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Contents

Dear readers!

We welcome you to the pages of the pre-New Year issue of the journal "Oncology and Radiology of Kazakhstan" 2024!

On behalf of the Editorial Board, let me congratulate you on the upcoming New Year! The past year has become a time of great professional growth and new challenges.

Together we have experienced many significant events and advanced in medicine, science and innovation.

In oncology and radiology, we strive to implement advanced technologies, find better diagnostic and treatment solutions, and strengthen our professional community.

This issue presents the research findings of domestic and foreign oncologists and specialists in related fields. It offers articles on new biomarkers for early detection of therapeutic approaches to gastric cancer, discusses the prospects for using extracellular neutrophil trap levels in colorectal cancer, and describes the first experience of VATS bronchoplastic lobectomy in Kazakhstan.

With each new issue, we try to offer a useful tool for professionals in oncology and radiology. We share the latest advances, scientific research, and practical recommendations that help us grow and maintain high levels of medical care. In the coming year, we will continue improving the quality of our content, expanding our audience, and building our community.

May the coming year bring you many bright and joyful moments and an inspiration for new accomplishments and professional achievements! May every day be filled with energy for work and aspiration for new heights. I wish you health, happiness, and success in every endeavor!

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

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ANALYSIS OF CERVICAL CANCER CASES AND HUMAN PAPILLOMA VIRUS PREVALENCE IN ZHAMBYL REGION IN 2021-2023

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ABSTRACT

Relevance: *There are strategies of the World Health Organization (WHO) for the prevention and screening of cervical cancer (cervical cancer), but the annual incidence of cervical cancer and mortality from this disease continue to force the world community to look for ways to improve approaches to its prevention and early detection. The possibilities of prevention and early detection of breast cancer are among the most difficult in practical oncogynecology.*

The study aimed to *evaluate the incidence of cervical cancer in the Zhambyl region for 2021-2023 and determine the spread and prevailing type of human papillomavirus in cervical cancer.*

Methods: *The study was conducted based on data from medical records of patients diagnosed with breast cancer registered with the state municipal enterprise on the right of economic management Zhambyl Regional Multidisciplinary Center of Oncology and Surgery (Zhambyl, Kazakhstan) from 2021 to 2023. Statistical data analysis was performed using the descriptive statistics program of the Statistica 8.0 computer software package (StatSoft, Russia). The data were described as the frequen-cy and proportion (%) of the total cases for categorical variables.*

Results: *In 2021, the average age of patients with cervical cancer (cervical cancer) will be 52 years, with a range from 29 to 83 years. In 2022, the average age dropped to 50 (28-73) years. In 2023, the population's average age will increase to 53.8 years (33-82 years). This indicates a possible age dynamic among patients. Diagnostic effectiveness: in 2023, 99 cases of cervical cancer were identified, of which 51% of patients tested positive for human papillomavirus (HPV). In 2023, the effectiveness of screening programs significantly increased; 23 screening cases were identified, compared with 16 cases in 2021 and 8 in 2022.*

Conclusion: *Analysis of data on the Zhambyl region for 2021-2023 revealed an increase in the average age of women with breast cancer, which requires further study. Improved screening programs and better public awareness have increased early case detection, positively affecting treatment outcomes. Against the background of the high prevalence of HPV, especially its types 16 and 18, the need for timely diagnosis and vaccination against this virus becomes especially urgent.*

Keywords: *prevention of cervical cancer, screening for cervical cancer, barriers to the prevention of cervical cancer, precancerous lesions of the cervix, modern cervical cancer prevention strategies.*

Introduction: In 1996, the World Health Organization, the European Research Organization on Genital Infections and Neoplasia, and the National Institutes of Health Consensus Conference on Cervical Cancer recognized the role of human papillomavirus (HPV) in the development of cervical cancer (cervical cancer) [1]. Based on the degree of association with invasive tumors, HPV genotypes were divided into those that pose high oncogenic risk, low oncogenic risk, and uncertain risk. High oncogenic risk (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) is associated with an increased risk of developing cervical cancer [2].

HPV is one of the most dangerous human carcinogens [3, 4]. However, most HPV genotypes do not cause cancer: according to IARC, only 12 of the documented 448 HPV types are currently reliably classified as carcinogenic ones (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), and HPV type 68 is probably carcinogenic [5]. According to other data, several HPV types are classified as having a low risk of oncogenicity, such as 6, 11, 42, 43, and 44; others as high-risk HPV types - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82; the literature also describes cases when cervical cancer was caused by other types of HPV [6]. Regardless of the accepted classification, HPV type 16 is the most carcinogenic type of HPV worldwide, causing about 60% of HPV-associated cervical cancer; HPV types 18 and 45 are highly carcinogenic, and the remaining types vary in both prevalence and degree of association with cancer depending on the geographical region.

There are World Health Organization (WHO) strategies for preventing and screening cervical cancer. However, the annual incidence of cervical cancer and mortality from the disease continue to compel the global community to seek ways to improve approaches to prevention and early detection of cervical cancer [1]. Currently, the arsenal of the most effective treatments for precancerous cervical lesions includes strategies aimed at sequential treatment, identification of early molecular

markers, and determination of the influence of the vaginal microbiota on viral excretion [6-8]. One of the least explored areas for improvement of screening programs is the application of artificial intelligence to ensure quality screening in regions with a shortage of qualified specialists [9]. Another equally important issue is the shift from the principle of screening and treatment to the principle of screening, triage, and treatment in the management of patients with cervical abnormalities, including precancerous abnormalities [10, 11].

According to statistics provided by the press service of the Kazakh Research Institute of Oncology and Radiology of the Ministry of Health of the Republic of Kazakhstan, cancer care in Kazakhstan is developed within the framework of the Strategic Plan of the Ministry of Health and the Comprehensive Plan for Cancer Control for 2023-2027 a total of 218,213 cancer patients are under dynamic observation (2022 - 205,822 patients) as of the end of 2023. The growth is 5.7%. In terms of incidence, breast cancer is in first place (13.3%, 5,507 cases), colorectal cancer is second (9.5%, 3,939 cases), lung cancer is third (9.3%, 3,872 cases), stomach cancer is fourth (6.9%, 2,874 cases), and cervical cancer is fifth (4.9%, 2,035 cases) [12].

Existing methods of primary prevention influenced the dynamics of cervical cancer incidence and contributed to its downward trend. Nevertheless, the incidence of cervical cancer is increasing in many countries [13]. According to the National Cancer Registry, cervical cancer is the most common type of cancer in Kazakhstan, ranking second among neoplastic diseases in women and fifth among all malignant neoplasms in both sexes. Despite the implementation of screening programs, the incidence of cervical cancer is growing, and mortality rates from this disease remain consistently high [14-17].

The study aimed to evaluate the incidence of cervical cancer in the Zhambyl region for 2021-2023 and determine the spread and prevailing type of human papillomavirus in cervical cancer.

Study methods: The study was conducted based on medical records of patients diagnosed with cervical cancer registered in the Zhambyl Regional Multidisciplinary Center of Oncology and Surgery from 2021 to 2023.

The following materials were used for epidemiological analysis:

1. International Classification of Diseases, Tenth Edition (ICD-10), by regions;

2. Data from the official report of regional oncological dispensaries in the Republic of Kazakhstan, "Report on malignant neoplasm diseases" (registration form No. 7) for the period from 2021 to 2023;

3. Records of patients with the first diagnosis of malignant neoplasms (registration form 090/U);

4. Data of the Agency of the Republic of Kazakhstan on Statistics on the number, gender, and age structure of the population by regions and districts;

5. Form 030-6/u "Dispensary Observation Card";

6. Data from the National Cancer Registry (electronic register of cancer patients) on malignant neoplasms and cervical cancer;

7. Data from the report of the National Center for Healthy Lifestyles on the results of screening studies in the target population of the Republic of Kazakhstan for the period 2021-2023

The admission cards of 235 patients admitted to the Department of Gynecologic Oncology of the Zhambyl Regional Multidisciplinary Center of Oncology and Surgery with a diagnosis of cervical cancer of various stages were analyzed. Patients admitted on an outpatient basis for elective diagnostic and therapeutic procedures were excluded from the study. Statistical data analysis was conducted using Statistica 8.0 (StatSoft, Russia). The data were described as frequency and proportion (%) of total cases for categorical variables. The continuous variables are presented as mean ± standard deviation and were compared using the Student's t-test. The total patient statistics are presented in a general way for categorical variables.

Results:

Age of patients: In 2021, the average age of women with cervical cancer was 52 years. The 95% confidence interval ranged from 49 to 56 years, suggesting a significant variation in age. The minimum age of patients was 29 years, while the oldest age was 83 years.

In 2022, there is a slight decrease in the average age to 50. The confidence interval remained relatively narrow, covering the range of 47 to 52 years. The minimum age among patients was 28 years; the maximum was 73 years this year. A standard deviation of 11.38 years indicates a moderate dispersion of age-related values around the mean one.

Interestingly, in 2023, the average age of women with this diagnosis increased again to 53.79 years, which may indicate an age trend in the patient population. This year, the confidence interval ranged from 51.56 to 56.02 years, showing that most patients were over 50. The minimum age has increased to 33 years.

HPV and types of cancer: HPV type 16 predominated in women who tested positive for HPV. It was found in 76.9% of patients. The study highlights the importance of early diagnostics, HPV vaccination, and improvement of the efficiency of screening programs to improve cervical cancer treatment outcomes.

Cervical cancer stage in detection: In 2021, most patients were diagnosed at stage 1, while in 2023, there was an increase in the proportion of patients diagnosed at stage II (Figure 1). According to the data, the number of diagnostic cases at earlier stages increased in 2023. It may be due to the improvement of diagnostic methods.

An analysis of new cervical cancer cases by age revealed an increase in the number of new cervical cancer

cases in younger age groups in 2023 compared to 2021. The shift in the peak incidence towards younger ages confirms the need to improve and expand screening among young and middle-aged women.

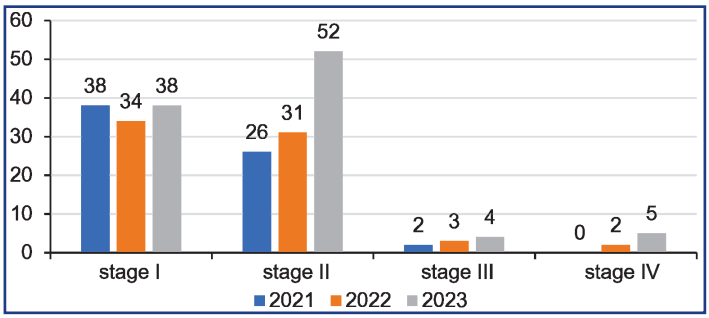

Figure 1 – Stages of cervical cancer found in 2021-2023, %

Types of cervical cancer found: Morphological analysis of the tumors shows that the most common types are adenocarcinoma and squamous cell carcinoma.

In 2023, 99 cases of cervical cancer were found, of which 51% were HPV-positive, indicating a significant prevalence of cervical cancer infection. The efficiency of the screening program has increased significantly in 2023: 23 cases were diagnosed by screening, compared to 8 in 2022 and 16 in 2021. 27.6% of patients tested negative for HPV and 21.4% did not undergo HPV screening, making it difficult to further classify them (Figure 2).

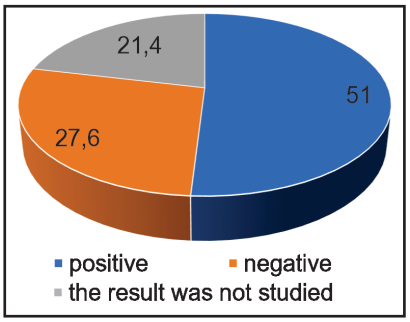

Figure 2 – HPV test results among women with cervical cancer in 2023, %

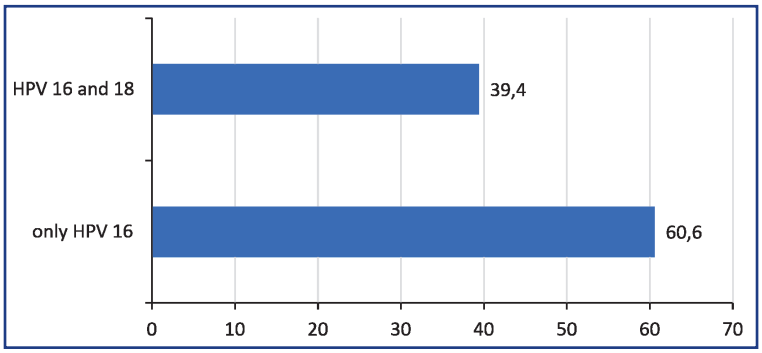

Figure 3 – Distribution of HPV types among women who tested positive for HPV, %

The remaining 23.1% of cases were diagnosed with a combination of HPV types 16 and 18, indicating the prevalence of these strains among infected women with cervical cancer (Figure 3). A 95% confidence interval was calculated for the proportion of women who tested positive for HPV [41.4% to 60.6%]. This interval confirms the reliability of estimates and indicates that more than half of the study sample has HPV infection.

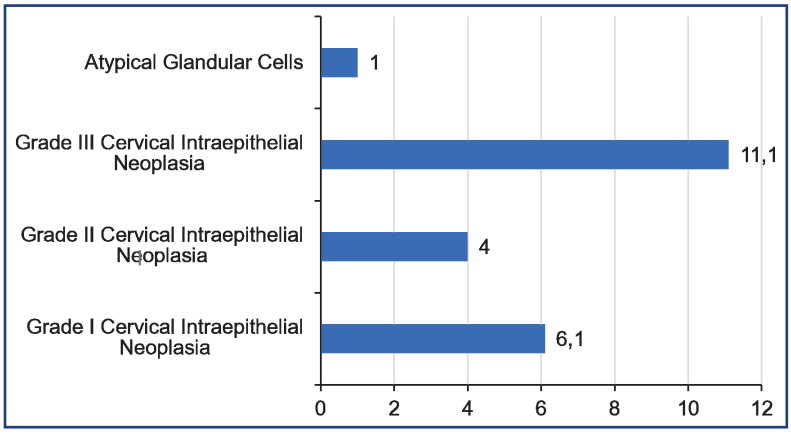

Figure 4 – Proportion of cervical cancer cases among various forms of dysplasia, %

Relationship between cervical cancer and dysplasia: 22 cases of cervical cancer (22.2%) were associated with previous diagnoses of cervical intraepithelial neoplasia (CIN) or atypical glandular cells (AGC). The distribution of these

cervical cancer cases by type of dysplasia is presented below: Grade I CIN – 6 cervical cancer cases (6.1% of the total), grade II CIN – 4 cervical cancer cases (4.0%), grade III CIN – 11 cervical cancer cases (11.1%), AGC – 1 cervical cancer case (1.0%).

The 95% CI for the proportion of cervical cancer cases associated with CIN III was [0.050; 0.172], indicating a significant level of uncertainty but confirming a higher likelihood of cervical cancer in women with CIN III. Figure 4 shows the proportion of cervical cancer cases in the presence of various forms of dysplasia.

Discussion: At the moment, the ability of countries to achieve the goals of the WHO global strategy to accelerate cervical cancer elimination is limited by their level of social and economic well-being. Researchers from different countries suggest the following to improve the efficiency of primary prevention measures:

Raising awareness of the risks associated with HPV and the role of the virus in tumorigenesis not only among women but also among men;

Inclusion of HPV vaccination for boys in national immunization plans;

Developing new HPV vaccines to extend vaccination to middle- and middle-income countries.

To increase the efficiency of secondary prevention measures (early screening for precancerous lesions of the cervix), the following is proposed:

More intensive study of the efficiency of the analysis of self-collected samples;

Search for molecular markers of carcinogenesis in self-collected samples;

Use of artificial intelligence to identify abnormalities in samples for the Pap test;

Use of artificial intelligence in doctor-led cervical biopsy to improve the accuracy of histological examinations;

Development of diagnostic and therapeutic approaches for treatment based on the analysis of the vaginal microbiome [10].

Cervical cancer is one of the main problems in the region [5, 6], and efforts should be made to remove obstacles to the elimination of this disease. Therefore, preventive methods should include vaccination, screening, and public awareness. More and more patients become ill young [7, 8]. The Pap test is an important and effective way to detect cervical cancer. It has high-quality and reliable screening, and the number of cases of this type of cancer can be reduced to 90% [9, 10]. It is recommended that the National Immunization Program include HPV vaccination so that it can be integrated with screening (with a Pap test/HPV DNA) and national cancer control programs, reducing the cost of vaccines and low awareness of effective prevention. Both print and audiovisual media can be crucial to achieve this goal.

According to domestic researchers, the HPV vaccine reduces the risk of cervical cancer and precancerous HPV-associated genital warts without negatively affecting reproductive health. This important observation underscores the safety and efficacy of the human papillomavirus vaccine in preserving the typical well-being of girls and young women. Thus, the HPV vaccine is an important immunization that not only prevents the development of dangerous diseases but also does not affect the reproductive function of a woman. It confirms the safety and efficacy of the HPV vaccination program, which is generally considered a public health measure [11].

Since 2005, preventive gynecological screening has been conducted in Kazakhstan. In 2008, the Ministry of Health of the Republic of Kazakhstan issued Order No. 607, "On Improvement of Preventive Screening of Certain Categories of the Adult Population," and in 2009 – Order No. 685, "On Approval of the Rules for Preventive Screening of the Target Population." Since 2008, the National Cervical Cancer Screening Program has been implemented using Pap tests, assessed according to the Bethesda classification [18]. Studies are conducted at five-year intervals among women aged 30 to 60 years. The program was implemented in stages: training specialists who consult women and providing colposcopy to women [19]. Since 2011, liquid cytology has been actively introduced. It has many advantages over traditional methods. This examination method allows for quick and easy sample collection and is highly sensitive to mild and severe pathologies.

