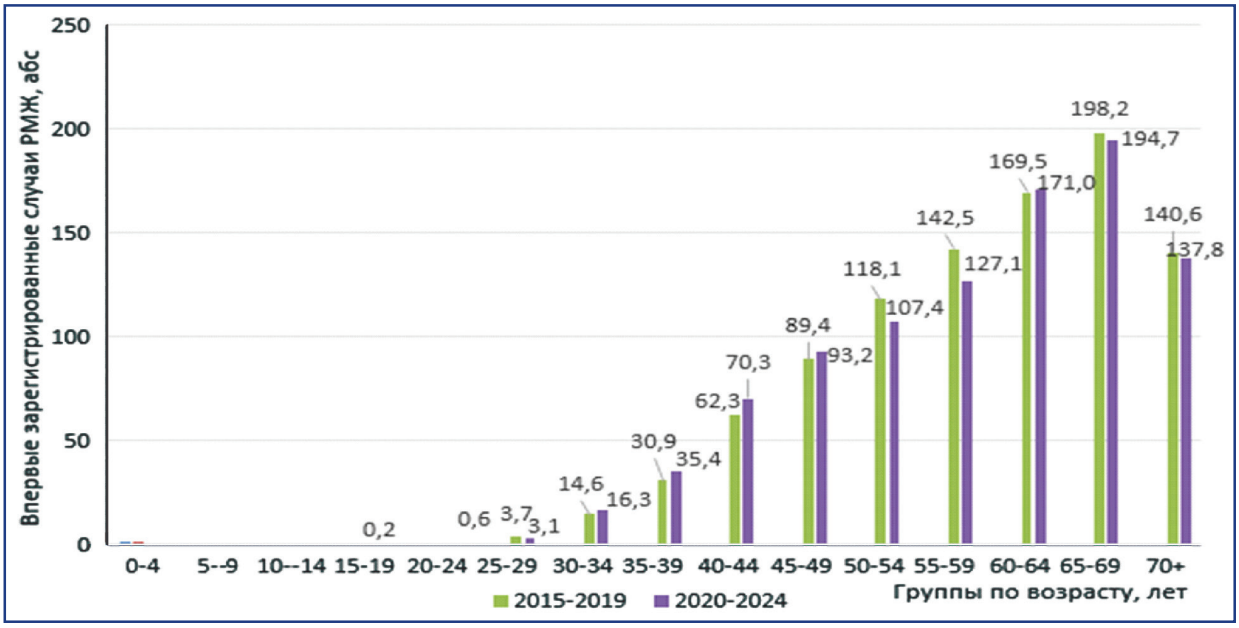
Legend: Y axis – Share of new breast cancer cases (%); X axis – Stage at detection

Figure 6 – Distribution of breast cancer cases by stage at detection, Kazakhstan: A – in 2015, B – in 2024

An analysis of the age structure of breast cancer incidence showed a clear tendency for rates to increase with age. The lowest incidence rates are observed in age groups up to 25 years, where the values do not exceed 3.7 per 100,000 women. From the age of 30, a gradual increase is observed: from 14.6-16.3 per 100 thousand among women aged 30-34 years to maximum rates in the 60-64 and 65-69 age groups. The highest incidence rate was recorded in the 65-69 age category: 198.2 per 100 thousand in 2015-2019 and 194.7 per 100 thousand in 2020-2024. They are followed by the 60-64 year old group (169.5 and 171.0 per 100 thousand) and 70+ (140.6 and 137.8 per 100 thousand), which confirms the predominant development of the disease in older age groups. It is clear that the increase in morbidity in the second five-year period compared to the first was observed in all age cohorts starting from 35 years and was most pronounced in the 35–39-year-old group (an increase from 30.9 to 35.4 per 100 thousand) (Fig. 7).

Discussion: The obtained data reflect global trends in oncology: an increase in morbidity with a simultaneous decrease in mortality from breast cancer. This may be due to improved accessibility of diagnostics, the introduction of screening programs, modernization of oncology services, and more active oncology alertness among both the population and primary care physicians.

Similar epidemiological shifts have been recorded in some CIS countries. Thus, in the Republic of Belarus, standardized incidence rates of breast cancer have increased significantly in all regions over the past decades, especially in Minsk, which confirms a real increase in incidence rates that is not due solely to population aging [12]. In the Russian Federation, over the period 2000-2015, the standardized incidence rate increased by 30.4%, with the largest increase in the group of women aged 65-79, which is consistent with the results of the present analysis, where the peak incidence rate is also observed at the age of 65-69 [13].



Legend: Y axis – First registered breast cancer cases, abs.; X axis – Age groups, years

Figure 7 – Comparison of breast cancer incidence by age groups in Kazakhstan,2015-2019 and 2020-2024

Data from the Kyrgyz Republic confirms that breast cancer often affects Kyrgyz women at a younger age, with the highest increase recorded at the ages of 40-49 and 50-59 [14]. This requires adaptation of screening approaches depending on the ethnic and age characteristics of the populations. Similar findings are presented in studies on Uzbekistan and Tajikistan: mortality from breast cancer has a significant impact on the life expectancy of women, and the highest incidence is recorded at the age of 40-59 [15]. These data emphasize the universality of the breast cancer problem in the region and the need for coordinated interstate efforts for early diagnosis, access to treatment, and prevention. In Kazakhstan, despite the introduction of a national screening program, significant regional differences in incidence and mortality rates remain. According to previous studies, higher rates were recorded in the North Kazakhstan, Pavlodar, and Karaganda regions, as well as in Almaty, which is probably due to higher availability of diagnostics and oncological care [16]. The increase in the proportion of breast cancer among all malignant neoplasms (from 20.1% to 22.3%) may be due to both the growth of the female population and improved screening coverage. A significant increase in the number of patients under observation for more than 5 years (almost doubling in a decade) confirms the positive dynamics in survival rates.

A significant increase in the proportion of stages I-II at the time of diagnosis indicates the effectiveness of the screening program implemented in Kazakhstan. At the same time, there is a decrease in the frequency of detection of the disease at stage III by almost two times. However, the proportion of stage IV remains stable, which requires a separate analysis of the reasons for late treatment in this group of patients.

The increase in the share of early detection of breast cancer in the Republic of Kazakhstan (up to 88.7% in 2024) demonstrates the effectiveness of the implemented preventive measures. However, the stable share of stage IV, as well as the increase in incidence in young women, indicates the need for further improvement of the age structure of screening and increased cancer alertness among primary care physicians.

The increase in incidence in older age cohorts, especially after 50 years, emphasizes the importance of targeted prevention and expanded coverage within age-specific screening. The steady decline in standardized mortality rates against the background of increasing incidence can be interpreted as a result of improved quality of treatment, including drug and surgical care, the introduction of a multidisciplinary approach, and expanded access to high-tech medical care. However, persistent regional and age differences require additional attention from the healthcare system, including sociological studies of the reasons for late treatment, barriers to screening, and the level of public awareness.

Dynamics of stages of breast cancer detection (2015 and 2024) A comparative analysis of the stage of the disease at primary diagnosis in 2015 and 2024 demonstrates a positive trend towards earlier detection of breast cancer. In 2015, the propor-

tion of patients in whom the disease was detected at stages I–II was 81.5%, of which 13.8% were at stage III and 4.7% at stage IV.

In 2024, stage I accounted for 37.4% of cases, stage II – 51.3%, which in total means the early detection rate of 88.7%. An increase in early detection compared to 2015 reflects positive dynamics in breast cancer timely diagnosis. 7.1% of cases were detected at Stage III, and 4.2% at Stage IV.

The share of early diagnosis (stages I-II) increased by 7.2 percentage points over the decade, while the share of stage III decreased almost twofold, from 13.8% to 7.1%. This indicates an increase in the effectiveness of screening programs and early patient referrals, as well as the development of the early diagnosis system as a whole.

Conclusion: Thus, in the period from 2015 to 2024, the Republic of Kazakhstan has seen an increase in breast cancer incidence, while mortality has decreased and early detection rates have improved. These trends indicate a positive impact of screening programs, increased diagnostic activity, and the development of cancer care in the country. Continuation and expansion of preventive measures, as well as targeted coverage of vulnerable age groups, should become a priority for further reducing cancer mortality from breast cancer.

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АҢДАТПА

ҚАЗАҚСТАНДАҒЫ СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ЭПИДЕМИОЛОГИЯСЫ: 2015-2024 ЖЫЛДАРДАҒЫ СЫРҚАТТАНУШЫЛЫҚ, ӨЛІМ-ЖІТІМДІ ЖӘНЕ АУРУДЫҢ САТЫЛАРЫН ТАЛДАУ

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Өзектілігі: *Сүт безі қатерлі ісігі (СБҚІ) Қазақстан Республикасындағы әйелдерде барлық қатерлі ісіктердің таралуы бойынша бірінші орында. 2015-2024 жылдар кезеңінде сырқаттанушылықтың тұрақты өсуі байқалады, бұл ретте ауру егде жастағы топтар-*

дағы әйелдерде жиі анықталады. Іске асырылып жатқан скринингтік бағдарламаларға қарамастан, СБҚІ онкологиялық өлім-жітімнің маңызды себебі болып қала береді. Алғаш рет сырқаттанушылық, өлім-жітім, кезеңділік және бес жылдық өмір сүру динамикасын бағалай отырып, СБҚІ бойынша ұлттық деректерге кешенді 10 жылдық талдау жүргізілді.

***Зерттеудің мақсаты** – ауруды ерте анықтау және емдеу жөніндегі іс-шаралардың тиімділігін бағалау мақсатында ҚР әйелдерде СБҚІ 2015-2024 жылдардағы аурушаңдық, өлім-жітім, өмір сүру және сатылық көрсеткіштеріндегі өзгерістерді талдау.*

***Әдістері:** СБҚІ бойынша аурушаңдық пен өлім-жітімнің талдауы 2015–2024 жылдар аралығында №7 және №090/У нысандары, сондай-ақ онкологиялық регистр деректері негізінде жүргізілді. Демографиялық көрсеткіштер ҚР Стратегиялық жоспарлау және реформалар агенттігінің ашық деректерінен алынды. Статистикалық өңдеу SPSS бағдарламасының (23.0 нұсқасы) көмегімен сипаттамалық статистика әдістерін қолдану арқылы жүргізілді: орташа мәндер, сенімді аралықтар және көрсеткіштердің өзгеру қарқыны есептелді.*

***Нәтижелері:** Талдау кезеңінде СБҚІ бойынша аурушаңдықтың көрсеткіші 100 000 әйелге шаққанда 45,7-ден 47,6-ға дейін өсті, ал өлім-жітім 14,2-ден 7,8-ге дейін төмендеді. Бесжылдық өмір сүру 81%-ға артып, 16 740-тен 30 267 пациентке дейін өсті. Аурудың ерте сатыларында (I–II) анықталу үлесі 81,5%-дан 88,7%-ға дейін жоғарылады, ал III сатының үлесі екі есеге жуық қысқарды. Ең жоғары аурушаңдық 65–69 жас аралығындағы топта тіркелді.*

Скринингпен қамту мен өлім-жітімнің төмендеуі арасында байланыс орнатылды. Алынған нәтижелер бұрын ұсынылған өңірлік деректерді нақтылайды және кеңейтеді және профилактикалық бағдарламаларды жетілдіру және онкологиялық көмектің тиімділігін арттыру үшін негіз бола алады.

***Қорытынды:** Қазақстанда СБҚІ аурушаңдығының тұрақты өсуі аясында өлім-жітімнің төмендеуі мен ерте диагностика деңгейінің жақсаруы байқалады. Бұл үрдістер скринингтік бағдарламалардың және онкологиялық көмектің тиімділігін көрсетеді, алайда IV сатыдағы жағдайлардың тұрақты деңгейі ерте жүгіну алдындағы кедергілерді жою қажеттігін көрсетеді.*

***Түйінді сөздер:** эпидемиология, сүт безі қатерлі ісігі, Қазақстан, аурушаңдық, өлім-жітім, өмір сүру, скрининг.*

АННОТАЦИЯ

ЭПИДЕМИОЛОГИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ В КАЗАХСТАНЕ: АНАЛИЗ ЗАБОЛЕВАЕМОСТИ, СМЕРТНОСТИ И СТАДИЙ ЗАБОЛЕВАНИЯ В 2015-2024 ГОДАХ

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***Актуальность:** Рак молочной железы (РМЖ) занимает первое место по распространённости среди всех злокачественных новообразований у женщин в Республике Казахстан. За период 2015–2024 гг. отмечается устойчивый рост заболеваемости, при этом РМЖ всё чаще выявляется у женщин старших возрастных групп. Несмотря на реализуемые скрининговые программы, РМЖ остаётся значимой причиной онкологической смертности. В данном исследовании впервые проведён комплексный 10-летний анализ национальных данных по РМЖ с оценкой динамики заболеваемости, смертности, стадийности и пятилетней выживаемости.*

***Цель исследования** – проанализировать изменения в показателях заболеваемости, смертности, выживаемости и стадийности рака молочной железы у женщин в Республике Казахстан за 2015-2024 годы с целью оценки эффективности мероприятий по раннему выявлению и лечению заболевания.*

***Методы:** Анализ заболеваемости и смертности от РМЖ в РК за период 2015-2024 гг. выполнен на основе данных форм №7 и №090/У, а также сведений онкологического реестра. Демографические показатели получены из открытых источников Агентства по стратегическому планированию и реформам РК. Статистическая обработка осуществлялась с применением SPSS (версия 23.0) с использованием методов описательной статистики, включая расчёт средних значений, доверительных интервалов и темпов изменения показателей.*

***Результаты:** За анализируемый период стандартизированный показатель заболеваемости РМЖ вырос с 45,7 до 47,6 на 100 000 женщин, в то время как смертность снизилась с 14,2 до 7,8. Пятилетняя выживаемость увеличилась на 81% – с 16 740 до 30 267 пациенток. Доля выявления на ранних стадиях (I-II) повысилась с 81,5% до 88,7%, а доля III стадии снизилась почти вдвое. Наибольшая заболеваемость отмечена в возрастной группе 65-69 лет.*

Установлена связь между охватом скринингом и снижением смертности. Полученные результаты уточняют и расширяют ранее представленные региональные данные и могут служить основой для совершенствования профилактических программ и повышения эффективности онкологической помощи.

***Заключение:** В Казахстане наблюдается устойчивый рост заболеваемости РМЖ при одновременном снижении смертности и улучшении ранней диагностики. Эти тенденции подтверждают эффективность программ скрининга и онкологической помощи, но сохраняющееся постоянство IV стадии подчёркивает необходимость устранения барьеров к раннему обращению.*

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

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NUTRITIONAL SUPPORT OF PATIENTS WITH HEPATOPANCREATODENAL TUMORS: A KEY ELEMENT OF INTENSIVE CARE IN THE POSTOPERATIVE PERIOD

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ABSTRACT

Relevance: *Effective intensive therapy of complications arising from malignant neoplasms of the hepatopancreatoduodenal region remains an urgent task. It aims to eliminate energy deficiency, restore body weight, and normalize plastic processes that are disrupted due to severe hypercatabolism, increased body needs for nutrients, and the development of intoxication syndrome, especially in the postoperative period.*

The study aimed to *research the key aspects of nutritional support in patients with tumors of the hepatopancreatoduodenal region by studying and comparing the effectiveness of isolated enteral, parenteral, and mixed nutritional therapy in the early postoperative period.*

Methods: *The study involved 91 patients over 18 years old with hepatopancreatobiliary malignancies. Patients were divided into three groups depending on the type of nutritional support. The study assessed nutritional status indicators, including screening results, body mass index, basal metabolic rate, and key laboratory indicators: the level of lymphocytes in the blood, total protein, total bilirubin, and ALT and AST activity.*

Results: *With parenteral nutritional support according to the screening protocols used, by Days 10-12, 17 patients maintained a "normal" nutritional status, 14 patients had "moderate malnutrition" with regression of "severe malnutrition" in 1 patient (3.2%). In the mixed nutrition group, by Days 10-12 of the postoperative period, there was an increase in patients with "moderate malnutrition" according to the SGA and NRI scales by 10% and 6.7%, respectively, with complete elimination of signs of "severe malnutrition" according to the given nutritional assessment scales ($p<0.005$).*

Conclusion: *In the group with isolated parenteral nutrition, sufficient effectiveness in stabilizing and maintaining the nutritional status of patients was achieved, which was manifested in an increase in the number of patients with "moderate" and "normal" nutritional status, as well as a decrease in the number of patients with severe and moderate nutritional deficiency.*

Mixed nutritional support can be considered a promising alternative to parenteral nutrition since the indicators of the nutritional status of patients achieved in this group were statistically similar to the results of parenteral therapy.

Keywords: *nutritional status, nutritional deficiency, nutritional support, sipping, oncology, nutrition, tumors of the hepatopancreatoduodenal region.*

Introduction: Treatment of hepatopancreatoduodenal tumors and their complications is one of the key tasks of oncologists and intensive care specialists. The relevance of this problem is due to the increase in the number of patients with oncological diseases of the abdominal cavity, which require external energy supplementation and correction of nutritional status in the postoperative period. This growth is observed even against the background of improvement of non-invasive diagnostic methods for tumors of the abdominal cavity and hepatopancreatoduodenal zone [1, 2].

Tumors of the hepatopancreatoduodenal zone occupy a special place among malignant neoplasms, as they are often accompanied by complications such as mechanical jaundice, liver failure, and nutritional deficiency in the perioperative period, which significantly increases the risk of death.

To identify nutritional deficiencies, screening methods recommended by the international clinical nutrition associations ASPEN (American Society of Clinical Nutrition and Metabolism) and ESPEN (European Society of Clinical Nutrition and Metabolism) are used. These methods include patient questionnaires, the use of standard anthropometric and laboratory indicators, which allow for an objective assessment of nutritional status and the degree of its impairment [3, 4].

Early detection of tumors and assessment of nutritional status at the outpatient examination stage could reduce the risk of complications through the use of modern screening methods and assessment scales (Subjective Global Assessment, SGA; Nutritional Risk Index, NRI). These tools allow the timely initiation of nutritional therapy in combination with surgical treatment [4, 5].

Particular attention should be paid to the prevention of early postoperative complications, since up to 70-80% of cancer patients suffer from varying degrees of nutritional deficiency. This condition is aggravated by severe hy-

percatabolism and an increased need for nutrients, which contributes to the development of complications in the postoperative period.

The choice of the optimal nutrition method remains a pressing issue for many clinicians and researchers. The need for an individual approach is due to the complexity of surgical interventions in the hepatopancreatoduodenal zone. However, existing methods and strategies are still insufficiently covered in the literature, which emphasizes the need for further study and implementation of these approaches in clinical oncology.

The study aimed to research the key aspects of nutritional support in patients with tumors of the hepatopancreatoduodenal region by studying and comparing the effectiveness of isolated enteral, parenteral, and mixed nutritional therapy in the early postoperative period.

Objectives of the study: 1) to conduct a comparative assessment of the dynamics of nutritional deficiency and nutritional status of patients operated on for malignant tumors of the hepatopancreatoduodenal zone in the early postoperative period using isolated enteral, isolated parenteral and mixed types of nutrition; 2) to analyze the dynamics of protein and carbohydrate metabolism, the viability of liver function in cancer patients operated on for malignant tumors of the hepatopancreatoduodenal zone using the presented types of energy supplementation in the early postoperative period. This material is a continuation of the previous article [6], in which we analyzed the main aspects and published the intermediate result. This article contains the final results of the study, discussions, and conclusions.

Materials and Methods: This prospective, longitudinal, parallel study and retrospective analysis of treatment results involved 91 patients over 18 years old with hepatopancreatobiliary malignancies, including 49 men and 44 women.

Depending on the volume, severity, and prevalence of the oncological process, the appropriate volume of surgical intervention was undertaken, which was radical or palliative: 1) resection of various segments of the liver; 2) hemihepatectomy; 3) transhepatic drainage of the right and left hepatic duct; 4) bypass gastroenteroanastomosis or cholecystoenteroanastomosis with interintestinal entero-enteroanastomosis according to Brown; 5) gastro-pancreatoduodenal resection; 6) corporocaudal resection of the pancreas with splenectomy.

The most common (84.7%) were combined surgical interventions affecting the intestines, liver, and pancreas simultaneously. This was due to the significant volume and growth of the oncological process in this area, which was associated with complete temporary intestinal failure in the early postoperative period.

In some patients (n=28, 30%), the disease was accompanied by obstructive jaundice, which required a preliminary or intraoperative decompression of the bile ducts. Postoperative jaundice lasted for 15.5±3.3 days on average.

Group I included patients on enteral nutrition after surgery (n=30); Group II – patients on parenteral nutrition (n=31); and Group III – patients on mixed nutrition as a type of partial parenteral nutrition regimen (n=30).

At the first stage, the clinical condition of patients was assessed according to the SGA and NRI screening protocols before surgery and on Days 10 and 12 after surgery.

A comparative assessment of the clinical effectiveness of using types of nutritional support in a complex of therapeutic measures after the specified operations in the hepatopancreatoduodenal zone was carried out.

The main indicators of nutritional status were also assessed: body mass index (weight was measured before surgery, on Day 10 and Day 12), basal metabolic rate (calculated using the Harris-Benedict equation based on the patient's anthropometric data (gender, age, weight and height), laboratory indicators: blood lymphocytes, total protein, total bilirubin, ALT, AST levels, related to routine methods of assessing nutritional status [6, 7].

In each group of patients, nutritional support in the postoperative period was carried out from Day 2, based on the average calculated value of energy requirement of 35 kcal/kg, using highly concentrated glucose solutions (10%, 20%), which allowed achieving the required energy supply in the postoperative period without increasing the volume of daily volume support. 20% glucose solutions were administered from Day 3 till the transfer of patients to the specialized department. To assimilate separately administered glucose, short-acting insulin was used at the rate of 1 U of insulin per 4 grams of dry glucose [8-10].

Patients in the group with isolated enteral nutrition were given nutritional mixtures through a nasogastric tube at a rate of 25-35 ml/single administration in a total volume of 500-700 ml/day, with a subsequent increase in volume in the following days by 10-20%, provided that it was absorbed. The frequency of administration of the mixture varied depending on the clinical condition of the patients and the results of laboratory examination. In this case, the maximum rate of administration of the mixture did not exceed 125 ml/hour. Administration was carried out for 18-20 hours during the day, then a break was taken, usually at night.

Patients in the mixed feeding group received combined nutritional support parenterally from Day 2. Once intestinal peristalsis appeared, vomiting and severe gastrointestinal paresis were absent, and they were provided with oral or nasogastric tube feedings at the specified rate. In case of persistence of gastrointestinal paresis, the percentage of the enteral part was reduced in favor of parenteral dosing of plastic materials to ensure the required daily caloric intake [10, 12].

Methods of statistical data analysis

The quantitative and qualitative indicators obtained

during the study were analyzed using descriptive and analytical statistics. Pairwise comparisons of laboratory indicators were performed depending on the time of the survey using the Wilcoxon T-test, significance level α (taking into account the Bonferroni correction). The Friedman criterion was used to analyze repeated measurements.

The resulting level of statistical significance "P" characterized the compliance of the distribution with the normal law (if p>0.05, the distribution was considered to correspond to the normal distribution; if p≤0.05, the distribution was considered to not correspond to the normal distribution. The level of statistical significance was fixed at the error probability level of 0.05.

Results: The nutritional status of patients in all three groups before surgery and during Days 10-12 after surgery relative to the clinical scales for assessing nutritional status, SGA, and NRI was assessed as normal, moderate, and severe malnutrition (Figures 1-3).

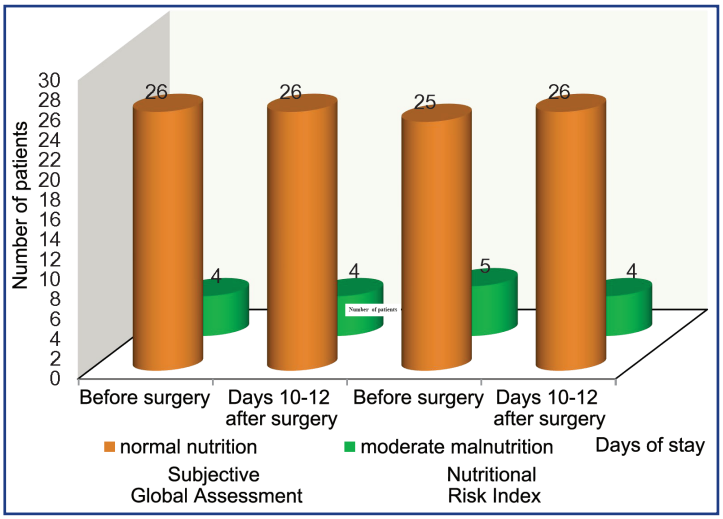

Figure 1 – Dynamics of nutritional status of patients in Group 1 with enteral support

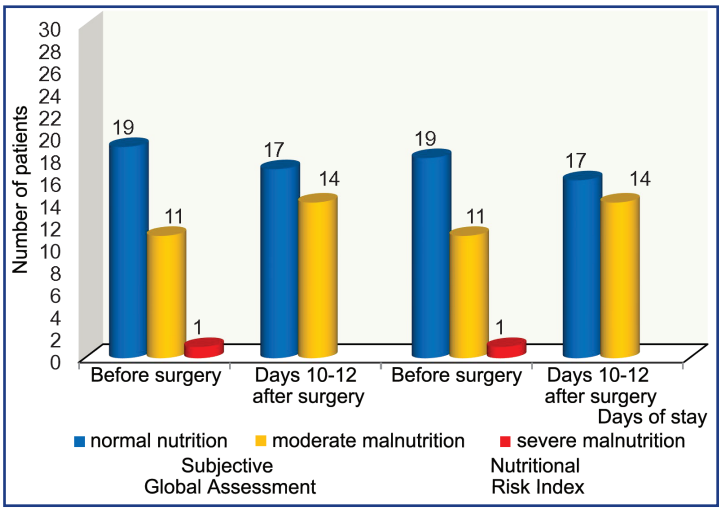

Figure 2 – Dynamics of nutritional status of patients in Group 2 with parenteral support

As can be seen from the data presented in Figures 1-3, in the preoperative period, according to the SGA scale, 24 patients of Group 1 (80%), 19 patients of Group 2 (61.3%) and 17 patients of Group 3 (56.7%) had a normal nutritional status before surgery compared to patients with "moderate" and "severe" malnutrition. The assessment of the nutritional status before surgery using the NRI scale made it possible to confirm the nutritional status in the overwhelming majority of patients in all groups (n=62) as relatively "normal" or true negative (normal) nutritional status [1, 2, 5]. True positive (moderate malnutrition) nutritional status was observed in 26 patients, and severe malnutrition in 3 patients. The NRI data in this period had a strong correlation with the SGA scale results (p<0.005).

On Days 10-12 after surgery, the results of the assessment according to the SGA scale remained unchanged in patients of Group 1; according to the NRI assessment scale, an increase in "moderate malnutrition" was noted per patient (3.3%).

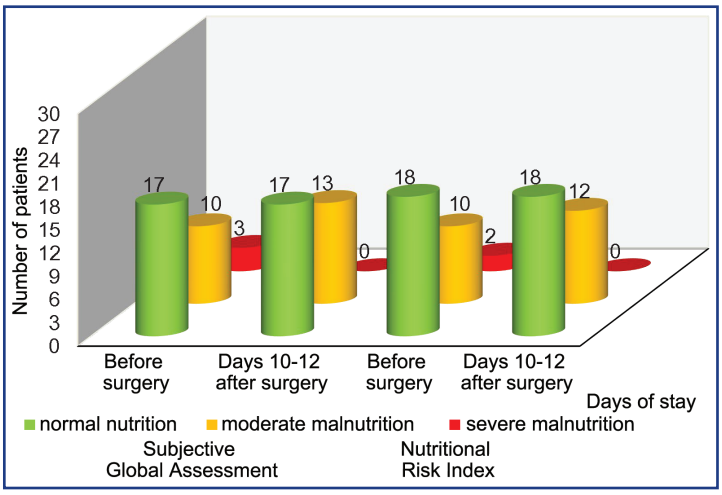

Figure 3 – Dynamics of nutritional status of patients in Group 3 with a mixed type of nutritional support

With parenteral nutritional support, 17 patients had "normal nutrition", 14 patients had "moderate malnutrition," with regression of "severe malnutrition" in 1 patient (3.2%). In the mixed nutrition group, there was a complete elimination of signs of "severe malnutrition" according to the given scales ($p<0.005$), but with an increase of 10% (SGA) and 6.7% (NRI) of patients with "moderate malnutrition".

In patients in the groups with enteral and parenteral nutrition, by the end of these types of energy supplementation (10-15 days), the level of basal metabolism was observed to approach its initial values – 2500.1±353.4 kcal/day and 2350.0±330.5 kcal/day, respectively, which indirectly confirmed the effectiveness of the types of nutritional support used.

With a mixed type of nutrition, a statistically significant approach of the basal metabolic rate to its initial values was noted at an earlier stage – by Days 6-8 after surgery (2250.0±105.2 kcal/day), which allows us to conclude that this option of nutritional support is more effective in covering the energy costs of patients in comparison with isolated types of nutrition ($p<0.03$) (Figure 4).

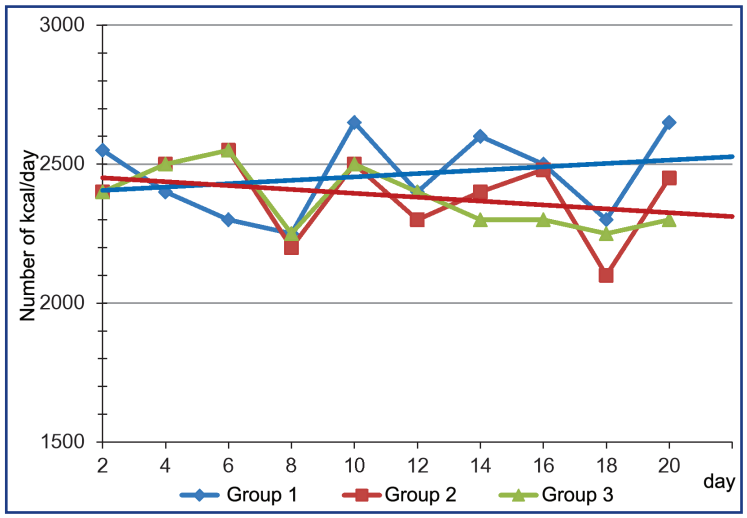

Figure 4 – Comparative analysis of the dynamics of the basal metabolic rate in patients of the three groups in the early postoperative period, kcal/day

The presented analysis of the dynamics of the basal metabolic rate in patients of three groups indicates an earlier detection of the compliance of the basal metabolic rate in patients with a mixed type of nutrition compared to the initial one, which may, in turn, indicate a faster "coverage" of the energy deficit in patients after surgery, despite the increased number of patients with "moderate malnutrition".

In this case, it can be argued that what is important is not so much the speed of covering the calculated value of the basal metabolism, but the target effectiveness of the type of nutrition used to eliminate nutritional deficiency.

Evaluation and subsequent analysis of the average results of laboratory examination in groups of patients in a comparative aspect showed a relatively slow and gradu-

al decrease in the level of total blood protein by Day 5 after surgery, on average, by 6.8±0.95% of the initial values, which, apparently, was due to increased catabolism and ongoing protein losses (exudation, drainage, etc.) with a fairly reliable increase by the end of nutritional support, on average by 8.47% of the initial values.

Thus, a statistically significant increase in the level of total blood protein was noted in the mixed nutrition group (p=0.004). In the groups with enteral and parenteral nutrition, differences in the dynamics of the level of total protein were found at the level of statistical tendency: p=0.108 and p=0.129, respectively (Table 1).

Table 1 – Laboratory parameters of blood tests by study groups

Laboratory indicators	Groups					
	Group 1 (n=30)		Group 2 (n=31)		Group 3 (n=30)	
	Before surgery	Days 10-12 after surgery	Before surgery	Days 10-12 after surgery	Before surgery	Days 10-12 after surgery
Total protein	52.2-62.4±6.2 g/l (M=55.6 g/l)	58.0-68.2±5.1 g/l (M=61.3 g/l)	53.8-61.4±4.2 g/l (M=57.3 g/l)	55.0-63.3±3.7 g/l	56.5-65.4±5.2 g/l (M=52.3 g/l)	60.0-70.2±4.2 g/l (M=58.7 g/l)
Lymphocytes	8.4-16.0±4.2% (M=11.2%)	16.1-23.5±4.2% (M=8.95%)	10.2-14.7±3.1% (M=8.95%)	11.6-19.4±4.3% (M=10.35%)	7.8-16.3±4.2% (M=15.4%)	12.4-23.7±4.0% (M=19.9%)
ALT and AsAT	78.2%	40.15%	81.6%	66.7%	72.6%	63.8%

When analyzing the change in the number of blood lymphocytes, it should be noted that before the operation, the relative level of blood lymphocytes in the three groups was significantly reduced (25.9±3.7%), but, given the methods and volumes of the operation, the stress of the cellular and humoral links of the immune system, the dynamics of their level was expressed in the form of a statistically significant increase in the level of lymphocytes in the postoperative period by Days 10-12 – a stable increase in the level of blood lymphocytes by Day 10 after surgery by 8.95% (p=0.000) in Group 1, 10.35% (p=0.003) in Group 2, and 10.91% (p=0.000) in Group 3.

A comparative analysis of the dynamics of the ALT and AST blood levels in the study groups on Days 10-12 after surgery revealed an initial excess of their normal values after surgery in some patients, by tens of times on Day 1, followed by a decrease.

In particular, the dynamics of blood transaminase levels in most patients of Group 1 (n=23, 78.2%) by Day 10 were expressed as a decrease in ALT (by 32.1%) and AST (by 40.15%) from the initial preoperative level.

The overwhelming majority of patients in Group 2 (81.6%, n=26) also showed a statistically significant decrease in the level of these blood transaminases, on average, by 72.2% by Day 5 and by 66.7% by Day 10 after surgery compared to the baseline.

With a mixed type of nutritional support, by Day 5 after surgery, the average statistically significant decrease in transaminases was, on average, up to 72.6% of the initial values (p=0.000), by Day 10, their level decreased to 63.8% of the previous value achieved on Day 5 (p=0.008).

Regarding the dynamics of the level of total bilirubin in the blood, it should be noted that its high values persisted during Day 1 after surgery, which was most likely due to temporary swelling of the bile ducts and difficulty in the outflow of bile into the intestinal lumen, which caused the total bilirubin in the blood to exceed the norm by more than 10 times (p=0.000).

On average, on Days 5-7, all study groups showed a 5-6-fold decrease in their level from the baseline, with a gradual decrease to normal values by Days 10-12, which persisted in some patients until their discharge (p=0.004).

In comparative quantitative equivalent, in patients of Group 1, a decrease in the level of total bilirubin was recorded, on average, by 12.7% only by Day 10 after surgery (p=0.187). In Group 2, the total bilirubin in blood decreased on average by 40.09% by Day 5 and by 45.0% by Day 10 from the baseline (preoperative period) (p=0.002).

Patients in the 3rd group showed a slower regression of this indicator: a decrease, on average, of 20.0% by Day 5 and 44.0% by Day 10 after surgery.

Discussion: Assessing the results of the study, in particular the dynamics of nutritional status according to the NRI and SGA scales, it can be noted that the most pronounced tendency to normalize nutritional status was observed with parenteral support. This was expressed in an increase in the number of patients with "moderate malnutrition" by an average of 9.7% (n=3) on both scales, which was associated with the complete elimination of severe nutritional deficiency, and not with an absolute increase in the number of patients with "moderate malnutrition".

Similar results in terms of stabilization of nutritional status were demonstrated by the group with a mixed type of nutrition, where an increase in the proportion of patients with "moderate malnutrition" by 10% and 6.7% on the scales was also noted, which is also associated with a complete regression of severe nutritional deficiency. In this group, despite the lack of a significant increase in patients with "moderate malnutrition", an improvement in laboratory parameters and a more rapid restoration of the basal metabolic rate were observed.

Patients receiving isolated enteral support demonstrated relatively better results according to the assessment scales. The increase in the number of patients with "moderate malnutrition" in the postoperative period was only 3.3% (n=1) according to the NRI scale. However, in comparison with other groups, this category did not

show complete elimination of moderate nutritional deficiency and the transition of patients to the category with "normal" nutritional status, which indicates the absence of pronounced dynamics of nutritional improvement in this group.

The results of this work, indicating the presence of nutritional deficiency in patients before surgery, are consistent with the studies of V. M. Khomyakov and A. D. Ermoshin (2015). Their work presents data on the use of nutritional status screening scales (NRS, SGA, and NRI) to assess the condition of cancer patients at the preoperative examination stage. This made it possible to promptly identify early signs of nutritional deficiency and develop recommendations for the initiation of early nutritional support aimed at reducing the risks of postoperative complications and accelerating the recovery of patients [1].

Confirmation of the presence of nutritional deficiency in patients with pancreatic cancer before surgery is also presented in the study by N. Bibby et al. (2023). Their work analyzed data from 137 patients who underwent surgery for the underlying disease. The results showed that in 62.3% of patients, malnutrition led to a weight loss of more than 5%, and in 29.2% of hospitalized patients, more than 10% of the initial weight over the past 6 months [5].

The improvement in nutritional status in the postoperative period noted in this study was achieved due to the nutritional methods used. According to their data, the average weight gain in patients was 1.8% over two weeks, with an overall improvement in weight of 7.9%. Similarly, in the study by N. Bibby, an increase in the Patient-Performing Subjective Global Assessment (PG-SGA) scale was observed by an average of 6.19% [5].

The dynamics of the restoration of the basal metabolic rate, as reflected in the trend analysis, show that with enteral and parenteral support, it reached the initial values only by Days 10-12 after surgery (2500.1±353.4 kcal/day and 2350.0±330.5 kcal/day, respectively). However, with the mixed type of nutritional support, the basal metabolic rate approached the initial value (2250.0±105.2 kcal/day) faster by Days 6-8 after surgery. This acceleration, however, was not accompanied by an earlier restoration of independent nutrition of patients and did not ensure the complete elimination of moderate nutritional deficiency. Instead, an increase in the number of patients with this type of nutritional status disorder was noted.

The correspondence between the level of the calculated basal metabolism and the "energy intensity" of the total nutritional subsidy with a mixed type of nutrition and isolated enteral support is probably due to the preservation or restoration of parietal digestion in the gastrointestinal tract in the early postoperative period, even in the presence of intestinal paresis of varying degrees.

The dynamics of protein metabolism showed that by the time patients were transferred from intensive care to a specialized department, the mixed type of nutritional support provided a more pronounced and statistically significant increase in the level of total blood protein.

The increase in the level of blood lymphocytes recorded in all groups can be considered as the body's response to surgical intervention, which probably indicates a positive effect of these changes on the immune status of patients.

An increase in the level of blood lymphocytes may indirectly indicate a positive effect on the immune status of patients when using all studied types of nutrition in the postoperative period in this contingent.

As for the dynamics of the level of transaminases and total bilirubin in the blood, statistically significant increases in the levels of ALT and AST, and, to a lesser extent, total bilirubin, are observed in patients of all three groups (n=91, 100%). These changes can be explained, first of all, by the surgical intervention itself and its volume, as well as by the underlying disease of the hepatopancreatoduodenal zone, which is associated with the development of cytolytic syndrome against the background of cholestasis.

Between Days 5-6 and Days 10-12 post-surgery, blood transaminase levels decreased. A strong direct correlation was observed between the total bilirubin level in the blood and the decrease in transaminase levels in patients across all groups. This is probably due to the creation of adequate intraoperative bile outflow due to drainage of the bile ducts and elimination of the cause of mechanical jaundice (tumor).

Although nutritional support had a certain effect on the dynamics (including the decrease) of serum transaminases and total blood bilirubin, surgical intervention also played a significant role in these changes. It contributed to the improvement of bile outflow, the elimination of mechanical jaundice (tumor removal), and a resulting decrease in the severity of cytolytic syndrome due to the surgical intervention.

The results of this study, aimed at targeted and early initiation of nutritional support in the considered group of patients, closely correlate with the results of the meta-analysis by F. Yang et al. (2018), taking into account the results of 2307 cases from 26 studies. This meta-analysis emphasizes the effectiveness of early initiation of nutritional support as a safe and manageable means of facilitating the recovery of patients in China. In particular, it contributes to a more rapid recovery of gastrointestinal motility and a reduction in the duration of postoperative hospital stay of patients [8].

Conclusion: 1. According to the NRI and SGA nutritional status assessment scales, parenteral and mixed nutrition throughout the study period demonstrated higher efficacy in stabilizing the clinical condition of patients and in reducing severe nutritional deficiency compared to the group receiving isolated enteral nutrition.

2. A mixed type of nutrition in the postoperative period in patients operated on for malignant neoplasms of the

hepatopancreatoduodenal zone, based on the totality of the dynamics of clinical and laboratory indicators, can be considered as an alternative method of isolated parenteral nutrition, mainly due to the complete regression of severe nutritional deficiency and the preservation of a higher percentage of patients with a "normal" nutritional status in the perioperative period.

3. Although the rate of restoration of the calculated level of basal metabolism approaches the initial values before surgery, this indicator, regardless of the type of nutritional support, cannot serve as a completely reliable criterion for the effectiveness of nutrition in the postoperative period, since there is no clear correlation between the dynamics of its values and the elimination of different degrees of nutritional deficiency.

In patients with malignant tumors of the hepatopancreatoduodenal zone, when there is an indication for nutritional support in the early postoperative period, it is necessary to assess the degree of nutritional status using the SGA and NRI screening scales. In signs of mild nutritional deficiency, one of the three methods of nutritional support is allowed: isolated enteral, isolated parenteral, or mixed nutrition, due to their statistically equivalent effect on the level of basal metabolism and laboratory test results. In cases of moderate and severe nutritional deficiency, it is recommended to use a mixed type of nutritional support, which promotes faster restoration of protein balance, a decrease in the value of basal metabolism, and, in this regard, a reduction in the duration of hospitalization.

It is recommended to begin nutritional support from Day 2 after surgery, regardless of the scope of the surgical intervention, the severity of the patient's condition in the preoperative period, and the degree of the initial nutritional status, to avoid worsening nutritional deficiency.

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АҢДАТПА

ГЕПАТОПАНКРЕАТОДУОДЕНАЛЬДЫ ІСІКТЕРІ БАР НАУҚАСТАРДЫ ТАҒАМДЫҚ ҚАМТАМАСЫЗ ЕТУ: ОПЕРАЦИЯДАН КЕЙІНГІ КЕЗЕҢДЕГІ ҚАРҚЫНДЫ ТЕРАПИЯНЫҢ НЕГІЗГІ ЭЛЕМЕНТІ

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Өзектілігі: *Гепатопанкреатодуоденальды аймақтың қатерлі ісіктерінен туындайтын асқынулардың тиімді қарқынды терапиясы өзекті мәселе болып қала береді. Ол энергия тапшылығын жоюға, дене салмағын қалпына келтіруге және ауыр гиперкатаболизмнің нәтижесінде бұзылған пластикалық процестерді қалыпқа келтіруге, ағзаның қоректік заттарға қажеттілігін арттыруға және интоксикация синдромын дамытуға бағытталған, әсіресе операциядан кейінгі кезеңде.*

Мақсаты: *Операциядан кейінгі ерте кезеңде гепатопанкреатодуоденальды аймақтың ісіктері бар науқастарда тамақтануды қамтамасыз етудің негізгі аспектілерін зерттеу.*

Әдістері: *Зерттеу гепатопанкреатодуоденальды аймақтың қатерлі ісіктері бар 18 жастан асқан 91 науқаста жүргізілді. Науқастар тағамдық қолдау түріне байланысты үш топқа бөлінді. Зерттеу скрининг нәтижелерін, дене салмағының индексін, базальды метаболизм жылдамдығын және негізгі зертханалық көрсеткіштерді қоса алғанда, тамақтану күйінің көрсеткіштерін бағалады: қандағы лимфоциттердің деңгейі, жалпы ақуыз, жалпы билирубин және ALT және AST белсенділігі.*

Нәтижелері: *Қолданылған скринингтік хаттамаларға сәйкес парентеральді тамақтануды қолдау кезінде 10-12-ші күндері 17 науқаста «қалыпты» тамақтану күйі сақталды, 14 науқаста 1 науқаста (3,2%) «ауыр жеткіліксіз тамақтану» регрессиясымен «орташа тамақтанбау» болды. Аралас тамақтандыру тобында операциядан кейінгі кезеңнің 10-12-ші күндерінде белгілердің толық жойылуымен SGA және NRI шкалалары бойынша «орташа тамақтанбауы» бар науқастардың сәйкесінше 10% және 6,7% артуы байқалды. Берілген тамақтануды бағалау шкаласына сәйкес «ауыр жеткіліксіз тамақтану» (p<0,005).*

Қорытынды: *Оқшауланған парентеральді тамақтану тобында пациенттердің тамақтану жағдайын тұрақтандыру және сақтауда жеткілікті тиімділікке қол жеткізілді, бұл «орташа» және «қалыпты» тамақтану жағдайы бар пациенттер санының өсуімен көрінді, сондай-ақ ауыр және орташа тамақтану тапшылығы бар науқастар санының төмендеуі.*

Тамақтануды қолдаудың аралас түрі, өз кезегінде, парентеральды тамақтанудың перспективті баламасы ретінде қарастырылуы мүмкін, өйткені осы топтағы пациенттердің тамақтану жағдайының көрсеткіштері парентеральды терапия нәтижелеріне статистикалық түрде ұқсас болды.

Түйінді сөздер: *тамақтану жағдайы, тағамдық жетіспеушілік, тағамдық қамтамасыз ету, жүту, онкология, тамақтану, гепатопанкреатодуоденальды аймақтың ісіктері.*

АННОТАЦИЯ

НУТРИЦИОННАЯ ПОДДЕРЖКА ПАЦИЕНТОВ С ОПУХОЛЯМИ ГЕПАТОПАНКРЕАТОДУОДЕНАЛЬНОЙ ЗОНЫ: КЛЮЧЕВОЙ ЭЛЕМЕНТ ИНТЕНСИВНОЙ ТЕРАПИИ В ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ

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Актуальность: *Эффективная интенсивная терапия осложнений, возникающих при злокачественных новообразованиях гепатопанкреатодуоденальной области, остается актуальной задачей. Она направлена на устранение энергодефицита, восстановление массы тела и нормализацию пластических процессов, которые нарушаются в результате выраженного гиперкатаболизма, повышенных потребностей организма в питательных веществах и развития интоксикационного синдрома, особенно в послеоперационном периоде.*

Цель исследования *– улучшение нутриционного статуса онкологических больных после операций на гепатопанкреатодуоденальной зоне за счёт изучения и сравнения эффективности изолированной энтеральной, парентеральной и смешанной нутриционной терапии в ранний послеоперационный период.*

Методы: *В исследовании участвовал 91 пациент старше 18 лет с злокачественными опухолями гепатопанкреатодуоденальной зоны. Пациенты были разделены на три группы в зависимости от типа нутриционной поддержки. В рамках исследования была проведена оценка показателей нутриционного статуса, включая результаты скрининга, индекс массы тела, величину основного обмена, а также ключевые лабораторные показатели: уровень лимфоцитов в крови, общего белка, общего билирубина, а также активности АлАТ и АсАТ.*

Результаты: *При парентеральной нутриционной поддержке согласно используемым скрининг-протоколам к 10-12 суткам 17 пациентов сохраняли «нормальный» нутриционный статус, 14 пациентов – «умеренное недоедание» при регрессе «тяжелого недоедания» у 1 пациента (3,2%). В группе смешанного питания к 10-12 суткам послеоперационного периода наблюдалось увеличение числа пациентов со статусом «умеренное недоедание» по шкалам SGA и NRI на 10% и 6,7%, соответственно, при полной ликвидации признаков «тяжелого недоедания» по указанным шкалам (p<0,005).*

Заключение: *В группе с изолированным парентеральным питанием была достигнута достаточная эффективность в стабилизации и поддержании нутриционного статуса пациентов, что проявилось в увеличении числа пациентов с «умеренным» и «нормальным» нутриционным статусом, а также сокращении количества больных с тяжелой и умеренной нутриционной недостаточностью. Смешанный тип нутриционной поддержки, в свою очередь, может рассматриваться как перспективная альтернатива парентеральному питанию, поскольку показатели нутриционного статуса пациентов, достигнутые в данной группе, оказались статистически схожими с результатами парентеральной терапии.*

Ключевые слова: *пищевой статус, нутриционная недостаточность, нутриционная поддержка, онкология, питание, опухоли гепатопанкреатодуоденальной зоны.*

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BRCA-NEGATIVE HIGH-GRADE SEROUS OVARIAN CANCER WITH RECURRENT PROGRESSION: A CLINICAL CASE

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ABSTRACT

Relevance: *High-grade serous ovarian cancer (HGSOC) is characterized by pronounced genomic instability, frequent mutations in BRCA1/2 genes, and high clinical and molecular heterogeneity. In some patients, the disease is accompanied by a homologous recombination deficiency (HRD), which causes sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. However, the efficacy of these drugs remains limited in BRCA wild-type patients.*

This study aimed to *analyze and describe a clinical case of BRCA-negative serous ovarian cancer complicated by multiple progressions and the formation of drug resistance.*

Methods: *This study presents a clinical case of a patient with a common form of HGSOC, without mutations in BRCA1/2 genes but with a moderately positive HRD status. Molecular genetic analysis was performed by next-generation sequencing using the Foundation Medicine platform. The effectiveness of the treatment was assessed through positron emission tomography combined with computed tomography, magnetic resonance imaging, and computed tomography, alongside serial measurements of the CA-125 tumor marker.*

Results: *The patient underwent cytoreductive surgery followed by five successive lines of chemotherapy, including platinum-based regimens, bevacizumab, liposomal doxorubicin, gemcitabine, and olaparib as a PARP inhibitor. Although transient partial responses were achieved, the disease subsequently progressed. Molecular genetic analysis confirmed the absence of BRCA1/2 mutations and revealed an HRD score of 20.1%, indicative of limited sensitivity to PARP inhibition. As the patient's general condition declined, a transition to palliative care was initiated in February 2025. The patient passed away in March 2025.*

Conclusions: *The presented case highlights the limited therapeutic possibilities in BRCA-negative HGSOC with moderate HRD status and demonstrates the need to develop new personalized treatment strategies in patients with an unfavorable molecular profile.*

Keywords: *high-grade serous ovarian cancer (HGSOC), BRCA-negative status, homologous recombination deficiency (HRD), PARP inhibitors, clinical case, chemotherapy, molecular profiling.*

Introduction: High-grade serous ovarian carcinoma (HGSOC) is the most common and aggressive histological subtype of epithelial ovarian cancer. This disease is characterized by pronounced genomic instability, a high frequency of somatic and germinal mutations, impaired *DNA* repair mechanisms, and activation of cellular stress signaling pathways. In most cases, the tumor develops against the background of molecular disorders in the TP53, *BRCA1/2 genes,* or other elements of the homologous recombination system. HGSOC is clinically characterized by an aggressive course, early intraperitoneal dissemination, and pronounced histological and molecular heterogeneity, complicating treatment response prediction and necessitating a personalized therapeutic approach [1, 2]. According to the international cancer registries, the median 5-year survival rate in patients with advanced HGSOC does not exceed 27%. This is significantly lower than in low-grade or early-stage tumors, where the survival rate can reach 70-90%. The main reasons for such unfavorable outcomes are late diagnosis, pronounced heterogeneity of the tumor, a tendency to rapid intraperitoneal spread, and the development of chemoresistance after the first courses of therapy [3,4]. According to molecular genetic studies, about 30-35% of HGSOCS are associated with disorders in the BRCA1 or BRCA2 genes, including germinal and somatic mutations and epigenetic inactivation, such as hypermethylation of promoter regions. These molecular defects lead to homologous recombination deficiency (HRD), forming the so-called HRD phenotype [5]. HRD is a central mechanism underlying genomic instability in epithelial ovarian cancer. It is associated with impaired high-precision repair of double-stranded DNA breaks. According to current molecular studies, signs of HRD are detected in approximately 50% of patients with HGSOC. This phenotype forms the therapeutic vulnerability of the tumor to poly (ADP-ribose) polymerase (PARP) inhibitors, whose action is based on the principle of synthetic lethality. In this regard, determining the HRD status is of key importance for choosing personalized therapy and evaluating the potential effectiveness of PARP inhibitors in this category of patients [6-8]. Poly inhibitors (ADP-ribose) polymerases (PARP) were initially developed as a maintenance therapy for patients with recurrent ovarian cancer who have achieved a complete or partial response to repeated chemotherapy with platinum preparations. Their clinical efficacy was convincingly demonstrated in three large, randomized phase III trials –

NOVA (ENGOT-OV16), SOLO-2 (ENGOT-OV21), and ARIEL3 – where there was a significant improvement in progression-free survival (PFS) compared to placebo. The results of these studies led to the approval of niraparib, olaparib, and rukaparib as maintenance therapy for recurrent platinum-sensitive ovarian cancer, regardless of the presence of mutations in *BRCA1/2* or other biomarkers. This expanded the indications for using PARP inhibitors and confirmed their role as one of the key components of a personalized approach to treating recurrent tumors [9, 10].

This study aimed to analyze and describe a clinical case of *BRCA*-negative serous ovarian cancer complicated by multiple progressions and the formation of drug resistance.

Materials and methods: This paper presents a clinical case of a patient with a common form of HGSOC under observation at the Almaty Cancer Center. An integrated approach was used to assess the molecular and immunohistochemical profile of the tumor.

A next-generation molecular genetic sequencing (NGS) study was performed in Foundation Medicine Inc.'s (USA) laboratory to assess the mutation status. The test evaluated mutations in the BRCA1/2 genes and the level of genomic instability (HRD), which revealed the absence of BRCA mutations and the HRD status of 20.1%.

An immunohistochemical study of the tumor tissue was performed using antibodies to the WT1, PAX8, p53, p16, Ki-67 markers, estrogen and progesterone receptors (ER/PR), and the folate α receptor. The study was performed on the VENTANA BenchMark ULTRA (Roche) platform using the BN3.2 monoclonal antibody (Novocastra/Leica). Mutation-specific overexpression of p53 and Ki-67 at 30% and moderate and strong expression of folate receptor α in 35% of tumor cells were found. Expression of ER and PR was absent.

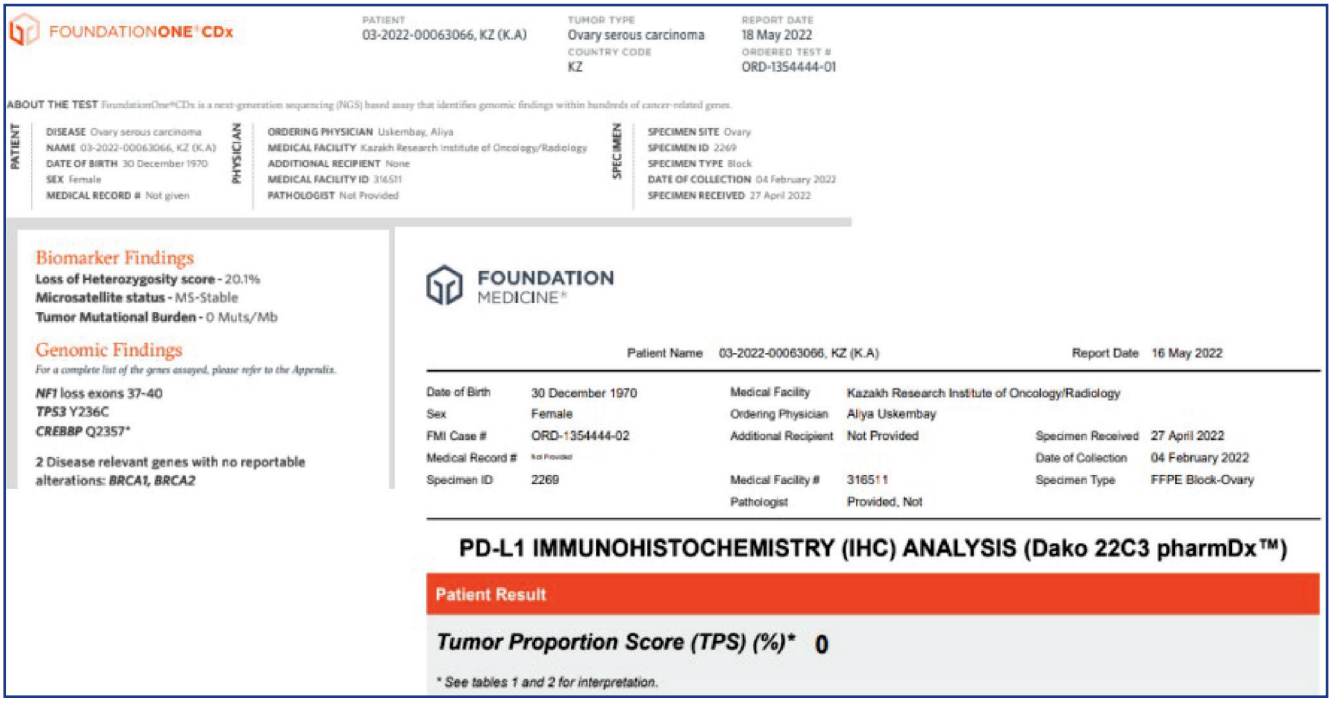
In contrast to the clinical case described in our previous article [11], which documented a rare *BRCA1* mutation *(p.181T>G; p.Cys61Gly)* associated with prolonged tumor stabilization exceeding three years, this patient had no *BRCA1/2* mutations and an HRD score of 20.1%, indicating limited expected benefit from PARP inhibitor therapy. Variations in the molecular profile proved to be critical determinants in selecting therapeutic strategies, prognostication of treatment response, and prediction of disease trajectory. Disease progression and therapeutic response were dynamically monitored through serial imaging studies, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography/computed tomography (PET/CT), complemented by sequential measurements of serum CA-125 levels.

Clinical case:

Patient Information: Patient A. was 42 years old at the diagnosis. She presented in February 2022 with clinical signs necessitating immediate surgical intervention. Primary cytoreductive surgery was performed with an extensive surgical approach, including total abdominal hysterectomy with bilateral salpingo-oophorectomy, resection of the round ligament of the liver, excision of a tumor mass from the left paracolic gutter, total omentectomy, and pelvic and para-aortic lymph node dissection. Histological analysis confirmed HGSOC, FIGO stage IIIC (pT3C pN1c M0).

Between March and June 2022, the patient received six cycles of chemotherapy consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m^2), administered intravenously every 21 days. A favorable treatment response was observed, as evidenced by a decline in the CA-125 tumor marker level to 32 U/mL by July 2022.

In June 2022, the tumor molecular genetic profiling was done by NGS using Foundation Medicine Inc. USA). No pathogenic variants were identified in the *BRCA1/2 genes*, indicating a *BRCA wild-type status*. The HRD score of 20.1% evidenced moderate genomic instability and suggested limited sensitivity to PARP inhibitor therapy (Figure 1).


FOUNDATIONONE CDx

PATIENT 03-2022-00063066, KZ (K.A)
TUMOR TYPE Ovary serous carcinoma
COUNTRY CODE KZ
REPORT DATE 18 May 2022
ORDERED TEST # ORD-1354444-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Ovary serous carcinoma
NAME 03-2022-00063066, KZ (K.A)
DATE OF BIRTH 30 December 1970
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN
ORDERING PHYSICIAN Uskembay, Aliya
MEDICAL FACILITY Kazakh Research Institute of Oncology/Radiology
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 316511
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Ovary
SPECIMEN ID 2269
SPECIMEN TYPE Block
DATE OF COLLECTION 04 February 2022
SPECIMEN RECEIVED 27 April 2022

Biomarker Findings
Loss of Heterozygosity score - 20.1%
Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.
NF1 loss exons 37-40
TP53 Y236C
CREBBP Q2357*

2 Disease relevant genes with no reportable alterations: *BRCA1, BRCA2*

FOUNDATION MEDICINE

Patient Name 03-2022-00063066, KZ (K.A) Report Date 16 May 2022

Date of Birth	30 December 1970	Medical Facility	Kazakh Research Institute of Oncology/Radiology		
Sex	Female	Ordering Physician	Aliya Uskembay		
FMI Case #	ORD-1354444-02	Additional Recipient	Not Provided	Specimen Received	27 April 2022
Medical Record #	Not Provided			Date of Collection	04 February 2022
Specimen ID	2269	Medical Facility #	316511	Specimen Type	FFPE Block-Ovary
		Pathologist	Provided, Not		

PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)

Patient Result

*Tumor Proportion Score (TPS) (%)** 0

* See tables 1 and 2 for interpretation.

Figure 1 – Molecular genetic and immunohistochemical analysis was performed using next-generation sequencing (FoundationOne® CDx, Foundation Medicine, Cambridge, USA)

An immunohistochemical study of the tumor was also performed at the Charité University Hospital (Berlin, Germany). Mutational type of p53 expression, Ki-67 proliferative activity index at the level of 30%, expression of folate receptor α in 35% of tumor cells, and negative expression of hormone receptors ER and PR were found.

To evaluate the disease extent, a PET/CT scan performed in February 2022 revealed increased metabolic activity in the mesenteric lymph nodes (SUVmax 3.8–6.1). Follow-up imaging in November 2022 showed no evidence of disease recurrence (Figure 2).

In December 2022, the clinical case was reviewed during a multidisciplinary consultation at the Kazakh Institute of Oncology and Radiology, with the participation of specialists from Charité University Hospital. Considering the absence of disease recurrence on the PET/CT scan from November 2022 and a platinum-free interval exceeding six months, the patient was classified as platinum-sensitive. Based on the results of the discussion, repeated platinum-containing chemotherapy in combination with bevacizumab is recommended, followed by the appointment of a PARP inhibitor when the disease stabilizes.

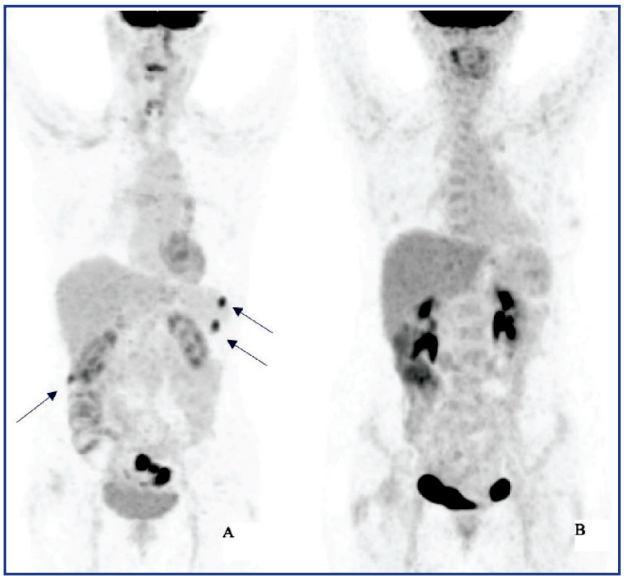


Figure 2 – PET/CT scan: A – an increased metabolic activity in the abdominal lymph nodes (arrows), consistent with active disease (February 2022); B – a marked reduction in metabolic activity of previously hypermetabolic lymph nodes (November 2022)

From April to September 2023, the patient underwent six cycles of second-line chemotherapy consisting of carboplatin (AUC 5), paclitaxel (175 mg/m^2), and bevacizumab (15 mg/kg), administered intravenously every 21 days. The treatment was well tolerated. A positive treatment response was observed, reducing the CA-125 tumor marker level from 115 to 48 U/mL. Follow-up PET/CT imaging in August 2023 demonstrated decreased metabolic activity in the previously affected lymph nodes, consistent with a partial metabolic response (Figure 3).

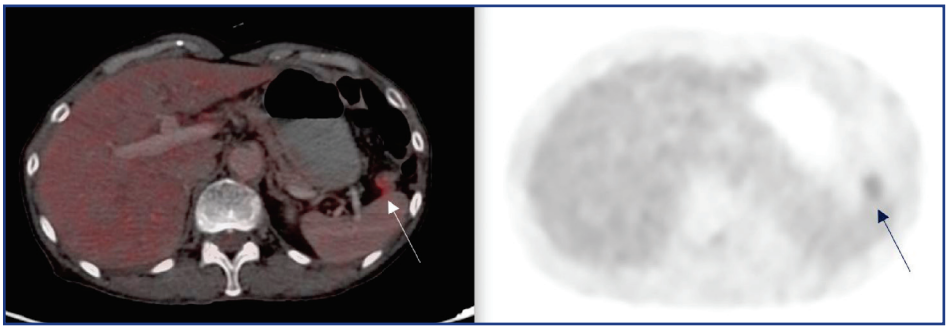


Figure 3 – A PET/CT scan from August 2023: reduced metabolic activity in the affected lymph nodes (arrows) indicates a favorable response to second-line chemotherapy

From October 2023 to February 2024, the patient received maintenance therapy with olaparib at a dose of 300 mg twice daily. This regimen was initiated following a favorable response to second-line treatment and was in alignment with international guidelines for the use of PARP inhibitors in patients with platinum-sensitive disease despite the absence of *BRCA* mutations. However, in March 2024, both biochemical and radiological evidence of disease progression was observed: CA-125 levels increased to 151 U/mL, and PET/CT imaging revealed new metabolically active lesions in the cervical, mediastinal, para-aortic, mesenteric, and paracaval lymph nodes, as well as radiophar-

maceutical uptake in the skin of the neck and the anterior abdominal wall (Figure 4).

From April to June 2024, the patient received chemotherapy consisting of paclitaxel at a dose of 160 mg administered intravenously on days 1, 8, and 15 of each 21-day cycle, in combination with bevacizumab 15 mg/kg every 21 days. A total of three cycles were completed. During treatment, the patient developed grade 2 leukopenia. A PET/CT scan performed in July 2024 revealed signs of peritoneal carcinomatosis, ascites, and enlargement of the mesenteric and para-aortic lymph nodes, along with cystic lesions in the liver suspected to be of metastatic origin.

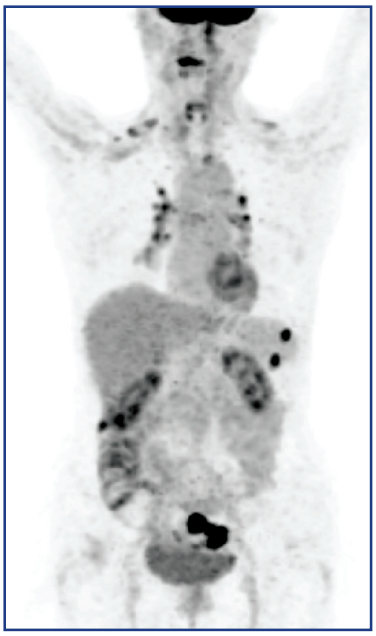


Figure 4 – PET/CT image: New metabolically active lesions in the lymph nodes, the skin of the neck, and the abdominal wall

From July to October 2024, the patient received sequential chemotherapy with continued use of bevacizumab. Two cycles of liposomal doxorubicin (40 mg/m2 intravenously) with bevacizumab (15 mg/kg) were initially administered. Due to the absence of clinical or biochemical improvement, the treatment regimen was modified to include three cycles of gemcitabine (1000 mg/m^2 on days 1 and 8 of each 21-day cycle), again combined with bevacizumab at the same dosage. Despite these interventions, no objective treatment response was achieved. PET/CT and MRI scans performed in October 2024 revealed multiple metastatic lesions in the liver and peritoneum (Figure 5), as well as bilateral pleural effusions.

A CT scan performed in February 2025 confirmed intestinal obstruction, multiple hepatic metastases, and bilateral pleural effusions. Due to progressive clinical deterioration, the patient underwent laparotomy, followed by a relaparotomy with gastrostomy and cecostomy. At that time, the CA-125 level exceeded 1100 U/mL, and the patient's performance status was assessed as ECOG 3. In light of the lack of therapeutic response, the extensive progression of the disease, and the overall decline in clinical condition, a decision was made in February 2025 to transition the patient to palliative care. Despite supportive measures, the patient succumbed to disease progression in March 2025.

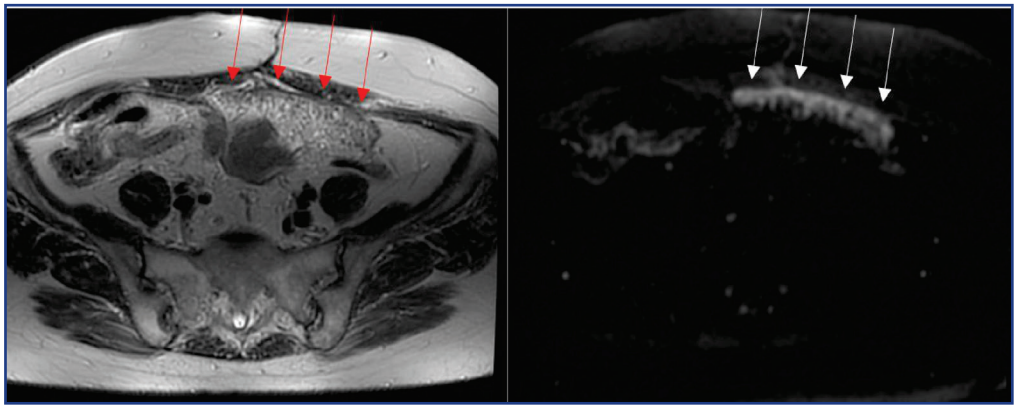


Figure 5 – Axial pelvic MRI: Signs of peritoneal carcinomatosis. The T2-weighted image (left) and diffusion-weighted image (right) reveal irregular thickening and nodularity along the peritoneal surfaces (arrows), consistent with metastatic peritoneal involvement

Results: The patient underwent complex treatment, including cytoreductive surgery, five lines of chemotherapy, targeted therapy, and maintenance treatment with a PARP inhibitor. After the first line of chemotherapy, partial remission was achieved with a biochemical decrease in CA-125 levels to 32 U/ml. PET/CT from November 2022 showed no signs of relapse. Considering the platinum sensitivity (over more than 6 months), repeated platinum-containing chemotherapy in combination with bevacizumab was started in April 2023. At the end of six cycles, partial metabolic remission was achieved, and the CA-125 level decreased to 48 U/ml. Since October 2023, maintenance therapy with olaparib was performed, but by March 2024, biochemical and visual progression was recorded: an increase in CA-125 to 151 U/ml and the detection of active metastatic lymph nodes. Due to documented disease progression, treatment with weekly paclitaxel in combination with bevacizumab was initiated between April and June 2024. However, follow-up PET/CT imaging revealed continued disease spread. Subsequent chemotherapy regimens incorporating liposomal doxorubicin and gemcitabine likewise failed to elicit an objective response. Trends in CA-125 levels throughout treatment, showing initial response followed by progressive elevation during later lines of therapy and transition to palliative care (Figure 6), and PET/CT imaging from October 2024 demonstrated multiple metastatic lesions. NGS revealed no pathogenic mutations in *BRCA1/2* and HRD score of 20.1%, indicative of moderate genomic instability and limited expected benefit from PARP inhibitor therapy. Due to disease progression and functional decline (ECOG performance status 3), the patient was transitioned to palliative care in February 2025. A fatal outcome was recorded in March 2025 (Table 1).

The timeline of this clinical case is provided in Table 1.

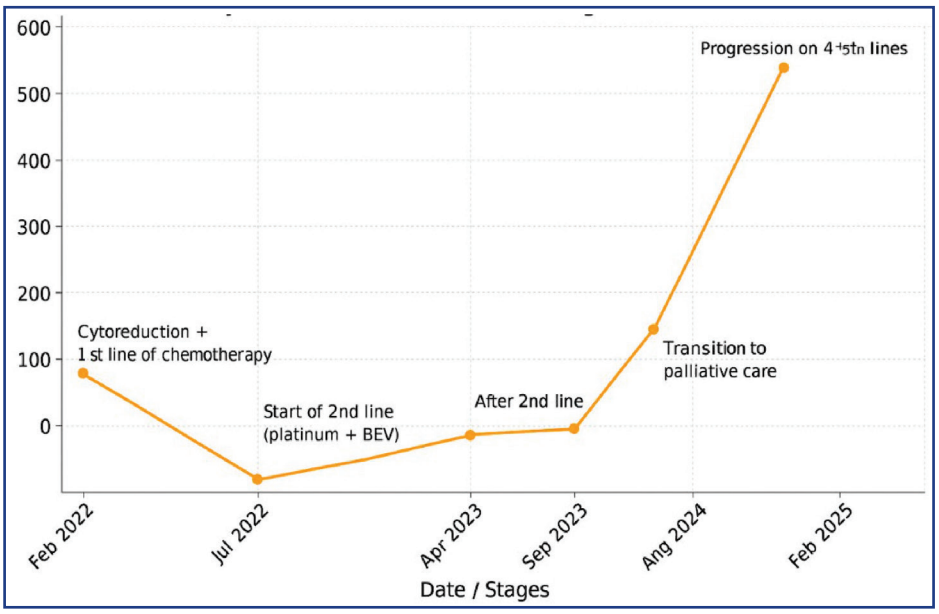


Figure 6 – Changes in CA-125 levels during treatment

Table 1 – Timeline of the clinical case of *BRCA*-negative serous ovarian cancer with multiple progressions and drug resistance

Date	Event
February 2022	Initial presentation and primary cytoreductive surgery. Diagnosis: HGSOC, FIGO IIIC.
March - June 2022	First-line chemotherapy (carboplatin + paclitaxel), favorable response (CA-125 decrease to 32 U/mL).
June 2022	NGS: BRCA-negative, HRD 20.1% confirmed.
November 2022	PET/CT: No signs of recurrence.
April - September 2023	Second-line chemotherapy (carboplatin + paclitaxel + bevacizumab): partial metabolic response, CA-125 decreased to 48 U/mL.
October 2023 - February 2024	Maintenance therapy with olaparib.
March 2024	A progression was detected: CA-125 increased to 151 U/mL; new metastatic lesions on PET/CT.
April - June 2024	Third-line chemotherapy (weekly paclitaxel + bevacizumab): the progression continued.
July - October 2024	Fourth-line chemotherapy: liposomal doxorubicin + bevacizumab; switch to gemcitabine + bevacizumab; no response.
October 2024	MRI and PET/CT: Liver metastases, peritoneal carcinomatosis, pleural effusion.
February 2025	Intestinal obstruction: palliative surgeries (gastrostomy, cecostomy); ECOG 3; transition to palliative care.
March 2025	Patient deceased.