It is known that the main problems in the implementation of screening programs are low coverage of the female population, low compliance with screening, low level of training of medical personnel, and high cost in countries that do not allocate national funding for cervical cancer screening. The main problems and obstacles to cervical cancer screening and proposed ways to solve them were studied in several international studies [20]. Educational activities for healthcare professionals (e.g., continuing education, training in cervical cancer diagnostics, especially screening) have effectively increased adherence and coverage. Female-targeted education campaigns on cervical cancer screening, HPV testing, and HPV vaccination should be conducted at the local, provincial, and national levels. Cervical cancer screening is undoubtedly an important step towards the reduction of the global burden of cervical cancer. However, a comprehensive approach based on the study and improvement of adherence to screening among the female population is required to achieve the ultimate goal of reduction of morbidity and mortality [21].

The results of an epidemiological study of cervical cancer morbidity and mortality in Almaty from 2005 to 2022 showed the need to improve and intensify screening among women of reproductive age and the introduction of vaccination and screening programs with HPV testing [22].

Conclusion: The data analysis results for the Zhambyl region for 2021 and 2023 emphasize the importance of continuing work in the field of early diagnostics and prevention of cancer. Improving screening programs and public awareness can reduce morbidity and improve treatment outcomes. There is a trend towards an increase in the average age of cervical cancer patients during the period under study. This fact requires further identification of possible factors affecting this age dynamics. The study demonstrates a significant HPV prevalence among women with cervical cancer, highlighting the importance of early diagnostics and timely HPV vaccination, especially against types 16 and 18.

It is necessary to perform active explanatory work among the female population, with coverage in the media and social networks, to reduce the burden of cervical cancer and increase the coverage of cervical cancer screening and HPV vaccination in order to improve prevention programs and raise awareness among the population of the Zhambyl region. It is necessary to give recommendations on physical activity for women of different age groups: lead a healthy lifestyle, avoid bad habits, practice sports, and walk in the fresh air. Promoting a healthy lifestyle should contribute to increasing women's responsibility for their health, forming a healthy lifestyle, creating a favorable social environment for maintaining health and preventing diseases, and forming a society with a strong and healthy population.

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АНДАТПА

2021-2023 жж. ЖАМБЫЛ ОБЛЫСЫ БОЙЫНША ЖАТЫР МОЙНЫ ОБЫРЫ ЖӘНЕ АДАМ ПАПИЛЛОМАВИРУСЫНЫҢ ТАРАЛУЫН ТАЛДАУ

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Өзектілігі: *Дүниежүзілік денсаулық сақтау ұйымының (ДДҰ) жатыр мойны обырының (ршм) алдын алу және скринингі бойынша стратегиялары бар, алайда ршм сырқаттанушылығы мен осы аурудан болатын өлім-жітімнің жыл сайынғы көрсеткіштері әлі де әлемдік қауымдастықты оның алдын алу және ерте анықтау тәсілдерін жетілдіру жолдарын іздеуге мәжбүр етеді. РШМ алдын алу және ерте анықтау мүмкіндіктері практикалық онкогинекологиядағы ең күрделі болып табылады.*

Зерттеудің мақсаты болып *– Жамбыл облысы бойынша 2021-2023 жылдары жатыр мойны обырында адам папилломавирусының таралуы мен басым түрін анықтаумен бірге жатыр мойны обырымен сырқаттану көрсеткіштерін бағалау табылады.*

Әдістері: *Зерттеу 2021 жылдан 2023 жылға дейін Жамбыл облыстық онкология және хирургия көпсалалы орталығы (ЖОМЦОиХ ШЖҚ МКК) шаруашылық жүргізу құқығындағы мемлекеттік коммуналдық кәсіпорнында тіркелген РШМ диагнозы қойылған пациенттердің медициналық карталарының деректері негізінде жүргізілді.. Деректер категориялық айнымалылар үшін жағдайлардың жалпы санының жиілігі мен үлесі (%) ретінде сипатталды.*

Нәтижелері: *2021 жылы Жатыр мойны обыры (ЖМО) бар науқастардың орташа жасы 29-83 жас аралығындағы 52 жасты құрайды.2022 жылы орташа жас 50 жасқа дейін төмендеді (28-73 жас). 2023 жылы халықтың орташа жасы 53,8 жасқа (33-82 жас) дейін өседі. Бұл пациенттер арасындағы жас динамикасын көрсетеді. Диагностиканың тиімділігі: 2023 жылы ЖМО-ның 99 жағдайы анықталды, оның 51%-ы адам папилломавирусына (АПВ) оң нәтиже берді.2023 жылы скринингтік бағдарламалардың тиімділігі едәуір артты, 2021 жылы 16 және 2022 жылы 8 жағдаймен салыстырғанда 23 скринингтік жағдай анықталды.*

Қорытынды: *Жамбыл облысы бойынша 2021-2023 жылдардағы деректерді талдау жатыр мойны обыры бар әйелдердің орта жасының өсуін анықтады, бұл одан әрі зерттеуді қажет етеді. Скринингтік бағдарламалардың жақсаруы және халықтың хабардарлығының артуы ерте кезеңдерде диагноз қойылған жағдайлардың көбеюіне әкелді, бұл емдеу нәтижелеріне оң әсер етеді. АПВ-ның, әсіресе оның 16 және 18 түрлерінің жоғары таралуы аясында бұл вирусқа қарсы уақтылы диагноз қою және вакцинациялау қажеттілігі әсіресе өзекті болып отыр.*

Түйінді сөздер: *жатыр мойны обырының алдын алу, жатыр мойны обырының скринингі, жатыр мойны обырының алдын алу жолындағы кедергілер, жатыр мойны обырына дейінгі зақымданулар, жатыр мойны обырының алдын алудың заманауи стратегиялары.*

АННОТАЦИЯ

АНАЛИЗ СЛУЧАЕВ РАКА ШЕЙКИ МАТКИ И РАСПРОСТРАНЁННОСТИ ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА В ЖАМБЫЛСКОЙ ОБЛАСТИ В 2021-2023 гг.

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Актуальность: *Существуют стратегии Всемирной организации здравоохранения (ВОЗ) по профилактике и скринингу рака шейки матки (РШМ), однако ежегодные показатели заболеваемости РШМ и смертности от данного заболевания по-прежнему вынуждают мировое сообщество искать пути совершенствования подходов к его профилактике и раннему выявлению. Проблемы профилактики и раннего выявления РШМ являются одними из наиболее сложных в практической онкогинекологии.*

Цель исследования *– оценить показатели заболеваемости раком шейки матки в Жамбылской области за 2021-2023 гг. с определением распространения и превалирующего типа вируса папилломы человека при раке шейки матки.*

Методы: *Исследование проведено на основе данных медицинских карт пациенток с диагнозом РШМ, зарегистрированных в ГКП на ПХВ «Жамбылский областной многопрофильный центр онкологии и хирургии» с 2021 по 2023 гг. Статистический анализ данных выполняли с использованием программы «Statistica 8.0» (StatSoft, Россия). Данные были описаны как частота и доля (%) от общего числа случаев для категориальных переменных.*

Результаты: *В 2021 году средний возраст женщин с РШМ составил 52 года (диапазон: 29-83 года). В 2022 году средний возраст снизился до 50 лет (28-73 года), а в 2023 году средний возраст снова увеличился до 53,8 года (33-82 года). Это свидетельствует о возможной возрастной динамике среди пациенток с РШМ.*

В 2023 году было выявлено 99 случаев РШМ, из которых 51% пациенток имели положительный результат на вирус папилломы человека (ВПЧ). В 2023 году значительно возросла эффективность скрининговых программ: было выявлено 23 случая благодаря скринингу, в сравнении с 16 случаями в 2021 году и 8 в 2022 году.

Заключение: *Анализ данных по Жамбылской области за 2021-2023 гг. выявил рост среднего возраста женщин с РШМ, что требует дальнейшего изучения. Улучшение скрининговых программ и повышение информированности населения привели к увеличению числа случаев, диагностированных на ранних стадиях, что положительно сказывается на исходах лечения. На фоне высокой распространенности ВПЧ, особенно типов 16 и 18, необходимость в своевременной диагностике и вакцинации против этого вируса становится особенно актуальной.*

Ключевые слова: *профилактика рака шейки матки, скрининг рака шейки матки, барьеры на пути профилактики рака шейки матки, предраковые поражения шейки матки, современные стратегии профилактики рака шейки матки.*

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EPIDEMIOLOGICAL ASSESSMENT OF CANCER INCIDENCE IN THE RURAL POPULATION OF THE ALMATY REGION

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ABSTRACT

Relevance: *In recent decades, there has been an increase in oncological diseases in Kazakhstan, becoming a serious medical and social problem. The relevance of this topic is due to the need to study the causes and dynamics of morbidity in various regions, including rural areas. A lower level of accessibility to medical services, including diagnosis and treatment of oncological diseases, characterizes rural areas of Kazakhstan. Insufficient medical care, difficult socioeconomic conditions, and the possible impact of harmful environmental factors make rural populations more vulnerable to diseases, including cancer. Reliable data on the level and characteristics of cancer is needed to make adequate management decisions in healthcare. Epidemiological analysis in the region's context will optimize resource allocation and improve the availability and quality of cancer care for the rural population of the Almaty region.*

The study aimed to *provide an epidemiological assessment of cancer incidence in the rural population of the Almaty region.*

Methods: *The study included a retrospective analysis of the indicators of the oncological service of the Almaty region, materials on the incidence of malignant neoplasms based on the screening program's results (2015-2020), and statistical processing of indicators.*

Results: *Despite a slight decrease in morbidity and precancerous conditions, the mortality rate did not decrease significantly. The ranking of districts by the general incidence of malignant neoplasms revealed that the "disadvantaged" districts included the Enbekshikazakh, Ili, Karasay, and Talgar districts; the "relatively prosperous" – Zhambyl and Uygur; and the "prosperous" – the Balkhash and Raiymbek districts. The increase in the incidence of malignant neoplasms in almost all localizations in the Almaty region was due to increased cases among the able-bodied population and the rejuvenation of the disease.*

Conclusion: *Summarizing the results of an epidemiological study of the nature and trends of the incidence of malignant neoplasms in the rural population of the Almaty region allows us to formulate the main directions of managerial efforts to change the situation. It is necessary to pay attention to the increase in cancer incidence in the Almaty region (the growth rate is 0.5%). The incidence of malignant neoplasms in almost all localizations of the Almaty region is due to the intensive increase in the incidence of the able-bodied part of the population's "rejuvenation." Therefore, prevention and early diagnosis at the age of 40-60 years with the formation of high-risk groups should lead to a decrease in morbidity and mortality.*

Keywords: *public health, morbidity, epidemiological assessment, screening, cancer awareness, prevention, early cancer diagnosis.*

Introduction: According to the World Health Organization, 19.3 million cancer incidences and 10 million mortalities were registered in 2020 [1]. Cancer incidences increased in developing countries, including Kazakhstan. Cancer morbidities are prevalent among rural residents due to the impact of socio-economic and environmental factors. Growing access to healthcare services is crucial in addressing cancer epidemiology [2]. Canadian studies proved that rural residents' access to medical oncology services is limited. It increases cancer incidence and mortality [3]. According to comparative analysis, cancer treatment outcomes are higher in regions with better health care. Similar studies in Europe proved that smoking, limited physical activity, and limited access to healthcare services increase cancer incidence in rural areas [4, 5].

According to the Ministry of Health of the Republic of Kazakhstan, cancer incidences among rural residents are high. However, the characteristics of this group have not been sufficiently studied.

The studies conducted in other countries demonstrated the necessity of a more in-depth analysis of oncological diseases in rural areas to develop effective prevention and treatment methods [6].

Screening is the most important aspect of early cancer detection. That is cancer detection through mass preliminary population examinations [7]. The main goal of screening is to detect asymptomatic tumors early and treat them. For early detection of diseases in the Republic of Kazakhstan, the National Screening Program provides for preliminary medical examination among target population groups. Early diagnosis of a tumor allows for a complete cure for the disease. Late detection complicates treatment by the risk of tumor spread [8]. Screening studies increased early cancer detection. This positive trend indicates patients' condition improvement and screening programs' effectiveness [9].

The study aimed to provide an epidemiological assessment of cancer incidence in the rural residents of the Almaty region.

Materials and Methods: We analyzed the Almaty region oncology service indicators based on the screening program results, collected data on malignant neoplasm incidence, and statistically processed their indicators.

We used information on the number of cancer incidences and the prevalence by type of cancer among age groups from the Ministry of Health of the Republic of Kazakhstan. We used detailed information on the patient's condition, time and place of diagnosis, and treatment results from oncology registries. We also used the international Globocan database for comparative characteristics [10]. It allowed us to compare cancer incidence and mortality in Kazakhstan with other countries and regions.

Results: According to the World Health Organization [1], cancer incidence in Central Asia is higher than in other regions. According to Globocan 2020 [10], the incidence in Kazakhstan is 89 cases per 100,000 population. It is very close to the rates in neighboring countries such as Kyrgyzstan and Uzbekistan. The Almaty region's rural population makes up a significant part of its population. According to the latest census [11], about 40% of the region's population lives in rural areas. It is approximately 1.5 million people.

These settlements are distinguished by their ethnic diversity, in which many Russians and other nationalities live along with Kazakhs. In the Almaty region, 8,902 cancer patients are registered under dynamic control. In 2018, the incidence rate was 1,670 (relative mass 123.0); in 2019, 1,700 newly diagnosed patients were registered (relative mass 124.1).

Based on the overall cancer incidence rate in the Almaty region (Figure 1), the following «unfavorable" districts are identified: Enbekshikazakh, Ili, Karasay, and Talgar (marked red on the map), and "relatively favorable" districts: Zhambyl and Uygur (marked yellow on the map), and «favorable" districts: Balkhash and Raiymbek (marked green on the map).

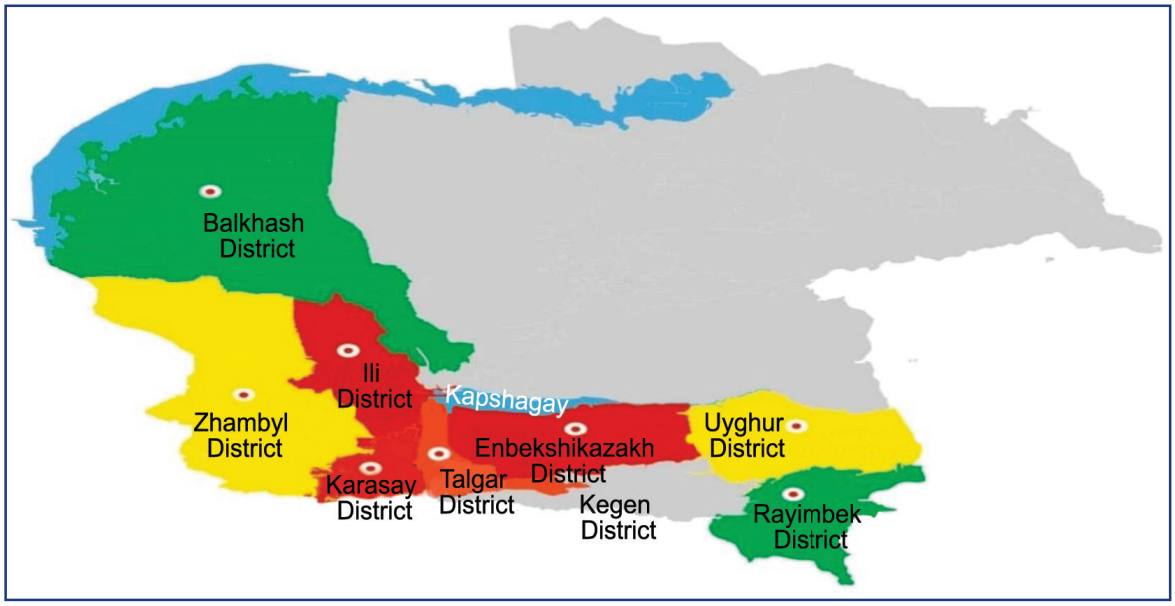

Figure 1 – Differentiation of districts by overall cancer incidence

The cancer incidence among the population increases with age. For example, in the US studies, over 60% of cancer cases occur in people over 65 years [12]. Dividing the population into age groups (0-17, 18-44, 45-64, 65+) is important to analyze which age groups cancer is most common. Analysis of age-related malignant neoplasm incidence in 2019 showed the predominance of breast and cervical cancer in age categories. That is: 40-49 age (Breast cancer – 49 cases, cervical cancer – 19 cases), 50-59 age (Breast cancer – 45 cases, cervical cancer – 30 cases), 60-69 age (Breast cancer – 59 cases, cervical cancer – 20 cases). Also, in the age category of 30-39 years (Breast cancer – 19 cases, cervical cancer – 14 cases) (Figure 2). Although cancer is more common in older people, blood cancer and breast cancer are most common among young people.

Cancer occurs with different frequencies in men and women. For example, lung and liver cancer are more common in men. And breast cancer is more common in women. According to the World Health Organization, in 2020, breast cancer was the highest among women worldwide [13]. In the Almaty region, lung cancer is more common among men, and breast cancer is in first place among women.

As of 2021, lung cancer accounts for 27% of all cancer cases among men. Breast cancer in women accounts for 32% [14]. According to the study, the average age of patients diagnosed with colon cancer was 65.2 ± 7.45 years, and among men – 64.8 ± 4.48 years, and among women – 65.5 ± 5.06 years. Age-related features of this disease are characterized by reaching the progression threshold even at 70 ages and older, with an increase for each subsequent decade of the disease (Figure 3).

In the Almaty region, cancer incidence is distributed by age group and gender. This data is crucial in differentiating the epidemiological situation and planning preventive

measures and medical resources. In the age group from 0 to 17 years, the incidence in this group remains relatively low, but some cancer cases, such as leukemia and central nervous system tumors, are still registered. In 2021, about 30 cases of cancer were registered among children in Almaty region, which is less than 1% of the total. In 2021, about 800 cases of cancer were registered. This is 32% of the total incidences. Among the population over 65 years old, this is the highest rate. Based on the results of the incidence rate of rectal cancer by regions, the following can be classified as "unfavorable" districts: Enbekshikazakh, Zhambyl, and Ili; the "relatively unfavorable" districts include Karasay, Talgar, and Rayimbek; and the "favorable" districts include Balkhash and Uyghur districts (Figure 4).

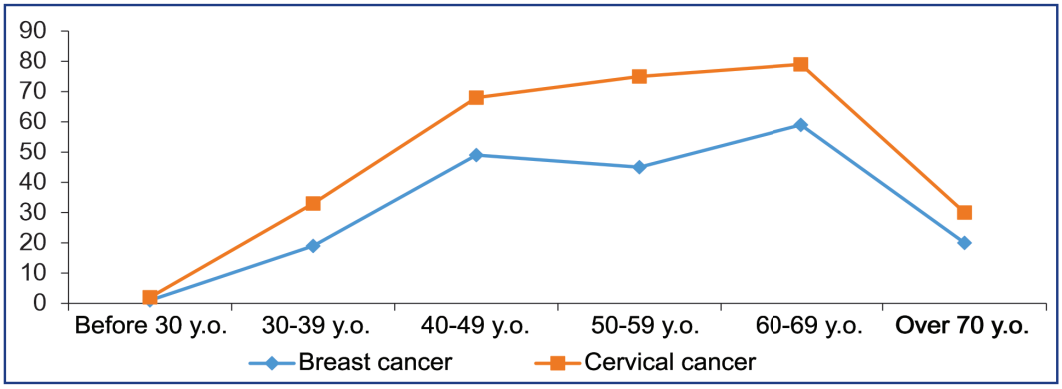

Figure 2 – Breast cancer and cervical cancer incidence in the southern part of Almaty region, 2019

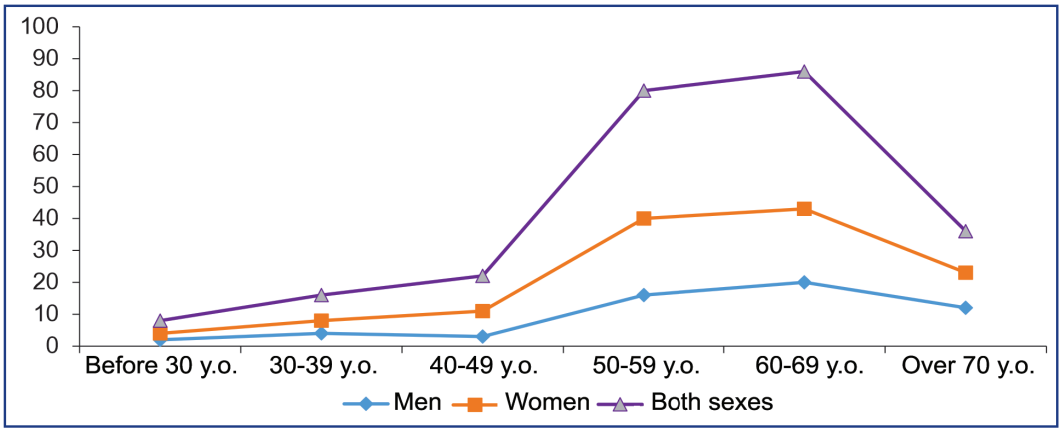

Figure 3 – Colon cancer incidence in the southern part of Almaty region by age and sex

Based on the analysis of breast cancer incidences, a rating of «unfavorable" districts was identified: Enbekshikazakh, Ili, Talgar; "relatively favorable" districts: Zhambyl, Karasay and Uyghur, and «favorable" districts: Balkhash and Rayimbek (Figure 5).

The «unfavorable" districts in assessing the epidemiological situation by the incidence of cervical cancer include Enbekshikazakh, Karasay, and Talgar; "relatively favorable" districts are Zhambyl, Balkhash, and Uyghur; and "favorable" districts are Ili and Rayimbek (Figure 6).

It is known that the incidence of rural populations is influenced by socio-economic, environmental, medical-demographic, and many other factors. During studies, we have become convinced of the importance of lifestyle and environmental risk factors.

However, it is hard to determine the exact impact of each of them individually. Therefore, we adopted a differentiated approach at the initial stage of this study. To be completely sure of this, it is necessary to conduct an individual statistical development of data on the incidence of rural residents based on the characteristics of their socio-economic living conditions.

Many factors influence the development of malignant neoplasms. These include environmental pollution, radiation, rape conditions, hormonal changes in the body, and industrial zones. Another reason is vitamin deficiency. Genetics also plays a big role. One of the important factors in the development of the disease depends on age. For example, the risk of developing colon cancer among the population after 50 years doubles with each decade. All these factors are due to appropriate preventive measures, which include vaccination against oncogenic infections. By influencing these risk factors, it is possible to reduce the incidence and mortality of cancer. Screening coverage for cervical, breast, and colorectal cancer varies by region in the region. The analysis showed that despite a slight decrease in incidence rates and detection of precancerous conditions, the mortality rate does not decrease significantly. The results of the district rating by the level of general incidence of oncological diseases showed:

in the "unfavorable" districts such as the Enbekshikazakh, Ili, Karasay, and Talgar; in the "relatively favorable" districts such as the Zhambyl and Uyghur, and "favorable" districts, including the Balkhash and Rayimbek.

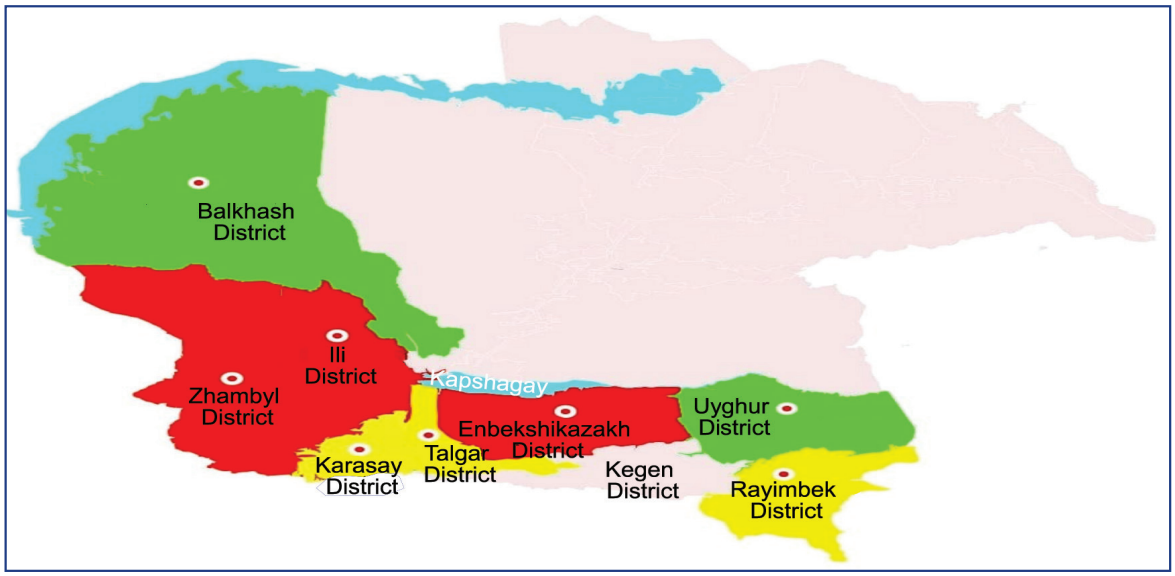

Figure 4 – Rating of incidence of rectal cancer in the Almaty region

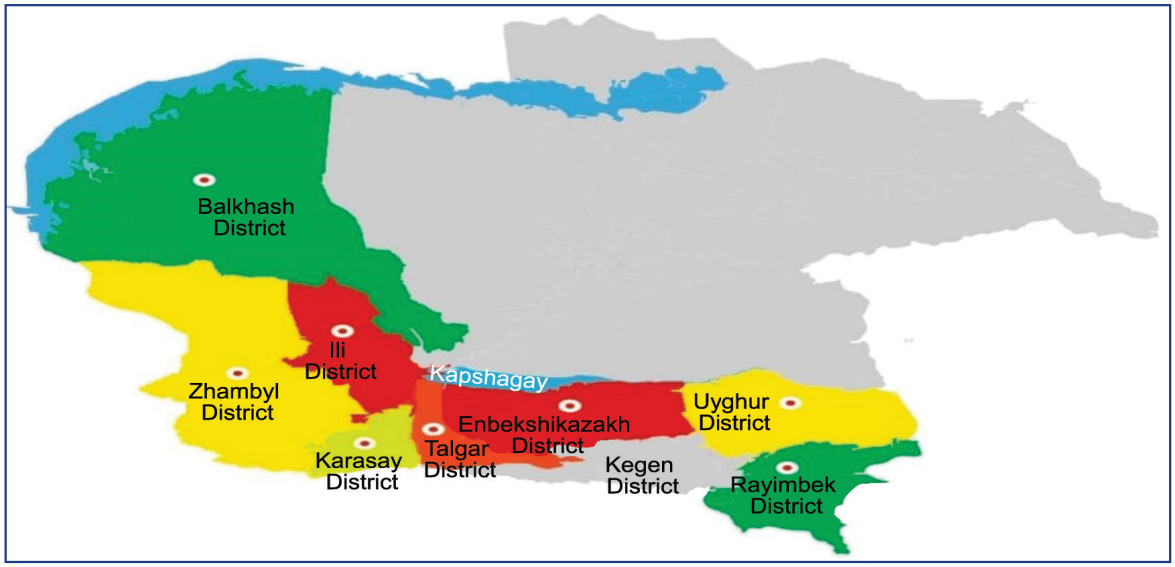

Figure 5 – Rating of districts by incidence of breast cancer

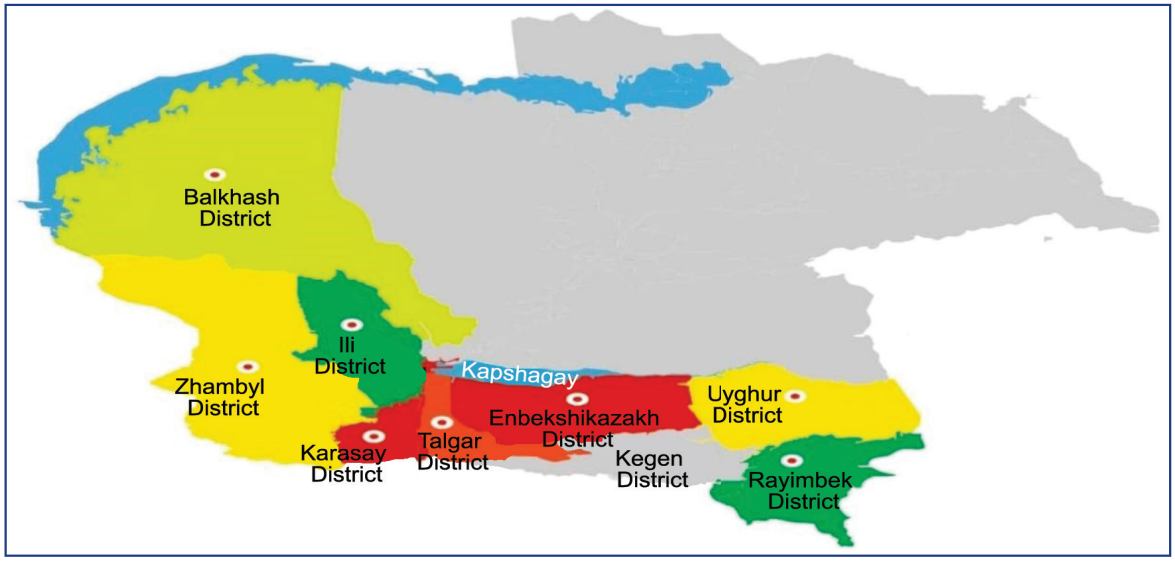

Figure 6 – Differentiation of districts by cervical cancer incidence

The analysis and study of specialized literature showed the relationship between various endogenous and exogenous risk factors affecting cancer development and the risk of developing the disease. In rural areas, oncological auras are a serious problem that requires attention. Comparative data from international studies again emphasize the need to develop effective strategies to improve diagnostic indicators, improve the availability of medical care, and implement preventive programs. This is especially true for rural residents of the Almaty region. Such studies can significantly improve health and reduce the incidence of cancer.

As a model of a protective factor, the well-being of cancer patients can serve as a risk factor. Among women, in most cases, household and socio-economic status as risk factors can further affect the stage of cancer and the effectiveness of therapy. Early diagnosis of cancer can increase the life expectancy of the disease.

Conclusion: Analysis of current data on cancer incidence and mortality provided by international and national sources shows that cancer remains one of the most pressing and complex public health problems worldwide. The results of epidemiological studies of cancer incidence in rural areas of the Almaty region show alarming trends, such as a steady increase in incidence and "rejuvenation" of cancer, especially among the working-age population. In this regard, to effectively manage the situation and improve its epidemiological situation in the region, it is necessary to focus the main work on stabilizing and further reducing the incidence among men and preventing the intensive growth of oncological pathology among women.

Despite significant advancements in cancer diagnostics and treatment, there remains a pressing need to enhance the prevention of known risk factors and improve the organizational framework of cancer care. Raising public awareness about cancer prevention methods and associated risk factors is crucial, particularly through widespread information and educational initiatives targeting rural communities. Enhancing access to medical services requires establishing mobile medical teams to conduct preventive examinations in remote and hard-to-reach areas.

Efforts should address modifiable risk factors such as smoking, poor nutrition, lack of physical activity, and exposure to harmful environmental factors. Additionally, greater emphasis should be placed on promoting regular preventive examinations and participation in screening programs for breast, cervical, and colorectal cancers. These measures significantly increase the likelihood of early detection.

Targeted interventions in high-incidence districts, including Enbekshikazakh, Ile, Karasay, and Talgar, underscore the importance of localized efforts in expanding and optimizing cancer screening programs. Such focused strategies are essential for improving early diagnosis rates and reducing cancer burden.

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АНДАТПА

АЛМАТЫ ОБЛЫСЫНДАҒЫ АУЫЛ ТҰРҒЫНДАРЫНЫҢ ОНКОЛОГИЯЛЫҚ АУРУ-ШАҢДЫЛЫҒЫН ЭПИДЕМИОЛОГИЯЛЫҚ БАҒАЛАУ

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Өзектілігі: *Соңғы жылдары Қазақстанда онкологиялық аурулардың өсуі байқалады. Бұл тақырыптың өзектілігі ауылдық жерлердегі аурудың себептері мен динамикасын зерттеу қажеттілігіне байланысты. Қазақстанның аудандарында онкологиялық ауруларды диагностикалау, емдеу медициналық қызметтердің қолжетімділігінің төмен деңгейімен ерекшеленеді. Медициналық көмектің жеткіліксіздігі, күрделі әлеуметтік-экономикалық жағдайлар және қоршаған ортаға зиянды факторлардың әсер етуі ауыл тұрғындарын аурушаңдылыққа әкелуде. Денсаулық сақтауда тиісті басқару шешімдерін қабылдау үшін онкологиялық аурушаңдылық деңгейі мен ерекшеліктері туралы сенімді деректер қажет. Өңірдегі эпидемиологиялық талдау ресурстарды бөлуді оңтайландырады. Ол ауыл тұрғындары үшін онкологиялық көмектің қолжетімділігі мен сапасын жақсартуға мүмкіндік береді.*

Зерттеудің мақсаты *– Алматы облысының ауыл тұрғындарының онкологиялық аурушаңдылығын эпидемиологиялық бағалау.*

Материалдар мен әдістер: *Алматы облысының онкологиялық қызметінің көрсеткіштеріне, қатерлі ісіктермен сырқаттанушылық бойынша материалдар мен көрсеткіштерге статистикалық өңдеу жүргізе отырып, скринингтік бағдарламаның (2015-2020 жж.) нәтижелері бойынша ретроспективті талдау жүргізілді*

Нәтижелері: *мақалада аурушаңдық пен қатерлі ісікке дейінгі жағдайлардың аздап төмендеуіне қарамастан, өлім-жітім айтарлықтай төмендемейтіні көрсетілген. Қатерлі ісіктердің жалпы аурушаңдылығы бойынша аудандарды саралауды талдау" қолайсыз "аудандарға Еңбекшіқазақ, Іле, Қарасай және Талғар;" салыстырмалы түрде қолайсыз" Жамбыл және Үйғыр; ал "қолайлы" Балқаш және Райымбек аудандары жататынын анықтады. Алматы облысында қатерлі ісіктермен аурушаңдылықтың барлық дерлік таралуының артуы еңбекке қабілетті халық арасында жағдайлардың көбеюімен және аурудың жасаруымен байланысты.*

Қорытынды: *Алматы облысының ауыл тұрғындарының қатерлі ісіктермен аурушаңдылығының сипаты мен үрдістерін эпидемиологиялық зерттеу нәтижелерін жалпылау жағдайды өзгерту бойынша басқарушылық күш-жігердің негізгі бағыттарын тұжырымдауға мүмкіндік береді. Алматы облысы бойынша қатерлі ісік ауруы бойынша аурушаңдығы көрсеткішінің өсуіне назар аудару қажет (өсу қарқыны – 0,5%). Алматы облысында қатерлі ісіктермен аурушаңдылық барлық таралуына қарай халықтың еңбекке қабілетті бөлігінің аурушаңдылығының қарқынды өсуіне, оның "жасаруына" байланысты. Сондықтан 40-60 жас аралығындағы алдын-алу және ерте диагностика жоғары қауіпті топтардың қалыптасуымен аурушаңдылық пен өлім-жітімнің төмендеуіне әкелуі керек.*