Discussion: The presented clinical case illustrates the course of FIGO IIIC HGSOC in a *BRCA-negative* patient with moderate genomic instability. Despite complete cytoreductive surgery, two consecutive platinum regimens, targeted therapy with bevacizumab, and maintenance treatment with olaparib, the disease was char-

acterized by a progressive and resistant course [12]. In contrast to the clinical case presented in a previously published paper [11], where the detection of a rare *BRCA1 gene* mutation (p.181T>G; p. Cys61Gly) allowed us to achieve long-term stabilization of the tumor process for more than three years on the background of PARP-inhibitor therapy; in our case, the molecular profile was different [13].

The patient had no mutations in the BRCA1/2 genes, and the HRD level was 20.1%, indicating a limited sensitivity to PARP inhibitors. Despite similar maintenance therapy with olaparib, the effect was short-lived, and disease progression was recorded [14]. This highlights the importance of molecular profiling in the early management of patients with epithelial ovarian tumors. In addition, high p53 expression, absence of ER/PR receptors, and moderate folate α receptor expression (35%) reflect the aggressive molecular phenotype of the tumor.

Repeated changes in chemotherapy regimens, including liposomal doxorubicin, gemcitabine, and weekly paclitaxel, did not provide a stable response. These lines' lack of clinical efficacy highlights the limitations of available treatment strategies in patients with an unfavorable molecular profile. In conditions of aggressive course and cumulative toxicity, timely transition to palliative care plays a key role.

Conclusions: The presented clinical case of HGDOC, FIGO stage IIIC, in a *BRCA-negative* patient with moderate genomic instability (an HRD score of 20.1%) illustrates an aggressive disease course with limited response to multi-line therapy. Despite optimal primary cytoreduction, sequential platinum-based chemotherapy, and targeted antiangiogenic therapy, the patient experienced recurrent relapses and multiple episodes of disease progression. The absence of *BRCA1/2 mutations* and a borderline HRD score likely contributed to reduced sensitivity to PARP inhibition and the lack of durable treatment response. This case highlights the urgent need to develop novel individualized treatment strategies and identify additional therapeutic targets in patients with unfavorable molecular profiles. Emphasis should be placed on early detection of resistance predictors and the implementation of truly personalized oncologic care tailored to the genetic and phenotypic characteristics of the tumor.

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АҢДАТПА

BRCA-ТЕРІС АНАЛЫҚ БЕЗДІҢ ЖОҒАРЫ ДӘРЕЖЕЛІ СЕРОЗДЫ ҚАТЕРЛІ ІСІГІ, ҚАЙТАЛАНАТЫН ҮДЕУІ: КЛИНИКАЛЫҚ ЖАҒДАЙДЫ

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Өзектілігі: *Аналық бездің жоғары дәрежелі серозды қатерлі ісігі (HGSOC) айқын геномдық тұрақсыздықпен, BRCA1/2 гендеріндегі жиі мутациялармен және жоғары клиникалық және молекулалық гетерогенділікпен сипатталады. Кейбір науқастарда ауру гомологиялық рекомбинацияның (HRD) жетіспеушілігімен бірге жүреді, бұл PARP ингибиторларына сезімталдықты тудырады. Алайда, Бұл препараттардың BRCA-жабайы түрі ісіктердегі тиімділігі шектеулі болып қалады.*

Зерттеу мақсаты *– бірнеше үдеумен және дәріге төзімділіктің қалыптасуымен асқынған BRCA-теріс аналық бездің серозды қатерлі ісігі бар науқасты емдеудің клиникалық жағдайын талдау және сипаттау.*

Әдістер: *Бұл зерттеу BRCA1/2 гендерінде мутациясы жоқ, бірақ орташа оң HRD мәртебесі бар HGSOC жалпы формасы бар науқастың клиникалық жағдайын ұсынады. Молекулалық-генетикалық талдау Foundation Medicine платформасында келесі ұрпақ секвенциясы арқылы жүргізілді. Емдеудің тиімділігі CA-125 ісік маркерін сериялық өлшеумен қатар компьютерлік томографиямен біріктірілген позитронды-эмиссиялық томография, магниттi резонансты томография және компьютерлік томография арқылы бағаланды.*

Нәтижелері: *Науқас циторедуктивті операциядан өтті, содан кейін платина негізіндегі режимдерді, бевацизумабты, липосомалық доксорубицинді, гемцитабинді және поли(АДФ-рибоза) полимераза (ПАРП) ингибиторлары олапарибті қоса алғанда, химиотерапияның қатарынан бес бағыты жүргізілді. Өтпелі ішінара реакцияларға қол жеткізілгенімен, кейіннен ауру асқынып кетті. Молекулалық-генетикалық талдау BRCA1/2 мутацияларының жоқтығын растады және HRD 20,1% көрсеткішін анықтады, Бұл ПАРП тежелуіне шектеулі сезімталдықты көрсетеді. Науқастың жалпы жағдайы нашарлағандықтан, 2025 жылдың ақпанында паллиативтік көмекке көшу басталды. Науқас 2025 жылдың наурыз айында қайтыс болды.*

Қорытынды: *Ұсынылған жағдай орташа HRD мәртебесі бар BRCA-теріс HGSOC препараттарының шектеулі емдік мүмкіндіктерін көрсетеді және қолайсыз молекулалық профилі бар науқастарды емдеудің жаңа жекелендірілген стратегияларын әзірлеу қажеттілігін көрсетеді.*

Түйін сөздер: *аналық бездің жоғары дәрежелі серозды қатерлі ісігі (HGSOC), BRCA-теріс статусы, гомологиялық рекомбинация тапшылығы (HRD), ПАРП ингибиторлары, клиникалық жағдайы, химиотерапия, молекулалық профильдеу.*

АННОТАЦИЯ

BRCA-НЕГАТИВНЫЙ СЕРОЗНЫЙ РАК ЯИЧНИКОВ ВЫСОКОЙ СТЕПЕНИ ЗЛОКАЧЕСТВЕННОСТИ С РЕЦИДИВИРУЮЩИМ ПРОГРЕССИРОВАНИЕМ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Серозный рак яичников высокой степени злокачественности (high-grade serous ovarian cancer, HGSOC) характеризуется выраженной нестабильностью генома, частыми мутациями в генах BRCA1/2 и высокой клинической и молекулярной гетерогенностью. У некоторых пациентов заболевание сопровождается дефицитом гомологичной рекомбинации (homologous recombination deficiency, HRD), что обуславливает чувствительность к ингибиторам поли(АДФ-рибозо)полимеразы (ПАРП). Однако эффективность этих препаратов при BRCA дикого типа остается ограниченной.*

Цель исследования *– проанализировать и описать клинический случай лечения пациентки с BRCA-негативным серозным раком яичников, осложненным множественными прогрессиями и формированием лекарственной устойчивости.*

Методы: *В данной публикации представлен клинический случай пациента с распространенной формой HGSOC, без мутаций в генах BRCA1/2, но с умеренно положительным статусом HRD. Молекулярно-генетический анализ проводился с использованием секвенирования нового поколения на платформе Foundation Medicine. Эффективность лечения оценивалась с помощью позитронно-эмиссионной томографии в сочетании с компьютерной томографией, магнитно-резонансной томографии, компьютерной томографии, а также последовательных измерений опухолевого маркера CA-125.*

Результаты: *Пациентке была проведена циторедуктивная операция, за которой последовали пять последовательных курсов химиотерапии, включая схемы на основе платины, бевацизумаб, липосомальный доксорубицин, гемцитабин и ингибитор ПАРП олапариб. Хотя были достигнуты временные частичные ответы, впоследствии заболевание прогрессировало. Молекулярно-генетический анализ подтвердил отсутствие мутаций BRCA1/2 и выявил дефицит гомологичной рекомбинации (HRD), который составил 20,1%, что указывает на ограниченную чувствительность к ингибированию ПАРП. Поскольку общее состояние пациента ухудшилось, в феврале 2025 года был начат переход на паллиативную помощь. Пациент скончался в марте 2025 года.*

Заключение: *Представленный случай подчеркивает ограниченные терапевтические возможности при BRCA-негативном HGSOC с умеренным HRD статусом и демонстрирует необходимость разработки новых персонализированных стратегий лечения пациентов с неблагоприятным молекулярным профилем.*

Ключевые слова: *серозный рак яичников высокой степени злокачественности (HGSOC), BRCA-негативный статус, дефицит гомологичной рекомбинации (HRD), ингибиторы поли(АДФ-рибозо)полимеразы (ПАРП), клинический случай, химиотерапия, молекулярное профилирование.*

Transparency of the study: *Authors take full responsibility for the content of this manuscript.*
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WILMS' TUMOR IN HORSESHOE KIDNEY: POSSIBILITIES OF ORGAN-PRESERVING TREATMENT (A CLINICAL CASE)

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ABSTRACT

Relevance: *Horseshoe kidney is the most typical kidney fusion anomaly among children (0.25%) and is associated with various urological and non-urological abnormalities. Wilms' tumor is the most common malignant neoplasm of the kidneys and the third most common solid malignant neoplasm in pediatrics.*

The study aimed to *present a clinical case of Wilms' tumor detected in a horseshoe kidney, describing the diagnostic and treatment methods.*

Methods: *The article describes a clinical case of Wilms' tumor in the horseshoe kidney of a 4-year-old girl treated at the Moscow Regional Oncological Dispensary (Balashikha, Russia).*

Results: *A combined treatment was performed, including neoadjuvant and adjuvant chemotherapy and surgical resection of the left half of the horseshoe kidney at the isthmus level. At the time of writing, there were no manifestations of the disease.*

Conclusion: *The clinical case highlights the importance of a timely diagnosis of Wilms' tumor and the initiation of treatment, which significantly contributes to a favorable outcome. Early diagnosis and treatment allowed a particular patient to evaluate all possible outcomes and determine further tactics. This made it possible to remove Wilms' tumor localized in the horseshoe kidney with minimal loss of renal and urinary system function.*

Keywords: *pediatrics, surgical treatment, nephroblastoma, Wilms' tumor, horseshoe kidney, chemotherapy.*

Introduction: Wilms' tumor, also known as nephroblastoma, is the most common kidney tumor in children [1-3]. Kidney tumors account for approximately 5% of malignant neoplasms in children under 15 years old and 3.6% of malignant neoplasms in children under 18 years old. Among the 9,731 patients enrolled in the National Renal Tumor Research Group (NWTSG) (1969–2002), nephroblastoma accounted for the vast majority of childhood kidney tumors (92%), followed by clear cell renal sarcoma (3.4%), congenital mesoblastic nephroma (1.7%), malignant rhabdoid tumor (1.6%), and rare neoplasms, including primitive neuroectodermal tumor, synovial sarcoma, neuroblastoma, and cystic nephroma (1.1%). Although renal cell carcinoma has not historically been included in NWTSG studies, it accounts for 8% of kidney tumors in children from birth to 19 years old, according to the Surveillance, Epidemiology, and Outcomes (SEER) Program [2]. Horseshoe kidney is the most common abnormality of kidney formation [4].

The primary kidney migrates from the pelvic cavity to the level of the upper lumbar vertebrae during the formation and development of the renal system, accompanied by additional rotation and fixation of the organ in its typical position [5]. Renal fusion anomalies can occur during rotation and kidney elevation during the 9th week of ontogenesis [6]. The isthmus of a horseshoe kidney may contain a functioning renal parenchyma or a fibrous band [7]. In up to 80% of horseshoe kidney cases, the isthmus contains functional renal parenchyma tissue, and in 90% of cases, fusion occurs at the lower pole [8]. Horseshoe kidneys are often asymptomatic and are usually discovered by chance, often due to symptoms or secondary disorders of the genitourinary system, such as genitourinary infections or obstructions [8]. It is believed that these patients are at increased risk of developing malignant neoplasms, such as Wilms' tumor [6]. Nephroblastoma is the most common malignant kidney tumor detected in childhood [7]. The risk of developing Wilms' tumor in children with horseshoe kidney is 2-6 times greater than in children in general [7]. Approximately 50% of Wilms' tumors in horseshoe kidneys develop from the isthmus, probably due to abnormal proliferation of the metanephric blastema [6]. The same abnormality that causes the development of a horseshoe kidney can also lead to the development of Wilms' tumor [8]. Nephroblastoma is asymptomatic; approximately 10% are detected accidentally after injury, while 25% are found to have microhematuria or hypertension, which occurs against the background of hyperproduction of renin [1].

Ultrasound is used to diagnose a horseshoe kidney, whereas computed tomography (CT) and magnetic reso-

nance imaging (MRI) are used in staging the process [3]. On ultrasound, the tumor appears as a large mass that can be solid or cystic, characterized by large hypoechoic areas resulting from central necrosis and cyst formation [1]. The areas are characterized by fat deposits, calcifications, or hemorrhages [1]. CT scans show tumors with a lower density and are less visualized than the normal renal parenchyma [4]. Tumors are often characterized by heterogeneous enhancement and may have inclusions in the form of accentuated calcifications [4]. In magnetic resonance imaging, tumors exhibit low signal intensity in T1-weighted images, varying signal intensity in T2-weighted images, and limited diffusion in diffusion-weighted images [5]. CT is also used to detect lung metastasis or local recurrence [5].

Wilms' tumor may contain inclusions of embryonic renal elements, including blastema, epithelium, and stroma [4]. Wilms' tumor can be divided into 2 types based on the prognosis: favorable (more than 90%) and unfavorable (6–10%) [5]. Histopathological analysis is the modern gold standard for diagnosing Wilms' tumor.

Surgery, chemotherapy, and radiation therapy are used to treat Wilms' tumor [6]. The National Wilms' Tumor Study Group (NWTSG)/Children's Oncology Group (COG) and the International Society of Pediatric Oncology-Renal Tumor Study Group (SIOP) have established main guidelines for the management of patients with Wilms' tumor [8]. SIOP recommends the use of preoperative chemotherapy to reduce tumor size and prevent intraoperative complications due to tumor rupture [7]. In contrast, the NWTSG/COG recommends the use of primary surgery before any conservative therapy [2]. The overall survival rate for children with Wilms' tumor in the horseshoe kidneys is similar to that for children with Wilms' tumor in normal kidneys: NWTS-4 stage I-IV (event-free survival – 80.6%-94.9%, overall survival – 93%-98.7%) [6].

The study aimed to present a clinical case of Wilms' tumor detected in a horseshoe kidney, describing the diagnostic and treatment methods.

Description of the clinical case.

Patient's data: A 4-year-old girl, 4 months from the 8th pregnancy, second childbirth. The weight at birth was 2980 g. No chronic diseases. There were no surgeries or injuries. The ultrasound results revealed the formation of the abdominal cavity during a routine examination at the place of residence. The child was hospitalized in the Moscow Regional Oncology Dispensary (Balashikha, Russia).

Diagnostics: During the examination, palpation revealed a volumetric formation of tightly elastic consistency, painless and immobile, on the right side. General urinalysis revealed microhematuria. Blood pressure was higher than the norm for the age. A CT scan of the abdominal cavity with intravenous contrast enhancement was performed on 04.09.24: CT scan of a horseshoe kidney, a tumor mainly of the right half of the kidney with a size of 6.6×8.3×8 cm, heterogeneous structure. Renal veins contrast homogeneously (Figure 1).

The diagnosis was established based on instrumental research methods: "Nephroblastoma of the horseshoe kidney on the right."

The child was admitted to the Moscow Regional Oncology Dispensary to determine further treatment tactics and receive specific treatment.

Treatment: From 06.09.2024, after the diagnosis, the child began to receive therapy according to the Umbrella SIOP 2016 protocol, AV block:

Week 1 (06.09.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg), Actinomycin D 45 µg/kg IV bolus (single dose of 0.72 mg).

Week 2 (13.09.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg).

Week 3 (20.09.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg), Actinomycin D 45 µg/kg IV bolus (single dose of 0.72 mg).

Week 4 (27.09.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg).

Due to technical difficulties during surgery at Week 5, an additional injection of vincristine was administered following the recommendations of the RF Ministry of Health.

Week 5 (04.10.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg).

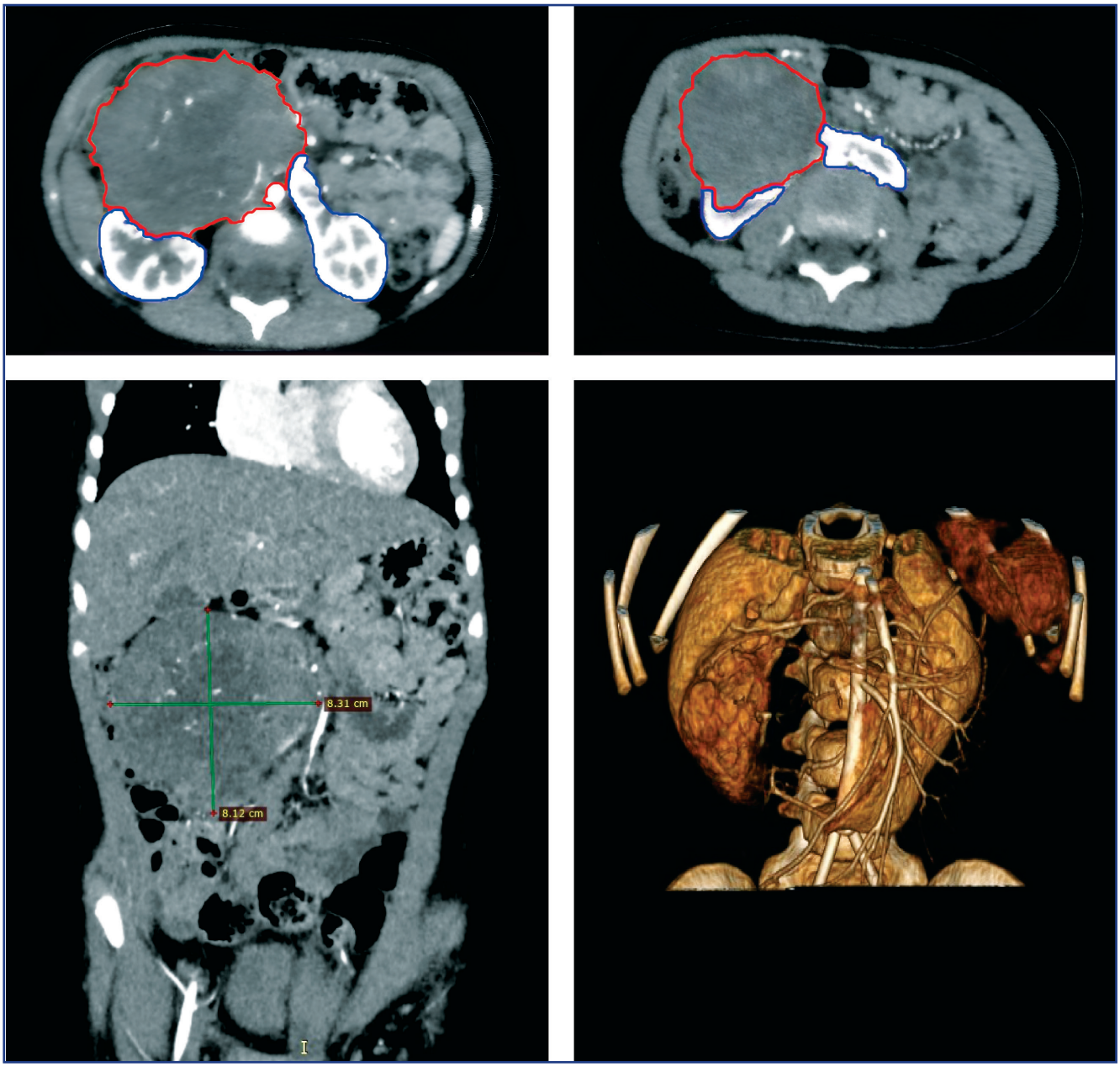
Against the background of preoperative chemotherapy, a CT scan of the abdominal cavity and retroperitoneal space with intravenous contrast showed a reduction in the size of the tumor node from 6.6×8.3×8 cm (230 cm^3) to 5.1×5.7×5.7 cm (86 cm^3). The tumor has decreased by 62.6% of its initial volume (Figure 2).

It was decided to perform surgery after neoadjuvant maintenance chemotherapy within the framework of the Umbrella SIOP 2016 protocol.

The surgical intervention was performed on October 14, 2024. The access was via median laparotomy. The revision revealed no pathology in the abdominal organs. A rounded tumor of 6×6×5 cm was visualized in the retroperitoneal space in the centre and to the right at the level of the lower poles of the kidneys. It emanated from the isthmus of the horseshoe kidney and spread to a greater extent to the lower parts of the right half of the horseshoe kidney. The right ureter passed along the anterior edge of the tumor node; the inferior vena cava (compressed by the tumor) was posterior to the tumor, and there was the bifurcation of the aorta. The right lateral canal was opened, and the right half of the horseshoe kidney, including the tumor and the isthmus to the level of the left part, was mobilized. The right ureter was isolated and mobilized to the right pelvis (Figure 3).

The inferior vena cava was abruptly separated from the tumor node, and the aorta was mobilized at the bifurcation level. A feeding vessel extending from the aorta to the isthmus of the horseshoe kidney was found, li-

gated, and dissected. The left ureter was checked. Acute resection of the left half of the horseshoe kidney was performed at the level of the isthmus within healthy tissues. Suturing of the lower group of calyces of the left half of the horseshoe kidney was performed with Prolene 4-0 thread. The encircling stitch was made with Vicryl 0 thread on the lower pole of the left kidney half. Acute resection of the right half of the horseshoe kidney was performed at the level of the lower pole within healthy tissues. Suturing of the lower group of calyces of the right half of the horseshoe kidney was performed with Prolene 4-0 thread. The encircling stitch was made with Vicryl 0 thread on the lower pole of the right kidney half (Figure 4).



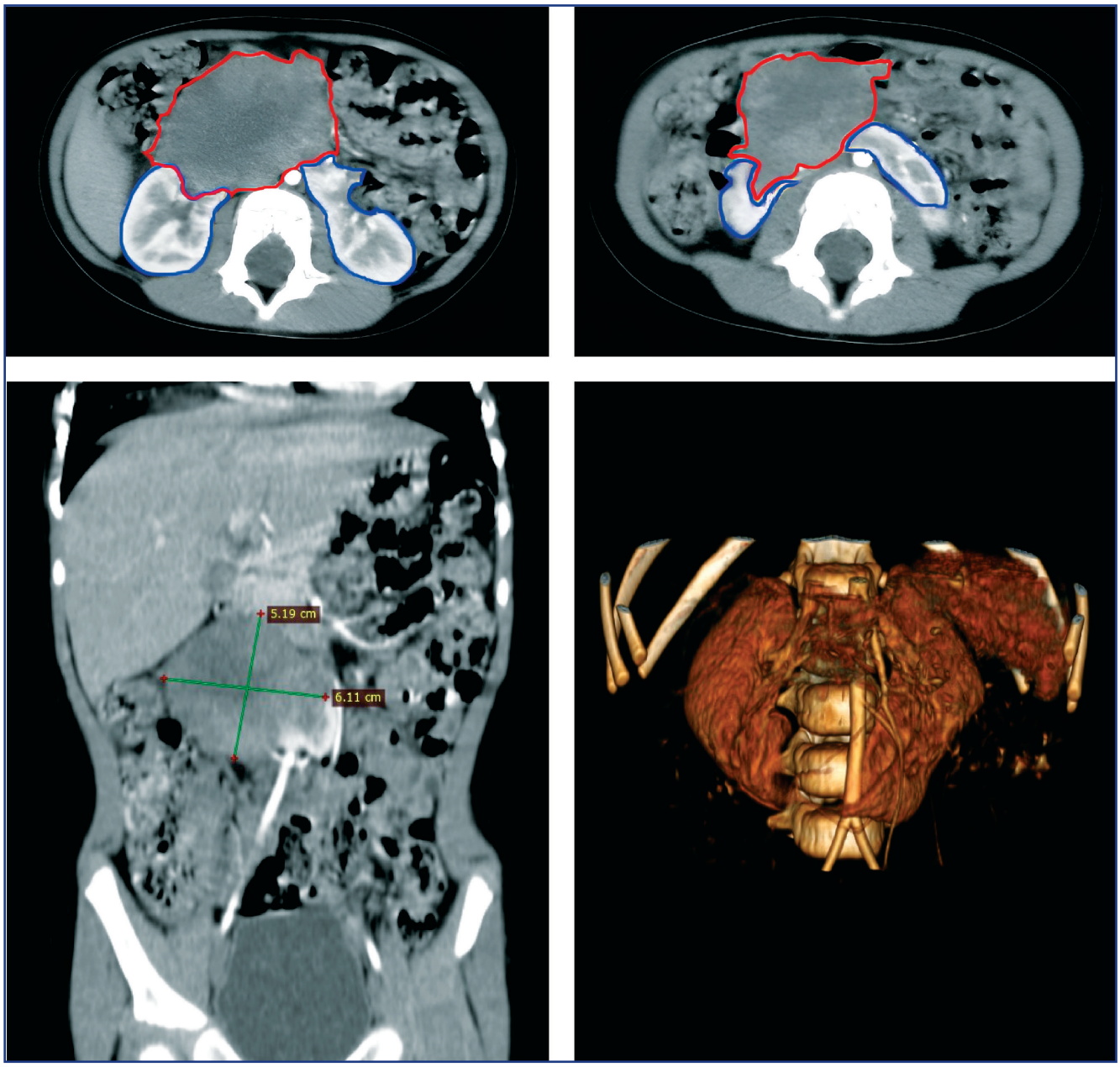
Blue line – Boundaries of normal renal tissue; Red line – Boundaries of the neoplasm
Figure 1 – Computed tomography of the abdominal cavity and retroperitoneal space with intravenous contrast dated 04.09.2024, arterial phase

Hemostasis during the operation – dry. The revision revealed no pathological findings; the sutures were consistent, with no leaks. The following procedures were performed: drainage of the pelvis with a silicone tube led through a counter-aperture on the right; plastic surgery of the right lateral canal; layer-by-layer suturing of the postoperative wound; cosmetic skin suture. Urine was drained through a Foley catheter inserted into the urethra.

The material obtained during the operation was sent for pathomorphological examination (Figure 5).

The child in stable condition was transferred from the intensive care unit to the children's oncology department on the 2nd day after the operation. Blood pressure was

within the normal range for the age. Urine outflow through the urethral catheter was adequate, without pathological inclusions or discoloration. Discharge through the drainage was below 100 ml.



Blue line – Boundaries of normal renal tissue; Red line – Boundaries of the neoplasm

Figure 2 – Computed tomography of the abdominal cavity and retroperitoneal space with intravenous contrast dated 02.10.2024

The drainage was removed along with the urethral catheter on the 7th day after surgery.

Histochemical study dated 16.10.2024: Nephroblastoma, epithelial type, intermediate risk group, R0-resection. pT2N0M0.

The final clinical diagnosis was established: Nephroblastoma on the right, epithelial type, intermediate risk group, local stage 1.

The child began to receive adjuvant chemotherapy according to the Umbrella SIOP 2016 protocol for the intermediate histological risk group block AV1 from 24.10.2024, after surgical treatment:

Week 1 (24.10.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 1.0 mg).

Week 2 (01.11.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 0.9 mg), Actinomycin D 45 µg/kg IV bolus (single dose= 0.65 mg).

Week 3 (08.11.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 0.9 mg).

Week 4 (15.11.2024) – Vincristine 1.5 mg/m^2 IV bolus (single dose of 0.9 mg).

Control computed tomography of the abdominal organs and retroperitoneal space with intravenous contrast enhancement was performed on 21.11.2024: functionally sound

right and left kidneys were visualized, with dimensions of 34×37×76 mm on the right, and 52×27×90mm on the left. The pelvic system of both kidneys was not deformed or dilated, and radiopaque concrements were not found (Figure 6).

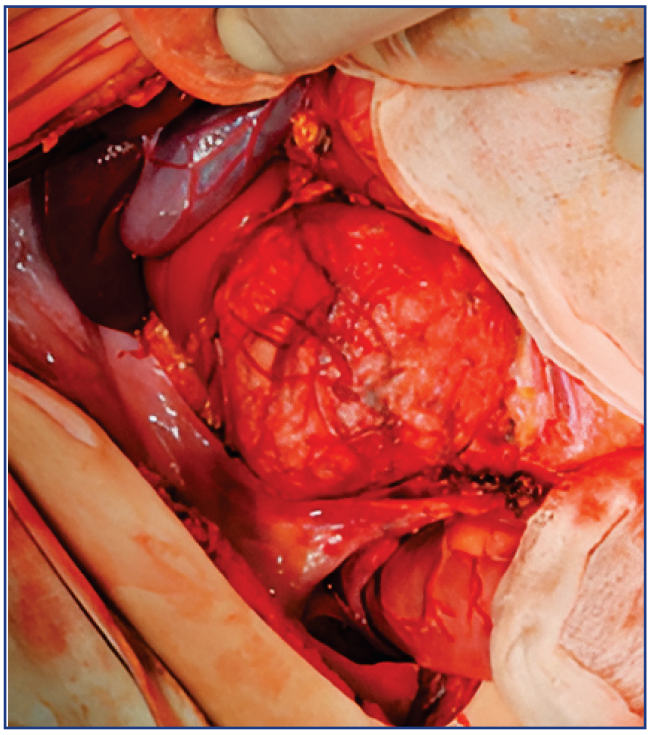


Figure 3 – Horseshoe kidney mobilization and formation

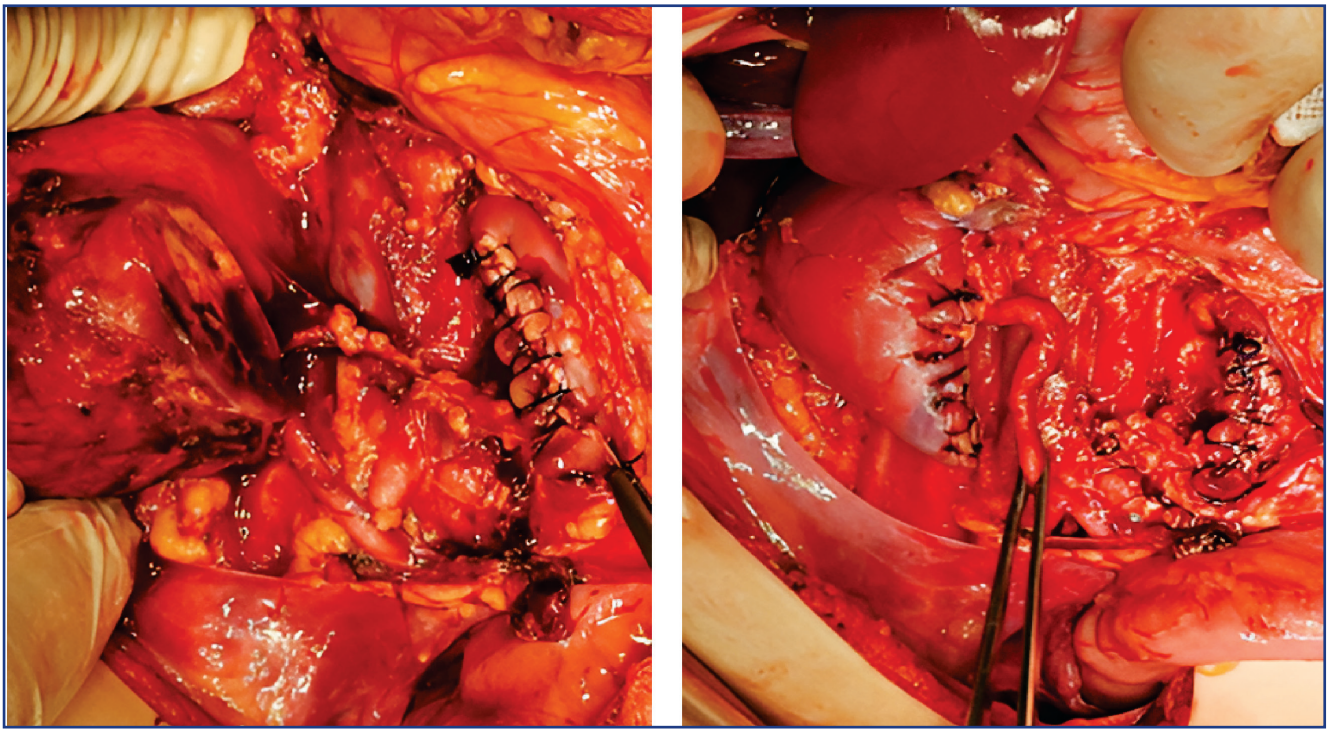


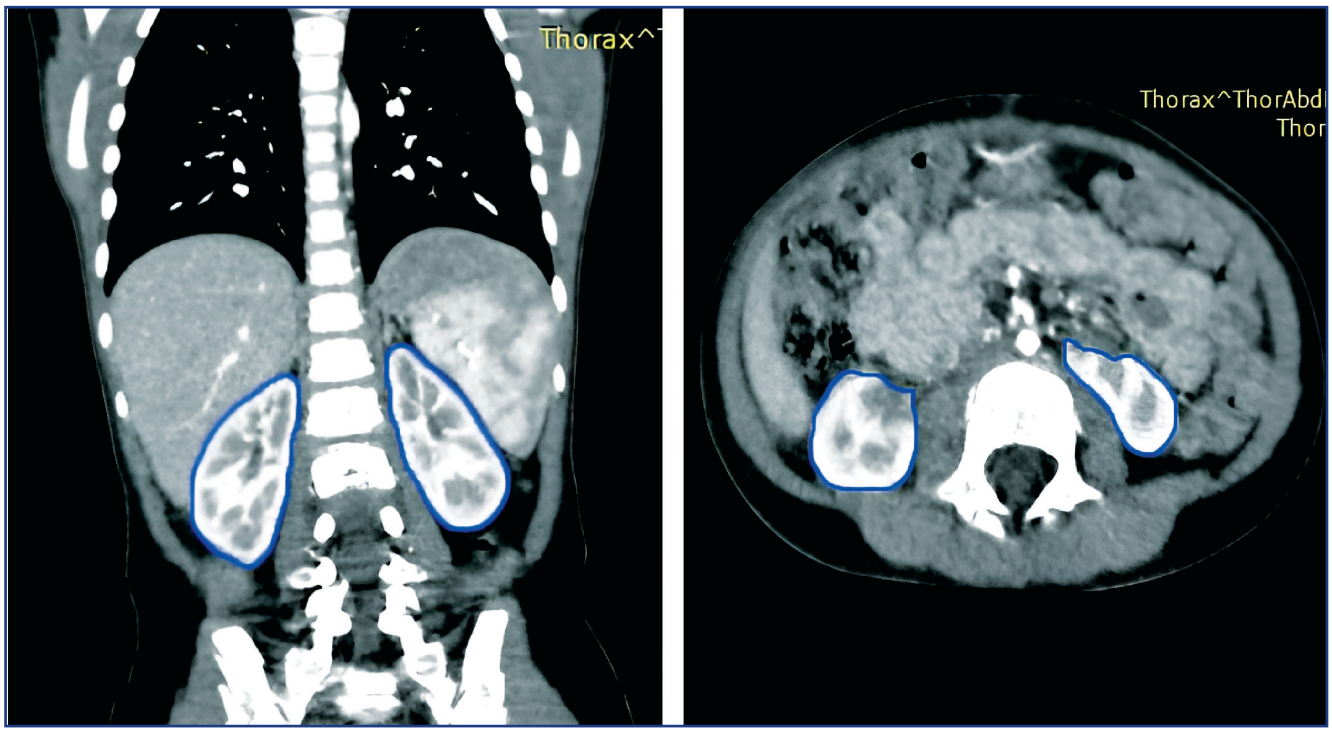
Figure 4 – Suturing of the lower poles of the right and left kidneys

Results: A combined treatment was performed, including neoadjuvant and adjuvant chemotherapy and a resection of the left half of the horseshoe kidney at the isthmus. The primary indicators, including blood pressure and a general urinalysis, were monitored during treatment. These indicators demonstrated the positive dynamics of the patient, from the moment of admission to the moment of withdrawal, as erythrocytes ceased to be detected in the general urinalysis, and BP values stabilized within the age norm. In dynamics, radiation di-

agnostic methods showed a positive trend in response to chemotherapy. A follow-up examination at the time of withdrawal from treatment made it possible to verify the efficiency of the therapy and the integrity of the urogenital system after reconstructive plasty. There were no manifestations of the disease at the time of writing the article.

The timeline of the clinical case is presented in Figure 7.

Figure 5 – Taken gross specimen



Blue line – Borders of normal renal tissue

Figure 6 – Computed tomography of the abdominal cavity and retroperitoneal space with intravenous contrast dated 21.11.2024

Discussion: Wilms' tumor is the most common kidney malignant neoplasm in children and the fifth most common malignant neoplasm in children in general [1]. Horseshoe kidney is a kidney fusion abnormality characterized by the fusion of the kidneys through the isthmus at the lower pole in approximately 90% of cases. This isthmus is predominantly composed of functional renal tissue, although it can sometimes appear as a fibrous band [1, 3]. Horseshoe kidney is a risk factor for kidney malignant neoplasms [8]. Despite the increased risk compared to the general population, horseshoe kidney is not currently recommended as a condition requiring Wilms' tumor screening [6]. Since horseshoe kidney is usually asymptomatic [3, 4], most cases described in the literature were diagnosed at the same time as the tumor itself [8].

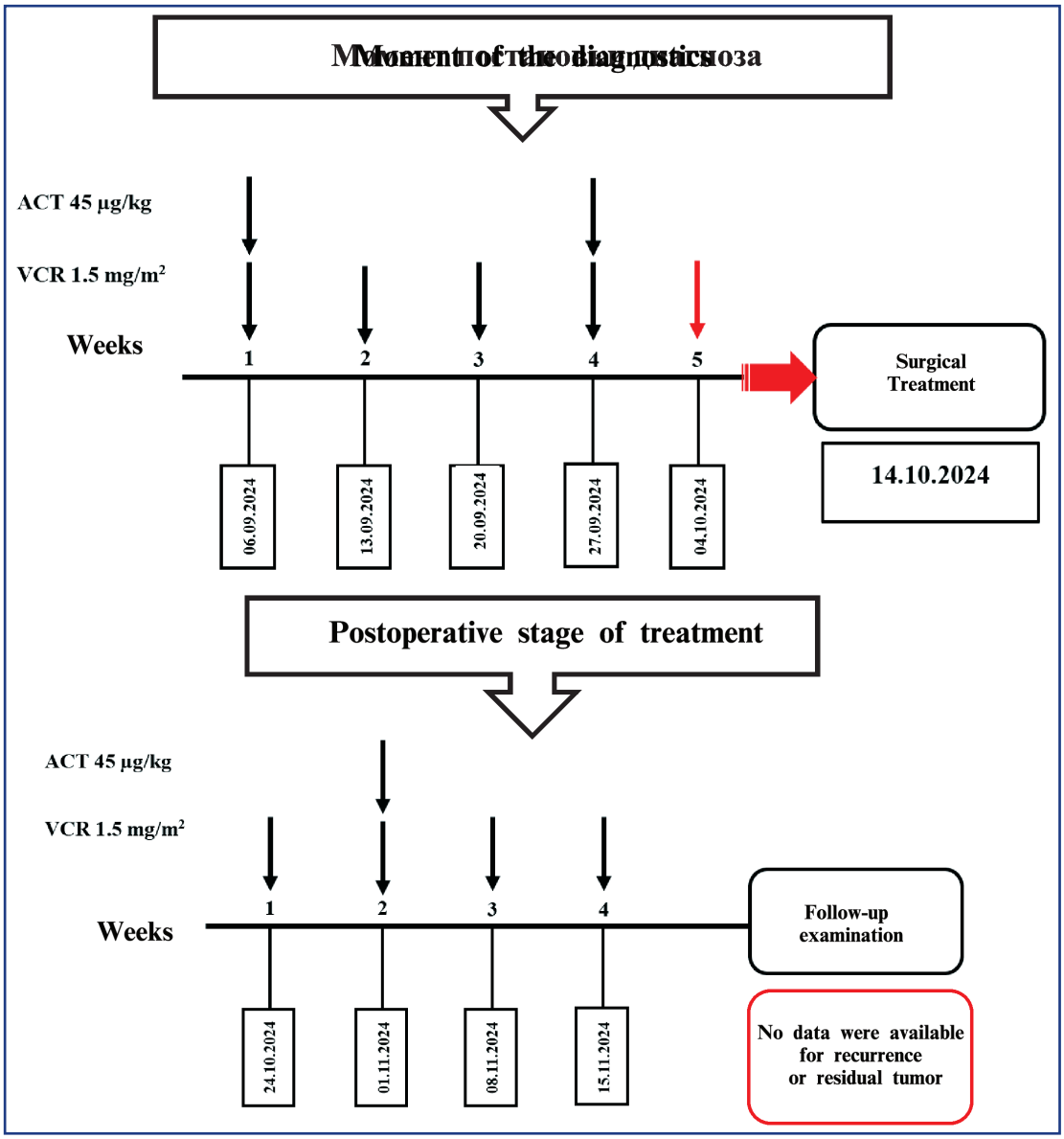


Figure 7 – Timeline of the clinical case of Wilms' tumor in a horseshoe kidney in a 4-year-old girl

Radical nephroureterectomy with lymph node removal using a wide transverse, transperitoneal approach is recommended for adequate tumor resection [8]. Complete removal of the affected kidney, along with the isthmus and tumor, is recommended in case of a unilateral tumor in the horseshoe kidney. When the tumor is located in the isthmus, an organ-preserving treatment method is possible [7, 8].

In the presented case, the tumor node was removed along with the isthmus, with the simultaneous formation of two separate kidneys.

Conclusion: Wilms' tumor is the most common malignant neoplasm of the kidneys among the pediatric population. This nosology can be associated with various congenital anomalies, such as sporadic aniridia, hemihypertrophy, and genitourinary anomalies, which in some cases make it possible to verify the diagnosis at an early stage, during the process of studying background conditions. But in most cases, nephroblastoma is diagnosed at the stage of visual changes in the child's body, when parents begin to see body asymmetry and can palpate the formation. It of-

ten leads to several complications, such as rupture of the tumor capsule, which in turn is an unfavorable prognosis in terms of contamination of the surrounding tissues and organs located in the abdominal cavity and retroperitoneal space with tumor cells.

Early diagnostics of concomitant renal pathologies makes it possible to adequately route patients and plan management tactics.

Preoperative chemotherapy allows for the avoidance of several possible complications during surgery.

A combined anomaly of the structure of the kidneys and neoplasms requires a highly qualified surgical team to perform one-stage removal of the tumor and use a reconstructive method.

The rational performance of computed tomography of the abdominal cavity and retroperitoneal space enables the adequate assessment of the effect of each stage of treatment, as well as the comparison of dynamics relative to the initial data obtained during the detection of the formation.

If it is impossible to perform surgery at the appointed time, it is worth considering the option to add a course of chemotherapy in order to maintain the therapeutic effect of the block until the moment when surgery becomes possible.

This clinical case highlights the importance of timely diagnosis of Wilms' tumor and the initiation of treatment, which contributes to a favorable outcome. Early diagnostics and treatment made it possible to assess all possible outcomes in a particular patient and determine further tactics; as a result, Wilms' tumor, localized in the horseshoe kidney, could be corrected with minimal loss of kidney function and urinary system function.

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АҢДАТПА

АТТАСҚАН БҮЙРЕКТЕ ДАМЫҒАН ВИЛЬМС ІСІГІ: АҒЗАЛАРДЫ САҚТАУ ЕМІНІҢ МҮМКІНДІКТЕРІ (КЛИНИКАЛЫҚ ЖАҒДАЙ)

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Өзектілігі: *Аттасқан (таға тәрізді) бүйрек – балаларда жиі кездесетін бүйрек қосылу аномалиясы (0,25%) болып табылады және ол әртүрлі урологиялық және бейурологиялық ауытқулармен байланысты. Вильмс ісігі – балалардағы ең жиі кездесетін қатерлі бүйрек ісігі және үшінші жиі кездесетін қатты тіндік қатерлі ісік болып саналады.*

Зерттеу мақсаты: *Аттасқан бүйректе анықталған Вильмс ісігінің клиникалық жағдайын сипаттау, диагностика және емдеу әдістерін баяндау.*

Әдістер: *Бұл мақалада 4 жастағы қыз баланың аттасқан бүйрегінде анықталған Вильмс ісігінің клиникалық жағдайы сипатталады. Емдеу Мәскеу облыстық онкологиялық диспансерінде (Балашиха, Ресей) жүргізілген.*

Нәтижелері: *Неоадъювантты және адъювантты химиотерапияны және аттасқан бүйректің сол бөлігін мойын тұсында резекциялау көлемінде жасалған операцияны қамтитын кешенді ем жүргізілді. Мақала жазу кезінде аурудың көріністері тіркелмеген*

Қорытынды: *Бұл клиникалық жағдай Вильмс ісігін дер кезінде анықтап, емдеудің маңыздылығын көрсетеді, бұл қолайлы нәтижеге қол жеткізуге мүмкіндік берді. Ерте диагностика мен ем нақты науқастың барлық мүмкін нәтижелерін бағалап, әрі қарайғы ем тактикасын анықтауға септігін тигізді. Соның арқасында аттасқан бүйректе орналасқан Вильмс ісігін бүйрек пен несеп шығару жүйесінің функциясына барынша аз зиян келтіре отырып емдеуге мүмкіндік болды.*

Түйінді сөздер: *педиатрия, хирургиялық ем, нефробластома, Вильмс ісігі, аттасқан бүйрек, химиотерапия.*

ABSTRACT

WILMS' TUMOR IN HORSESHOE KIDNEY: POSSIBILITIES OF ORGAN-PRESERVING TREATMENT (A CLINICAL CASE)

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Relevance: *Horseshoe kidney is the most typical kidney fusion anomaly among children (0.25%) and is associated with various urological and non-urological abnormalities. Wilms' tumor is the most common malignant neoplasm of the kidneys and the third most common solid malignant neoplasm in pediatrics.*

The study aimed to *present a clinical case of Wilms' tumor detected in a horseshoe kidney to describe diagnostic and treatment methods.*

Methods: *The article describes a clinical case of Wilms' tumor in the horseshoe kidney of a 4-year-old girl treated at the Moscow Regional Oncological Dispensary (Balashikha, Russia).*

Results: *A combined treatment was performed, including neoadjuvant and adjuvant chemotherapy and surgical resection of the left half of the horseshoe kidney at the isthmus level. At the time of writing, there are no manifestations of the disease.*

Conclusion: *The clinical case reflects the need for a timely diagnosis of Wilms' tumor and initiation of treatment, which contributes to a favorable outcome. Early diagnosis and treatment allowed a particular patient to evaluate all possible outcomes and determine further tactics. This made it possible to remove Wilms' tumor localized in the horseshoe kidney with minimal loss of renal and urinary system function.*

Keywords: *pediatrics, surgical treatment, nephroblastoma, Wilms' tumor, horseshoe kidney, chemotherapy.*

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A MODERN APPROACH TO T-CELL LYMPHOMA TREATMENT: DEMONSTRATING A THERAPEUTIC STRATEGY (A CLINICAL CASE)

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ABSTRACT

Relevance: *Primary central nervous system (PCCNS) lymphomas are a rare type of lymphoma, accounting for 2% of all CNS lymphomas, and are associated with a poor prognosis. According to data from the Republic of Kazakhstan EROB Information System, in 2023-2024, the «CNS lymphoma» diagnosis was morphologically confirmed in 13 individuals. Among primary CNS lymphomas, the ALK-negative subtype of anaplastic large-cell T-cell lymphoma is a highly malignant tumor with an aggressive clinical course. Treatment of such patients remains challenging, requiring an expanded evidence base and more clinical case reports.*

The study aimed to *demonstrate the effectiveness of combined chemo-targeted therapy with autologous bone marrow transplantation in a patient with ALK-negative anaplastic large cell CNS lymphoma (a T-cell lymphoma subtype) through a clinical case and literature review.*

Methods: *This article presents a literature review and a clinical case of a patient with T-cell lymphoma of the central nervous system. Diagnostic assessments included computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) of the brain, as well as histopathological and immunohistochemical examination of postoperative tissue samples. The disease course and response to treatment are described.*

Results: *A patient with a provisional clinical diagnosis of «Primary anaplastic CNS lymphoma, ALK-negative subtype» underwent microsurgical tumor resection. Given the rare nature and localization of the tumor, a histopathological re-evaluation with immunohistochemical analysis of the postoperative specimen was performed. A therapeutic strategy was selected, including using the targeted agent brentuximab vedotin. This case illustrates the potential of combined chemo-targeted therapy in treating ALK-negative anaplastic CNS lymphoma, taking into account the tumor's biological characteristics and the patient's individual features.*

Conclusion: *The correct choice of treatment strategy depends on timely and accurate diagnosis, making diagnostic workup - including morphological and immunohistochemical evaluation - a key step in patient management. In recent years, the strategy of choice for improving prognosis and survival in such patients has been developing and implementing combined therapeutic approaches, incorporating both intensive chemotherapy regimens and modern targeted therapies.*

Keywords: *central nervous system (CNS) lymphoma, epidemiology, T-cell lymphomas, anaplastic large cell lymphoma (ALCL), targeted therapy.*

Introduction: Primary central nervous system lymphoma (PCNSL) is a rare and aggressive type of non-Hodgkin lymphoma (NHL) affecting the brain, meninges, eyes, and spinal cord [1]. PCNSL account for approximately 5% of all primary CNS tumors and 1% of all NHLs. According to population studies in Western Europe, North America, and Asia, the incidence of PCNSL ranges from 0.3 to 0.5 per 100,000 population [2]. According to the "Electronic Register of Cancer Patients of the Republic of Kazakhstan" Information System, in 2023–2024, CNS lymphomas were morphologically confirmed in 13 people.

Histologically, the most common type is diffuse large B-cell lymphoma (DLBCL), while T-cell lymphoma variants are rare, accounting for only 2% of all CNS lymphomas. A unique type of T-cell lymphoma is anaplastic T-cell lymphoma (ATCL). This lymphoma is divided into two subtypes depending on the expression of anaplastic lymphoma kinase (ALK): ALK-positive and ALK-negative [2,3].

ALK-positive ATCL is more common (70-80% of cases), whereas the ALK-negative form is rare and is characterized by a more aggressive course, diagnostic difficulties, and limited therapeutic options [3, 4].

In recent years, the use of combined treatment methods, including chemotargeted therapy and cell technologies, in the treatment of ATCL has been actively studied. This article presents a clinical case of a patient diagnosed with ALK-negative ATCL. The patient underwent successful microsurgical removal of the tumor followed by spe-

cific chemotargeted therapy, which resulted in a stable remission for 18 months.

The study aimed to demonstrate the effectiveness of combined chemo-targeted therapy with autologous bone marrow transplantation in a patient with ALK-negative anaplastic large cell CNS lymphoma (a T-cell lymphoma subtype) through a clinical case and literature review.

Materials and methods: To conduct a literature review, a systematic search of scientific literature was conducted in PubMed, Web of Science, and Scopus electronic databases, covering the period from January 2010 to January 2024.

The search was conducted using a combination of the following keywords and Medical Subject Headings (MeSH) terms: "T-cell anaplastic lymphoma," "ALK-negative status," and synonyms and derivatives of these terms (in English).

The analysis included publications that met the following inclusion criteria: articles published in peer-reviewed scientific journals with the full text available in English; articles containing data from randomized controlled trials, cohort studies, meta-analyses, and systematic reviews; and publications describing individual clinical cases. Exclusion criteria: incomplete publications (e.g., conference abstracts, presentations); articles not indexed in leading databases or published in journals with a low impact factor and questionable scientific reputation; articles with a citation index below the average for the subject during the search period according to Scopus/Web of Science.

The initial search yielded approximately 20 publications. After applying the inclusion and exclusion criteria, 16 of the most relevant sources were selected for analysis. Two researchers conducted the article selection.

The article also describes the clinical situation and medical history of a 47-year-old patient diagnosed with ALK-negative anaplastic large cell lymphoma. The following research methods were employed during the diagnostic search: positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and immunohistochemical studies of morphological and histopathological material.

Clinical situation:

Patient information: A 47-year-old man was admitted to the Bone Marrow Transplant and Hematology Center of the Kazakh Research Institute of Oncology and Radiology for the first time with complaints of headache in the occipital region, nausea, muscle weakness in the left arm and leg.

Clinical data: The disease lasted for several months; examination revealed left-sided hemiparesis.

Diagnosis: Contrast-enhanced MRI of the brain revealed a 6.5 cm tumor in the right parietal lobe. Additional CT of the chest, abdomen, and pelvis, as well as bone marrow puncture, did not reveal a primary lesion or metastases. An intraparenchymal soft mass measuring 6.5×4.7 cm with unclear borders and a density of 40 HU was found in the right parietal lobe. Extensive perilesional edema and compression of the lateral ventricles around the first ventricle were noted (Fig. 1).

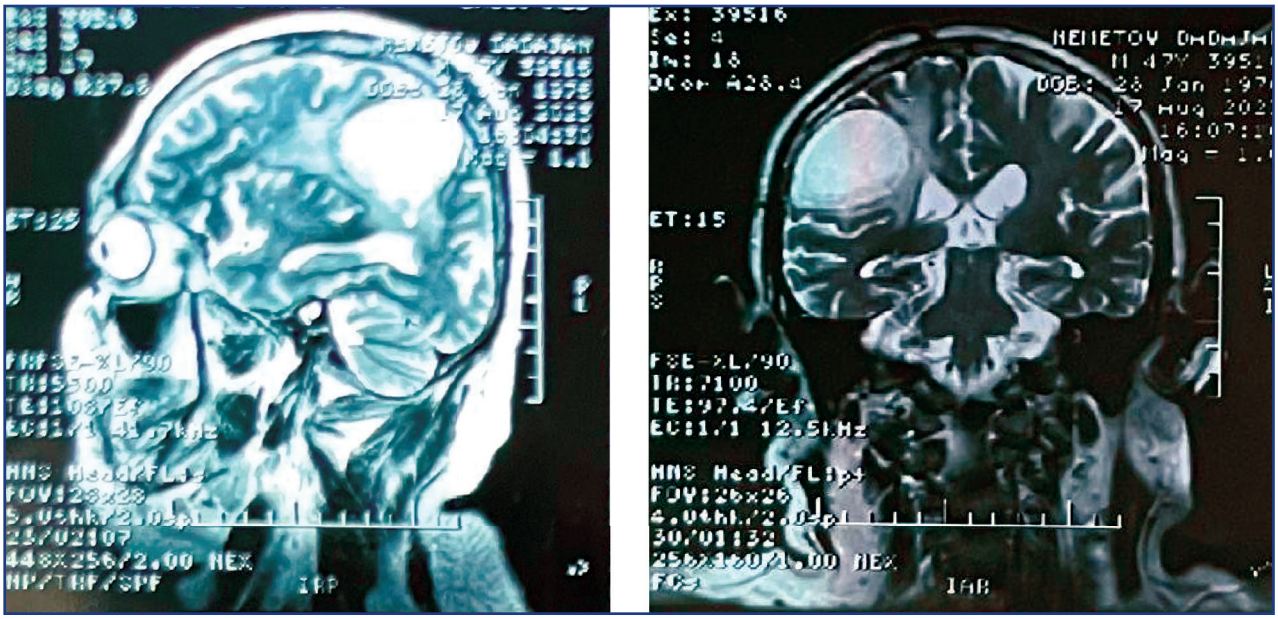

Figure 1 – MRI data from February 2023: a soft mass in the right parietal region, perilesional edema, and ventricular compression were determined.

Histological examination of the I-cell biopsy revealed diffuse infiltration of the brain tissue by atypical cells with large, hyperchromatic, ovoid, and bean-shaped nuclei characteristic of this tumor. The differential diagnosis included germ cell tumors and various large cell lymphomas. Immunohistochemical examination showed that the tumor cells were positive for CD45, CD30, and CD8 markers, but negative for the ALK marker. Based on the results obtained, the diagnosis of ALK-negative anaplastic large T-cell lymphoma (ALCL) was confirmed (Figure 2).

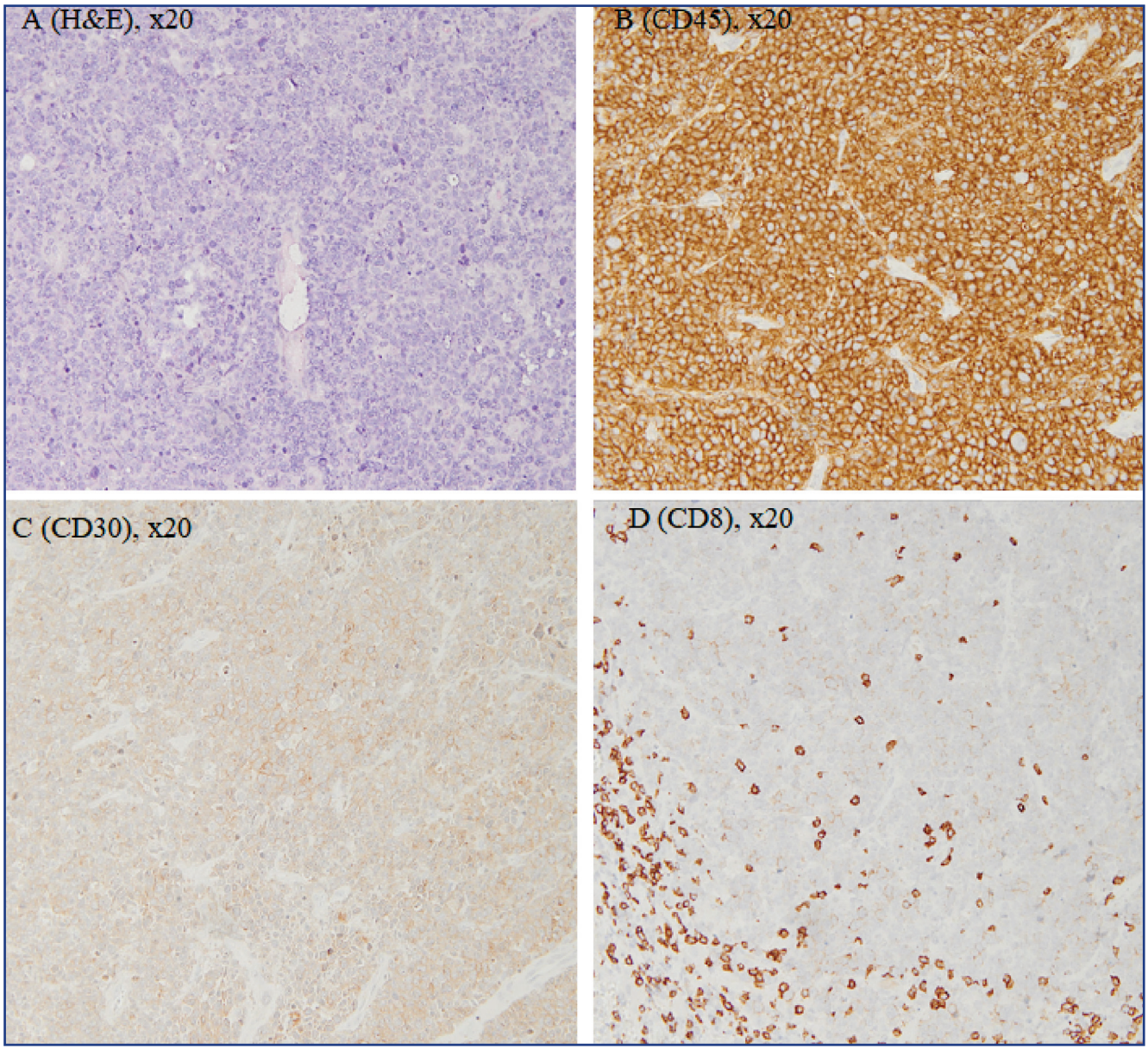

Figure 2 - (A) Diffuse proliferation of large atypical lymphoid cells. Intense diffuse immunostaining for CD45 (B), CD30 (C), and weakly positive immunostaining for CD8 (D)

PET-CT revealed accumulation of fluorodeoxyglucose F18 only in the brain; no other foci were detected. No tumor cells were detected in the cerebrospinal fluid.

Differential diagnosis includes glioblastoma, metastases from solid tumors, and brain lymphoma.

Treatment: The first tumor was completely removed microsurgically after 2 months. Pathological examination confirmed an ALK-negative ALCL. The tumor in the right parietal lobe was removed microsurgically using neuronavigation. Since the patient was diagnosed with ALK-negative ALCL, the treatment followed the Bre-HyperCVAD protocol considering the marker expression and status (cycles 1,3,5,7: brentuximab vedotin (1.8 mg/kg), cyclophosphamide (2×300 mg/m^2), vincristine (2 mg), doxorubicin (50 mg/m^2); cycles 2,4,6,8: brentuximab vedotin (1.8 mg/kg), methotrexate (1 g/m^2), cytarabine (2 g/m^2). A total of 8 cycles of chemotargeted therapy and autologous hematopoietic stem cell transplantation (autoHSCT) in a treosulfan-conditioned regimen were performed.

During chemotherapy, grade 1-2 side effects were registered: mild anemia and mild thrombocytopenia. Maintenance therapy: dexamethasone, leucovorin. After four courses of the Bre-HyperCVAD protocol, complete remission was achieved, and stem cells were collected in a volume of 5×10^6/kg. Conditioning was carried out on days 1–3 with treosulfan at a dose of 16 g/m^2, and autologous HSCT was performed on April 7, 2024 (Day 0). Neutrophil recovery was noted on Day 14.

Results: After completing combination therapy, including chemotargeted therapy according to the Bre-Hyper CVAD regimen (8 courses) and subsequent autologous bone marrow transplantation, a control MRI examination of the brain performed 12 months later revealed no signs of disease recurrence (Figure 3).

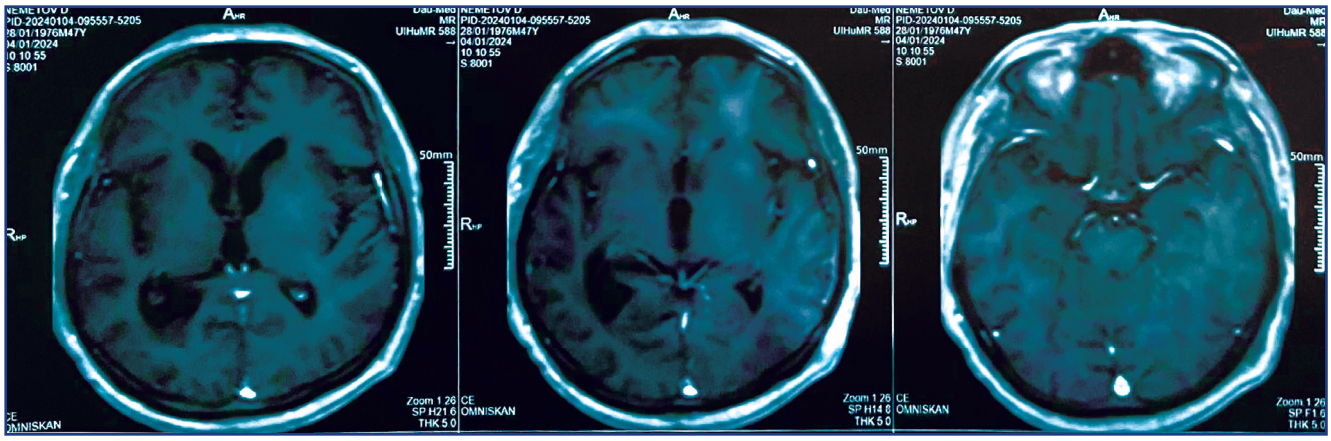

Figure 3 – Cystic mass (1.5×4.5 cm). Multiple vasogenic foci were detected in the white matter of the brain. Right-sided sinusitis. (April 2025)

Table 1 – Timeline of a clinical case of ALK-negative anaplastic large T-cell lymphoma

Date	Event
January 2023	The disease began with severe headaches in the occipital region. The patient consulted a neurologist and underwent outpatient treatment, which had a temporary effect.
February 2023	The symptoms worsened: headache, double vision, weakness in the left arm and leg. MRI revealed a large mass in the right parietal lobe.
April 2023	12.04 – Surgery performed: craniotomy of the right occipital lobe. The tumor was removed microsurgically using neuronavigation. 15.04 – Pathomorphological examination: According to the results of the IHC study, the morphology and immunophenotype corresponded to non-Hodgkin's lymphoma. CD45 exhibited a diffuse positive reaction, while CD20 was positive in rare B-lymphocytes, and CD79a was positive in B-lymphocytes. CD3 was positive in T-lymphocytes, CD99 was negative, FLI1 was focally positive, panceratin (AE1/AE3) was negative, and CD138 was positive in single plasma cells.
May 2023	03.05 – repeated IHC study was performed at KazNIIOiR: CD20, PanCK, PAX5, CD3, CD138, ALK, CD15, CD4, Granzyme B, CD5, CD79a – negative; MUM1, CD45, CD30, CD8, p63 – positive. Conclusion: Tumor morphology and immunophenotype corresponded to ALK-negative anaplastic large cell lymphoma. 25.05 – MRI of the brain (with contrast): hypervascular formations, edema, and displacement of brain structures were determined in the right frontal-parietal region and left frontal region.
June 2023	11.06 – Results of MDT at KazNIIOiR: treatment according to the Bre-HyperCVAD scheme was recommended; the patient underwent 1 course.
July 2023	09.07 – 2nd course according to the Bre-HyperCVAD scheme
August 2023	06.08 – 3rd course according to the Bre-HyperCVAD scheme
September 2023	11.09 – Mobilization of stem cells (5 million cells collected)
October 2023	15.10 – 4th course according to the Bre-HyperCVAD scheme
November 2023	25.11 – 5th course according to the Bre-HyperCVAD scheme
December 2023	25.12 – 6th course according to the Bre-HyperCVAD scheme
January 2024	18.01 – 7th course according to the Bre-HyperCVAD scheme
February 2024	20.02 – 8th course according to the Bre-HyperCVAD scheme
March-April 2024	09.03 – Pre-transplant preparation started: conditioning regimen RIC-treosulfan 16 mg/m² on days 1-3. 24.03 – The patient underwent autologous hematopoietic stem cell transplantation (autoHSCT) (Day 0) 07.04 – On D+14, restoration of neutrophils was recorded.
April 2025	MRI of the brain: no signs of relapse found.

Discussion: According to the literature, fewer than 20 confirmed cases of ALK-negative CNS ALCL have been registered worldwide, predominantly in patients over 40 years old, with a male predominance [5, 6]. The disease presents with nonspecific symptoms, including headache, aphasia, weakness, and confusion. An MRI of the brain often reveals solitary or multifocal lesions [7,8]. Morphologically, this lymphoma is characterized by large, atypical cells with horseshoe-shaped nuclei expressing CD30. Immunohistochemical studies reveal the presence of T-cell markers (CD4, CD43, Granzyme B), but ALK expression is absent. In some patients, genetic studies have revealed *TP53 gene deletions, complex karyotypes, and DUSP22 rearrangements (including DUSP22-IRF4),* which may impact the disease prognosis [9-13].

The standard approach to treating PCNSL is a combination of rituximab with high-dose methotrexate and cytarabine. During the consolidation phase, autologous bone marrow transplantation is performed using a myeloablative or non-myeloablative regimen, which enhances treatment effectiveness and facilitates long-term remission [14]. Previously, radiation therapy to the brain was used in the consolidation phase, as well as additional (boost) radiation directed at the tumor [15]. Given the rarity of PCNSL and its aggressive course, the search for effective treatment methods for this patient group is an urgent problem [16]. Although the ability of brentuximab vedotin (BV) to penetrate the blood-brain barrier (BBB) has not been proven, its penetration through the BBB is theoretically possible as a result of systemic spread of lymphoma to the CNS [17, 18].

According to the literature, BV is effective in treating systemic T-cell lymphomas. However, its use in PCNSL is limited and has been described in only a few clinical cases. Combination approaches, such as BV plus high-dose methotrexate or HyperCBAD (modified HyperCVAD with BV instead of vincristine), have been successfully used in two patients with refractory ALCL involving the CNS and in one patient with CD30-positive DLBCL [19-20].

T. Mitsunobu et al. described a case of ALK-negative ALCL in an 11-year-old boy. The boy presented with secondary CNS involvement and was treated with intensive chemotherapy consisting of BV and high-dose methotrexate in the induction phase, sequentially [20].

In 2016, W. *Delacruz* et al. reported two clinical cases. The first clinical case is a patient with stage IV ALCL with cranial nerve involvement. This patient experienced disease progression during first-line treatment with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) and second-line HyperCVAD. However, a positive response was observed after using BV instead of vincristine (HyperCBAD regimen). The second patient was a man with stage IV DLBCL with leptomeningeal involvement. The disease progressed during first-line treatment with R-CHOP and second-line treatment with R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin). However, the combination of BV with topotecan showed significant improvement [19].

In addition to histological type and ALK positivity, the study of CD30 expression in lymphoma has resulted in the development of important therapeutic approaches. Currently, numerous clinical trials are underway to develop more effective treatment regimens that utilize BV in combination with other drugs, such as chemotherapy or immunotherapy. Additionally, various approaches are employed to target CD30-positive cells. These include the use of bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy [21].

Conclusion: Treatment of PCNSL is a challenging task for oncohematologists. The choice of treatment tactics is made taking into account the tumor localization, its morphological structure, the presence of perifocal edema, the presence or absence of genetic abnormalities, immunophenotype, and often the patient's comorbidities. T-cell PCNSL, particularly ALK-negative ALCL, is a rare disease, and its treatment options are limited. However, active research is currently underway to develop new treatment strategies for ALK-negative ALCL, including modifications of existing treatment regimens. In this clinical setting, we demonstrated the effectiveness of BV and chemotargeted therapy in combination with an integrated approach that includes autologous hematopoiesis. Nevertheless, despite the development of new, promising methods for treating ALCL, the prognosis for these patients remains unfavorable. In this regard, studying the pathological mechanisms of the disease, collecting data on patients with this rare disease, monitoring the course of the disease, and analyzing its outcomes will pave the way for the development of successful treatment strategies and the widespread use of existing therapeutic options, thereby increasing the life expectancy of patients in this group.

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АҢДАТПА

Т-ЖАСУШАЛЫ ЛИМФОМАНЫ ЕМДЕУДЕГІ ЗАМАНАУИ ТӘСІЛ: ТЕРАПИЯЛЫҚ СТРАТЕГИЯНЫ КӨРСЕТУ (КЛИНИКАЛЫҚ ЖАҒДАЙ)

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Өзектілігі: *Орталық жүйке жүйесінің біріншілік лимфомалары (ОЖЖБЛ) - лимфомалардың сирек кездесетін түрлерінің бірі болып табылады, олар ОЖЖ-нің барлық лимфомаларының 2%-ын құрайды және болжамы қолайсыз болып есептеледі. Қазақстан Республикасындағы ЭРОБ Ақпараттық Жүйесінің деректеріне сәйкес, 2023-2024 жылдары «ОЖЖ лимфомасы» диагнозы морфологиялық түрде 13 адамда расталған. ОЖЖБЛ ішінде анапластикалық лимфома киназа (АЛК)-теріс анапластикалық Т-жасушалы лимфома - жоғары дәрежелі қатерлі ісік түрі, ағымы агрессивті болады. Мұндай науқастарды емдеу мәселелері әлі толық шешілмеген, бұл өз кезегінде дәрелді деректер қорын кеңейтуді және клиникалық бақылаулар санын арттыруды талап етеді.*

Зерттеудің мақсаты *– клиникалық жағдай мен әдеби деректер негізінде ОЖЖ-нің АЛК-теріс анапластикалық ірі жасушалы лимфомасы (АІЖЛ) – Т-жасушалық лимфомамен ауыратын науқаста химио-таргеттік біріктірілген терапияны аутологиялық сүйек кемігінің трансплантациясымен қатар қолданудың тиімділігін көрсету.*

Әдістері: *Мақалада ОЖЖ-нің Т-жасушалық лимфомасы бар науқастың клиникалық жағдайы мен әдеби шолу сипатталған. Осындай зерттеу деректері ұсынылған: компьютерлік томография (КТ), позитронды-эмиссиялық томография (ПЭТ), бас миына жасалған магниттік-резонанстық томография (МРТ), сондай-ақ операциядан кейінгі материалға жүргізілген патоморфологиялық және иммуногистохимиялық зерттеу. Аурудың динамикасы мен емге жауабы баяндалған.*

Нәтижелері: *«ОЖЖ-нің біріншілік анапластикалық лимфомасы, АЛК-теріс түрі» деген клиникалық диагнозы бар науқасқа микрохирургиялық жолмен ісік алынып тасталғаннан кейін, аурудың сирек кездесетін нұсқасы мен ісіктің орналасуын ескере отырып, операциядан кейінгі материалға патоморфологиялық және иммуногистохимиялық зерттеу жүргізіліп, препараттарды қайта қарау жүзеге асырылды. Емдеу тактикасы ретінде таргеттік препарат – брентуксимаб ведотинді қамтитын біріктірілген ем таңдалды. Ұсынылған клиникалық жағдай АЛК-теріс түріндегі ОЖЖ-нің анапластикалық лимфомасын емдеуде ісіктің биологиялық ерекшеліктері мен науқастың жеке жағдайын ескере отырып, химио-таргеттік біріктірілген терапияны қолданудың әлеуетін көрсетеді.*

Қорытынды: *Дұрыс ем тактикасын таңдау дәл диагноздың уақытында қойылуына тікелей байланысты, сондықтан диагностика – науқасты жүргізу алгоритміндегі негізгі буын болып табылады. Осыған орай, морфологиялық және иммуногистохимиялық зерттеулер жүргізу аса маңызды. Мұндай науқастардың болжамын жақсарту және өмір сүру көрсеткіштерін арттыру мақсатында соңғы жылдары емдеудің таңдаулы стратегиясы ретінде қарқынды химиотерапиялық схемалар мен заманауи таргеттік препараттарды қамтитын біріктірілген емдеу тәсілдерін әзірлеу және қолдану ұсынылып отыр.*

Түйін сөздер: *орталық жүйке жүйесінің біріншілік лимфомалары (ОЖЖБЛ), эпидемиология, Т-жасушалық лимфомалар, анапластикалық ірі жасушалы лимфома (АІЖЛ), таргеттік терапия.*

АННОТАЦИЯ

СОВРЕМЕННЫЙ ПОДХОД К ЛЕЧЕНИЮ Т-КЛЕТОЧНОЙ ЛИМФОМЕ: ДЕМОНСТРАЦИЯ ТЕРАПЕВТИЧЕСКОЙ СТРАТЕГИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Актуальность: *Первичные лимфомы центральной нервной системы (ПЛЦНС) являются редким видом лимфом, встречаются в 2% от всех лимфом ЦНС и являются прогностически неблагоприятными. Согласно данным Информационной Системы ЭРОБ*

в Республике Казахстан, в 2023-2024 годах диагноз «лимфома ЦНС» был морфологически подтвержден у 13 человек. Среди первичных лимфом центральной нервной системы, ALK-негативная анапластическая крупноклеточная лимфома (АККЛ) является высокозлокачественной опухолью с агрессивным характером течения. Вопросы лечения таких пациентов остаются нерешенными, что требует расширения доказательной базы и большего количества клинических наблюдений.