Түйінді сөздер: *халықтың денсаулығы, аурушаңдылық, эпидемиологиялық бағалау, скрининг, онкологиялық сақтық, алдын алу, қатерлі ісіктің ерте диагностикасы.*

АННОТАЦИЯ

ЭПИДЕМИОЛОГИЧЕСКАЯ ОЦЕНКА ОНКОЗАБОЛЕВАЕМОСТИ СЕЛЬСКОГО НАСЕЛЕНИЯ АЛМАТИНСКОЙ ОБЛАСТИ

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Актуальность: *За последние десятилетия в Казахстане наблюдается рост онкологических заболеваний, что становится серьезной медико-социальной проблемой. Актуальность этой темы обусловлена необходимостью исследования причин и динамики заболеваемости в различных регионах, включая сельскую местность. Сельские районы Казахстана отличаются более низким уровнем доступности медицинских услуг, включая диагностику и лечение онкологических заболеваний. Недостаточное медицинское обслуживание, сложные социально-экономические условия и возможное воздействие вредных факторов окружающей среды делают сельское население более уязвимым перед заболеваниями, включая рак. Для принятия адекватных управленческих решений в здравоохранении необходимы достоверные данные об уровне и особенностях онкозаболеваемости. Эпидемиологический анализ в разрезе региона позволит оптимизировать распределение ресурсов, улучшить доступность и качество онкологической помощи для сельского населения Алматинской области.*

Цель исследования *– эпидемиологическая оценка онкозаболеваемости сельского населения Алматинской области.*

Методы: *Проведен ретроспективный анализ показателей онкологической службы Алматинской области, материалов по заболеваемости злокачественными новообразованиями (ЗНО) по результатам скрининговой программы (2015-2020 гг.) и статистическая обработка показателей.*

Результаты: *Несмотря на небольшое снижение заболеваемости и предраковых состояний, уровень смертности от злокачественных новообразовании среди сельского населения Алматинской области существенно не снижается. Анализ ранжирования районов по общей заболеваемости злокачественных новообразовании выявил, что к «неблагополучным» районам относятся Енбекшиказахский, Илийский, Карасайский и Талгарский; к «относительно благополучным» — Жамбылский и Уйгурский; а к «благополучным» — Балхашский и Райымбекский. Рост заболеваемости злокачественных новообразовании почти всех локализаций среди населения Алматинской области связан с увеличением числа случаев среди трудоспособного населения и омоложением болезни.*

Заключение: *Обобщение результатов эпидемиологического исследования характера и тенденций заболеваемости злокачественных новообразовании сельского населения Алматинской области позволяет сформулировать основные направления управленческих усилий по изменению ситуации. Необходимо обратить внимание на рост показателя заболеваемости ЗН по Алматинской области (темп прироста – 0,5%). Заболеваемость ЗНО в Алматинской области практически всех локализаций обусловлена интенсивным ростом заболеваемости трудоспособной части населения, ее «омоложением». Поэтому профилактика и ранняя диагностика в возрасте 40-60 лет с формированием групп повышенного риска должна вести к снижению заболеваемости и смертности.*

Ключевые слова: *здоровье населения, заболеваемость, эпидемиологическая оценка, скрининг, онконастороженность, профилактика, ранняя диагностика рака.*

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ANALYSIS OF THE INCIDENCE OF MALIGNANT NEOPLASMS OF THE ORAL CAVITY IN THE CITY OF SHYMKENT

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ABSTRACT

Relevance: *In Kazakhstan, an exponentially growing number of people live with bad habits (smoking, drinking alcohol, drug abuse, etc.), which are the main cause of oral cancer. It is necessary to inform the population about preventive measures and periodically conduct screening examinations.*

The study aimed to *analyze the incidence and mortality rates of the population from oral cancer for 2019-2022 in the city of Shymkent.*

Methods: *A retrospective study of patients with oral cancer in the oncology dispensary of Shymkent from 2019 to 2022 was conducted.*

Results: *The low percentage of early detection of this pathology in the city of Shymkent creates the need to intensify the work of the Shymkent city clinic on the early detection of oral cancer.*

Conclusion: *Within the guaranteed volume of medical care, we recommend that men aged 40 to 70 with bad habits not only in rural areas but also in cities undergo examination once a year for early detection of oral cancer.*

Keywords: *oral cancer, risk factors, oral thrush, prevention, morbidity.*

Introduction: A growing number of people living in our country have harmful habits (smoking, alcohol consumption, drug use, etc.), which are the main cause of oral cancer. Oral cancer is often detected late due to its asymptomatic course [1]. Oral cancer is the second most common cause of death after cardiovascular disease. Its incidence is due to both qualitative and quantitative factors. Smokers and drug abusers have an 8.4 times higher incidence of oral cancer than those who are free of such habits [2]. Oral cancer is more common in countries such as India, Taiwan, Sri Lanka, Pakistan, and Bangladesh. It is particularly prevalent among low-income populations with poor living conditions and widely spread among people at risk factors such as environmental carcinogens, alcohol consumption, infectious agents, and smoking. Oropharyngeal cancer is one of the most dominant cancers globally. Tobacco and alcohol are the main risk factors for oral cancer. Smokeless tobacco also causes oral cancer, as confirmed by the International Agency for Research on Cancer [3, 4]. Other numerous risk factors include smoking, alcohol consumption, poor diet, HPV virus, excessive use of alcohol-based mouthwashes, poor oral hygiene, weakened immune system, and genetic factors. Oral cancer has a profound impact on the normal physiology of the oral cavity. Disturbance of normal physiology leads to malignant diseases such as leukoplakia, erythroplakia, submucosal fibrosis, cleft palate, and actinic keratosis, common in smokers.

The study aimed to analyze the incidence and mortality rates of the population from oral cancer for 2019-2022 in the city of Shymkent.

Materials and Methods: This retrospective study involved patients with oral cancer registered at the Shymkent Oncology Dispensary from 2019 to 2022. Data was taken from patients' medical records with their prior consent. All analyzed patients were newly or previously diagnosed with oral cancer.

The diagnosis in newly diagnosed patients was established:

a. when self-seeing a doctor
b. during medical check-ups
c. during screening

Among patients included in the study, we measured if:

- The diagnosis was morphologically verified
- The stage of the disease was established

Some patients were deregistered for oral cancer due to:

a. Non-verified diagnosis
b. Loss for follow-up.
c. A basal cell carcinoma was diagnosed
d. The patient's death for other diseases.

Patients registered in the past 4 years were 40 to 60 years old.

The study subjects included tongue, oral cavity, pharynx, and palate cancers.

The data was entered into Microsoft Excel and analyzed using the Statistical Package for Social Sciences (SPSS) version 16.

Results: The study included a total of 68 patients with oral cancer, aged 40 to 60 years, both sexes. Among the enrolled patients, 19 were diagnosed with oral cancer in 2019, 14 in 2020, 15 in 2021, and 20 in 2022.

The diagnosis in newly diagnosed patients was established:

In 2019:

a. When self-seeing a doctor – 15 people

p. During medical check-ups – 0

c. During screening – 0

In 2020:

a. When self-seeing a doctor – 13 people

p. During medical check-ups – 0

c. During screening – 0

In 2021:

a. When self-seeing a doctor – 9

p. During medical check-ups – 6

c. During screening – 1

In 2022:

a. When self-seeing a doctor – 5

p. During medical check-ups – 14

c. During screening – 0

The number of patients with laboratory-confirmed diagnoses among patients registered in the past 5 years amounted to 4 patients in 2019, 19 in 2020, 25 in 2021, and 4 in 2022. Tables 1-4 contain information about patients with oral cancer registered at the Shymkent Oncology Center in 2019-2022. The analysis was made in four general areas. The patients were divided into four large groups: patients registered in the relevant year, newly diagnosed patients, patients deregistered for oral cancer during the year, and patients registered with cancer in the past 5 years.

Table 1 – Characteristics of patients with oral cancer registered at the Shymkent Oncology Center in 2019

Indicator	Values		
Among patients registered that year	Patients with a previously established diagnosis		4
	Newly diagnosed patients		15
Among newly diagnosed patients	When self-seeing a doctor	Total	15
		Including 1-2 stages	8
	During medical check-ups	Total	
		Including 1-2 stages	
		Total	
	During screening	Including 1-2 stages	
Among patients deregistered that year	The diagnosis was morphologically verified		15
	The stage of cancer was established		
	Stage I		2
	Stage II		6
	Stage III		2
	Stage IV		5
	Total		90
	Patients deregistered for oral cancer during the year		86
	Non-verified diagnosis		
	Loss for follow-up.		1
	A basal cell carcinoma was diagnosed		
	Death for another disease		3
Patients on record for cancer for the previous 5 years			27

Table 2 – Characteristics of patients with oral cancer registered at the Shymkent Oncology Center for 2020

Indicator	Values		
Among patients registered that year	Patients with a previously established diagnosis		1
	Newly diagnosed patients		13
Among newly diagnosed patients	When self-seeing a doctor	Total	9
		Including 1-2 stages	9
	During medical check-ups	Total	
		Including 1-2 stages	
		Total	
	During screening	Including 1-2 stages	

Table 2 (continued)

Among patients deregistered that year	The diagnosis was morphologically verified	14
	The stage of cancer was established	
	Stage I	3
	Stage II	6
	Stage III	2
	Stage IV	2
	Total	9
	Patients deregistered for oral cancer during the year	3
	Non-verified diagnosis	
	Loss for follow-up.	
	A basal cell carcinoma was diagnosed	
	Death for another disease	6
Patients on record for cancer for the previous 5 years		19

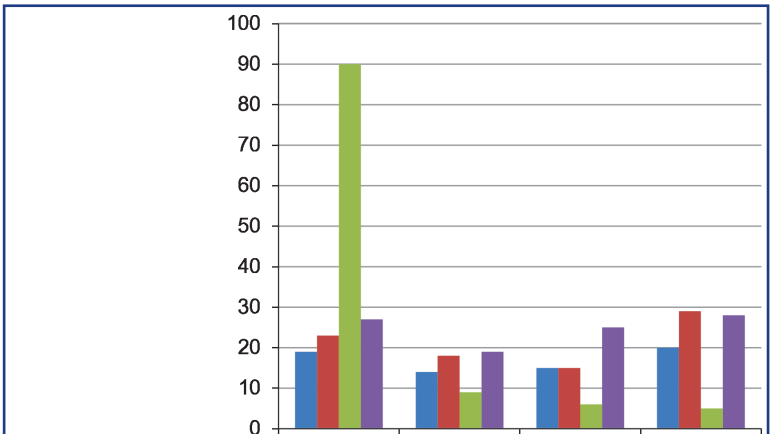
Table 3 – Characteristics of patients with oral cancer registered at the Shymkent Oncology Center for 2021

Indicator	Values		
Among patients registered that year	Patients with a previously established diagnosis		
	Newly diagnosed patients		15
Among newly diagnosed patients	When self-seeing a doctor	Total	9
		Including 1-2 stages	5
	During medical check-ups	Total	6
		Including 1-2 stages	2
		Total	
	During screening	Including 1-2 stages	
Among patients deregistered that year	The diagnosis was morphologically verified		15
	The stage of cancer was established		
	Stage I		1
	Stage II		6
	Stage III		6
	Stage IV		
	Total		6
	Patients deregistered for oral cancer during the year		
	Non-verified diagnosis		
	Loss for follow-up.		
	A basal cell carcinoma was diagnosed		
	Death for another disease		6
Patients on record for cancer for the previous 5 years			25

Table 4 – Characteristics of patients with oral cancer registered at the Shymkent Oncology Center for 2022

Indicator	Values		
Among patients registered that year	Patients with a previously established diagnosis		
	Newly diagnosed patients		20
Among newly diagnosed patients	When self-seeing a doctor	Total	5
		Including 1-2 stages	2
	During medical check-ups	Total	14
		Including 1-2 stages	8
		Total	
	During screening	Including 1-2 stages	
Among patients deregistered that year	The diagnosis was morphologically verified		20
	The stage of cancer was established		
	Stage I		4
	Stage II		6
	Stage III		7
	Stage IV		3
	Total		5
	Patients deregistered for oral cancer during the year		3
	Non-verified diagnosis.		
	Loss for follow-up.		
	A basal cell carcinoma was diagnosed		
	Death for another disease		2
Patients on record for cancer for the previous 5 years			28

According to our findings, 19 patients were registered for oral cancer in 2019, 14 – in 2020, 15 – in 2021, and 20 – in 2022. The number of patients under monitoring has increased by 2022. Among newly diagnosed patients, 23 patients have been diagnosed in 2019, 11 – in 2020, 18 – in 2021, 15 – in 2022, and 20 – in 2023. Of those deregistered in the same year, 90 patients had been registered in 2019, 9 – in 2020, 6 – in 2021, and 5 – in 2022. Of the patients registered during the past 5 years, 27 were registered in 2019, 19 – in 2020, 25 – in 2021, and 28 – in 2022. We divided our identified indicators into subgroups. As shown in Tables 1-4, the highest number of registered patients, newly diagnosed patients, the patients on record for cancer during the past 5 years, and the lowest number of those deregistered during the same year were registered in 2022.



	2019	2020	2021	2022
Among patients registered that year	19	14	15	20
Among newly diagnosed patients	23	18	15	29
Patients deregistered for oral cancer during the year	90	9	6	5
Patients on record for cancer for the previous 5 years	27	19	25	28

Figure 1 – Cohorts of patients registered for oral cancer at the Shymkent Oncology Center in 2019-2022

At early stages, oral cancer is painless and has no obvious onset, so patients seek medical help only when symptoms appear. Tumors usually manifest as white, red, or spotted lesions on the oral mucosa. The oral cavity is often affected first; later, the pathological process passes to the pharynx. Most oral lesions are in the oral cavity (oral mucosa, vestibular apparatus mucosa, and alveolar tumor).

We identified age-related risk factors for oral cancer. Out of 68 patients in this study, 40 (22.18%) were registered with oral cancer at the age of 40-50 years, and 28 (18.75%) – at the age of 50-60 years. Among people with harmful habits, 48 (75.5%) were smokers and 20 (24.5%) were drinkers.

Discussion: Our study did not reveal an overall increase in oral cancer prevalence. Oral cancer can be successfully treated only when detected at an early stage. Early detection of oral cancer is critical because it helps prescribe the right therapy on time, leading to better outcomes. The participants in this study only noticed oral cancer after the onset of clinical symptoms such as weight loss and others. Late detection and diagnosis are directly proportional to morbidity and mortality [6].

Oral cancer is difficult to detect at early stages due to its asymptomatic nature. Therefore, early detection is crucial to improving patient survival. When detected early, the survival rate in oral cancer reaches 80-90% [5, 6].

Delayed detection of the disease increases mortality. Although several treatment options are available, survival rates have not yet improved. Therefore, prevention is the main tool to reduce and control oral cancer mortality. Despite recent advances in treatment strategies, oral cancer survival rates remain low. Thus, the survival rate of patients with locally advanced (stage III or IV) OSCC is below 50% compared to patients with early-stage disease because cervical lymph node metastases are usually associated with poor prognosis in patients with oral cancer. Except for salivary gland pathology, most oral lesions in our study occurred after the age of 45, which confirms the findings of other studies [7, 8]. These could be due to the accumulation of bad habits and parafunctions in the oral cavity and iatrogenic factors. Removable prostheses, extensive sensations, iatrogenic factors, and habits are typical for older people [9, 10].

Despite advances in surgical techniques and adjuvant chemotherapy, the prognosis for patients with oral cancer remains poor. At the same time, five-year overall survival has slightly improved with concurrent postoperative chemotherapy (as shown by the studies of the Radiation Therapy and Oncology Group and the European Organization for Research and Treatment of Cancer). However, to further improve survival and other outcomes in patients with oral cancer, it is necessary to take into account the complex relationships between the patient, the tumor, and the underlying disease. Early detection of malignant tumors and other possible oral malignancies requires timely screening procedures [11].

Conclusion: The oral cavity is a place where various lesions of the mucous membrane occur. Their occurrence can be limited by early identification and elimination of harmful habits and iatrogenic factors, especially those that are prone to lesions, such as the oral and labial entrances. In conclusion, we recommend the following preventive measures:

1. Passing timely preventive check-ups.

2. Excluding all possible odontogenic and iatrogenic causes of oral mucosal lesions.

3. Identifying and eliminating bad habits.

4. Identifying and eliminating all causative factors before surgical treatment to reduce the risk of recurrence.

In addition, we recommend that rural and urban men aged 40 to 70 with harmful habits undergo an annual examination to detect oral cancer early within the state-funded guaranteed volume of medical care.

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АНДАТПА

ШЫМКЕНТ ҚАЛАСЫ БОЙЫНША АУЫЗ ҚУЫСЫНЫҢ ҚАТЕРЛІ ІСІКТЕРІМЕН СЫРҚАТТАНУШЫЛЫҚТЫ ТАЛДАУ

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Өзектілігі: *Қазақстанда ауыз қуысының қатерлі ісігінің негізгі себебі болып табылатын зиянды әдеттермен (темекі шегу, алкогольді ішу, есірткі қолдану және т.б.) өмір сүретін адамдардың саны еселеп өсуде. Ауыз қуысы қатерлі ісігі ұзақ уақыт симптомсыз жүретіндіктен,өте кеш сатысында анықталады. Бұл жағдайды алдын алу мақсатында халықты профилактикалық шаралармен ақпараттандыру, скринингтік тексерістер уақытылы өткізу болып табылады.*

Зерттеу мақсаты: *Шымкент қаласы бойынша 2019-2022 жылдарға арналған ауыз қуысы қатерлі ісігінен халықтың аурушаңдық және өлім-жітім көрсеткіштерін талдау.*

Әдістері: *Шымкент қаласының онкологиялық диспансерінде 2019-2022 жж. аралығындағы ауыз қуысының қатерлі ісігі бар науқастарға ретроспективті зерттеу жүргізілді.*

Нәтижелері: *Шымкент қаласында осы патологияны ерте кезеңде анықтау пайызының төмендігі ауыз қуысы қатерлі ісігіктерін ерте анықтау бойынша Шымкент қаласындағы дәрігерлік амбулатория қызметінің жұмысын жандандыру қажеттілігін тудырады.*

Қорытынды: *Медициналық көмектің кепілдік берілген көлемі аясында тек ауылдық жерлерде ғана емес, қалаларда да зиянды әдеттері бар 40 жастан 70 жасқа дейінгі ерлер ауыз қуысы қатерлі ісігін ерте анықтау мақсатында жылына бір рет тексерілуден өтуді ұсынамыз.*

Түйінді сөздер: *ауыз қуысының қатерлі ісігі, қауіп факторлары, ауыз қуысы, профилактика, аурушаңдық.*

АННОТАЦИЯ

АНАЛИЗ ЗАБОЛЕВАЕМОСТИ ЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ ПОЛОСТИ РТА В ГОРОДЕ ШЫМКЕНТЕ

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Актуальность: *В Казахстане растет в геометрической прогрессии количество людей, живущих с вредными привычками (курение, употребление алкоголя, употребление наркотических средств и т.д.), которые являются основной причиной рака полости рта. Необходимо информировать население о профилактических мерах, периодически проводить скрининговые обследования.*

Цель исследования *– проанализировать показатели заболеваемости и смертности населения от рака полости рта за 2019-2022 годы в городе Шымкенте.*

Методы: *Проведено ретроспективное исследование больных раком полости рта в онкологическом диспансере г. Шымкента в 2019-2022 гг.*

Результаты: *Низкий процент раннего выявления данной патологии в городе Шымкенте создает необходимость активизации работы поликлиники города Шымкента по раннему выявлению рака полости рта.*

Заключение: *В рамках гарантированного объема медицинской помощи мы рекомендуем мужчинам в возрасте от 40 до 70 лет с вредными привычками не только в сельской местности, но и в городах проходить обследование один раз в год с целью раннего выявления рак полости рта.*

Ключевые слова: *рак полости рта, факторы риска, молочница полости рта, профилактика, заболеваемость.*

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EFFICIENCY OF ENDOSCOPIC SEDATED EXAMINATIONS: EXPERIENCE OF THE NATIONAL RESEARCH ONCOLOGY CENTER (ASTANA, KAZAKHSTAN)

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ABSTRACT

Relevance: *The purpose of sedation during endoscopic procedures is to reduce patient discomfort, including anxiety and pain, while maintaining a minimum frequency of side effects associated with taking medications.*

The study aimed to *investigate the effectiveness of sedation in endoscopic examinations at the National Scientific Oncology Center (NSOC, Astana, Kazakhstan) in 2023, determine the effect of sedatives on the quality of colonoscopy, and provide more theoretical evidence for the clinical use of sedatives.*

Methods: *In 2023, sedation for endoscopic examinations at the outpatient stage was available in 11 clinics in Astana. A retrospective analysis of endoscopic studies under sedation and without sedation conducted in the conditions of the NSOC endoscopic department for 2023 was carried out.*

Results: *The total number of endoscopic examinations in Astana in 2023 is 56,143, of which 10,651 studies were conducted under sedation with propofol. The average cost of sedation in Astana was KZT 18,600, from a minimum of KZT 13,000 to a maximum of KZT 32,000. The number of sedations during endoscopic examinations in 2023 in Astana varied from a minimum of 312 to a maximum of 4,593 per clinic. In 2023, 2 cases of colon perforation were recorded during colonoscopy under propofol sedation; both cases occurred in private centers, and patients were urgently operated with colostomy removal.*

In a single-center study of the results of performed colonoscopies without sedation and with sedation in the conditions of the NROC, the number of detected malignancies during sedated colonoscopy was 3% higher, and the number of identified polyps was 0.3% more than with non-sedative, which, as a result, improves the quality of screening colonoscopy as a whole.

Conclusion: *The increased use of sedation at the outpatient level will have a positive impact on the quality of esophagogastroduodenoscopy and screening colonoscopy, which means that it will increase the incidence of early forms of stomach and intestinal cancer. Given the data on sedation during endoscopic examinations in the city's clinics, it is safe to say that there is a good growth potential for the widespread introduction of sedation.*

Keywords: *endoscopy, sedation, analgesia, polyp, colorectal cancer.*

Introduction: The challenge of population aging around the world is gradually worsening, while the incidence of colorectal cancer (CRC) is also increasing with age. CRC is the third most common malignant tumor in the world and the second leading cause of cancer death.

In 2023, the incidence rate in the Republic of Kazakhstan amounted to 208.7 per 100 thousand population, and 41,515 new malignant neoplasms (MNs) have been registered. Gender composition of identified patients with malignant neoplasms made in total: women (56.9% – 23,613 cases) fell ill more often than men (43.1% – 17,902 cases).

CRC rose to second place in cancer incidence structure, compared to fifth in 2022. It now accounts for 9.3% of cancer cases, with 3,939 cases. Of them, 55.6% of patients are people of working age, 18 to 64 years old. In 2023, 1,973 new cases of CRC were reported in men and 1,970 in women. Also, in 2023, the mortality rate was 7.6 per 100,000 men and 6.5 per 100,000 women. Of the newly diagnosed CRC cases in 2023, 501 belonged – to stage 1, 1862 – to stage 2, 912 – to stage 3, and 536 have been attributed – to stage 4.

The elevation of detection of CRC in 2023 was noted across all regions of the country. A colonoscopy allows for detecting and removing potential precancerous lesions and preventing metachronous cancer. A colonoscopy is considered an effective method for lowering the rate of CRC early detection and reducing mortality. However, the effectiveness of colonoscopy depends entirely on the quality of its performance.

Sedatives allow patients to tolerate unpleasant endoscopic procedures, relieving anxiety, discomfort, or pain. It also reduces the risk of physical injury to the patient during endoscopic procedures while providing the endoscopist with adequate conditions for a relevant, comprehensive examination. Therefore, many endoscopists consider sedation an important component of gastrointestinal endoscopy. The goal of sedation in endoscopic procedures is to reduce the patient's discomfort, including anxiety and pain while maintaining a minimal incidence of medication-related side effects. Sedatives allow patients to endure unpleasant procedures, relieving anxiety, discomfort,

or pain, and also reduce the risk of physical injury to the patient during endoscopic procedures by providing the endoscopist with adequate conditions for a detailed examination.

Factors affecting the quality of colonoscopy;

1. Specialist-independent factors: a) the quality of bowel preparation; b) sedation.

2. Specialist-dependent factors: practical skills of an endoscopist.

The quality of bowel preparation depends on the drug used for bowel preparation, the volume of the drug solution drunk, and, of course, the patient's conscientious implementation of all recom According to the Boston Bowel Preparation Scale, the large intestine is conventionally divided into 3 sections: right, middle, and left. The quality of bowel preparation is rated from 0 to 3 points, where 3 points means a clean intestinal section. The recommended number of points for a satisfactory quality of bowel preparation is 6-9 points.

In Kazakhstan, sedation is performed only by anesthesiologists; therefore, it does not depend on the competence of the endoscopist performing the colonoscopy. However, the success of cecal intubation depends on the practical skills and experience of the endoscopist in performing endoscopy.

According to recent data from a multicenter study conducted by J.W. Zhou et al., which included the results of a colonoscopy of 216,400 patients, the detection rates of adenomas (32.24% vs. 31.63%, $p<0.05$) and polyps (20.61% vs. 20.21%, $p<0.05$) increased in the sedated endoscopy group, especially in flat adenomas (44.80% vs. 43.95%, $p<0.05$) and adenomas of 0-5 mm size (66.99% vs. 66.24%, $p<0.05$). In addition, the number of colonoscopy biopsies was significantly higher in the selected group (0.79=0.93 vs. 0.56=0.80, $p<0.001$) [1].

Q. Zhang et al. reviewed the results of 63,417 colonoscopies, including 11,417 sedation-free and 52,000 sedated colonoscopies. The share of colonoscopic examinations with the use of sedatives was 82.0%. The detection rate of adenomas was significantly higher in cases with sedation compared to cases without sedation (adenoma detection rate was 22.5% versus 17.0%). In addition, this study considered the effect of the specialist's experience on the rate of adenoma detection and the percentage of cecum intubation [2].

For successful and safe sedation, endoscopists must consider procedural and patient factors. Procedural factors include the duration of the endoscopic examination, the level of discomfort during the examination, and the patient's prolonged static position during the procedure. Factors related to the patient include drug intolerance, sensitivity to pain, medical history, age, and body weight.

Before the procedure, the doctor must discuss with the patient the benefits, risks, and limitations associated with the use of sedatives, and as a result of the discussion, the patient should sign an informed consent [3].

Medical history and thorough physical examination are needed for all patients before the endoscopic procedures. The anamnesis elements that may affect the quality of sedation include the clinical history and physical examination.

The minimum patient monitoring requirements for gastrointestinal sedation include assessment of blood pressure, heart rate, pulse oximetry, visual assessment of ventilation activity, level of consciousness, and discomfort [4].

The most common benzodiazepines used in sedation are midazolam and diazepam. The efficacy of sedation of these two drugs is the same, but most endoscopists prefer midazolam because of its rapid action onset, short duration of sedation, lower risk of thrombophlebitis, and high amnestic properties. When using midazolam, sleep occurs quickly, after 15 minutes with intramuscular injection and after 1-1.5 minutes with intravenous administration. Besides, it has almost no effect on sleep structure and has almost no aftereffects. Midazolam is not registered in Kazakhstan and, therefore, is not included in the clinical formulary, although it is preferable to propofol in terms of quality.

The use of anesthesiologist-monitored propofol sedation for endoscopic procedures is widespread in the United States and Europe. It is also the most common method of choice in Kazakhstan.

The drug has sedative, hypnotic, amnestic, antiemetic, and anticonvulsant effects but is devoid of analgesic effects. The time from injection to the onset of sedation is 30 to 60 seconds, and its action lasts 4 to 8 minutes [5,6].

Currently, most outpatient endoscopic examinations in Kazakhstan are carried out without sedation, and sedation is performed only at the patient's request on a paid basis. No order obliges to conduct all endoscopic sedated examinations. The only regulation of the Minister of Health of the Republic of Kazakhstan is the order of April 26, 2023, No.78, "On Approval of the standard for the organization of anesthesia and resuscitation care performance in the Republic of Kazakhstan" [7]. Annex No.4 to this order contains the Classification scale for the patient's physical status from the American Society of Anesthesiologists' Endoscopy Manual on Sedation.

Most importantly, any sedation for all outpatient and inpatient endoscopic interventions in Kazakhstan can only be performed by anesthesiologists. An endoscopist can be admitted to sedation, but only if there is a certificate of completion of certification courses on anesthesiology. However, according to American guidelines, self-sedation of the patient by gastroenterologists or endoscopists is justified and recommended only for routine diagnos-

tic procedures, such as colonoscopy and gastroscopy. In surgical endoscopic interventions, sedation is carried out only by doctors-anesthesiologists since the intraprocedural introduction of the patient requires the attention of a separate specialist and a separate nurse.

Also, Annex No.5 to this order specifies the scope of preoperative examination of patients, considering the urgency of surgical intervention (in case of emergency and planned hospitalization), but does not specify the exact list of tests required for sedation in outpatient cases.

This study aimed to investigate the effectiveness of sedation in endoscopic examinations at the National Scientific Oncology Center (NSOC, Astana, Kazakhstan) in 2023, determine the effect of sedatives on the quality of colonoscopy, and provide more theoretical evidence for the clinical use of sedatives.

Materials and methods: In 2023, sedation for endoscopic examinations at the outpatient stage was available in 11 clinics in Astana. A retrospective analysis of endoscopic studies under sedation and without sedation conducted in the conditions of the endoscopic department of the National Scientific Oncology Center (NSOC, Astana, Kazakhstan) was performed.

In a sedated colonoscopy, patients received intravenous propofol to achieve deep sedation or general anesthesia. At the beginning of the procedure, propofol was administered at a dose of 80-120 μg/kg of body weight. A maintenance dose of 20-50 mcg/kg was repeated depending on the patient's response, operator experience, and technical difficulties encountered, while patients undergoing traditional colonoscopy remained conscious during the procedure. All patients were monitored with pulse oximetry, continuous ECG, and noninvasive blood pressure assessment every 5 minutes. Supplemental oxygen is supplied to patients under sedatives through a nasal catheter.

Results: In 2023, the total number of endoscopic examinations performed in Astana comprised 56143, of which 10651 were carried out under propofol sedation. The average cost of sedation in Astana amounted to KZT 18,600, from a minimum of KZT 13,000 to a maximum of KZT 32,000. The number of sedations during endoscopic examinations performed in 2023 in Astana ranged from a minimum of 312 to a maximum of 4,593 per clinic. In 2023, 2 cases of perforation of the large intestine during colonoscopy under sedation with propofol were recorded, and both cases occurred in private centers, followed by the patients urgently operated with the colostomy egestion. According to Table 4, sedation during endoscopic examinations at the outpatient stage is available in 11 clinics in Astana. However, in 5 clinics, the tests for sedation are not required at all 5 clinics only a general blood count and ECG are required from the necessary tests, and only in one clinic 5 tests are required (complete blood count, blood test for HIV and hepatitis, ECG and plain X-ray of the lungs). Based on data from Table 1, it can be stated that the list of tests requested by the anesthesiologist before sedation is not regulated by the Order No.78 of the Ministry of Health of the Republic of Kazakhstan and depends on the preferences of the anesthesiologist. The number of sedations depends only on the staffing of intensive care and anesthesiology departments; hence, the potential for growth of sedated endoscopies directly depends on the number of anesthesiologists in the clinic.

Table 1 – Use of sedation in endoscopy at the outpatient stage in Astana (Kazakhstan), 2023

Aspects	Name of Clinic										
	NRMC	MDMC	NSOC	State hospital №1	State hospitalNo2	State hospital №3	Hospital of the Department for Presidential Affairs RK	I-clinic	Green Clinic	Alanda	Umit
1. No. of studies in 2023	5880	4734	4833	7788	7922	6553	9674	1600	3559	2100	1500
2. No. of sedated examinations	312	500	478	1040	320	348	4593	1280	316	864	600
3. Cost of sedation?	32000	20000	18000	29500	13000	13000	15000	22000	24000	18000	25000
4. What tests are required?	Not required	Not required	CBC, HIV, hepatitis, ECG, X-ray of lungs	CBC, UA, ECG	Not required	Not required	CBC, ECG	CBC, ECG	CBC, ECG	CBC, ECG	Not required

According to Table 2, the total number of endoscopic examinations performed in the Department of Expert Endoscopy of the NSOC steadily increases yearly, even though the department employs only 3 endoscopists and only 2 colonoscopes are available. Also, according to Table 2, it can be seen that the number of recto-colonoscopy examinations and the number of initially diagnosed cases of CRC is also growing, although the clinic does not belong to a primary care medical facility.

Table 2 – Performance indicators of the Department of Expert Endoscopy of the NSOC, 2019-2023

Indicator	Years				
	2019	2020	2021	2022	2023
Total number of endoscopic examinations	1226	2130	2684	2676	4833
Number of biopsies in all endoscopic examinations	294	1577	693	1452	1721
Rectocolonoscopy	78	351	503	555	968
Number of biopsies in rectocolonoscopies	29	301	176	308	353
Number of malignant neoplasms detected during recto-colonoscopies	22	10	32	37	50

According to Table 3, the number of sedated colonoscopy procedures performed at the NSOC Endoscopy Center of Expertise was lower than non-sedated procedures, with an annual increase in the proportion of sedated endoscopy examinations. Besides, Table 3 confidently proves that sedated examinations detected more cases of terminal ileum and cecal intubation and benign neoplasms, including flat neoplasia. Thus, in 2019-2023, benign tumors were detected 3-11% more often during sedated colonoscopy than during non-sedated examinations. Accordingly, this has improved the quality of screening colonoscopy in general.

Table 3 – Results of colonoscopy examinations conducted at the Center for Expert Endoscopy of the NSOC, 2019-2023

Indicator	Years				
	2019	2020	2021	2022	2023
Number of colonoscopies, abs.	40/38***	202/149	289/214	305/250	490/478
CIR, %*	89.1/93.8	91.2/94.1	91.0/94.7	92.5/94.3	91.7/96.3
ADR, %**	17/22.5	18/22.4	17.9/25.6	19.1/27.2	20.9/32.1

*Notes: *CIR is an indicator of cecum intubation; **ADR – adenoma detection rate; The first digit in the results refers to non-sedated colonoscopy, the second to sedated colonoscopy*

The statistical analysis of differences in the incidence of cecum intubation and the incidence of adenomas with and without sedation was carried out using the Welch t-test. The two-sample Welch t-test, which compared adenoma detection between the sedated and non-sedated groups, revealed a significant difference between the groups (t=-3.8431, p=0.0075), with the sedation group having a higher mean adenoma detection rate (23.72), compared to the non-sedation group (18.58). The 95% confidence interval for the mean difference composed [-8.36, -1.92] indicates a significant effect of sedation status.

Sedation during colonoscopy makes it possible to examine the mucous membrane of the large intestine more thoroughly using chromoendoscopy and electron chromoendoscopy, increasing the number of biopsies and ultimately increasing the adenoma detection rate (ADR).