***Цель исследования** – на примере клинического случая и литературных данных показать эффективность применения химио-таргетной комбинированной терапии в сочетании с аутологичной трансплантацией костного мозга у пациента с Т-клеточной лимфомой (АККЛ ЦНС).*

***Методы:** В статье описан литературный обзор и клинический случай пациента с Т-клеточной лимфомой ЦНС. Представлены данные исследований: компьютерная томография, позитронно-эмиссионная томография, магнито-резонансная томография головного мозга, а также патоморфологическое исследование с иммуногистохимическим исследованием послеоперационного материала. Описана динамика заболевания, ответ на лечение.*

***Результаты:** Пациент с направительным клиническим диагнозом «Первичная анапластическая лимфома ЦНС, ALK-негативный подтип», после микрохирургического удаления опухоли. Учитывая редкий вариант заболевания, локализацию образования, был проведен патоморфологический пересмотр препаратов с иммуногистохимическим исследованием послеоперационного материала и выбрана тактика терапии с включением таргетного препарата брентуксимаб ведотин. Представленный случай показывает потенциал применения комбинированной химиотаргетной терапии в лечении АККЛ ЦНС с учётом биологических особенностей опухоли и индивидуальных особенностей пациента.*

***Заключение:** Выбор верной тактики лечения зависит от своевременно уставленного точного диагноза, что делает диагностику ключевым звеном в алгоритме ведения пациента, в связи с чем необходимо проведение морфологического, иммуногистохимического исследования. С целью улучшения прогноза и показателей выживаемости таких пациентов, в последние годы стратегией выбора является разработка и применение комбинированных лечебных подходов, включающих как интенсивные химиотерапевтические схемы, так и современные таргетные препараты.*

***Ключевые слова:** лимфома центральной нервной системы (ЦНС), эпидемиология, Т-клеточные лимфомы, анапластическая крупноклеточная лимфома (АККЛ), таргетная терапия.*

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SURGICAL TREATMENT AND RECONSTRUCTION OF RECURRENT AMELOBLASTOMA OF THE MANDIBLE COMPLICATED BY OROSTOMY: A CLINICAL CASE

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ABSTRACT

Relevance: *Ameloblastoma is one of the most common benign jaw tumors, characterized by locally invasive growth and a high recurrence rate. Despite its benign nature, the disease presents a significant clinical challenge due to bone destruction, the risk of functional impairment, and the need for complex maxillofacial reconstruction. Diagnostic and treatment methods such as MRI, CT, biopsy, and surgical resection remain essential. However, frequent relapses necessitate new therapeutic strategies and improved reconstructive approaches.*

This report presents a clinical case of a female patient suffering from recurrent ameloblastoma of the mandible since 1997. Following initial tumor resection in 2002, multiple recurrences required repeated surgeries. In 2022, the patient was admitted again, highlighting the aggressive course of the disease.

This publication aimed to *analyze a clinical case of recurrent ameloblastoma of the mandible complicated by orostomy, with an evaluation of the effectiveness of surgical treatment and reconstruction.*

Clinical presentation: *A rare clinical case involving a 63-year-old woman diagnosed and treated for mandibular ameloblastoma is described. The tumor was first diagnosed in 1997, with subsequent surgeries in 2002, 2009, 2016, and 2020 due to recurrences. In 2022, a combined surgery was per-formed, including tumor resection and soft tissue reconstruction using a skin-muscle flap. Histology confirmed the follicular type of ameloblastoma with epithelial nests, palisading cell arrangement, and stellate structures resembling the enamel organ. MRI in May 2025 showed no signs of recurrence. The patient has remained in stable remission for three years. The disease has been tracked over nearly 30 years. The case confirms the effectiveness of a comprehensive surgical approach.*

Conclusion: *Despite its benign character, ameloblastoma requires active surgical management and long-term follow-up. This case underscores the importance of individualized treatment planning and interdisciplinary cooperation to improve outcomes and patient quality of life.*

Keywords: *ameloblastoma, recurrence, reconstructive surgery, clinical case.*

Introduction: Ameloblastoma is classified as a benign tumor of odontogenic origin. It is localized mainly in the jawbone. The development of ameloblastoma is probably associated with the transformation of residual cells of the dental plate, epithelial cell rests of Malassez, or basal cells of the oral mucosa epithelium [1].

The global incidence of ameloblastoma in 2020 amounted to 0.92 per 1 million people. The incidence of ameloblastoma worldwide is mainly spread around the age of 30 years. In Europe and North America, ameloblastoma is mainly found in elderly individuals (50-60 years); in Africa and South America, ameloblastoma is mainly found in young people (about 30 years), with the highest incidence registered in Asia (30-60 years) [2].

In 2017, the World Health Organization (WHO) included ameloblastoma in the list of benign epithelial odontogenic tumors [3]. According to the latest WHO classification, published in 2022 and updated in 2024, ameloblastoma has five clinical forms: typical (solid/multicystic), unicystic, adenoid, metastatic, and peripheral/extraspinous [4, 5].

Extended jaw resection, although effective in preventing recurrence of ameloblastoma, can lead to significant aesthetic and functional impairments [6].

This publication aimed to analyze a clinical case of recurrent ameloblastoma of the mandible complicated by orostomy, with an evaluation of the effectiveness of surgical treatment and reconstruction.

Materials and methods: The article describes a rare case of diagnosis and treatment of ameloblastoma of the lower jaw in a 63-year-old patient. The patient provided a signed informed consent to the manipulations, as well as to the use of the results of her treatment in scientific studies.

Patient Information:

Clinical findings: Local status: The face was asymmetrical due to a tumor of the parotid masticatory region and a defect in the lower jaw. The skin above the formation was purple-bluish, did not gather in a fold, and had a dense consistency on palpation. Additionally, two fistulas were detected. In the oral cavity, there was an exophytic forma-

tion in the area of the transitional fold of the upper jaw, rightward, a heterogeneous structure, painful on palpation, and densely elastic. Regional lymph nodes were not enlarged (Figure 1).

Diagnostics: Magnetic resonance imaging of the brain, performed in February 2022, revealed the presence of a volumetric formation of soft tissues of the face in the right half with involvement of neighboring muscles and destructive changes in the lower jaw and auditory arch. In addition, single foci of gliosis were found in the brain substance of vascular origin. A retrocerebral arachnoid cyst has also been detected (Figure 2).

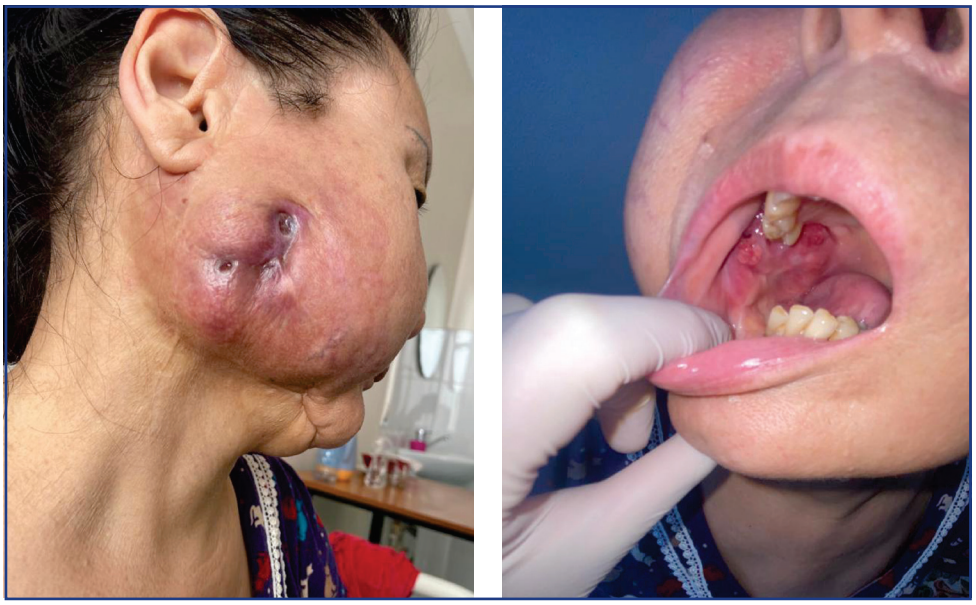

Figure 1 – Picture of a formation in the lower jaw in a 63-year-old patient diagnosed with "Ameloblastoma of the mandible. Recurrence."

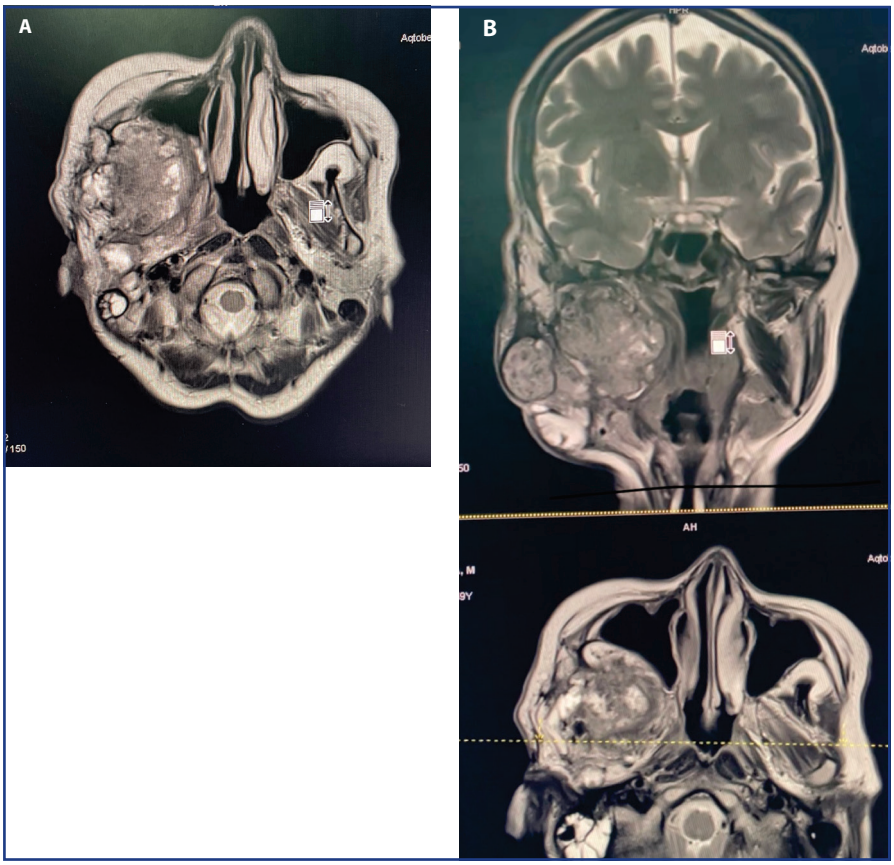

Figure 2 – MRI picture of a volumetric formation in the lower jaw in a 63-year-old patient diagnosed with "Ameloblastoma of the mandible. Recurrence: A – axial projection, B – frontal projection.

Magnetic resonance imaging of the cervical spine, performed in February 2022, showed an enlargement of the cervical lymph nodes, mainly to the right.

Treatment: After preoperative preparation, on 22.02.2022, surgical treatment was carried out as planned: Combined removal of a recurrent tumor of the middle zone of the right half of the face with extirpation of the right parotid salivary gland and buccal mucosa. Plastic surgery of the postoperative defect with a musculocutaneous flap along the pectoralis major muscle. Tracheostomy (Figure 3).

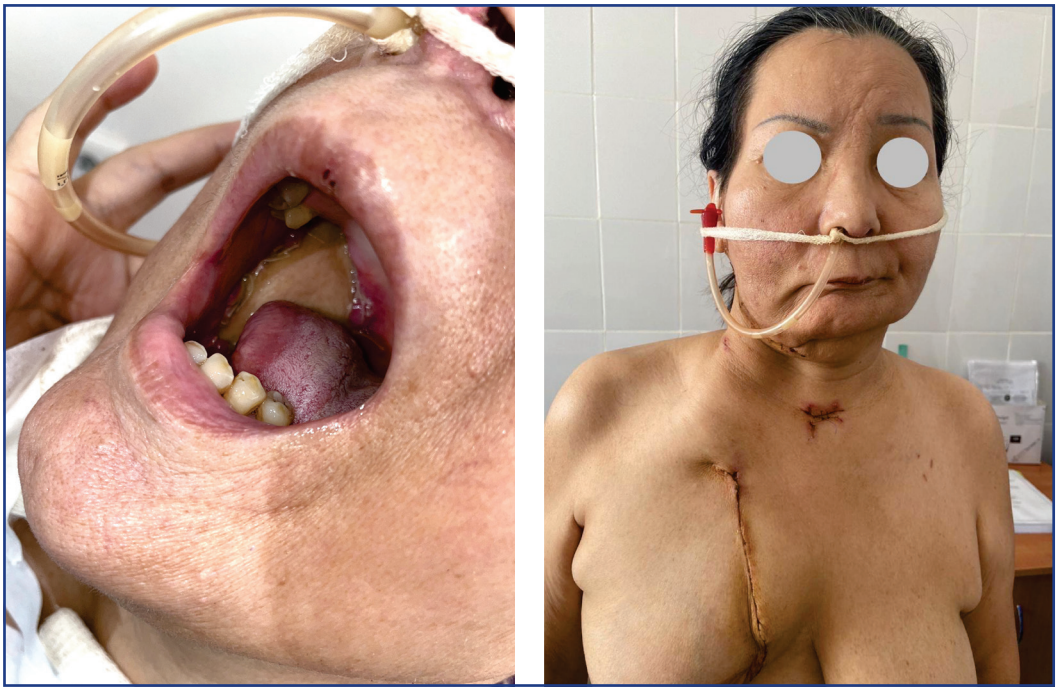

Figure 3 – Final view after surgery, "Combined removal of a recurrent tumor of the middle zone of the right half of the face with extirpation of the right parotid gland and buccal mucosa. Plastic surgery of the postoperative defect with a musculocutaneous flap along the pectoralis major muscle. Tracheostomy."

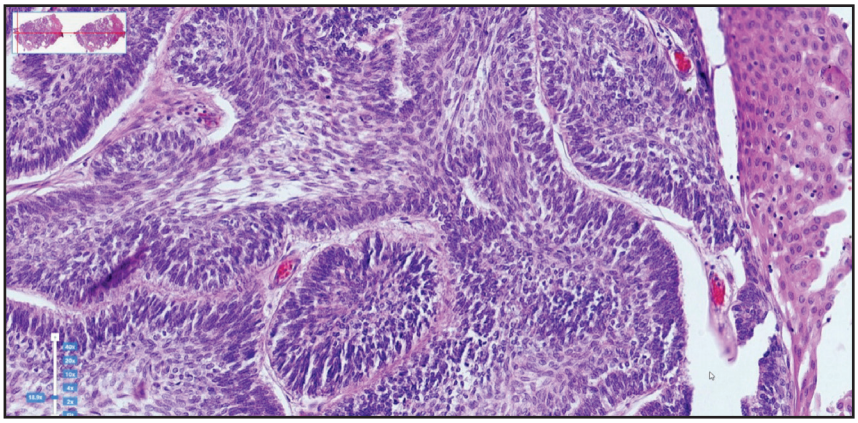

Figure 4 – Histological structure of the formation in the lower jaw in a 63-year-old patient diagnosed with Ameloblastoma of the mandible. Recurrence.

Results: Histological examination showed a tumor growth from a single-layer epithelium of structural tissue in the form of lymphocytes. Follicular ameloblastoma, reactive follicular changes in the detected lymph nodes (Figure 4).

Microscopic description: The structure consisted of round, oval, or irregular islands of epithelium that attempted to mimic the epithelium of an enamel organ. Nests and islets showed a peripheral palisade of columnar cells with reverse polarity. The central part of the insula included angular cells, resembling a stellate network of a developing tooth bud. A mature fibrous connective tissue stroma separated the nests.

MRI of the brain as of 05/25/2025: Retrocerebellar cyst. MRI signs of dyscirculatory encephalopathy. Condition after removal of ameloblastoma from the projection of the right mandible. The use of adipose and musculocutaneous tissue in the postoperative defective zone. Area with diffuse restriction in the parotid region. Residual tissue is not excluded (Figure 5).

The patient is currently healthy; no clinical or radiological signs of relapse were detected during 3 years' follow-up.

The timeline of the clinical case of "Ameloblastoma of the lower jaw on the right" is presented in Table 1.

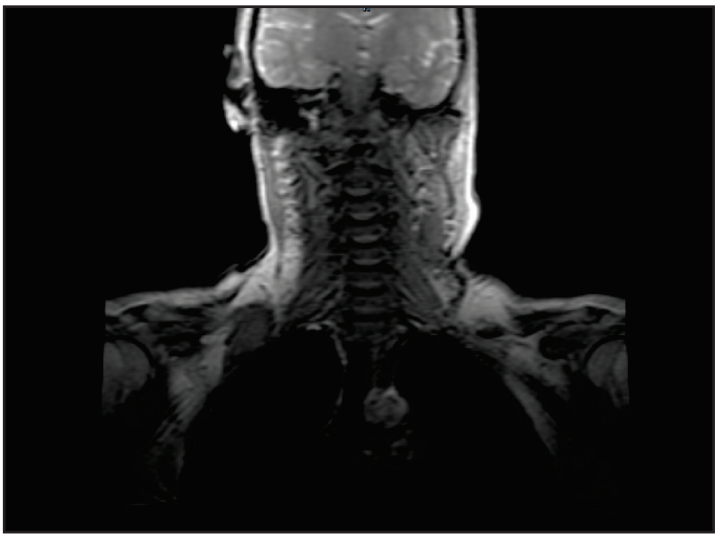

Figure 5 – Results of MRI of the brain, frontal projection: no data for recurrence were revealed in a 63-year-old patient diagnosed with Ameloblastoma of the lower jaw on the right. Recurrence.

Table 1 – Timeline of a clinical case of recurrent ameloblastoma of the mandible complicated by an orostomy

Date	Event	Symptoms
1997	A neoplasm was detected after the wisdom tooth extraction	Pain and swelling in the area of the wisdom tooth
1998	Admission to the Regional Clinical Hospital in Uralsk. Ameloblastoma was first diagnosed.	Increased jaw volume, dis-comfort when chewing
2002	Resection of the right half of the lower jaw	Pain, facial deformity, occlu-sion disorder
2009	Removal of recurrence in Orenburg	Repeated volume gain, facial asymmetry
2016	Repeated resection of recurrence in Orenburg	Swelling, a feeling of pres-sure in the jaw area
2020	Surgical removal of a recurrent tumor in Tash-kent	Pain, limitation of mouth opening, recurrent course
February 2022	Hospitalization at the M. Ospanov Medical Center (Aktobe), MRI, diagnosis of relapse	Pain, speech disorders
22 February 2022	A combined operation with reconstruction of a musculocutaneous flap was performed.	Postoperative pain, recovery of functions
May 2022	First postoperative control: satisfactory condition, remission	No complaints
January 2023	MRI of the head and lower jaw – no signs of re-currence were revealed	No complaints
March 2024	Repeated MRI, consultations with an oncologist and a dentist – stable remission	No complaints
May 2025	Last MRI: postoperative changes with no signs of recurrence. No complaints	The condition is stable; no signs of recurrence

Discussion: Ameloblastoma is the most common tumor of the oral cavity, developing from residual odontogenic epithelium [7, 8]. The most common type of ameloblastoma (57-63.8% of cases) is ordinary ameloblastoma [9]. It is predominantly localized in the lower jaw [10], showing no obvious dependence on gender or ethnicity. Clinically, conventional ameloblastoma is manifested by slow and asymptomatic growth of bone tissue. With a significant tumor size, loosening of the teeth, facial asymmetry, masticatory function disorders, and pain can be observed. Unlike other types of ameloblastoma, the ordinary form is characterized by a more aggressive course and an increased likelihood of recurrence. The most effective treatment method is radical surgery [11].

The goal of surgical treatment of ameloblastoma is to achieve maximum efficiency in preventing recurrences of the disease while restoring the full functionality and aesthetic appearance of the patient, while minimizing the risk of complications in the area of donor material. Currently, the standard treatment for classic ameloblastoma (solid/multicystic) is a radical operation, involving a complete block resection with an adequate supply of healthy tissues. In this case, segmental or marginal osteotomy is used for the lower jaw, and partial or total maxillectomy is used for the upper jaw. Given the high probability of recurrence after conservative treatment, especially in cases of hard/multicystic form of ameloblastoma, it is recommended to perform a wide resection with an indentation from the bone edges by 1-1.5 cm. Radical surgery, despite its effectiveness, can lead to aesthetic defects, functional disorders, and psychological discomfort in patients [12]. In order to minimize such complications, conservative surgery was reviewed, including removal of abnormal focus, enucleation, curettage, as well as their various combinations using Carnoy solution and cryotherapy, which was performed for that patient.

However, as a recent meta-analysis has shown, conservative approaches are characterized by a high relapse rate (up to 40%). Moreover, in the treatment of primary solid/multicenter ameloblastoma, conservative methods were three times more prone to recurrence compared to radical methods [13]. Similarly, another meta-analysis covering four studies of radical and conservative treatment of ameloblastoma found a statistically significant increase in recurrence rates in conservative treatment compared with surgery intervention [14]. The prognosis of ameloblastoma is determined by a set of factors, including the patient's age and the tumor's location, size, histological type, degree, and stage of development [15].

According to studies, there is a risk of recurrence after treatment of ameloblastoma. A Chinese study indicates an overall recurrence rate of 9.8% [16], while a European multicenter study [17] fixes this figure at the level of 19.3%. Tumors larger than 6 cm in diameter or affecting neighboring anatomical structures, including soft tissues, are associated with an increased risk of recurrence, regardless of the chosen method of surgical intervention [17]. An increased recurrence rate is also observed in granular and follicular histological variants of the tumor [3]. Ameloblastoma is characterized by slow growth. According to a meta-analysis, the average annual growth rate of this tumor is 87.8% [12]. However, if left untreated, ameloblastoma can reach a significant size, which can lead to airway compression and a life-threatening condition [18].

Histological analysis in all cases confirmed the diagnosis of ameloblastoma, which excludes the possibility of a different nature of the tumor. According to the WHO classification 2024, the most common form is classic ameloblastoma, characterized by infiltrative growth and a higher tendency to recurrence. Given the repeated relapses, we can assume exactly this form of the disease in this case.

Another important feature of the presented case is the wide geography of the patient's treatment, including medical institutions of Kazakhstan, the Russian Federation, and Uzbekistan. This may indicate the difficulty of managing such patients in the long term, as well as the need for a standardized approach to the treatment of ameloblastoma at the international level. Based on this clinical follow-up, it can be concluded that the optimal treatment tactics for ameloblastoma are radical surgery followed by careful monitoring of the patient. An important role is also played by a multidisciplinary approach, including dental surgeons, oncologists, and reconstructive specialists, which not only reduces the risk of recurrence but also improves the patient's quality of life after surgery.

Conclusion: Ameloblastoma is a benign but aggressive tumor prone to recurrence. The optimal treatment tactic is radical resection with reconstruction, since conservative methods are ineffective. The presented case demonstrates the importance of timely diagnosis, an interdisciplinary approach, and long-term follow-up. Standardization of ameloblastoma treatment remains a critical task.

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АҢДАТПА

ОРОСТОМАМЕН АСҚЫНҒАН ТӨМЕНГІ ЖАҚ СҮЙЕГІНІҢ ҚАЙТАЛАНАТЫН АМЕЛОБЛАСТОМАСЫН ХИРУРГИЯЛЫҚ ЕМДЕУ ЖӘНЕ РЕКОНСТРУКЦИЯЛАУ: КЛИНИКАЛЫҚ ЖАҒДАЙДЫ

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Өзектілігі: *Амелобластома — жақ сүйегінің жиі кездесетін қатерсіз ісіктерінің бірі, ол жергілікті инвазиялық өсуімен және жиі қайталануымен сипатталады. Қатерсіз сипатына қарамастан, бұл ауру сүйек тінінің бұзылуы, функционалдық бұзылыстар қаупі және жақ-бет ақауларын қалпына келтірудегі күрделілік салдарынан маңызды клиникалық мәселе болып табылады. Қазіргі таңда магнитті-резонанстық және компьютерлік томография, биопсия және хирургиялық резекцияны қоса алғанда, диагностика мен емдеудің заманауи әдістері бұл науқастарды басқаруда негізгі құрал болып қала береді. Дегенмен, рецидивтердің жиілігі жаңа терапиялық тәсілдерді іздеуді және реконструктивті әдістерді жетілдіруді талап етеді.*

Бұл басылымның мақсаты *– оростомамен күрделенген төменгі жақтың қайталанатын амелобластомасының клиникалық жағдайын талдау, хирургиялық емдеу мен реконструкцияның тиімділігін бағалау.*

Әдістері: *Мақалада 63 жастағы әйелде төменгі жақтың амелобластомасын диагностикалау және емдеу бойынша сирек клиникалық жағдай сипатталған.*

Нәтижелері: *Амелобластома алғаш рет 1997 жылы анықталған, кейін 2002, 2009, 2016 және 2020 жылдары бірнеше рет рецидивтермен және хирургиялық араласулармен байқалған. 2022 жылы қайталанған ісікті резекциялау және тері-бұлшықеттік қақпақша арқылы ақауды қалпына келтірумен біріктірілген операция жасалды.*

Гистологиялық тұрғыдан фолликулярлық типтегі амелобластома расталды: палисад тәрізді орналасқан жасушалары мен эмальді органды еліктіретін жұлдыз тәрізді құрылымдары бар эпителиальды ұяшықтар анықталды. 2025 жылдың мамырындағы МРТ нәтижесі бойынша рецидив белгілері байқалмаған. Үш жылдық бақылау барысында пациент тұрақты ремиссияда.

Ауру уақыт шкаласы бойынша шамамен 30 жыл бойы бақыланды. Алынған деректер кешенді хирургиялық әдістің және реконструкцияның тиімділігін растайды.

Қорытынды: *Амелобластома қатерсіз ісік бола тұра, белсенді хирургиялық араласуды және ұзақ мерзімді динамикалық бақылауды қажет ететін патология ретінде ерекшеленеді. Жекелендірілген емдеу жоспары мен пәнаралық тәсіл науқас жағдайын жақсартуға мүмкіндік береді.*

Түйінді сөздер: *амелобластома, рецидив, реконструктивті хирургия, клиникалық жағдай.*

АННОТАЦИЯ

ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ И РЕКОНСТРУКЦИЯ РЕЦИДИВИРУЮЩЕЙ АМЕЛОБЛАСТОМЫ НИЖНЕЙ ЧЕЛЮСТИ, ОСЛОЖНЕННОЙ ОРОСТОМОЙ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Амелобластома – одна из наиболее распространённых доброкачественных опухолей челюсти, характеризующаяся локально инвазивным ростом и высокой склонностью к рецидивированию. Несмотря на доброкачественную природу, заболевание представляет серьёзную клиническую проблему вследствие разрушения костной ткани, риска функциональных нарушений и необходимости сложной реконструкции челюстно-лицевых дефектов. Современные методы диагностики и лечения, включая магнитно-резонансную и компьютерную томографию, биопсию и хирургическую резекцию, остаются ключевыми в ведении таких пациентов. Однако высокая частота рецидивов обусловливает необходимость поиска новых подходов к терапии и усовершенствования реконструктивных методов.*

Цель публикации *– анализ клинического случая рецидивирующей амелобластомы нижней челюсти, осложненной оростомой, с оценкой эффективности хирургического лечения и реконструкции.*

Методы: *В статье описан редкий случай диагностики и лечения амелобластомы нижней челюсти у пациентки 63 лет.*

Результаты: *Амелобластома у пациентки впервые выявлена в 1997 году, с последующими рецидивами и хирургическими вмешательствами в 2002, 2009, 2016 и 2020 годах. В 2022 году выполнена комбинированная операция с резекцией рецидивной опухоли и реконструкцией дефекта кожно-мышечным лоскутом.*

Гистологически подтверждён фолликулярный тип амелобластомы: выявлены эпителиальные гнёзда с палисадным расположением клеток и звездчатоподобными структурами, имитирующими эмалевый орган. По данным МРТ от мая 2025 года, признаков рецидива не выявлено. На протяжении трёх лет наблюдения пациентка находится в устойчивой ремиссии.

Заболевание прослежено на временной шкале в течение почти 30 лет. Полученные данные подтверждают эффективность комплексного хирургического подхода с реконструкцией.

Заключение: *Данный клинический случай демонстрирует, что амелобластома, несмотря на доброкачественный характер, требует активного хирургического подхода и длительного наблюдения. Представленный опыт подтверждает важность индивидуализированного плана лечения и междисциплинарного взаимодействия специалистов для повышения эффективности терапии и улучшения качества жизни пациентов.*

Ключевые слова: *амелобластома, рецидив, реконструктивная операция, клинический случай.*

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QUALITY OF LIFE IN WOMEN WITH BREAST CANCER AFTER TREATMENT

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ABSTRACT

Relevance: *Breast cancer (BC) is one of the most common oncological diseases among women. Despite advances in treatment methods, factors affecting patients' quality of life and psy-cho-emotional state remain insufficiently studied. In the post-treatment period, changes in physical, emotional, sexual, and social well-being have a significant impact on patients' quality of life (QoL).*

The study aimed to *assess the quality of life of women treated for breast cancer based on the EORTC QLQ-BR23 questionnaire.*

Methods: *Data collection was conducted from January 15, 2024, to January 1, 2025, at the Medical Center of West Kazakhstan Marat Ospanov Medical University (Aktobe, Kazakhstan) using the EORTC QLQ-BR23 questionnaire. A total of 103 women participated in the study. The EORTC QLQ-BR23 is a standardized tool for assessing the QoL in BC.*

Results: *According to the study, 69.9% of patients rated their health status as satisfactory, while 30.1% reported a significant decline in the QoL (p=0.000). Major concerns included physical functioning and body image satisfaction (p=0.000), deterioration of sexual function (p=0.000), and uncertainty about the future (p=0.000). Additionally, systemic therapy side effects (p=0.000), breast symptoms (p=0.000), and hair loss (p=0.000) had a negative impact on the QoL.*

Conclusion: *The study results reaffirm the relevance of this issue and underscore the im-portance of comprehensive support measures in enhancing the QoL for BC survivors. Psychological support, rehabilitation programs, and measures to reduce treatment side effects may contribute to better patient social adaptation. The findings provide a foundation for further improvement of medical and psychological support for BC patients.*

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

Introduction: Breast cancer (BC) ranks first in cancer incidence in women, with a statistically stable growth [1]. GLOBOCAN 2022 predicts BC to become the second most common cancer in both sexes and the first among women globally. 2.3 million new cases are registered every year. BC accounts for 23.8% of all new cancer cases in women [2]. The BC mortality rate is 7%. BC causes 1 of 4 cancer cases and 1 of 6 cancer deaths, ranking first in incidence even in emerging and transitional economies [3].

Despite a trend of stabilization in overall cancer incidence in Kazakhstan, BC incidence in the country is increasing, in line with global indicators [4]. According to GLOBOCAN 2022, BC accounts for 12.6% of new cancer cases in Kazakhstan, ranking first among all tumor incidences. The mortality from BC is 10.9%, and the 5-year prevalence is 17.9 per 100,000 people [5].

Despite significant advances in BC diagnostics and treatment, it has a significant negative impact on the quality of life (QoL) of affected women [6]. One of the most important areas in medicine is the study of the QoL of patients, which is understood as the satisfaction of a person in physical, social, psychological, and spiritual terms, that is, conditional well-being in all spheres of life, which a person evaluates according to the totality of his subjective experiences [7]. Assessing QoL can help the doctor personalize symptomatic therapy and obtain important information to predict the disease. QoL can serve as the basis for the development of rehabilitation programs for cancer patients. QoL assessment in clinical trials improves the research quality [8].

Although advances in science and medicine in recent years have led to a significant increase in the number of healthy survivors from BC, the physical health of women at risk due to the disease and the side effects of treatment, as well as their social and emotional well-being, still challenge their QoL [9]. BC diagnosis and treatment affect all aspects of women's health: physical, psychological, social, economic, and spiritual [10]. In oncology, the concept of growth is of particular importance due to the peculiarities of pathology and the radicality of treatment methods (surgical, radiation, and chemotherapy) [11]. Various research studies have evaluated differences in the QoL depending on the method of surgery for BC [12].

It is known that different options for surgical treatment of BC can have different effects on post-surgery QoL of women [11]. Surgical treatment of the mammary gland is generally considered very aggressive, considering the aesthetic effect of the treatment. This causes fear, anxiety, and uncertainty of consequences in the context of the underlying disease [6]. Surgical intervention has not only physiological, but also psychological and social consequences, since a woman can lose one of the main signs of femininity – the mammary gland. At the same time, the therapy was long centered on oncological safe-

ty, leaving the aesthetic result or assessment of personal well-being without attention [13]. On the one hand, radical surgery for BC helps inhibit the disease progression for several years. However, on the other hand, they lead to functional disorders associated with organ loss, disability, and, as a result, deep emotional disorders that inhibit the process of recovery, adaptation, and re-socialization, which prevents the achievement of a full-fledged therapeutic result [14]. Radical mastectomy for many years will be the only surgical method to treat BC. This intervention is often accompanied by post-mastectomy syndrome and has a permanent traumatic effect on the woman's psyche. The presence of a cosmetic defect after surgery forces a woman to change her usual lifestyle in order to hide her problem from others. This inevitably causes problems in personal life, contributes to the development of disorders in the sexual sphere, emotional isolation, and the emergence of bad habits. According to scientists, the presence of BC is a "very strong stress" for a woman, since she must accept not only the presence of a potentially fatal disease, but also the need to remove the mammary gland [15]. Assumptions about the etiology and course of cancer indicate the importance of studying the interaction of various biological, psychological, and social factors [16].

The study aimed to assess the quality of life of women treated for breast cancer based on the EORTC QLQ-BR23 questionnaire.

Materials and methods: A survey was conducted among patients of the Medical Center of West Kazakhstan Marat Ospanov Medical University (WKMOMU) from January 15, 2024, to January 1, 2025. During the planning of the research work, f2=0.35 and power = 0.8 were calculated based on the estimated impact size for the regression analysis. The sample size was 82 people, with a margin of error of +20 %, resulting in a total sample size of 98 people. The survey involved 103 women.

Inclusion criteria: admission to the WKMOMU Medical Center in the postoperative period; newly detected BC; consent to fill out the questionnaire.

Exclusion criteria: newly diagnosed BC for the first time, but are not subject to surgery; patients who have undergone surgery for a benign tumor; those who do not give consent to filling out the questionnaire.

Data collection consisted of 2 stages:

I – Determination of socio-demographic and clinical data of the survey participants, such as age, marital status, number of children, level of education, place of work, place of residence, method of diagnosis, and type of surgery;

II – The use of the EORTC QLQ-BR23 questionnaire to determine the effect of treatment on the QoL of sick women.

EORTC QLQ-BR23 is a standardized, widely used questionnaire for measuring the QoL of patients with BC, widely used in foreign countries and Russia. In 1996, it was developed by the European Organization for Research and Treatment of Cancer (EORTC) QoL Study Group. The questionnaire consists of 23 questions divided into 4 functional (Body Image, Sexual Functioning, Sexual Enjoyment, Future Perspective) and 4 symptomatic (Systemic Therapy Side Effects, Arm Symptoms, Breast Symptoms, Upset by Hair Loss) scales. Each question is evaluated on a scale from "Not at All" (1) to "A Little" (2), "Quite a Bit" (3), and "Very Much" (4).

According to the EORTC measurement guide, the assessment included summing up the initial scores for the corresponding points and their linear conversion. The given formulas were used to derive the resulting linear scale, ranging from 0 to 100. A high score on functional scales corresponded to a high (good) level of functioning, while a high score on symptomatic scales and for individual symptoms indicated an increase in symptoms and the feeling of discomfort. The remaining points were accounted for according to the survey instructions: a "no answer" on a scale meant the "no data" value [17].

Research ethics. Prior to the study, the local Bioethical Commission of WKMOU approved the scientific research work in strict compliance with all necessary ethical standards and rules (Protocol No. 9, 02.10.2023).

A permission No. 13/8-21-77 was obtained from E. E. Smailov, Head of the Medical Center of WKMOMU, to conduct a study of women undergoing treatment with BC. Each participant was to sign a Personal Data Sharing Consent Agreement in order to participate in the study.

At the beginning of each survey, information was provided about the study's goals and objectives, its importance, and participants' rights to refuse participation at any time. It was also noted that the data would be confidential and that the anonymity of their identity would be preserved.

Statistical methods for processing the results obtained. Descriptive statistics. Statistical processing of results using IBM SPSS Statistics version 25.0. (IBM Corp., Armonk, NY). The normality of distribution of numerical variables was tested using the Shapiro-Wilk test. The main indicators of descriptive statistics were calculated: for numerical variables, the arithmetic mean (M) and standard deviation (SD) ($\mu \pm \sigma$); and for categorical variables, as well as for categorical variables (high/low) after dichotomization according to the mean, frequency (N), and percentage (%). For functional and health status/QoL scales, 0-50 indicated a low level, and 51-100 indicated a high level. For symptomatic scales, a score of 0-50 indicated a high level, while a score of 51-100 indicated a low level. The statistical significance of the difference between the "high" and "low" groups on the functional and symptomatic scales (p-value) was assessed using the Mann-Whitney U test criterion. Differences in values were considered statistically significant at $p<0.05$.

Results: Socio-demographic and clinical characteristics of the respondents in the study are presented in Table 1. The average age of the women was 58.4 (SD=10.89) years; the youngest patient was 25 years old, and the oldest was over 75 years old. By age group, the largest share was 39.8% of respondents aged 56-65 (SD=30.4-49.3), and the smallest group included patients aged 25-35 (SD=-0.3-6.2). Most of the study participants were urban residents (81.6%, SD=74.1-89.0), while the proportion of those living in rural areas was 18.4% (SD = 11.0-25.9). Depending on the level of education, the majority (70.9%) had secondary education (SD=62.1-79.6), and patients with higher education accounted for 29.1% (SD=20.4-37.9). In terms of employment, most patients were employed, at 43.7% (SD=34.1-53.3), and retired, comprising 39.8% (SD=30.4-49.3), while the share of unemployed patients was 16.5% (SD=9.3-23.7). According to marital status, 54.4% of respondents (SD=44.7-64.0) are married, and 45.6% (SD=36.0-55.3) are single. The largest share of children was 65.0% (SD=55.8-74.3) of patients with 2-3 children, 18.4% (SD=11.0-25.9) had 0-1 child, and 16.5% (SD=9.3-23.7) had 4 or more children. Regarding the method of diagnosis, more than half of the respondents identified the disease through screening (52.4%; SD=42.8-62.1), while 47.6% (SD=37.9-57.2) reported feeling symptoms and visiting the doctor on their own initiative. In terms of treatment methods, most patients (70.9%; SD=62.1-79.6) underwent radical mastectomy (RME), the remaining 29.1% (SD=20.4-37.9) underwent organ-saving surgery with extended sectoral breast resection (ESBR).

Table 1 – Socio-demographic and clinical characteristics of women undergoing treatment with breast cancer

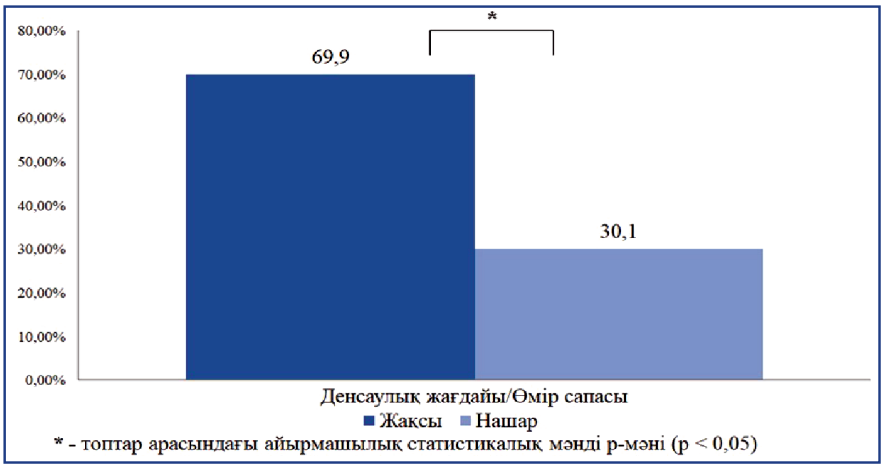
Variables Age	Number of patients (n=103)	Recurrence rate, %	Confidence interval 95%
25-35	3	2,9	-0,3-6,2
36-45	11	10,7	4,7-16,6
46-55	21	20,4	12,6-28,2
56-65	41	39,8	30,4-49,3
66-75	22	21,4	13,4-29,3
75 and older	5	4,9	0,7-9,0
Place of residence			
Urban	84	81,6	74,1-89,0
Rural	19	18,4	11,0-25,9
Education level			
Higher Education	73	70,9	62,1-79,6
High School	30	29,1	20,4-37,9
Employment			
Unemployed	17	16,5	9,3-23,7
Employed	45	43,7	34,1-53,3
Retired	41	39,8	30,4-49,3
Marital Status			
Married	56	54,4	44,7-64,0
Single	47	45,6	36,0-55,3
Number of children			
0-1	19	18,4	11,0-25,9
2-3	67	65,0	55,8-74,3
4 and more	17	16,5	9,3-23,7
Diagnosed via			
Screening	54	52,4	42,8-62,1
Visit to a doctor on the patient's initiative	49	47,6	37,9-57,2
Type of surgery			
RME	73	70,9	62,1-79,6
ESBR	30	29,1	20,4-37,9

The study showed significant differences in the health status and QoL indicators in patients.

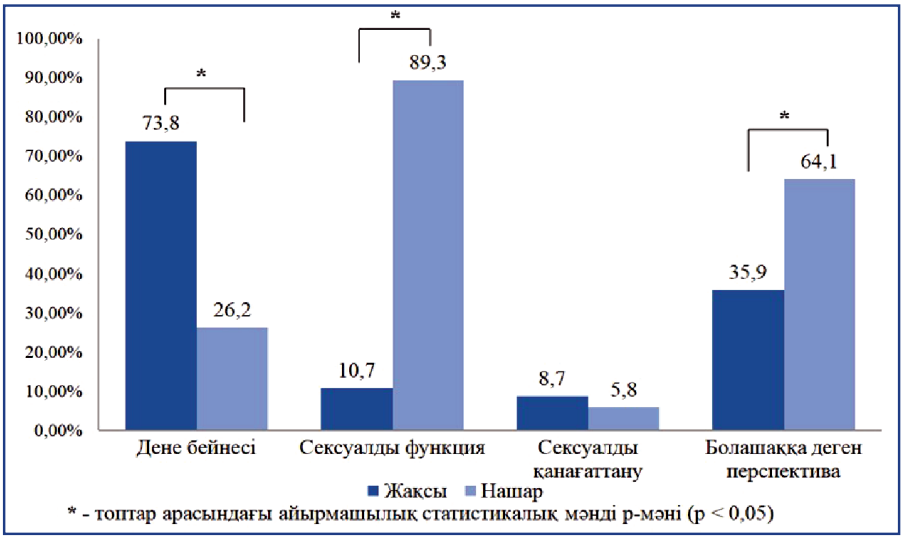
The difference between the "high" and "low" groups *on the QoL scale* was statistically significant (p=0.000). 69.9% of the patients who participated in the study assessed their state of health and QoL as high, while the remaining 30.1% considered it to be low (Figure 1).

When analyzing the indicators of *functional scales,* a statistically significant difference was found between the groups, primarily in terms of the level of satisfaction with body image (p=0.000). Most patients, 73.8%, reported being satisfied with their body image, while 26.2% expressed dissatisfaction. In addition, there was a decrease in sexual functioning (p=0.000). Only 10.7% of patients rated their sexual functioning as high, and 89.3% considered this indicator to be low or low level. This factor can seriously affect the psycho-emotional state of patients and the QoL in general. Even in terms of a future perspective, there was a significant difference between patients (p=0.000). 35.9% of the study participants expressed confidence in their future, while 64.1% reported reduced hope for the future or felt insecure (Figure 2).

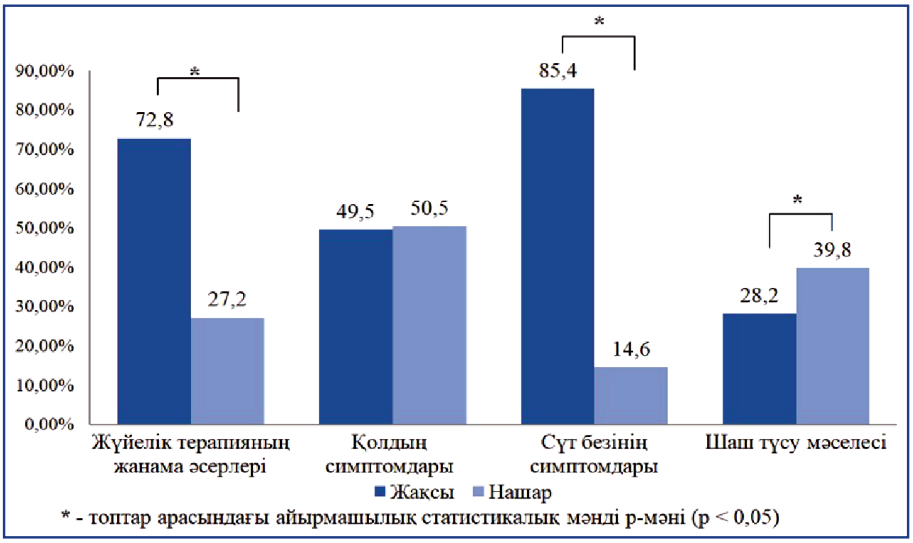
Statistically significant differences were observed between the "high" and "low" groups on both *symptomatic scales*. When evaluating the side effects of systemic therapy, 72.8% of patients reported no adverse effects, while 27.2% noted that these effects were more noticeable (p=0.000).



*Legend: Денсаулық жағдайы/Өмір сапасы – Health status / Quality of life; Жақсы – High; Нашар – Low; * - топтар арасындағы айырмашылық статистикалық мәнді р-мәні – The statistical difference between groups was significant (p<0.05)*
Figure 1 – Levels on the Health Status/Quality of Life scale in women being treated for breast cancer



*Legend: Дене бейнесі – Body Image; Сексуалды функция – Sexual Functioning; Сексуалды қанағаттану – Sexual Enjoyment; Болашаққа деген перспектива – Future Perspective; Жақсы – High; Нашар – Low; * - топтар арасындағы айырмашылық статистикалық мәнді р-мәні – The statistical difference between groups was significant (p<0.05)*
Figure 2 – Levels on functional scales in women being treated for breast cancer



*Legend: Жүйелік терапияның жанама әсерлері – Systemic therapy side effects; Қолдың симптомдары – Arm symptoms; Сүт безінің симптомдары – Breast symptoms; Шаш түсу мәселесі – Upset by hair loss; Жақсы – High; Нашар – Low; * - топтар арасындағы айырмашылық статистикалық мәнді р-мәні – The statistical difference between groups was significant (p<0.05)*
Figure 3 – Levels on the symptomatic scale in women being treated for breast cancer

A significant difference was also found between the two groups in terms of breast symptoms (p=0.000). In 85.4% of the patients in the study, these symptoms were not observed, and in 14.6% they showed a pronounced manifestation. The problem of hair loss was also one of the most important factors contributing to the QoL of patients (p=0.000). In 28.2% of patients, this problem was not observed at all, while 39.8% reported significant hair loss (Figure 3).

Discussion: The study results revealed significant differences between QoL levels in patients. The findings show that reconstructive plastic surgery plays an important role in improving the QoL of patients with BC, which is indicated by higher scores on all scales of the questionnaire compared to women after radical mastectomy [1]. The difference between the "high" and "low" groups on the QoL/health status scale was statistically significant (p=0.000). In the results of other scales scores, significant differences were reported between the following sub-scales of the functional scales of the QLQ-BR23 questionnaire: body image (p=0.003), sexual functioning (p=0.007) and sexual enjoyment (p=0.005), and in the case of symptom scales, the differences were related to shoulder-related diseases (p=0.024) [6]. Even in our research, significant differences were observed in the scores on functional scales, especially in terms of satisfaction with body image (p=0.000). In addition, a decrease in sexual functioning is also considered an important factor (p=0.000). This indicates that functional changes affect the psychological state of patients and negatively affect their self-perception. These findings support the results of the previous studies. Worth noting that women had the lowest score during functional assessment was given to sexual functioning (17.49±23.56, Me=0.00). Sexual functioning, sexual enjoyment, and body image were assessed as high by women who underwent organ-saving surgery, while respondents who underwent mastectomy assessed low. In the group of women who underwent mastectomy, decreased libido was often observed, which led to a decrease in their QoL. In these studies, although 80% of patients were satisfied with their appearance, only 54% of them were able to accept their naked bodies [6]. Attitude towards the future is also an important indicator; 64.1% of the participants expressed uncertainty about the future (p=0.000). These scores support the findings of previous studies, which have shown that fear is a common emotion among patients. They are worried about cancer relapse or metastasis. Female patients are also very worried about the likelihood that their daughters will inherit the disease [3].

Significant differences were also found on the symptomatic scales. Side effects of systemic therapy were observed in 27.2% of patients (p=0.000). However, the level of observation of breast symptoms also differed (p=0.000). The problem of hair loss was also identified as an important factor. According to the results of our study, 39.8% of patients experienced significant hair loss (p=0.000). These figures support the data from other research cited in the literature, which states that the duration of adjuvant treatment can last for years after surgery and that patients may experience side effects and late effects during this period. For example, radiation therapy can cause skin changes, systemic chemotherapy and/or endocrine therapy are known to cause polyneuropathy, musculoskeletal pain, hair loss, and fatigue, which can affect cognitive and social functions [18]. In some studies, physical functions, role function, body image, financial difficulties, and symptoms such as fatigue, pain, shortness of breath, as well as symptoms associated with side effects of breast, arm, and systemic therapy, significantly worsened after the completion of treatment [19].

Overall, the results of this study highlight the main factors influencing the QoL of cancer patients. The results obtained are consistent with the data described in the literature and once again confirm the need for comprehensive support to improve the QoL of patients.

Conclusion: BC is a complex disease that has a significant impact on the QoL due to various factors. This study revealed physical and psycho-emotional changes, functional disorders, and side effects of therapy in women who underwent treatment. In the study, women rated their QoL as high (p < 0.000). Namely, 73.8% of patients were satisfied with their body image, while 26.2% were dissatisfied (p = 0.000). Decreased sexual functioning (p=0.000) and uncertainty about the future (p=0.000) were found. Side effects of systemic therapy (p=0.000), breast symptoms (p=0.000), and hair loss (p=0.000) were observed on the symptomatic scales.

The results of this study once again confirm the relevance of this problem and emphasize the importance of comprehensive support to improve the QoL of women with BC. Psychological support, rehabilitation programs, and comprehensive medical supervision help patients adapt to everyday life. These aspects of the study play a crucial role in enhancing the effectiveness of early detection, treatment, and rehabilitation of patients with BC. Moreover, scientific research in this area can serve as the basis for improving national and regional strategies to combat cancer. Thus, this study contributes to the formation of important practical and theoretical foundations for improving the QoL of women with BC.

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АНДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІ БАР ЕМДЕУДЕН ӨТКЕН ӘЙЕЛДЕРДІҢ ӨМІР САПАСЫ

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Өзектілігі: *Сүт безі қатерлі ісігі (СБҚІ) – әйелдер арасында кең таралған онкологиялық аурулардың бірі. Бұл дерттің емдеу әдістері жетілдірілгенімен, науқастардың өмір сапасы мен психоэмоционалдық жағдайына әсер ететін факторлар толық зерттелмеген. Емдеуден кейінгі кезеңде науқастардың физикалық, эмоционалдық, сексуалды және әлеуметтік жағдайының өзгеруі олардың өмір сапасына елеулі ықпал етеді.*

Зерттеу мақсаты *– сүт безі қатерлі ісігі бар емдеуден өткен әйелдердің өмір сапасын EORTC QLQ-BR23 сауалнамасы негізінде зерттеу.*

Әдістері: *Деректерді жинау 2024 жылғы 15 қаңтар мен 2025 жылғы 1 қаңтар аралығында Марат Оспанов атындағы Батыс Қазақстан медициналық университетінің медициналық орталығында EORTC QLQ-BR23 сауалнамасы арқылы жүргізілді. Сауалнамаға 103 әйел қатысты. EORTC QLQ-BR23 – СБҚІ бар науқастардың өмір сапасын бағалауға арналған стандартталған құрал.*

Нәтижелері: *Зерттеу нәтижелері бойынша, науқастардың 69,9%-ы өз денсаулық жағдайын қанағаттанарлық деп бағаласа, 30,1%-ы өмір сапасының айтарлықтай төмендегенін атап өтті (p=0,000). Физикалық функциялар мен дене бей-несіне қанағаттану деңгейі (p=0,000), сексуалдық функцияның нашарлауы (p=0,000) және болашаққа деген сенімсіздік (p=0,000) маңызды мәселелер ретінде анықталды. Сонымен қатар, жүйелік терапияның жанама әсерлері (p=0,000), сүт безі симптомдары (p=0,000) және шаш түсу проблемасы (p=0,000) өмір сапасына теріс әсер етті.*

Қорытынды: *Алынған зерттеу нәтижелері мәселенің өзектілігін тағы бір рет растай отырып, СБҚІ емделген науқастардың өмір сапасын арттыру үшін жан-жақты қолдау шараларының маңыздылығын көрсетеді. Психологиялық көмек, оңалту бағдарламаларын дамыту және емдеудің жанама әсерлерін азайтуға бағытталған шаралар пациенттердің әлеуметтік бейімделуін жақсартуға ықпал етуі мүмкін. Алынған мәліметтер науқастарға медициналық және психологи-ялық көмекті одан әрі жетілдіру үшін негіз бола алады.*

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

АННОТАЦИЯ

КАЧЕСТВО ЖИЗНИ У ЖЕНЩИН С РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ, ПЕРЕНЕСШИХ ЛЕЧЕНИЕ

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Актуальность: *Рак молочной железы (РМЖ) — одно из наиболее распространенных онкологических заболеваний среди женщин. Несмотря на усовершенствование методов лечения, факторы, влияющие на качество жизни и психоэмоциональное состояние пациенток, до сих пор недостаточно изучены. В период после лечения изменения физического, эмоционального, сексуального и социального состояния пациенток оказывают существенное влияние на их качество жизни.*

Цель исследования *– изучить качество жизни женщин с раком молочной железы, перенесших лечение, на основе анкеты EORTC QLQ-BR23.*

Методы: *Сбор данных был проведен с 15 января 2024 года по 1 января 2025 года в медицинском центре Западно-Казахстанского медицинского университета имени Марата Оспанова (Актобе, Казахстан) с использованием анкеты EORTC QLQ-BR23. В исследовании приняли участие 103 женщины. EORTC QLQ-BR23 — это стандартизированный инструмент для оценки качества жизни пациенток с РМЖ.*

Результаты: *По результатам исследования, 69,9% пациенток оценили свое состояние здоровья как удовлетворительное, в то время как 30,1% отметили значительное снижение качества жизни (p=0,000). Уровень удовлетворенности физическими функциями и телесным образом (p=0,000), ухудшение сексуальной функции (p=0,000) и неуверенность в будущем (p=0,000) были определены как важные проблемы. Также побочные эффекты системной терапии (p=0,000), симптомы РМЖ (p=0,000) и проблема выпадения волос (p=0,000) оказали негативное влияние на качество жизни.*

Заключение: *Полученные результаты исследования еще раз подтверждают актуальность проблемы и подчеркивают важность комплексной поддержки для повышения качества жизни пациенток, перенесших РМЖ. Психологическая помощь, развитие реабилитационных программ и меры, направленные на снижение побочных эффектов лечения, могут способствовать улучшению социальной адаптации пациенток. Полученные данные могут стать основой для дальнейшего совершенствования медицинской и психологической помощи пациенткам.*

Ключевые слова: *женщина, рак молочной железы (РМЖ), качество жизни, EORTC QLQ-BR23.*

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ADAPTATION INTO KAZAKH AND RELIABILITY ASSESSMENT OF THE MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT (MSPSS)

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ABSTRACT

Relevance: *Social support is crucial for the physical and emotional well-being of individuals with cancer. A cancer diagnosis causes psychological stress, leading to fear, hopelessness, depression, and isolation. Support from family, friends, colleagues, and healthcare providers is vital in such cases. It helps patients stay connected to society, return to work, and improve quality of life while promoting social integration and adaptation to normal life.*

The study aimed to *adapt the Multidimensional Scale of Perceived Social Support (MSPSS) into Kazakh and assess its reliability.*

Methods: *The study design is a cross-sectional momentary study. A survey was conducted to determine the level of social support among cancer patients receiving treatment at the Medical Center of West Kazakhstan Marat Ospanov Medical University (Aktobe, Kazakhstan) using the MSPSS scale. The questionnaire consisted of 12 questions assessing support from family, friends, and significant others. Interpretation of results: 12-35 points – low level, 36-60 points – medium level, 61-84 points – high level. SSPSS version 25.0 was used for statistical analysis.*

Results: *Among 89 participants, the average MSPSS score was 80.54 ұ 6.80, indicating a high level of social support. The Kazakh version of the MSPSS scale showed high internal consistency, with a Cronbach's α of 0.84 and values ranging from 0.39 to 0.95 across three subscales. The item-result correlation coefficients ranged from 0.32 to 0.95, confirming no redundancy in the items.*

Conclusion: *The study results demonstrated that the Kazakh version of the MSPSS questionnaire has high reliability (Cronbach's α=0.84), confirming its suitability for use in scientific research. The questionnaire effectively assesses the level of social support among cancer patients, allowing for the exploration of various aspects of social support, identification of social issues, and provision of solutions for their resolution.*

Keywords: *oncology, MSPSS, social support, reliability.*

Introduction: The diagnosis of cancer can be a very stressful situation for patients, as it is a life-threatening [1] and life-changing disease [2, 3]. In recent years, the life expectancy of cancer patients has increased thanks to advances in technology and Medical Sciences. However, patients face many difficulties, such as poor treatment effects, the presence of side effects, the high cost of treatment, anxiety, and fear of disease recurrence, as well as psychological and physical stress [4]. The psychological state of cancer patients is a crucial indicator; in this regard, it is necessary to assess their condition and conduct an analysis. This can increase awareness and improve the overall quality of treatment. Cancer has physical, emotional, social, and economic consequences. Cancer is often diagnosed before symptoms appear, or they might develop gradually, so routine screening tests and self-examination by patients are required. From this stage onwards, the patients need social support from family, friends, and others. After diagnosis, social support becomes increasingly important for patients as they face the challenges of diagnostic tests, invasive procedures, and complex treatments with little warning and limited ability to adapt to their condition [5].

Social support refers to the assistance and support received from other people, particularly individuals. The specific social support received by the patient is considered objective social support. Subjective social support refers to the support that a patient receives and evaluates from their perspective, based on how they perceive and interpret the social support provided [6]. The sources of accepted social support can range from spouses, friends, and family members to healthcare providers and other professionals. Social support provides care and attention to cancer patients, helping them overcome their fear and anxiety about the disease, as well as alleviate the difficulties they face at different stages of the disease [7, 8]. Thus, social support plays a crucial role in the psychological well-being of patients. Improving the quality of life of cancer patients is also associated with adequate social support [9]. Mortality rates are also positively correlated with a lack of social support [8].

Social support is an important source of reducing negative psychological reactions such as despair and depression. Thanks to this effect, social support helps mitigate the adverse effects of negative life events on physical health and emotional well-being, and also serves as a buffer against stress. A social support group typically consists of family members, the environment (including relatives and friends), and a medical team (such as doctors, nurs-

es, social service specialists, and psychologists). Therefore, in addition to the fact that caring for patients diagnosed with cancer is a key factor in increasing hope [10], each social connection can become a belief in survival, providing social support [11].

In most cases, cancer leads to serious physical and psychological consequences, material discomfort, and social pressure. The patient's usual lifestyle changes, family relationships are disrupted, and the possibility of severe stressful situations and the number of threats that completely affect family relationships increases. The families learn to cope with the illness of a loved one, fear for their health and life, distrust of the successful completion of the disease, daily household chores, medication, money, search for treatment methods, consultation with doctors, fatigue, and despair [12, 13].

Family is an important resource for patients during their adaptation to the disease [11]. In the study of S. I. Boyarkin, the family was an adaptation factor for cancer patients, because cancer affects the disease as a factor leading to psychological maladaptation. Psychiatrist Jimmy Holland defined the organization of psychotherapeutic services in cancer hospitals and the inclusion of the patient's family in the "circle of care" as a crucial condition for effective medical care. In the family, crisis periods appear from the moment of diagnosis. Difficulties can arise from both objective factors (such as an increase in financial burden, a change in regime, a change in place of residence or work) and subjective factors (such as loss of life prospects, anxiety, fear, and fatigue). Such support helps families rationally utilize their internal and external resources and transition to a new stage of development, adapting to changing guidelines and values [13].

Social support typically encompasses all the social contacts a person receives when facing difficulties. Such support helps reduce depression by creating a safe environment that allows you to talk openly about difficult situations [14]. Additionally, social support can generate and expand the resources necessary to raise expectations [15].

A useful way to study the role of hope and resilience in cancer conditions is to support them socially [16-18]. Social support can protect cancer patients from negative psychological effects and acts as a buffer against cancer-related stress [16, 19, 20]. The above research shows that social support not only determines the direct effect but also indirectly affects depression through trigger mediators, and it has been proven that hope and vitality mediate the relationship between a priori variables and emotional outcomes in cancer patients [21, 22].

It is important in determining the impact and level of social support on the quality of life and vitality of patients. One of the defining questionnaires of social support in the patient environment is the Multidimensional Scale of Perceived Social Support (MSPSS). Since the use of the MSPSS questionnaire for the Kazakh-speaking population is limited, it is essential to verify its reliability before incorporating it into research work.

The study aimed to adapt the Multidimensional Scale of Perceived Social Support (MSPSS) into Kazakh and assess its reliability.

Methods:

The study design is a cross-sectional momentary study.

Study object. MSPSS is a common tool to measure social support. It is an open-use questionnaire created by Kenti-Mitchell and Zimet to assess the elements of social support, which consists of 12 questions: the social support of family (questions 3, 4, 8 and 11), friends (questions 6, 7, 9 and 12) and special people (questions 1, 2, 5 and 10). The scale ranges from 1, "strongly disagree," to 7, "strongly agree". The overall score ranges from 12 to 84, with scores of 69 to 84 indicating a high level of support, 49 to 68 – a medium level, and 12 to 48 – a low level [23, 24].

A survey was conducted to determine the level of social support among cancer patients receiving treatment at the Medical Center of West Kazakhstan Marat Ospanov Medical University (WKMOMU) in Aktobe, Kazakhstan, using the MSPSS scale. The data were collected from the WKMOMU Medical Center in Aktobe, Kazakhstan, with the consent of the WKMOMU Medical Center Director, as per Decision #3/2 dated October 7, 2024.

The study consisted of three stages: 1) translation into Kazakh and assessment of the validity of the content, 2) pilot testing, and 3) assessment of the reliability of the MSPSS Kazakh translation. During pilot testing, the sample or number of patients was selected according to the following criteria.

- *Inclusion criteria*: Recipients of treatment at the WKMOMU Medical Center, Aktobe, Kazakhstan; over 18 years of age; those who agreed to participate in the study.

- *Exclusion criteria:* the presence of cognitive disorders; patients with Stage IV cancer (due to the severity of health conditions, the attending physicians did not have permission); those who did not agree to participate in the study.

Stage 1: translation and adaptation of the questionnaire. Translation into Kazakh. Using the translation system proposed by Guillemin et al. [25] to translate the MSPSS into Kazakh, it included 5 steps: (1) direct and reverse translation, (2) synthesis, (3) evaluation by a team of experts, (4) evaluation of substantive reliability, and (5) pilot test.

The original English version was independently translated into Kazakh by two translators who were fluent in both English and Kazakh; one of them was a healthcare professional, while the other was not. Each translation version was translated back into English again by MSPSS and two other translators who were unaware of social support. Later, four translators discussed it together and made the final version in Kazakh.

This version was later reviewed and edited by experts in oncology (2), public health (2), psychology, and translation (4). Experts assessed the importance and clarity of each sentence and approved the final version. This version was again translated back into English and reviewed by another professional translator to ensure it was equivalent to the original text.

Stage 2: Pilot study. As part of a pilot study, patients who received treatment from November 1, 2024, to February 1, 2025, at the WKMOMU Medical Center in Aktobe were included in the study using a holistic sample method. The translated version of MSPSS was piloted among 89 cancer patients selected according to the inclusion and exclusion criteria. All participants easily understood the translated version. No changes were made to the translated version after the pilot study.

Stage 3: Assessment of the reliability of the MSPSS Kazakh translation. Eighty-nine participants were selected for analysis to confirm the reliability of the MSPSS structure in this study. In addition to the MSPSS survey, socio-demographic characteristics were summarized.

Statistical analysis. The data were processed, encoded, and analyzed using Statistical Package for the Social Sciences (SPSS) 25.0. The internal reliability (internal stability) of the MSPSS was measured using the Cronbach's α coefficient. Kronbach shows that alpha questions on a certain scale constantly measure something, the value of which is $\alpha \geq 0.90$ – it is considered to be very high reliability, $0.80 \leq \alpha < 0.90$ – high reliability, $0.70 \leq \alpha < 0.80$ – good reliability, $0.60 \leq \alpha < 0.70$ – medium reliability, $\alpha < 0.60$ – low reliability [26]. This resource discusses the value of Cronbach's α and what its scales should be.

Results: Adaptation and translation into the Kazakh language, as well as pilot testing, followed the aforementioned research methods. The final translation proved to be of high content reliability and was deemed suitable for use during pilot testing. The majority of participants said that the scale was clear and easy to answer, and there were no conclusions that could complicate or confuse the meaning of the question. No suggestions were received regarding the processing of words and phrases. Thus, no changes were made after pilot testing.

Socio-demographic characteristics of the respondents in the study: the average age of the 89 respondents was 53.8±1.3, with 32.6% being men and 67.4% being women. Of these, 67.4% are urban and 32.6% are rural. 77.5% of the participants were married, 2.2% were divorced, and 20.2% were widowed or single. 28.1% of participants had more than four children, 69.7% had fewer than four children, and 2.2% had no children. Additionally, 64.0% of participants had a secondary education, while 36.0% had higher education; 53.9% were engaged in public or private business, and 46.1% were unemployed 14.6% of the study participants were diagnosed through screening, and 85.4% them were examined due to pain. Of them, 69.7% of respondents knew their stage of cancer (Table 1).

Table 1 – Socio-demographic characteristics of respondents (N=89)

Variables	N	%
Age [53,8±1,3]		
21-30 31-40 41-50 51-60 61-70 71 and older	5 16 13 28 18 9	5.6 18.0 14.6 31,5 20.2 10.1
Gender		
Male Female	29 60	32.6 67.4
Place of residence		
Urban Rural	60 29	67.4 32.6
Education level		
Higher Education High School	32 57	36.0 64.0
Place of work		
Unemployed Retired Civil Servant Individual Entrepreneur Disabled Other	12 24 29 19 2 3	13.5 27.0 32.6 21.3 2.2 3.4
Family status		
Married Widowed (single) Divorced	69 18 2	77.5 20.2 2.2
Number of children		
Non <4 >4	2 62 25	2.2 69.7 28.1
Cancer stage		
I II III Unknown	24 29 9 27	27.0 32.6 10.1 30.3

According to the survey results, the average overall score on the MSPSS scale was 80.54 ± 6.8, indicating a relatively high level of social support accepted by the studied population (Table 2).

Table 2 – The level of social support of respondents based on the MSPSS survey results

Level of social support on the Likert scale		
Low	Medium	High
–	9%	91%

The average scores for the sub-categories of "family" (27.5±1.3) and "special person" (27±3.04) were higher than for the sub-categories "friends" – 26±4.6" (Table 3). The Kazakh translation of the MSPSS scale had a high intrinsic harmony with the Cronbach's α on the general scale varying from 0.84 to 0.39 to 0.95 for the three sub categories. The "element-result" correlation coefficients were in the range from 0.32 to 0.95, indicating that not all questions on the scale were redundant or content repeating.

Table 3 – Reliability of MSPSS and its internal scales

Description	Average score ɣSD	Correlation between the element and the result	Cronbach's α
Sub-category "Family"	27.5±1.3		0.39
- My family is trying to help me		0.32	
- I get the help and support I need from my family.		0.32	
- I can talk to my family about my problems.		0.43	
- My family is ready to help with the decision.		0.45	
Sub-category "Friends"	26±4.6		0.95
- My friends are trying to help me.		0.79	
- I can trust my friends when everything goes wrong.		0.95	
- I have friends with whom I can share my joys and sorrows.		0.82	
- I can talk to my friends about my problems.		0.94	
Sub-category "Special person"	27±3.04		0.91
- There is a special person who will be with me when I need it.		0.65	
- There is a special person with whom I can share my joys and sorrows.		0.87	
- I have a special person who is a real source of comfort and joy for me.		0.85	
- There is a special person who perceives my feelings and worries as important.		0.89	
MSPSS overall score	80.54±6.8		0.84

**MSPSS – multidimensional scale of acceptable social support; SD – standard deviation.*

Discussion: Social support can contribute to maintaining a healthy lifestyle, increasing commitment to treatment, and improving the quality of life of cancer patients [27]. Although social support has played an important role in alleviating the psychological and physical challenges associated with cancer [28], prior to this study, there was no linguistically valid tool for assessing social support among cancer patients in Kazakhstan. Our results show that the Kazakh translation of the MSPSS scale is a reliable and effective tool for assessing the accepted social support of cancer patients.

At stages 1 and 2 of this study, we officially translated the original MSPSS questionnaire into the Kazakh language. These stages are important under the translation procedure proposed by Guillemin et al. [25]. In practice, research questionnaires are not always correctly translated before being used in New temporal, cultural, or linguistic contexts, which runs the risk that the translations do not accurately reflect the concepts that should be measured in the original questionnaire.

In our study, the translation was performed in both directions by four independent translators, including health professionals and other experts. This made it possible to ensure the authenticity and reliability of the translation. The results of Stages 1 and 2 showed that the translation was correctly formulated and accurately reflected the meaning of the original MSPSS tool. This translation is suitable for use not only for cancer patients, but also for everyone in Kazakhstan [29, 30].

In our study, the internal consistency of the MSPSS scale (α = 0.84) is high. Our results are similar to those obtained in the original study and other studies conducted in various countries worldwide [31, 32]. The internal consistency of the translated MSPSS scale was α = 0.89 for Malay [33], α = 0.90 for Korean [34], α = 0.92 for Spanish and Thai [35, 36], and α = 0.91 for Russian [37]. The searches [32-34, 36] describe the countries that adapted this questionnaire to their language and determined its reliability, providing Cronbach's α values.

Social support has a significant impact on treatment commitment and improves the quality of life of cancer patients [38]. Measuring social support allows you to obtain important information regarding the health and treatment of cancer patients. To our knowledge, this study is the first to evaluate the reliability of the MSPSS scale among patients with cancer. The demand for research tools tailored to the culture and language of each country and region is high, particularly in low- and middle-income countries, as it enhances the quality of research [39, 40]. Researchers and health professionals can utilize the MSPSS scale for cancer patients as a screening tool, thereby contributing to the improvement of daily clinical care provided to patients. The MSPSS scale is simple and highly reliable. The use of such tools may help reduce the lack of information about social support and improve the quality of life of cancer patients.

Conclusion: The study's results demonstrated that the Kazakh version of the MSPSS questionnaire has high reliability (Cronbach's α = 0.84), indicating its suitability for use in scientific research. The questionnaire can not only be used as an effective tool for assessing the level of social support among cancer patients, but also allows you to study various aspects of social support and identify social problems, suggesting ways to solve them.