Discussion: Sedated colonoscopy has been carried out in clinics in Astana and Kazakhstan over the past decades. It is widely used in clinical practice in public hospitals and private centers. At NSOC, sedatives are used in 42.4-49.3% of cases, and ADR rate and cecal intubation rate (CIR) increase year to year with more sedatives used. The growth of the proportion of sedated endoscopic examinations in clinics depends on the availability of doctors-anesthesiologists and anesthetists in the anesthesiology and resuscitation departments. For example, NSOC has significantly increased the rate of sedated colonoscopies and ADR and CIR rates. However, there is a shortage of anesthesia service staff.

In this study, we did not consider the years of experience and the number of colonoscopies performed by each endoscopist of the Expert Endoscopy Department since only three doctors worked there, which was not enough to compare the indicators.

The main limitation of this study was the insufficiency of indicators reflecting the quality of colonoscopy. Two important indicators of colonoscopy quality, including ADR and CIR, have been studied. However, other indicators, such as patient comfort and satisfaction, were not considered. This retrospective study lacked data on patient satisfaction, so the relevant indicators could not be examined. In addition, sedation may lead to increased complications and financial burdens on patients not assessed in that study. Further studies are needed to assess sedatives' complications and potential economic impact on colonoscopy.

Conclusion: Further development of effective and safe sedation in endoscopy requires further high-quality multicenter randomized trials in cooperation with professional societies of anesthesiologists and resuscitators, modifying the legislative framework, and the research of the pharmaco-economic efficacy of specified changes. Expanded use of sedation at the outpatient level could improve the quality of endoscopic examinations and, therefore, increase the detection of early forms of bowel cancer. Data on the use of sedation during endoscopic examinations in Astana clinics evidences a good growth potential for a wider introduction of sedation and improving the quality of colonoscopies (ADR, CIR). The increase in ADR and timely curing of identified adenomas will have a positive delayed cumulative effect on the CRC incidence and mortality due to this disease among the population of Kazakhstan. This study's results suggest sedatives can help inexperienced and experienced endoscopists achieve better colonoscopy quality.

Also, in our opinion, it is necessary to work out the issue of proper and adequate reimbursement of the cost of sedation under the CSHI package at the outpatient stage.

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АҢДАТПА

СЕДАЦИЯ КЕЗІНДЕГІ ЭНДОСКОПИЯЛЫҚ ЗЕРТТЕУЛЕРДІҢ ТИІМДІЛІГІ: ҰЛТТЫҚ ҒЫЛЫМИ ОНКОЛОГИЯЛЫҚ ОРТАЛЫҚТЫҢ ТӘЖІРИБЕСІ (АСТАНА, ҚАЗАҚСТАН)

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Өзектілігі: *Эндоскопиялық процедураларды жүргізу кезінде седацияның мақсаты пациенттің ыңғайсыздығын, соның ішінде мазасыздық пен ауырсынуды азайту, дәрі-дәрмекпен байланысты жанама әсерлердің минималды жиілігін сақтау болып табылады.*

Зерттеудің мақсаты *– Ұлттық ғылыми онкологиялық орталық (ҰҒО, Астана, Қазақстан) жағдайында эндоскопиялық тексерулер кезінде седативтерді қолданудың тиімділігін зерттеу 2023 ж., седативтердің колоноскопия сапасына әсерін анықтау және седативтердің клиникалық қолданылуына көбірек теориялық дәлелдер келтіру.*

Әдістері: *2023 жылы амбулаториялық кезеңде эндоскопиялық зерттеулер кезінде седация Астана қаласындағы 11 клиникада қолжетімді болды. 2023 жылы Ұлттық ғылыми онкологиялық орталықтың (Астана, Қазақстан) эндоскопиялық бөлімшесі жағдайында жүргізілген седациямен және седациясыз эндоскопиялық зерттеулерге ретроспективті талдау жүргізілді.*

Нәтижелері: *2023 жылы Астана қаласы бойынша эндоскопиялық зерттеулердің жалпы саны 56143-кетең, оның ішінде пропофол седациясымен 10651 зерттеу жүргізілді. Астана қаласы бойынша седацияның орташа құны 18600 теңгегетең, ең төменгі құны – 13 мың теңге және ең көбі 32 мың теңгеге дейін жетеді. 2023 жылы Астана қаласы бойынша эндоскопиялық зерттеулер кезінде седациялардың ең аз саны 312, ең көп саны – 4593 құрады.*

2023 жылы пропофол седациясының астында колоноскопия кезінде тоқ ішектің перфорациясының 2 жағдайы тіркелді; екі жағдай да жеке орталықтарда болды, науқастарға колостомияны жою үшін шұғыл операция жасалды. Седациясыз және седациямен жүргізілген колоноскопиялардың нәтижелерін бір орталықты зерттеуде седативті колоноскопияда анықталған қатерлі ісіктердің саны седативті емес колоноскопияға қарағанда 3%-ға, ал анықталған полиптердің саны 0,3%-ға көп болды, нәтижесінде жалпы скринингтік колоноскопияның сапасы артады.

Қорытынды: *Амбулаториялық деңгейде седацияны қолдануды кеңейту эзофагогастродуоденоскопия мен скринингтік колоноскопияның сапасына оң әсер етеді, яғни асқазан мен ішек қатерлі ісігінің ерте түрлерінің пайда болуын арттырады. Қала клиникаларында эндоскопиялық зерттеулерде седация деректерін ескере отырып, седацияны кеңінен енгізу үшін жақсы өсу әлеуеті бар деп айтуға болады.*

Түйінді сөздер: *эндоскопия, седация, анальгезия, полип, колоректальды қатерлі ісік.*

АННОТАЦИЯ

ЭФФЕКТИВНОСТЬ ЭНДОСКОПИЧЕСКИХ ИССЛЕДОВАНИЙ ПОД СЕДАЦИЕЙ: ОПЫТ НАЦИОНАЛЬНОГО НАУЧНОГО ОНКОЛОГИЧЕСКОГО ЦЕНТРА (АСТАНА, КАЗАХСТАН)

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Актуальность: *Целью седации при проведении эндоскопических процедур является уменьшение дискомфорта пациента, включая беспокойство и боль, при сохранении минимальной частоты побочных эффектов, связанных с приемом лекарств.*

Цель исследования *– изучить эффективность применения седации при эндоскопических исследованиях в условиях Национального научного онкологического центра (ННОЦ, Астана, Казахстан) в 2023 году, определить влияние седативных препаратов на качество колоноскопии и предоставить больше теоретических доказательств для клинического применения седативных препаратов.*

Методы: *В 2023 г. седация при эндоскопических исследованиях на амбулаторном этапе была доступна в 11 клиниках г. Астана. Проведен ретроспективный анализ эндоскопических исследований под седацией и без седации, проведенных в условиях эндоскопического отделения Национального научного онкологического центра (Астана, Казахстан).*

Результаты: *Общее количество эндоскопических исследований по г. Астана за 2023 год равна 56143, из них под седацией пропофолом проведено 10651 исследование. Средняя стоимость седации по г. Астана равна 18600 тенге, минимальная стоимость – 13 тысяч тенге и максимально доходит до 32 тысяч тенге. Минимальное количество седаций при эндоскопических исследованиях в 2023 г. по г. Астана составило 312, максимальное количество – 4593.*

За 2023 год зафиксировано 2 случая перфорации толстого кишечника во время колоноскопии под седацией пропофолом; оба случая произошли в частных центрах, пациенты были экстренно прооперированы с выведением колостомы.

В одноцентровом исследовании результатов проведенных колоноскопий без седации и с седацией в условиях ННОЦ количество выявленных злокачественных образований при седативной колоноскопии было больше на 3%, а количество выявленных полипов – больше на 0,3 %, чем при неседативной, что, в итоге, повышает качество скринингoвой колоноскопии в целом.

Заключение: *Расширение использования седации на амбулаторном уровне окажет положительное влияние на качество эндоскопических исследований, а значит, повысит выявляемость ранних форм рака кишечника. Учитывая данные по проведению седации при эндоскопических исследованиях в клиниках г. Астаны, можно с уверенностью сказать, что есть хороший потенциал роста для повсеместного внедрения седации и роста качества проводимых колоноскопий.*

Ключевые слова: *эндоскопия, седация, анальгезия, полип, колоректальный рак (КРР).*

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ANALYSIS OF THE EXPRESSION OF APOPTOSIS MARKERS ON PERIPHERAL BLOOD LYMPHOCYTES AND BLAST CELLS IN ACUTE LEUKEMIA IN CHILDREN

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ABSTRACT

Relevance: *A topical issue of oncohematology is the search for effective approaches to therapy and methods of predicting the course of acute leukemia. A promising direction in this field is the study of changes in the expression of molecular markers on the cell surface in the dynamics of chemotherapy.*

The study aimed to *determine the expression level of proteins annexin V, Bcl-2, CD95, and p53 on peripheral blood lymphocytes and leukemic bone marrow cells in children diagnosed with acute leukemia.*

Methods: *the study design was cross-sectional. Research method: immunophenotyping. Peripheral blood and bone marrow of 106 patients with acute leukemia diagnosed for the first time at 1 month to 16 years (study group) and peripheral blood of 23 conditionally healthy children aged 2 to 17 years (control group) served as the study materials. The obtained data were subjected to statistical processing.*

Results: *The study of Bcl-2 expression in B-ALL did not reveal reliable differences; in T-ALL, Bcl-2 expression was significantly higher on peripheral blood lymphocytes than on blasts. In OML, Bcl-2 expression was significantly higher in the blast cell population than in lymphocytes. When CD95 expression was analyzed in ALL, expression was significantly higher on peripheral blood lymphocytes than on the membrane of leukemic cells. The results of the analysis of the expression of annexin V showed that lymphocytes expressed a marker of early apoptosis significantly more than bone marrow blasts. This phenomenon is a dangerous sign indicating a decrease in antitumor immunity. Comparative analysis of p53 protein expression on the surface of lymphocytes and blast cells showed no significant differences in leukemia variants.*

Conclusion: *The study indicated the prognostic significance of Bcl-2 and CD95 in acute leukemia. Annexin V and p53 did not show reliable sensitivity and specificity, which allows not to include these markers in the leukemia immunophenotyping panel.*

Keywords: *acute leucosis, blast cells, markers of apoptosis, Bcl-2, CD95.*

Introduction: Significant progress has been made in diagnosing and treating acute leukemia (AL) over the past decade. The clinicians' main problem remains the presence of resistant forms of the disease and the frequency of relapses. Accordingly, the search for effective methods of treatment, diagnostics, and prognosis of the AL course is one of the main topics of domestic and foreign oncohematology. In this area, the study of the biological characteristics of leukemia cells, particularly changes in the expression of molecular markers on the surface of cells during chemotherapy dynamics, seems to be a promising area [1, 2].

It is known that an important role is played by an imbalance between proliferation and the ability of cells to die naturally (apoptosis) in the development of most malignant tumors. The main function of apoptosis is to eliminate transformed cells, including virus-infected, tumor-infected, or irreversibly damaged cells. Induction of apoptosis is the main mechanism of action of most chemotherapy drugs used in the intensive treatment of AL [2-11]. Currently, two main interrelated mechanisms of apoptosis are actively investigated: mitochondrial and receptor ones. They function with a balanced interaction of pro- and anti-apoptotic factors, such as proteins of the Bcl-2 family, p53, and CD95 proteins [2].

Thus, H.F. Ebian et al. found that increased regulation of Bcl-2 was paradoxically associated with increased apoptosis and low rates of early mortality in AML patients [12]. Low Bcl-2 expression levels indicated inhibition of antiapoptosis and chemosensitivity in malignant cells [2].

The CD95 protein is known to be directly involved in the initiation and regulation of apoptosis. The results of studies showing a significant increase in CD95 expression on the surface of cells obtained from patients with acute leukemia, breast cancer, and glioblastoma after chemotherapy or radiation treatment are presented in [13-16]. A high level of CD95 expression predicted a favorable response to chemotherapy in acute lymphocytic leukemia (ALL) [2]. At the same time, M. Tiribelli et al. have shown an association between increased Bcl-2 expression and chemotherapy resistance and low survival in AML [17].

A key element in ensuring the genomic stability of a cell is the transcription factor p53, known as the "im-

mortality protein" or "guardian of the genome." It is involved in the regulation of l death receptor genes (DR5, Fas); l genes responsible for stopping cell division (P21, GADD45, etc.); l genes that trigger apoptosis (I-VM, KILLER DR5, PIG, etc.); l causes repression of genes that inhibit apoptosis (BCL-2, RELLA). Dysfunction of p53 is found among many malignant diseases, including AL. In adult ALL, p53 gene mutations are found in 13% of cases, but in children, this figure is much lower at 2% of cases. It may lead to a more favorable prognosis and a high frequency of remission in children [2]. Studying the p53 expression in patients with various AML variants, A. Ahmádzadeh et al. found a poor prognosis in patients with high levels of this protein expression [18]. Therefore, studying the complex of apoptotic (annexin V, CD95, p53) and anti-apoptotic antigens (Bcl-2) will make it possible to identify differences in the signaling pathways of apoptosis in different variants of acute leukemia. It may be helpful to look for abnormalities in programmed cell death mechanisms to determine methods to predict leukemia cells' sensitivity and/or resistance. Analysis of the role of annexin V, CD95, p53, and Bcl-2 markers controlling apoptosis will make it possible to develop recommendations for improvement of the panel of surface antigens in cell immunophenotyping at various stages of therapy.

The study aimed to determine the expression level of proteins annexin V, Bcl-2, CD95, and p53 on peripheral blood lymphocytes and leukemic bone marrow cells in children diagnosed with acute leukemia.

Materials and methods:

The study design is cross-sectional.

The study materials were the peripheral blood and bone marrow from 106 patients (the study group) diagnosed with acute leukemia and the peripheral blood of 23 conditionally healthy children (the control group). The patients' age varied from 1 month up to 16 years in the study group and from 2 to 17 years in the control group.

All patients with AL received appropriate therapy at the Scientific Center for Pediatrics and Pediatric Surgery (Almaty, Kazakhstan). The stay of patients diagnosed with ALL in the inpatient regime was 8 months, for patients with AML - 4-5 months.

Samples from patients with marked leukopenia and in the absence of signed informed consent or informed waiver from the study prior to initiation of therapy were excluded from the study.

Research method: immunophenotyping of bone marrow and peripheral blood. The acute leukemia diagnostic panel included 51 immunophenotypic markers. The samples were analyzed on a flow cytometer FacsCantoII (Planet Dickéncon, USA) in the DIVA program. The data were collected under several parameters in the DIVA software of the flow-through cytometer FacsCantoII: forward light scattering (FSC), side light scattering (SSC), and 8 fluorescence channels. The linearity and subvariant of acute leukemia were determined at the first stage using a multicolor panel of monoclonal antibodies. The same samples on bone marrow blast cells and peripheral blood lymphocytes of patients with AL were tested for annexin V, Bcl2, CD95, and p53 protein expression before treatment.

Statistical methods: The SPSS statistical program was used for statistical data processing. The Mann-Whitney U-test was used to analyze the differences between the two independent variables. The significance level was set to $p<0.05$ to determine reliability.

Results: The linearity and subvariant of acute leukemia in children were determined with the use of a panel of monoclonal antibodies; the expression of apoptotic (annexin-V, CD95, p53) and anti-apoptotic antigen (Bcl-2) on bone marrow blast cells and peripheral blood lymphocytes was found for the same sample.

The structure of AL immunological variants in the studied patients is presented in Figure 1.

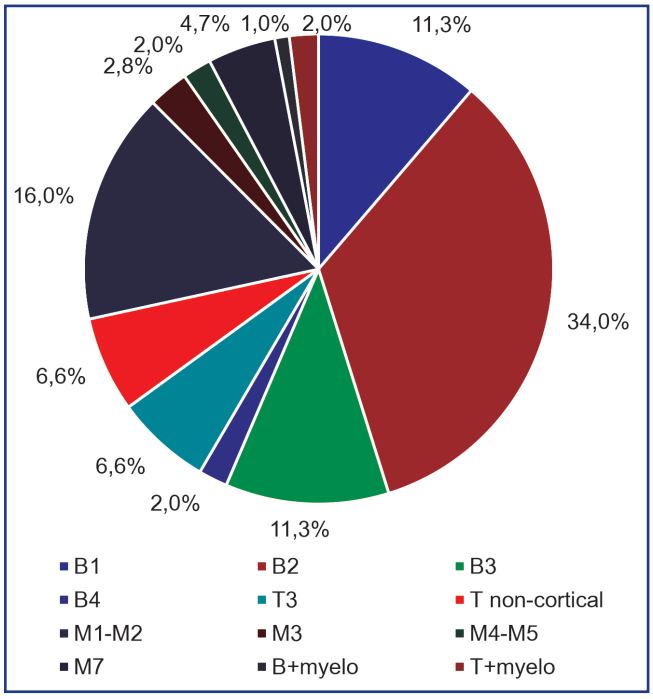


Figure 1 – Structure of AL immunologic variants (106 patients)

Thus, most ALL cases were B-ALL cases (46.1%), among which the B2 variant prevailed (34.0%). The next most common cases were AML, which accounted for 38.7% of all ALs. T-ALL accounted for 13.2% of cases, while T-cortical (T3) and non-cortical (non-T3) variants were equally common – 6.6% of the total number of ALLs. The mixed-cell phenotype of AL (biphenotypic OL) was the rarest, accounting for 2% of all leukemias. Figure 2 shows a CD45/SSC scattergram showing the gating of a blast population (R2) that has a paler (CD45) luminescence for the total leukocyte antigen CD45 compared to the lymphocyte population (R1).