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АНДАТПА

«MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT» (MSPSS) САУАЛНАМАСЫН ҚАЗАҚ ТІЛІНЕ БЕЙІМДЕУ ЖӘНЕ СЕНІМДІЛІГІН АНЫҚТАУ

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Өзектілігі: *Онкологиялық науқастарға әлеуметтік қолдау – олардың физикалық және психоэмоционалдық әл-ауқатын жақсартудың маңызды факторы. Қатерлі ісік диагнозы науқастарға үлкен психологиялық салмақ түсіріп, қорқыныш, үмітсіздік, депрессия және әлеуметтік оқшаулану сияқты жағымсыз эмоцияларға себеп болуы мүмкін. Мұндай жағдайда отбасы мүшелері, достар, әріптестер және медициналық қызметкерлер тарапынан көрсетілетін моральдық, эмоционалдық және практикалық көмек – ерекше маңызды. Әлеуметтік қолдау науқастың қоғаммен байланысын сақтап, олардың жұмысқа қайта оралуына, өмір сапасын арттыруына ықпал етеді. Сонымен қатар, мұндай қолдау әлеуметтік интеграцияны қамтамасыз етіп, науқастың қалыпты өмірге бейімделуіне және толыққанды өмір сүруіне мүмкіндік береді.*

Зерттеу мақсаты *– Multidimensional scale of perceived social support (MSPSS) сауалнамасын қазақ тіліне бейімдеу және сенімділігін анықтау.*

Әдістері: *зерттеу дизайны бір сәттік көлденеңді. MSPSS сауалнамасы М.Оспанов атындағы Батыс Қазақстан медицина университетінің Медициналық орталығында (Ақтөбе, Қазақстан) емделіп жатқан онкологиялық науқастарды әлеуметтік қолдау деңгейін анықтау мақсатында жүргізілді. Сауалнама отбасынан, достарынан және ерекше адамдардан келетін әлеуметтік қолдауды бағалауға арналған 12 сұрақтан тұрады. Нәтижені бағалау шкаласы 12-35 ұпай болса төмен, 36-60 ұпай аралығында орташа, ал 61-84 ұпай аралығында жоғары деп бағаланады. Статистикалық талдау SPSS бағдарламасының 25.0 нұсқасы көмегімен жүргізілді.*

Нәтижелері: *89 қатысушы арасында сауалнама нәтижелері бойынша MSPSS шкаласының орташа жалпы көрсеткіші 80,54ұ6,8 болды, бұл зерттелген популяцияда қабылданатын әлеуметтік қолдау деңгейінің салыстырмалы түрде жоғары екенін көрсетеді. MSPSS шкаласының қазақ тіліндегі аудармасы жоғары ішкі үйлесімділікке ие, шкала бойынша Кронбах альфасы 0,84, ал үш субшкала бойынша 0,39-дан 0,95-ке дейінгі аралықта өзгерді. «Элемент-нәтиже» корреляция коэффициенттері 0,32-ден 0,95-ке дейінгі диапазонда болды, бұл шкаладағы барлық сұрақтардың артық немесе мазмұнды қайталайтын емес екенін көрсетті.*

Қорытынды: *Зерттеу нәтижелері MSPSS сауалнамасының қазақ тіліндегі нұсқасының жоғары сенімділікке ие екенін көрсетті (Cronbach's α=0,84) және оны ғылыми зерттеулерде қолдануға болатынын дәлелдейді. Сауалнама онкологиялық науқастардың әлеуметтік қолдау деңгейін бағалауға тиімді құрал ретінде қолданылып қана қоймай, сонымен қатар әлеуметтік қолдаудың түрлі аспектілерін зерттеуге және әлеуметтік мәселелерді анықтап, оларды шешудің жолдарын ұсынуға мүмкіндік береді.*

Түйінді сөздер: *онкология, MSPSS, әлеуметтік қолдау, сенімділік.*

АННОТАЦИЯ

АДАПТАЦИЯ НА КАЗАХСКИЙ ЯЗЫК И ОПРЕДЕЛЕНИЕ НАДЕЖНОСТИ ШКАЛЫ «MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT» (MSPSS)

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Актуальность: *Социальная поддержка онкологических пациентов – важный фактор улучшения их физического и психоэмоционального благополучия. Диагноз злокачественного новообразования оказывает на пациентов сильное психологическое давление, вызывая такие негативные эмоции, как страх, безнадежность, депрессия и социальная изоляция. В такой ситуации моральная, эмоциональная и практическая помощь со стороны членов семьи, друзей, коллег и медицинских работников имеет особое значение. Социальная поддержка способствует сохранению связи пациента с обществом, возвращению к трудовой деятельности и повышению качества жизни. Кроме того, она обеспечивает социальную интеграцию, помогая пациенту адаптироваться к нормальной жизни и жить полноценно.*

Цель исследования *– адаптация опросника Multidimensional Scale of Perceived Social Support (MSPSS) на казахский язык и оценка его надежности.*

Методы: *Дизайн исследования — поперечный моментный. Для определения уровня социальной поддержки у онкологических пациентов, получающих лечение в Медицинском центре ЗКМУ им. М. Оспанова (Актобе, Казахстан), было проведено анкетирование с использованием шкалы MSPSS. Анкета состояла из 12 вопросов, оценивающих поддержку от семьи, друзей и значимых других. Интерпретация результатов: 12-35 баллов – низкий уровень, 36-60 баллов – средний, 61-84 балла – высокий уровень. Статистический анализ проводился с использованием программы SPSS версии 25.0.*

Результаты: *Среди 89 участников, средний общий показатель по шкале MSPSS составил 80,54±6,8, что свидетельствует о сравнительно высоком уровне социальной поддержки, принимаемой исследуемой популяцией. Перевод шкалы MSPSS на казахский язык имеет высокую внутреннюю согласованность, коэффициент альфы Кронбаха по шкале составил 0,84, а по трем субшкалам варьировался от 0,39 до 0,95. Корреляционные коэффициенты «элемент-результат» варьировались от 0,32 до 0,95, что подтверждает отсутствие избыточных или повторяющихся вопросов в шкале.*

Заключение: *Результаты исследования показали, что казахская версия анкеты MSPSS обладает высокой надежностью (Cronbach's α=0,84), что подтверждает ее применимость в научных исследованиях. Анкета не только эффективно оценивает уровень социальной поддержки у онкологических больных, но также позволяет исследовать различные аспекты социальной поддержки и выявлять социальные проблемы, предлагая пути их решения.*

Ключевые слова: *онкология, MSPSS, социальная поддержка, надежность.*

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THE LAUREN CLASSIFICATION PROGNOSTIC VALUE AND SURVIVAL ANALYSIS IN PATIENTS WITH GASTRIC CANCER

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ABSTRACT

Relevance: *Numerous pathohistological classification systems are used to diagnose gastric cancer (GC). Several studies have examined the relationship between the pathohistological characteristics of gastric cancer and various patient-related aspects, as well as factors influencing the course and prognosis of the disease. The Lauren classification system remains an accessible and widely used method for classifying gastric cancer, having been correlated with the clinical, histological, and molecular features of these tumors. This article presents a statistical analysis and evaluates the prognostic significance of the Lauren pathohistological classification system for gastric cancer, aiming to determine the most relevant classification for predicting overall survival in patients with this disease.*

The study aimed to *investigate the clinicopathological characteristics of gastric cancer based on the Lauren classification and to assess its value in predicting the overall survival of patients with gastric cancer.*

Methods: *In this retrospective cohort study, a multidisciplinary team reviewed and discussed the data of 161 patients with GC from Aktobe. All patients met the criteria of the diagnostic and treatment protocol for oncology patients in the Republic of Kazakhstan (Order No. 174, dated November 21, 2022) for surgical treatment and were newly diagnosed with gastric cancer at any stage, aged 18 years or older. Data analysis was performed using SPSS v.25 (SPSS Inc., Chicago, Illinois, USA). The Pearson chi-square test was used to analyze the association between the Lauren classification and clinicopathological factors. The study was conducted at the Medical Center of West Kazakhstan Marat Ospanov Medical University based on pathomorphological reports collected from January 2020 to August 2024.*

Results: *In the analysis of 161 gastric cancer cases, the Lauren classification showed a statistically significant association with the clinicopathological characteristics of the disease and patients' overall survival. The diffuse type was associated with a more aggressive course and worse prognosis. The intestinal type was more frequently observed in patients with favorable prognostic features. Statistical analysis using the Pearson chi-square test revealed significant differences in survival rates between the Lauren subtypes.*

Conclusion: *The Lauren classification remains a clinically significant and reliable tool for the prognostic stratification of gastric cancer patients. According to Lauren, the tumor type enables the assessment of disease aggressiveness and prognosis, supporting informed therapeutic choices and a personalized approach to treatment.*

Keywords: *gastric cancer (GC), Lauren classification, overall survival, prognosis.*

Introduction: Gastric cancer (GC) is a malignant neoplasm with an aggressive course, most often diagnosed at advanced stages, particularly in Western countries [1, 2]. GC ranks fifth in prevalence among oncological diseases and third in mortality, according to WHO data [3]. In East Asian countries, such as Japan, the Republic of Korea, and Mongolia, an increase in incidence has been reported. In contrast, rates in North America, Northern Europe, and several African regions remain significantly lower, following a trend observed over recent decades [4]. In the Republic of Kazakhstan, GC ranks third in prevalence among oncological diseases, with an incidence rate of 15.8 cases per 100,000 population, and also holds third place in mortality, with 11.4 cases per 100,000 population [5].

Currently, the gold standard for GC prognosis and treatment guidance is the anatomical classification of tumors, lymph nodes, and metastases (TNM), developed by the American Joint Committee on Cancer (AJCC) [6, 7]. It is widely used in many clinical practices without considering histopathology, as the significance of the morphological characteristics of GC in determining clinical outcomes remains limited [8].

Most studies have identified the Lauren subtype as an independent prognostic factor in GC [9 - 11]. Recent studies conducted in Asia have also suggested that the Lauren classification may serve as a reliable prognostic tool for GC patients [12, 13].

Depending on tumor architecture, growth pattern, and cell morphology, this classification divides GC into intestinal, diffuse, and mixed types [14 - 16]. Intestinal-type GC consists of glandular structures accompanied by papillary or solid components. On the other hand, diffuse-type GC consists of loosely cohesive cells that grow in small clusters or as scattered cells, exhibiting an infiltrative pattern. This classification is differently associated with clinicopathological features [17, 18]. According to well-established experiments, *Helicobacter pylori* is the primary factor in the development of malignant changes in the stomach; however, the influence of factors such as diet, genetic predisposition, and the patient's socioeconomic status cannot be excluded in

this multistep process [19]. Intestinal tumors are more frequently found in elderly males and are associated with *Helicobacter pylori* infection and environmental factors. Moreover, most studies have identified the Lauren subtype as an independent prognostic factor in GC [20 - 22]. Thus, in the era of molecular medicine, the Lauren system is a cost-effective and widely used classification that is associated with clinical, pathological, prognostic, and molecular features. Lauren subtypes can be considered distinct entities that differ in histology, biology, and clinical behavior, and the identification of easily accessible prognostic factors in patients with intestinal and diffuse-type tumors may significantly improve risk assessment and patient stratification in GC [23].

The study aimed to investigate the clinicopathological characteristics of gastric cancer based on the Lauren classification and to assess its value in predicting the overall survival of patients with gastric cancer.

Materials and methods:

Study design: In this retrospective cohort study, data from 161 patients aged 18 years and older with a newly diagnosed GC of any grade who underwent surgical treatment following the Protocol for Diagnosis and Treatment of Oncology Patients of the Republic of Kazakhstan No. 174 dated 21.11.2022, were reviewed and discussed by a multidisciplinary team. The study was conducted at the Medical Center of the West Kazakhstan Marat Ospanov Medical University NCJSC based on histological reports compiled from January 2020 to August 2024.

Inclusion Criteria:

– Age over 18 years;

– Patients with pathomorphologically confirmed diagnosis of GC;

– Disease stages I, IIa, IIb, IIIa - IIIc according to the 8th edition of the TNM classification;

– Tumor located in any anatomical region of the stomach;

– Operable and resectable growing tumor;

– Histological tumor type according to Lauren classification: intestinal and diffuse types of GC.

Exclusion Criteria:

– Patients with newly diagnosed GC with primary multiple metachronous and synchronous tumor growth;

– Diagnosis established postmortem;

– Mixed type GC (dimorphic tumors);

– Neuroendocrine tumors of the stomach;

– Sarcomas, lymphomas of the stomach;

– Gastrointestinal stromal tumors (GIST) of the stomach.

Within the framework of the retrospective study, patients were divided into subgroups based on the morphological type of GC according to Lauren's histological classification:

– Diffuse type: poorly differentiated carcinoma, signet-ring cell carcinoma, and undifferentiated carcinoma.

– Intestinal type: papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, and well-differentiated adenocarcinomas.

Disease staging was determined according to the TNM classification of the American Joint Committee on Cancer (AJCC), 8th edition.

Patients were also stratified into subgroups according to tumor localization in:

– Cardiac part of the stomach (C16.0 - C16.1)

– Body of the stomach (C16.2 - C16.8)

– Antral part of the stomach (C16.3)

Statistical Analysis: Survival time was presented as the median and interquartile range (IQR, 25th-75th percentiles). Pearson's chi-square test was used to analyze the relationship between the Lauren classification and clinicopathological factors. Five-year survival rates were assessed using the Kaplan–Meier method, with group differences evaluated by the log-rank test. A 95% confidence interval was applied, and p-values < 0.05 were considered statistically significant.

Ethical Approval: The study was conducted in compliance with bioethical standards related to the use of patients' pathomorphological data. The study design and protocol were approved at a local meeting of the Bioethical Experimental Committee of West Kazakhstan Marat Ospanov Medical University, Aktobe (Protocol No. 10, dated October 27, 2023).

Results: A total of 161 GC patients underwent surgical treatment at the Aktobe Oncology Medical Center from 2020 to 2023 (Table 1).

Table 1 – Descriptive Characteristics of Patients with Newly Diagnosed Gastric Cancer (n=161)

Demographic Data and Tumor Characteristics	Number of Patients	%
Gender		
Men	110	68.3
Women	51	31.7
Age		
Under 60 years	37	23
Over 60 years	124	77
Tumor Location		
Cardia of the stomach	58	36.0
Body of the stomach	56	34.8
Antrum of the stomach	47	29.2
Disease Stage		
I	15	9.3
II	8	5.0
III	138	85.7
Tumor (T)		
T1	12	7.5
T2	8	5.0
T3	11	6.8
T4	130	80.7
Node (N)		
N0	72	44.7
N1	28	14.7
N2	43	26.7
N3	17	10.6
Histological Type (Lauren Classification)		
Diffuse type	110	68.3
Intestinal type	51	31.7
Grade		
1	6	3.7
2	51	31.7
3	84	52.2
4	20	12.4

In our study, the incidence of GC was twice as high among men as among women. A total of 80.7% of patients had large invasive gastric tumors, with 73.9% of those in locally advanced stages. In 36% of patients, the tumor was localized in cardia of the stomach. Lymphatic metastasis was identified in 55% of GC patients. Diffuse-type GC was diagnosed twice as often as the intestinal type (68% vs. 32%). Poorly differentiated tumors accounted for 52% of all cases.

According to the Lauren classification, the diffuse type predominated in both sexes (Table 2). Advanced tumor growth (pT) was more commonly observed in diffuse-type GC (75.4% vs. 25%; p<0.001). Distant lymphatic metastasis (pN) was also more frequently noted in diffuse-type cases (65% vs. 35%), although the difference was not statistically significant. In diffuse-type GC, the tumor was most frequently localized in cardia of the stomach (98%), whereas in intestinal-type GC, the tumor was predominantly found in the antral region (79%; p<0.001). By stage, the intestinal type significantly prevailed (80%) in early-stage GC, whereas the diffuse type predominated in locally advanced forms (74%) (p<0.001).

Table 2 – Clinicopathological Characteristics According to the Lauren Classification

Parameters	Diffuse Type, abs. (%)	Intestinal type, abs. (%)	Total, abs. (%)	p*
Gender				p=0.502
Women	33 (64.7%)	18 (35.3%)	51 (31.7%)	
Men	77 (70%)	33 (30%)	110 (68,3%)	
pT stage				p<0.001
T1	2 (16.7%)	10 (83.3%)	12(7.5%)	
T2	3 (37.5%)	5 (62.5%)	8 (4.9%)	
T3	7 (63.6%)	7 (36.4%)	11 (6.8%)	
T4	98 (75.4%)	32 (24.6%)	130 (80.7%)	
Tumor Location				p<0.001
Cardia of the stomach	57 (98.3%)	1 (1.7%)	58 (36.02%)	
Body of the stomach	43 (76.8%)	13 (23.2%)	56 (35%)	
Antrum of the stomach	10 (21.3%)	37 (78.7%)	47 (29.2%)	
pN stage				p=0.280
N0	47 (65.3%)	25 (34.7%)	72 (44.7%)	
N1	18 (64.3%)	10 (35.7%)	28 (17.4%)	
N2	34 (79.1%)	9(20.9%)	43 (26.7%)	
N3	11 (64.7%)	6(35.3%)	17 (10.6%)	
Stage				p<0.001
1	3 (20%)	12(80%)	15 (100.0%)	
2	5 (62.5%)	3 (37.5%)	8 (100.0%)	
3	102 (73.9%)	36(26.1%)	138 (100.0%)	

*Note: *- Pearson's Chi-square test was used*

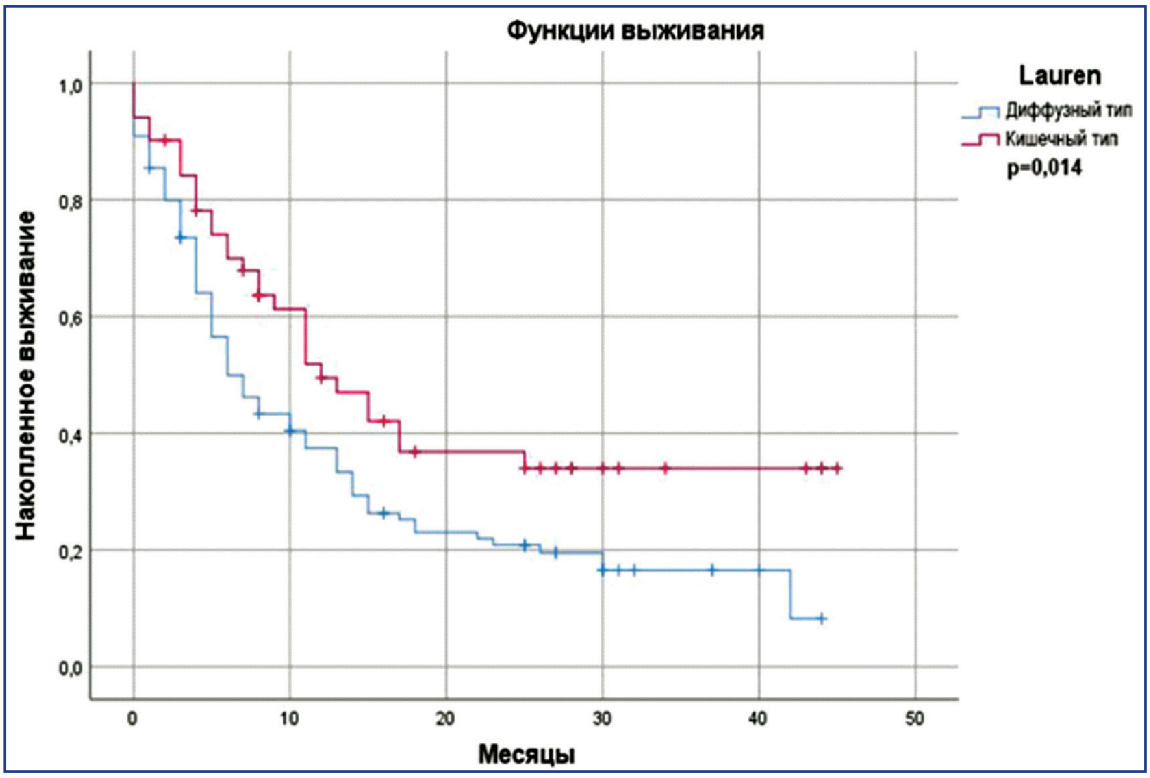
Survival Analysis in Patients with Gastric Cancer: The overall survival rate among patients was 15%, with a median survival time of 8 months. The analysis of survival in relation to tumor size (pT) and lymphatic metastasis (pN) revealed a reliable association: The best survival outcomes were observed in patients with early-stage tumors (T1 – T2) and absence of lymph node metastasis (N0 – N1), where the median survival was around or more than 13 months. The worst prognosis was noted in patients with advanced tumor stages (T3-T4) and multiple lymph node metastases (N3-N4), where median survival decreased to 3-6 months (p<0.001). The survival analysis revealed an overall survival rate of 15%, with a median survival time of 8 months. A statistically significant difference in survival was observed depending on tumor size (pT) and presence of lymphatic metastasis (pN) (p<0.001) (see Table 3).

Table 3 – Overall and Median Survival Depending on Tumor Stage (pT) and Lymphatic Metastasis (pN)

Disease Indicator	Overall survival, % (95% CI)	Median Survival, $Q_{50}(Q_{25}$-$Q_{75})$
pT stage		
T1	32.19% [23.19-41.19]	∞
T2	33.39% [21.83-44.96]	∞
T3	12.15% [6.05-18.26]	11 [5.72-16.28]
T4	13.25% [6.05-18.26]	6 [3.94-8.06]
pN stage		
N0	20.08% [15.60-24.55]	13 [9.03-16.96]
N1	16.37% [11.80-20.94]	13 [9.54-16.45]
N2	12.11% [7.65-16.57]	5 [3.45-6.54]
N3	6.47% [3.80-9.13]	6 [1.96-10.03]

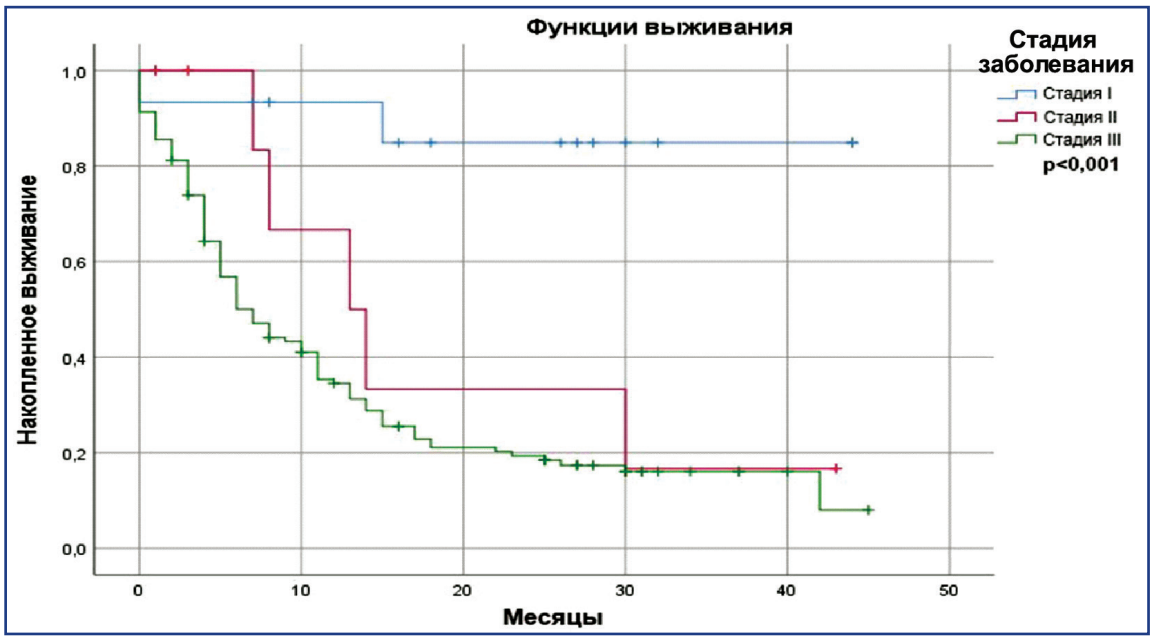
Survival Dependence on Gastric Cancer Type: According to the Lauren classification, the best survival rate was observed in patients with the intestinal type of gastric cancer: the overall survival rate was 20.88% [95% CI: 15.6-26.17], and the median survival time was 12 months [95% CI: 7.48-16.51]. In contrast, patients with the diffuse type had an overall survival rate of 13.58% [95% CI: 10.72-16.44], and the median survival time was 6 months [95% CI: 3.84-8.15]. Statistical significance: p<0.001 (see Figure 1).

Survival Dependence on Tumor Stage: A direct correlation was found between survival and the stage of tumor development. Thus, the overall survival rate at Stage I was 38% [95% CI: 31.64-45.56], while in patients with Stage III, it was 13.30% [95% CI: 10.74-15.85]. The median survival time for all Stage III patients was 7 months [95% CI: 5.01-8.98]. Statistical significance: p<0.001 (see Figure 2).



Legend: Накопленное выживание – Accumulated survival; Функции выживания – Survival functions; Месяцы – Months; Диффузный тип – Diffuse type; Кишечный тип – Intestinal type

Figure 1 – Five-Year Survival Rate considering the Lauren classification

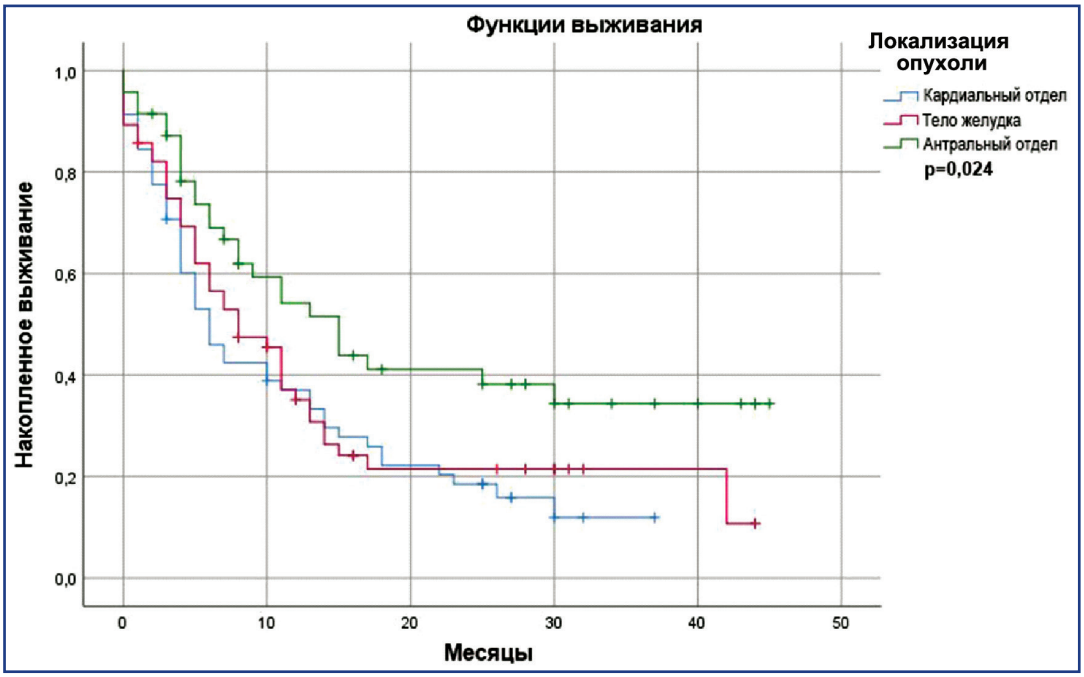


Legend: Накопленное выживание – Accumulated survival; Функции выживания – Survival functions; Месяцы – Months; Стадия – Stage

Figure 2 – Five-Year Survival Rates by Stage

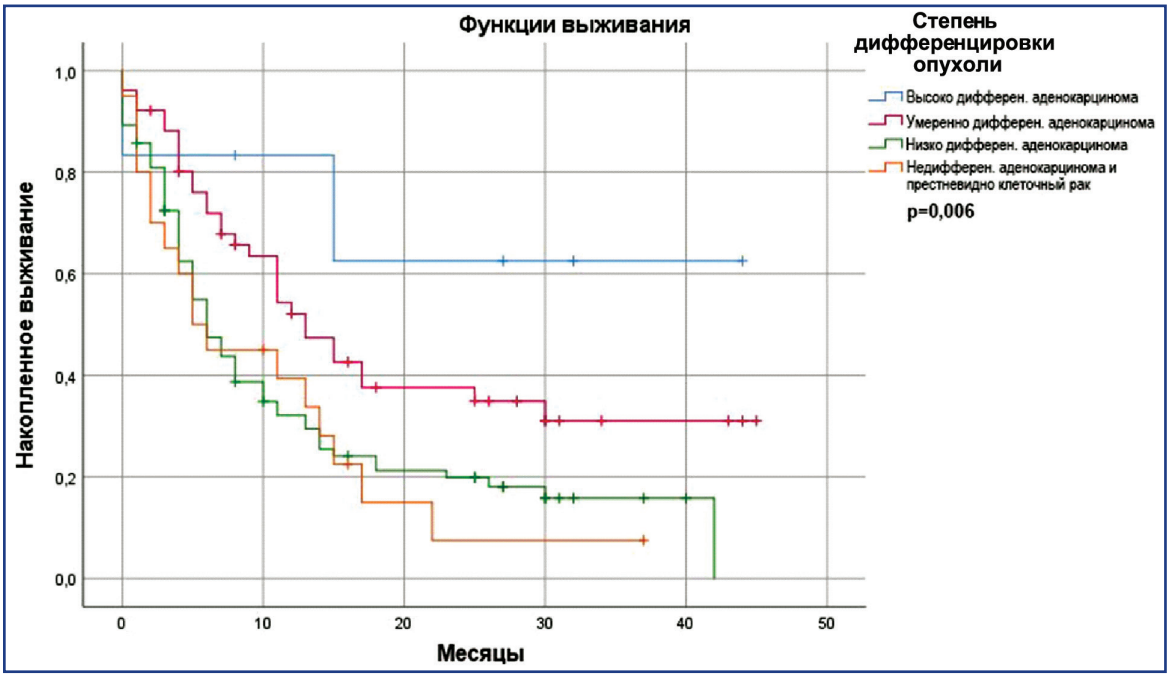
Survival Dependence on Tumor Location: For tumors located in cardia of the stomach, the overall survival rate was 11.79% [95% CI: 8.61-14.97], and the median survival time was 6 months [95% CI: 3.80-8.19]. In the body of the stomach, the overall survival rate was 14.48% [95% CI: 10.17-18.79], with a median survival time of 8 months [95% CI: 4.59-11.40]. The best survival outcomes were observed in tumors located in the antrum, with an overall survival rate of 21.68% [95% CI: 16.17-27.20], and a median survival time of 15 months [95% CI: 9.12-20.87]. Statistical significance: p=0.024 (see Figure 3).

Survival Dependence on Tumor Differentiation: In patients with well-differentiated adenocarcinoma, the overall five-year survival rate was 30% [95% CI: 15.61-45.63], while in cases of undifferentiated and signet-ring cell carcinoma, the overall survival rate was 10% [95% CI: 5.51-14.84]. Statistical significance: p=0.006 (see Figure 4).



Legend: Накопленное выживание – Accumulated survival; Функции выживания – Survival functions; Месяцы – Months; Кардиальный отдел – Cardia of the stomach; Тело желудка – Body of the stomach; Антральный отдел – Antrum of the stomach

Figure 3 – Five-Year Survival Rates Depending on Tumor Location



Legend: Накопленное выживание – Accumulated survival; Функции выживания – Survival functions; Месяцы – Months; Высокодифференцированная аденокарцинома – Well-differentiated adenocarcinoma; Умеренно дифференцированная аденокарцинома – Moderately differentiated adenocarcinoma; Низкодифференцированная аденокарцинома – Poorly differentiated adenocarcinoma; Недифференцированная аденокарцинома и перстневидно-клеточный рак – Undifferentiated adenocarcinoma and signet-ring cell carcinoma

Figure 4 – Five-Year Survival Rates Depending on Tumor Differentiation

Discussion: There are several histopathological classifications of GC due to the pronounced morphological heterogeneity of this disease [24]. However, the question of which classification is superior remains a matter of controversy. Tumor grades of differentiation are commonly used to describe GC, and four types are defined: well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated [12]. It is widely believed that poorly differentiated tumors are typically more widespread at the time of surgery compared to well-differentiated ones, and that patients with more differentiated tumors have clear survival advantages after curative resection [25, 26]. However, recent studies have reported that tumor differentiation grade does not have a significant association with the prognosis of GC patients [27-30]. In the present study, tumor differentiation was significantly associated with prognosis, as determined by the log-rank test; however, it was not an independent prognostic factor for overall survival (OS). This inconsistency may be due to the mixing of differentiated and undifferentiated histologies in GC [29, 31]. Therefore, further research is needed to understand the significance of tumor differentiation grade in GC.

According to the results of our study based on the Lauren classification, the diffuse type predominates among both sexes. Diffuse tumors were mostly advanced (75.4% vs. 24.6%; p<0.001). Distant lymphatic metastasis (pN) was also observed more frequently in the diffuse type (65% vs. 35%), although the difference was not statistically significant. In the diffuse type, the tumor was most commonly located in cardia of the stomach (98%), whereas the intestinal type was more often located in the antral region (79%; p<0.001). By stage: at early stages, the intestinal type of GC predominated (80%), while in locally advanced cases, the diffuse type accounted for the majority (74%, p<0.001).

Our study showed a direct correlation between tumor stage and survival rate. According to our results, survival at stage I was 38% [95% CI: 31.64-45.56], while in patients with stage III, overall survival was 13.30% [95% CI: 10.74-15.85], and median survival was 7 months [95% CI: 5.01-8.98] with statistical significance of p<0.001.

By tumor location: In cardia of the stomach, overall survival was 11.79% [95% CI: 8.61-14.97], and the median survival time was 6 months [95% CI: 3.80-8.19]; In the body of the stomach – 14.48% [95% CI: 10.17-18.79], with a median survival time of 8 months [95% CI: 4.59-11.40]; the best survival outcome was observed in GC located the antral part of the stomach – 21.68% [95% CI: 16.17-27.20], and a median survival time of 15 months [95% CI: 9.12-20.87], with statistical significance of p=0.024.

By tumor differentiation grade: The overall five-year survival in patients with well-differentiated adenocarcinoma was 30% [95% CI: 15.61-45.63]; In cases of undifferentiated and signet-ring cell carcinoma, overall survival was 10% [95% CI: 5.51-14.84], with statistical significance of p=0.006.

Based on the data from our study, the incidence in men was twice that of women. Among them, 80.7% of patients had massive invasive gastric tumors. In the majority of patients, the tumor was located in cardia of the stomach (36%). In addition, 55% of patients with gastric cancer had lymphatic metastasis.

In our study, the diffuse type GC was twice as common as the intestinal type (68% vs. 32%).

The Lauren classification of GC is one of the widely used morphological classification systems applied for survival prediction [15]. There is evidence that tumor subtypes under the Lauren classification respond differently to chemotherapy, resulting in different survival outcomes [14].

The specific pathogenetic and morphological features of the intestinal and diffuse types may underlie their differing behaviors [16]. The epidemiological intestinal type of cardia cancer, especially in the antral part, is often closely associated with chronic inflammation due to *Helicobacter pylori* infection [32, 33]. Anatomically proximal GC can be classified as the third type, in which inflammation of a different origin may be the driving force of carcinogenesis [34]. In addition, the anatomical location of GC has clinical relevance, with proximal third gastric cancers being associated with worse prognosis than middle or distal third cancers [35].

Several studies have shown that the Lauren classification has better discriminatory ability and monotonicity [11, 12]. In this study, the Lauren classification demonstrated superior model discrimination, fitting efficiency, and net benefit compared to other classifications. The five-year survival based on the Lauren classification showed similar results when stratified by morphological type, tumor stage, location, and differentiation grade.

The solution curve analysis revealed that the use of this classification model yields greater clinical benefits compared to alternative approaches. Nomograms are visual tools that enable individualized survival prediction based on a patient's unique clinical data [36], providing improved prognostic accuracy and comprehensive outcomes for various types of cancer [37]. Based on the Lauren classification, considering tumor stage, location, and differentiation, we developed a new prognostic nomogram. This new prognostic model demonstrated higher discriminatory ability, better model fitting, and net advantages compared to the 8th edition AJCC TNM classification. These findings confirm that incorporating a broader range of factors encompassing various aspects of the disease is the most promising approach to enhancing the clinical treatment of GC. However, the results of this study should still be interpreted with caution, as specific intervention factors, such as surgical procedures, chemotherapy and radiotherapy regimens, and drug dosages, were not controlled.

Conclusion: Thus, the Lauren classification exhibits high discriminatory ability, effective model calibration, and clear advantages compared to classification based on tumor differentiation grade and the Lauren classifica-

tion itself. This classification also demonstrates good applicability in various clinical scenarios. The new prognostic nomogram, based on the Lauren classification, also demonstrates high discriminatory ability, model fitting performance, and notable advantages. Nevertheless, the results of this study require further confirmation.

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АНДАТПА

АСҚАЗАН ҚАТЕРЛІ ІСІГІ БАР НАУҚАСТАРДА LAUREN КЛАССИФИКАЦИЯСЫНЫҢ БОЛЖАМДЫҚ МӘНІ ЖӘНЕ ӨМІР СҮРУ ТАЛДАУЫ

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Өзектілігі: *Асқазан обырын диагностикалау үшін қолданылатын көптеген патогистологиялық классификациялық жүйелер бар. Бірқатар зерттеулерде асқазан рагының патогистологиялық сипаттамалары мен науқастардың әртүрлі аспектілері, сондай-ақ аурудың ағымына және оның болжамына әсер ететін факторлар арасындағы өзара байланыс зерттелді. Lauren жіктеу жүйесі асқазан ісіктерінің клиникалық, гистологиялық және молекулалық сипаттамаларына негізделген және асқазан ісіктерін жіктеудің қолжетімді және кеңінен қолданылатын әдісі болып қала береді. Осы мақалада асқазан обырын (АО) үшін Лаурен патогистологиялық классификациясының статистикалық анализі мен прогностикалық маңызы, сондай-ақ осы аурумен ауыратын науқастардың жалпы өмір сүруін болжау үшін ең маңызды классификацияны анықтау ұсынылған.*

Зерттеу мақсаты *– асқазан рагының клиникалық-патологиялық сипаттамасын Лаурен классификациясы бойынша зерттеуге және асқазан обырын бар науқастардың жалпы өмір сүруін болжауға бағытталған.*

Әдістері: *Осы ретроспективті когорттық зерттеуде Қазақстан Республикасының 2022 жылғы 21 қарашадағы № 174 онкологиялық науқастарды диагностикалау және емдеу хаттамасына сәйкес хирургиялық ем тағайындалған кез келген дәрежедегі асқазан обыры жаңадан анықталған 18 жастан асқан және одан жоғары 161 науқастың деректері мультидисциплиналық топта зерттеліп, талқыланды. Есептеу үшін SPSS.v.25 бағдарламасы қолданылды. Категориялық деректер Пирсон X^2 тесті арқылы бағаланды.*

Зерттеу КеАҚ Марата Оспанов атындағы БҚМУ медицина орталығы базасында 2020 жылдың 01 айынан 2024 жылдың 08 айына дейінгі патоморфологиялық сипаттама негізінде жүргізілді.

Нәтижелері: *Асқазан обырының 161 жағдайын талдау Лаурен классификациясының аурудың клиникалық-патологиялық сипаттамаларымен және науқастардың жалпы өмір сүруімен статистикалық маңызды өзара байланысты растайтынын көрсетті. Диффузды рак түрі агрессивті ағыммен және нашар болжаммен байланысты болды. Ішек түрі көбінесе қолайлы прогностикалық белгілері бар науқастарда кездеседі. Пирсон X^2 критерийін қолдану арқылы статистикалық өңдеу Лаурен типіне байланысты өмір сүру бойынша топтар арасында сенімді айырмашылықтарды көрсетті.*

Қорытынды: *Лаурен бойынша асқазан обырын классификациялау науқастарды прогностикалық стратификациялау үшін клиникалық маңызды және сенімді құрал болып қала береді. Лаурен бойынша ісік түрі процестің агрессивтілігін және болжамды бағалауға мүмкіндік береді, бұл терапияны негізделген таңдау мен жекелендірілген тәсілді қамтамасыз етеді.*

Түйінді сөздер: *асқазан обыры, Лаурен классификациясы, жалпы өмір сүру, болжам.*

АННОТАЦИЯ

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ КЛАССИФИКАЦИИ LAUREN И АНАЛИЗ ВЫЖИВАЕМОСТИ У ПАЦИЕНТОВ С РАКОМ ЖЕЛУДКА

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Актуальность: *Существует множество патогистологических классификационных систем, применяемых для диагностики рака желудка (РЖ). В ряде исследований изучалась взаимосвязь между патогистологическими характеристиками РЖ и различными аспектами пациентов, а также факторами, влияющими на течение болезни и её прогноз. Система классификации Lauren привязана к клиническим, гистологическим и молекулярным характеристикам опухолей желудка и остается доступным и широко используемым методом классификации РЖ. В данной статье представлен статистический анализ и прогностическая значимость системы*

патогистологической классификации Lauren для РЖ, а также определена наиболее значимая классификация для прогнозирования общей выживаемости пациентов с РЖ.

***Цель исследования** – изучение клинико-патологической характеристики рака желудка по классификации Lauren и прогнозирования общей выживаемости пациентов с раком желудка.*

Методы: В данном ретроспективном когортном исследовании были изучены и обсуждены на мультидисциплинарной группе данные 161 пациента в возрасте от 18 лет с впервые установленным диагнозом РЖ любой степени дифференцировки, которым было показано оперативное лечение согласно протоколу диагностики и лечения онкологических больных РК №174 от 21.11.2022 г. Исследование проводилось в МЦ НАО ЗКМУ имени Марата Оспанова на основании гистологических описаний, составленных с 01.2020 г. по 08.2024 г. Для анализа данных использовали программу SPSS.v.25 (SPSS Inc., Чикаго, Иллинойс, США), связь между классификацией Lauren и клинико-патологическими факторами исследовали при помощи теста хи-квадрат Пирсона.

Результаты: Анализ 161 случая РЖ показал, что классификация Lauren подтверждает статистически значимую взаимосвязь с клинико-патологическими характеристиками заболевания и общей выживаемостью пациентов. Тип диффузного рака ассоциировался с более агрессивным течением и худшим прогнозом. Кишечный тип чаще встречался у пациентов с более благоприятными прогностическими признаками. Статическая обработка с использованием критерия хи-квадрат Пирсона показала достоверные различия между группами по выживаемости в зависимости от типа Lauren.

Заключение: Классификация РЖ по Lauren остается клинически значимым и надежным инструментом для прогностической стратификации пациентов. Тип опухоли по Lauren позволяет оценить агрессивность процесса и прогноз, что способствует обоснованному выбору терапии и персонализированного подхода.

Ключевые слова: рак желудка (РЖ), классификация Lauren, общая выживаемость, прогноз.

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FEATURES OF THE TNM-9 CLASSIFICATION FOR LUNG CANCER AND INTEGRATION OF TNM-8 LIMITATIONS

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ABSTRACT

Relevance: *Lung cancer ranks among the leading causes of morbidity and mortality in oncological diseases both in Kazakhstan and worldwide. Accurate tumor staging is crucial for choosing patient management strategies, considering the continuously advancing diagnostic and treatment methods. The 8th edition of the Tumor-Node-Metastasis (TNM) classification, introduced in 2017, brought significant changes to the staging approach, thereby improving its precision. However, accumulated data have demonstrated the need for further refinement, particularly in assessing mediastinal lymph nodes and systemic metastasis. Therefore, the 9th edition of TNM came into force on January 1, 2025. It includes important updates that require adaptation in radiological practice.*

The study aimed to *compare the 8th and 9th editions of the TNM classification in lung cancer and identify key changes to improve staging accuracy and facilitate multidisciplinary treatment planning.*

Methods: *This study conducted a structured review of the changes introduced in TNM-9 compared to TNM-8, with a focus on interpreting the N and M categories. The analysis utilized clinical guidelines from the International Association for the Study of Lung Cancer (IASLC) and recent publications reflecting current approaches to tumor staging.*

Results: *In the TNM-9 classification, the N and M categories were refined by introducing new subcategories, N2a/N2b and M1c1/M1c2. The staging of several combinations of T and N categories was also revised. Particular emphasis was placed on the need for more detailed anatomical characterization of lymph nodes and the systemic nature of metastases.*

Conclusion: *Understanding the new provisions of TNM-9 is essential for accurate stage assessment, improving communication during multidisciplinary tumor boards, and optimizing therapeutic decision-making.*

Keywords: *lung cancer, staging, TNM, TNM-9.*

Introduction: Lung cancer ranks first in morbidity and mortality among all oncological diseases. According to the Kazakh Research Institute of Oncology and Radiology (KazRIOR), in 2023, 3,872 new cases of lung cancer were registered in the Republic of Kazakhstan, which is 9.3% of the total number of oncological diseases. Despite the decrease in incidence, lung cancer remains the leading cause of cancer mortality in the country: in 2023, 2,034 persons died from it, that is 15.7% of all cancer deaths [1].

In recent years, the diagnostics and treatment of lung cancer have advanced significantly. If earlier surgery was the primary method of treatment only in the early stages, and chemotherapy and radiotherapy were used for more advanced forms, today, a multidisciplinary approach is implemented. Local methods are increasingly used in advanced processes, while systemic treatment is employed at early stages. It requires a more accurate assessment of the anatomical spread of the tumor, especially in high categories N and M [2].

The TNM (Tumor-Node-Metastasis) system, developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [3], remains a key staging tool in international clinical practice and serves as the standard for describing the extent of a malignant process worldwide. The use of the TNM system provides a standardized anatomical staging system for malignant neoplasms. The TNM system is based on an assessment of three key components. The first component, T (Tumor), reflects the size of the primary tumor and the degree of its invasion into the surrounding structures. The second component, N (Nodes), characterizes the presence and degree of involvement of regional lymph nodes. The third component, M (Metastasis), indicates the presence or absence of distant metastases in other organs and systems [3, 4]. Each of these categories is further subdivided into subcategories (e.g., T1, T2; T1a, T1b), and their combinations form a certain stage of the disease, as recommended by the International Association for the Study of Lung Cancer (IASLC) [4].

Since January 1, 2017, the use of TNM-8 has been recommended worldwide for staging non-small cell and small cell lung cancer. This publication is based on the results of a large-scale IASLC study, which analyzed data from over 77,000 patients from various regions worldwide. Despite the significant contributions of the 8th edition to standardizing disease staging and improving predictive stratification, subsequent clinical experience and analysis have revealed several limitations. In particular, there was a need for a more accurate gradation of mediastinal lymph nodes, as well as for

a detailed characterization of the metastatic lesion. Taking into account the accumulated data and the needs of clinical practice, the UICC and AJCC, with the participation of IASLC, approved TNM-9, the official use of which will begin on January 1, 2025 [5-7]. Radiologists need to familiarize themselves with the new provisions to accurately reflect the stages of the disease in their reports and participate in decision-making at multidisciplinary boards.

The study aimed to compare the 8th and 9th editions of the TNM classification in lung cancer and identify key changes to improve staging accuracy and facilitate multidisciplinary treatment planning.

Materials and methods: This review is an analytical study based on a comparative analysis of the changes reported in TNM-9 compared to TNM-8, specifically concerning lung cancer staging. The basis for the analysis was the official publications of the IASLC, AJCC, and UICC, published from 2017 to 2024 [3-7].

Results:

Major updates in TNM-9. There were no changes in category T in the TNM-9 classification. As before, the key criterion for staging remains the maximum tumor diameter measured by thin-slice CT (≤1.5 mm) in the pulmonary windows. In this case, only a solid component of mass is taken into account; the ground-glass component or the lepidic component, if any, shall not be included in the measurement. In the presence of multiple solid foci, classification is performed according to the largest of them. If it is difficult to assess the dimensions, multiplane reconstructions can be used. Category T is subdivided as follows: T1 includes tumors up to 3 cm and is divided into T1a (≤1 cm), T1b (>1-2 cm), and T1c (>2-3 cm); T2 encompasses tumors 3 to 5 cm in size and is divided into T2a (>3-4 cm) and T2b (>4-5 cm), or invasion of the visceral pleura, adjacent lobe, involvement of the main bronchus, or the presence of atelectasis/obstructive pneumonia; T3 corresponds to sizes from 5 to 7 cm, as well as when the chest wall, parietal pleura, phrenic nerve, pariental pericardial membrane or the presence of individual tumor nodes within the same lobe as the primary tumor; T4 - tumors of 7 cm or more or with invasion of the vertebral body, large vessels (including subclavians), adipose tissue of the mediastinum or other mediastinal structures, trachea, esophagus, visceral pericardium, diaphragm, thymus or brachial plexus, as well as the presence of individual tumor nodes in another part of the lung on the same side, but in a different lobe. Individual neoplasms with distinct histological structures are considered independent primary tumors and are classified separately according to the TNM system.

The Tis (preinvasive tumor in situ) and T1mi (minimally invasive adenocarcinoma) categories also remain, as they reflect the growth features of the lepidic component. The Tis category includes in situ adenocarcinomas and squamous cell carcinomas. For adenocarcinomas, it means a ≤3 cm ground-glass lesion on CT scan with no invasive component. A lesion >3 cm with signs of lepidic growth without invasion is classified as T1a. T1mi is a partially solid node measuring ≤3 cm, where the invasive (dense) component is ≤0.5 cm. If the dense part is >0.5 cm, then this lesion is classified as T1. These criteria remain important for the accurate assessment of stage and prognosis in lung adenocarcinomas with lepidic growth.

Consolidation and the "pneumonic" form of cancer. In the case of diffuse consolidation without bronchial obstruction (referred to as invasive mucinous adenocarcinoma), staging is determined by the number of lobes: one lobe is classified as T3. In contrast, different lobes of the same lung are classified as T4 (Figure 1), and involvement of both lungs is classified as M1a (Figure 2).

Division of category N2 into subcategories N2a and N2b. In TNM-8, category N was determined solely by the anatomical location of the affected lymph nodes, regardless of their number or extent. The classification was based on the location of the lesion and did not take into account either the number of lymph nodes or the number of anatomical stations affected.

However, it has been observed in clinical practice that patients with lesions confined to a single mediastinal station (e.g., the subcarinal station) have a significantly better prognosis compared to those with lesions involving two or more stations (e.g., parallel lesions of the paratracheal and subcarinal nodes). This difference was not reflected in the eighth edition and may have influenced therapeutic decision-making, particularly in potentially resectable cases.

In this regard, the ninth edition of TNM clarified the N2 category by dividing it into two subcategories: N2a – metastases in one anatomical station of ipsilateral mediastinal and/or subcarinal lymph nodes; N2b – metastases in two or more anatomical stations in the same regions (Figure 3). It is emphasized at the same time that the assessment should be based on the number of affected stations, rather than individual lymph nodes. The basis for this change was the data from the IASLC database, which demonstrated significant differences in survival between the N2a and N2b groups, regardless of age, gender, histological type of the tumor, and other factors [8, 9].

The ninth edition retains its reliance on the IASLC International Lymph Node Map, where groups are numbered from 1 to 14 and are indicated by side (e.g., 4R, 4L, 7). The ninth edition also clarifies that lymph nodes not included in the IASLC map (e.g., diaphragmatic, cervical, intercostal, axillary) are not classified as regional, but are treated as distant metastases (category M1). This is crucial for accurate staging.

Thus, the ninth edition of TNM emphasizes the need for accurate anatomical localization of affected stations in radiological reports. This means that the radiologist must indicate the numbers and sides of suspicious stations (e.g., 4R) and note whether one or more stations are affected, allowing for the differentiation between N2a and N2b. Such a description is important for multidisciplinary tumor boards and can influence the choice of therapy. For example, surgery may be considered for N2a, but becomes less likely for N2b, especially if there is more severe or multiple lymph node involvement.

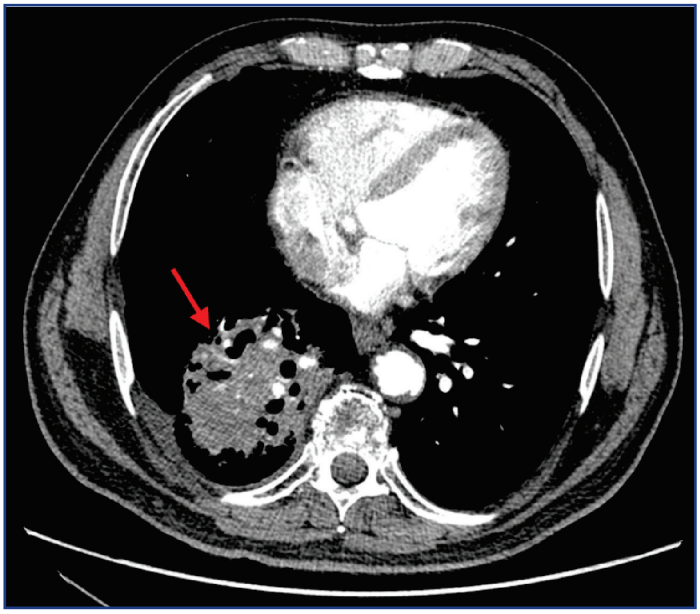

Figure 1 - Pneumonia-like form of cancer in segments S6, S9, S10 of the right lung with marked enlargement of segmental and subsegmental bronchi in a 60-year-old woman; the tumor process spreads to different lobes of one lung, which corresponds to category T4 according to TNM-9 [Source: author's collection]

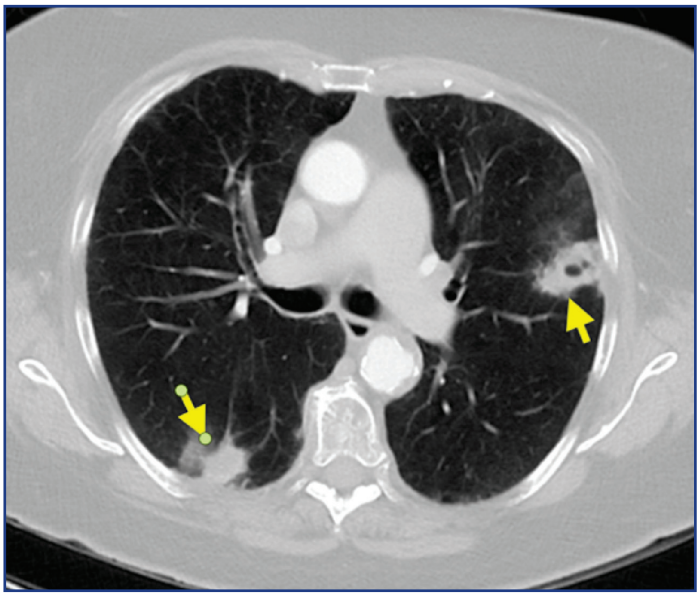

Figure 2 - Two masses up to 3 cm in diameter in the lungs of a 71-year-old woman. The lesion in the right lung is treated as a metastatic lesion, which corresponds to category M1a according to TNM-9 [Source: author's collection]

Division of category M1c into subcategories M1c1 and M1c2. The M category was divided into three levels in the eighth edition of the TNM classification: M1a, M1b, and M1c. The M1a subcategory included signs of intrathoracic metastasis, such as tumor nodes in the contralateral lung, malignant pleural or pericardial effusion, and pleural or pericardial tumor nodes. M1b corresponded to the presence of a single extrathoracic metastatic focus in one organ. The M1c subcategory included multiple extrathoracic metastases regardless of the number of organs affected. This division enabled the refinement of prognoses for patients with varying metastatic loads, particularly in stage IV.

The ninth edition of TNM clarifies the M1c category by dividing it into two levels: M1c1 and M1c2. The M1c1 subcategory corresponds to multiple metastases within a single organ system. M1c2 refers to the involvement of two or more organ systems (Figure 4). In this case, both single organs (for example, the liver or brain) and paired organs (such as the adrenal glands or kidneys) or diffuse

anatomical structures (such as the skeletal system) are considered part of an organ system. Thus, multiple bone metastases, regardless of the number of foci, are classified as M1c1. If metastases are found, for example, simultaneously in the bones and liver, this situation is interpreted as M1c2.

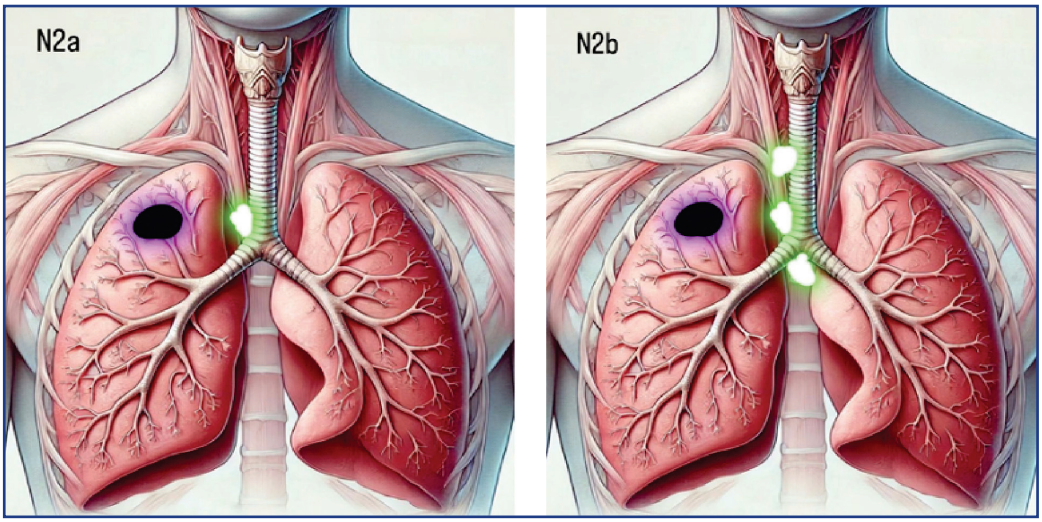

Figure 3 - Division of N2 (ipsilateral lymph nodes) into single (N2a) and multiple ipsilateral stations (N2b) according to TNM-9 [Source: author's collection]

The additional division of M1c into M1c1 and M1c2 reflects the desire for a more accurate stratification of patients based on their prognosis and the extent of systemic tumor spread. Quantitative criteria (for example, the number of foci within one organ) are not defined in the new classification; the emphasis is on the number of organ systems involved [7-9]. It is essential for the radiologist not only to record the presence of multiple metastases but also to specify exactly which organ systems are involved, for accurate staging and informed therapeutic decision-making (Table 1).

Table 1 – Staging of lung cancer according to TNM-9 (from 2025) [5, 6, 14]

Component	Subcategory	Short description
T – Tumor	T1a,b,c	≤3 cm (in 1 cm increments: a – up to 1 cm, b – from 1 to 2 cm, c – from 2 to 3 cm)
	T2a,b	>3–5 cm, T2a – 3 to 4 cm, T2b 4 to 5 cm, also invasion of the visceral pleura, adjacent lobe, involvement of the main bronchus, or the presence of atelectasis/obstructive pneumonia
	T3	>5 to 7 cm, involvement of the chest wall, parietal pleura, phrenic nerve, parietal pericardial membrane, or the presence of individual tumor nodes within the same lobe as the primary tumor
	T4	>7 cm, with invasion to the vertebral body, large vessels (including subclavians), adipose tissue of the mediastinum or other mediastinal structures, trachea, esophagus, visceral pericardium, diaphragm, thymus or brachial plexus, as well as the presence of separate tumor nodes in another part of the lung on the same side, but in a different lobe
N – Lymph nodes	N0	No metastases in regional lymph nodes
	N1	Ipsilateral peribronchial and/or hilar lymph nodes
	N2a	New subcategory: one ipsilateral mediastinal/subcarinal station
	N2b	New subcategory: two or more ipsilateral mediastinal lymphatic stations
	N3	Contralateral or supraclavicular lymph nodes
M – Metastases	M0	Absence of distant metastases
	M1a	Contralateral foci, pleural or pericardial effusion/node
	M1b	One extrathoracic metastasis
	M1c1	A new subcategory: multiple metastatic foci localized within a single anatomical system (e.g., liver, brain, skeletal system, paired organs such as kidneys and adrenal glands).
	M1c2	New subcategory: metastases in two or more organ systems (for example, in the liver and in the skeletal system at the same time)

Redistribution of stages according to changes in N and M categories. Comparative analysis shows that:

T1N1 now belongs to stage IIA, instead of IIB in the eighth edition;

T1N2a – to stage IIB, instead of IIIA in the eighth edition (Figure 5);

T1N2b and T2N2a remain in stage IIIA (unchanged);

T2N2b – stage IIIB (eighth edition – IIIA);

T3N2a – stage IIIA;

T3N2b – stage IIIB;

T4N2a and T4N2b – both combinations remain in stage IIIB, as before (Figure 6) [11, 12].

These changes enable potential downstaging, thereby expanding the indications for surgical treatment (Table 2) [2, 8, 9].

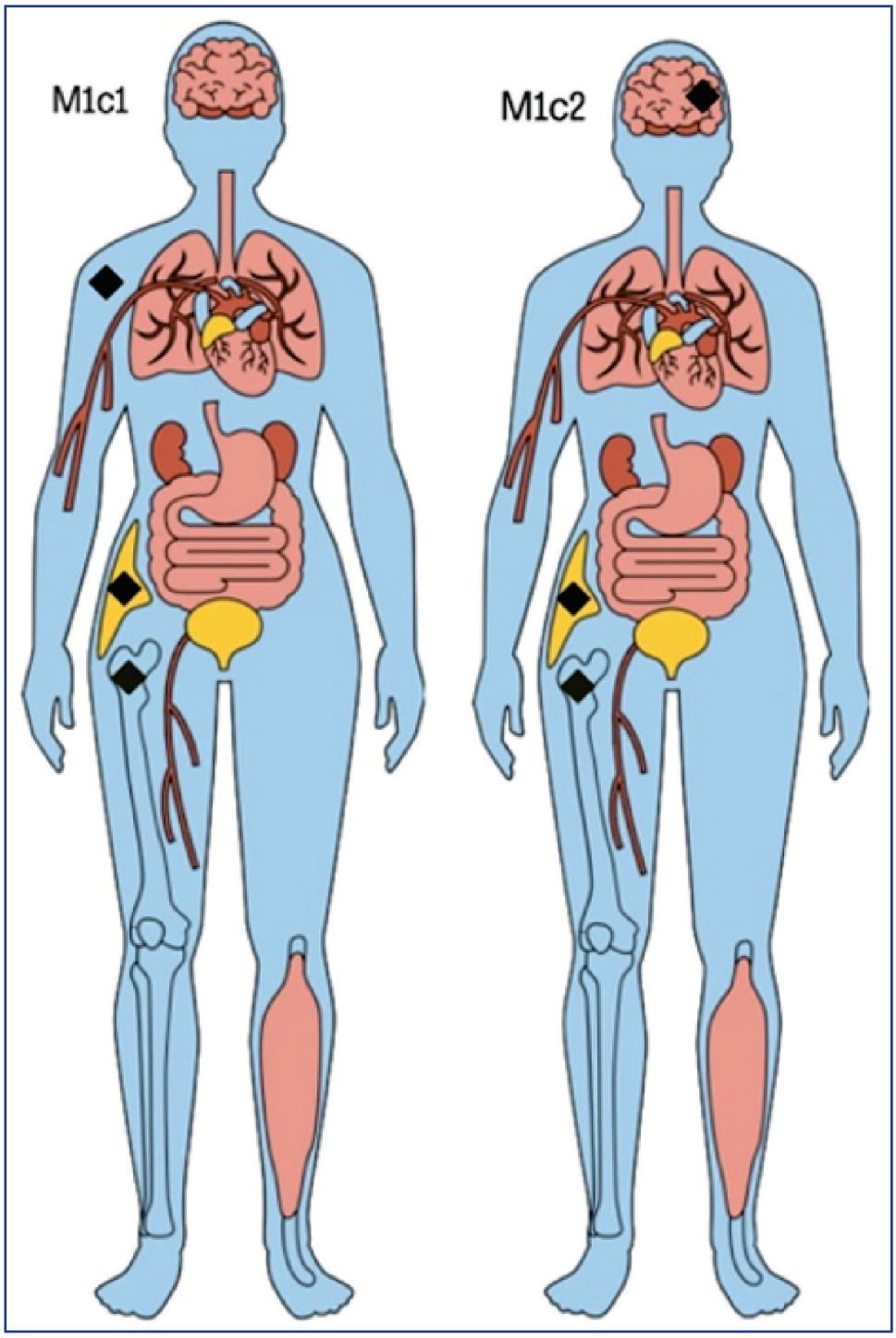

Figure 4 – Division of the subcategory M1c (multiple extrathorocal metastases) into metastases in one organ/system and metastases in several organ systems according to TNM-9. Picture A demonstrates multiple metastases to bone structures, corresponding to the category M1c1. Figure B demonstrates metastases to bone structures and the brain. They reflect lesions of two organ systems and are categorized as M1c2 [Source: author's collection].

TNM-9 in the structure of the radiological report.

The T category is determined based on the maximum diameter of a solid tumor component as imaged on a high-resolution CT scan with a slice thickness of no more than 1 mm, excluding the ground-glass and lepidic components. The T1 category encompasses tumors measuring up to 3 cm in size and is further divided into T1a (tumors measuring up to 1 cm), T1b (tumors measuring 1 to 2 cm), and T1c (tumors measuring 2 to 3 cm). The T2 category includes tumors 3 to 5 cm in size, as well as cases involving the visceral pleura, proximal bronchus, or accompanied by atelectasis/obstructive pneumonitis. T3 corresponds to tumors measuring 5 to 7 cm or invasions of the chest wall, diaphragm, pericardium, and other structures. T4 includes tumors larger than 7 cm or cases of invasion of large vessels, spine, trachea, and other critical anatomical formations. Multiple tumor foci are classified based on localization and histological identity as T3, T4, or M1a.

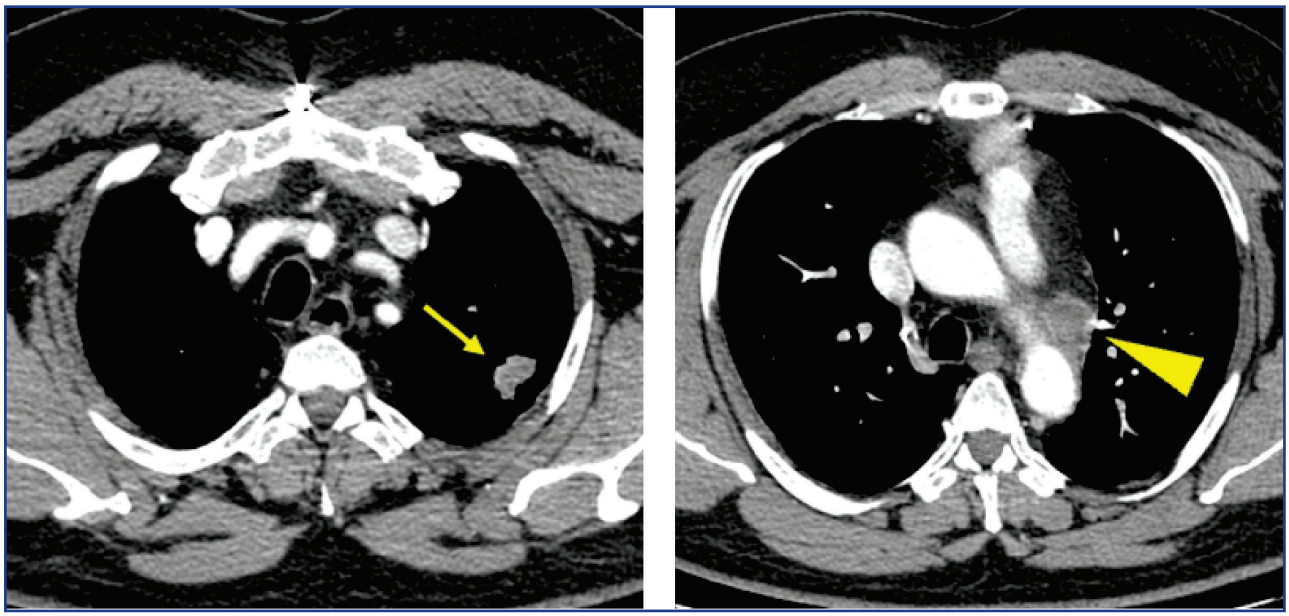

Figure 5 – Lung adenocarcinoma (T1c) 2 cm in the left upper lobe (yellow arrow) with single-position subaortic lymphadenopathy (arrowhead) (N2a) in a 51-year-old man. According to the TNM-9 classification, this patient is classified as T1cN2aM0, which corresponds to stage IIB. In contrast, the TNM-8 classification would classify this patient as T1cN2M0, corresponding to stage IIIA.

Table 2 – Grouping of lung cancer stages according to TNM-9 [5, 9, 10]

Stage	Combinations (T, N, M)
IA1	T1mi/T1a, N0, M0
IA2	T1b, N0, M0
IA3	T1c, N0, M0
IB	T2a, N0, M0
IIA	T2b, N0, M0 or T1, N1, M0
IIB	T2a/b, N1, M0 or T1, N2a, M0 or T3, N0, M0
IIIA	T1–3, N2b, M0 or T4, N0, M0
IIIB	T3–4, N2b, M0 or T1–2, N3, M0
IIIC	T3–4, N3, M0
IVA	Any T, any N, M1a, or M1b
IVB	Any T, any N, M1c1, or M1c2

Note: A high-resolution CT scan (≤1 mm) should be used for visual assessment, and only the solid tumor component should be measured. Atelectatic and inflammatory changes are not taken into account when determining the tumor size, but are automatically equated to T2 in the absence of signs of invasion into neighboring structures.

Regional lymph node (N) lesion categories include N0, N1, and N3, while N2 is now subdivided into N2a, when a single mediastinal lymphatic station is involved, and N2b, when two or more stations are involved. Clarification of the number of affected stations is recognized as an important prognostic factor.

The M categories remain the same: M0, M1a, and M1b, but the M1c category is now subdivided into M1c1 when there are multiple metastases within the same organ system (e.g., bone lesions only) and M1c2, when two or more organs metastatically are affected. The importance of a comprehensive assessment of oligometastatic disease, as well as the possibility of future integration of the molecular and biological characteristics of the tumor into the staging system, is separately emphasized.

Conclusion: The TNM-9 classification provides an enhanced and clinically sound anatomical framework, building upon the improvements introduced in TNM-8. Many of the changes in TNM-9 logically build upon the TNM-8 methodology, based on a global analysis of survival data from more than 70,000 patients. Particular attention is paid to improving the stratification of stages depending on the number of lymphatic stations, the number and localization of metastases, as well as the configuration of multiple tumor foci.

Understanding and active implementation of the TNM-9 classification by radiologists will significantly improve the accuracy of staging and the quality of multidisciplinary management of patients with lung cancer.