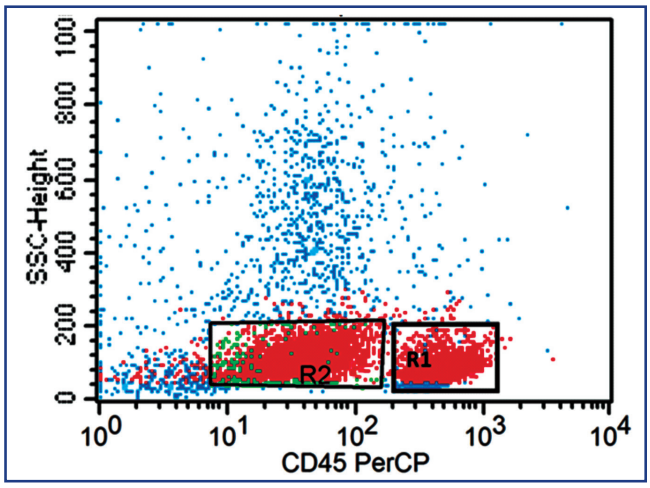


Figure 2 – CD45/SSC scattergram

Comparison of the expression of apoptotic antigens on peripheral blood lymphocytes in patients with AL and conditionally healthy children. Table 1 presents the analysis results for the expression level of the proteins - annexin V, Bcl-2, CD95, and p53 on peripheral blood lymphocytes in patients with ALL and conditionally healthy children.

A comparison of the early apoptosis marker, annexin V, expression on peripheral blood lymphocytes found the following. The mean expression of this marker in the control group did not significantly differ from the corresponding indicator in patients with almost all leukemia subvariants except for the mature B4 variant and the M7 variant of AL. At that, annexin expression was notably lower than in the control group.

Table 1 – Comparison of the expression levels of apoptosis markers on peripheral blood lymphocytes in patients with ALL (n=106) and the control group (n=23), M±m

AL variant Number of patients (N)	Markers of apoptosis							
	annexin V		P53		Bcl-2		CD95	
	Early apoptosis,%	Medium value	%	Medium value	%	Medium value	%	Medium value
B2 (n=36)	60.8±3.4	42.5±6.1	2.9±1.3	7.1±1.9	17.8±5.8	6.0±3.3	33.3±4.3	11.6±2.5
B1 (n=12)	68.5±7.3	50.4±5.6	2.8±1.5	7.6±1.7	12.9±1.5	5.6±1.4	23.1±1.9	12.0±3.3
B3 (n=12)	57.2±3.2	48.3±6.8	4.7±2.2	8.8±2.9	8.9±2.9	6.0±0.5	25.9±3.2	11.1±3.6
B4 (n=2)	50.4±5.5	39.2±2.1	11.4±2.9	11.1±2.7	15.4±4.6	4.5±2.3	46.5±2.1	9.4±3.9
T3 (n=7)	70.9±1.6	40.5±3.9	1.7±1.7	9.6±1.7	10.1±3.6	4.3±0.8	43.1±3.9	12.1±3.8
T4 (n=7)	70.7±4.8	47.5±3.9	3.8±4.5	8.4±1.5	17.7±4.0	3.6±1.4	37.6±2.9	7.4±4.1
M1-M2 (n=17)	54.1±2.9	51.9±4.4	3.5±4.3	7.8±2.1	26.0±3.2	6.1±2.3	30.2±2.8	8.9±2.8
M3 (n=3)	57.6±3.4	32.1±3.4	3.6±3.3	7.6±1.6	6.0±5.1	4.2±1.6	27.2±1.3	7.9±1.1
M4-M5 (n=2)	53.7±11.7	28.7±7.8	5.9±1.9	6.4±1.2	2.8±2.8	6.6±2.9	8.3±12.7	12.2±8.8
M7 (n=5)	49.2±4.5	64.8±7.1	4.1±4.2	7.1±1.7	9.6±1.9	5.5±2.6	16.0±2.5	10.0±1.5
T+myelo (n=2)	55.6±11.5	42.6±5.5	2.8±6.0	7.4±2.7	8.8±10.9	7.1±3.9	21.1±3.4	11.5±2.0
B+myelo (n=1)	65.0	3025.2	2.9	15.8	11.6	11.7	39.1	12.1
Control group (n=23)	66.1±3.7	21.9±2.5	3.6±2.1	6.1±0.9	10.9±2.3	4.4±1.2	20.3±3.2	7.3±1.1

Note: Arithmetic Mean (M), Standard Deviation (±m)

Analysis of annexin expression within the leukemia variant showed a significant difference between the group with B1 ALL (68.57.3, $p<0.05$) and B4 ALL (50.4±5.5%) among B-lymphoblastic ALs. No significant difference was found within the T-ALL groups. There was also no significant difference in annexin expression on peripheral blood lymphocytes among the myeloblastic and biphenotypic leukemia variants.

More significant changes were observed in the study of the annexin fluorescence intensity, which turned out to be significantly lower in the control group than in the corresponding indicator in all other subgroups. It should be noted that the fluorescence intensity of annexin V in the biphenotypic variant (B+myelo) of leukemia increased manifold, even though its expression did not differ from that of the control group. Fluorescence intensity is probably a more sensitive indicator for determining the course and outcome of the disease.

The apoptotic marker p53 expression ($t>2.2$; $p<0.05$) was significantly higher only in the subvariant with the mature B-form of ALL (B4), both compared to the control group and other leukemia subvariants. However, no convincing changes in fluorescence intensity (mean for p53 antigen) were determined in the analysis between the control group and leukemia variants, as well as within the groups, in contrast to annexin. According to these findings, p53 is not specific in its expression or fluorescence intensity in oncohematological diseases. However, the limited number of patients in each group reduced the reliability of the presented findings. The number of leukemia subvariant studies shall be increased to achieve statistically significant groups.

Comparing the anti-apoptotic marker Bcl-2 expressions on lymphocytes in conditionally healthy children and patients with leukemia, we found that the Bcl-2 expression on peripheral blood lymphocytes in healthy children was significantly higher than in patients with any ALL subvariant. At the same time, no significant differences in the Bcl-2 protein expression were found in the control group and patients with AML and biphe-

notypic variant of AL, and there were no differences in the fluorescence intensity. There is an assumption that there will be an increase in the expression level of the Bcl-2 anti-apoptotic marker on the patients' lymphocytes due to the activation of the cellular link [19]. However, this hypothesis was confirmed only in patients with ALL. This could be due to the statistically small number of studies conducted, which indicates the need for further study.

In the CD95 apoptosis marker parameter analysis, the mean value of the control group was significantly lower than the corresponding value in ALL and biphenotypic leukemia patients. In contrast, high CD95 expression was determined only in M1-M2 variants of AML in the groups of AML patients. No significant difference in fluorescence intensity was determined between the control and study groups. We assumed that increased CD95 expression on peripheral blood lymphocytes in leukemia patients indicates inhibition of immune system activity by suppressor factors produced by tumor cells to avoid immunological surveillance. This assumption was confirmed only for ALL. In comparing the expression and intensity of CD95 fluorescence between leukemia subvariants, the intensity reached the maximum in the B4 and T3-cortical variants and the minimum in the M4-M5 variants. However, interpreting these findings is impossible due to the small sample size (n=1).

Expression analysis of apoptotic markers on peripheral blood lymphocytes and bone marrow blast cells in patients with lymphoblastic AL. Analysis of the apoptotic marker annexin V expression showed a significant increase in protein expression on peripheral blood lymphocytes of patients compared to bone marrow blasts. Among B-ALL, a significant increase was characteristic of the B1 and B2 subvariants, T-ALL for the T3-cortical subvariant, AML for the M1-M2 and M4-M5 subvariants, as well as in biphenotypic variants of AL (B+myelo and T+myelo) ($p<0.05$, $t>2.2$). The fluorescence intensity was significantly higher in T3, M7, and biphenotypic leukemia. In our opinion, the pronounced expression of the early apoptosis marker on lymphocytes is an unfavorable prognostic factor, indicating the focus of immunocompetent cells on programmed death and a decrease in antitumor immunological surveillance.

Table 2 – Expression of apoptosis markers in bone marrow blast cells in patients with acute lymphoblastic leukemia, M±m

AL variant, quantity Patients (N)	Apoptosis markers							
	annexin V		P53		Bcl-2		CD95	
	Early apoptosis,%	Mean	%	Mean	%	Mean	%	Mean
B2 (n=36)	44.4±7.8	27.8¥5.4	4.8¥7.2	8.7¥2.3	17.2¥16.4	6.9¥8.7	8.1¥2.7	6.1¥7.2
B1 (n=12)	29.0¥13.0	33.5¥26.5	4.3¥4.5	7.6¥1.0	10.8¥13.2	5.7¥1.6	2.8¥2.2	4.8¥1.4
B3 (n=12)	55.6¥8.7	37.7¥10.1	3.9¥5.2	8.6¥1.2	26.5¥19.0	6.6¥2.1	5.3¥3.1	5.2¥1.0
B4 (n=2)	37.8¥18.2	15.6¥2.5	29.2¥20.7	16.8¥7.8	9.6¥1.3	3.4¥1.8	3.0¥0.4	4.8¥0.1
T3(n=7)	36.4¥7.2	16.7¥4.8	3.0¥1.5	6.2¥2.6	2.1¥1.3	3.8¥2.5	3.0¥1.5	5.0¥1.8
T-non-cort (n=7)	62.7¥2.8	39.3¥5.5	4.2¥3.1	6.4¥3.3	8.3¥11.8	5.1¥4.3	4.2¥3.1	5.3¥2.5
M1-M2 (n=17)	37.1¥14.7	44.5¥24.5	5.0¥6.0	13.0¥4.2	11.0¥17.4	8.0¥6.0	16.4¥13.2	13.3¥4.9
M3 (n=3)	56.5¥11.2	36.9¥7.5	1.9¥2.4	14.6¥1.6	57.5¥2.0	12.9¥0.7	10.5¥6.8	16.8¥1.7
M4-M5 (n=2)	35.0¥11.7	37.4¥7.8	3.5¥1.9	11.3¥1.2	2.9¥2.8	7.3¥2.9	30.6¥12.7	17.5¥8.8
M7 (n=5)	53¥14.5	43¥6.6	5.2¥2.0	13.4¥1.1	1.8¥1.1	5.5¥1.1	3.8¥2.3	8.6¥2.9
T+myelo (n=2)	23.9¥11.5	27.5¥5.5	6.8¥6.0	11.0¥2.7	15.9¥10.9	7.8¥3.9	3.5¥3.4	8.1¥2.0
Biphenotypic B+myelo (n=1)	40.1	33.1	84.7	31.1	0.21	17.9	24.2	8.7

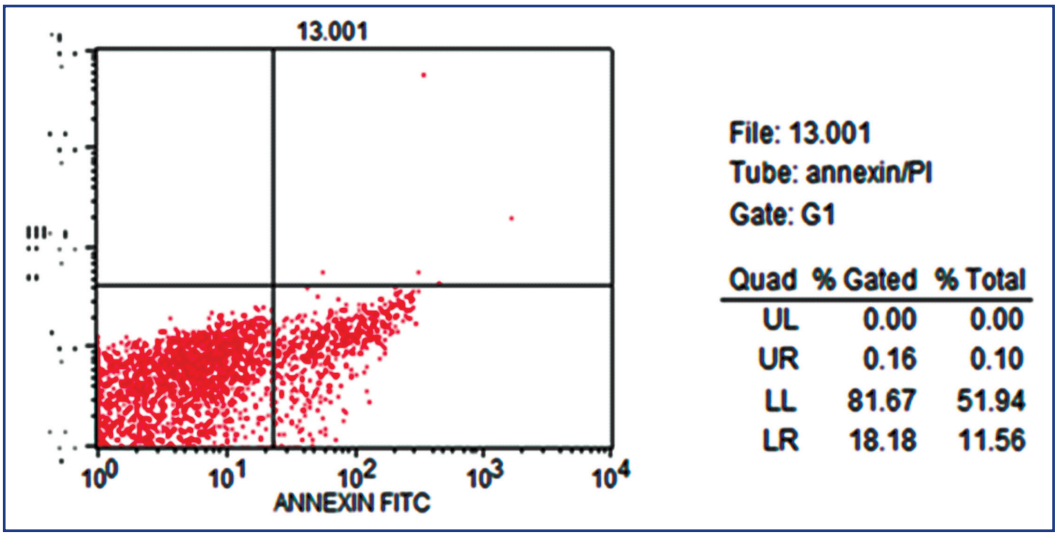
Note: Mean is the arithmetic mean (M). The data is presented as M±m, where m is the standard deviation

While comparing the annexin V expression on bone marrow blasts in different ALL subvariants, the minimum expression was found in the B1 variant and the biphenotypic form (T+myelo), indicating the pronounced viability of the blasts. The maximum expression was found in the B2, B3, T4, M3, and M7 variants. An increase in fluorescence intensity was also characteristic of these leukemia subvariants. It has been shown that B3 and M3 linear leukemias have a favorable prognosis, and T-non-cortical ones are more favorable compared to the cortical form. Probably, the presence of a larger number of apoptotic proteins on the surface of blasts will contribute to their accelerated death. It is not the expression of annexin itself that should be considered but the indicator that has shown great sensitivity, i.e., the fluorescence intensity. An increase in the patient samples and future studies could affect the search results. However, we can say that even based on the data obtained, it is necessary to analyze this marker on the blasts and lymphocytes of patients in order to predict the disease course.

Among T-ALL, the early apoptosis marker expression on blast cells was significantly reduced in the group with the T3-cortical variant (36.4±7.2%) compared to the group of non-cortical T-ALL (62.7±2.8%) ($p<0.05$, $t=2.9$), while the annexin expression was maximum in peripheral blood lymphocytes in these types of leukemia. The mean value is also lower in patients with T3-cort ALL (16.7± 4.8 c.u.) compared to the corresponding indicator of non-cortical T-ALL (39.3±5.5 c.u.).

Among AML, the annexin-V expression on peripheral blood lymphocytes was significantly higher than on blast cells in the M1-M2 and M4 subvariants of AML. Acute promyelocytic leukemia (AML M3) and acute megakaryocytic leukemia (AML M7) are known to have an aggressive course and an unfavorable outcome compared to other types of AML. Thus, it was implied that the annexin-V marker expression on tumor cells in these AML subvariants would be lower than in the groups with B-ALL characterized with a more favorable course, but no significant differences were found.

In our opinion, the significantly low expression of annexin on blasts in the biphenotypic (T+myelo) variant compared to the B+myelo variant is interesting.

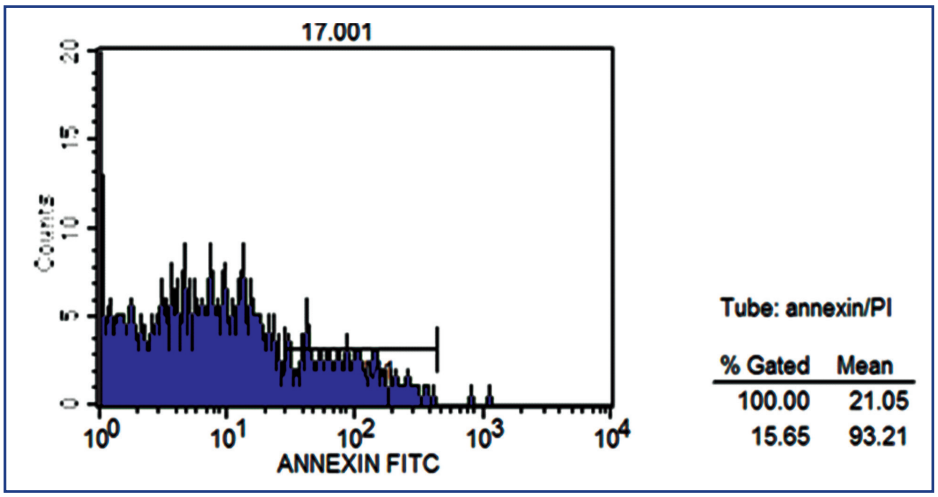


Legend: UL (upper left) – upper left quadrant, UR (upper right) – upper right quadrant, LL (lower left) – lower left quadrant, LR (lower right) – lower right quadrant, Gated – area of cells, Quad – quadrant, Total – total percentage

Figure 3 – Expression of fluorescein-labeled annexin V (FITC) on blast cells

The lower right quadrant of the graph (LR) shows blast cells that are annexin-V positive, i.e., at the stage of early apoptosis (18.18%). The left lower quadrant (LL) contains cells that are annexin-V negative, hence alive (81.57%), the left upper quadrant (UL) contains dead cells (0.00%), and the right upper quadrant (UR) contains cells in the late apoptosis stage (0.16%) (Figure 3).

The mean value of FITC-positive cells containing annexin-V was 21.05 units (Figure 4).



Legend: Gate is the area of cells; Mean is the average intensity of fluorescence

Figure 4 – One-parameter histogram of annexin V fluorescence intensity (mean)

In the groups with myeloid ALs, the annexin V expression on peripheral blood lymphocytes was significantly higher than on blast cells in leukemia subvariants M1-M2 and M4-M5 ($p<0.05$, $t=11.2$). At the same time, no significant differences were found in the groups with M3 and M7 subvariants. High expression of annexin-V on lymphocytes may signal a more unfavorable course of the disease due to the accelerated withdrawal of lymphocytes from participation in antitumor immunity. In the future, we intend to analyze the correlation between the disease's clinical course and the expression of apoptosis markers. No signif-

icant differences have been determined in annexin mean fluorescence intensity.

Thus, the analysis of an early marker of apoptosis in patients with ALL and AML shows that this antigen is expressed higher on peripheral blood lymphocytes than on tumor cells. A similar picture was observed concerning the fluorescence intensity.

Expression analysis of p53 protein. The analysis of the p53 protein expression on peripheral blood lymphocytes and blast cells in various AL subvariants showed a significant increase in this marker expression only in peripheral blood lymphocytes of patients with the B4 subvariant compared to lymphocytes of other groups. The same pattern was observed when comparing the p53 expression on blast cells. ($p<0,05$; $t>2.2$) (Figure 5, Table 1).