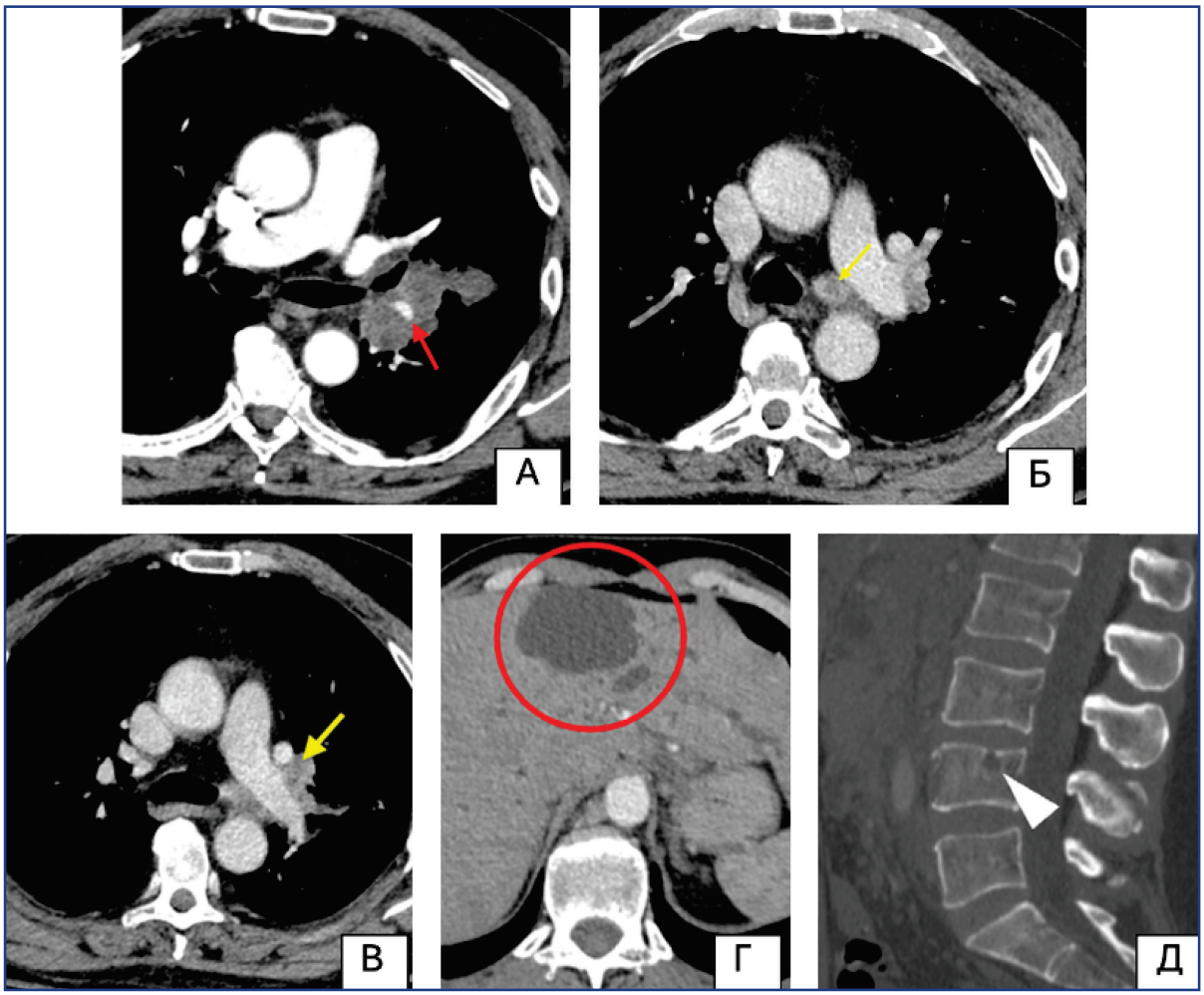

Figure 6 – Lung adenocarcinoma infiltrating the left pulmonary artery (T4) (red arrow on A), in a 58-year-old man. Ipsilateral lymphadenopathy is also visualized in the paratracheal (yellow arrow on B) and bronchopulmonary groups (yellow arrow on B) (N2b), as well as metastases in the liver (red circle on G) and in the vertebral body L4 (white arrowhead on D) (M1c2) followed by stage IVB (stage unchanged according to TNM 9)
[Source: Author's collection]

TNM	Описание	N0	N1	N2a	N2b	N3
T1a	до 1 см	IA1	IIA	IIB	IIIA	IIIB
T1b	от 1 до 2 см	IA2	IIA	IIB	IIIA	IIIB
T1c	от 2 до 3 см	IA3	IIA	IIB	IIIA	IIIB
T2a	от 3 до 4 см висцеральная плева/центральная инвазия	IB	IIB	IIIA	IIIB	IIIB
T2b	от 4 до 5 см	IIA	IIIB	IIIA	IIIB	IIIB
T3	от 5 до 7 см инвазия соседних структур отдельные узлы в той же доле	IIB	IIIA	IIIA	IIIB	IIIC
T4	от 7 см инвазия крупных магистральных структур отдельные узлы в других долях того же лёгкого	IIIA	IIIA	IIIB	IIIB	IIIC
M1a	узлы в противоположном лёгком злокачественый плеврит/перикардит	IVA	IVA	IVA	IVA	IVA
M1b	единичные внегрудные метастазы	IVA	IVA	IVA	IVA	IVA
M1c1	множественные метастазы в 1 системе	IVB	IVB	IVB	IVB	IVB
M1c2	множественные метастазы в нескольких системах	IVB	IVB	IVB	IVB	IVB

Figure 7 – Stages of lung cancer according to TNM-9 with color differentiation of changes: yellow indicates new positions, green indicates positions carried over from the previous edition unchanged [adapted from: 9]

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АНДАТПА

ӨКПЕ ОБЫРЫНЫҢ TNM-9 ЖІКТЕМЕСІНІҢ ЕРЕКШЕЛІКТЕРІ ЖӘНЕ TNM-8 ШЕКТЕУЛЕРІНІҢ ИНТЕГРАЦИЯСЫ

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Өзектілігі: *Өкпе обыры бүкіл әлемде сонымен қатар Қазақстандада онкологиялық аурулар арасында сырқаттанушылық пен өлім-жітім бойынша алдыңғы орындарды иеленеді. Диагностика мен емдеу әдістері уздіксіз жетілдіріліп жатқан жағдайда, ісік процесін дәл сатылау пациенттерге ем жүргіз тактикасын таңдауда маңызды рөл атқарады. 2017 жылы енгізілген tumor-node-metastasis (TNM) жіктемесінің 8-ші басылымы сатылауға қатысты маңызды өзгерістер енгізіп, оның дәлдігін арттырған болатын. Алайда жиналған мәліметтер медиастинальды лимфа түйіндері мен жайылмалы метастаздарды бағалауда қосымша нақтылықты қажет ететінін көрсетті. Осыған байланысты, 2025 жылдың 1 қаңтарынан бастап маңызды өзгерістерді қамтитын TNM-нің 9-шы басылымы қолданысқа енді және бұл радиологиялық практикаға бейімделуді талап етеді.*

Зерттеудің мақсаты *– Өкпе обырының TNM жіктемесінің 8-ші және 9-шы редакцияларын салыстыра талдау жүргізіп, сатылаудың дәлдігін арттыру және ем кезіндегі мультидисциплинарлық жоспарлауды тиімді ұйымдастыру мақсатында негізгі өзгерістерді анықтау.*

Әдістері. *Осы зерттеуде TNM жіктемесінің 9-шы редакциясын 8-ші редакциямен салыстырғанда енгізілген өзгерістер құрылымды түрде қаралып, негізінен N және M категорияларының трактовкасына назар аударылды. Талдау барысында Өкпе обырын зерттеу бойынша халықаралық қоғамның (IASLC) клиникалық ұсыныстары және ісік процесінің сатылауындағы қазіргі әдістемелерді көрсететін заманауи басылымдар пайдаланылды.*

Нәтижелері. *TNM жіктемесінің тоғызыншы редакциясында N және M категориялары нақтыланып, N2a/N2b және M1c1/M1c2 жаңа подкатегориялары енгізілді. Сонымен қатар, T және N категорияларының кейбір комбинацияларының сатылауы қайта қаралды. Лимфа түйіндерінің анатомиялық егжей-тегжейлі сипаттамасы мен метастаздардың жүйелік сипатына ерекше мән берілді.*

Қорытынды. *TNM-9 жаңа ережелерін түсіну сатыны дәлірек бағалауға, мультидисциплинарлық консилиумдардағы қарым-қатынасты жақсартуға және емдеу шешімдерін оңтайландыруға маңызды.*

Түйінді сөздер: *өкпе обыры, сатылау, TNM, TNM-9.*

АННОТАЦИЯ

ОСОБЕННОСТИ КЛАССИФИКАЦИИ TNM-9 ПО РАКУ ЛЁГКОГО И ИНТЕГРАЦИЯ ОГРАНИЧЕНИЙ TNM-8

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Актуальность: *Рак лёгкого занимает лидирующие позиции по заболеваемости и смертности среди онкологических заболеваний в Казахстане и во всём мире. В условиях постоянно совершенствующихся методов диагностики и лечения точное стадирование опухолевого процесса играет ключевую роль в выборе тактики ведения пациентов. Восьмое издание классификации Tumor-Node-Metastasis (TNM), внедрённое в 2017 году, внесло значимые изменения в подход к стадированию, повысив его точность. Однако накопленные данные продемонстрировали необходимость дальнейшей детализации, особенно в оценке медиастинальных лимфоузлов и системного метастазирования. В связи с этим с 1 января 2025 года вступило в силу 9-е издание TNM, содержащее важные изменения, которые требуют адаптации в радиологической практике.*

Цель исследования *– провести сравнительный анализ 8-й и 9-й редакций классификации TNM при раке лёгкого и выявить ключевые изменения с целью повышения точности стадирования и участия в мультидисциплинарном планировании лечения.*

Методы: *В настоящем исследовании проведён структурированный обзор изменений, внесённых в 9-е издание классификации TNM по сравнению с 8-м изданием, с фокусом на трактовку категорий N и M. Для анализа использованы клинические рекомендации Международного общества по изучению рака лёгкого (IASLC), а также современные публикации, отражающие актуальные подходы к стадированию опухолевого процесса.*

Результаты: *В 9-м издании классификации TNM были уточнены категории N и M с введением новых подкатегорий N2a/N2b и M1c1/M1c2. Кроме того, пересмотрено стадирование ряда комбинаций категорий T и N. Особое внимание уделено необходимости более детальной анатомической характеристики лимфатических узлов и системного характера метастазирования.*

Заключение: *Понимание новых положений TNM-9 важно для точной оценки стадии, улучшения коммуникации на мультидисциплинарных консилиумах и оптимизации лечебных решений.*

Ключевые слова: *рак лёгкого, стадирование, TNM, TNM-9.*

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HER2 AND BCL-2 ALTERATIONS IN NON-SMALL CELL LUNG CANCER, BIOLOGICAL AND CLINICAL SIGNIFICANCE, THERAPEUTIC PERSPECTIVES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Lung cancer remains one of the leading causes of cancer mortality worldwide. Accord-ing to WHO, more than 2.2 million new cases are detected annually, and the mortality rate exceeds 1.8 million. Despite advances in diagnostics and treatment, the prognosis for non-small cell lung cancer (NSCLC), especially in the late stages, remains unfavorable. Molecular genetic biomarkers play a significant role in improving diagnostics and choosing therapy. Bcl-2 and HER2 proteins, in-volved in regulating apoptosis and proliferation, may be associated with the aggressive course of NSCLC and resistance to therapy. Their study is relevant for the development of a personalized ap-proach to the treatment of this disease.*

The study aimed to *assess the biological and clinical significance of HER2 and Bcl-2 alterations in non-small cell lung cancer and to analyze their impact on disease prognosis and the effectiveness of various therapeutic strategies.*

Methods: *The search for electronic medical sources was conducted in the PubMed, Web of Science, and Google Scholar databases using the keywords: "biomarkers," "non-small cell lung cancer," "di-agnosis," "prognosis," and "survival." The review included full-text articles in Russian and English, published over the past five years and available in open access, devoted to the role of biomarkers in lung cancer early detection and prognosis.*

Results: *The expression of Bcl-2 and HER2 plays a significant role in the pathogenesis of NSCLC. Bcl-2, a key regulator of apoptosis, is detected in 30-50% of patients and may be associated with tumor aggressiveness and improved survival, depending on histological subtype and disease stage. HER2 alterations are found in 1-30% of cases, more commonly in adenocarcinomas among non-smoking women, and are associated with poor prognosis and therapy resistance. Targeted therapies like venetoclax and HER2 inhibitors (trastuzumab deruxtecan, pyrotinib) improve progression-free survival.*

Conclusion: *Bcl-2 and HER2 are promising biomarkers and therapeutic targets in NSCLC. Their study supports personalized treatment and should be integrated into clinical practice to improve out-comes.*

Keywords: *biomarker, non-small cell lung cancer (NSCLC), diagnosis, prognosis, survival.*

Introduction: Lung cancer (LC) is the leading malignant neoplasm in terms of morbidity and mortality worldwide [1].

According to the Global Cancer Observatory (GLOBOCAN 2022), lung cancer in Kazakhstan still ranks first among malignant neoplasms in men and is among the five most common in women. The standardized incidence rate is 20.4 per 100,000 population, and the proportion of lung cancer among all cancers in the country is about 9.7%. These findings highlight the continuing high burden of the disease and the need for further improvement of early diagnostics and personalized treatment [2].

Oncological diseases remain one of the priority medical and social health problems of the Republic of Kazakhstan, having a significant impact on the overall mortality rate and life expectancy of the population. In the structure of malignant neoplasms, lung cancer is of particular epidemiological importance, which is characterized by high prevalence and marked mortality. A significant contribution of this disease to the overall cancer mortality is due mainly to the latent clinical course in the early stages, which complicates timely diagnosis, as well as an unfavorable prognosis, especially when detected at late stages [3].

Recent studies have shown that, in addition to extrinsic carcinogens, ethnicity and genetic predisposition (associated with mutations in known genes associated with a high or moderate risk of cancer) can significantly affect the risk of developing LC and its molecular profile [4].

As part of a global analysis conducted by F. Islami et al., trends in lung cancer mortality by major morphological forms in 48 countries over the past decades were studied. The results of the study demonstrated significant changes in the structure of LC histological types. The authors noted that in most countries of the world, including high- and middle-income countries, there is a steady trend towards an increase in the proportion of non-small cell lung cancer (NSCLC), especially adenocarcinoma. The study highlights that adenocarcinoma has become the predominant histo-

logical type of lung cancer among both men and women, in virtually all countries involved in the analysis. In addition, F. Islami et al. focused on the fact that despite the general trend towards a decline of overall mortality from lung cancer in several countries, the proportion of lethal outcomes due to adenocarcinoma continues to be high. This is due to the difficulties of early diagnosis of this histological type, the tendency to metastasis in the early stages, and the variability of the molecular characteristics of tumors, which determines the relevance of further research in the field of molecular genetic profiling and the development of personalized approaches to NSCLC therapy [5].

According to R.L. Siegel et al., NSCLC accounts for about 81% of all lung cancer cases in the United States, remaining the most common form of the disease [1].

According to GLOBOCAN 2022, lung cancer has the highest mortality rate among all malignant tumors. Non-small cell lung cancer (NSCLC) accounts for about 82-85% of all lung cancer cases in all regions of the world, with a remaining upward trend of adenocarcinoma, especially among women and never-smokers. In the NSCLC structure, the major share is occupied by adenocarcinoma, which has been the leading subtype for more than 10 years. This is due to a change of smoking style (switching to filter cigarettes) and an elevation of the proportion of cases among non-smokers [2].

The choice of NSCLC as a study object is due to its high prevalence, prognostic and biological diversity, as well as the possibility of molecular profiling necessary for the development of personalized approaches to therapy. In the context where late diagnosis and resistance to treatment remain the key problems, the emphasis on the NSCLC study allows identifying new biomarkers and approaches to risk stratification, which is a critical task of modern oncology.

With the development of molecular medicine and the creation of drugs targeting specific molecular targets, the treatment of non-small cell lung cancer (NSCLC) has become personalized in recent years. It focuses on molecular aspects of the disease pathogenesis.

As of today, personalized targeted therapy based on molecular tumor profiling is actively used in the treatment of NSCLC, especially in patients with mutations in the epidermal growth factor (EGFR) gene and rearrangements of the anaplastic lymphoma kinase (ALK) gene. According to D.R. Camidge et al., the introduction of tyrosine kinase inhibitors EGFR and ALK significantly improved survival and disease control in these patient groups. Concurrently, despite the success of targeted therapy, the prognosis of most patients with NSCLC remains unfavorable due to the high rate of late diagnostics and a limited number of available molecular targets [6].

One of the promising prognostic and potential therapeutic biomarkers is the Bcl-2 protein, an anti-apoptotic regulator, that plays a key role in the mechanisms of cellular survival. As noted by T. Miyashita et al. [7] and J. Ni et al. [8], overexpression of Bcl-2 is associated with tumor cell resistance to apoptosis, decreased chemotherapy efficacy, and poor prognosis in patients with NSCLC. The identification of such molecular markers and their further study opens up prospects for the development of new therapeutic strategies in the treatment of that pathology.

Human Epidermal Growth Factor Receptor 2 (HER2) is a transmembrane receptor protein in the epidermal growth factor receptor family that plays an important role in carcinogenesis. It was initially investigated as a key biomarker for breast cancer, but in recent years, scientists have focused on its significance in NSCLC [9]. HER2 mutations and amplifications are detected in approximately 2-4% of patients with lung adenocarcinoma, which makes it a promising target for targeted therapy [10]. Recent clinical studies have shown the efficacy of HER2 inhibitors such as trastuzumab deruxtecan in treating patients with HER2-positive NSCLC, opening up new opportunities for personalized therapies [11].

The study of the role of Bcl-2 and HER2 as biomarkers of lung cancer is an important direction of modern oncology. This allows not only a better understanding of tumor biology, but also the development of personalized approaches to patient treatment, by improving its effectiveness. This review is devoted to the analysis of the role of Bcl-2 and HER2 in the pathogenesis, diagnosis, and prognosis of lung cancer, as well as their possible use in personalized therapy of patients.

The study aimed to assess the biological and clinical significance of HER2 and Bcl-2 alterations in non-small cell lung cancer and to analyze their impact on disease prognosis and the effectiveness of various therapeutic strategies.

Materials and methods: An electronic search of the medical literature using the PubMed, Web of Science, and Google Scholar databases was conducted within this study. The search was carried out by the following keywords: “biomarkers”, “lung cancer”, “lung cancer diagnosis”, “lung cancer prognosis “, “survival”. A total of 252 sources were found; the review involved 27 full-text publications in English and Russian, published over the past 5 years, available in the public domain, and devoted to the study of the role of biomarkers in the early diagnosis and prognosis of lung cancer.

Results: The HER2 and Bcl-2 alterations occur in a significant proportion of patients with NSCLC, affecting the tumor aggressiveness, its resistance to standard therapy, and disease prognosis.

The discovery of the BCL2 gene in 1984-1985 as an oncogene involved in the specific translocation t(14; 18) (q32; q21) in follicular B-cell lymphomas has become one of the key events in molecular oncology [7]. This was the first time that an oncogene was associated not with increased proliferation, but with dysregulation of apop-

tosis - a physiological process of controlled cell death [12]. Later, this discovery was confirmed by the identification of the homologous anti-apoptotic gene ced-9 in the nematode Caenorhabditis elegans, which proved the universality of apoptosis mechanisms in eukaryotes [13]. Modern studies have confirmed that the Bcl-2 protein is localized predominantly in the outer membrane of mitochondria, playing a central role in controlling the mitochondrial-dependent apoptosis pathway through the regulation of pro- and anti-apoptotic members of the Bcl-2 family [14]. This became the basis for the concept of apoptosis as the most important mechanism for maintaining tissue homeostasis and the target of antitumor therapy, which is reflected in the drug development, for example, the Bcl-2 inhibitor Venetoclax, which is actively used in the treatment of hematological and some solid tumors [15].

Bcl-2 is a key anti-apoptotic protein that regulates the survival of tumor cells. In NSCLC, Bcl-2 expression occurs in 30-50% of patients, especially in adenocarcinomas. In small cell lung cancer, Bcl-2 levels are elevated in 75-90% of cases. High expression of Bcl-2 in SCCL is associated with resistance to chemotherapy and a more aggressive course of the disease. In NSCLC, Bcl-2 may be a marker of a better prognosis because it correlates with a less aggressive phenotype [16].

The HER2 amplification is detected in 2-4% of patients with lung adenocarcinoma. HER2 mutations are more common in non-smoking patients and women, and HER2 mutations (insertions in exon 20) are detected by next-generation sequencing (NGS) [17].

HER2-positive NSCLC is characterized by a more aggressive course and rapid progression. Patients with HER2 mutations show worse survival in the absence of targeted therapy [18]. Bcl-2 inhibitors, such as Venetoclax, have shown promising results in the treatment of some forms of lung cancer. The combination of Bcl-2 inhibitors with chemotherapy may increase the sensitivity of the tumor to treatment [19]. HER2 inhibitors (Afatinib, Trastuzumab, Trastuzumab deruxthecan) significantly improve the prognosis of patients with HER2-positive lung cancer. Trastuzumab deruxtecan showed an improvement of progression-free survival for 9.3 months in HER2-positive patients [20]. Analysis of the expression of Bcl-2 and HER2 proteins in NSCLC revealed their significant role in the progression of the tumor process and response to therapy.

According to N.F. Underwood et al., HER2 changes occur in 7-27% of cases of de novo NSCLC and are a mechanism of resistance in 10% of mutated EGFR-NSCLC cases. The most common mutation is the insertion of HER2 exon 20, which leads to increased activity of the PI3K/Akt and MEK/ERK signaling pathways, which promotes oncogenesis and disease progression. The studies show that patients with HER2 amplification and overexpression demonstrate lower progression-free survival and overall survival, compared to HER2-negative patients [21].

E. Loeffler et al. note that HER2 is a receptor tyrosine kinase of the EGFR/ErbB family, and its disorders can occur in the form of gene mutation, gene amplification, protein overexpression, and hyperphosphorylation.

HER2 abnormalities contribute to abnormal proliferation, angiogenesis, mesenchymal tumor properties, and immune response evasion, making HER2 a significant target for targeted therapy. HER2 mutations occur in 1-4% of patients with NSCLC, HER2 amplification in 2-5%, and overexpression in 2-30% of patients. HER2 mutations are more common in women, non-smoking patients, and in adenocarcinoma. High HER2 expression is associated with a worse prognosis and lower efficacy of standard chemotherapy and immunotherapy [22].

M. Miladinović et al. found that HER2 was overexpressed in 7.4% of patients with lung adenocarcinoma when using HercepTest, and in 2.7% of patients when testing with the 4B5 antibody. In 90.9% of cases, a correlation was found between high HER2 expression and amplification of the HER2 gene, which confirms its importance as a molecular target [23].

In a study of W. Chen et al., HER2 mutations were more common in younger patients and non-smokers. Such tumors tend to show slower growth, compared to wild-type HER2 [24].

Discussion: The data obtained confirm the importance of HER2 and Bcl-2 molecular alterations in the pathogenesis and clinical course of non-small cell lung cancer (NSCLC). Both targets are involved in the regulation of key processes of tumor growth and apoptosis, determining the aggressiveness of the tumor, its sensitivity to treatment, and the disease prognosis.

The Bcl-2, being an important anti-apoptotic protein, affects the survival of tumor cells by suppressing the mitochondrial-mediated pathway of apoptosis. Bcl-2 overexpression is most frequent in small cell lung cancer, where it reaches 75-90%, while in NSCLC, it occurs in 30-50% of cases. However, the role of Bcl-2 in NSCLC remains controversial: on the one hand, high protein expression is associated with resistance to chemotherapy, on the other hand, it can serve as a marker of a less aggressive tumor phenotype. This highlights the need for further research to clarify the prognostic and predictive value of Bcl-2 in different histological subtypes of NSCLC, as well as to optimize the use of Bcl-2 inhibitors as part of combination regimens of therapy.

HER2, in turn, is a receptor tyrosine kinase of the EGFR/ErbB family, the alterations of which include mutations, amplification, and overexpression. HER2 mutations occur in 1% to 4% of patients with NSCLC, mainly in women, non-smokers, and patients with adenocarcinoma. The most common option is insertion in exon 20, resulting in activation of the PI3K/Akt and MEK/ERK signaling path-

ways and promoting tumor progression. HER2 amplification and overexpression also demonstrate an association with poor prognosis and reduced efficacy of standard chemotherapy and immunotherapy. At the same time, the presence of HER2 alterations predetermines the possibility of prescribing targeted drugs such as Afatinib, Trastuzumab, and Trastuzumab deruxtecan, the use of which has already demonstrated improvement in progression-free survival and overall survival of patients with HER2-positive NSCLC.

Of particular interest are the data on the relationship between HER2 amplification and overexpression of its protein, which emphasizes the need for a comprehensive assessment of these parameters to optimize the choice of therapy. In addition, HER2 alterations play the role not only in primary oncogenesis, but also as a mechanism of acquired resistance in patients with EGFR-mutated NSCLC, which is important for the subsequent selection of therapy after disease progression.

Accordingly, HER2 and Bcl-2 are topical biomarkers and therapeutic targets in the treatment of NSCLC. Their study allows not only to enhance the understanding of the molecular basis of the tumor process, but also to justify the feasibility of personalized treatment selection, including targeted therapy and combined regimens. Further multicenter studies with enrollment of large patient cohorts and standardized diagnostic methods are needed to refine the prognostic value of these biomarkers and optimize the treatment approaches.

Conclusion: The findings highlight the important role of HER2 and Bcl-2 molecular alterations in the pathogenesis, prognosis, and individualization of therapy for non-small cell lung cancer. These biomarkers have a significant impact on tumor biological behavior, sensitivity to therapy, and patient survival. Expression of Bcl-2 shows a dual role: in NSCLC, it may be associated with a less aggressive course, while in small cell lung cancer, it correlates with resistance to chemotherapy. Taking into account the above, the inclusion of HER2 and Bcl-2 assays in the algorithm of molecular tumor profiling seems appropriate and can contribute to more accurate stratification of patients, optimization of treatment tactics, and increased effectiveness of personalized treatment in NSCLC. Further studies are needed to validate these markers in routine clinical practice and develop the combined therapeutic strategies.

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АҢДАТПА

HER2 ЖӘНЕ BCL-2 АЛЬТЕРАЦИЯЛАРЫНЫҢ ҰСАҚЕМЕСЖАСУШАЛЫ ӨКПЕ ОБЫРЫНДАҒЫ БИОЛОГИЯЛЫҚ ЖӘНЕ КЛИНИКАЛЫҚ МАҢЫЗЫ, СОНДАЙ-АҚ ТЕРАПИЯЛЫҚ ӘДІСТЕРДІҢ ПЕРСПЕКТИВАЛАРЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Өкпенің қатерлі ісігі бүкіл әлемде қатерлі ісік өлімінің жетекші себептерінің бірі болып қала береді. Дүниежүзілік денсаулық сақтау ұйымының мәліметі бойынша, жыл сайын бұл аурудан 2,2 миллионнан астам жаңа жағдай және 1,8 миллион адам қайтыс болады. Диагностика мен емдеудегі жетістіктерге қарамастан, ұсақемесжасушалы өкпе обырының (ҰЕЖӨО) болжамы, әсіресе соңғы кезеңдерінде, қолайсыз болып қала береді. Молекулярлық және генетикалық биомаркерлер диагностиканы жақсартуда және терапияны таңдауда маңызды рөл атқарады. Апоптозды және пролиферацияны реттеуге қатысатын Bcl-2 және HER2 ақуыздары ҰЕЖӨОагрессивті ағымымен және терапияға төзімділікпен байланысты болуы мүмкін. Олардың зерттеуі осы ауруды емдеудің жеке көзқарасын дамыту үшін өзекті болып табылады.*

Зерттеу мақсаты *– ұсақемесжасушалы өкпе обыры кезінде HER2 және Bcl-2 өзгерістерінің биологиялық және клиникалық маңыздылығын бағалау, сондай-ақ олардың аурудың болжамына және әртүрлі терапевтік стратегиялардың тиімділігіне әсерін талдау.*

Әдістері: *Бұл шолуда PubMed, Web of Science және Google Scholar дерекқорларында «биомаркерлер», «ұсақемесжасушалы өкпе обыры», «диагностика», «болжам», «тірі қалу қабілеттілігі» кілт сөздері бойынша медициналық әдебиеттерге электрондық іздеу жүргізілді. Шолуда соңғы бес жылда жарияланған, өкпе обырының ерте диагностикасы мен болжамындағы биомаркерлердің рөліне арналған орыс және ағылшын тілдеріндегі толық мәтінді мақалалар қамтылды.*

Нәтижелері: *Bcl-2 және HER2 экспрессиясы ҰЕЖӨО патогенезінде маңызды рөл атқарады. Апоптоздың реттеушісі Bcl-2 30-50% науқастарда анықталады және бұл ісіктің түрі мен сатысына байланысты өршумен де, өмір сүрудің жақсаруымен де байланысты болуы мүмкін. HER2-дегі өзгерістер науқастардың 1-30%-ында кездеседі, көбінесе темекі шекпейтін әйелдердегі аденокарциномаларда байқалады және қолайсыз болжаммен әрі терапияға төзімділікпен байланысты. Қазіргі нысаналы препараттар, соның ішінде венетоклакс және HER2-ингибиторлары (трастузумаб дерукстекан, пиротиниб) тиімділігін көрсетіп, рецидивсіз өмір сүру ұзақтығын арттырады.*

Қорытынды: *Bcl-2 және HER2 зерттеу ҰЕЖӨО-ның молекулярлық механизмдерін түсінуге және емдеуге жекелендірілген тәсілді дамытуға мүмкіндік туғызады. Бұл ақуыздар перспективті биомаркерлер және емдеу үшін нысаналар болып табылады, сонымен қатар оларды кешенді бағалау емдеудің тиімділігін жоғарылату және болжамды жақсарту үшін клиникалық практикаға енгізілуі керек.*

Түйінді сөздер: *биомаркер, ұсақемесжасушалы өкпе обыры (ҰЕЖӨО), диагностика, болжам, тірі қалу қабілеттілігі.*

АННОТАЦИЯ

АЛЬТЕРАЦИИ HER2 И BCL-2 ПРИ НЕМЕЛКОКЛЕТОЧНОМ РАКЕ ЛЕГКИХ: БИОЛОГИЧЕСКОЕ И КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ, ПЕРСПЕКТИВЫ ТЕРАПЕВТИЧЕСКИХ МЕТОДОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак легкого остается одной из ведущих причин онкологической смертности в мире. По данным ВОЗ, ежегодно выявляется более 2,2 млн новых случаев, а смертность превышает 1,8 млн. Несмотря на достижения в диагностике и лечении, прогноз при немелкоклеточном раке легкого (НМРЛ), особенно на поздних стадиях, остаётся неблагоприятным. Существенную роль в улучшении диагностики и выборе терапии играют молекулярно-генетические биомаркеры. Белки Bcl-2 и HER2, участвующие в регуляции апоптоза и пролиферации, могут быть связаны с агрессивным течением НМРЛ и устойчивостью к терапии. Их изучение актуально для развития персонализированного подхода в лечении данного заболевания.*

Цель исследования *– оценить биологическое и клиническое значение изменений HER2 и Bcl-2 при немелкоклеточном раке легких, а также проанализировать их влияние на прогноз заболевания и эффективность различных терапевтических стратегий.*

Методы: *В обзоре проведён электронный поиск медицинской литературы в базах PubMed, Web of Science и Google Scholar по ключевым словам: «биомаркеры», «рак легкого», «диагностика», «прогноз», «выживаемость». Включены полнотекстовые статьи на русском и английском языках, опубликованные за последние пять лет и доступные в открытом доступе, посвящённые роли биомаркеров в ранней диагностике и прогнозировании рака легкого.*

Результаты: *Экспрессия Bcl-2 и HER2 играет важную роль в патогенезе НМРЛ. Регулятор апоптоза Bcl-2 выявляется у 30-50% пациентов и может ассоциироваться как с агрессивностью опухоли, так и с улучшенной выживаемостью в зависимости от подтипа и стадии. Альтерации HER2 обнаруживаются у 1-30% больных, чаще при аденокарциномах у некурящих женщин, и связаны с неблагоприятным прогнозом и резистентностью к терапии. Современные таргетные препараты, включая венетоклакс и HER2-ингибиторы (трастузумаб дерукстекан, пиротиниб), демонстрируют эффективность, повышая безрецидивную выживаемость.*

Заключение: *Изучение Bcl-2 и HER2 способствует пониманию молекулярных механизмов НМРЛ и развитию персонализированных подходов к терапии. Эти белки являются перспективными биомаркерами и мишенями для лечения, а их комплексная оценка должна быть внедрена в клиническую практику для повышения эффективности лечения и улучшения прогноза.*

Ключевые слова: *биомаркер, немелкоклеточный рак легкого (НМРЛ), диагностика, прогноз, выживаемость.*

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EVALUATION OF QUALITY ASSURANCE STRATEGIES FOR IMMUNOHISTOCHEMISTRY TESTING IN BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *External quality assessment (EQA) programs should be used alongside the technique to achieve accurate and reliable results when performing Immunohistochemistry (IHC) tests and diagnostics. Ensuring the accuracy of tumor biomarker tests is critically important in precision medicine since individualized treatment plans are now common in oncology.*

The study aimed to *systematically review evidence related to EQA in reducing inter-laboratory discrepancies and interpretative concordance variability in human epidermal growth factor receptor 2 (HER2) IHC testing for breast cancer and to identify current challenges and future directions.*

Methods: *This study's systematic literature search revealed 306 records, of which 25 full-text articles were included in the final analysis. The review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020).*

Results: *Recent studies suggest that EQA programs greatly improve the agreement and accuracy of HER2 IHC testing done in several laboratories. Global standards ensure standardized, reliable, and consistent HER2 testing procedures throughout the process. Moreover, new approaches like digital pathology, algorithms, and messenger RNA (mRNA)-based tests hold great potential for improving the consistency of results and reducing judgment errors in manual reviews.*

Conclusion: *Implementing EQA programs has reduced variation in results from HER2 IHC across different laboratories. With the introduction of the HER2-low classification, testing methods are moving from subjective approaches to using various forms of data to improve the test's importance to doctors. Participation in EQA enhances the efficiency of testing HER2 receptors, with the same results in several places worldwide. Having a team of experts improves the diagnosis and repeatability of breast cancer.*

Keywords: *Immunohistochemistry (IHC), External Quality Assessment (EQA), Breast Cancer, HER2, Quality Control (QC).*

Introduction: Breast cancer's diverse biological characteristics remain a serious challenge despite new developments in screening, diagnostics, and therapies. Ensuring an accurate evaluation of HER2 status is vital for treatment strategy selection. IHC testing is commonly used as the initial method for assessing HER2 status due to its widespread availability, low cost, and rapid turnaround time. However, its diagnostic accuracy can be affected by variability in antibody selection, staining protocols, and pathologists' subjective interpretation of it. The mentioned variability can misjudge the HER2 status of some cancer cells, leading to faulty treatment decisions. EQA programs have been adopted and standardized across countries to help hospitals stay consistent in testing and diagnoses [1, 2].

Using the quality control case in HER2 IHC scoring for breast cancer, we present a systematic review that summarizes authoritative international quality assessment initiatives, associated standards, and the documented impact of EQA programs on enhancing inter-laboratory reproducibility and diagnostic consistency.

The study aimed to systematically review evidence related to EQA in reducing inter-laboratory discrepancies and interpretative concordance variability in HER2 IHC testing for breast cancer and to identify current challenges and future directions.

Materials and Methods: This research conducted a systematic review of 306 records. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, the study assessed quality control measures in immunohistochemistry laboratories for HER2 testing in breast cancer on a global scale [3]. The exclusion criteria included studies not related to breast cancer (n=65), those not focusing on EQA (n=50), studies lacking sufficient methodological details (n=18), publications published before 2020 (n=4), and non-English language articles (n=3). We selected 25 full-text articles for final analysis.

Search Strategy: A thorough search was conducted within PubMed, Scopus, Web of Science, and Google Scholar databases for the literature released between 2020 and 2025. The search applied such terms as "immunohistochemistry" or "IHC" with "quality assessment," "quality assurance," or "quality control," in addition to the terms "breast cancer" and "HER2". In addition, manual citation searches were done, and Rayyan was used to manage references and complete the research.

Study Selection Process: The review followed a clear workflow to ensure robust findings closely aligned with quality control in breast cancer immunohistochemistry testing, as illustrated in Figure 1.

Results:

1. The Present Condition of Quality Control Research in Breast Cancer Immunohistochemistry (IHC)

This study conducts a systematic search and analysis of 25 research articles published between the years 2020

and 2025 in order to provide a quantitative overview and academic summary of the current research landscape on quality control of HER2 IHC analysis.

1.1. Publication Trends Over the Last Five Years

According to bibliometric analysis, the number of publications on EQA of HER2 IHC testing in breast cancer has shown an overall increasing trend despite some fluctuations (Figure 2). In 2023, the number of publications reached its highest point. This upward trajectory may be strongly associated with the growing clinical recognition of the role of HER2-low subtypes in guiding targeted treatment decisions. Notably, the timing of this increase aligns with the release of updated guidelines from two major international bodies — the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) and the European Society for Medical Oncology (ESMO) [1, 4]. As of April 2025, four studies have been published, meaning that research activity in this area continues to be strong. It is expected that the total number of publications for the year will remain at a relatively high level.

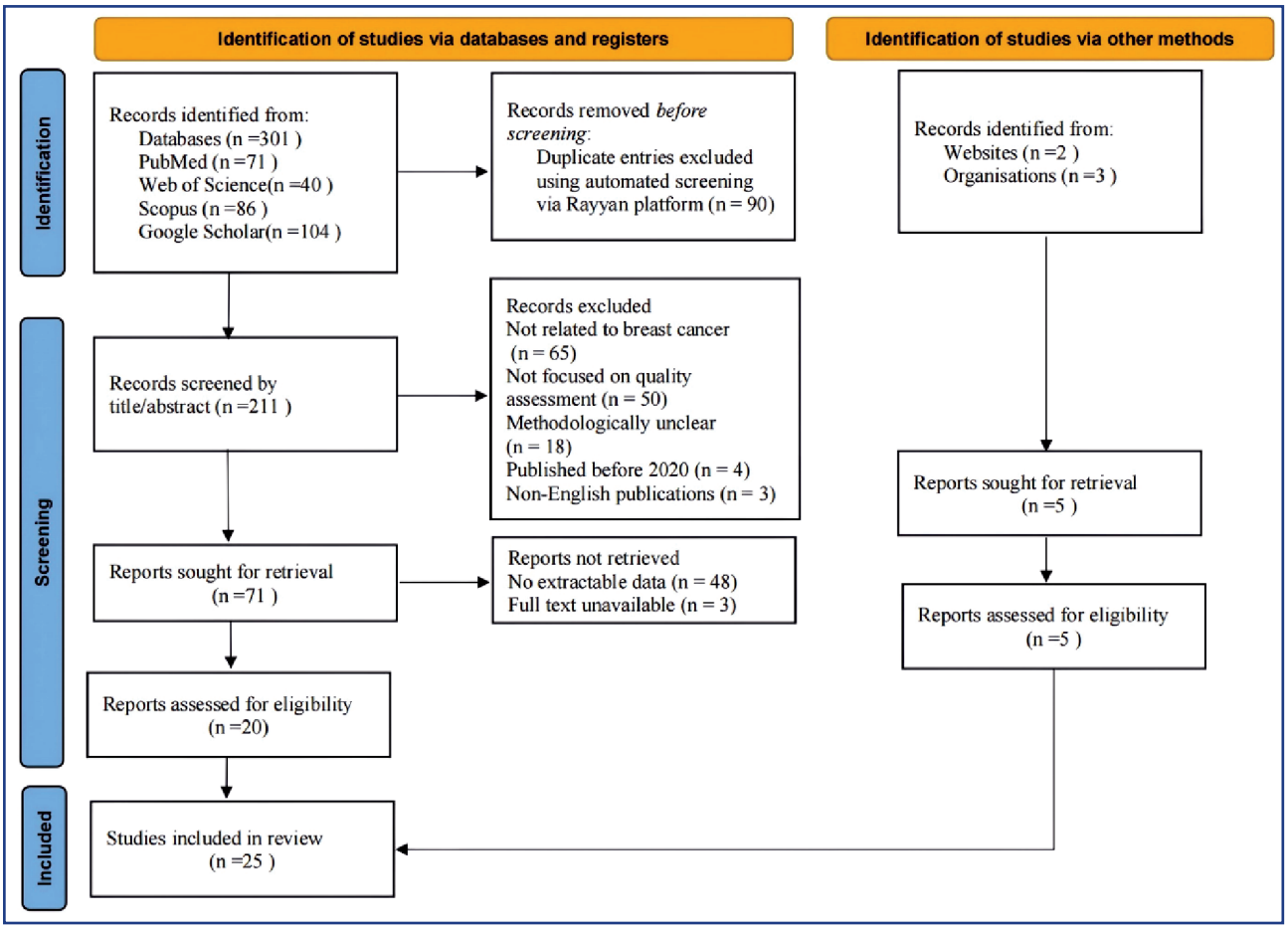

Figure 1 – PRISMA flow diagram of HER2 IHC EQA review

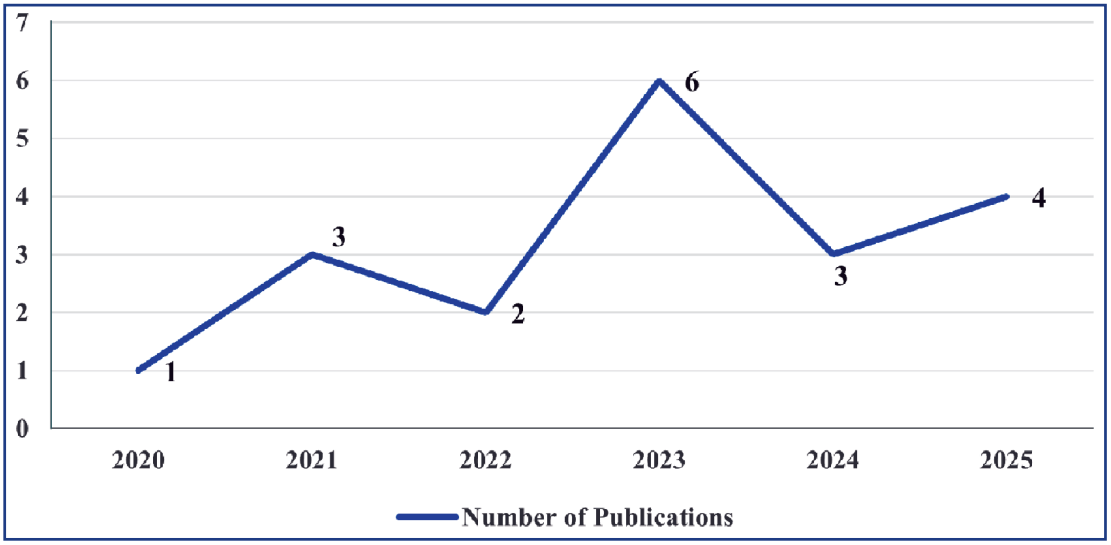

Figure 2 – Annual number of publications on EQA of HER2 IHC testing in breast cancer (2020-2025)

All in all, these trends evidence the ongoing global focus on HER2 IHC testing standardization, increased concordance of scoring, and the establishment of strong EQA programs. This increased awareness is sparked not only because of the newly defined HER2-low category used in enhanced therapeutic selection for breast cancer but also because of the importance of precision pathology in making individualized treatment options both accessible and effective.

1.2. Geographic Dispersion of Publications

As illustrated in Figure 3, In terms of single-country studies, the United States provided four publications, reflecting its dominant role in HER2 testing validation and establishing associated regulations. China independently contributed two studies, reflecting an ongoing national-level commitment to proficiency testing and diagnostic standardization. Likewise, Denmark, Australia, and the Netherlands contributed two studies, reflecting their respective engagement in HER2-related quality assurance. Italy contributed to one study. However, most of the investigations in this review emerged from international collaborative multinational studies, with six studies classified as multinationals, representing the largest proportion of all identified. This finding demonstrates the growing dependence on international cooperation around the quality assurance of HER2 IHC testing and a significant need for harmonized international standards. International collaborative studies often aim to improve scoring concordance, share methodology, and collaboratively advance clinical practice guidelines.

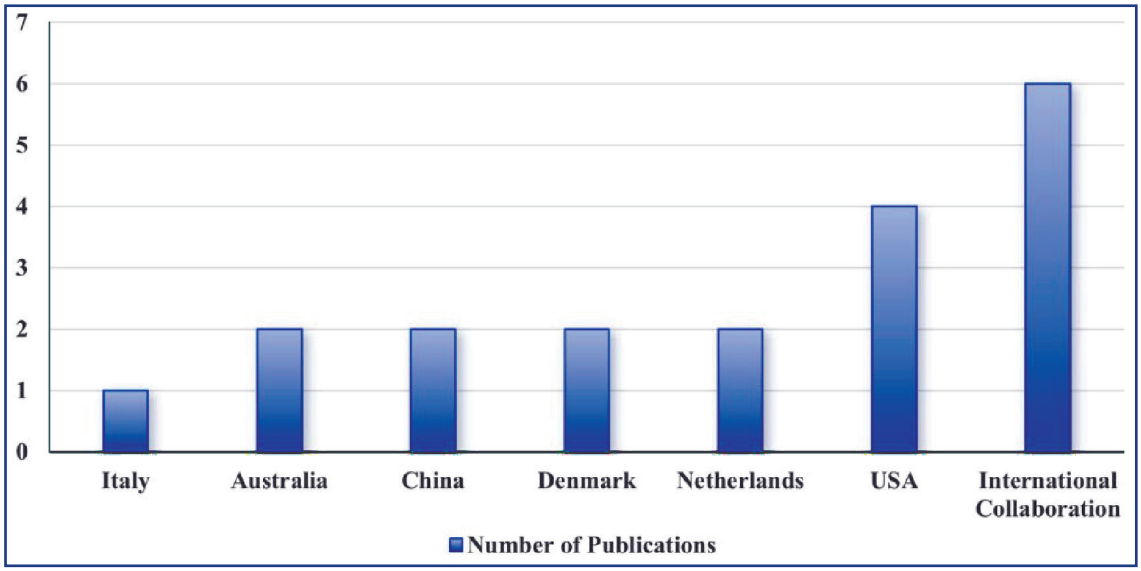

Figure 3 – Distribution of cited publications by country/international collaboration

1.3. Distribution of Research Themes

As depicted in Figure 4, the literature reviewed comprises diverse research topics about HER2 testing in breast cancer. The three areas addressed most frequently were interobserver agreement and reproducibility, HER2-low subtyping and management, and the utilization of artificial intelligence and digital pathology, with 21% of the literature comprising each area (n=4 per category).

In total, 16% of studies (n=3) explored molecular diagnostics and proficiency testing on the following components: fluorescence in situ hybridization (FISH) confirmation in IHC 2+ cases, inter-laboratory reproducibility of mRNA detection assays, and an increased need to establish concordance between IHC and molecular-level assays in borderline cases. Two studies (11%) focused on quality assurance and EQA systems, including themes such as EQA program design, pathologists' interpretive performance, and laboratory compliance analysis. These findings indicate an actionable pathway towards standardization of HER2 testing workflows and ultimately improving diagnostic quality overall.

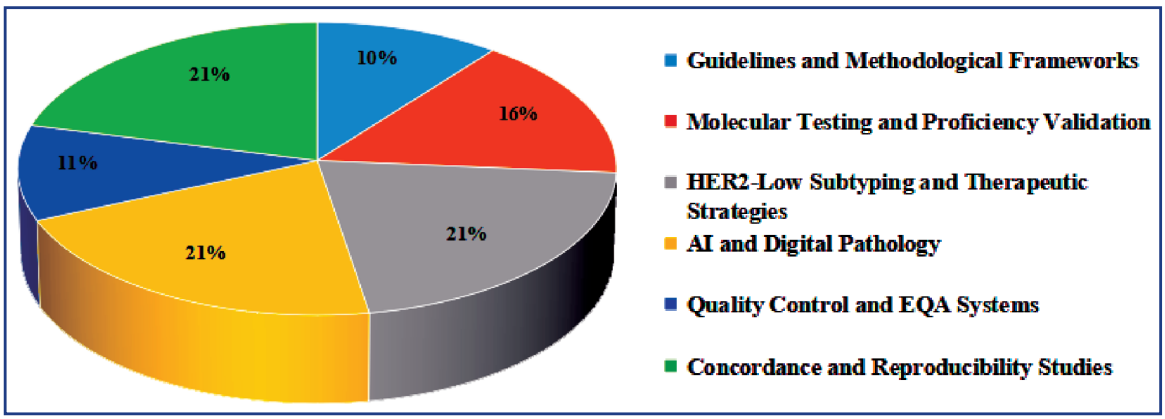

Figure 4 – Research focus distribution in HER2 IHC EQA studies

In conclusion, the diversity found in Figure 4 indicates the obstacles and challenges faced when performing HER2 testing in an HER2-low setting. Even though targeted therapeutic options continue to be developed, limitations in clinically applying HER2-low as a biomarker arise due to consistent scoring concordance, reproducibility of the assay, and variability of methods. As a result, enhancing the precision and reliability of IHC-scored will continue to be an important area of focus and direction in active HER2 research.

1.4. HER2 IHC testing scoring concordance

Due to more individualized treatment of breast cancer, there has been increasing scrutiny on the issue of concordance in HER2 IHC scoring, especially for classification and treatment decisions around the "HER2-low" subtype. HER2-low tumors are primarily defined as those with an IHC score of 1+ or 2+ and a negative FISH result and may now benefit from targeted therapies such as trastuzumab deruxtecan (T-DXd). However, substantial inter-laboratory and inter-observer variability, particularly in distinguishing IHC 0 from 1+, remains a major challenge to accurate patient stratification.

Multiple multicenter scoring studies have supported this trend. In a study of 18 breast pathology experts conducted in the United States by Robbins et al., the overall concordance rate for HER2 IHC 0 was only 25%. The concordance for 1+ and 2+ was similarly low, with a Fleiss' κ coefficient of only 0.49, indicating poor reliability of the current scoring system for interpreting HER2-low cases [5]. This conclusion was further supported by a consensus study conducted in the United Kingdom and Ireland. In this study, 16 experienced pathologists independently reviewed 50 digitized HER2 IHC slides. The participants agreed upon only about 6% of the evaluated cases. Notably, overall agreement increased to 86% when scores were dichotomized into 0 versus non-0, suggesting that score aggregation strategies may help reduce inter-observer variability [6].

Simultaneously, data from the real world also demonstrated variability in HER2 scoring at the laboratory level. A population-based cohort study using a national registry in Denmark with 50,714 breast cancer cases showed differences of 25.5 percentage points in the classification of HER2-low tumors by laboratory. The testing laboratory was identified as an independent variable associated with HER2 0 versus HER2-low from the multivariate regression, providing evidence that there was still low laboratory concordance with HER2 0 and HER2-low concordance even under standardized testing conditions [2].

The National Cancer Center of China has embarked on a proficiency testing (PT) program designed in practice to assess the consistency of HER2 scoring in three categories: 0, 1+, and 2+ (FISH-negative). The concordance rate for HER2 0 was 78.1%, while for HER2 2+, some institutions scored less than 59%, demonstrating systematic biases in scoring. The PT program, conducted using ISO/IEC 17043 quality criteria, exemplifies the variation in scoring methods and the importance of training and subsequent feedback in scoring concordance [7].

By contrast, an Australian study offers an encouraging example of improving interpretive concordance. The research group implemented a HER2-low-specific scoring protocol, which was validated based on two scoring rounds against a cohort of 64 HER2-negative breast cancer samples. Their results included a reported accuracy rate of 89.58% and Cohen's κ coefficient of 0.81, denoting "excellent agreement." This study provides all-important evidence that targeted training and scoring workflow optimization can improve reproducibility regarding the interpretation of HER2-low [8].

Comprehensive descriptions of the previous studies are provided in Table 1. The table represents a summary of the HER2 scoring studies, methodological characteristics of the studies, and scoring concordance results. As well as different dimensions of evidence to support scoring consistency and quality control in HER2 immunohistochemistry.

Table 1 – Overview of concordance studies in HER2 IHC testing for breast cancer

Study / Project	Study Type	Sample Size	Key Findings
Robbins et al. (USA)	Multi-institutional scoring concordance study	170 biopsy specimens	Overall concordance for HER2 0 was only 25%; low agreement for 1+ and 2+; Fleiss' κ=0.49
Zaakouk et al. (UK/ Ireland)	Expert consensus scoring study	50 digital slides	Absolute concordance was achieved in only 6% of cases and increased to 86% when grouped as 0 vs. non-0
Nielsen et al. (Denmark)	Nationwide registry study	50,714 breast cancer cases	The proportion of HER2-low cases ranged from 46.3% to 71.8% across different pathology departments (P<0.0001, relative difference 0.55); the pathology department was a significant independent factor influencing HER2 scoring (P<0.0001).
Xue et al. (China)	National proficiency testing program	HER2 slides from 173 institutions	Concordance for HER2 0 was 78.1%; some labs showed <59% accuracy for 2+ scoring
Farshid et al. (Australia)	HER2-low focused scoring system validation	64 HER2-negative breast cancer cases	Achieved 89.58% mean accuracy for HER2-low vs non-low classification; Cohen's κ=0.81, indicating excellent interobserver concordance

In summary, the interpretation of HER2 IHC scores within the HER2-low range, specifically 0 to 1+, continues to be a real challenge that has shown considerable variability across countries, laboratories, and observers. Improving agreement on the score will require establishing a standardized assessment system using HER2-low as a case example, internationally harmonized interpretive frameworks, and implementation of digital pathology, external proficiency testing programs, and artificial intelligence-assisted tools. Several approaches shall be applied simultaneously to improve the reliability, standardization, and clinical utility of HER2-low breast cancer classification.

2. Quality Assessment Programs for Immunohistochemistry Testing in Breast Cancer

As precision medicine continues to advance and breast cancer treatments become more individualized, the accuracy and reproducibility of HER2 testing have become increasingly critical. Standardized EQA systems are essential to ensure diagnostic reliability and support clin-

ical decision-making. Growing concern about inter-laboratory variability in testing has prompted international organizations to actively promote the quality of HER2 testing through EQA initiatives. Table 2 summarizes key global EQA providers and their specific focus in assessing the quality of HER2 testing.

Table 2 – The functions of global EQA organizations in quality assessment of HER2 IHC testing

EQA Organization	Description
College of American Pathologists (CAP) [9]	CAP is the number one major proficiency testing body and laboratory accreditation agency in the U.S. Its Immunohistochemistry Proficiency Testing Program (CAP IHC PT) is a proficiency test that tests for necessary breast cancer biomarkers such as HER2, ER, and PR to enhance inter-laboratory agreement and analytical accuracy.
Nordic Immunohistochemical Quality Control (NordiQC) [10]	NordiQC offers EQA programs for several predictive biomarkers (HER2, ER, PR, and Ki-67). It evaluates staining outcomes and concordance, providing technical evaluation to standardize and enhance diagnostic precision.
UK National External Quality Assessment Service for Immunocytochemistry (UK NEQAS ICC) [11]	UK NEQAS ICC provides EQA schemes for IHC and ISH, emphasizing the inter-laboratory achievability of consensus in HER2 biomarker analysis, achieved through standardized scoring and feedback.

Notes: CAP=College of American Pathologists; NordiQC=Nordic Immunohistochemical Quality Control; UK NEQAS ICC= UK National External Quality Assessment Service for Immunocytochemistry.

These initiatives have significantly contributed to the global standardization of HER2 IHC testing and the reduction of inter-laboratory variability, thereby improving diagnostic accuracy and reinforcing the reliability of treatment decisions in breast cancer care. As a whole, EQA organizations have become essential features of HER2 testing quality assurance.

Multiple reputable global guidelines in HER2 IHC testing for breast cancer have created organized frameworks for testing, validation, and quality assurance (Table 3). Specifically, the joint guidelines from the American Society of Clinical Oncology (ASCO) and College of CAP from 2007, 2013, 2018, and 2023 established standardized interpretation criteria for HER2 IHC and in situ hybridization (ISH) assays. These guidelines utilize evidence-based recommendations to guide testing methodology, scoring, and interpretations [1, 12].

Furthermore, the International Organization for Standardization (ISO) 15189:2022 specifies the requirements for a quality management system and technical competency for medical laboratories established by the ISO and provides a fundamental basis for their validity, reliability, and comparability of test results [13]. A complete revision of earlier versions has made ISO 17043:2023 a pillar for the organization's standardization, implementation, and evaluation of proficiency testing schemes. It sets sounder technical requirements and procedures for risk management, statistical data analysis, and results reporting for EQA programs to ensure their scientific soundness, impartiality, transparency, and practicality [14]. Together, these standards and guidelines provide an internationally accepted framework for quality control for HER2 assays in breast cancer biology, giving standardized referential and institutional acceptances for laboratory quality control.

Table 3 – International Guidelines and Standards for Quality Assurance of HER2 IHC Testing in Breast Cancer

Program	Description
ASCO/CAP HER2 Testing Guideline [12]	Developed by ASCO and CAP. This guideline identifies HER2 IHC and ISH testing and interpretation standards, scoring systems, and laboratory accreditation requirements. It is the world's most authoritative guideline for HER2 testing.
ISO 15189:2022	Developed by the ISO, this standard provides requirements for the quality and competence of medical labs. It is relevant to laboratories doing HER2 testing for reliability and quality control.
ISO 17043:2023	ISO also released this standard, which describes the general requirements for proficiency testing providers. It sets standards for the development, implementation, and evaluation of the outcome of EQA programs, maintaining scientific validity, fairness, and transparency in the process.

Notes: ASCO/CAP = American Society of Clinical Oncology / College of American Pathologists; ISO=International Organization for Standardization

In conclusion, internationally recognized guidelines and standards provide the technical support and evaluation criteria for HER2 testing. EQA systems support ongoing improvements in quality through localized operationalization. These guidelines, standards, and EQA systems establish the foundation for quality assurance in HER2 testing for breast cancer as part of the precision medicine paradigm.

3. The challenges of external quality assurance for breast cancer testing with immunohistochemistry

Despite the presence of relatively well-established EQA systems to support HER2 IHC testing, an issue remains with inter-laboratory variability, driven by different technical issues and subjective interpretative factors involved at every stage of the testing process. Laboratory-based variability in interpreting HER2 IHC testing is a significant problem, and a variety of pre-analytical and analytical factors, including inconsistent tissue processing, variability from staining platforms, antibody sensitivity, antibody clone selection, non-specific background staining, variations in protocols, and subjective interpretation influences this variability. Addressing the contribution of these issues to variability is fundamental to improving the accuracy and reproducibility of HER2 testing.

Table 4 provides key procedural steps and recommendations for HER2 IHC testing in the pre-analytical, analytical, and post-analytical settings to aid this targeted intervention framework. Each of these procedural steps aims to help optimize and standardize aspects of laboratory quality control.

Studies have underscored considerable inter-platform variability concerning staining intensity and staining reproducibility when assessing the efficacy of various automated IHC staining platforms for HER2 assessment. Jiang et al. established that the combined use of standardized cell lines and algorithm-based real-time monitoring can

detect the relative level of staining variability attributed to the instrument and counterbalance for potential slot position effects. This methodology supports routinized evaluation and maintenance, which ultimately enhances the consistency and reliability of staining [15]. In addition, different staining protocols (NordiQC, Protocol 1, and Protocol 2) influence HER2 IHC results, especially when examining HER2-low cases. In particular, great differences were observed in the NordiQC compared to the other staining protocols, emphasizing the importance of standardizing staining protocols in limiting pre-analytical variables among laboratories [16].

Table 4 – Crucial processing steps and best practice recommendations for each phase of HER2 IHC testing [1, 12]

Phase	Critical Steps	Recommendations
Pre-analytical	Biopsy/Surgical Excision, Tissue Fixation, Processing, Paraffin Embedding, Sectioning	Cold ischemic time should be less than 1 hour. Transporting at a controlled temperature is advised. To ensure antigenicity, tissue samples should be fixed in 10 % (neutral buffered formalin) for 6-72 hours. Laboratories should make use of internal quality control and EQA programs. Paraffin sections should not be greater than 5 µm thick, and sections stored longer than 6 weeks should be avoided to avoid antigen degradation.
Analytical	Antibody Selection, Staining Platform, Antigen Retrieval, Tissue Controls, Interpretation, Recognition of Aberrant Expression and Unusual Staining Patterns	Apply FDA-approved IHC antibody clones, PATHWAY anti-HER-2 /neu (4B5), or HercepTest pharmDx. Use validated automated staining platforms such as Ventana BenchMark and Dako Omnis. Apply standardized protocols of antigen retrieval. Every staining run must include adequate low-level and high-level positive and negative controls. ASCO/CAP criteria must be referred to, especially when dividing IHC scores 0 vs. 1+. Pay particular attention to the staining heterogeneity and aberrant patterns that need re-evaluation.
Post-analytical	SOP Adherence, Pathologist Training, Report Annotation (e.g., IHC 0 vs. 1+ distinction), Reference Materials for Varying HER2 Expression Levels	All HER2 testing procedures have to conform to institutional SOPs. The continuous training of pathologists and credentialing should be sustained. IHC results and interpretation notes should be kept in the patient's clinical record. Reports should specify the differences between the weak IHC 0 and the weak plus (IHC +) cases, including HER2-negative (the IHC 0, 1+, and equivocal 2+/ISH−). The verification of detection sensitivity should involve reference materials for 1+ expression.

The choice of antibody clones and their compatibility with staining platforms is an important factor influencing the correct identification of HER2-low expression. In a comparison study, Hempenius et al. found that the 4B5 antibody had a higher agreement and lower background staining in samples in the HER2-low category when used with the OptiView detection system; therefore, this approach should be considered a better option for detecting this expression category [17]. These observations continue to highlight the importance of optimized matching of antibody clones and staining platforms in improving the accuracy of HER2-low detection and inter-laboratory reproducibility of HER2 IHC testing.

Furthermore, Fernandez et al., leveraging data from the CAP proficiency testing program and a multi-institutional scoring dataset provided by Yale, observed low concordance in HER2 IHC scoring (0 and 1+) at only 26%, compared to a higher concordance of 58% in 3+ cases [18]. These results illustrate greater subjectivity and less reproducibility in the HER2-low scoring range, warranting improved and standardized interpretive guidelines and targeted training in that interval that creates diagnostic ambiguity for more consistent diagnostics.

In conclusion, there continues to be meaningful inter-laboratory variability for HER2 IHC testing regarding the interpretation of staining, antibody choice, and execution of protocols, which can be a significant barrier to diagnostic accuracy. Incorporating digital pathology and enhanced laboratory accreditation may represent meaningful deliveries toward the standardization of testing pathways. The prospect of artificial intelligence (AI)-based automated scoring systems represents a significant pathway to deliver the quality of HER2 assessment as an essential of precision oncology.

Discussion: With the advancement of precision medicine, the drawbacks of traditional single-modality HER2 testing, that is, its ability to accurately diagnose and reproducibly detect HER2 status, have garnered increasing interest in the subtype of breast cancer setting. In response to a growing interest in providing more reliable diagnosis, recently, there has been a transition toward a more integrated approach, in which digital technologies, artificial intelligence, and multi-omics are increasingly incorporated into testing [19, 20].

Utilizing AI and digital image analysis (DIA) within the HER2 testing workflow mitigates many intrinsic limitations of conventional manual test scoring. An AI-based scoring system will be trained on large datasets of well-annotated histopathological images. The system can quantitatively measure both membrane staining intensity and the proportion of tumor cells that exhibit positive staining. The AI systems have a particular advantage in resolving interpretative issues in the HER2 0 vs 1+ scoring range. Several studies demonstrated the clinical value of these tools. Sode et al. demonstrated that DIA improved interpretative concordance in HER2-low cases, especially in interpreting IHC 0 vs. 1+, which often has high uncertainty [21]. Likewise, Glass et al. constructed a quality control tool using machine learning that identified inter-laboratory differences in scoring HER2. The tool improved HER2 assessment reproducibility and diagnostic accuracy, even when assessing sub-category classifications such as <2+, 2+, and 3+ cross-laboratory [22].

Currently, complementary molecular assays have become valuable options to enhance the accuracy of determining HER2 status in equivocal or inconsistent results with IHC or FISH. For example, reverse transcription-quantitative polymerase chain reaction (RT-qPCR) allows for accurate quantification of HER2 mRNA expression and shows promise as a complementary tool in intermediate or otherwise uncertain cases. HER2 mRNA levels evaluated by RT-qPCR were almost perfectly concordant with the results of IHC in the study by Caselli et al. [23]. This suggests that RT-qPCR represents a viable test for confirming HER2 status, specifically in cases with intermediate results with IHC.

At the same time, the EQA framework for assessing HER2 testing is also at a tipping point of improvement. Most EQA programs historically have been based on cases with well-defined HER2-positive or HER2-negative testing [24]. More recently, studies have recommended that EQA programs begin to include cases scored as 0, 1+, and 2+ with defined interpretation criteria, specifically with borderline cases. Also, new techniques, including AI-assisted interpretation and mRNA-based assays, should have incremental inclusion into the EQA structure to help pave the way for a multimodal quality assessment system for testing HER2 (i.e., for genomic, transcriptomic, and proteomic quality assessments). For example, the EQA structure that Badrick et al. suggested includes how molecular diagnostics fit into pathology quality assurance and outlines a pathway to develop quality HER2-low testing standards [20].

Global standardization of HER2 testing will require coordinated collaboration at an international level. Significant variances exist across and within countries in HER2 testing guidelines, antibody clone selection); scoring criteria, and implementation of EQA programs [25]. Developing a comprehensive global standardized HER2 testing framework allows for the comparability of results across diagnostic platforms and the recognizability of data amongst laboratories. Such a framework would be increasingly important in reducing diagnostic variances from regional practices. Creating this comprehensive framework would improve diagnostic accuracy and patient accessibility for receiving appropriate treatment for breast cancer across the globe.

In conclusion, the assessment of HER2 IHC quality is moving from subjective, single-method, and experience-based approaches to objective, integrated, and evidence-based assessments. Integrating digital pathology, laboratory accreditation, and AI-based automated scoring represents new standardization approaches to HER2 testing within a move to precision oncology.

Conclusion: EQA has become a critical quality assurance component in HER2 testing and is developing into an internationally recognized framework. Beyond evaluating test results, it provides critical feedback on staining, interpretation, and workflow, enhancing inter-laboratory consistency. The classification of HER2-low introduces new demands, requiring alignment with updated guidelines.

As international collaboration increases, laboratory participation in EQA programs will encourage us to establish a uniform and highly comparable quality assurance framework for immunohistochemical testing; we will be able to provide the most reliable and reproducible diagnostic pathology support for patients with breast cancer.

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АҢДАТПА

СҮТ БЕЗІ ОБЫРЫ КЕЗІНДЕ ИММУНОГИСТОХИМИЯЛЫҚ ЗЕРТТЕУЛЕРДІҢ САПАСЫН ҚАМТАМАСЫЗ ЕТУ СТРАТЕГИЯЛАРЫН БАҒАЛАУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сапаның сыртқы бақылау бағдарламалары (EQA) иммуногистохимиялық (ИГХ) тесттер мен диагностикалық зерттеулерді орындау кезінде нақты және сенімді нәтижелерге қол жеткізу үшін әдістемемен қатар қолданылуы тиіс. Ісік биомаркерлерін анықтау дәлдігін қамтамасыз ету дәл медицинада өте маңызды, өйткені онкологияда жекелендірілген емдеу әдістері кеңінен қолданыла бастады.*

Зерттеу мақсаты *– сапаның сыртқы бағалау бағдарламаларының сүт безі обыры кезінде адам эпидермалдық өсу факторының 2-типті рецепторын (HER2) анықтауға арналған иммуногистохимиялық (ИГХ) тестілеудегі зертханалар арасындағы айырмашылықтар мен интерпретациялық өзгергіштікті төмендетудегі рөлін жүйелі түрде шолу, сондай-ақ қазіргі қиындықтар мен болашақ даму бағыттарын анықтау.*

Әдістері: *Бұл зерттеу аясында жүргізілген жүйелі әдебиеттерді шолу барысында 306 жарияланым анықталып, оның ішінде 25 толық мәтінді мақала соңғы талдауға енгізілді. Шолу жүйелі шолулар мен метаанализдерге арналған PRISMA 2020 нұсқаулығына сәйкес жүргізілді.*

Нәтижелері: *Соңғы зерттеулер сапаның сыртқы бағалау бағдарламалары HER2 ИГХ тестілеуінің дәлдігі мен сәйкестігін әртүрлі зертханаларда айтарлықтай жақсартатынын көрсетіп отыр. Ғаламдық стандарттар HER2 тестілеуінің барлық кезеңдерінде стандартталған, сенімді және үйлесімді процедураларды қамтамасыз етеді. Сонымен қатар, цифрлық патология, алгоритмдер және мРНҚ (мессенджер РНҚ) негізіндегі тесттер сияқты жаңа әдістер нәтижелердің бірізділігін арттырып, қолмен жүргізілетін сараптамаларда қателіктерді азайтуға зор мүмкіндік береді.*

Қорытынды: *Сапаның сыртқы бақылау бағдарламаларын енгізу HER2 ИГХ нәтижелерінің әртүрлі зертханалар арасындағы айырмашылықтарын азайтты. HER2-low санаттамасының енгізілуімен тестілеу әдістері субъективті тәсілдерден деректердің әртүрлі түрлерін қолдануға қарай ауысып жатыр, бұл дәрігерлер үшін тесттің клиникалық маңызын арттырады. Сапаның сыртқы бақылау бағдарламаларына қатысу HER2 рецепторларын тестілеу тиімділігін арттырып, әлемнің әртүрлі бөліктерінде бірдей нәтижелер алуға мүмкіндік береді. Сарапшылар тобының болуы сүт безі обырын диагностикалау мен нәтижелердің қайталануын жақсартады.*

Түйінді сөздер: *иммуногистохимия, сыртқы сапаны бағалау (EQA), сүт безі обыры, HER2, сапаны бақылау (QC).*

АННОТАЦИЯ

ОЦЕНКА СТРАТЕГИЙ ОБЕСПЕЧЕНИЯ КАЧЕСТВА ИММУНОГИСТОХИМИЧЕСКОГО ТЕСТИРОВАНИЯ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *При проведении иммуногистохимических (ИГХ) тестов и диагностических исследований для достижения точных и надёжных результатов помимо методики проведения исследований следует также применять программы внешнего контроля*

качества (EQA). Обеспечение точности тестов на опухолевые биомаркеры имеет критически важное значение в прецизионной медицине, поскольку индивидуализированные схемы лечения стали обычной практикой в онкологии.

***Цель исследования** – провести систематический обзор данных, касающихся роли внешней оценки качества в снижении межлабораторных расхождений и вариабельности интерпретации при иммуногистохимическом определении рецептора эпидермального фактора роста человека 2-го типа (HER2) при раке молочной железы, а также выявить текущие проблемы и возможные направления развития.*

***Методы:** Систематический обзор литературы в рамках данного исследования выявил 306 публикаций, из которых 25 полнотекстовых статей были включены в окончательный анализ. Обзор проводился в соответствии с руководством по предпочтительным элементам отчётности для систематических обзоров и метаанализов (PRISMA 2020)*

***Результаты:** Последние исследования показывают, что программы внешней оценки качества значительно повышают согласованность и точность ИГХ-тестирования HER2, проводимого в различных лабораториях. Глобальные стандарты обеспечивают стандартизированные, надёжные и последовательные процедуры тестирования HER2 на всех этапах. Кроме того, новые подходы, такие как цифровая патология, алгоритмы и тесты на основе мРНК (мессенджер РНК), обладают большим потенциалом для повышения согласованности результатов и снижения ошибок при ручной интерпретации.*

***Заключение:** Внедрение программ внешнего контроля качества позволило снизить расхождение результатов HER2 ИГХ между различными лабораториями. С введением классификации HER2-low методы тестирования переходят от субъективных подходов к использованию различных видов данных, что повышает клиническую значимость теста для врачей. Участие в программах внешнего контроля качества повышает эффективность тестирования рецепторов HER2, обеспечивая воспроизводимые результаты в разных частях мира. Наличие команды экспертов улучшает точность диагностики и повторяемость результатов при раке молочной железы.*

***Ключевые слова:** иммуногистохимия, внешняя оценка качества (EQA), рак молочной железы, HER2, контроль качества (QC).*

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AIR POLLUTION AND CANCER RISKS: A REVIEW OF META-ANALYSES

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ABSTRACT

Relevance: *Air pollution, recognized by the World Health Organization as a global threat due to its contribution to the development of chronic and oncological diseases, is of particular concern in megacities such as Almaty, where pollution levels significantly exceed acceptable norms and pose a serious risk to vulnerable population groups.*

The study aimed to *systematically review meta-analyses focused on the effect of air pollution on the risk of developing various types of cancer, most relevant to the Republic of Kazakhstan.*

Methods: *This systematic review included publications from the PubMed, Web of Science, Scopus, Embase, and Cochrane Library databases from 2000 to February 18, 2025. Only meta-analyses were included to investigate the association of air pollutants (PM2.5, PM10, NO2, SO2, O3, VOCs, and others) with cancer. Relative risk (RR) parameters and pollutant concentrations were extracted for the analysis.*

Results: *The review revealed significant correlations between exposure to air pollutants and an in-creased risk of developing several cancers. The effect of pollutants on the risk of cancer is presented.*

Conclusion: *Air pollution is recognized as a significant risk factor for cancer and cancer mortality. In this regard, it is necessary to develop state and individual environmental measures, including the implementation of IT and hardware solutions for monitoring and improving air quality in residential and workspaces.*

Keywords: *air pollution, cancer, cancer risk, meta-analysis, PM2.5, NO2, Kazakhstan.*

Introduction: Today, the negative impact of air pollution on the respiratory and cardiovascular systems, as well as overall quality of life, is recognized as a significant problem in various geographical areas [1-3]. The connection between pollution and the development of cancer has also attracted the attention of researchers [4, 5]. According to the World Health Organization (WHO), air pollution causes millions of premature deaths every year, and its contribution to the development of chronic diseases and cancer pathologies is recognized as a global threat [6].

According to a UNICEF policy brief [7], air pollution is the main environmental health risk for children. Young children are particularly at risk of death and illness from air pollution [7]. According to the Institute for Health Metrics and Evaluation (IHME, UK), in 2021, 6,441 child and adolescent deaths from air pollution-related causes were recorded in 23 countries and territories in Europe and Central Asia, and the vast majority (85%) died in the first year of life [8].

Among the major cities with high levels of pollution, Almaty, Kazakhstan's largest metropolis, holds a special place. The city suffers from intense emissions from industrial enterprises, vehicle exhaust gases, and unfavorable natural conditions, including its geographical location in a basin that limits natural air ventilation [9]. According to environmental reports, concentrations of pollutants such as PM2.5, PM10, nitrogen dioxide (NO2), and sulfur dioxide (SO2) in Almaty often exceed the maximum permissible levels [9, 10]. According to IQAir [11], a global air quality monitoring platform, PM 2.5 concentrations in Almaty regularly exceed WHO ambient air quality guidelines by 17 times during the winter months [11]. Additionally, according to a new World Bank study, cleaner residential heating is one of the key factors in reducing air pollution in Kazakhstan's cities [12].

The growing scale of the air pollution problem necessitates not only environmental action but also a comprehensive understanding of its health implications. This article reviews the results of meta-analyses devoted to the impact of air pollution on the risk of various types of cancer.

The study aimed to systematically review meta-analyses focused on the effect of air pollution on the risk of developing various types of cancer, most relevant to the Republic of Kazakhstan.

Materials and methods:

Data sources and search strategy. This systematic review comprised articles from the largest medical and environmental databases, including PubMed, Web of Science, Scopus, Embase, and the Cochrane Library. The

search was conducted for the period from 2015 to 2025. The following keywords and their combinations were used: "air pollution", "carcinogenesis", "cancer risk", "meta-analysis", "particulate matter (PM2.5, PM10)", "volatile organic compounds (VOCs)", "nitrogen dioxide (NO2)", "ozone (O3)". The review included only meta-analyses that: (1) were published in peer-reviewed journals, (2) contained data on the relationship between air pollutants (PM2.5, PM10, NO2, SO2, O3, volatile organic compounds (VOCs) and others) with the risks of developing cancer of the most common types of cancer in the Republic of Kazakhstan.

Figure 1 – Typical state of the air basin in Almaty in winter (left) and autumn (right) periods

Study selection process. All retrieved publications were uploaded to the EndNote bibliography manager. Duplicate records were removed. Two independent researchers performed the initial screening based on titles and abstracts. Full texts of the retrieved articles were reviewed to determine whether they met the inclusion criteria. The following parameters were extracted for data analysis: (1) relative risk (RR), odds ratio (OR), or hazard ratio (HR) for developing cancer, (2) air pollution levels in the analyzed studies.

Ethical aspects. Since the work was based on the analysis of already published data, ethical approval was not required. All studies included in the review met the ethical standards set for primary data.

Results:

Breast cancer and traffic-related air pollution. Traffic-related air pollution increases the risk of breast cancer by 1.5% for every 10 μg/m3 increase in NO2 exposure [13]. Additionally, combustion-related nitric oxide (NO) is oxidized in air to form NO2, which plays a role in several stages of cancer, including angiogenesis, apoptosis, cell cycle progression, invasion, and metastasis [14-16].

A systematic review by J. Tippila et al. included 25 parallel studies on the association between air pollution and breast cancer, with a primary focus on PM2.5, PM10, and NO2 [17]. In a study by JY Ou et al. [18], in a group of young patients under 39 years of age, PM2.5 concentrations ≥ 12 μg/m^3 were associated with increased breast cancer mortality, HR for 5 years = 1.50 (95% CI from 1.29 to 1.74), HR for 10 years = 1.30 (95% CI from 1.13 to 1.50) [18]. A study by A. Amadou et al. (2021) showed that long-term exposure to benzo(a)pyrene in the ambient air is associated with an increased risk of developing breast cancer - for every 1 interquartile range (IQR) increase in benzo[a]pyrene concentration (1.42 ng/m^3), there was an increase in the OR=1.15 (95% CI: from 1.04 to 1.27), higher rates were observed in women who had experienced the menopausal transition and in patients with hormone-positive tumors [19].

Proximity to roads is also a danger for children – one study reported a borderline association (HR=1.4; 95% CI: 1.0-1.9) between breast cancer risk and childhood proximity to a road with characteristics of high exposure to traffic-related pollutants. The influencing factors included (1) proximity, (2) presence of a median/barrier, (3) multiple lanes, and (4) heavy traffic [20].

Lung cancer: Pooled estimates showed that NO2, EC, and PM2.5 were associated with mortality from all causes, cardiovascular diseases, coronary heart disease, respiratory diseases, and lung cancer (RR=1.04; 95% CI: 1.01-1.07) [21].

The study by B. Brunekreef describes the connections between long-term effect of four pollutants (PM2.5, NO2, BC, and O3) on health. The researchers found significant positive associations between PM2.5, NO2, and BC and death from natural causes, respiratory, cardiovascular diseases and lung cancer, with moderate to high heterogeneity between cohorts – for lung cancer, an increase in HR was found only for PM 2.5, HR 1.13 (95 % CI: 1.05-1.23) [22].

A meta-analysis by Ramamoorthy et al. [23] involved 61 studies, including 53 cohort studies and 8 case-control studies. PM 2.5 was the exposure pollutant in half (55.5%) of the studies, and lung cancer was the most commonly studied cancer, in 59% of the studies [23]. A pooled analysis of exposure from cohort and case-control stud-

ies and cancer incidence showed a significant association, RR=1.04 (95% CI: 1.02-1.05). Significant associations were observed between exposure to pollutants such as PM2.5 (RR=1.08; 95% CI: 1.04-1.12) and nitrogen dioxide (NO2) (RR=1.03; 95% CI: 1.01-1.05) and the incidence of lung cancer. The association between air pollutant exposure and cancer mortality showed a significant association (RR=1.08; 95% CI: 1.07-1.10). Among the four pollutants, PM2.5 (RR=1.15; 95% CI: 1.08-1.22) and NO2 (RR=1.05; 95% CI: 1.02-1.08) were significantly associated with lung cancer mortality. The study confirms the association between air pollution exposure and lung cancer incidence and mortality [23].

JS meta-analysis by Pyo et al. included 19 studies that assessed exposure to PM2.5 and PM10 [24].

The analysis showed that the incidence of lung cancer was significantly increased by PM2.5 exposure (RR=1.172; 95% CI: 1.002-1.371). All-cause mortality and lung cancer mortality were significantly increased by PM 2.5 exposure (HR=1.143; 95% CI: 1.011-1.291 and HR=1.144; 95% CI: 1.002-1.307, respectively) [6].

Thus, the above meta-analyses confirm that air pollution is a significant risk factor for the development of a number of cancers. It should also be taken into account in terms of long-term exposure and the effect on rare cancers.

Colorectal cancer. A meta-analysis of seven observational studies confirmed an association between PM2.5 exposure (per 10 μg/m^3 increment) and an increased risk of colorectal cancer (RR=1.42; 95% CI: 1.12-1.79). At the same time, a higher Air Pollutants Exposure Score, proposed by the study working group, was associated with an increased risk of colorectal cancer (RR=1.03; 95% CI: 1.01-1.06) and worse survival (RR=1.13; 95% CI: 1.03-1.23), especially among participants with insufficient physical activity and ever-smoking [25].

A meta-analysis of 30 cohort studies found that a 10 μg/m^3 increase in PM2.5, PM10, and nitrogen dioxide (NO2) levels was associated with an increased odds of cancer mortality of 17% (95% CI: 11-24%), 9% (95% CI: 4-14%), and 6% (95% CI: 2-10%), respectively. In particular, a 6.5 parts per billion (ppb) increase in NO2 was associated with an increased odds of colorectal cancer mortality of 6% (95% CI: 2-10%) [26].

A meta-analysis including 13 studies found that PM2.5 exposure was associated with a 12% (95% CI: 1-24%) increased risk of developing gastrointestinal cancer. The largest associations were found for liver cancer, where the risk increased by 31% (95% CI: 7-56%), and for colorectal cancer, where the risk increased by 35% (95% CI: 8-62%) [27].

A meta-analysis by P. Fu et al. found an association between PM2.5 exposure and an 18% (95% CI: 9-28%) increase in the risk of colorectal cancer incidence and a 21% (95% CI: 9-35%) increase in mortality from it [28].

Discussion: Environmental problems in Kazakhstan are linked to urban growth, the use of coal and oil for electricity and heating, and the mining industry [29]. The intensive development of natural resources, often without considering their environmental impact, inevitably leads to land and soil pollution [29]. Worth noting, Almaty, the largest city in Kazakhstan, has one of the highest levels of air pollution [30]. The main sources of pollution are emissions from industry, motor vehicles, and heating systems [9]. The city's geographical location in a basin at the foot of the mountains significantly limits natural air ventilation, exacerbating the situation with air pollution [9-11].

In winter, the concentration of pollutants such as PM2.5, PM10, NO2, and SO2 can exceed the maximum permissible levels by 10 to 17 times [11]. This poses a direct threat to the health of city residents, increasing the risk of developing cancer, respiratory, and cardiovascular diseases. It should be noted that current scientific work focuses on the impact of pollution on cancer incidence, but does not assess the condition of cancer patients after cancer-related interventions. This direction can be a point of growth in assessing outcomes after interventions, as well as in comparing the effectiveness of various interventions in patients across regions with differing environmental conditions.

Figure 2 – UAVs developed by the research group and an example of analysis of city pollution by solid household waste using artificial intelligence

Given the risks described, it is necessary to take proactive measures to minimize the impact of air pollution on public health. This includes both government initiatives to adopt environmentally friendly technologies and enhance air quality monitoring, as well as individual efforts, such as utilizing modern software and engineering solutions to improve air quality in residential and workspaces. Environmental education programs, the introduction of energy-efficient technologies, and the development of public transport can also become an important part of the risk mitigation strategy. One of the areas that the CUES scientific group is proactively pursuing is the development of monitoring the city's environmental status using uncrewed aerial vehicles (UAVs) [29]. The introduction of UAVs will help to better monitor the environmental status and assess the danger of individual areas of the city, and, together with other technologies, provide a contour for assessing personal environmental safety and identifying measures to reduce risks.

Thus, decisive actions and coordination of efforts at the state, public, and individual levels are necessary to improve the environmental situation and reduce the negative impact of air pollution on public health in Almaty and other cities with similar geographical conditions.

Conclusion: The above material suggests the need to develop environmental measures to counteract air pollution that affects oncological diseases. It is necessary to conduct educational activities among oncologists to increase awareness of the risks associated with environmental pollution.

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АҢДАТПА

АУАНЫҢ ЛАСТАНУЫ ЖӘНЕ ОНКОЛОГИЯЛЫҚ АУРУЛАРДЫҢ ДАМУ ҚАУПІ: МЕТА-АНАЛИЗДЕРГЕ ШОЛУ

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Өзектілігі: *Созылмалы және онкологиялық аурулардың дамуына әсері үшін Дүниежүзілік денсаулық сақтау ұйымы тарапынан жаһандық қауіп ретінде танылған ауаның ластануы, ластану деңгейі рұқсат етілген шектерден айтарлықтай асып түсетін және әсіресе осал халық топтары үшін қауіп төндіретін Алматы секілді мегаполистерде ерекше алаңдаушылық тудырады.*

Зерттеудің мақсаты *– бұл зерттеудің мақсаты Ауаның ластануының Қазақстан Республикасы үшін негұрлым өзекті болып табылатын онкологиялық аурулардың әртүрлі түрлерінің даму қаупіне әсеріне арналған мета-талдауларға жүйелі шолу болып табылады.*

Әдістері: *Жүйелі шолу PubMed, Web of Science, Scopus, Embase және Cochrane Library дерекқорларындағы 2000 жылдан 2025 жылғы 18 ақпанға дейінгі кезеңде жарияланған еңбектер негізінде жасалды. Ауаны ластаушы заттардың (PM2.5, PM10, NO2, SO2, O3, VOCs және т.б.) қатерлі ісікпен байланысын зерттейтін мета-талдаулар ғана қамтылды. Талдау үшін салыстырмалы тәуекел параметрлері (RR) және ластаушы заттардың концентрациясы алынды.*

Нәтижелері: *Шолу ауаны ластаушы заттардың әсері мен бірқатар онкологиялық аурулардың даму қаупінің жоғарылауы арасындағы айтарлықтай корреляцияны анықтады. Ластаушы заттардың қатерлі ісік қаупіне әсері ұсынылған.*

Қорытынды: *Ауаның ластануы қатерлі ісік пен қатерлі ісік ауруынан болатын өлім-жітімнің маңызды қауіп факторы ретінде танылды. Осыған байланысты тұрғын және жұмыс орындарындағы ауа сапасын бақылау және жақсарту үшін IT - және hardware шешімдерін енгізуді қоса алғанда, мемлекеттік және жеке экологиялық шараларды өзірлеу талап етіледі.*

Түйінді сөздер: *ауаның ластануы, онкологиялық аурулар, қатерлі ісік даму қаупі, мета-талдау, PM2.5, No2, Қазақстан.*

АННОТАЦИЯ

ЗАГРЯЗНЕНИЕ ВОЗДУХА И РИСКИ РАЗВИТИЯ ОНКОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЙ: ОБЗОР МЕТА-АНАЛИЗОВ

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Актуальность: *Загрязнение воздуха, признанное Всемирной организацией здравоохранения глобальной угрозой из-за его вклада в развитие хронических и онкологических заболеваний, вызывает особую тревогу в мегаполисах вроде Алматы, где его уровни значительно превышают нормы и особенно опасны для уязвимых групп населения.*

Цель исследования *– систематический обзор мета-анализов, посвященных влиянию загрязнения воздуха на риск развития различных видов онкологических заболеваний, наиболее актуальных для Республики Казахстан.*

Методы: *Систематический обзор был выполнен на основе публикаций из баз данных PubMed, Web of Science, Scopus, Embase и Cochrane Library за период с 2015 по 2025 годы. Включались только мета-анализы, исследующие связь загрязнителей воздуха (PM2,5, PM10, NO2, SO2, O3 и других) с онкологическими заболеваниями. Для анализа извлекались параметры относительного риска (RR) и концентрации загрязняющих веществ.*

Результаты: *Обзор выявил значительные корреляции между воздействием загрязнителей воздуха и повышенным риском развития ряда онкологических заболеваний. Представлено влияние загрязнителей на риск онкологических заболеваний.*

Заключение: *Загрязнение воздуха признано значимым фактором риска развития рака и смертности от онкологических заболеваний. В связи с этим требуется разработка государственных и индивидуальных экологических мер, включая внедрение программных и инженерных решений для мониторинга и улучшения качества воздуха в жилых и рабочих помещениях.*

Ключевые слова: *загрязнение воздуха, онкологические заболевания, риск развития рака, мета-анализ, PM2,5, NO2, Казахстан.*

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THE ROLE OF INTRAOPERATIVE RADIATION THERAPY IN BREAST CANCER TREATMENT: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Breast cancer is one of the most common cancers in women. In 2022, GLOBOCAN reported 2,296,842 new cases of breast cancer and 666,103 deaths from this disease. Breast cancer ranks 1st in the world in the structure of oncopathologies in women.*

In the Republic of Kazakhstan, 37,038 new cancer cases were registered in 2023, except for skin cancer. The number of cases of malignant neoplasms increased by 1,959, or 5.6%, compared to the previous year. The "stable" incidence per 100,000 population was 186.1 per year, with a growth rate of 3.5%; the standardized rate was 0.8%, with a growth rate of 159.6.

It is also worth paying attention to the main directions and principles of SCC treatment. The types of SCC treatment depend on the stage of the disease. Tumor treatment includes surgical removal, radiation therapy, chemotherapy, and hormonal therapy. Currently, intraoperative radiation therapy (IRT) is relevant as an op-timal method of SCC treatment. According to oncologists, mammologists, and radiation oncologists, this treatment method also requires in-depth analysis to improve treatment outcomes and five-year survival rates for this disease.

The study aimed to *examine the world experience in the use of IORT in the treatment of breast cancer.*

Methods: *This article reviews PubMed sources from 2003 to 2023 on the use of IORT in treating breast can-cer.*

Results: *This review presents the results of large studies, including multicenter prospective ones, on evaluat-ing the efficacy, the effect on survival, and the features and possible limitations of IORT in treating breast cancer.*

Conclusion: *IORT is a fairly promising and innovative treatment method that reduces the risk of side effects and the duration of treatment. Considering the positive short-term and long-term results of IORT application, it is advisable to recommend its full use in clinical protocols within Kazakhstan's healthcare system.*

Keywords: *intraoperative radiation therapy (IORT), breast cancer, survival rate, long-term results, recurrence rate.*

Introduction: Every year, about 2.3 million new cases of breast cancer (BC) are registered in the world, and the number of deaths exceeds 700 thousand. Countries with high prevalence include the USA, Denmark, France, Australia, New Zealand, Sweden, and Canada. Countries with low incidence rates include the Democratic Republic of the Congo, Mali, China, Vietnam, and India. Countries with a high incidence in the CIS countries include Armenia, Moldova, Kyrgyzstan, and Ukraine. Breast cancer ranks first. It is followed by: lung and bronchial cancer, colorectal cancer, stomach cancer, cervical cancer, esophageal cancer, prostate cancer, kidney, ovarian, pancreatic, endometrial, and liver cancer [1]. According to data in our country: According to the latest data, in 2023, 37,038 cases of almost all types of cancer, except for skin cancer, were detected for the first time in the Republic of Kazakhstan (in 2022 - 35,079 cases). The number of cases increased by 1959, or 5.6%, compared to the previous year (2507 cases, or 7.7%). The normal incidence rate per 100,000 population was 186.1 (2022 – 179.9), with a growth rate of 3.5% (+5.6%) per year. The standard rate was 159.6 (158.4), with a growth rate of 0.8% (+3.8%) (Table 1) [2].

Table 1 – Incidence of certain types of malignant neoplasms (excluding skin cancer) among the population of the Republic of Kazakhstan ("normal" indicators) (the table presents data on the most common types of cancer)

Location of tumors	Number of people diagnosed with cancer for the first time in their lives				Growth rates
	Absolute number		Per 100,000		
	Total cases – 15,885 (2022)	Total cases – 16,336 (2023)	2022	2023	
High-risk areas for cancer development include:	13951	14301	81.3	82.2	3.5
Breast	5171	5505	26.5	27.7	4.3
Lung and respiratory tract cancer	3925	3873	20.1	19.5	-3.3
Stomach	2915	2873	14.9	14.4	-3.4
Colon	1940	2050	9.9	10.3	3.6

Due to the high prevalence of this type of cancer, it is necessary to make certain efforts for its early diagnosis and treatment. Radiation therapy is a widely used method of treating all types of cancer, even for palliative care. The use of intraoperative radiation therapy (IRT) in the treatment of breast cancer is becoming increasingly relevant. IRT is a method of treating breast cancer using direct radiation therapy during surgery. It can be used as an alternative or an addition to standard adjuvant radiation therapy after surgery. A variety of high-tech methods are used for adjuvant radiation therapy. For example, adjuvant radiation therapy is intensively modulated and image-guided, and hypofractionated breast treatment is used instead of the traditional total dose of 50 Gy (2 Gy x 25 days). This type of treatment has a set of features that enable the near-complete cure of almost all tumors, regardless of their location and severity [3]. However, the role of IOST in the treatment of squamous cell breast cancer has been studied in several clinical trials and has shown positive results as an alternative or adjunct to adjuvant radiotherapy [4].

Some studies have also shown that IOST can be safe and convenient for patients. Since it allows for a single dose of radiotherapy to be delivered during surgery, whereas standard radiotherapy is administered a few weeks after surgery and is carried out over several weeks [5]. According to oncologists, mammologists, and radiologists, this approach is an optimal option, requiring an in-depth analysis of both the treatment and the five-year survival rate after treatment. Numerous studies confirm this. The use of IOST immediately after surgical removal of breast cancer was widely studied in this scientific study, which led to a positive attitude towards IOST among specialists. In squamous cell breast cancer, 44,752 patients were treated with IOST in 35 countries over 20 years, with the administration of intraoperative radiotherapy immediately after tumor removal. Evidence suggests that the treatment has saved 30 million kilometers of travel time and approximately 2,000 lives [6].

The study aimed to examine the world experience in the use of IORT in the treatment of breast cancer.

Materials and methods: We searched the PubMed database from 2003 to 2023 using the following keywords: intraoperative radiotherapy, "IOST and breast cancer", "breast cancer treatment", "IOST application", "IOST side effects", "IOST advantages". Based on the critical analysis, 28 literature references were included in this review.

Results: IOST was first used to treat squamous cell carcinoma in 1998. It is designed to replace traditional radiation therapy after surgery. IOST is a method that delivers radiation directly during surgery, reducing the amount of tissue exposed to radiation and shortening the treatment time. This method was originally proposed by the Medical College of Ohio (MCO) in the United States and the Montpellier Regional Cancer Center (CRLC) in France, based on reports of 72 patients treated with intraoperative electron beam therapy. Compared with SCC, SCC shows different sensitivity to high doses. In the 2000s, Fowler proposed an alpha/beta ratio of 4 for SCC, which is the best approximation to the 10-point scale for most SCCs. Clinical results from Canadian and British hypofractionation studies further support this value. A lower dose per fraction may result in greater sensitivity compared to a higher dose. This is a clear argument in favor of IOST. In a linear-quadratic model using an alpha/beta value of 4, the IOST dose per 10 Gy is 35 QED. Therefore, a single dose of 10 Gy of IOST is equivalent to approximately 24 Gy of ablation [7]. Despite evidence of improved treatment efficacy and patient quality of life, concerns remain regarding long-term outcomes and local recurrence rates [8]. IOST can be delivered in several ways. The most common is electronic IOST. IOST is currently the standard therapeutic approach for patients with early-stage, low-risk squamous cell carcinoma as part of breast-conserving surgery. Studies have shown that IOST is an effective treatment for squamous cell carcinoma. One study found that IOST reduced the risk of squamous cell carcinoma recurrence by 80% [9]. Other studies have also demonstrated that IOST achieves high control rates and favorable survival rates for squamous cell carcinoma [10,11]. However, there are several limitations to the use of IOST in the treatment of squamous cell breast cancer. First, IOST is designed for relatively small tumors, making it difficult to use. Second, not all centers offer IOST, making it inaccessible to some patients. Despite the above limitations, IOST is still an effective treatment option for squamous cell breast cancer. For patients with relatively small tumors, IOST has proven to be more cost-effective than traditional radiation therapy. IOST is also very useful for patients who cannot undergo long courses of traditional radiation therapy, including those who live far from the cancer center or have transportation and mobility issues [12]. However, IOST is not effective for all patients and may not be completely suitable for all cases of squamous cell breast cancer. Some studies have also shown an increased risk of disease recurrence after IOST. However, these studies did not take into account tumor characteristics, age, geographic location, and race [13]. Limitations of radiotherapy dosing regimens may be associated with certain risks and limitations, such as limited availability of IOST for some patients [14]. Overall, numerous studies and data suggest that IOST may be an effective and convenient treatment option for squamous cell carcinoma. However, further studies and evaluations are needed to better understand its efficacy and safety, as well as to identify patients suitable for this treatment. One of the most well-known studies is the randomized TARGIT-A trial. This study assessed the effectiveness of low-energy IOST on treatment outcomes. Initially, 3451 women were randomized to IOST or total breast irradiation. 15% of patients received additional IOST. It is worth noting that the study included 2 groups: those who received IOST during surgery and those who received IOST

as a second treatment (after pathological examination). The authors published the first results after 5 years (29 months of follow-up). It showed an increase in recurrence. (Note that 3.3% in the IOST group and 1.3% in the TBBI group, but within the non-inferiority criteria) for the entire study population. In the post-pathology cohort, there was an increased recurrence rate with IOST (5.4% for IOST and 1.7% for TBBI, which exceeded the efficacy threshold), as observed in the surgery cohort (2.1% vs 1.1%, respectively, with efficacy criteria not being weak) [15]. Later, the TARGIT-A investigators published an update. However, the results were criticized and questioned by oncologists because they were not in the same population [16]. In the post-cohort (1153 patients), 5-year follow-up revealed an increased recurrence rate in the IOST group (IOST 3.96%, TBBI 1.05%), which is below the efficacy threshold and should not be recommended for patients at this time [17, 18]. In the IOST surgical cohort, the 5-year recurrence rates were 0.95%–2.11%, but within the non-inferiority criteria. Long-term Kaplan-Meier curves were not presented at the time [19]. However, a major concern with the methodology of these updates is that the study reported local recurrence-free survival (LRFS) rather than long-term absolute recurrence rates. This is an important study because concerns have been raised about composite endpoints such as LRFS that include mortality. Additionally, other breast or breast radiotherapy studies have shown long-term recurrence rates, highlighting the importance of counseling patients about radiotherapy options [19, 20]. The results that formed the basis for e-IOST are the largest multicenter trial to date, the ELIOT trial. In it, 1305 women were randomized to IOST or ablation. At 5 years, IOST was associated with an increased local recurrence rate (4.4% vs. 0.4%) [21]. However, long-term results of the ELIOT trial have not yet been published. On the other hand, Leonardi et al followed 1822 patients who underwent IOST at a single institution outside the context of a clinical trial. They found that patients who met the criteria of the American Society for Radiation Oncology (ASTRO) had lower 5-year recurrence rates [22]. This clearly indicates that IOST treatment requires further study. Clinicians, including breast surgeons and radiation oncologists, may wonder what the role of IOST is for patients with early-stage squamous cell carcinoma. Current ASTRO guidelines recommend that patients with IOST should always seek medical advice if they are at increased risk of local recurrence. ASTRO guidelines emphasize that IOST should only be used in prospective studies and that only eligible patients should be considered for its use. The American Brachytherapy Society does not support IOST outside of prospective studies (although this was published before the TARGIT-A trial updates were released). The guidelines emphasize that IOST using electronic devices should be limited to eligible patients [16, 21, 22]. One of the most important recent studies is ELIOT (Electronic Intraoperative Radiotherapy for Breast Cancer) [21]. This study investigated the use of IOST in patients with early squamous cell breast cancer. The study results showed a 5-year overall survival of 95.5% and a disease-free survival of 98.1%. These results were compared with standard radiotherapy, and the authors concluded that IOST is a safe and effective treatment option for patients with early squamous cell breast cancer [21]. Another study from 2018 showed that IOST may be an effective treatment option for patients with multiple, non-bulky breast tumors. This study included 203 patients who were given IOST instead of standard radiotherapy. The study results showed a 5-year local recurrence-free survival rate of 96.4%. This is comparable to standard radiotherapy. The researchers concluded that IOST may be an effective treatment option for this patient group [18]. A study was also conducted to evaluate the efficacy of IOST in combination with liposomal doxorubicin (L-Dox) for the treatment of patients with localized squamous cell carcinoma [23]. This study included 79 patients who were randomly assigned to two groups: one group received IOST in combination with L-Dox, and the other group received IOST alone. The study results showed that patients who received IOST plus L-Dox had a higher rate of local recurrence and poorer disease-free survival compared to patients who received IOST alone. These results suggest that the combination of IOST and L-Dox may be a more effective treatment option for patients with localized squamous cell carcinoma. Some studies have also investigated the use of IOST as an alternative to standard radiation therapy for patients with other types of squamous cell carcinoma. For example, a 2016 study [24] demonstrated that IOST may be a safe and effective treatment option for patients with low rates of locoregional recurrence. This study also found that patients treated with IOST had higher treatment satisfaction than those treated with standard radiation therapy. However, not all studies support the effectiveness of IOST in treating squamous cell carcinoma. A 2020 study found no statistically significant differences in survival or disease recurrence between patients treated with IOST and those treated with standard radiation therapy [25].

Discussion: In summary, several studies have demonstrated the efficacy of IOST in treating SCC, although all aspects of the treatment method have not yet been thoroughly studied. Radiation therapy is rapidly evolving every day. This is evidenced by the capabilities of spiral tomotherapy, adjuvant radiotherapy (which is performed with intensity-modulated and image-guided techniques), and adjuvant ionizing radiation. However, additional studies are certainly needed to determine the best indications for the use of IOST and to assess its long-term impact on the survival and quality of life of patients with SCC. An important aspect of using IOST in the treatment of SCC is the selection of patients who can effectively benefit from the treatment method. In the main studies, we observed that IOST may be more effective in patients with small tum-

ors, a low invasion rate, the absence of lymphatic metastases, and high sensitivity to radiotherapy [18, 23]. It has also been shown that several other factors need to be taken into account, including the patient's age, general health condition, presence of comorbidities, and their treatment. Another important aspect of using IOST in the treatment of squamous cell carcinoma is controlling the optimal dose and distribution of radiation [26]. Compared with adjuvant radiotherapy, IOST allows for more precise delivery of radiation to the tumor, reducing the amount of radiation received by healthy tissues. The use of IOST in the treatment of breast cancer is becoming increasingly relevant. Since IOST is a method of treating squamous cell carcinoma with direct radiation therapy during surgery, it can be used as an alternative or in addition to standard adjuvant radiotherapy after surgery [3]. The role of IOST in treating squamous cell carcinoma has been investigated in several clinical trials. The results of many studies suggest that IOST may be an effective alternative to standard radiotherapy.

Additionally, the optimal dose of radiotherapy may vary depending on several factors, including tumor size and location, the presence of metastases, and the level of sensitivity to radiotherapy. Additional aspects to consider include skin burns, edema, and changes in skin texture. In some cases, the above-mentioned side effects can be significant and affect the patient's quality of life [27, 28]. However, it is known that modern technologies and methods of using IOST can reduce side effects and increase the safety of this treatment method.

Conclusion: Overall, IOST is safer and more effective than standard radiation therapy in some cases. It is also an effective treatment for patients with locally advanced squamous cell carcinoma. Numerous studies have demonstrated that IOST can enhance survival and decrease the risk of recurrence in squamous cell carcinoma. However, the limitations of IOST may make it inaccessible to some patients. Given the currently available results and evidence-based recommendations, the use of IOST in early-stage squamous cell carcinoma certainly requires additional practical studies. As part of shared decision-making, oncologists should inform patients about potential concerns related to the IOST results.

Nevertheless, the method is quite promising and innovative, reducing the risk of side effects and shortening the treatment period. Despite this, there are limitations to the use of IOST. Additional theoretical and experimental studies are necessary for a more comprehensive understanding of the application of this technique in the treatment of squamous cell carcinoma in our country. Once the research has a solid foundation and evidence base regarding the immediate and long-term patient outcomes, the method will undoubtedly be introduced into clinical protocols as an alternative to traditional ablative radiotherapy, and guidelines and recommendations for consultation will be developed.

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІН ЕМДЕУДЕГІ ИНТРАОПЕРАЦИЯЛЫҚ СӘУЛЕЛІ ТЕРАПИЯНЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сүт безі қатерлі (СБҚ) ісігі әйелдерде жиі кездесетін ісіктердің бірі. GLOBOCAN деректері бойынша 2022 жылы сүт безі обырының 2 296 842 жаңа жағдайы және осы аурудан 666 103 өлім тіркелді. Әйелдер арасында онкопатология құрылымында таралуы бойынша әлемде 1-ші орында.*

Қазақстан Республикасында 2023 жылы тері қатерлі ісігін қоспағанда ең алғаш рет қатерлі ісікпен тіркелген аурудың саны 37 038 жағдай анықталды. Алдыңғы жылдың деңгейіне қарағанда қатерлі дертке шалдыққандар саны 1959-ға немесе 5,6%-ға өсті. Сырқаттанушылықтың 100 мың халыққа шаққандағы «қалыпты» көрсеткіші 186,1 құрады өсу қарқынымен жылына 3,5%, стандартты көрсеткіші – 0,8%-дық өсу қарқынымен 159,6-ны құрады.

Сондай-ақ СБҚ ісігін емдеудегі негізгі бағыттар мен принциптерге назар аударған жөн. СБҚ ісігін емдеу түрлері аурудың сатысына байланысты. Ісікті емдеу: хирургиялық алып тастау, сәулелі терапия, химиотерапия және гормондық терапияны қамтиды. Қазіргі уақытта интраоперациялық сәулелі терапияны (ИОСТ) СБҚ ісігін емдеуде оңтайлы әдіс ретінде қолдану өзекті болып отыр. Онкологтардың, маммологтардың және радиациялық онкологтардың пікірінше, бұл емдеу тәсілі, ем нәтижесі мен бес жылдық өмір сүру мерзімі көрстекішін жақсарту үшін де терең талдауды қажет етеді.

Зерттеудің мақсаты *– сүт безі қатерлі ісігін емдеуде интраоперациялық сәулелі терапияны қолданудың әлемдік тәжірибесін зерттеу.*

Әдістері: *Рандомизациялы ем мен мета-анализ нәтижелері негізінде 2003-2023 жылдардағы PubMed базасынан СБҚ ісігін емдеудегі ИОСТ қолдану туралы дереккөздерге шолу берілді.*

Нәтижелері: *Әдеби шолуда ем тиімділігі, өмір сүру ұзақтығына ем әсерін бағалау бойынша ірі зерттеулердің, соның ішінде көп орталықты оң нәтижелі зерттеулердің, сондай-ақ СБҚ ісігін емдеуде ИОСТ қолданудың ерекшеліктері мен мүмкін болатын шектеулері ұсынылды.*

Қорытынды: *ИОСТ ем алудан кейінгі жанама әсерлердің қаупін төмендетумен қатар, СБҚ ісігін емдеу ұзақтығын азайтады. СБҚ ісігін емдеуде осы әдістемені қолдануды жақсырақ түсіну үшін қосымша зерттеулер қажеті анық. Қысқа мерзімді және ұзақ*

мерзімді оң нәтижелер болған жағдайда, ИОСТ-ны толығымен қолдану мен емдеу мекемелерінде клиникалық хаттамаларға енгізу үшін ұсынылуы хақ.

Түйін сөздер: *интраоперациялық сәулелі терапия (ИОСТ), сүт безі қатерлі ісігі (СБК), өмір сүру деңгейі, ұзақ мерзімді нәтижелер, дерт қайталану жиілігі.*

АННОТАЦИЯ

РОЛЬ ИНТРАОПЕРАЦИОННОЙ ЛУЧЕВОЙ ТЕРАПИИ В ЛЕЧЕНИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак молочной железы (РМЖ) является одним из самых распространенных видов рака у женщин. По данным GLOBOCAN за 2022 год зарегистрировано 2,296,842 новых случаев РМЖ и 666,103 случаев смерти от данного заболевания. По распространенности занимает 1-е место в мире в структуре онкопатологии у женщин.*

В Республике Казахстан в 2023 году зарегистрировано 37,038 новых случаев рака, за исключением рака кожи. Число заболевших злокачественными новообразованиями увеличилось на 1,959, или на 5,6% по сравнению с уровнем предыдущего года. «Стандартизированный» показатель заболеваемости на 100 тыс. населения составил 186,1 в год с темпом прироста 3,5%, стандартизированный показатель – 0,8% с темпом прироста 159,6.

Также стоит обратить внимание на основные направления и принципы лечения РМЖ. Виды лечения РМЖ зависят от стадии заболевания. Хирургическое удаление опухоли может включать лучевую терапию, химиотерапию и гормональную терапию. В настоящее время актуальным становится использование интраоперационной лучевой терапии (ИОЛТ) в качестве оптимального метода лечения РМЖ. По мнению онкологов-хирургов, маммологов и радиационных онкологов подход к лечению путем использования ИОЛТ требует глубокого анализа для улучшения результата лечения и пятилетней выживаемости у пациентов с данным недугом.

Цель исследования *– изучение мирового опыта применения интраоперационной лучевой терапии в лечении рака молочной железы.*

Методы: *В статье представлен обзор источников из базы PUBMED за 2003-2023 гг. по применению ИОЛТ в лечении РМЖ.*

Результаты: *В обзоре представлены результаты крупных исследований, в том числе мультицентровых проспективных, по оценке эффективности, влиянии на выживаемость, а также об особенностях и возможных ограничениях применения ИОЛТ в лечении РМЖ.*

Заключение: *ИОЛТ является достаточно перспективным и инновационным методом лечения, который позволяет снизить риск развития побочных эффектов и уменьшить продолжительность лечения. Учитывая положительные краткосрочные и долгосрочные результаты применения ИОЛТ, целесообразно рекомендовать полноценное использование данного метода в клинических протоколах в системе здравоохранения Казахстана.*

Ключевые слова: *интраоперационная лучевая терапия (ИОЛТ), рак молочной железы (РМЖ), выживаемость, отдаленные результаты, частота рецидивов.*

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THE ROLE OF NEUTROPHIL EXTRACELLULAR TRAPS IN THE DEVELOPMENT OF BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Neutrophil extracellular traps (NETs) are extracellular networks released by neutrophils. They are extracellular strands of decondensed DNA fiber, combined with histones and proteins from neutrophil granules, which immobilize pathogens to facilitate their subsequent elimina-tion.*

NET formation (netosis) was first discovered as an immune response to bacterial infection. However, it has since been proven that netosis occurs abnormally in several other inflammatory conditions, including cancer.

Breast cancer (BC) is the most commonly diagnosed malignant disease in women. In this review, we will focus on the role of NETs in BC development and their potential use as diagnostic biomarkers and/or therapeutic targets in cancer.

The study aimed to *evaluate the role of NETs in the pathogenesis of breast cancer based on literature data.*

Methods: *The search in the Web of Science, PubMed, and Scopus databases for 2014-2024 revealed about 600 articles. Of these, 53 were analyzed following the inclusion and exclusion crite-ria.*

Results: *The NET role in tumor development is related to cancer immunoediting and the interaction between the immune system and cancer cells. NETs play a key regulatory role in the tumor microenvironment, contributing to the development of distant metastases and exacerbating the tumor's aggressiveness, thereby increasing its ability to invade. NETs play a significant role in regulating the tumor microenvironment. NETs also have an antitumor effect since their components directly kill cancer cells.*

NETs' production in cancer requires interaction between various cells and blood components, including platelets, leukocytes, metastatic tumor cells, and the primary tumor site.

Today, there are no generally accepted methods of using NETs to treat cancer. These treatment methods are under development, and work is underway to target various points and components of the NETs.

Conclusion: *In BC, netosis is associated with accelerated disease progression, metastasis, and complications. The study identifies potential NET-specific targets that should be investigated and used to develop treatment methods. A better understanding of the interaction between cancer and NETs will facilitate the development of precision treatments and diagnostics tailored specifically to NETs.*

Keywords: *breast cancer (BC), extracellular neutrophil traps (NETs).*

Introduction: Neutrophils are the most common leukocytes formed in the bone marrow. Neutrophils constitute the first line of defense against non-indigenous pathogens, utilizing the primary effector mechanisms of phagocytosis, degranulation, and neutrophil extracellular trap (NET) formation [1]. Neutrophil extracellular traps (NETs) are extracellular networks that are released by neutrophils and are extracellular strands of decondensed DNA fiber in combination with histones and granule proteins neutrophils, including matrix metalloproteinase (MMP), neutrophil elastase (NE), myeloperoxidase (MPO), cathepsin G, complement factors, and other enzymatically active proteases and peptides that immobilize pathogens to facilitate their subsequent elimination [2].

The NETs formation, known as NETosis, was first discovered as an immune response to bacterial infection. Histones and the released granular contents of neutrophils have antimicrobial properties, and the fibrous structure of the networks can physically capture and render harmless bacteria. However, it has since been proven that NETosis occurs abnormally in several other inflammatory conditions, including cancer. NETosis occurs when proteases enter the neutrophil nucleus, leading to chromatin decondensation through citrullination. These loosely bound filaments are eventually ejected from the cell, destroying it or leaving the membrane intact. The subsequent integrity of the membrane depends on the nature of the stimulus that provokes NETosis [3-6].

According to the data of the Global Cancer Observatory, 2,296,840 cases of breast cancer (BC) and 666,103 deaths from this disease were registered in the world in 2022. The incidence was 46.8 cases per 100,000 people, and the mortality was 12.7 deaths per 100,000. In Kazakhstan, the absolute number of BC cases amounted to 5,171 in 2022. The incidence was at 26.5 per 100,000, and the mortality was 5.4 per 100,000 [7, 8].

This review focuses primarily on the NET role in BC development. It is well established that NETs exhibit both antitumor and protumorigenic effects. This review en-

compasses the established and potential stimuli that contribute to oncogenic NETosis at the molecular level, and also describes the interactions between neutrophil species, other blood components, and the tumor cells themselves. The review also presents the consequences of NETosis and its role in the progression of BC. NET is further considered a diagnostic biomarker and/or a possible therapeutic target in malignant tumors.

The study aimed to evaluate the role of NETs in the pathogenesis of breast cancer based on literature data.

Methods: For this literature review, a systematic search of the scientific literature in the Web of Science, PubMed, and Scopus databases was conducted from January 2014 to January 2024. In exceptional cases, publications published earlier than 2014 were included in the review, as they represented basic research that had a significant impact on the development of the topic [9, 10].

The search was conducted using combinations of keywords and medical subject headings (MeSH terms), such as "breast cancer" and "neutrophil extracellular traps", as well as their synonyms and derivatives in English.

The following search strategy was used (example for PubMed):

(«breast neoplasms»[MeSH Terms] OR «breast cancer») AND ("neutrophil extracellular traps" OR "NETs")

Publications were included in the analysis according to the following inclusion criteria:

• articles published in peer-reviewed scientific journals;

• availability of the full version of the article in English;

• articles containing data from randomized controlled trials, cohort studies, meta-analyses, and systematic reviews;

• studies directly relating to the role of neutrophil extracellular traps (NETs) in BC pathogenesis, progression, or treatment.

Exclusion criteria included:

• incomplete publications, including conference abstracts, presentations, and short communications;

• articles describing only isolated clinical cases (case reports);

• publications in journals with a dubious scientific reputation, determined by the lack of indexing in leading databases and a low impact factor;

• articles with a citation index below the average for the subject (according to Scopus/Web of Science data at the time of search).

As a result of the initial search, about 600 publications have been identified. After applying the inclusion and exclusion criteria to the analysis, 53 of the most relevant sources were selected. A detailed selection scheme is presented in Figure 1. The selection of articles was carried out by two researchers. The level of convergence of views regarding the inclusion of articles was 98%. All disagreements were resolved through discussion and consensus.

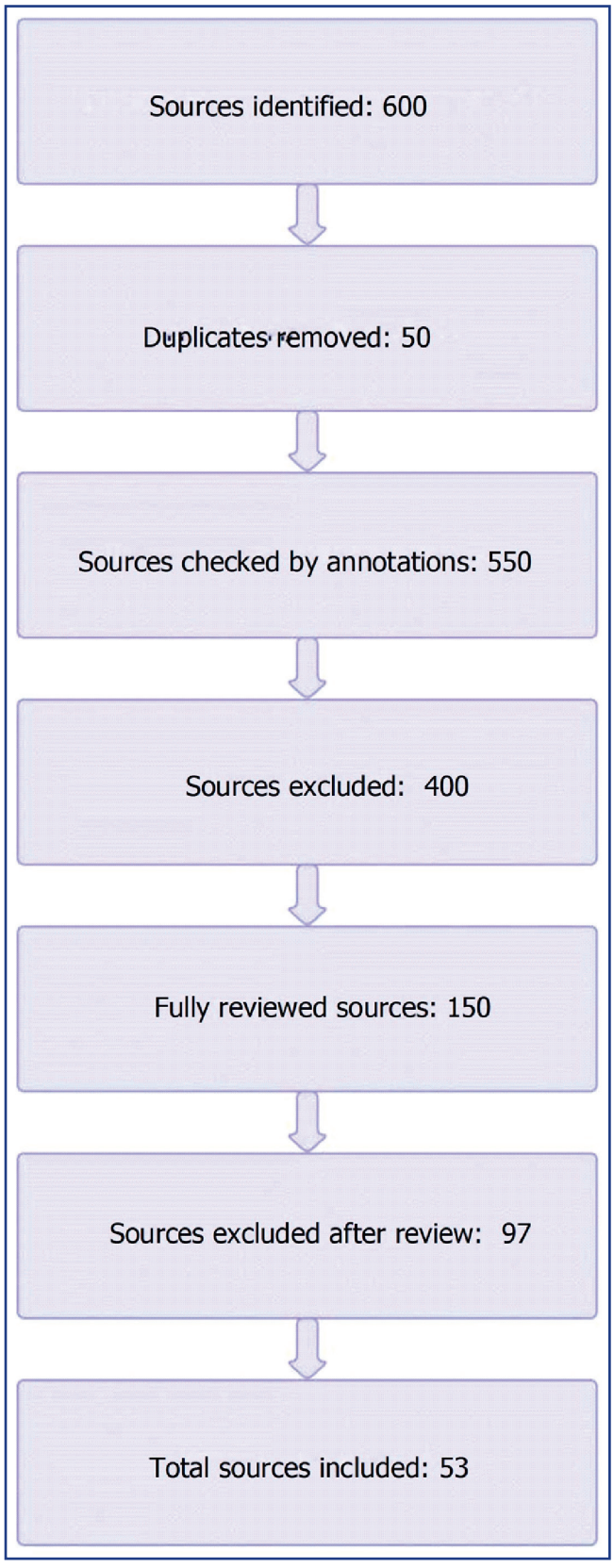

Figure 1 – Stages of selection of sources for the review

Results: In a scientific first, V. Brinkmann et al. reported on NETs in 2004, when electron microscopy was used to obtain images of activated neutrophils involved in antimicrobial processes [9]. An in vitro study of neutrophils activated with IL-8, phorbol-12-myristate-13-acetate (PMA)

showed the formation of distinctive extracellular fibers. This concept has been further confirmed in vivo, where these structures have been identified under infection conditions in both preclinical models and humans.

In 2012, M. Demers et al. were the first to report on the role of traps in oncological processes. In the main part, the authors studied melanoma B16F10 and leukemia AML. In this study, NET has been associated with tumor progression for the first time [10]. Later, several authors demonstrated that breast tumors generate neutrophils, which are predisposed to forming NETs. The number of traps increases with the progression of the tumor stage. NET was identified by an increase in plasma DNA content, as well as by immunofluorescence staining of extracellular histone and DNA around neutrophils. These markers represent the process of NETosis, in which neutrophils release decondensed enzymatic granules containing chromatin into the extracellular space, typically resulting in non-apoptotic cell death [11, 12].

The NETs' antitumor effect can theoretically be exerted by activating the immune system or directly destroying malignant cells. It has been shown that NETs components, such as NE and MPO in vitro, as well as histones, can destroy cancer cells, thereby blocking further cell growth and the development of distant metastases [13, 14].

Numerous studies have shown that granulocyte colony-stimulating factor (G-CSF) contributes to the production of NETs. Demonstration of NETs in mice with tumors has been made possible by tumor-derived neutrophil G-CSF priming, which can be neutralized by treating mice with an anti-G-CSF antibody. Additionally, neutrophils from mice treated with recombinant G-CSF were more predisposed to platelet formation when stimulated by platelet-activating factor in vivo. Thus, NETs have been shown to induce a prothrombotic state in the lungs of mice with a tumor and also participate in tumor growth [15, 16].

Several studies have shown higher preoperative levels of MPO-DNA, a well-known marker of systemic neutralization, in the serum of patients with metastatic cancer compared to healthy controls. These rates were associated with low disease-free survival and overall survival. NETs can promote the growth of stressed cancer cells by altering their bioenergetics, while inhibiting traps leads to the death of cancer cells. Thus, serum levels of MPO-DNA may represent a possible prognostic biomarker [17-19].

NETs have also been recognized as a crucial component of the dynamic tumor immune microenvironment (TIME), which can significantly contribute to the prevention of metastatic spread [20, 21]. Several factors have been identified that contribute to the formation of TIME. Among them are cancer-associated fibroblasts (CAFs), which are considered one of the most important protumor factors. Regarding the effect of NETs on CAFs, it has been reported that trap formation occurs in these fibroblasts within pancreatic ductal adenocarcinoma, thereby creating a protumor microenvironment [22]. However, due to the difficulty of converting normal fibroblasts into CAFs, further research is required to study the specific mechanisms mediated by NETs regulation.

Neutrophil elastase (NE), a key granular protein in reticulated microvesicles, has been shown to disrupt the extracellular matrix and activate the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway in cancer cells. Induction of the PI3K signaling pathway promotes the proliferation and migration of cancer cells [23, 24]. Another representative of granule proteins, a matrix metalloproteinase (MMP), has also been reported to promote tumor growth and metastasis through extracellular matrix proteolysis [25, 26].

Patients with malignant tumors show an increase in platelet activation [27]. NETs have been shown to contribute to the formation of arterial, venous, and cancer-related thrombosis [28, 29]. The traps induce intravascular activation of the coagulation cascade, which promotes primary tumor growth, cancer aggressiveness, progression, and metastasis. According to L.G. Lima et al., there is a significant correlation between the incidence of thromboembolic complications and a worsening of the prognosis of tumor diseases. These authors suggested that the traps collect on the scaffold with the thrombus and may play a crucial role in the pathogenesis of cancer, in conjunction with the hemostasis system [30]. Subsequently, H.S. Jung et al. demonstrated that NETs stimulate cancer-associated thrombosis, which correlates with a worse clinical outcome [31]. It is well known that the incidence of thromboembolic diseases is markedly dependent on the type of cancer. For example, patients with BC have a low incidence of thromboembolic complications, while patients with pancreatic cancer have a high incidence [32].

Methods to identify neutrophil extracellular traps: The detection of NETs in peripheral blood enables the separation of patients at higher risk of venous thromboembolism and metastasis. This is especially important in clinical practice for a personalized approach in the choice of treatment tactics. The traps can be used as a biomarker for risk stratification and treatment adaptation. However, as of today, the literature does not outline the reference values for the NET level. One of the available ways to determine in vivo networks is to measure the NETs components, such as circulating cell-free DNA, citrullinated histone H3 (citH3), NE, and MPO.

In the study of the blood of patients with established diagnoses of colorectal cancer and BC, freely circulating DNA was detected by quantitative analysis of nucleic acid staining [33]. A correlation was found between circulating DNA and the size of the breast tumor, as well as the degree of its malignancy. A disadvantage of this study was the lack of specificity in measuring NETosis. The elevation of DNA in blood serum can also be attributed to the consequences of cell necrosis and apoptosis. A solution in this situation

may be to measure the circulating MPO-DNA conjugates, which are more specific in NETs formation, compared to assessing cell-free DNA alone [34].

The most specific marker of traps is citrullinated histone H3 (citH3). It is formed during the NETs formation within PAD4-mediated citrullination and has an important predictive value. In patients with advanced cancer, high levels of citH3 are a significant indicator of short-term death, surpassing even those of critically ill patients without cancer [35].

Neutrophil derivatives - neutrophil elastase and myeloperoxidase - cannot be reliable and specific markers for NETs, since these enzymes are released during degranulation of neutrophils, regardless of the trap's formation. Additionally, in the study of seriously ill patients, no significant differences were found between these markers, regardless of whether a malignant tumor was present or absent [6].

From the above, it follows that citH3 is the most stable indicator of NETosis, as it is highly specific for netosis. The CitH3 may be effective in understanding the differences between other biomarkers associated with NETs. The CitH3 levels are also predictors of venous thromboembolism (VTE) risk in newly diagnosed patients, further supporting its diagnostic usefulness [35, 36].

Extracellular neutrophil traps and breast cancer: BC is one of the three most commonly diagnosed cancers worldwide [7, 36], as well as one of the most studied cancers. In the previously mentioned work, additional experiments by Demers et al. also studied the BC in a mouse model (4T1) for the first time, finding that in a mouse model of BC, the formation of NETs corresponded to cancer-associated thrombosis in the lung. The development of thrombosis in patients with BC is associated with an increased risk of death, both due to the thromboembolic complication itself and due to the progression of the malignant process, against which thrombosis may reflect a more aggressive course of the disease [10]. It was found that the release of cancerous extracellular chromatin networks (CECN) occurred due to high levels of *Padi4* gene expression in 4T1 BC cells of mice and PAD4-mediated traps. The deletion of Padi4 genes in mouse models significantly slowed the proliferation and migration of BC cells, indicating that PAD4-mediated NETs stimulate breast tumor growth and liver metastasis [37]. In addition, NETs have been shown to stimulate the prometastatic phenotype in human BC cells by inducing an epithelial-mesenchymal transition program [38].

It was also revealed that the activation of neutrophil lipopolysaccharides awakens dormant BC cells, leading to the production of NETs. The obtained NETs reconstruct laminin, utilizing MMP-9 and NE proteases. The reconstructed laminin further activates the signaling of integrin α3β1 to awaken BC cells. Inhibition of NETs formation via cleavage by DNase I or by inhibition of protein-dezincinase 4 prevents the activation of dormant cancer cells [40]. Besides, metastatic BC cells are also able to activate neutrophils, thereby promoting NET formation even in the absence of infection. Activation of neutrophils by cancer cells occurs through the secretion of G-CSF. Blocking the NETs formation by DNase I showed the prevention of lung metastasis in mice [41].

Therapeutic capacity of neutrophil extracellular traps: There are currently no approved medicines that target NETs. These treatments are under development. There are several ways to inhibit NETosis, each with different potential for clinical therapy. According to several studies, DNase I treatment disrupts networks, leading to the loss of reticular structure and a reduced ability to induce metastasis [41-43]. In addition, DNase I has been shown to reduce the tumor volume in rats when administered intramuscularly or intraperitoneally in combination with other proteases (papain, trypsin, and chymotrypsin). However, it is not known whether these effects were primarily due to inhibition of NETs [44].

Inhibition of trap components integral to NETosis, such as NE or PAD4, is likely to have similar off-target effects due to their involvement in other key pathways, potentially disrupting normal neutrophil function. Low-molecular-weight irreversible PAD4 inhibitors, Cl-amidin and F-amidine, are being actively studied as they inactivate the calcium-related PAD4. The disadvantage of these inhibitors is their lack of specificity and the potential for interaction with other enzymes within the PAD family. Lewis et al. synthesized two reversible inhibitors, GSK199 and GSK484, which overcome this obstacle. Both exhibit high specificity for PAD4 and inhibit NETosis in both mouse and human neutrophils. GSK484 has been shown to prevent tumor-associated renal dysfunction in mice, which NETs mediate. The inhibitory effects of GSK484 were as effective as DNase I [45].

Alternatively, there is an example of adaptations of FDA-approved drugs that contribute to the development of effective methods to combat NETs. For example, the inhibitory effect of aspirin on the network has yielded some promising results in animal models. M.J. Lapponi et al. showed that aspirin prevented NET-induced damage to the lung endothelium by inhibiting platelet activation and subsequent formation of NETs in mice. The authors found that aspirin treatment effectively suppressed NETs in human neutrophils in vitro, but led to an increase in bacteria in mice with aggravated infection in vivo, suggesting a loss of normal NET functionality [46]. There is evidence of a positive effect of aspirin in clinical practice. Thus, it was found that daily aspirin, regardless of the dose, can reduce the risk of cancer mortality and the development of distant metastases, in particular in adenocarcinomas, and that in patients with BC, aspirin affects the reduction of metastasis [47].

The FDA-approved hydroxychloroquine, originally used to treat malaria, was also found to inhibit NETosis. Although the mechanism underlying hydroxychloroquine's

inhibition of NETs is unclear, it may be related to autophagy inhibition [48-50]. A phase II clinical trial in patients with advanced pancreatic cancer had little clinical benefit. However, the authors suggest that combination therapy may be more effective than hydroxychloroquine monotherapy [51]. Additionally, the use of hydroxychloroquine as a neoadjuvant treatment in the early stages of the disease holds significant promise [52].

L. Yang et al. studied the therapeutic targets associated with NETs in the treatment of BC and revealed a potential specific mechanism of the effect of NETs on BC metastasis. The researchers demonstrated that the DNA components of NETs can function as a chemotactic factor, attracting BC cells and contributing to the development of liver metastases in patients with early-stage BC. It was assumed that the transmembrane protein CCDC25 could be a potential receptor for the DNA components of NETs in BC cells, by reading information from cell-free DNA. Activation of CCDC25 contributed to the improvement of cell motility by activating the ILK-B-PARVIN pathway. These results highlight the potential of using CCDC25 as a target for the development of a therapeutic strategy aimed at preventing cancer metastasis [53].

Discussion: The role of NETs in tumor development increasingly involves the cancer immunoediting and the interaction between the immune system and cancer cells. According to the accumulated evidence, NET awakens dormant cancer cells, thereby causing tumor recurrence, as well as its uncontrolled growth and spread [16]. NETs play a significant role in regulating the tumor microenvironment, particularly in the formation of distant metastases, by secreting matrix metalloproteinases and pro-inflammatory cytokines. Additionally, NET enhances the tumor's ability to invade and spread, contributing to its increased aggressiveness. The data obtained show that NET induces the epithelial-mesenchymal transition in tumor cells through the activation of the highly mobile group protein box 1, which also enhances their invasive properties. NET proteinases can also disrupt the extracellular matrix, promoting the extravasation of cancer cells. Moreover, the traps can capture and grip circulating cancer cells, thereby promoting metastasis. NET directly triggers the proliferation of tumor cells through their proteases or activating signals.

Studies have shown that in cancer, the formation of NETs is associated with a complex interaction between different cells and blood elements, including platelets, white blood cells, metastatic tumor cells, and the primary tumor. NETs contribute to the development of an inflammatory microenvironment, creating a vicious cycle: NETs enter the bloodstream, damage endothelial cells, which increases inflammation and activates platelets and neutrophils. This, in turn, can lead to additional release of NETs. Platelet activation induced by NETs may also contribute to several negative effects associated with late-stage metastatic BC, including VTE.

NETs also have an antitumor effect. Various NETs components, such as MPO or histones, have been shown to directly kill the cancer cells.

To date, the effect of NETs on the tumor process is being actively studied, and therapeutic strategies targeting NETs are being developed; however, they are still in the preclinical stage. It is worth noting that relevant work is underway aimed at various points and components of NETs [41-43, 53]. Each method has its advantages and disadvantages. The prognostic consequences of cancer-related NETosis are being studied in addition to the development of new therapeutics to improve the outcomes in patients with BC. Future research should focus on finding new specific targets for the prevention of concomitant complications, such as increased risk of venous thromboembolism and metastasis, which adversely affect the prognosis of patients with BC.

Conclusion: BC is the most commonly diagnosed malignant disease in women. Immunological experiments over the past two decades have addressed many important questions regarding the causal relationship between chronic inflammation and carcinogenesis.

Accordingly, there is now more and more evidence that NETs play a significant role in the formation of the inflammatory component of the tumor microenvironment and can contribute to the progression of cancer. The data presented in the review relate to both classical inducers of NETs and specific stimuli capable of triggering NETosis in malignant neoplasms, although the mechanisms of their action are still insufficiently studied. The review also examines the negative consequences triggered by NETs and identifies potential therapeutic targets associated with them, which are of interest for future preclinical and clinical studies. One of the next important steps is to determine the relationship between neutrophils, tumor cells, endothelial cells, platelets, and extracellular vesicles, as well as to define the impact of other components of the innate and adaptive immune system on cancer progression. NET-targeted therapy has shown success in preclinical models of cancer and may prove to be a valuable clinical goal in slowing or stopping the tumor progression in patients with BC.

A better understanding of the interaction between cancer and NETs will enable the development of precision diagnostic and therapeutic strategies focused on NETs. This will make it possible to identify the tumors with the potential for metastasis, carry out an early diagnosis, and provide more effective and personalized treatment for patients with BC.

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ДАМУЫНДАҒЫ ЖАСУШАДАН ТЫС НЕЙТРОФИЛЬДІ ТҰЗАҚТАРДЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Нейтрофильді жасушадан тыс тұзақтар (НЖТТ) – нейтрофилдер шығаратын жасушадан тыс торлар. Олар гистондар және нейтрофилді түйіршік ақуыздарымен біріктірілген деконденсацияланған ДНҚ талшығының жасушадан тыс жіптері болып табылады, олар патогендерді кейіннен жоюды жеңілдету үшін иммобилизацияланады.*

НЖТТ түзілуі (нетоз) алғаш рет бактериялық инфекцияға иммундық жауап ретінде анықталды. Алайда, содан бері нетоздың қалыптан тыс бірқатар басқа қабыну жағдайларында, соның ішінде қатерлі ісіктерде болатындығы дәлелденді.

Сүт безінің қатерлі ісігі (СБҚІ) – әйелдер арасындағы қатерлі ісіктерден ең жиі қойылатын диагнозы. Бұл мақалада НЖТТ-нің СБҚІ дамуындағы рөліне, НЖТТ-ны ықтимал диагностикалық биомаркерлер және/немесе қатерлі ісікке арналған клиникалық емдік мақсаттар ретінде пайдалануға назар аударамыз.

Зерттеудің мақсаты *– әдебиет деректері негізінде сүт безі қатерлі ісігінің патогенезіндегі NSCLC рөлін бағалау.*

Әдістері: *2014-2024 жылдар аралығында келесі мәліметтер базасында іздеу жүргізілді: Web of Science, Pubmed, Scopus. 600-ге жуық мақала табылды, қосу және алып тастау критерийлеріне сәйкес 53 мақала талданды.*

Нәтижелері: *Ісіктің дамуындағы НЖТТ рөлі-қатерлі ісіктің иммунередактациясы және иммундық жүйе мен қатерлі ісіктің жасушаларының өзара әрекеттесуі. НЖТТ ісік микроортасында, алыс метастаздардың дамуында негізгі реттеуші рөл атқарады, ісіктің агрессивтілігін күшейтеді, қатерлі ісіктің таралуын және инвазия қабілетін арттырады. НЖТТ сонымен қатар ісікке қарсы әсері де анықталған: тұзақтардың компоненттері қатерлі жасушаларды тікелей жояды.*

Қатерлі ісік кезіндегі НЖТТ өндірісі тромбоциттер, лейкоциттер, метастатикалық ісік жасушалары және бастапқы ісік аймағының өзін қоса алғанда, әртүрлі жасушалар мен қан компоненттері арасындағы өзара әрекеттесуді қамтиды.

Қазіргі уақытта НЖТТ көмегімен қатерлі ісік ауруын емдеудің жалпы қабылданған әдістері жоқ. Бұл емдеу әдістері даму сатысында, НЖТТ-нің әртүрлі нүктелері мен компоненттеріне бағытталған жұмыстар жүргізілуде.

Қорытынды: *сүт безі қатерлі ісігінде нетоз аурудың жедел дамуымен, метастазбен және асқынулармен байланысты. Мақалада НЖТТ-ге тән ықтимал мақсаттар анықталған, оларды зерттеу және емдеу әдістерін әзірлеу үшін пайдалану керек. Қатерлі ісік пен НЖТТ арасындағы өзара әрекеттесуді жақсырақ түсіну НЖТТ-ге бағытталған дәл емдеу мен диагностиканы жасауға мүмкіндік береді.*

Түйінді сөздер: *сүт безі қатерлі ісігі, жасушадан тыс нейтрофильді тұзақтар.*

АННОТАЦИЯ

РОЛЬ ВНЕКЛЕТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК В РАЗВИТИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Нейтрофильные внеклеточные ловушки (ВНЛ) — это внеклеточные сети, высвобождающиеся нейтрофилами. Они представляют собой внеклеточные нити из деконденсированного ДНК-волокна в комплексе с гистонами и белками гранул нейтрофилов, которые иммобилизуют патогены для облегчения их последующей элиминации.*

Образование ВНЛ (нетоз) впервые было обнаружено как иммунный ответ на бактериальную инфекцию. Однако с тех пор было доказано, что нетоз происходит аномально и при ряде других воспалительных состояний, включая рак.

Рак молочной железы (РМЖ) является наиболее часто диагностируемым злокачественным заболеванием у женщин. В этом обзоре мы сосредоточимся на роли ВНЛ в развитии РМЖ, на использовании ВНЛ в качестве потенциальных диагностических биомаркеров и/или клинических терапевтических мишеней при раке.

Цель исследования *– оценить роль внеклеточных нейтрофильных ловушек в патогенезе рака молочной железы на основе данных литературы.*

Методы: *Поиск в базах данных Web of Science, Pubmed, Scopus за 2014-2024 гг. выявил около 600 статей. Проанализировано 53 публикации согласно критериям включения и исключения.*

Результаты: *Роль ВНЛ в развитии опухоли- иммунноредактирование рака и взаимодействие между иммунной системой и раковыми клетками. ВНЛ являются регуляторами микроокружения опухоли, участвуют в распространении опухоли и в развитии отдаленных метастазов, способствуют повышению агрессивности опухоли и усиливают способность к инвазии. ВНЛ играют значимую роль в регуляции микроокружения опухоли, а также оказывают противоопухолевое действие, поскольку компоненты ВНЛ напрямую убивают раковые клетки.*

Продукция ВНЛ при раке включает взаимодействие между различными клетками и компонентами крови, включая тромбоциты, лейкоциты, метастатические опухолевые клетки и сам участок первичной опухоли.

В настоящее время нет общепринятых способов лечения рака с использованием ВНЛ. Данные методы лечения находятся на стадии разработки, ведутся работы по нацеливанию на различные точки и компоненты ВНЛ.

Заключение: *Нетоз при РМЖ связан с ускоренным прогрессированием заболевания, метастазированием и осложнениями. В работе определены потенциальные специфичные для ВНЛ цели, которые следует исследовать и использовать для разработки методов лечения. Лучшее понимание взаимодействия между раком и ВНЛ позволит разработать прецизионные методы лечения и диагностики, нацеленные на ВНЛ.*

Ключевые слова: *рак молочной железы (РМЖ), внеклеточные нейтрофильные ловушки (ВНЛ).*

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MODERN METHODS FOR DETERMINING HOMOLOGOUS RECOMBINATION DEFICIENCY IN OVARIAN CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *As scientists continue to explore and deepen their understanding of cancer genomics, they are increasingly able to identify broader molecular "fingerprints" characteristic of various forms of cancer. One such marker is homologous recombination deficiency (HRD), which is gaining importance in understanding the biology of different cancer types.*

The study aimed to *review the available methods used in clinical practice to assess homologous recombination deficiency status in ovarian cancer.*

Methods: *This review utilized various literature sources, including scientific articles and reviews. Literature search was conducted in databases such as PubMed, Cochrane Library, Scopus, and Web of Science using keywords like "ovarian cancer," "homologous recombination deficiency", and "homologous recombination repair". Articles were included in the review based on their content and relevance to the research topic. The search covered a period of 5 years (2020-2025).*

Results: *Each method presented in the review has specific advantages and disadvantages. It is important to compare the available tests with the gold standard (BRCA1/2, GIS) in clinical trials to better characterize their prognostic value and integrate them into treatment regimens. The combination of multiple tests may provide higher prognostic value. It is crucial to consider the technical heterogeneity that characterizes internal HRD tests. Variations in certain technical characteristics (e.g., reference range, analyzed genomic markers, panel expansion) highlight the importance of harmonizing analytical procedures before implementing internal HRD tests.*

Conclusion: *HRD status analysis is essential in treating ovarian cancer. However, several pre-analytical and analytical factors can influence its clinical testing in surgical pathology laboratories. In recent years, numerous HRD tests have appeared on the market, but their clinical implementation is still far from routine practice. Multicenter efforts should determine the best approaches to ensure adequate HRD testing for all patients with HGSOC.*

Keywords: *ovarian cancer, homologous recombination deficiency (HRD), biomarker, mutation.*

Introduction: As scientists continue to explore and delve deeper into the fundamentals of cancer genomics, they are increasingly able to identify broader molecular "fingerprints" characteristic of various forms of malignancies. One such hallmark is homologous recombination deficiency (HRD), which is gaining importance in the context of understanding the biology of different cancer types – including ovarian, breast, and pancreatic tumors, as well as cancers of the uterus, genitourinary system, colorectal tract, gastrointestinal tract, hepatocellular carcinoma, biliary tract cancer, sarcoma, and malignant neoplasms of the prostate. HRD is a complex genomic feature that arises when cells lose the ability to repair DNA double-strand breaks through the homologous recombination repair (HRR) pathway. Cells must efficiently resolve DNA damage to maintain genomic stability and proper cellular function [1]. This repair system ensures the integrity of chromosomal DNA and maintains cellular viability.

The study aimed to review the available methods used in clinical practice to assess homologous recombination deficiency status in ovarian cancer.

Materials and Methods: This literature search identified approximately 200 different sources, including scientific articles and reviews, of which 51 were selected for analysis. The search was conducted in databases such as PubMed, Cochrane Library, Scopus, and Web of Science using the keywords "ovarian cancer," "homologous recombination deficiency," and "homologous recombination repair." Articles were included in the review based on their content and relevance to the research topic. The search covered a period of 5 years (2020-2025).

Results: Numerous genes are involved in the homologous recombination process, among which BRCA1 and BRCA2 play a key role [3 - 7] (Table 1). When the HRR pathway is disrupted, damaged DNA regions are not properly repaired, and the cell resorts to a less accurate mechanism, known as non-homologous end joining. This may lead to genomic instability, manifested as characteristic "scars" in the genome, which contributes to the development of malignant tumors [8].

Genomic markers associated with HRD are also known as "genomic scars" (Table 2).

Table 1 – Most significant genes involved in the homologous recombination repair pathway [1]

ARID1A	EMSY	MSH2
ATM	FANCA	NBN
ATR	FANCC	PALB2
BRCA1/2	FANCE	PTEN
BARD1	FANCF	RAD50
BAP1	FANCD2	RAD51
BRIP1	FANCG	RAD51B
BLM	FANCI	RAD51C
CDK12	FANCL	RAD51D
CHEK1	H2AX	RAD54L
CHEK2	MRE11	TP53

Table 2 – Types of "genomic scars" included in the genomic instability score [9 - 11]

Name	Characteristics
Loss of heterozygosity	One of the two alleles of a given gene is lost, resulting in the cell becoming homozygous for that gene. If the second allele also be-comes nonfunctional, this may promote malignant transformation.
Telomeric allelic imbalance	Occurs when the allele ratio at the telomeric region of a chromosome is disrupted, meaning one chromosome in the pair contains more alleles than the other.
Large-scale transitions	Represent regions of chromosomal breaks that disrupt the normal structure and concordance of paired chromosomes.

HRD status can be determined either by analyzing mutations in key genes involved in homologous recombination (such as BRCA1, BRCA2, and other HRR genes) or by assessing the presence of characteristic genomic scars. Today, several diagnostic tests are available to determine HRD status, each using its criteria [12]. Some existing tests focus solely on evaluating loss of heterozygosity (LOH). However, recent studies indicate that more accurate identification of HRD-positive tumors is achieved through a comprehensive analysis that combines multiple genomic indicators - LOH, telomeric allelic imbalance (TAI), and large-scale transitions (LST) [13, 14]. This approach provides a sensitive and reliable characterization of HRD and other oncology-related genomic alterations present in the sample.

Homologous recombination deficiency (HRD) in ovarian cancer (OC). HRD is an emerging biomarker with both predictive and prognostic value in high-grade serous ovarian carcinoma (HGSOC). According to data from The Cancer Genome Atlas (TCGA), approximately 50% of patients with HGSOC exhibit signs of HRD. The underlying mechanisms can be diverse, and many of them remain incompletely understood. Most commonly, HRD is caused by inactivating mutations or epigenetic alterations in the BRCA1/2 genes, as well as in several other key players in the HRR pathway such as ATM, BARD1, BRIP1, H2AX, MRE11, PALB2, RAD51, RAD51C/D, RPA, and Fanconi anemia-associated genes [1, 15, 16] (see Table 1). These molecular alterations are considered significant contributors to HRD development in HGSOC.

Poly(ADP-ribose) polymerase (PARP) inhibitors were developed based on the concept of synthetic lethality, implying their selective efficacy against tumor cells with HRD. The enzyme PARP1 (poly(ADP-ribose) polymerase 1) plays a crucial role in the repair of single-strand DNA breaks, particularly via base excision repair mechanisms [16, 18]. When damage occurs, PARP inhibitors block PARP1 activity, preventing the repair of single-strand breaks [19]. As a result, such lesions can evolve into more severe double-strand breaks (DSBs), particularly during replication. Cells harboring mutations in BRCA1/2 or other components of the HRD pathway are unable to efficiently repair DSBs, leading to the accumulation of genomic damage and eventual cell death. These mechanisms form the basis for using HRD as a potential predictive biomarker for PARP inhibitor therapy in HGSOC, as well as in breast, pancreatic, and prostate cancers [19-23].

BRCA gene mutation testing can be performed on both tumor tissue and peripheral blood samples, allowing detection of both somatic and germline (inherited) variants. According to current guidelines, all patients with low-grade or unspecified OC should undergo testing for somatic BRCA mutations at the time of diagnosis. If a tumor sample tests positive, subsequent genetic testing on a blood sample is required to differentiate between germline and somatic mutations. Germline alterations necessitate genetic counseling and may warrant testing of close relatives [1, 24-26].

It is important to note that HRD can be observed not only in the presence of germline or somatic BRCA1/2 mutations, but also in cases of epigenetic suppression of BRCA1 expression or dysfunction of other key DNA repair genes such as ATM, ATR, BARD1, BRIP1, EMSY, PALB2, RAD51, as well as Fanconi anemia-related genes [1, 27 - 32]. Patients with such molecular alterations exhibit the so-called "BRCAness" phenotype, which resembles the clinical picture of BRCA1/2 mutation carriers. It is characterized by a serous histological subtype, high sensitivity to plati-

num-based chemotherapy, prolonged recurrence-free intervals, and a more favorable overall survival prognosis [33-36].

Identifying the BRCAness phenotype enables stratification of a subgroup of patients with sporadic OC who have a better prognosis [19] and demonstrate high sensitivity to platinum agents and PARP inhibitors [37]. Currently, PARP inhibitors are approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of high-grade serous carcinoma (HGSC) in various clinical settings:

1. As first-line maintenance therapy for patients who achieved a complete or partial response to platinum-based chemotherapy.

2. As maintenance therapy following platinum-sensitive recurrence, regardless of BRCA mutation or HRD status.

3. As monotherapy in HGSC with confirmed BRCA mutations (Olaparib or Rucaparib), or with a positive HRD status (Niraparib), after two lines of chemotherapy [1, 38].

The publication of the SOLO-1 trial results in 2018 marked a turning point, after which the EMA and FDA approved Olaparib as first-line maintenance therapy for patients with BRCA1/2 mutations. This decision laid the foundation for a new treatment standard. In 2019, data from three major Phase III randomized trials–PRIMA, PAOLA-1, and VELIA–were presented, evaluating the efficacy of PARP inhibitors in first-line therapy for both BRCA-mutated tumors and in combination therapeutic regimens. These studies formed the basis for expanded indications: Niraparib was approved as maintenance therapy regardless of biomarker status, and the combination of Olaparib with Bevacizumab was approved for advanced OC with a positive HRD status [39].

Homologous Recombination Deficiency (HRD) Testing in Clinical Practice. Clinical tests aimed at determining HRD status are based on the analysis of specific genomic alterations that reflect HRD. HRD determination plays a key role in selecting patients who may benefit from PARP inhibitor therapy or other agents that act by inducing DNA damage, especially in the treatment of ovarian cancer. However, for correct interpretation of results and optimal use of these tests in clinical practice, a clear understanding of both their methodological foundations and existing limitations is required [40] (see Table 3).

Table 3 – Advantages and limitations of homologous recombination deficiency (HRD) testing methods [40]

Type of test	Principle	Advantages	Limitations
Genetic testing (BRCA and HRR genes)	Analysis of germline and/or somatic mutations in BRCA1/2 and other HRR genes	Allows identification of hereditary and acquired mutations; an accessible method	Does not always reflect functional HRR status; it does not account for other HRD mechanisms.
Genomic scar analysis (LOH, TAI, LST)	Evaluation of structural genome alterations using SNP arrays or NGS	Widely used in clinical practice	Reflects "historical" instability rather than the current HRR function
Composite genomic instability score	Integration of LOH, TAI, and LST to calculate the overall HRD score	Validated in randomized trials	Requires standardization; limited use in other cancer types
Mutational signatures (WGS/WES)	Whole-genome or exome sequencing to identify specific mutation patterns	Potentially more accurate prediction of HRD and therapy sensitivity	Requires fresh-frozen samples; expensive; not widely implemented
Functional tests (RAD51)	Measurement of RAD51 protein activity involved in HRR	Reflects current functional HRR status; applicable to FFPE samples	Requires standardization; limited availability of laboratories

Note: FFPE – formalin-fixed, paraffin-embedded tissue; LOH – loss of heterozygosity; LST – large-scale chromosomal transitions; TAI – telomeric allelic imbalance; WGS – whole-genome sequencing; WES – whole-exome sequencing, covering only coding genomic regions (exons); RAD51 – protein involved in the homologous recombination DNA repair process.

Although HRD testing is currently FDA-approved only for ovarian cancer, it also has potential significance in the treatment of prostate, pancreatic, and breast cancers. Therefore, in such cases, testing is recommended on an individual basis. The primary objective remains the development of tests capable of accurately identifying the HRD phenotype of a tumor and predicting sensitivity to PARP inhibitors, allowing for more precise patient selection and maximizing therapeutic benefit [41].

There are three main approaches to HRD testing:

1. Analysis of germline and somatic mutations in HRR pathway genes;

2. Detection of "genomic scars" or mutational profiles indicating genomic instability;

3. Assessment of the functional status of the HRR system (Figure 1) [42].

Mutations in HRR Genes. The BRCA1 and BRCA2 genes play a key role in the HRR mechanism. Disruption of their function is one of the main factors contributing to the development of HRD in tumors [12]. All patients with newly diagnosed epithelial OC are recommended to undergo both germline and somatic BRCA testing. BRCA1/2 mutations are the most common cause of hereditary OC and are detected in approximately 20% of cases [44].

The BRCA genes function independently, ensuring genomic stability through the homologous recombination mechanism [45]. Testing helps identify patients who are potentially sensitive to PARP inhibitor therapy. Even with negative results for germline mutations, somatic testing may reveal additional mutation cases (an additional 6-7%) [28].

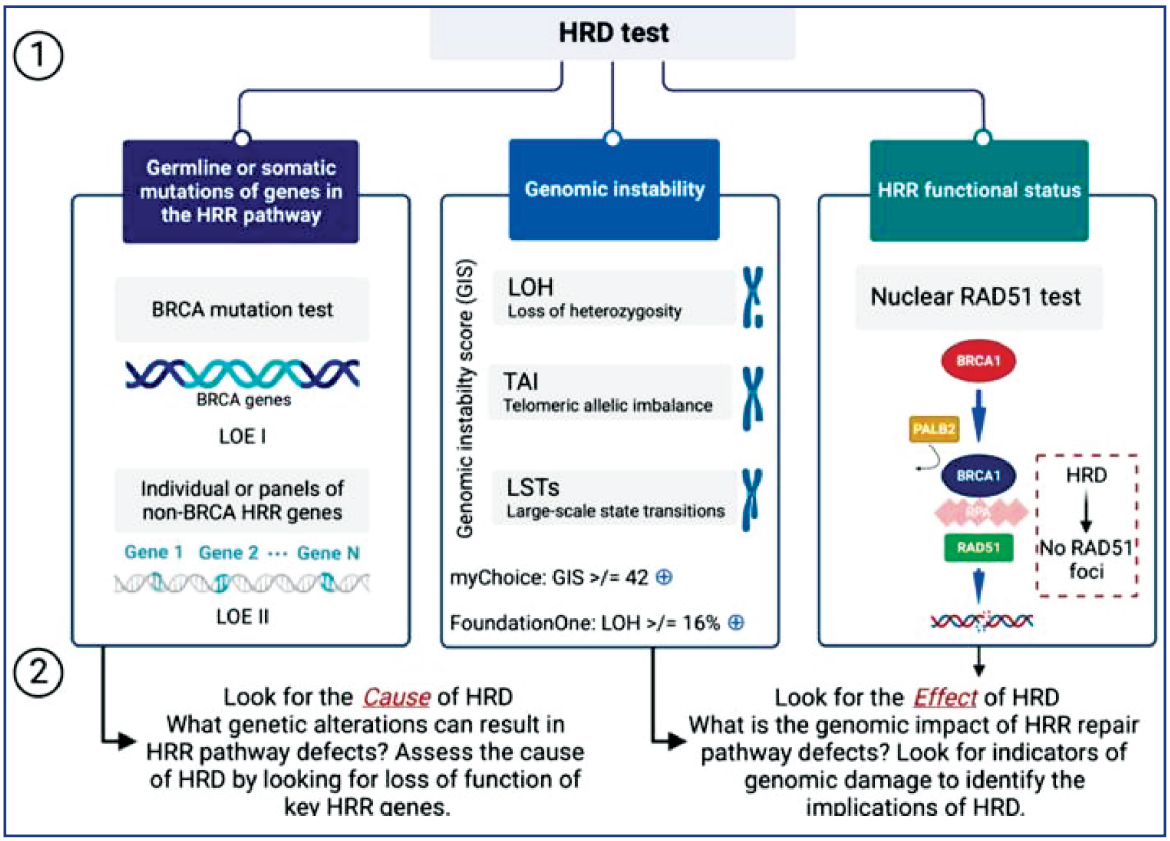

Figure 1 – Main approaches to HRD testing [adapted from: 1]

According to TCGA data, approximately 30% of patients with HGSOC exhibit alterations in HRR genes [28]. Mutations in RAD51C, RAD51D, BRIP1, and other pathway components, including ATM, CHEK1, CHEK2, and CDK12, also increase sensitivity to DNA repair inhibitors [34, 44, 45]. Amplification of the EMSY gene (a BRCA2 inhibitor) is associated with HRD, while CCNE1 amplification correlates with intact homologous recombination and poor prognosis [48].

Clinical data show that somatic mutations in HRR genes (beyond BRCA) may also provide comparable survival outcomes and sensitivity to platinum-based therapy. However, due to the rarity of these mutations, their impact is assessed collectively [38].

Genomic Scars and Mutational Markers of Genomic Instability. Modern HRD tests often use SNP microarrays to analyze somatic copy number variations (CNV). Several studies have used CNV analysis to assess BRCA status, measuring parameters such as LST [101], LOH [9], and TAI [10]. Combining these indicators increases the accuracy of distinguishing tumors with intact versus deficient HRR function [13].

Among commercial tests, FoundationOne (Foundation Medicine, USA) uses LOH analysis, while myChoice HRD (Myriad Genetics, USA) calculates a genomic instability score by integrating LOH, TAI, and LST (Figure 2).

The genomic instability index (GIS) assessment method is the only one validated in randomized clinical trials [38]. Although mutation-based tests using whole-genome sequencing potentially offer greater accuracy, they require fresh-frozen samples, while in clinical practice, formalin-fixed and paraffin-embedded (FFPE) blocks are more commonly available. Moreover, there is currently insufficient data to confirm the effectiveness of such tests in predicting response to PARP inhibitors in HGSOC.

Functional Tests for Homologous Recombination Deficiency. All available HRD tests are based on DNA analysis, reflecting mutations accumulated in the tumor. However, therapeutic pressure may induce resistance, particularly in metastatic tumors, which reduces the accuracy of such tests.

A functional alternative is the assessment of nuclear RAD51 protein levels, which is involved in homologous recombination. RAD51 forms foci in the nucleus upon DNA damage, and this process depends on the BRCA1-PALB2-BRCA2 complex. In model systems, reduced RAD51 activity is associated with BRCA deficiency and sensitivity to PARP inhibitors [48].

The RAD51 test has demonstrated reliability in FFPE tissues, particularly in selecting patients with ovarian and breast cancer who respond to PARP inhibitors [49, 50].

Homologous Recombination Deficiency Testing in Laboratory Practice. HRD testing methods vary and include cause-based and effect-based analyses, sequencing, and SNP-based techniques to evaluate genomic instability. Various HRD tests are available on the market, intended for laboratories equipped with high-throughput NGS plat-

forms. European academic centers are developing their tests, aiming to replicate the results of Myriad MyChoice CDx – for example, the Leuven test, developed within the ENGOT European initiative.

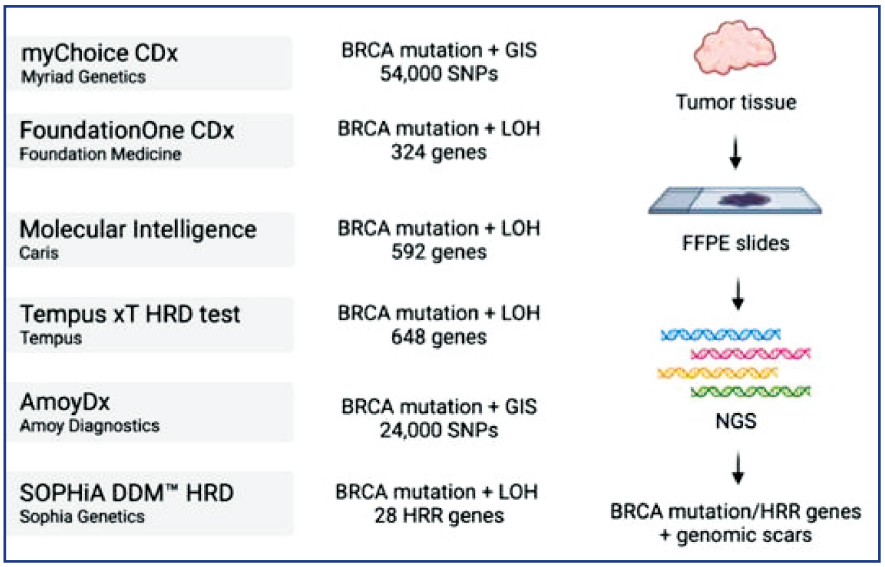

Figure 2 – Methods to assess HRD status in commercial tests [adapted from: 41]

The PAOLA-1/ENGOT-ov25 study, which analyzed 468 ovarian cancer samples, demonstrated a strong correlation between the Leuven HRD test and Myriad myChoice PLUS results. Modern tests such as AmoyDX HRD Focus, Oncomine Comprehensive Assay Plus, SOPHiA DDM HRD Solution, and Illumina TruSight Oncology 500 HRD offer different thresholds to determine HRD status. To more precisely characterize their prognostic value, these tests need to be compared with the gold standard (BRCA1/2, GIS) [1] in clinical studies, which will help determine their role in therapy selection. Moreover, the combined use of several such tests may enhance prognostic significance and requires further investigation, as results must be aligned with the treatment initiation timeline.

Currently, several HRD tests are commercially available. However, implementation of this testing strategy in routine clinical practice remains an open question. The study by Fumagalli et al. evaluated the technical feasibility of the HRD Focus Assay (Amoy Diagnostics, China), which can detect pathogenic BRCA1/2 alterations and calculate HRD scores [51]. In a retrospective series of 95 HGSOC patients who underwent external testing using the myChoiceCDx solution (Myriad Genetics, USA), the success rate of the internal testing strategy was 84.2%. Furthermore, a statistically significant degree of concordance (97.3%) was observed between the molecular BRCA1/2 assessments obtained using these two methodological approaches. The internal testing approach demonstrated outstanding negative predictive value (100.0%) and encouraging positive predictive value (83.3%) compared to the external solution.

One of the key advantages of performing internal tests is the ability to control sample quality and quantity, as well as select the most appropriate material. However, the technical heterogeneity inherent in internal HRD testing must be taken into account. Differences in parameters such as reference ranges, analyzed genomic indicators [1], and the composition of extended panels emphasize the need for standardization of analytical processes before the broad implementation of internal HRD testing.

Limitations of Homologous Recombination Deficiency (HRD) Analysis.

1. FFPE Material. The selection of appropriate tumor material for HRR gene analysis is a critical step. In cases of disease recurrence, preference is given to formalin-fixed paraffin-embedded (FFPE) material, as the tumor's HRD profile may change between the initial diagnosis and disease relapse. However, in some cases, the quantity and quality of FFPE tissue may be insufficient, rendering the sample unsuitable for analysis. In such situations, it is preferable to use the material obtained at the time of the primary diagnosis. Nevertheless, this is not always feasible, especially when treatment has been administered across different medical institutions at various stages of the disease. In such cases, and if the laboratory's technical capabilities allow, germline BRCA mutation analysis should be considered (Figure 3).

Moreover, FFPE samples frequently present alterations that are not true mutations but rather artifacts, such as base deamination or severe DNA fragmentation. These artifacts are often difficult to interpret accurately. Incorrect fixation – whether due to delayed initiation or excessively prolonged fixation – significantly affects sample quality and the reliability of molecular genetic analysis.

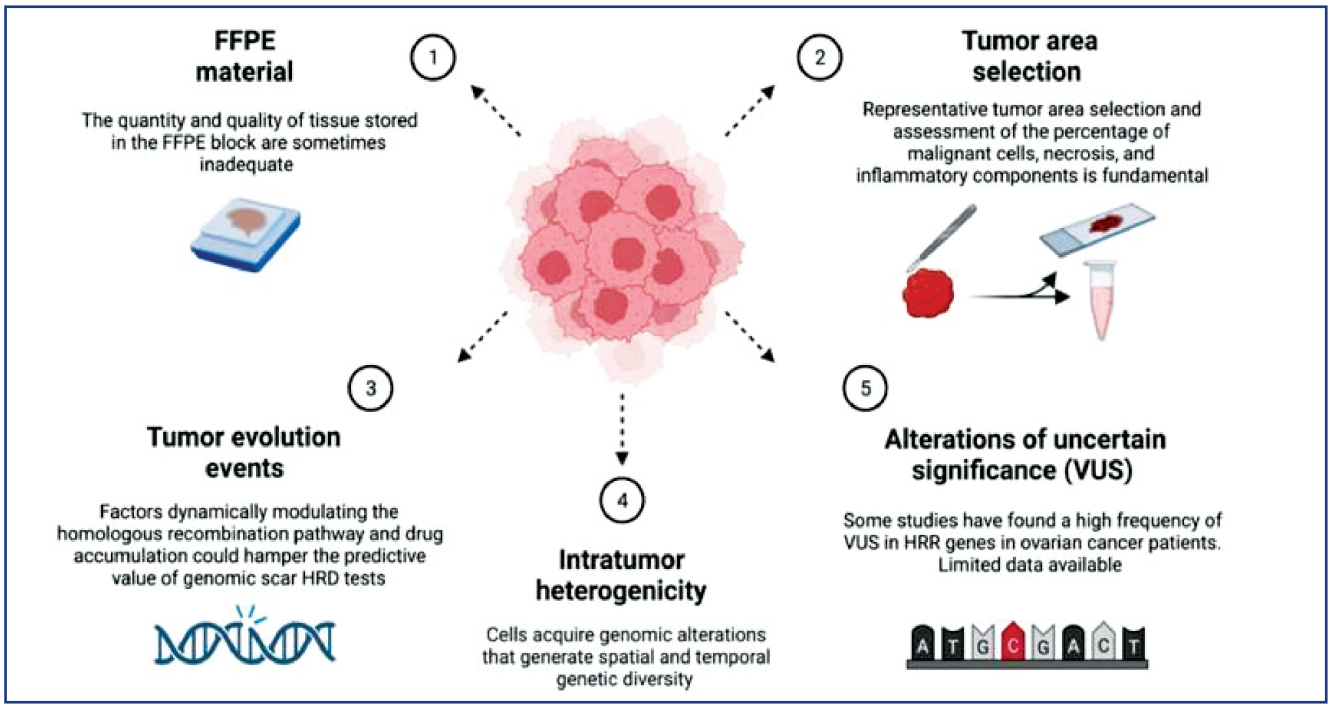

Figure 3 – Limitations of Homologous Recombination Deficiency Analysis

Therefore, it is recommended that molecular laboratories and pathology departments adhere to recognized national and international standards, such as ISO 15189. This is essential to ensure high quality at both the pre-analytical and analytical stages.

2. Selection of a Representative Tumor Area. Choosing the correct tumor area for investigation and assessing parameters such as the percentage of malignant cells, necrosis, and inflammatory infiltration play a key role in the molecular assessment of HRD. To allow for the reliable detection of genetic alterations, the tumor cell content in the tested sample should be at least 30%, and at least 40% for certain tests. This condition can be challenging to meet in tumors with marked inflammatory cell infiltration, which is frequently observed in HRD-associated cancers.

3. Tumor Evolution Events. The clinical relevance of HRD testing in OC is currently assessed primarily in the context of predicting PARP inhibitor efficacy, rather than as a direct indicator of HRD biological status. Beyond BRCA1/2 mutations, a major unresolved issue is whether genomic scars can serve as prognostic biomarkers that predict tumor sensitivity to platinum salts or PARP inhibitors. One of the key limitations of current genomic scar tests is their inability to detect tumor evolution events, such as the restoration of homologous recombination activity in response to therapy. These factors, which dynamically modulate the homologous recombination pathway and drug accumulation, may significantly reduce the predictive value of HRD "genomic scar" tests.

Furthermore, there are currently no documented cases where secondary mutations or BRCA1/2 reversions restore homologous recombination ability. Although a BRCA mutation may initially cause a genomic scar indicative of HRD, the tumor may regain homologous recombination proficiency even if the scar remains visible. This is especially relevant in OC, where approximately half of all BRCA-mutated tumors resistant to platinum-based therapy eventually restore BRCA function after platinum treatment. Additionally, many mechanisms of resistance to PARP inhibitors unrelated to BRCA1 mutations cannot be detected using HRD "genomic scar" tests.

For example, membrane transporters may play a key role in both innate and acquired resistance. In this regard, tests that enable the functional assessment of homologous recombination activity in tumor material may become a valuable tool in clinical practice, offering significant advantages. For a more precise approach within personalized medicine, the ideal strategy would be to integrate data on platinum sensitivity, "genomic scars", mutational markers, and functional tests - providing a comprehensive view of the presence of HRD and the tumor's DNA repair capability throughout treatment.

4. Intratumoral Heterogeneity. One of the major challenges to effective diagnosis and therapy is intratumoral heterogeneity, which refers to genetic differences between the primary tumor, biopsy site, and metastatic areas. Within a single tumor, multiple subclones of cells with distinct mutational profiles may coexist. Studies investigating the mutational spectrum in various segments of tumor tissue have shown significant variation in genetic alterations depending on the location of the sampled tissue [15]. These data confirm the presence of spatial genomic heterogeneity, which can significantly

impact the reliability of results when analyzing biomarkers such as "genomic scars". Such discrepancies may arise even when analyzing individual biopsy samples [16], which complicates data interpretation and underscores the need for a careful approach in selecting material for molecular analysis.

Thus, the same tumor may be classified as either HRD-positive or HRD-negative depending on the biopsy site, which is explained by potential sampling bias. This phenomenon includes both biological differences observed between separate biopsies and technical artifacts inherent to the method, including even minor variations in tissue composition between samples. It is also important to consider the genetic diversity that may exist within different parts of the same tumor specimen.

Variants of Uncertain Significance. The high frequency of variants of uncertain significance (VUS) in other HRR-related genes is most likely due to the limited data available for interpreting mutations outside BRCA1 and BRCA2. When analyzing HRR genes, various databases are often used, which may contain contradictory or ambiguous information, as the clinical significance of many such alterations remains undetermined. Some studies [1, 3] have reported a high frequency of VUS in HRR genes among patients with ovarian cancer. However, they also emphasize that two decades of research on BRCA1 and BRCA2 have led to a substantial reduction in the frequency of VUS in these genes, resulting in VUS rates that are lower than in most other genes.

Discussion: Based on the data obtained, several key points can be identified that confirm the importance of testing for homologous recombination deficiency (HRD) in the treatment of ovarian cancer, particularly when using PARP inhibitors and other DNA-damaging agents.

The Significance of HRD in Ovarian Cancer Therapy. Homologous recombination deficiency serves as an important prognostic indicator to identify patients who are most likely to benefit from therapies targeting DNA repair mechanisms, including PARP inhibitors. Various factors can cause HRD, the most extensively studied of which are mutations in the BRCA1/2 genes, as well as alterations in other components of the DNA repair system, such as ATM, RAD51, and PALB2, among others [17]. Such genetic and epigenetic alterations render tumor cells more vulnerable to certain types of therapy, which can significantly improve clinical outcomes.

The Importance of Accurate Testing. The methods used to detect HRD vary in sensitivity and specificity, underscoring the need for their standardization and unification. Differences in technical execution, such as the gene panels used, threshold values, or the types of genomic alterations analyzed, can significantly impact the reliability of the data obtained. Therefore, it is especially important to correlate the results of various methods with an established reference standard, such as the detection of mutations in the BRCA1/2 genes. This approach enables a more objective evaluation of the prognostic value of each test, thereby enhancing the clinical accuracy of diagnosis.

Genetic Heterogeneity of the Tumor and Spatial Genomic Heterogeneity. The presence of mutational diversity within a single tumor represents a major challenge for molecular diagnostics and disease prognosis. Genetic heterogeneity, resulting from differences between regions of the same tumor, may lead to discrepancies in HRD test results depending on the site of biopsy sampling. This is due to both the tumor's intrinsic biological characteristics and technical factors, including the biopsy site and analysis of different tissue regions, requiring a cautious approach to result interpretation.

The Issue of Variants of Uncertain Clinical Significance (VUS). The high frequency of variants of uncertain significance in genes responsible for DNA repair in patients with ovarian cancer complicates the accurate interpretation of molecular tests and the making of informed therapeutic decisions. However, with the accumulation of data and improvements in mutation classification, there is a trend toward a decreasing proportion of VUS—particularly in BRCA1/2 genes—which positively influences diagnostic accuracy and prognostic evaluation.

Collaboration Between Institutions and the Development of New Diagnostic Approaches. Despite the availability of various methods to determine HRD status, their routine implementation in clinical practice remains limited. To overcome this barrier, active collaboration between research and clinical institutions is needed to develop, validate, and standardize testing approaches. Reliable and reproducible diagnostic methods, including functional assays, should become an integral part of the treatment protocol for all patients with high-grade serous ovarian carcinoma (HGSOC).

Conclusion: Determination of HRD status plays a key role in the personalized treatment of ovarian cancer, particularly in the administration of PARP inhibitors. However, the effectiveness of this approach largely depends on the quality and accuracy of the tests used, as well as on the ability of the methods to adequately reflect the spectrum of genetic alterations present in the tumor. It is essential to consider not only laboratory parameters but also clinical factors, including the spatial heterogeneity of the neoplasm and the influence of biological features on test results.

Successful implementation of HRD testing in clinical practice requires addressing issues of method standardization and optimization, as well as conducting additional studies aimed at improving tests and deepening the understanding of the mechanisms underlying tumor resistance. Multi-institutional efforts to develop a unified

approach to HRD testing will contribute to more accurate identification of patients eligible for PARP inhibitor therapy and improve treatment outcomes.

Looking ahead, it is essential to develop a comprehensive strategy that integrates all available data, from mutational markers to functional HRD analyses, and can serve as a foundation for a more precise and effective approach to ovarian cancer therapy, thereby ensuring the best possible outcomes for each patient.

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АҢДАТПА

АНАЛЫҚ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ГОМОЛОГИЯЛЫҚ РЕКОМБИНАЦИЯ ТАПШЫЛЫҒЫН АНЫҚТАУДЫҢ ЗАМАНАУИ ӘДІСТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Ғалымдар қатерлі ісік геномикасының негіздерін зерттеуді және тереңірек зерттеуді жалғастыра отырып, олар қатерлі ісіктің әртүрлі формаларына тән барған сайын кеңірек молекулалық саусақ іздерін табуда. Осындай белгілердің бірі әртүрлі қатерлі ісіктердің биологиясын түсінуде барған сайын маңызды болып келе жатқан гомологиялық рекомбинация тапшылығы (homologous recombination deficiency, HRD) болып табылады.*

Зерттеудің мақсаты *– аналық безі қатерлі ісігінде гомологтық рекомбинация тапшылығы статусын бағалау үшін нарықта және клиникалық тәжірибеде қолданылатын қолданыстағы әдістерге шолу жасау.*

Әдістері: *Бұл шолуда әртүрлі әдебиет көздері пайдаланылды, соның ішінде ғылыми мақалалар, шолулар. Әдебиеттерді іздеу PubMed, Cochrane library, Scopus және Web of Science дерекқорларында «жұмыртқа безінің рагы», "homologous recombination deficiency", "homologous recombination repair" деген кілт сөздермен жүргізілді. Мақалаларды шолу жұмысына қосу олардың мазмұны мен зерттеу тақырыбына сәйкес келуіне негізделді. Іздеу тереңдігі 5 жылды (2020-2025 ж.) қамтыды.*

Нәтижелері: *Шолуда ұсынылған әр әдістің өз артықшылықтары мен кемшіліктері бар, сондықтан қолдағы тесттерді клиникалық зерттеулерде алтын стандартпен (BRCA1/2, GIS) салыстыру өте маңызды, бұл олардың болжамдық мәнін жақсырақ сипаттауға және оларды емдеу схемасына енгізуге мүмкіндік береді. Бірнеше тесттің комбинациясы жоғары болжамдық мәнді қамтамасыз етуі мүмкін. HRD ішкі тестілерін сипаттайтын техникалық біртекті еместікті ескеру маңызды. Кейбір техникалық сипаттамалардағы вариациялар (мысалы, референттік ауқым, талданатын геномдық көрсеткіштер, панельді кеңейту) ішкі HRD тестілерін енгізбестен бұрын аналитикалық процедураларды үйлестірудің маңыздылығын көрсетеді.*

Қорытынды: *HRD статусын талдау аналық безі қатерлі ісігі бар науқастарды терапевтикалық емдеуде қажет. Алайда бірнеше преаналитикалық және аналитикалық факторлар оның хирургиялық патология зертханаларындағы клиникалық сынақтарына әсер етуі мүмкін. Соңғы жылдары нарықта көптеген HRD тестілері пайда болды, бірақ олардың клиникалық қолданылуы әлі күнге дейін күнделікті тәжірибе болып табылмайды. Көп салалы күш-жігер аналық бездердің жоғары дәрежелі серозды карциномасы бар барлық пациенттер үшін сәйкес HRD тестін қамтамасыз ететін ең жақсы тәсілдерді анықтауы керек.*

Түйінді сөздер: *аналық безі қатерлі ісігі, гомологиялық рекомбинация тапшылығы (HRD), биомаркер, мутация.*

АННОТАЦИЯ

СОВРЕМЕННЫЕ МЕТОДЫ ОПРЕДЕЛЕНИЯ ДЕФИЦИТА ГОМОЛОГИЧНОЙ РЕКОМБИНАЦИИ ПРИ РАКЕ ЯИЧНИКОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *По мере того, как учёные продолжают изучать и углубляться в основы раковой геномики, им удаётся выявлять всё более обширные молекулярные «отпечатки», характерные для разных форм онкологических заболеваний. Одним из таких признаков является дефицит гомологичной рекомбинации (homologous recombination deficiency, HRD), значение которого возрастает в контексте понимания биологии различных видов рака.*

Цель исследования *– обзор существующих на рынке и в клинической практике методов оценки статуса дефицита гомологичной рекомбинации при раке яичников.*

Методы: *В данном обзоре были использованы различные источники литературы, включая научные статьи, обзоры. Поиск литературы был осуществлен в базах PubMed, Cochrane Library, Scopus и Web of Science, используя ключевые слова «рак яичников»,*

«homologous recombination deficiency», «homologous recombination repair». Включение статей в обзор происходило на основе их содержания и релевантности для темы исследования. Глубина поиска составила 5 лет (2020-2025 г.).

***Результаты:** Каждый из рассмотренных методов обладает своими сильными и слабыми сторонами. Для более точной оценки прогностической значимости различных тестов необходимо проводить их сравнение с признанными эталонными методами, такими как BRCA1/2 и геномный индекс нестабильности, в рамках клинических исследований. Использование комбинации нескольких тестов может повысить точность прогноза. При этом важно учитывать технические различия, характерные для локально разрабатываемых HRD-тестов. Разнообразие в технических параметрах — таких как диапазон референсных значений, геномные показатели, входящие в анализ, и состав панелей — подчеркивает необходимость стандартизации лабораторных процедур до широкого клинического внедрения таких тестов.*

***Заключение:** Определение HRD-статуса играет важную роль в выборе терапии для пациентов с раком яичников, однако на результативность тестирования могут повлиять как преаналитические, так и аналитические факторы, особенно в условиях лабораторий хирургической патологии. Несмотря на появление множества коммерчески доступных HRD-тестов в последние годы, их использование в повседневной клинической практике остаётся ограниченным. Требуются совместные усилия различных учреждений для выработки оптимальных стратегий, которые обеспечат качественное и стандартизированное определение HRD у всех пациентов с серозной карциномой яичников высокой степени злокачественности.*

***Ключевые слова:** рак яичника (РЯ), дефицит гомологичной рекомбинации (HRD), биомаркер, мутация.*

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ARTIFICIAL INTELLIGENCE IN THE DIAGNOSIS OF BREAST PATHOLOGIES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Timely diagnosis of breast cancer remains one of the key challenges in healthcare, as this disease continues to be a leading cause of mortality among women worldwide. In recent years, artificial intelligence (AI) has become an integral part of medical imaging, demonstrating broad applicability and potential. Current diagnostic modalities, such as mammography and magnetic resonance imaging (MRI), serve as essential tools for detecting breast pathologies; however, they have certain limitations regarding sensitivity and specificity. This literature review presents an overview of contemporary approaches to the application of AI in the diagnosis of breast cancer.*

The study aimed to *analyze the methods of applying artificial intelligence in diagnosing breast cancer, including its capabilities in prediction, interpretation of results, and improving the accuracy of imaging techniques.*

Methods: *A comprehensive search was conducted using PubMed, Medline, Cochrane Library, and Google Scholar databases. The review includes scientific articles focused on the application of AI in the diagnosis of breast diseases.*

Results: *The review demonstrated that AI systems, such as convolutional neural networks, can detect microcalcifications on mammograms with high accuracy (up to 94.5%) and reduce false-positive results by 11%. In MRI image analysis, using hybrid models, such as CNN-RNN architectures, improves the diagnostic accuracy of malignant tumors by 15% and reduces error rates by 20%. Radiomics shows high accuracy (87%) in predicting therapeutic response while integrating multiomics data provides sensitivity up to 92%.*

Conclusion: *Using AI in breast cancer diagnostics enhances the accuracy of imaging techniques, facilitates data interpretation, and contributes to the personalization of treatment strategies. However, challenges remain, including the availability of high-quality data for model training and ethical considerations in decisionmaking processes.*

Keywords: *breast cancer, artificial intelligence, mammography, MRI, radiomics, prediction.*

Introduction: Timely detection of breast cancer (BC) remains a top priority in healthcare, as this disease ranks among the leading causes of mortality among women worldwide. According to data from the World Health Organization, more than 2.3 million new cases of BC are diagnosed annually, accounting for approximately 25% of all cancers in women [1].

Imaging methods such as mammography and magnetic resonance imaging (MRI) are key tools to detect breast pathologies; however, they have limitations related to insufficient sensitivity and specificity at the early stages of the disease. Studies by S.M. McKinney et al. indicate that in routine clinical practice, mammography may miss up to 20% of BC cases, especially in women with high breast tissue density [2]. In this context, the use of modern technologies, such as artificial intelligence (AI), opens up new opportunities for improving diagnostic accuracy, which is particularly important for early-stage detection, when treatment is most effective [3-5].

Artificial intelligence (AI) utilizing Deep Neural Networks (DNN) has demonstrated its effectiveness in analyzing mammograms and MRI scans. Systems based on Convolutional Neural Networks (CNN) achieve accuracy rates of up to 94.5% in detecting pathologies on mammograms [6]. Moreover, the application of hybrid models, such as Convolutional Recurrent Neural Networks (CNN-RNN), enhances the analysis of dynamic contrast-enhanced MRI, resulting in a 20% reduction in false-positive diagnoses [7, 8].

The study aimed to analyze the methods of applying artificial intelligence in diagnosing breast cancer, including its capabilities in prediction, interpretation of results, and improving the accuracy of imaging techniques.

Materials and Methods: This review covered publications focused on the application of AI in breast disease diagnosis, sourced from the PubMed, Medline, Cochrane Library, and Google Scholar databases. The last search was conducted on March 10, 2025. The following keywords were used for the search: breast cancer, artificial intelligence, deep learning, radiomics, machine learning, diagnosis, mammography, MRI, neural networks. Keyword combinations included logical operators AND/OR. Languages of publication: English and Russian. Inclusion criteria: original research studies and meta-analyses published

in the past 10 years (2015 - 2025), articles in which AI was applied for the diagnosis of breast diseases, availability of quantitative data (sensitivity, specificity, area under the curve (AUC), etc.). *Exclusion criteria:* review articles, case reports, letters to the editor, and conference abstracts. Out of 350 identified publications, after removing duplicates and assessing for compliance with the inclusion criteria, the final review included 20 of the most relevant studies.

Results: Modern AI systems in the diagnosis of breast pathology employ various approaches and algorithms, such as classical machine learning methods, DNN, and hybrid approaches combining multiple technologies. Among the most widely used models are CNN, which demonstrate high accuracy in image processing and feature extraction [3]. For example, U-Net is actively used for segmentation tasks, including tumor delineation in MRI scans. The study focused on the development and evaluation of a model for medical image segmentation tasks. Particular attention was given to improving the traditional U-Net architecture through the use of enhanced skip connections. These modifications significantly enhanced the accuracy and efficiency of medical image analysis, particularly in applications such as breast MRI. The U-Net model demonstrated an average segmentation accuracy exceeding 92% on standard datasets, including the Breast MRI Dataset. This improvement enables more precise delineation of tumor boundaries, which is particularly important for surgical planning and radiotherapy. One of the key achievements of the model was the 70% reduction in image processing time, enhancing its applicability in real-world clinical practice [7].

Another important direction is the use of explainable AI methods, which make model operations more understandable to physicians, including the use of heatmap visualizations [8]. Combined systems, such as CNN-RNN, enable the analysis of temporal data, which is particularly useful in dynamic studies, such as dynamic contrast-enhanced MRI (DCE-MRI). The use of AI to analyze DCE-MRI data has helped reduce the number of false positives by 20%, thereby decreasing unnecessary biopsies and reducing emotional stress for patients. In the study by A. Landsmann et al., DCE-MRI data from patients with various types of breast neoplasms were analyzed. Special attention was given to the textural characteristics of tumors, such as heterogeneity, contrast, and signal intensity distribution. The objective was to identify parameters that consistently demonstrate differences between benign and malignant lesions at various time points following contrast administration [9].

Application of AI in Detecting Microcalcifications. Mammography is the primary method for breast cancer screening. AI is actively used to automate image analysis and enhance diagnostic accuracy. Examples of deep learning algorithm applications demonstrate strong potential for improving diagnostic precision and reducing errors.

Microcalcifications (small calcium deposits in breast tissue) are a key indicator of early-stage cancer. The use of deep learning algorithms, particularly CNN, enables the automatic identification of areas containing microcalcifications with high accuracy. S.M. McKinney et al. conducted a large-scale study involving over 25,000 patients. Their model demonstrated a sensitivity of 94.5% and a specificity of 88%, exceeding the performance of most Radiologists. The study also found that the algorithm reduced the likelihood of false-positive results by 11% [2].

H. Chougrad et al. explored the application of deep CNNs to improve BC screening accuracy. The researchers developed and tested a model using a dataset of 12,000 mammographic images, applying data augmentation techniques to enhance the training process. The results showed high model performance, with sensitivity reaching 96.8%, specificity at 97.5%, and an accuracy of 98.2% in detecting microcalcifications. Furthermore, the proposed approach reduced the number of false positives by 14% compared to traditional image analysis methods [10].

X. Wang et al. investigated the feasibility of automatic detection of microcalcifications in digital breast tomosynthesis using deep learning methods. The team applied three-dimensional image reconstructions and trained their model on a dataset of 2,500 tomosynthesis studies, with a specific focus on analyzing the spatial structure of microcalcifications. The results showed a sensitivity of 94.7% and specificity of 92.3%, confirming the high effectiveness of the method. The analysis time per case was only 3.2 seconds, and the number of missed cases was reduced by 15% compared to classical image processing techniques [11].

N. Dhungel et al. developed a fully automated method to classify mammographic images using deep residual neural networks (ResNet). The training dataset comprised 25,000 images, including both normal and pathological areas. The model analyzed tissue texture and density, achieving high diagnostic accuracy. Sensitivity reached 93.5%, and specificity was 90.2%. The use of the model reduced the number of false positives by 12% and outperformed traditional algorithms in accuracy by 6% [12].

In a large-scale study by T. Kooi et al., the model was trained on a dataset of 45,000 mammograms. The model effectively detected both individual microcalcifications and clusters. The algorithm achieved a sensitivity of 96.1% and a specificity of 94.8%. The processing time per image was minimal - only 2 seconds. The application of this method reduced the number of missed malignant changes by 20% [13].

Prediction of Malignancy in Neoplasms. The prediction of malignancy risk based on AI is becoming an increasingly popular area of research. The study by N. Wu et al. demonstrated that the use of DNN for mammogram analysis allows the prediction of cancer development with an accuracy of up to 89%. This study included 15,000 pa-

tients, and the model showed superiority in risk prediction compared to traditional assessment methods such as the Gail Model, which estimates the likelihood of BC in women based on risk factors including age, age at menarche, age at first childbirth, family history, and results of previous biopsies [14].

In 2021, researchers from the University of Massachusetts developed an AI model called Mirai, capable of predicting the risk of BC based on mammogram analysis. The model forecasts the probability of disease up to five years in advance, allowing physicians to make more informed decisions regarding the need for additional examinations or preventive measures. Mirai is a DNN trained on an extensive dataset comprising over 200,000 mammographic examinations, which ensures its high accuracy and reliability. Unlike traditional risk assessment methods, Mirai considers the individual characteristics of each patient, including breast tissue density and other factors, thereby providing a personalized prediction [15].

The study by M. Larsen et al. evaluated the ability of an AI algorithm to predict BC development in women. The study included 116,495 women aged 50-69 who had undergone at least three consecutive mammographic screenings at two-year intervals. The results showed that the AI algorithm could effectively identify women at high risk of future disease development, opening prospects for personalized screening approaches and earlier BC detection [16].

A study dedicated to evaluating the effectiveness of imaging methods and neural network algorithms in predicting the response of BC to neoadjuvant chemotherapy (NACT) included 342 patients with early and locally advanced disease. The authors compared the diagnostic accuracy of mammography, ultrasound, MRI, and a DNN algorithm. It was found that MRI demonstrated the highest sensitivity (80.0-83.3%) in detecting residual tumors, while neural network methods showed comparable results (69.2-72.0%), outperforming traditional mammography and ultrasound. These data suggest the potential of machine learning to enhance BC diagnostics, particularly in predicting the efficacy of antitumor therapy [17].

M. Bakker et al. presented an original study on the use of radiomics for classifying molecular subtypes of BC. The study focuses on utilizing digital mammographic images to extract key radiomic features that accurately predict the molecular profile of tumors. The authors utilized data from the large-scale OPTIMAM Mammography Image Database, which comprises digital mammograms and associated clinical information. The analysis included 186 patients diagnosed with BC, who were categorized into subtypes: luminal A, luminal B, HER2-positive, and triple-negative breast cancer (TNBC). To minimize errors at the tumor tissue extraction stage, automated segmentation algorithms were applied to accurately delineate tumor boundaries on mammograms. A total of 65 radiomic features were extracted from the images, covering texture, shape, and signal intensity characteristics. Based on the selected data, machine learning models were built, particularly using the Support Vector Machine (SVM) method. The results showed that SVM-based models achieved the highest predictive accuracy for the luminal A (AUC = 0.855) and luminal B (AUC = 0.812) subtypes. High sensitivity was also observed for the triple-negative subtype (AUC = 0.789) and the HER2-positive subtype (AUC = 0.755). These results confirmed the authors' hypothesis that radiomics can be used for non-invasive prediction of molecular subtypes of BC directly from mammographic images, which could reduce the need for biopsies and invasive procedures in the future [18].

The study by S. Montemezzi et al. is a successful example of using radiomic features to predict chemotherapy response in BC. Although the main focus of the study is radiomics, it is essential to note that radiomics plays an integral part in modern AI applications in medicine. Multivariate analysis methods and machine learning were used to process the extracted features, classifying the study within the scope of AI applications. The study investigated the potential of improving models to predict pathological complete response to NACT in BC patients using radiomic features extracted from MRI performed on a 3 Tesla scanner. The study included 60 patients, of whom 20 achieved complete response to NACT, and 40 did not. Geometric, first-order, and higher-order texture radiomic features were extracted from the pre-treatment contrast-enhanced MRIs, followed by feature selection. Five selected radiomic features were combined with other available data to build prediction models for complete response to NACT using three different classifiers: logistic regression, Support Vector Machine method, and random forest. All possible feature combinations were investigated. The AUC for predictors excluding radiomic features reached 0.89, while all three classifiers demonstrated AUCs above 0.90 when radiomic information was included (ranging from 0.91 to 0.98) [19].

In the study by M. Şep et al., the goal was to predict the hormonal status of BC (ER/PR) using radiomic features extracted from apparent diffusion coefficient maps obtained via MRI. The study considered data from 185 patients, supplemented by synthetic data from 25 patients using the Synthetic Minority Over-sampling Technique to balance classes, followed by division into training (n = 150) and testing (n = 60) cohorts. Manual tumor segmentation was performed over the entire volume, after which first-order radiomic features were extracted. The model based on these features demonstrated high diagnostic performance, with an AUC of 0.81 in the training cohort and 0.93 in the test cohort. When clinical and pathological data (Ki67% proliferation index and histological grade) were added, the combined model maintained a high AUC of 0.93. This model shows high potential for non-invasive

assessment of hormone receptor status in breast tumors, which may contribute to more accurate patient stratification and treatment personalization [20].

The study by C.C. Mireștean et al. focuses on the use of radiomics to characterize triple-negative breast cancer (TNBC), an aggressive subtype of BC with poor prognosis and high heterogeneity. Radiomics demonstrates the ability to differentiate TNBC from other tumor types based on features obtained through digital mammography and MRI. In particular, three TNBC subtypes were identified using voxel-level texture, shape, and size features. These subtypes showed a significant correlation with clinical response to NACT. The authors emphasize that standardizing radiomic methodologies is critical for their implementation in clinical practice. In the future, the study's results suggest the possibility of creating radiomic biomarkers and predictive models for a personalized approach to treating TNBC, which could improve outcomes and optimize therapeutic strategies [21].

A promising area of research is the use of contrast-enhanced mammography and radiomic microscopical analysis for the non-invasive characterization of breast tumors. M. Marino et al. conducted a study on the application of contrast-enhanced mammography combined with radiomic microscopical analysis for non-invasive assessment of tumor invasiveness, hormonal status, and malignancy grade in breast cancer. The retrospective study included 100 patients (103 tumor cases) who underwent contrast-enhanced mammography followed by radiomic microscopical analysis using the MaZda platform. The authors utilized various feature groups, including histograms, co-occurrence matrices, and run-length matrices. The model achieved the following accuracies: 87.4% in differentiating invasive and non-invasive tumors, 78.4% in determining hormonal receptor status, 97.2% in classifying HER2-positive and hormone-negative types, and 100% in differentiating TNBC and HER2+ hormone-positive tumors. Research Prospects: The high diagnostic value of the combined approach of contrast-enhanced mammography and radiomics has been demonstrated for non-invasive tumor stratification, which may significantly reduce the need for biopsies [22].

Discussion: AI technologies significantly enhance the diagnostic potential and contribute to the individualization of therapy for breast diseases. The obtained data align with global trends and confirm similar advancements in improving the accuracy of diagnostic procedures and the effectiveness of early detection programs for BC.

In international practice, particular attention is given to large-scale studies on the implementation of AI in screening processes. For example, the National Health Service (NHS) of the United Kingdom initiated the world's largest study on the use of AI for BC diagnosis, covering approximately 700,000 mammograms. The goal of this study is to evaluate the accuracy and reliability of AI compared to traditional analysis methods. Preliminary results show that AI can reduce the workload of Radiologists and accelerate the diagnostic process [23].

Similar results were obtained in Germany, where the use of AI in the screening program led to a 17.6% increase in the detection rate of BC cases without an increase in false-positive results. This confirms the potential of AI in improving the efficiency of diagnostic procedures and early disease detection [24].

The results of modern studies' analysis demonstrated the high promise of using AI in the diagnosis of breast pathologies. However, alongside the positive achievements, there are several limitations and challenges that hinder the widespread implementation of AI in clinical practice and require special attention for further development of AI technologies.

Limited effectiveness of AI in Digital Breast Tomosynthesis (DBT). AI has shown high accuracy in analyzing digital mammograms; however, its application in Digital Breast Tomosynthesis has been less successful. Studies have shown that AI performance in digital breast tomosynthesis is lower compared to traditional methods, which may be due to the limited availability of training data for this technology. A study published in the Korean Journal of Radiology in 2024 found that the use of AI in analyzing synthetic mammograms obtained through Digital Breast Tomosynthesis resulted in lower sensitivity compared to Full-Field Digital Mammography (FFDM). The sensitivity of the AI system when analyzing synthetic mammograms was 76.2%, whereas for Full-Field Digital Mammography it was 82.8%. The reduction in sensitivity was especially pronounced in cases with dense breast tissue and early cancer stages, such as T1 and Ductal Carcinoma In Situ (DCIS). The authors of the study emphasize that AI systems trained on FFDM data are not always effectively applicable to synthetic mammograms without additional adaptation or retraining. This is due to differences in image characteristics between these two imaging methods. Thus, the direct application of AI developed for FFDM to synthetic mammograms may lead to reduced diagnostic accuracy, particularly in cases with clinically significant findings. These findings highlight the need to develop and train AI models specifically designed to analyze synthetic mammograms, ensuring the high accuracy and reliability of diagnosis using Digital Breast Tomosynthesis [25].

Influence of Patient Characteristics on AI Accuracy. A study published in the journal Radiology found that patient characteristics such as race, age, and breast tissue density significantly influence the accuracy of AI algorithms used for BC screening. In particular, Black women had a 50% higher likelihood of false-positive results compared to White women. This indicator was also significantly higher in women with extremely dense breast tissue. Additionally, older women, especially those aged 61-70,

were more likely to receive false-positive results. These data underscore the need to include diverse data in training sets to reduce the risk of bias and improve the generalizability of AI algorithms [26].

Lack of superiority of AI over Radiologists in some studies. Despite the achievements of AI in the field of diagnostics, its performance does not always surpass that of experienced Radiologists. A study published in Radiology compared the effectiveness of an AI algorithm with the results of 552 Radiologists in interpreting mammograms. The results showed that AI reached a sensitivity level comparable to that of Radiologists but did not demonstrate significant superiority. This underscores that, despite AI's potential in BC diagnosis, its effectiveness may be limited compared to professional expertise. Therefore, AI should perhaps be considered a supportive tool rather than a replacement for the professional experience of Radiologists [27].

Lack of transparency and reproducibility in AI research. The study conducted by D. Bontempi et al. showed that many studies devoted to AI in medical imaging are characterized by insufficient transparency, lack of access to raw data and code, and a high risk of bias. This hampers the reproducibility of results and undermines trust in the conclusions of such studies. Thus, a systematic review published in Nature Communications noted that insufficient efforts to ensure reproducibility in AI research hinder the verification of claimed performance metrics, ultimately leading to overestimated accuracy and generalizability issues, which impede the clinical implementation of these systems [28].

Conclusion: The application of AI in mammography and MRI using radiomics demonstrates significant potential in improving the diagnosis and personalization of BC therapy. Modern algorithms enable the accurate detection of microcalcifications, the prediction of therapeutic response, and the development of personalized treatment plans. However, the future advancement of AI technologies requires data standardization, improved model interpretability, and adaptation to diverse populations.

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АҢДАТПА

ЖАСАНДЫ ИНТЕЛЛЕКТІНІ СҮТ БЕЗІ ПАТОЛОГИЯСЫН ДИАГНОСТИКАЛАУДА ҚОЛДАНУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сүт безі обырын уақытында диагностикалау денсаулық сақтау саласындағы басты міндеттердің бірі болып табылады, өйткені бұл ауру әлем бойынша әйелдер арасындағы өлім-жітімнің басты себебі болып қала береді. Жасанды интеллект (ЖИ) соңғы жылдары кеңінен қолданыла отырып, медициналық бейнелеудің ажырамас бөлігіне айналды. Маммография мен магнитті-резонанстық томография (МРТ) сияқты заманауи диагностикалық әдістер сүт безінің патологияларын анықтауда маңызды құралдар болып табылады, бірақ олардың шектеулері бар. Бұл әдебиет шолуы сүт безі обырын диагностикалауда ЖИ-ді қолданудың заманауи тәсілдерін сипаттайды.*

Зерттеудің мақсаты: *Сүт безі обырын диагностикалауда ЖИ-ді қолдану әдістеріне талдау жүргізу, соның ішінде болжау, нәтижелерді интерпретациялау және бейнелеу әдістерінің дәлдігін арттыру мүмкіндіктері.*

Әдістері: *PubMed, Medline, Cochrane Library және Google Scholar мәліметтер базаларында ғылыми жарияланымдарды іздеу жүргізілді. Шолу сүт безі ауруларын диагностикалауда ЖИ-ді қолдануға арналған мақалаларды қамтиды.*

Нәтижелері: *Шолу қондырмалы нейрондық желілер (CNN) сияқты ЖИ жүйелері маммограммалардағы микрокальцинаттарды жоғары дәлдікпен (94,5%-ға дейін) анықтауға және жалған оң нәтижелерді 11%-ға дейін төмендетуге мүмкіндік береді. МРТ кескіндерін талдауда CNN-RNN сияқты гибридті модельдерді қолдану қатерлі ісіктерді диагностикалаудың дәлдігін 15%-ға жақсартады және қателердің санын 20%-ға азайтады. Радиомика терапевтік жауапты болжауда жоғары дәлдікті 87%-дық көрсетеді, ал мультиомдық деректерді біріктіру сезімталдықты 92%-ға дейін қамтамасыз етеді.*

Қорытынды: *Сүт безін диагностикалауда ЖИ-ді қолдану бейнелеу әдістерінің дәлдігін арттырады, деректерді интерпретациялауды жеңілдетеді және терапияны жеке негізде жүргізуге мүмкіндік береді. Алайда, модельдерді оқыту үшін деректердің қолжетімділігі мен шешім қабылдаудың этикалық аспектілері сияқты қиындықтар әлі де бар.*

Түйінді сөздер: *сүт безі обыры, жасанды интеллект, маммография, МРТ, радиомика, болжам.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ ИСКУССТВЕННОГО ИНТЕЛЛЕКТА В ДИАГНОСТИКЕ ПАТОЛОГИИ МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Своевременная диагностика рака молочной железы является одной из ключевых задач здравоохранения, так как это заболевание остаётся ведущей причиной смертности женщин во всём мире. В последние годы технологии искусственного*

интеллекта (ИИ) прочно вошли в сферу медицинской визуализации, получив широкое распространение в клинической практике. Основные методы диагностики, включая маммографию и магнитно-резонансную томографию (МРТ), играют ведущую роль в обнаружении заболеваний молочной железы, однако имеют ряд ограничений. Настоящий обзор посвящён анализу современных возможностей применения ИИ для повышения эффективности диагностики рака молочной железы.

***Цель исследования** – проанализировать методы применения искусственного интеллекта в диагностике рака молочной железы, включая возможности прогнозирования, интерпретации результатов и повышения точности методов визуализации.*

***Методы:** Проведён поиск научных публикаций в базах данных PubMed, Medline, Cochrane Library и Google Scholar. В обзор включены статьи, посвящённые применению ИИ в диагностике заболеваний молочной железы.*

***Результаты:** Обзор показал, что системы ИИ, такие как свёрточные нейронные сети, позволяют с высокой точностью (до 94,5%) обнаружить микрокальцинаты на маммограммах и снижать количество ложноположительных результатов на 11%. МРТ в оценке прогнозирования ответа на неоадъювантную химиотерапию демонстрирует наибольшую чувствительность (80,0-83,3%) при выявлении остаточной опухоли, тогда как нейросетевые методы показали сопоставимые результаты (69,2-72,0%), превосходя при этом традиционную маммографию и ультразвуковое исследование. Радиомика демонстрирует высокую точность (87%) в прогнозировании терапевтического ответа, а интеграция мультиомных данных обеспечивает чувствительность до 92%.*

***Заключение:** Применение ИИ в диагностике молочной железы повышает точность методов визуализации, облегчает интерпретацию данных и способствует персонализации терапии. Однако остаются вызовы, такие как доступность данных для обучения моделей и этические аспекты принятия решения.*

***Ключевые слова:** рак молочной железы (РМЖ), искусственный интеллект (ИИ), маммография, магнитно-резонансная томография (МРТ), радиомика, прогнозирование.*

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RAMAN SPECTROSCOPY IN ONCOLOGY FOR PREDICTING MALIGNANT DISEASES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *This literature review examines scientific publications on the efficacy of optical spectroscopy methods, including Raman spectroscopy (RS), for the early diagnosis of tumors in oncology.*

The study aimed to *summarize the existing data, analyze their effectiveness in studying cancer located in different organs through Raman spectroscopy, and assess their diagnostic potential in oncology.*

Methods: *The literature search covered publications from 2015 to May 2025 using keyword-based database queries. After removing duplicates, articles were screened via abstracts and full texts. The research team reviewed all selected papers. All authors agreed upon a final list of 22 articles, with relevant data synthesized into this review.*

Results: *Optical spectroscopy (OS) has proven to be an effective tool for diagnosing, monitoring, and predicting malignant tumors in experimental and clinical studies. Over the past 20 years, RS has demonstrated 90% accuracy and specificity in early cancer detection and advantages in bioavailability, speed, clarity, and multiplex analysis-key factors driving its growing interest in biological research. However, foreign and domestic literature analysis revealed a lack of standardized protocols for RS in cancer diagnostics, highlighting the need for optimized, systematic guidelines.*

While promising, RS remains underexplored and requires further research to translate findings into routine clinical practice.

Conclusion: *Recent advancements in optical spectroscopy, particularly Raman methods, contribute to deeper cellular-level insights into oncological mechanisms and improve predictive diagnostics.*

Keywords: *oncology, malignant tumors, optical spectroscopy, predictive diagnostics, Raman spectroscopy, infrared spectroscopy.*

Introduction: Spectroscopy is a vibrational research method that combines various complementary methods.

Optical spectroscopy, including RS (RS), surface-enhanced RS (SERS), diffuse optical tomography, infrared spectroscopy, fluorescence spectroscopy, magnetic resonance spectroscopy, and electrical impedance spectroscopy, is a modern and optimal method for non-invasive diagnostics of oncological diseases.

Currently, cancer remains one of the leading causes of death and morbidity in the world [1].

Cancer has been one of the most important health problems worldwide for many years. This disease is associated with a disruption of cell growth and division regulation, leading to the uncontrolled proliferation of cells and the formation of tumors. In addition, tumors are characterized by heterogeneity, since they consist of different types of cells and extracellular components, which complicates their treatment. Another important feature is metastasis, i.e., the spread of cancer cells throughout the body via the blood or lymphatic system, resulting in the formation of secondary tumors in other organs [2].

Raman Spectroscopy as a Research Tool in Medicine: Among the optical spectroscopy methods, RS is one of the most well-known in medical research. This method is based on the Raman effect, discovered in 1928 by C. V. Raman and K. S. Krishnan. RS is a new method for studying biological tissues such as tumors [3, 4].

As a non-invasive, real-time, in vivo tool, RS ensures high specificity, sensitivity, and multiplexing capabilities, providing high spatial and temporal resolution to characterize the molecular basis of cancer [5].

Analysis of the correlation between the intensity of vibrational light scattering and frequency enables the identification of unique spectral structures associated with different samples. It is based on inelastic scattering of photons, known as vibrational conjugate scattering. Spectra of nucleic acids, proteins, lipids, and carbohydrates with Raman functional groups can be used to assess the metabolic state of various cells and tissues, each with its unique composition [6]. Monitoring the intensity of inelastic light scattering as a function of frequency enables the acquisition of a unique spectroscopic signature for a tissue sample [7].

The study aimed to summarize the existing data, analyze their effectiveness in studying cancer located in different organs through Raman spectroscopy, and assess their diagnostic potential in oncology.

Materials and methods: A literature review was conducted using keywords to search and select articles in databases for the period from 2015 to May 2025. After removing duplicates, articles were selected by reviewing their abstracts and full texts. The research team's authors reviewed all articles. The final list of selected articles was compiled after obtaining consent from all authors. Of these, 20 articles were selected; the relevant available data were analyzed and summarized in a review article.

Results:

Raman Spectroscopy in Oncology: New approaches to understanding disease pathogenesis may lead to the discovery of biological markers that will allow better monitoring of disease progression and improve prognosis. RS is a research and diagnostic tool that helps uncover the molecular basis of diseases and provides objective, quantitative molecular information for diagnosis and treatment evaluation. G.W. Auner and co-authors reviewed the use of RS for the detection of brain, ovarian, breast, prostate, and pancreatic cancer, as well as circulating tumor cells [8]. Domestic authors have described the use of electrical impedance spectroscopy for the early detection of skin malignant melanoma, specifically by analyzing electrical conductivity and impedance waves in the damaged layer of the skin compared to the healthy layer [9].

Raman Spectroscopy in Neuro-Oncology: The primary task during surgery is to distinguish between tumor and healthy tissue, as well as to identify tumor cells that have infiltrated beyond a clear pathological border. Determining the residual tumor load is of great importance, as complete resection is a favorable prognostic factor. In an experimental study by Marco Riva and co-authors, single-point RS was performed on biopsy samples of healthy and tumor-affected tissue from 63 patients with stage II-IV gliomas, as classified by the World Health Organization (WHO), who underwent surgery using neuronavigation. Raman spectral analysis of the active functional groups of nucleic acids, proteins, and lipids enabled a detailed characterization of biopsies from neoplastic and normal brain tissue. Averaged Raman spectra showed differences in molecular signatures between neoplastic and normal samples. A literature review of Raman scattering revealed 137 peak types, of which 60 peaks are known to have high specificity, and 19 new peaks useful for differentiating glioma from healthy tissue were identified. Analysis of these new bands may contribute to the further development of real-time tissue analysis, improving the accuracy and efficiency of neurosurgical interventions. This study makes a significant contribution to the application of this technology in oncological brain surgery [5].

Additionally, a domestic literature review describes the regulation of 2-hydroxyglutarate (2-HG) during tumor tissue division at the cellular level using magnetic resonance spectroscopy, a non-invasive method for diagnosing gliomas of the central nervous system [10].

Raman Spectroscopy in Hematology and Oncohematology: Diagnostics and treatment of hematological and oncological diseases are currently possible only through a combination of scientific advances and methods. For example, rapid detection of acute leukemia is essential for accurate and timely clinical decisions. The success of immunotherapy in hematological malignancies has created new diagnostic challenges, including the need to assess the immune status. In addition, despite the recent introduction of high-throughput genetics, which has revolutionized this field, many challenges remain to be addressed. Therefore, the development of new technologies that can overcome barriers such as inaccessibility, lengthy diagnostic times, and the need for highly trained personnel remains relevant.

Medical applications of mass spectrometry (MS), a molecular spectroscopy technique that provides detailed information on the chemical structure, phase, crystallinity, and molecular interactions of a sample, have been studied for several decades. Due to the rapid assessment of the metabolic state of cells in vivo, MS is of particular interest in hematology and oncology. The study of normal hematopoietic stem/progenitor cells and their progeny is associated with several challenges, including limited sample availability and difficulties in preserving their original state and functions. Due to the complex behavior of these cell populations, functional assays that measure cellular activity are often necessary for a comprehensive evaluation of hematopoietic cells. In addition, single-cell resolution and label-free protocols, another key feature of PCa hematology, provide important insights into the heterogeneity of stem and mature cell populations, as well as for assessing the developmental stages and activation status of cells [11].

Raman Spectroscopy in Cartilage Cancer: A study by F. Niccoli et al. in 10 patients with chondrosarcoma, a common primary bone tumor, demonstrated that it is challenging to distinguish between benign tumors (enchondroma) and chondrosarcoma grade 1 (CS1), as these two tissue types share common biochemical components. However, unlike standard procedures, the use of machine learning (ML) methods for multivariate analysis can enhance the classification of enchondroma in the form of CS1. This article presents the results of the best methods for improving multivariate analysis using ML algorithms. To differentiate the RS signals, two main methods were employed to distinguish between tissues, cells, and the extracellular matrix (ECM): principal component analysis (PCA) and linear discriminant analysis (LDA). PCA (an unsupervised method) includes projecting features onto a hyperplane that contains most of the variance (approxi-

mately 95%) of the data and its orthogonal complement. LDA (supervised method) is used to find a subspace of features that optimizes the separation of the analyzed cartilage tissues. For this purpose, the supervised method based on PCA+LDA algorithms is highly scalable and can be applied not only to large data sets, but also to cancer tissue of any type [12].

Raman Spectroscopy in Colon Cancer: About 30% of colorectal cancer (CRC) cases are caused by mutations in inherited genes. Approximately 15% are caused by malfunctioning repair genes, while another 80–85% are caused by mutations in the adenomatous polyposis coli (APC) gene. CRC can also develop as a result of inflammatory bowel disease.

Uncontrolled cell growth, a hallmark of cancer development, requires a continuous supply of nutrients. Carbohydrates and fats play an important role in tumor growth. Changes in lipid metabolism are a primary factor in the development of various diseases, including cancer. Therefore, this class of compounds is of increasing interest in clinical trials as biological markers to determine the role of lipidomics in cancer research. Among them (FA) - saturated (palmitic acid (PA, 16:0)), unsaturated (linoleic acid (LA, 18:2), eicosapentaenoic acid (EPA, 20:5)), and their potential in the diagnosis and treatment of colorectal cancer has been identified.

Evidence of lipid reprogramming in cancer cells was first described in the 1920s as the Warburg effect [13]. However, there is now a widespread trend towards the opposite of the Warburg effect: researchers have discovered that different types of cancer cells have unique metabolic characteristics, and some can synthesize adenosine triphosphate via oxidative phosphorylation [14].

In general, lipids can be characterized as a diverse group of compounds using LIPID MAPS [15]. K. Beton-Maysur et al. analyzed PA, LA, and EPA acids in normal (CD-18 Co) and malignant (Caco-2) human colon cells using Raman imaging and spectroscopy [14]. In addition, excessive intake of saturated fatty acids (SFAs), including PA, may increase the risk of obesity and digestive disorders. Many research groups have also proven a correlation between excessive PA intake and cancer development. Lipid analysis showed that PA may affect the aggressiveness of cancer cells [16].

This study demonstrated the possibility of visualizing the internal structures of individual cells (endoplasmic reticulum, mitochondria, lipid droplets, and nucleus) and analyzing fatty acid metabolism using Raman microscopy and cluster analysis. The distribution and metabolism of fatty acids in different cellular compartments were monitored by spectroscopic analysis of the intensity ratios of characteristic bands (I1656/I1444, I1444/I1256, I1444/I750 and I1304/I1256). The results showed LA to be the most effective membrane penetrator, having a significant impact on cell viability. Specifically, LA inhibits the growth of Caco-2 cancer cells while stimulating the proliferation of normal CCD-18 Co cells. PA, on the contrary, exhibits the opposite effect. The obtained data confirm the effectiveness of using Raman imaging to study the molecular mechanisms of colon carcinogenesis and to assess the effect of various fatty acids on cell metabolism [16].

Raman Spectroscopy in Lung Cancer: Lung cancer is the leading cause of cancer death worldwide. Due to its high mortality rate, the development of effective non-invasive diagnostic methods for this disease remains an urgent problem. Traditional diagnostic methods (computed tomography, sputum cytology, biopsy, and bronchoscopy) are often insufficient for early detection of the disease, as they are expensive, time-consuming, and may have insufficient sensitivity. On the other hand, these methods are less invasive and more convenient for the patient, without compromising the diagnostic accuracy. Vibrational spectroscopy, particularly Raman and Fourier transform infrared spectroscopy (FTIR), has been developed, enabling the detection of molecular-level changes with high sensitivity. These methods are non-invasive, non-destructive, do not require reagents, and leave no residues, providing detailed information on the composition and structural conformation of specific molecules [17–19]. FTIR spectroscopy measures the absorption of infrared light by a sample, revealing information about molecular vibrations, chemical bonds, and functional groups. On the other hand, RS measures the inelastic scattering effect and provides additional information about the molecular structure of a biological sample [20].

For RS, 1 µL of plasma from each individual was pipetted onto an aluminum foil attached to a glass slide and air-dried for 5 minutes. Aluminum foil was chosen due to its advantages, including high reflectivity, stability, flexibility, low background noise, and low cost. This makes it the most suitable base material for enhancing the Raman effect. FTIR spectroscopy was performed by attenuated total reflection (ATR) using a special crystal in direct contact with the sample [21].

In the study by H. Hano et al., 36 participants were recruited, including 18 patients with non-small cell lung cancer and 18 healthy participants. The information was obtained by combining Raman and FT-IR measurements in a single spectroscopic instrument. This instrument combines the two methods, enabling simultaneous measurements of a sample using two spectroscopic methods in a single location. Data fusion strategies can be divided into three types: low-level, mid-level, and high-level fusion. In low-level data fusion (LLDF), matrices from multiple data sources are directly combined to create a comprehensive dataset covering the full range of measured variables. Mid-level data fusion (MLDF) ad-

dresses the problem of high dimensionality. This method reduces data complexity by selecting or pruning features prior to data fusion, thereby preserving important information and enhancing model training efficiency. High-level data fusion (HLDF) combines the predicted results of models created for each data source, leveraging the strengths of each model to enhance the accuracy of predictions. In this study, the peak at 624 cm-1 in RS indicates C-C bond bending in phenylalanine and lipids. The peak at 966 cm-1 corresponds to the deformation of the CH3 group in the amino acids' tryptophan, valine, and proline. Of particular importance is the peak at 1125 cm-1, which indicates the stretching of the CC, CO, and CN bonds in lipids, glycogen, and proteins. The peak observed at 1587 cm-1 corresponds to the stretching of the C=C bond in tryptophan, while the amide I bands between 1632 and 1668 cm-1 correspond to changes in the secondary structure of the protein (α-helix and β-sheets) [22].

In FTIR spectroscopy, the vibration bands at 1055-1070 cm^{-1} indicate symmetric vibration of the PO^{-2} group in phospholipids, and the intense absorption band at 1699 cm^{-1} indicates stretching of the C=O bond in the amide I group.

These spectral markers enable the detection of changes in proteins and lipids at the molecular level in the diagnosis of lung cancer. Amide I bands indicate changes in protein structure, while phosphate and carbonyl group vibrations serve as important biological markers in the diagnosis of cancer. This study demonstrates the potential of Raman and FTIR spectroscopy in detecting malignant lung tumors using modern data fusion techniques [22].

Conclusion: According to the literature review, RS is one of the most widely used and proven methods in various fields of oncology.

Furthermore, numerous experimental studies have convincingly demonstrated the effectiveness of this method in characterizing biological tissues. However, to successfully transfer this technology into clinical practice, it is necessary to address several key challenges, including the creation of a comprehensive spectral database and the development of robust tissue classification methods that are thoroughly tested for compliance with established diagnostic standards. Solving methodological problems will enable RS to fully realize its potential and transition from the realm of research to everyday clinical practice, as well as establish a worthy place among modern diagnostic tools.

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АҢДАТПА

ҚАТЕРЛІ АУРУЛАРДЫҢ БОЛЖАУШЫЛАРЫН АНЫҚТАУ ҮШІН ОНКОЛОГИЯДАҒЫ РАМАН СПЕКТРОСКОПИЯСЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Мақалада онкологиядағы ісіктерді ерте диагностикалау үшін оптикалық спектроскопия әдістері соның ішінде Раман спектроскопиясы (РС) тиімділігі бойынша ғылыми жарияланымдарға әдеби шолу берілген.*

Зерттеу мақсаты *– бұл әдебиеттік шолу бар деректерді жинақтау, Раман спектроскопиясы арқылы әртүрлі мүшеде орналасқан қатерлі ісікті зерттеуде тиімділігін талдау және олардың онкологиядағы диагностикалық әлеуетін бағалау болып табылады.*

Әсілдері: *Әдеби шолу 2015 жылдан бастап 2025 жылдың мамыр айына дейінгі кезеңге арналған дерекқорлардағы мақалаларды іздеу және таңдау түйінді сөздерді қолдану арқылы жүзеге асырылды. Көшірмелерді жойғаннан кейін мақалалар олармен байланысты аннотациялар мен толық мәтіндерді қарау арқылы тексерілді. Барлық мақалалар зерттеу тобының авторларымен тексеріліп. Іріктеу жасалған мақалалардың соңғы тізімі барлық авторлармен келісілгенге дейін жүргізіліп, 22 мақала іріктеліп алынды, қолда бар тиісті деректер сарапталып, шолу мақаласы түрінде жинақталды.*

Нәтижелері: *Онкологияда оптикалық спектроскопия (ОС) қатерлі ісіктерді диагностикалау, бақылау және болжау үшін тәжірбиеде және клиникалық зерттеулерде тиімді құрал болып табылатынын көруге болады. Эксперименталды зерттеулердің нәтижелерінде көретін болсақ соңғы 20 жылда РС әдістер қатерлі ісіктердің ерте диагностикасында 90% дәлдігі және арнайылығын көрсетті, сонымен қатар биологиялық жетімділікте қолжетімділігімен тиімді, яғни спектроскопияға қызығушылықтың артуының оның биологиялық материалды зерттеуде жылдамдылығы, нәтиженің айқындылығы мен мультикомплексті болуы себеп болып табылады. Шетелдік және отандық әдебиеттерді талдауда қолданылған Раман спектроскопиясын онкологиялық ауруларды диагностикалауда бірыңғай әдістемелер туралы егжей-тегжейлі техникалық деректер жоқ екенін көрсетті, бұл пайдалануды реттейтін хаттамаларды жүйелі оңтайландыру қажеттілігін көрсетеді.*

РС әлі де жақсы түсінілмеген және кеңірек зерттеу қажет ететін және алынған нәтижелерді күнделікті тәжірибеге енгізуде ықпалы зор зерттеу әдістері болып табылады.

Қорытынды: *РС соңғы жылдары ОС-да әдістерінің медицина саласында дамуы онкологиялық аурулардың пайда болу механизмінің жасушалық деңгейде терең зерттеуге және оның болжаушыларын анықтауға көмектеседі.*

Түйін сөздер: *онкология, қатерлі ісіктер, оптикалық спектроскопия, болжаушылар, Раман спектроскопиясы, инфрақызыл спектроскопиясы.*

АННОТАЦИЯ

РАМАНОВСКАЯ СПЕКТРОСКОПИЯ В ОНКОЛОГИИ ДЛЯ ВЫЯВЛЕНИЯ ПРЕДИКТОРОВ ЗЛОКАЧЕСТВЕННЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *В статье представлен обзор научных публикаций, посвященных эффективности методов оптической спектроскопии, включая Рамановскую спектроскопию (РС), для ранней диагностики опухолей в онкологии.*

Цель исследования *– представляет собой сбор существующих данных, анализ эффективности исследования злокачественных новообразований, расположенных в различных органах, с помощью Рамановской спектроскопии, и оценку её диагностического потенциала в онкологии.*

Методы: *Поиск литературы проводился по публикациям с 2015 года по май 2025 года по ключевым словам в базах данных. После исключения дубликатов статьи отбирались на основе анализа аннотаций и полных текстов. Все публикации были проверены авторами исследования. Окончательный список из 22 статей был согласован всеми авторами, после чего соответствующие данные были проанализированы и систематизированы в виде обзора.*

Результаты: *Оптическая спектроскопия (ОС) является эффективным инструментом для диагностики, мониторинга и прогнозирования злокачественных опухолей как в экспериментальных, так и в клинических исследованиях. Результаты экспериментальных работ показали, что за последние 20 лет РС продемонстрировала 90% точность и специфичность в ранней диагностике рака, а также преимущества в биодоступности, скорости, четкости и мультиплексном анализе, что обуславливает растущий интерес к этому методу в биологических исследованиях. Однако анализ зарубежной и отечественной литературы выявил отсутствие единых стандартизированных методик применения РС в диагностике онкологических заболеваний, что подчеркивает необходимость разработки оптимизированных систематических протоколов.*

Несмотря на перспективность, РС остается недостаточно изученной и требует дальнейших исследований для внедрения полученных результатов в клиническую практику.

Заключение: *Современные достижения в области оптической спектроскопии, в частности Рамановских методов, способствуют углубленному изучению механизмов возникновения онкологических заболеваний на клеточном уровне и совершенствованию их предиктивной диагностики.*

Ключевые слова: *онкология, злокачественные опухоли, оптическая спектроскопия, предиктивная диагностика, Рамановская спектроскопия, инфракрасная спектроскопия.*

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COMPARATIVE EFFECTIVENESS OF LOBECTOMY AND SUBLOBAR RESECTIONS IN EARLY-STAGE NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Relevance: *Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality despite significant advances in diagnostic and therapeutic approaches. Anatomical lobectomy is traditionally considered the "gold standard" for stage I NSCLC, but the increasing detection of small-sized tumors through screening programs has renewed interest in sublobar resections.*

The study aimed to *compare the efficacy and safety of lobectomy versus sublobar resec-tions (segmentectomy and wedge resection) in patients with early-stage non-small cell lung cancer.*

Methods: *The meta-analysis was conducted following the PRISMA and AMSTAR guidelines. Literature was searched across PubMed, Embase, Cochrane Library, Scopus, Web of Science, and other databases for studies published between 2010 and 2024. Eligible studies included adult patients with stage I NSCLC undergoing either lobectomy or sublobar resection, with reported oncological or perioperative outcomes. Statistical analysis was performed using RevMan 5.4. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated; heterogeneity was assessed using the I^2 statistic.*

Results: *Twelve studies comprising 17,454 patients were included; 13,692 underwent lobectomy, and 3,762 received sublobar resection. No statistically significant difference in recurrence rates was found (RR=0.92; 95% CI: 0.65-1.31; p=0.66), although heterogeneity was substantial (I^2=87%). The risk of postoperative complications was significantly higher after lobectomy (RR=1.22; 95% CI: 1.08-1.37; p<0.01; I^2=0%). Five-year overall survival favored lobectomy (RR=1.08; 95% CI: 1.00-1.17; p=0.05), with high heterogeneity (I^2=91%).*

Conclusion: *Sublobar resections demonstrate comparable oncological outcomes to lobec-tomy in selected patients with tumors ≤2 cm, no signs of invasion, and reduced physiological reserve. These findings support the importance of an individualized surgical approach. Further multicenter randomized trials are warranted to confirm oncological equivalence and define clinical indications.*

Keywords: *non-small cell lung cancer (NSCLC), lobectomy, sublobar resection, segmentectomy, survival, recurrence-free survival, recurrence.*

Introduction: Lung cancer (LC) continues to be one of the leading causes of mortality from malignant neoplasms (malignant neoplasms) globally, despite significant progress in cancer diagnostics and treatment. According to GLOBOCAN data 2020, the total number of new cases of malignant neoplasms among women was 9,227,484, followed by colorectal cancer (865,630; 9.4%) and LC (770,828; 8.4%). Over the same period, 10,065,305 new cases of malignant neoplasms were registered in men, among which LC took the 1st place – 1,435,943 cases (14.3%), followed by prostate cancer (1,414,259; 14.1%) and colorectal cancer (1,065,960; 10.6%) [1].

In terms of cancer mortality, LC also occupies a leading position, causing about 1.8 million deaths, which comprises 18% of all deaths due to malignant neoplasms [1].

In Kazakhstan, according to D. Yessenbayev et al. (2023), 36,916 new cases of LC were registered over a ten-year period, of which 80.5% were recorded in men and 19.5% in women. The mean age of the cases was 64.2 ± 0.1 years. The highest incidence rates per 100,000 population were observed in the age groups of 65-69 years (147.6 ± 2.7), 70-74 years (159.3 ± 2.5), and 75-79 years (147.1 ± 3.2). The annual standardized average amounted to 22.2 cases per 100,000 population. At the same time, there is a trend towards a decline in incidence, especially among the male population, where the incidence rate is six times higher than in women [2].

As of today, surgery remains the main treatment option for non-small cell lung cancer (NSCLC). Anatomical lobectomy with systemic lymphatic dissection is traditionally considered the "gold standard" of the surgical approach, providing high rates of overall and recurrence-free survival. However, with the development of screening programs and the increase in the number of

small tumors (<2 cm) detected, approaches to the volume of resection are increasingly being revised [3, 4].

Although lobectomy remains an oncologically reliable method, sublobar resections – segmentectomy and wedge resection (wedge) – show comparable results in older patients with limited lung function and high levels of comorbidity. Due to their organ-preserving nature, such interventions become preferable in this category of patients [3].

According to the results of the analysis of data from 43,469 patients, the rate of postoperative complications in lobectomy reached 48%, while in sublobar resections it was 46.6%. Elevated rates were associated with severe baseline conditions, age, and comorbidities. In most studies, the complication rate for sublobar resections did not exceed 15.3%. The higher burden on the cardiovascular system during lobectomy explains the higher incidence of complications [5].

Regarding recurrences, the preference is given to lobectomy, with a risk of 32% compared to 53.4% with sublobar interventions. This is due to the greater radicality of the operation and the possibility of a full assessment of the lymph nodes, especially the 11th zone. If the tumor has spread, limited resections are associated with a higher risk of recurrence (42.6%, versus 12.7% after lobectomy) [6, 7].

In terms of overall survival, the 5-year rates after anatomical segmentectomy range from 43.8% to 49.9%, while after lobectomy they reach 78.4%. Sublobar interventions yield the best results in patients with lepidic-type tumors measuring less than 2 cm in diameter, detected at an early stage [5, 8, 9].

Thus, in modern conditions, revising surgical strategies for early NSCLC becomes extremely relevant. The present study aims to conduct a systematic review and meta-analysis to compare the efficacy and safety of lobectomy and sublobar resection in patients with early-stage NSCLC.

The study aimed to compare the efficacy and safety of lobectomy and sublobar resections (segmentectomy and wedge resection) in patients with early-stage non-small cell lung cancer.

Materials and methods: This study was conducted following the PRISMA and AMSTAR guidelines (Figure 1).

A systematic literature search was conducted in the international databases PubMed, Embase, Cochrane Library, Scopus, Web of Science, MedLine, as well as the Google Scholar search engine (the first 300 relevant results). In addition, to expand coverage, the clinical trial registration platform ClinicalTrials.gov was analysed, and references in previously published systematic reviews and meta-analyses were manually searched. All found articles were imported into EndNote X9 to remove duplicates.

The search period covered publications from January 1, 2014, to December 31, 2024. Articles in English and Russian were included. The following keywords and MeSH terms were used in various combinations: "non-small cell lung cancer", "NSCLC", "early-stage lung cancer", "lobectomy", "segmentectomy", "wedge resection", "sublobar resection", "surgical treatment", "meta-analysis", "survival", "recurrence", "postoperative complications".

Criteria for inclusion in the systematic review: adult patients with histologically confirmed early-stage NSCLC (stage I, T1–T2N0M0); anatomical lobectomy surgery; presence of a comparison group including patients undergoing segmentectomy or wedge resection; indication of at least one of the following outcomes: overall survival, recurrence-free survival, rate of recurrence or postoperative complications; study type – randomized controlled trials (RCTs), cohort studies, as well as retrospective comparative studies.

Publications that did not contain a direct comparison between lobectomy and sublobar resections, did not describe clinically significant outcomes, and reviews, case reports, experimental animal studies, duplicate publications, or sources with overlapping data have been *excluded*.

Data on patient characteristics, type of surgery, tumor size, presence of lymphatic dissection, clinical outcomes, and duration of follow-up were extracted from each included article. The comparability of the study groups was assessed by age, gender, resection volume, and concomitant diseases.

Meta-analyses were performed using RevMan 5.4 software (Cochrane Collaboration, London, UK). For binary variables, odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed using the I^2 score; studies with an I^2 value greater than 50% were analyzed using the random effects model. Statistical significance was determined at the p level < 0.05. The results were visualized using forest plots, and the presence of publication bias was estimated using funnel plots.

Results: The final meta-analysis included 12 studies published between 2014 and 2023, with a total of 17,454 participants. Of these, 13,692 patients (78.44%) underwent lobectomy (group L) and 3,762 patients (21.56%) underwent sublobar resection (SR groups), including segmentectomy and wedge resection. The analysis included studies with different designs: two RCTs [11, 19], two cohort studies [18, 21], and eight retrospective comparative studies (Table 1).

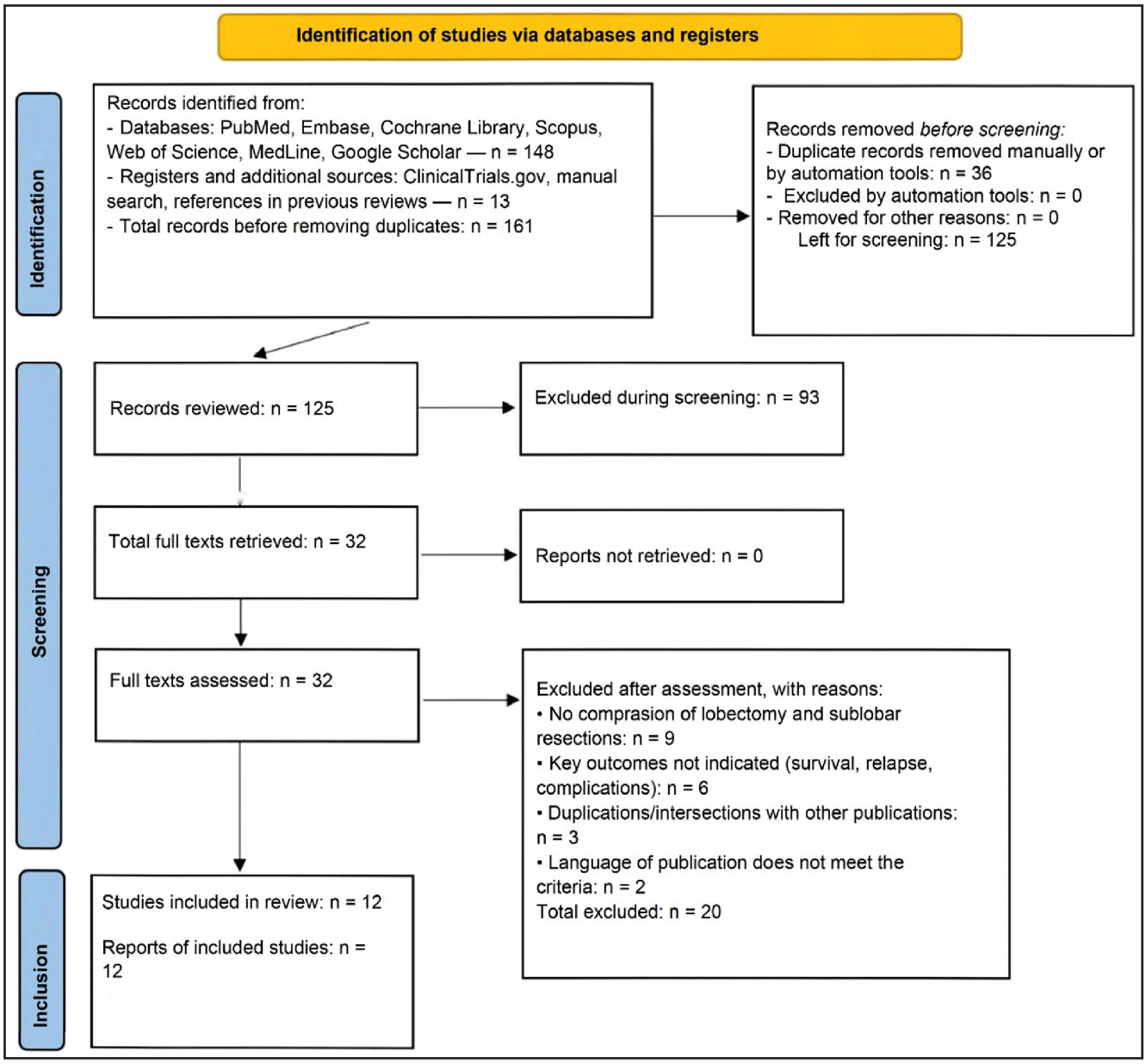

Figure 1 – Selection process for publications for systematic review and meta-analysis [10]

The mean age of patients in the L groups ranged from 59.8 to 77.9 years, while in the SR groups, it ranged from 59.7 to 79.2 years. However, in most studies, the average age in the SR group was slightly higher. The gender composition showed heterogeneity: in the L group, the proportion of men ranged from 41.2% to 86.4%, while in the SR group, women predominated in several studies, for instance, 59% [13], 63.3% [14], and 71.3% [18].

The duration of follow-up ranged from 30.3 to 109 months. The longest follow-up period was reported in the study by N. Altorki et al., which spanned over 84 months. [11], K. Kodama et al. – 87 months. [19], W. Nishio et al. – 109 months [20]. In the studies of A. Fiorelli et al. [13], A.V. Levitsky et al. [15], and R. Perez Holguin et al. [18] provided information on the timing of observation that was either absent or limited.

The average tumor size ranged from 1.42 to 2.29 cm in the L group and from 1.4 to 2.02 cm in the SR group. The average values for all studies were 9.4% and 7.5%, respectively.

Recurrence rates ranged from 0% to 29.3% in the L group and from 0% to 39% in the SR group, with a trend towards higher recurrence rates in the sublobar resection group in most publications.

The 30-day postoperative mortality rate in all studies was low, ranging from 0% to 1.6%, with no statistically significant differences between the interventions.

The five-year recurrence-free survival rates in the L group ranged from 60% to 91.5%, while in the SR group, they ranged from 36% to 92.7%. Five-year overall survival was higher in the lobectomy group (60.5% to 94.1%) compared with the sublobar resection group (45% to 95.7%), with an advantage of lobectomy in most studies.

Table 1 – Characteristics of the studies included in the meta-analysis comparing sublobar resection and lobectomy in patients with NSCLC

Authors	Study design	Follow-up (median), months.	Number of patients, abs.		Age, years		Gender (male/female), abs. (%)		Tumor size, cm		Complications after surgery, %		Recurrence rate, abs. (%)		Mortality on day 30, %		Five-year disease-free survival, %		Five-year overall survival, %	
			L	SR	L	SR	L	SR	L	SR	L	SR	L	SR	L	SR	L	SR	L	SR
Altorki N. (2023) [11]	РКИ	>84	357	340	67.6±13.0	68.3±11.4	147 (41.2%)/ 210 (58.8%)	150 (44.1%)/ 190 (55.9%)	н/д	н/д	13.5	8.17	103 (29.3%)	102 (30.4%)	1.1	0.6	63.6	64.1	80.3	78.9
Dziedzic R. (2017) [12]	Ретро.	36.9	5911	761	62.7±9.0	67.0±8.8	3444 (58.3%) /2467 (41.7%)	468 (61.5%)/ 293 (38.5%)	2.12±0.73	2.02±0.74	7.85	5.6	568 (9.6%)	93 (12.2%)	1.6	1.4	н/д	н/д	79.1	78.3
Fiorelli A. (2016) [13]	Ретро.	н/д	149	90	77.9ұ2.6	79.2±3.1	107 (72%)/ 42 (28%)	37 (41%)/ 53 (59%)	н/д	н/д	17	7	29 (19%)	21 (23%)	н/д	н/д	60	36	60.5	45
Mynard N. (2022) [14]	Ретро.	30.3	1916	275	65.6±9.5	67.6±9.6	805 (42.0%)/ 1111 (58.0%)	101 (36.7%)/ 174 (63.3%)	1.42±0.4	1.55±0.34	9.13	10.8	315 (16.4%)	63 (22.9%)	1.0	1.0	н/д	н/д	54	46
Левицкий А.В. (2021) [15]	Ретро.	н/д	78	38	60.6±8.5	59.7±8.5	61 (78.2%)/ 17 (21.8%)	27 (71.1%)/ 11 (28.9%)	1.95±0.49	1.82±0.37	3.56	2.4	0 (0%)	1 (2.6%)	0	0	85.2	76.2	82.0	74.8
Subramanian M. (2018) [16]	Ретро.	60	1354	333	66.3±10.0	69.6±9.6	579 (42.8%)/ 775 (57.2%)	158 (47.4%)/ 175 (52.6%)	2.0±0.7	1.7±0.6	8.9	7.4	0 (0%)	130 (39%)	н/д	н/д	н/д	н/д	61.8	55.6
Yaldız D. (2020) [17]	Ретро.	53.9	257	12	59.8±9.9	60.6±10.3	222 (86.4%)/ 35 (13.2%)	8 (66.7%)/ 4 (33.3%)	2.2±0.8	1.8±0.6	6.3	4.8	18 (7%)	0%	1.3	0.9	н/д	н/д	73.3	62.5
Perez Holguin R.A. (2023) [18]	Ког.	36.7	306	401	н/д	н/д	101 (33%)/ 205 (67%)	115 (28.7%)/ 286 (71.3%)	н/д	н/д	13.5	9.5	33 (10.8%)	25 (6.23%)	0.3	0.2	н/д	н/д	88.9	85.1
Kodama K. (2015) [19]	РКИ	87	69	69	62.1±9.52	62.6ұ7.81	32 (46.4%)/ 37 (53.6%)	33 (47.8%)/ 36 (52.2)	2.29±0.52	1.67±0.5	5.3	4.72	17 (24.6%)	3 (4.3%)	0	0	86.9	92.7	94.1	95.7
Nishio W. (2016) [20]	Ретро.	109	59	59	61±13.5	64ұ13	38 (64.4%)/ 21 (35.6%)	38 (64.4%)/ 21 (35.6%)	1.7±3.0	1.7±0.4	11.2	10.3	12 (19.5%)	5.6% (3.3%)	н/д	н/д	91.5	76.3	93.0	86.4
Okada M. (2014) [21]	Ретро.	34.2	479	155	66±14.8	66ұ14.5	223 (46.6%)/ 256 (53.4%)	74 (48.1%)/ 81 (51.9%)	1.7±0.4	1.5±0.4	7.15	5	37 (7.72%)	13 (8.3%)	0	0	86.9.	92.7	94.1	95.7
Stiles B.M. (2019) [22]	Ког.	40.15	2757	1229	74.3±5.5	75.6±5.7	1558 (56.6%)/ 1196 (43.4%)	731 (59.5%)/ 498 (40.5%)	1.5±0.4	1.4±0.4	13.4	11.7	256 (9.28%)	193 (15.7%)	0	0	90.8	82.8	65	48

Note: L – lobectomy; SR – sublobar resection; Retro - Retrospective study; RCT – randomized clinical trial; Cohort. – cohort study; not available – n/a.

Analysis of tumor recurrences. The total relative risk (RR) of recurrence was 0.92 [95% CI: 0.65-1.31], which does not indicate a statistically significant difference between lobectomy and sublobar resection (p=0.66). Thus, both surgical strategies have shown comparable efficacy in preventing recurrence in the early stages of NSCLC.

However, high inter-study heterogeneity was observed (I^2=87%, p<0.01), indicating significant differences between the included studies in design, population characteristics, duration of follow-up, and criteria for assessing relapse. For example, RR values ranged from 0.00 [0.00-0.02] in M. Subramanian et al. [16] to 5.67 [1.74-18.46] in K. Kodama et al. [19]. In a study of B.M. Stiles et al. [22], relapse occurred significantly more frequently after sublobar resection (RR=0.59 [0.50-0.70]) (Figure 2).

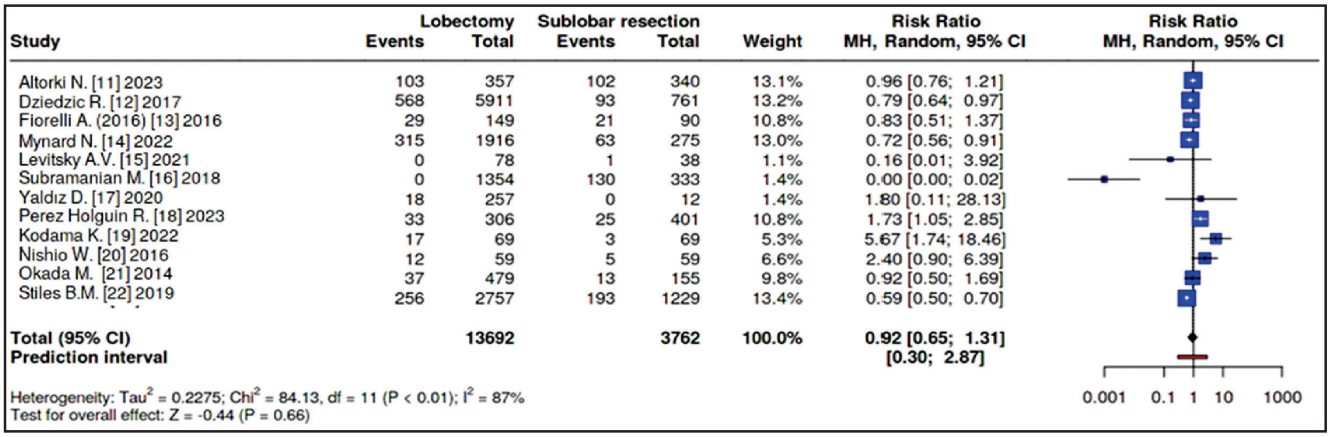

Figure 2 – Forest graph: risk of recurrence after lobectomy and sublobar resection (RR=0.92 [95% CI: 0.65 to 1.31]; p=0.66; I^2=87%)

Postoperative complications. Comparative analyses revealed a higher risk of postoperative complications in the lobectomy group (RR=1.22 [95% CI: 1.08-1.37]; p<0.01). This suggests that lobectomy is 22% more likely to develop complications, compared to SR (Figure 3).

The heterogeneity of the analysis was found to be minimal (I^2=0%; χ^2=10.62; df=11; p=0.48), indicating a high consistency of results between studies, regardless of region, clinical setting, and design.

Five-year overall survival. A meta-analysis of five-year overall survival showed an advantage of lobectomy over sublobar resection (RR=1.08 [95% CI: 1.00-1.17]; Z=1.96; p=0.05), but the difference is at the limit of statistical significance (Figure 4).

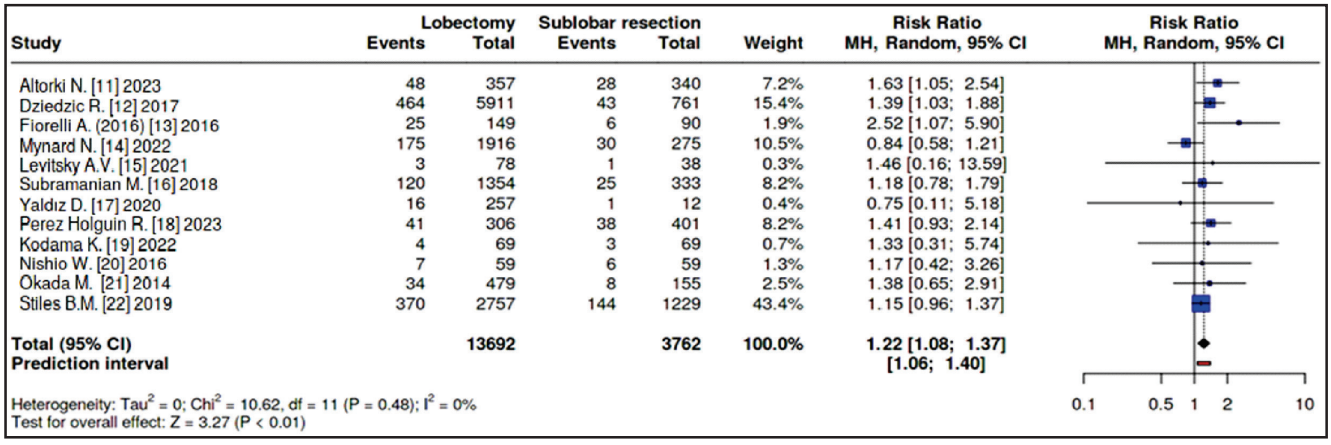

Figure 3 – Forest graph: incidence of postoperative complications (RR=1.22 [95% CI: 1.08 to 1.37]; p<0.01; I^2=0%)

Heterogeneity was pronounced (I^2=91%; χ^2=125.55; df=11; p<0.01), reflecting significant differences between studies. The prognostic interval [0.81-1.44] demonstrates potential variability in effect depending on the clinical context. This emphasizes the need for individualized selection of surgical tactics, taking into account the concomitant risk factors and the patient's overall condition.

Discussion: The results of the meta-analysis made it possible to comprehensively assess the oncological effectiveness and safety of lobectomy and sublobar resections (segmentectomy and wedge resection) in patients with stage I NSCLC. Even though lobectomy remains the standard of surgical treatment, the increased interest in organ-preserving interventions is due to the need to minimize surgical risks, especially in elderly and comorbid patients.

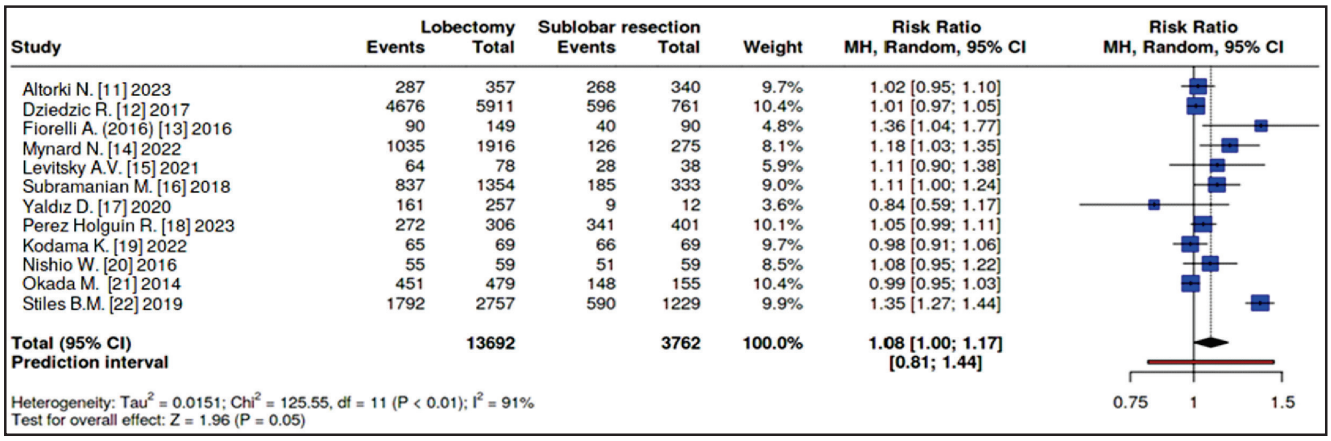

Figure 4 – Forest graph: five-year overall survival (RR=1.08 [95% CI: 1.00-1.17]; p=0.05; I^2=91%)

Analysis of recurrence rates revealed no statistically significant differences between lobectomy and sublobar resection (RR=0.92; 95% CI: 0.65-1.31; p=0.66). However, the high heterogeneity (I^2=87%) reflects variability in study designs, population characteristics, and evaluation criteria. The range of individual RR values from 0.00 to 5.67 emphasizes the importance of a stratified approach, taking into account tumor morphology, degree of invasion, and lepidic growth.

The incidence of postoperative complications was significantly higher after lobectomy (RR=1.22; 95% CI: 1.08-1.37; p<0.01), in the absence of inter-study heterogeneity (I^2=0%), confirming the persistence of the effect. These findings are particularly important for patients with limited functional reserve, who may prefer less invasive interventions.

Five-year overall survival was higher in the lobectomy group (RR=1.08; 95% CI: 1.00 to 1.17; p=0.05), but the effect was on the verge of statistical significance, with pronounced heterogeneity (I^2=91%) and a wide prognostic interval [0.81 to 1.44], which limits the universality of the findings. This emphasizes the need to individualize surgical tactics, taking into account the tumor's characteristics, size, localization, and risk factors for recurrence.

This meta-analysis is characterized by its coverage and strict adherence to the PRISMA and AMSTAR methodologies. Unlike previously published studies, this study includes various designs, covers key outcomes (relapses, complications, survival), and also contains a formal analysis of heterogeneity and confidence intervals, which increases the reliability of the conclusions.

The present study has several methodological limitations that should be considered when interpreting the results. Firstly, studies with different designs (randomized, cohort, and retrospective) were included in the meta-analysis, which, in itself, may be a source of heterogeneity. Pronounced variability in the duration of follow-up, patient characteristics, the volume of lymphatic dissection, and the use of additional methods of treatment also affects the comparability of results.

A key limitation is the aggregation of two different types of sublobar resections – anatomical segmentectomy and non-anatomical wedge resection – into one subgroup. These interventions differ significantly in radicality, volume of tissue removed, and the ability to assess resection margins and lymph nodes. Segmentectomy, as a rule, provides higher oncological reliability compared to wedge resection, a finding confirmed by several studies. Thus, combining these approaches in a single analysis could affect the accuracy of the cancer efficacy assessment and increase the heterogeneity of the results. Due to the limitations of the initial data and the lack of stratified data on the type of sublobar resection in separate publications, it was not possible to conduct a separate analysis of segmentectomy and wedge resection in this meta-analysis.

An additional limitation is the prevalence of retrospective studies with variable quality of initial data, which reduces the level of evidence. In addition, the lack of access to individual patient data limits the possibility of conducting an in-depth subgroup analysis on the morphological characteristics of the tumor, age, comorbidities, and other significant factors.

Conclusion: Sublobar resections demonstrate comparable oncological outcomes to lobectomy in patients with NSCLC, stage I. Despite the modest benefit of lobectomy in terms of five-year overall survival, the difference did not reach a clinically significant level and was accompanied by high heterogeneity. The recurrence rate did not differ statistically between groups; however, the risk of postoperative complications was significantly higher in the lobectomy group.

The data obtained confirm the validity of an individualized approach to determining the scope of intervention. Sublobar resections can be considered as a safe alternative to lobectomy in patients with tumors ≤2 cm, low invasiveness, and limited functionality.

Multicenter randomized trials with long-term follow-up, standardized inclusion criteria, and access to individual data are necessary for the final assessment of cancer equivalence.

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АҢДАТПА

ЕРТЕ САТЫДАҒЫ ҰСАҚ ЖАСУШАЛЫ ЕМЕС ӨКПЕ ҚАТЕРЛІ ІСІГІНДЕ ЛОБЭКТОМИЯ МЕН СУБЛОБАРЛЫҚ РЕЗЕКЦИЯЛАРДЫҢ САЛЫСТЫРМАЛЫ ТИІМДІЛІГІ: ЖҮЙЕЛІ ШОЛУ ЖӘНЕ МЕТА-ТАЛДАУ

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Өзектілігі: *Ұсақ жасушалы емес өкпе обыры (ҰЖЕӨО) – заманауи диагностика мен емдеудің жетістіктеріне қарамастан, онкологиялық өлім-жітімнің негізгі себептерінің бірі болып қалуда. I сатыдағы ҰЖЕӨО кезінде анатомиялық лобэктомия дәстүрлі түрде «алтын стандарт» болып саналады, алайда скринингтік бағдарламалардың дамуы және шағын өлшемді ісіктердің жиі анықталуы сублобарлық резекцияларға қызығушылықты арттыруда.*

Зерттеу мақсаты *– ұсақ жасушалы емес өкпе обырының ерте сатысында анатомиялық лобэктомия мен сублобарлық резекциялардың (сегментэктомия, клиновидті резекция) тиімділігі мен қауіпсіздігін салыстырмалы түрде бағалау мақсатында жүйелі шолу және мета-талдау жүргізу.*

Әдістері: *Мета-талдау PRISMA және AMSTAR әдістемелік ұсынымдарына сәйкес жүргізілді. 2010–2024 жылдар аралығындағы жарияланымдарға PubMed, Embase, Cochrane Library, Scopus, Web of Science және басқа да дереккорлар бойынша іздеу жүргізілді. Іріктеуге I сатыдағы ҰЖЕӨО диагнозы қойылған, лобэктомия немесе сублобарлық резекция жасалған ересек пациенттерге қатысты зерттеулер енгізілді. Статистикалық талдау RevMan 5.4 багдарламасы арқылы жүргізілді. Қауіп-қатердің салыстырмалы көрсеткіштері (RR) 95% сенімділік интервалымен есептелді, гетерогенділік I^2 индикаторы бойынша бағаланды.*

Нәтижелері: *Жалпы саны 17 454 науқасты қамтыған 12 зерттеу мета-талдауға енгізілді, олардың 13 692-сі лобэктомия, 3 762-сі сублобарлық резекциядан өтті. Рецидив жиілігі бойынша статистикалық айырмашылық байқалмады (RR=0,92; 95% CI: 0,65-1,31; p=0,66; I^2=87%). Лобэктомия тобында отадан кейінгі асқыну қаупі айтарлықтай жоғары болды (RR=1,22; 95% CI: 1,08-1,37; p<0,01; I^2=0%). Бесжылдық жалпы өмір сүру көрсеткіші лобэктомия тобында жоғары болды (RR=1,08; 95% CI: 1,00-1,17; p=0,05; I^2=91%).*

Қорытынды: *Сублобарлық резекциялар ≤2 см өлшемдегі ісіктері, инвазия белгілері жоқ және функционалдық резервтері шектеулі науқастар арасында онкологиялық тиімділік бойынша лобэктомиямен салыстыруға болатын нәтижелер көрсетеді. Хирургиялық тактиканы таңдауда жекелендірілген тәсілдің маңыздылығы арта түсуде. Бұл бағытта қосымша рандомизацияланған көпорталықты зерттеулер қажет.*

Түйінді сөздер: *ұсақ жасушалы емес өкпе обыры (ҰЖЕӨО), лобэктомия, сублобарлық резекция, сегментэктомия, өмір сүру, рецидивсіз өмір сүру ұзақтығы, рецидив.*

АННОТАЦИЯ

СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ЛОБЭКТОМИИ И СУБЛОБАРНЫХ РЕЗЕКЦИЙ ПРИ РАННЕЙ СТАДИИ НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЁГКОГО: СИСТЕМАТИЧЕСКИЙ ОБЗОР И МЕТА-АНАЛИЗ

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Актуальность: *Немелкоклеточный рак легкого (НМРЛ) остаётся одной из ведущих причин онкологической смертности, несмотря на прогресс в диагностике и лечении. Анатомическая лобэктомия традиционно считается «золотым стандартом» хирургического лечения НМРЛ I стадии, однако с развитием скрининга и увеличением числа выявленных опухолей малого размера растёт интерес к сублобарным резекциям.*

Цель исследования *– сравнительная оценка эффективности и безопасности лобэктомии и сублобарных резекций (сегментэктомии и клиновидной резекции) у пациентов с немелкоклеточным раком легкого на ранней стадии.*

Методы: *Мета-анализ выполнен в соответствии с рекомендациями PRISMA и AMSTAR. Поиск литературы проведён в базах PubMed, Embase, Cochrane Library, Scopus, Web of Science и других источниках за период с 2014 по 2024 год. Включались исследования с прямым сравнением лобэктомии и сублобарных резекций у взрослых пациентов с НМРЛ I стадии и оценкой клинически значимых исходов. Статистический анализ проводился с использованием программного обеспечения RevMan 5.4. Рассчитывались относительные риски (ОР) с 95% доверительными интервалами (ДИ), гетерогенность оценивали с помощью показателя I^2.*

Результаты: *В мета-анализ включены 12 исследований (n=17 454), из них 13 692 пациента перенесли лобэктомию, 3 762 – сублобарную резекцию. Частота рецидивов статистически не различалась между группами (ОР=0,92; 95% ДИ: 0,65-1,31; p=0,66), однако отмечалась высокая гетерогенность (I^2=87%). Частота послеоперационных осложнений была достоверно выше в группе лобэктомии (ОР=1,22; 95% ДИ: 1,08-1,37; p<0,01; I^2=0%). Пятилетняя общая выживаемость была выше после лобэктомии (ОР=1,08; 95% ДИ: 1,00-1,17; p=0,05), но с выраженной гетерогенностью (I^2=91%).*

Заключение: *Сублобарные резекции демонстрируют сравнимую с лобэктомией онкологическую эффективность при раннем НМРЛ, особенно у пациентов с опухолями ≤2 см, отсутствием инвазии и ограниченными функциональными резервами. Полученные данные подтверждают обоснованность индивидуализированного подхода при выборе объёма резекции. Необходимы дальнейшие рандомизированные исследования для окончательной оценки онкологической эквивалентности вмешательств.*

Ключевые слова: *немелкоклеточный рак легкого (НМРЛ), лобэктомия, сублобарная резекция, сегментэктомия, выживаемость, безрецидивная выживаемость, рецидив.*

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THE PROBLEM OF HUMAN PAPILLOMAVIRUS AND THE PREVENTION OF CERVICAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *The human papillomavirus (HPV) is the most common infection transmitted worldwide. It has high oncogenic activity and is the main reason for the development of cervical cancer. Cervical cancer is the leading cancer in women, especially in developing countries. Preventive measures, like vaccination, are of special significance in light of HPV's high prevalence and its connection with cancer.*

The study aimed to *examine current literature data on the role of HPV vaccination in the prevention of cervical cancer.*

Methods: *The analyzed data were obtained from scientific publications, clinical research, and systematic reviews on HPV and cervical cancer prevention. More than 120 full-text sources were examined, of which 27 publications were selected for inclusion in the review.*

Results: *An analysis of numerous epidemiological and clinical studies showed the high effectiveness of HPV vaccination in preventing HPV-associated diseases, including cervical cancer.*

Conclusion: *HPV vaccination is a powerful instrument of primary prevention of cervical cancer and other HPV-associated diseases. The widespread implementation of vaccination, especially in adolescence before the start of sexual activity, has the potential to significantly reduce the global burden of the RSM. However, given the long latent period of disease development, screening programs remain important and should be carried out in parallel with vaccination.*

Keywords: *Human papillomavirus (HPV), vaccination, cancer prevention, cervical cancer.*

Introduction: Human papillomavirus (HPV) is one of the most common sexually transmitted infections. According to epidemiological studies, almost every sexually active person encounters an HPV infection during their lifetime. The highest incidence of infection is observed between the ages of 15 and 25, which coincides with the first years of sexual activity. HPV can cause various diseases - from benign warts to malignant neoplasms, including cervical cancer (CC), anal canal, oropharynx, and other anogenital localizations [1].

Of particular concern is the oncogenic potential of certain HPV genotypes, of which types 16 and 18 are responsible for approximately 70% of cervical cancer cases worldwide. In this regard, primary prevention is of key importance, particularly HPV vaccination, which can prevent the development of malignant diseases associated with persistent viral infections.

The study aimed to examine current literature data on the role of HPV vaccination in the prevention of cervical cancer.

Materials and methods: A search and selection of articles was conducted in the PubMed, Web of Science, Scopus, and RSCI Up to Date databases using the main keywords and phrases: " *human papillomavirus* ", " *cervical cancer* ", " *cervical cancer prevention* ". The review included articles no more than 10 years old and related to the topic of this review. Reports of individual observations, correspondence, letters, and studies not conducted on humans were excluded from the review. To achieve the study's objective, an analysis of data from scientific publications, clinical trials, and systematic reviews on HPV vaccination and cervical cancer prevention was conducted. The following materials were used: the results of randomized controlled trials of HPV vaccines, data on the long-term effects of vaccination, including a reduction in the incidence of cervical cancer and other HPV-associated diseases, systematic reviews, and meta-analyses assessing the effectiveness of vaccines and the results of screening programs. More than 120 full-text sources were studied; the review included data from 27 publications.

Results: According to most authors, more than 88% of patients with invasive cervical cancer are HPV-infected. The etiological structure is dominated by HPV types 16 (70-72%), 18 (13-15%), and 45 (5-7%). Failure to detect high-risk HPV (HRHPV) in cervical cancer is associated, among other things, with false-negative test results. The conducted literature analysis revealed a relationship between HPV status and age, morphological form of the tumor, vi-

ral load, HRHV genotype, presence of deep stromal invasion, and metastatic lesions in the lymph nodes. Regarding the molecular genetic parameters of HPV HCR, such as viral load and HPV DNA integration, the association with prognostically important clinical indicators of cervical tumors, including disease stage, locoregional tumor process prevalence, and tumor histological type, remains a subject of discussion [2].

Many publications state the presence of a correlation between the HPV status and the HPV genotype of the HCR, with such an important factor influencing the results of cervical cancer treatment as the morphological form of the tumor. Ambiguous conclusions on the presence of a relationship between several molecular genetic parameters of HPV infection and the main prognostic factor - the stage of the disease (caused by both the heterogeneity of samples, the use of various test systems, and insufficiently complete consideration of the main parameters of HPV infection, primarily data on the integration of viral DNA), make it advisable to conduct further studies on a representative group of patients with homogeneous diagnostic protocols for determining the most complete spectrum of HPV parameters of the HCR. In addition, the conducted analysis of the literature showed the promise of searching for predictors of the effectiveness of specialized treatment of patients with cervical cancer among such HPV infection parameters as HPV status, HPV genotype of the HCR, and the significantly associated physical status of viral DNA [2].

However, recent research findings suggest opportunities for cervical cancer prevention in resource-limited settings by adopting a combined vaccination and screening strategy, which has been proven to be cost-effective in several low- and middle-income countries. The 2020 American Cancer Society guidelines update recommends that women initiate cervical cancer screening at age 25 years and undergo primary HPV testing every 5 years until age 65 years as the preferred option [3].

Further studies are needed to clarify the prognostic value of HPV DNA integration and other molecular parameters of these HPV genotypes. The relevance of this issue is likely to increase over time with widespread HPV vaccination, which is expected to reduce the prevalence of the more aggressive HPV genotypes 16 and 18 in cervical cancer [4].

Recently, three large Chinese cohort studies showed that 7.5-15.5% of patients with cervical carcinoma had negative HCR HPV test results on previous cytology specimens. These studies raise the question of whether these negative HCR HPV results represent true HCR HPV-negative carcinomas or false-negative HCR HPV test results due to limitations in cytology specimen testing. This is an increasingly important issue with the increasing push to use only HCR HPV testing for CC screening. This study shows that negative HPV testing on cervicovaginal cytology specimens in women subsequently diagnosed with cervical carcinoma can be explained by the occurrence of true HPV-negative carcinomas in more than half of the patients. These results should be considered in developing future CC screening guidelines [5].

Testing is more sensitive than cytology for the detection of cervical cancer and its precursors. However, there are limited and conflicting data on the efficacy of combining these two methods for screening cervical adenocarcinoma. This multicenter retrospective study examined the screening results of a cohort of Chinese patients subsequently diagnosed with invasive cervical adenocarcinoma to determine the optimal screening method for cervical adenocarcinoma. Both cytology and HCR HPV testing alone showed low screening efficacy, whereas their combination notably improved the primary screening efficacy for cervical adenocarcinoma. Thus, cytology and combined HCR HPV testing may be the most effective screening method for cervical adenocarcinoma [6].

Although cervical cancer is primarily caused by HPV infection, some types of cervical cancer test negative for HPV. Since these HPV-negative types of cervical cancer are often diagnosed at an advanced stage and have a poor prognosis, it is important to understand their molecular pathology. Although cervical cancer treatment is currently not stratified based on HPV positivity, there are cases of HPV-negative cervical cancer that have a worse prognosis than HPV-positive cervical cancer. For example, HPV-negative cervical cancer has been reported to have worse survival than HPV-positive cervical cancer [6]. However, false-negative HPV tests should also be considered, especially those due to improper specimen handling. In addition, metastasis to the cervix from cancers arising from other organs should be excluded, as treatment options vary widely. With the increased availability of HPV vaccines, the number of deaths from HPV-positive cervical cancer has steadily decreased. However, HPV-negative CC is expected to persist in the post-vaccination era, requiring intensive research into carcinogenic pathways and therapeutic targets [7].

Current estimates of HPV infection rates in China vary by geographic region (9.6-23.6%), with two age-specific prevalence peaks in women aged ≤20-25 years and 50-60 years. The most commonly detected HPV genotypes in the Chinese population are HPV-16, 52, and 58. Five HPV vaccines are licensed in China, and several others are in clinical trials. Although modeling studies in China suggest that HPV vaccination is cost-effective, population coverage and uptake are relatively low. Various policies have been implemented to raise awareness and increase vaccination coverage, with the long-term goal of eliminating cervical cancer in China [8, 9].

Most HPV genotypes are characterized by self-limiting infection, with the virus being eliminated by the immune system within 6–12 months. However, if the virus persists in cells, especially those with high oncogenic risk geno-

types, the likelihood of integrating the viral genome into the host DNA increases. This, in turn, can destabilize the cell cycle, disrupt apoptosis, and, potentially, lead to the development of malignant neoplasms [10-12].

Human Papillomavirus Epidemiology and Typification. HPV infection is one of the most common sexually transmitted viral infections. According to the World Health Organization, during their lifetime, up to 80–90% of sexually active men and women encounter infection with one or more types of the virus. The highest peak of infection occurs in the age range of 15–25 years, especially in the first years after the onset of sexual activity.

The human papillomavirus is a heterogeneous group comprising over 200 genotypes, of which about 40 affect the anogenital tract. Depending on the oncogenic potential, HPV is usually divided into types:

– high oncogenic risk (oncogenic) – 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68;

– low oncogenic risk (non-oncogenic) – 6, 11, 40, 42, 43, 44, 54, and others.

The most significant in terms of oncogenic potential are types **16 and 18,** causing about 70% of all cases of cervical cancer. Additionally, about 20% of cases are associated with types 31, 33, 45, 52, and 58. The remaining 10% are less common, but also dangerous types, such as 35, 39, 51, 56, 59, and 68 [13,14].

Types 6 and 11, in turn, do not have oncogenic potential, but are responsible for approximately 90% of cases of anogenital warts, as well as respiratory papillomatosis. The geographic distribution of HPV genotypes can vary, as can the frequency of occurrence of different types depending on the age group and sexual behavior of the population. This makes local epidemiological monitoring relevant, especially in countries with a high incidence of cervical cancer.

Thus, the high prevalence of HPV, the diversity of its types, and the direct link with the development of oncological diseases emphasize the need for large-scale preventive programs, primarily vaccination.

The Role of Human Papillomavirus in Cervical Cancer Development. Cervical cancer is one of the leading cancers in women worldwide. According to the International Agency for Research on Cancer, almost all cases of cervical cancer are associated with persistent HPV infection, mainly oncogenic types. Of these, HPV types 16 and 18 are found in approximately 70% of cases, while the remaining types comprise 31, 33, 45, 52, 58, and others [14,15].

Oncogenic HPV types cause high-grade squamous intraepithelial lesions that, if untreated, can progress to invasive cancer. The key event in the development of neoplasia is viral persistence, i.e., the long-term presence of the virus in epithelial cells without elimination by the immune system. Typically, the infection is eliminated within 6–12 months; however, during persistence, the virus can integrate into the host cell genome, disrupting cell cycle regulation. Integration of the viral genome leads to the overexpression of the E6 and E7 oncoproteins, which diminish the p53 and Rb tumor-suppressing functions, respectively. This contributes to uncontrolled cell division, disruption of apoptotic mechanisms, and accumulation of genetic mutations, which, in turn, lead to malignancy. The median age of detection of precancerous changes in the cervix is approximately 10 years after the onset of sexual activity, which emphasizes the long-term nature of infection progression. At the same time, early diagnosis (for example, using a Pap test and HPV testing) allows for the detection of pathological changes at the preclinical stage and significantly reduces mortality from cervical cancer [14-16].

It is also worth noting that oncogenic HPV types are involved not only in the pathogenesis of cervical cancer, but also other malignant neoplasms: anal cancer (up to 90% of cases - type 16), cancer of the oropharynx, vulva, vagina, and penis. This further increases the importance of combating HPV infection as a global medical and social problem [15,16].

Thus, the presence of persistent HPV VCR is a necessary, although not the only, condition for the development of cervical cancer. Prevention of infection through vaccination is an effective strategy for the primary prevention of this disease.

Vaccination as a Primary Method to Prevent Human Papillomavirus and Cervical Cancer. Vaccination against HPV is currently recognized as the most effective method of primary prevention of cervical cancer and other HPV-associated diseases. Vaccines are developed based on virus-like particles containing the capsid protein L1, which does not carry viral DNA, ensuring the safety and high immunogenicity of the vaccine.

There are three main groups of HPV vaccines on the market:

– The bivalent vaccine (Cervarix) is designed to protect against types 16 and 18;

– The quadrivalent vaccine (Gardasil) affects types 6, 11, 16, and 18;

– The nine-valent vaccine (Gardasil 9) protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The bivalent and quadrivalent vaccines have shown high efficacy in preventing infections and precancerous lesions caused by the corresponding HPV types. The nonavalent vaccine significantly expands the spectrum of protection, covering up to 90% of cervical cancer cases.

Clinical studies and meta-analyses have shown that vaccination:

– reduces the incidence of HPV infection;

– significantly reduces the prevalence of cervical intraepithelial neoplasia (CIN 2/3);

– reduces the incidence of anogenital warts;

– demonstrates a pronounced effect at the population level due to herd immunity.

Vaccines are most effective when administered before the onset of sexual activity. Vaccination is recommended for girls and boys aged 9 to 14 years, and in some countries is also administered to extended age groups up to 26 years and older.

Vaccination coverage of both sexes is of particular importance. Although the direct burden of HPV-associated diseases is higher in women, men are an important link in the chain of transmission of the infection. In addition, they are also susceptible to developing HPV-related cancers of the anus, oropharynx, and penis.

In several countries, there has been a decrease in the incidence of HPV infection and its complications 10–12 years after the introduction of mass vaccination. However, experts emphasize that the effect of vaccination does not appear immediately, and during the transition period, there remains a need for secondary prevention programs, including regular screening and testing for HPV.

Thus, vaccination is an effective, scientifically proven, and safe strategy for the primary prevention of cervical cancer and other diseases caused by HPV. Its widespread implementation allows for a significant reduction in HPV-related morbidity and mortality and is of great importance for public health.

Limitations of Vaccination and the Role of Secondary Prevention. The vaccine is most effective when administered before the onset of sexual activity, which limits protection among adults already infected with the virus.

Even the nine-valent vaccine does not cover *all* oncogenic HPV types. High-risk genotypes not included in the vaccine composition (e.g., 35, 39, 51, 56, 59, 68) continue to circulate worldwide, which, although less frequently, can also cause malignant transformations. And although there is a possibility of cross-protection due to antigenic similarity between types, it is not complete.

Additional limitations include: 1) *low vaccination coverage,* particularly in low- and middle-income countries; 2) *lack of gender parity* in vaccination (in many countries, only girls are vaccinated); 3) *lack of mass revaccination programmes* or antibody titer monitoring; 4) *hesitancy and low public awareness* of the importance of vaccination.

Given these factors, *secondary prevention* continues to play an important role in reducing morbidity and mortality from cervical cancer. The main methods of secondary prevention are: *Pap test* – to detect cellular atypia; *HPV testing* – to determine the presence of HPV HCR; *colposcopy and biopsy* – if the screening results are suspicious.

Early detection of precancerous changes in the cervical epithelium helps prevent the development of invasive cancer, even in the case of HPV infection.

Vaccination should be considered as part of a comprehensive approach to cervical cancer prevention, combined with regular screening, education, and improved access to health care.

Discussion: All are prophylactic vaccines designed to prevent primary HPV infection and subsequent HPV-associated lesions. In the United States, the 9-valent vaccine is specifically approved for the prevention of cancers and precancerous lesions of the cervix, vulva, vagina, anus, oropharynx, head and neck, and genital warts in women and for the prevention of anal, oropharyngeal, and other head and neck cancers, precancerous and dysplastic lesions of the anus, and genital warts in men [17].

Various models have shown that vaccinating both men and women is more beneficial in reducing HPV infection and disease than vaccinating women only, although vaccinating men is less cost-effective than vaccinating women [17,18]. However, cost-effectiveness analyses are limited by not including an estimate of the benefit of reducing other HPV-related diseases [1] in men, as discussed above, and by uncertainty about various variables that influence the impact of vaccinating men. These include vaccination coverage among women, the effect of herd immunity, the range of health outcomes included, and the impact of HPV-related diseases on quality of life [19,20].

According to the Advisory Committee on Immunization Practices (ACIP) guidelines, routine HPV vaccination is recommended for all women and men in the following age ranges in the United States:

– Routine HPV vaccination is recommended between the ages of 11 and 12. It can be administered starting at age 9.

– For adolescents and adults aged 13 to 26 years who have not previously received or completed the vaccination series, catch-up vaccination is recommended.

– For adults aged 27 years and older, catch-up vaccination is generally not recommended [1, 21].

It is noted that the decision to vaccinate people in this age group should be made on an individual basis. The likelihood of prior exposure to HPV vaccine types increases with age; thus, the population benefit and cost-effectiveness of HPV vaccination are lower among older patients [22, 23].

Recommendations from other expert groups for resource-limited settings vary somewhat. The World Health Organization (WHO) recommends that the primary target of HPV vaccination programmes should be girls aged 9–14 years, and that local public health programmes should recommend vaccination of older women only if it is available, cost-effective, and does not divert resources from vaccination of the key target population or screening for cervical cancer [24, 25].

Vaccination at a younger age is also supported by observational studies, which suggest that it is associated with a greater reduction in cervical cancer incidence compared to vaccination at a later age [26-28].

Conclusion: HPV is the leading cause of cervical cancer, as well as other anogenital and oropharyngeal malignancies. Its high prevalence, oncogenic potential of individu-

al genotypes, and ability to persist in the body for a long time make the problem of HPV infection relevant both in clinical and epidemiological terms. Analysis of world literature indicates high efficiency of HPV vaccination as a method of primary prevention of cervical cancer. In countries with high vaccination coverage, there is a reliable decrease in morbidity and mortality.

Modern HPV vaccines are an effective and safe tool for primary prevention. They help prevent infection with the most dangerous types of the virus, significantly reducing the risk of precancerous and malignant changes. However, the full effectiveness of vaccination requires broad population coverage, the start of immunization before the onset of sexual activity, and a gender-neutral approach to vaccination programs.

Limited vaccine coverage, the lack of universal immunity to all HPV types, and the impossibility of treating existing infections highlight the need for a comprehensive approach. In these circumstances, secondary prevention remains important – regular screening examinations aimed at early detection and treatment of precancerous lesions.

Thus, the fight against HPV-associated diseases should be based on the integration of primary and secondary prevention measures, as well as on raising awareness among the population and health workers. Only such an approach allows us to count on a sustainable reduction in morbidity and mortality from cervical cancer on a global scale.

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АҢДАТПА

АДАМ ПАПИЛЛОМАВИРУСЫНЫҢ ПРОБЛЕМАСЫ ЖӘНЕ ЖАТЫР МОЙНЫ ОБЫРЫНЫҢ АЛДЫН АЛУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Адам папилломасы вирусы (HPV) – әлемде берілетін ең көп кездесетін инфекция. Онда онкогендік белсенділігі жоғары және жатыр мойны обырын дамытудың негізгі себебі болып табылады. Жатыр мойны обырын әйелдерде, әсіресе дамушы елдерде қатерлі ісік аурулары арасындағы жетекші орындардың бірін алады. HPV-нің биік таралуы және оның қатерлі ісікпен байланысы аясында профилактикалық шараларды, мысалы, вакцинацияны енгізу ерекше мәнге ие болады.*

Зерттеудің мақсаты *– жатыр мойны обырының алдын алудағы HPV вакцинациясының рөлі туралы қазіргі әдебиет деректерін зерттеу.*

Әдістері: *Зерттеу мақсатына жету үшін ғылыми жарияланымдардан, клиникалық зерттеулерден және HPV-ге арналған клиникалық зерттеулер мен жүйелік шолулар мен жатыр мойны обырының алдын-алу бойынша мәліметтерді талдау жүргізілді. 120-дан астам толық мәтіндер зерттелді, шолулар 27 жарияланымнан мәліметтерді қамтыды.*

Нәтижелері: *Көптеген эпидемиологиялық және клиникалық зерттеулерді талдау HPV-аспиратталған аурулардың алдын-алу, оның ішінде жатыр мойны обырының алдын-алудағы адам папиллома вирусына қарсы вакцинацияның жоғары тиімділігін көрсетті.*

Қорытынды: *HPV вакцинациясы жатыр мойны обырының және басқа да HPV-аспиратталған аурулардың алғашқы алдын-алудың қуатты құралы болып табылады. Вакцинацияның, әсіресе жыныстық қатынас басталғанға дейін, әсіресе жасөспірімдерде Жасөспірімге дейін жатыр мойын обырынің жаһандық ауыртпалығын едәуір азайтуға мүмкіндігі бар. Алайда, аурудың ұзақ жасырын кезеңі, скринингтік бағдарламалар маңызды болып қала береді және вакцинациямен қатар жүргізілуі керек.*

Түйінді сөздер: *адам папилломавирусы, вакцинация, қатерлі ісіктің алдын алу, жатыр мойны обыры.*

АННОТАЦИЯ

ПРОБЛЕМА ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА И ПРОФИЛАКТИКА РАКА ШЕЙКИ МАТКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Вирус папилломы человека (ВПЧ) является самой распространенной инфекцией в мире, передающейся половым путем. Данный вирус имеет высокую онкогенную активность и считается главной причиной развития рака шейки матки (РШМ).*

РШМ занимает одно из ведущих мест среди онкологических заболеваний у женщин, особенно в развивающихся странах. В свете высокой распространенности ВПЧ и его связи с онкологическими заболеваниями, внедрение профилактических мер, таких как вакцинация, приобретает особую значимость.

***Цель исследования** – изучение актуальных данных литературы о роли вакцинации против ВПЧ в профилактике рака шейки матки.*

***Методы:** Для достижения цели исследования был проведён анализ данных научных публикаций, клинических исследований и систематических обзоров, посвящённых ВПЧ и профилактике РШМ. Было изучено более 120 полнотекстовых источников, в обзор вошли данные 29 публикаций.*

***Результаты:** Анализ многочисленных эпидемиологических и клинических исследований показал высокую эффективность вакцинации против ВПЧ в профилактике ВПЧ-ассоциированных заболеваний, в том числе РШМ.*

***Заключение:** Вакцинация против ВПЧ является мощным инструментом первичной профилактики РШМ и других ВПЧ-ассоциированных заболеваний. Широкое внедрение вакцинации, особенно в подростковом возрасте до начала половой жизни, имеет потенциал существенно снизить глобальное бремя РШМ. Однако, учитывая длительный латентный период развития заболевания, программы скрининга остаются важными и должны проводиться параллельно с вакцинацией.*

***Ключевые слова:** вирус папилломы человека (ВПЧ), вакцинация, профилактика рака, рак шейки матки (РШМ).*

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ORGANIZATION OF REHABILITATION ACTIVITIES FOR PATIENTS WITH BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *The high incidence of breast cancer in the world, leading to a high percentage of disability in the female population, requires not only the development of new technologies for early diagnosis and treatment, but also calls for the creation of effective approaches to rehabilitation measures, which indicates their socially significant nature.*

The study aimed to *identify the specific aspects of medical rehabilitation for breast cancer patients based on a literature analysis.*

Methods: *To achieve this goal, an analysis of available literary sources was conducted in leading electronic databases, including SpringerLink, PubMed, and Embase, with an emphasis on modern scientific achievements in the field of cancer patient rehabilitation. The selection of scientific publications was carried out according to the following key terms: "malignant neoplasms of the mammary gland", "rehabilitation medical strategies", "quality of life of cancer patients".*

Results: *A systematic analysis of scientific sources confirmed the need to introduce a multidisciplinary approach to the formation and implementation of medical rehabilitation programs for patients who have undergone breast cancer treatment. It has been proven that this category of patients faces many physiological, somatic, and psychological disorders that have a significant impact on their adaptation and social functioning. Significant changes in the physical and psycho-emotional state often lead to the loss of professional and social roles, which require the implementation of complex rehabilitation strategies. The complex nature of rehabilitation contributes to the comprehensive recovery of patients, ensuring an increase in their quality of life and social integration.*

Conclusion: *The use of integrated medical rehabilitation programs for patients who had breast cancer contributes to the restoration and/or optimization of lost functions of patients and their successful social adaptation.*

Keywords: *breast cancer, rehabilitation measures, quality of life.*

Introduction: Breast Cancer (BC) is the leading cause of cancer death in most countries of the world. According to the World Health Organization, 685,000 people died from breast cancer worldwide in 2020 and 670,000 in 2023 [1-3]. In Kazakhstan, breast cancer incidence also ranks first among other malignant neoplasms every year, making a significant contribution to both incidence rates (14.5% in 2020, 14.9% in 2023) and mortality rates (7.8% in 2020, 8.1% in 2023) [4]. At the same time, an annual reduction in these indicators of no more than 2-4% can be achieved only in those countries where not only modern, effective treatment technologies are introduced, but also methods of restorative medicine are widely adopted. The aggressiveness of the malignant process necessitates the use of techniques in antitumor therapy that aim not only to eliminate the primary tumor focus but also to restore the normal functioning of disrupted life processes, which significantly impact the quality of life of patients [5-7]. Considering the above data, the most vital task is the development and implementation of effective rehabilitation strategies aimed at minimizing the adverse effects of antitumor treatment and enhancing the functional state of patients [8, 9].

The study aimed to identify the specific aspects of medical rehabilitation for breast cancer patients based on a literature analysis.

Materials and methods: This review is based on a systematic analysis of published scientific sources devoted to the problems of medical rehabilitation of women who have had breast cancer. The information search was conducted in leading electronic bibliographic databases, including SpringerLink, PubMed, and Embase, with a focus on contemporary trends in restorative medicine. The following key terms were used as search criteria: "malignant neoplasms of the mammary gland", "rehabilitation medical strategies", "quality of life of cancer patients". The final analysis included 30 publications that met the criteria of scientific significance and methodological validity.

Results: Individualization of treatment and rehabilitation programs is a key area of modern medical rehabilitation of patients with breast cancer, similar to modern trends in the treatment of this disease. According to U. Olsson Möller et al., women who have undergone treatment for breast cancer face significant negative consequences, and their rehabilitation needs often remain unmet. Studies show that up to 43% of patients experience chronic dis-

tress, requiring a comprehensive therapeutic approach [10]. However, the problem of timely detection and restoration of individual physiological disorders in the body of women with breast cancer remains, which significantly reduces their chances of full rehabilitation [11, 12].

E. Wisotzky et al. in their study analyzed the functional interaction of specialists in rehabilitation teams and identified key problems in the distribution of responsibilities. It was found that the lack of a clear delineation of functions between attending physicians and rehabilitation specialists sometimes leads to duplication of certain responsibilities and the omission of others, ultimately resulting in a decrease in the effectiveness of rehabilitation measures. Based on the data obtained, the authors proposed an algorithm for optimizing interdisciplinary interaction, which allows for increased coordination of specialists' work and improved quality of rehabilitation care for patients with breast cancer [13].

Focusing on improving the quality of medical services, some authors offer an updated understanding of rehabilitation, which eliminates the boundaries between primary treatment, rehabilitation, and palliative care in oncology. The last two areas, in some interpretations by individual researchers, suggest similar activities, including symptomatic treatment to minimize the consequences of the tumor process and specialized treatment. These approaches are also aimed at optimizing healthcare resources by reducing the length of hospital stay and decreasing the number of unexpected rehospitalizations. Despite common goals, rehabilitation and palliative care use different methods [5]. Palliative care is aimed primarily at providing psychological and social support to the patient, creating comfortable conditions for his stay, and taking into account the spiritual aspects of the disease. In contrast, rehabilitation measures focus on restoring motor, cognitive, and psycho-emotional functions, reducing the level of disability, and improving the overall quality of life for patients [14].

S. Wittry et al. identify four key stages of rehabilitation of cancer patients: preventive, restorative, supportive, and palliative. The preventive stage, aimed at preparing the patient for specialized treatment, begins after diagnosis, with the patient being informed about the possible consequences of therapy and a personalized rehabilitation plan being developed. The recovery period encompasses rehabilitation measures implemented during and immediately following the completion of antitumor treatment. At this stage, physiotherapeutic, medicinal, and psychological methods are used to help minimize the side effects of therapy and restore the patient's functional capabilities. The supportive stage focuses on monitoring the condition and correcting functional and psychosocial parameters, while the palliative stage provides comprehensive symptomatic treatment to enhance the quality of life. Particular attention is paid to elderly patients with concomitant diseases, weakened musculoskeletal system, and risk of fractures, where an individualized approach is required with the involvement of family resources [15].

J. Weis and J. M. Giesler emphasize that oncological rehabilitation aims to reduce the impact of limitations caused by the disease and its treatment, promoting the social reintegration of the patient [16]. Given the increase in breast cancer incidence and the improvement of therapeutic approaches, the rehabilitation of cancer patients is of key importance in the healthcare system. In various countries, recommendations for follow-up care for women who have had breast cancer are being developed based on research results, emphasizing that to ensure the effectiveness of rehabilitation, a detailed personalized assessment of the patient's condition is required based on examination data from a multidisciplinary group of specialists, including specialized oncologists, specialized experts, rehabilitation specialists, psychologists, and social workers. To systematize information about the impact of the pathological process and treatment measures on various aspects of the patient's life, as well as to monitor the impact of external factors on the dynamics of rehabilitation, various classifications are being developed, for example, the International Classification of Functioning (ICF) of Disabilities and Health, aimed at diagnosing functional limitations [17].

A large-scale study by Spanish scientists has demonstrated that increased life expectancy, active implementation of early detection programs, and decreased mortality in breast cancer lead to an increase in the number of patients who require rehabilitation support over a long period. This fact is also explained by the fact that the disease and the corresponding antitumor treatment of patients complicate their integration into the professional environment, leaving significant physical and psychosocial consequences that can persist for a long time. In response to this problem, a guideline was developed to regulate the coordinated interaction of specialized and primary healthcare services. The proposed recommendations encompass aspects of post-therapeutic patient monitoring, the development of individualized rehabilitation strategies, and the organization of interdisciplinary specialist interaction. Additionally, the document contains general provisions aimed at maintaining a stable condition of female patients, including weight control, adherence to principles of rational nutrition, regular physical activity, cessation of smoking and alcohol consumption, use of auxiliary treatment methods (in particular, reflexology), monitoring of signs of possible relapse and strict control of compliance with hormonal therapy for 5-10 years. The issue of professional readaptation of female patients and their return to work is also considered [17].

J. Klocker et al. conducted a study of the effectiveness of a three-week inpatient rehabilitation program that included psychosocial support, correction of functional disorders, and training in the basics of a healthy lifestyle. The

sample included 3,233 patients, whose data were analyzed dynamically over a five-year period. The use of validated assessment scales (European Quality of Life – 5 Dimensions, EuroQol EQ-5D) revealed a significant improvement in the quality of life of patients immediately after completing the program, as well as during subsequent monitoring at 6 and 12 months. A decrease in anxiety and depression, as well as an increase in the level of psychological stability, were noted, which confirms the high effectiveness of rehabilitation measures based on biopsychosocial principles [18].

F. Di Iulio et al. conducted a systematic review of the literature, which analyzed cognitive impairment associated with antitumor therapy based on 29 studies. Based on the studies, the authors concluded that the combined use of hormonal therapy and chemotherapy in cancer patients affects the quality of life, in particular the deterioration of cognitive functions and the emergence of neuropsychological disorders. In patients with breast cancer, memory impairment, verbal abilities, and motor speed were most pronounced. The importance of neuropsychological diagnostics helps to objectively assess the effect of chemotherapeutic drugs not only on the tumor, but also on the central nervous system of patients with breast cancer, which can be regarded as a side effect of chemotherapy drugs and, in turn, is necessary for adequate rehabilitation measures [19].

The work by SL Bober et al. demonstrated that every year thousands of young women suffering from breast cancer face a difficult choice: to undergo drug suppression of ovarian function, leading to early menopause or sexual dysfunction, in order to reduce the risk of recurrence of the disease. The solution to this problem can be facilitated by the psycho-sexual rehabilitation complex developed by the authors, which is aimed not only at reducing sexual dysfunction, but also at combating psychological stress. The implementation of the developed rehabilitation complex was carried out during a study of 20 young patients with breast cancer, who underwent a 4-hour group treatment session, including cognitive therapy techniques based on mindfulness, exercises on "body awareness," and some questions related to sexual health. When analyzing the obtained data, a significant improvement in the psychological state of patients was revealed, including a decrease in anxiety levels and restoration of sexual function. Such results indicate the need for rehabilitation measures, which are especially relevant for young women with drug-induced menopause caused by breast cancer treatment [5, 20]. Surgical intervention in the treatment of breast cancer is also fraught with a violation of functional capabilities. Considering that more than half of breast cancer cases occur in middle-aged women (45 to 64 years old), preserving the function of the upper limbs becomes a key aspect, since this group of patients is often the main breadwinners of their families, is actively professionally active, and is at the peak of their careers [5].

Asian women have higher body fat percentage, lower physical activity levels, and lower bone mass than Western women, which may impact functional outcomes after surgery. In a single-center prospective cohort study with 6-week follow-up, the functional status of 44 patients (including 16 sector resections and 28 mastectomy patients) was assessed after early rehabilitation (from day 1 postoperatively) including a set of shoulder and upper extremity exercises. Shoulder range of motion and disability were assessed preoperatively, 2 weeks, and 6 weeks postoperatively. Results showed that at week 6, patients were able to regain active shoulder range of motion, but some patients experienced higher levels of disability, particularly in the group of women who underwent axillary lymph node dissection after sentinel lymph node exploration. The presented data further emphasize the importance of using active methods of early rehabilitation [5, 21].

Concerning the recovery of breast cancer patients after surgical treatment, numerous studies indicate the need for a comprehensive approach. Thus, WA Calo and colleagues developed the Strength After Breast Cancer (SABC) program, which included an online course for physiotherapists that incorporated specialized physical exercises. When surveying physicians who had completed the course, 76% of respondents reported implementing the program in their outpatient rehabilitation clinics, confirming the effectiveness of online training under this program [22].

A study of the effectiveness of magnetic therapy in the early stages after radical surgery in 64 patients with breast cancer showed a significant improvement in the quality of life, a decrease in pain syndrome (according to the following indicators: intensity, duration, frequency, irradiation), a decrease in muscle-tonic syndrome in the shoulder-scapular region, a decrease in the level of venous congestion in patients in the "magnetic therapy" group compared to the "placebo" group [23]. Based on the data obtained, it can be stated that the use of general magnetic therapy for 2-4 days after surgery is rational, as it helps improve patient condition.

Psychosocial support is also an important aspect of the comprehensive rehabilitation of patients with breast cancer. MK Derakhshan and MH Karbassian in their studies of cancer patients focused on the prevalence of mental disorders (depression, anxiety disorders, sleep disorders), which were especially common in women with breast cancer. The importance of non-drug treatments, such as cognitive behavioral therapy, was emphasized. The authors also point out that such disorders are often underestimated, although many patients need not only psychological but also psychiatric care. The results of using psychiatric drugs in the treatment of some patients with breast cancer were evidence of this. The researchers paid special attention to their interaction with other antitumor agents and hormonal drugs used for treatment. In conclusion, the researchers argue that psychiatrists should actively participate in rehabilitation teams, helping to identify psychosocial problems and develop individual plans for rehabilitation treatment [5, 24].

Modern technologies also play an important role in the rehabilitation of patients with breast cancer. J. Ollero et al. suggested monitoring such parameters as heart rate, energy expenditure, and hand mobility in their studies. To do this, the authors developed a system that can be controlled from three applications (for smart watches, smartphones, and a web application). Such technologies help patients and medical experts evaluate the effectiveness of rehabilitation [5, 25]. A similar program was used by M. Rutsch et al., who developed the ReNaApp mobile application for the rehabilitation of patients with breast cancer. This application proved effective in improving long-term rehabilitation outcomes and encouraged patients to participate more actively in physical activity, thereby enhancing their quality of life [26].

The last decade has also seen an increase in attention to patient involvement in research, particularly in planning individualized treatment and rehabilitation programs. This approach enhances the quality of research and enables the consideration of patients' opinions. As a result of such research, high acceptability of materials for participants is revealed and the general applicability of the data obtained increases [27]. A crucial aspect is the involvement of patients in the research process, which enhances the understanding of the problems being studied and strengthens the connections between researchers and the community [28].

A study by ER Nissen and colleagues demonstrates the benefits of establishing a working group to develop a psychosocial rehabilitation program for patients with breast cancer. The group included patient representatives, researchers, and a research assistant, who provided greater mutual understanding and increased relevance of the program. Involving patients in the design and implementation of the study brought significant benefits, despite the additional costs associated with this approach [29].

Discussion: Current trends in the field of rehabilitation treatment of patients with breast cancer confirm the need for a comprehensive multidisciplinary approach in developing medical rehabilitation programs for this group of patients. The rehabilitation period can and should begin with breast cancer prevention before a malignant tumor can appear (for example, during the treatment of fibrocystic mastopathy or other benign tumors of the female reproductive system) [30]. This is because patients with breast cancer develop both functional and organic somatic disorders, along with emotional, mental, and behavioral reactions that arise against the background of the disease. Together, these factors lead to severe psychosocial disorientation, impaired work activity and social adaptation, which requires comprehensive and targeted rehabilitation measures. Such an integrated approach will encompass all key aspects of patients' lives and help address the primary goal of medical rehabilitation: improving the quality of life. The implementation of a comprehensive medical rehabilitation program for women who have undergone treatment for breast cancer will ensure optimal recovery of their physical and psychosocial condition and support the process of their full reintegration into society, which is a prerequisite for achieving sustainable recovery.

Conclusion: An analysis of studies devoted to the rehabilitation of patients with breast cancer demonstrates the significant impact of this disease on their psycho-emotional state and overall quality of life. Breast cancer is accompanied by pronounced psychological reactions, including anxiety, depressive disorders, decreased concentration, a feeling of hopelessness, and emotional burnout. These factors determine the need for timely psychiatric diagnosis and therapy.

Women perceive the diagnosis of cancer as a threat to their physical condition and identity, and the consequences of the disease and the treatment often lead to complex functional and organic disorders. In this regard, patient rehabilitation should integrate an interdisciplinary approach that integrates oncological, psychiatric, and restorative medical care. Comprehensive rehabilitation is designed to minimize the negative consequences of treatment, restore lost functions, reduce the level of disability, enhance the quality of life, and prolong patients' active participation in social and professional spheres.

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АҢДАТПА

СҮТ БЕЗІ ОБЫРЫМЕН АУЫРАТЫН НАУҚАСТАРДЫ ОҢАЛТУ ІС-ШАРАЛАРЫН ҰЙЫМДАСТЫРУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Әлемде сүт безі обырымен ауыратын әйелдердің жоғары пайыз мүгедектігіне әкеп соғатын жоғары сырқаттану ерте диагностикалау мен емдеудің жаңа технологияларын дамытуды ғана емес, сондай-ақ оңалту іс-шараларын жүргізу кезінде тиімді тәсілдерді құруды да талап етеді, бұл олардың әлеуметтік-маңызды сипатын білдіреді.*

Зерттеу мақсаты *– әдеби деректерді талдау негізінде сүт безі обырымен ауыратын науқастарды медициналық оңалтудың ерекшеліктерін анықтау.*

Әдістері: *Алға қойылған мақсатты іске асыру үшін онкологиялық пациенттерді оңалту саласындағы қазіргі заманғы ғылыми жетістіктерге баса назар аудара отырып, Springer Link, PubMed және Embase қоса алғанда, жетекші электрондық дерекқорлардағы қол жетімді әдеби көздерге талдау жүргізілді. Ғылыми жарияланымдарды іріктеу мынадай негізгі терминдер бойынша жүзеге асырылды: «сүт безінің қатерлі ісіктері», «оңалтудың медициналық стратегиялары», «онкологиялық пациенттердің өмір сүру сапасы».*

Нәтижелері: *Ғылыми дереккөздерді жүйелендірілген талдау РМЖ-мен емдеуден өткен пациенттерді медициналық оңалту бағдарламаларын қалыптастыру және іске асыруға мультидисциплинарлық тәсілді енгізу қажеттігін растады. Науқастардың осы санаты олардың бейімделуі мен әлеуметтік жұмыс істеуіне елеулі әсер ететін көптеген физиологиялық, соматикалық және психологиялық бұзылуларға тап болатыны дәлелденді. Дене және психоэмоционалдық жағдайдағы айқын өзгерістер көбінесе кәсіби және әлеуметтік рөлдерді жоғалтуға әкеп соғады, бұл кешенді оңалту стратегияларын енгізуді талап етеді. Оңалтудың кешенді сипаты пациенттердің өмір сүру сапасын және әлеуметтік интеграциясын арттыруды қамтамасыз ете отырып, оларды жан-жақты қалпына келтіруге ықпал етеді.*

Қорытынды: *РМЖ-ға шалдыққан пациенттерді медициналық оңалтудың интеграцияланған бағдарламаларын қолдану пациенттердің жоғалтқан функцияларын қалпына келтіруге және/немесе оңтайландыруға және олардың табысты әлеуметтік бейімделуіне ықпал етеді.*

Түйінді сөздер: *сүт безінің қатерлі ісігі, оңалту іс-шаралары, өмір сүру сапасы.*

АННОТАЦИЯ

ОРГАНИЗАЦИЯ РЕАБИЛИТАЦИОННЫХ МЕРОПРИЯТИЙ БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Высокая заболеваемость раком молочной железы (РМЖ) в мире, приводящая к высокому проценту инвалидизации женского населения, требует не только развития новых технологий ранней диагностики и лечения, но и призывает к созданию эффективных подходов при проведении реабилитационных мероприятий, что обозначает их социально-значимый характер.*

Цель исследования *– выявление особенностей медицинской реабилитации больных раком молочной железы на основе анализа литературных данных.*

Методы: *Для реализации поставленной цели был проведен анализ литературных источников, представленных в ведущих электронных базах данных, включая Springer Link, PubMed и Embase, с акцентом на современные научные достижения в области реабилитации онкологических пациентов. Отбор научных публикаций осуществлялся по следующим ключевым терминам: «злокачественные новообразования молочной железы», «реабилитационные медицинские стратегии», «качество жизни онкологических пациентов».*

Результаты: *Систематизированный анализ научных источников подтвердил необходимость внедрения мультидисциплинарного подхода к формированию и реализации программ медицинской реабилитации пациенток, перенесших лечение РМЖ. Доказано, что данная категория больных сталкивается с множеством физиологических, соматических и психологических нарушений, которые оказывают значительное влияние на их адаптацию и социальное функционирование. Выраженные изменения в физическом и психоэмоциональном состоянии нередко приводят к утрате профессиональных и социальных ролей, что требует внедрения комплексных реабилитационных стратегий. Комплексный характер реабилитации способствует всестороннему восстановлению пациенток, обеспечивая повышение их качества жизни и социальной интеграции.*

Заключение: *Применение интегрированных программ медицинской реабилитации у пациенток, перенесших РМЖ, способствует восстановлению и/или оптимизации утраченных функций пациенток и их успешной социальной адаптации.*

Ключевые слова: *рак молочной железы (РМЖ), реабилитационные мероприятия, качество жизни.*

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