No significant difference in p53 protein expression was found among T-ALL (3.0±1.5% and 4.2±3.1%, respectively) ($p<0.05$; $t>2.2$). No significant difference was also found in the groups with AML (Table 1). Assessment of fluorescence intensity did not show significant differences in the studied groups. Therefore, it can be assumed that the p53 marker is not functionally significant for this study (Figure 5).

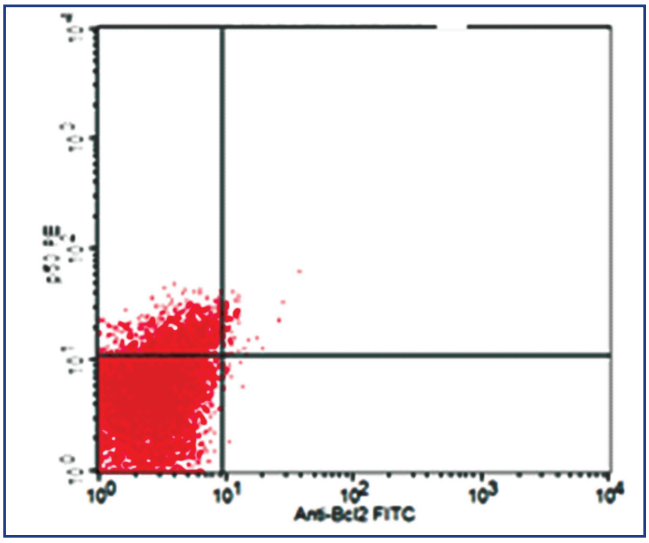


Figure 5 – Dot plot of the Bcl-2 marker and p53 protein expression

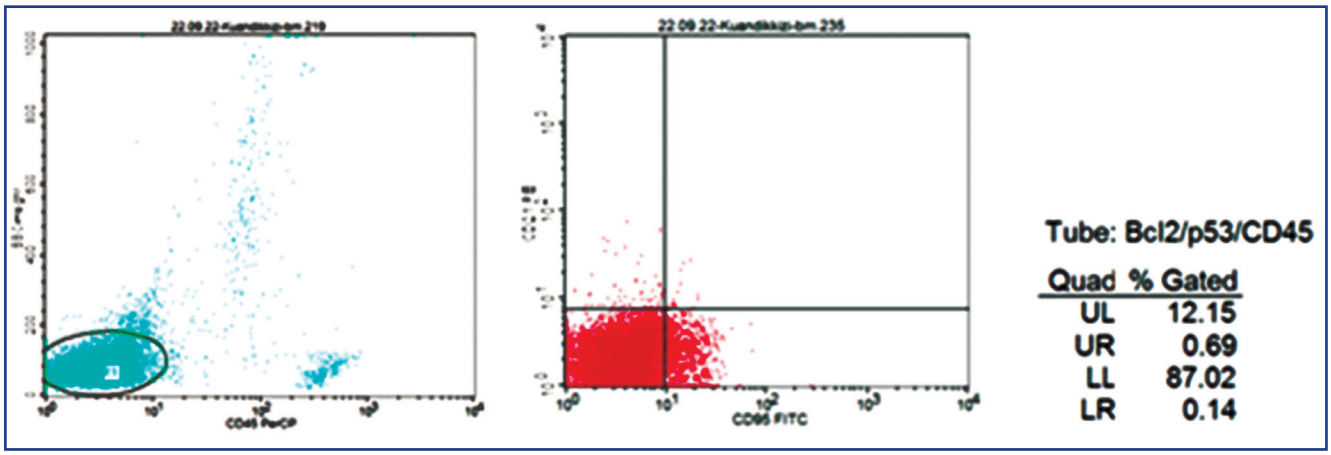
Expression analysis of anti-apoptotic marker Bcl-2. In our study, this marker's expression on peripheral blood lymphocytes was significantly lower in all patient groups before treatment than in healthy patients, except for the M1-M2 variants, where the Bcl-2 expression did not differ from the control group.

A comparative analysis of this marker expression on lymphocytes within groups showed that the highest expression was observed in the M1-M2 subtypes. We consider it a prognostically favorable sign, as it indicates the preservation of a certain functional activity of lymphocytes in AML. The expression of Bcl-2 in the blast cell population in different variants of B-ALL did not differ significantly but was significantly higher than in patients with T-ALL.

The bcl-2 expression was at minimum in the M3 variant on peripheral blood lymphocytes of patients in the group with AML and at maximum in the M1-M2 variant. The Bcl-2 expression on blast cells was the maximum in the M3 variant. The wide range of Bcl-2 expressions in the AML group compared to ALL could be due to the origin of blasts from different hematopoietic sprouts (myelocytic and lymphocytic ones). At the same time, it evidences a greater prognostic value of Bcl-2 in AML. A comparison of the expression results of this parameter between all the studied groups demonstrated that the minimum expression of the anti-apoptotic marker on blast cells was observed in ALL T3 and AML M4-M5. In contrast, the maximum was observed in AML M3 (Figure 6).

Expression analysis of the Fas ligand CD 95. Analysis of CD95 expression on peripheral blood lymphocytes within the groups did not show significant differences. At the same time, CD95 expression on blasts in all types of leukemia was notably lower than on the peripheral blood lymphocytes of these patients.

The percentage of antigen in the B2 group (8.1±2.7%) was increased compared with the B1, B3, and B4 subvariants (Table 1). There was no significant difference in the expression of the CD95 surface marker on the blasts within the groups of patients with T-ALL. Among AML, the expression of the CD95 ligand was significantly higher in the M4-M5 variants than in others. In the M7 variant, the expression of CD95 on the blasts was minimal, significantly lower than other AML variants. The highest expression of the CD95 marker was found in the M4-M5 OL group ($t=4.0$, $p<0.001$) (Figure 6) in summary table 1 for variants (B, T, myelo). The mean fluorescence intensity was also higher in the AML group (16.4±13.2 c.u.).



Legend: Gate is the region of cells, Q is the quadrant

Figure 6 – Gating strategy: 1) isolation of the blast population gate, 2) detection of expression of Bcl-2 and p53 antigens

Discussion: Apoptosis is known to be the primary mechanism by which most chemotherapeutic agents induce tumor cell death. It is more likely that the balance of expression (annexin V, CD95, p53) and anti-apoptotic protein (Bcl-2) can control the response of leukemia cells to chemotherapy and subsequently affect the patient's prognosis. Therefore, the task of this study was to determine the markers that will have prognostic significance for the studied leukemia variants.

This study area is relatively new, so only a few publications are available that determine the functional significance of apoptosis markers in predicting the course and response to therapy in patients with oncological and oncohematological diseases. In the presented work, we obtained data that partially corresponded to the already available results.

We also found a high expression of an early apoptosis marker, annexin V, on the lymphocytes of healthy patients. It does not correspond to the literature data, where the expression of annexin V in the healthy population is much lower. This result indicates the need for larger studies on a larger population sample. At the same time, the intensity of annexin fluorescence on lymphocytes in the healthy population is significantly lower than that of patients with leukemia. In the future, fluorescence intensity will probably be considered a more specific indicator for annexin V. However, we have not found any publications highlighting changes in its fluorescence intensity. Besides, a comparative analysis of annexin V expression on lymphocytes (the combined index of all groups of lymphoblastic leukemias is 63.8%) and blasts (44.3%) showed that this marker was significantly more expressed on lymphocytes than in the blast population, and it is an alarming sign in relation to the suppression of antitumor immunity. The expression of annexin V on lymphocytes was 58%I in myeloid leukemias, while it was 45.4% on blast cells but these differences were insignificant. No significant differences were also found when the expression of annexin within leukemia subvariants was considered. Therefore, this marker did not show pronounced specificity and cannot be recommended as a prognostic for monitoring and predicting the course of the pathological process.

Comparative analysis of p53 protein expression on the surface of lymphocytes and blast cells revealed no significant differences in leukemia variants. Available publications present the data from immunohistochemical studies of solid tumors (ovarian cancer, lung cancer, etc.), where this marker shows a certain diagnostic significance [20]. However, no significant differences in p53 expression were found in our study. Perhaps this marker is more specific for tumor cells of solid tumors. However, it is possible that there are no significant changes due to the small size of groups with rare leukemia subvariants, and therefore, there is a need for further study of this marker.

The study of the Bcl-2 protein expression on lymphocytes and blast cells in B-cell variants did not show significant differences, whereas this marker was expressed in significantly greater numbers in the T-cell variant on peripheral blood lymphocytes than in blasts. In AML, Bcl-2 expression was significantly higher in the blast cell population compared to lymphocytes. It may be one of the mechanisms of "tumor avoidance of immunological surveillance." As an anti-apoptotic marker, Bcl-2 contributes to prolonging the viability of the blast population, causing the phenomenon of "immortalization." At the same time, A. Cahyadi et al. [21] found no correlation between Bcl-2 expression and both response to induction chemotherapy and relapse rates in ALL, indicating that Bcl-2 expression levels have rather low prognostic significance. At the same time, it was quite surprising that all cell samples that showed a good response to the initial prednisolone therapy showed a significantly higher expression of Bcl-2 than those that did not respond well. Thus, high levels of Bcl-2 expression in ALL may indicate that in vivo tumor cell survival is dependent on cytokines. Glucocorticoids are known to have a potent anti-inflammatory ef-

fect due to the suppression of cytokine gene expression [22], and the treatment with prednisolone in vivo may result in an overall decrease in cytokine production. Thus, it is interesting to suggest that the prednisolone-induced reduction in cytokine expression may be responsible for the favorable response of blast cells (decreased apoptosis intensity) to prednisolone in ALL cell samples with high levels of Bcl-2 expression. The results of a study of Bcl-2 expression in ALL suggest that Bcl-2 expression levels may be higher in patients with a favorable response to treatment [23]. In the absence of published results of comparative analysis of the expression of apoptotic annexin-V, p53, CD95, and anti-apoptotic Bcl-2 markers on leukemia cells and lymphocytes, it is necessary to compare the level of expression with the clinical course of the disease in each case in order to establish the diagnostic significance of each marker, and it will determine the direction of further research.

According to the studies, the most diagnostically significant changes were shown in a comparative analysis of CD95 expression on lymphocytes and the blast population. CD95 expression on peripheral blood lymphocytes was significantly higher than on the blast population for any form of ALL, any subvariant of T-AL and B-AL. The results are consistent with the findings of A.Yu. Varishnikov et al., who showed that CD95 expression in blast cells is a favorable prognostic sign associated with an increase in relapse-free and overall survival. In contrast, the absence of CD95 antigen in blasts is an unfavorable sign for developing the disease. Thus, monitoring CD95 expression and CD95 function during in vivo chemotherapy may help to further determine the prognostic value of CD95 for drug-induced apoptosis in all patients. No significant differences were found in AML. It indicates the functional preservation of lymphocytes, but such a factor as a small number of patients could affect the results obtained.

Conclusion The results of the present studies indicate the prognostic significance of Bcl-2 and CD95 in acute leukemia. Further studies of these molecules are required and included in the standard panel of immunophenotyping in leukemia to identify favorable and/or unfavorable prognostic value in ALL in children. Annexin V and p53 showed no significant sensitivity and specificity. It allows not to include these markers in the immunophenotyping panel of leukemia.

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АҢДАТПА

БАЛАЛАРДАҒЫ ЖЕДЕЛ ЛЕЙКОЗДАРДАҒЫ ПЕРИФЕРИЯЛЫҚ ҚАН ЛИМФОЦИТТЕРІНДЕ ЖӘНЕ БЛАСТ ЖАСУШАЛАРЫНДА АПОПТОЗ МАРКЕРЛЕРІНІҢ ЭКСПРЕССИЯСЫН ТАЛДАУ

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Өзектілігі: *оЖедел лейкоз емінің тиімді тәсілдерін және емнің барысын болжау әдістерін іздеу онкогематологияның өзекті мәселесі. Бұл саладағы перспективалық бағыт химиотерапия барысында жасуша бетіндегі молекулалық маркерлер экспрессиясының өзгеруін зерттеу болып табылады.*

Зерттеудің мақсаты *– алғаш рет анықталған жедел лейкозы бар науқастарда перифериялық қан лимфоциттерінде және сүйек кемігінің бласт жасушаларында аннексин V, Bcl-2, CD95, p53 ақуыздарының экспрессиясын зерттеу.*

Әдістері: *Зерттеу дизайны – көлденең. Зерттеу әдісі: иммунофенотиптеу. Зерттеу материалдары 1 айдан 16 жасқа дейінгі "жедел лейкоз" диагнозы қойылған 106 пациенттің перифериялық қаны мен сүйек кемігі (зерттеу тобы) және 2 жастан 17 жасқа дейінгі шартты түрде сау 23 баланың перифериялық қаны (бақылау тобы) болды. Алынған мәліметтер статистикалық өңдеуден өтті.*

Зерттеу нәтижелері: *В-жасушалы жедел лейкоздарда BCL-2 экспрессиясын зерттеу сенімді айырмашылықтарды анықтаған жоқ, перифериялық қан лимфоциттеріндегі Т-жасушалы лейкоздарда бұл маркер бласттарға қарағанда сенімді түрде көбірек көрсетілді. Жедел миелобластты лейкозда BCL-2 экспрессиясы лимфоциттермен салыстырғанда бласттар популяциясында айтарлықтай жоғары болды. CD95 экспрессиясы лимфобластты лейкоздарда бласт жасушаларының мембранасына қарағанда перифериялық қан лимфоциттерінде айтарлықтай жоғары болды. Аннексин V экспрессиясын талдау ерте апоптоз маркерының экспрессиясы лимфоциттерде жоғары екенін анықтады. Бұл ісікке қарсы иммунитеттің төмен екенін көрсететін белгі. Лимфоциттер мен бласт жасушаларының бетіндегі p53 ақуызының экспрессиясын салыстырмалы талдау лейкоздың әртүрлі варианттарында сенімді айырмашылықтарды анықтаған жоқ.*

Қорытынды: *Жүргізілген зерттеудің нәтижесі жедел лейкоз кезінде BCL-2 және CD95 болжамдық маңыздылығының болуын көрсетті. Annexin V және p53 сенімді сезімталдық пен ерекшелікті анықтаған жоқ, бұл лейкоздың иммунофенотиптік панеліне осы маркерлерді қоспауға мүмкіндік береді.*

Түйінді сөздер: *жедел лейкоз, бласт жасушалар, апоптоз маркерлері, Bcl-2, CD95.*

АННОТАЦИЯ

АНАЛИЗ ЭКСПРЕССИИ МАРКЕРОВ АПОПТОЗА НА ЛИМФОЦИТАХ ПЕРИФЕРИЧЕСКОЙ КРОВИ И БЛАСТНЫХ КЛЕТКАХ ПРИ ОСТРЫХ ЛЕЙКОЗАХ У ДЕТЕЙ

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Актуальность: *Актуальным вопросом онкогематологии является поиск эффективных подходов терапии и методов прогнозирования течения острых лейкозов. Перспективным направлением в этой области является изучение изменений экспрессии молекулярных маркеров на поверхности клеток в динамике химиотерапии.*

Цель исследования *– определить уровень экспрессии белков annexin V, Bcl-2, CD95, p53 на лимфоцитах периферической крови и лейкемических клетках костного мозга у детей с диагнозом «острый лейкоз».*

Методы: *Дизайн исследования – поперечный. Метод исследования: иммунофенотипирование. Материалами исследования послужили периферическая кровь и костный мозг 106 пациентов с впервые установленным диагнозом «острый лейкоз» в возрасте от 1 мес. до 16 лет (исследуемая группа) и периферическая кровь 23 условно здоровых детей в возрасте от 2 до 17 лет (контрольная группа). Полученные данные были подвергнуты статистической обработке.*

Результаты: *Исследование экспрессии Bcl-2 при В-клеточных вариантах достоверных различий не выявило, при Т-клеточном варианте на лимфоцитах периферической крови данный маркер экспрессировался в достоверно большем количестве, нежели на*

бластах. При остром миелоидном лейкозе экспрессия Bcl-2 была достоверно выше на бластной популяции клеток, по сравнению с лимфоцитами. При анализе экспрессии CD95 при острых лимфобластных вариантах экспрессия была достоверно выше на лимфоцитах периферической крови, чем на мембране лейкемических клеток. Результаты анализа экспрессии annexin V показали, что лимфоциты экспрессировали маркер раннего апоптоза достоверно больше, чем бласты костного мозга. Данное явление является опасным признаком, указывающим на снижение противоопухолевого иммунитета. Сравнительный анализ экспрессии белка p53 на поверхности лимфоцитов и бластных клеток достоверных различий при различных вариантах лейкозов не выявил.

***Заключение:** Результаты проведенных исследований указывают на наличие прогностической значимости Bcl-2 и CD95 при остром лейкозе. Annexin V и p53 не выявили достоверной чувствительности и специфичности, что позволяет не включать данные маркеры в панель иммунофенотипирования лейкозов.*

***Ключевые слова:** острый лейкоз, бластные клетки, маркеры апоптоза, Bcl-2, CD95.*

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IMPACT OF CHARLSON COMORBIDITY INDEX ON POSTOPERATIVE COMPLICATIONS IN ELDERLY PATIENTS WITH HIGH-RISK PROSTATE CANCER

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ABSTRACT

Relevance: *The broad experience accumulated to date in performing radical prostatectomy (RPE) in high-risk patients has significantly reduced the frequency of perioperative complications. Studies that evaluate risk factors and scales to estimate the probability of complications for patients over 70 years are important.*

The study aimed to *determine the safety criteria for performing RPE in patients over 70 years of age with high-risk prostate cancer.*

Methods: *A total of 163 patients who underwent open RPE for high-risk prostate cancer from September 2018 and July 2021 were included in the study. The risk of postoperative complications was calculated using the Charlson Comorbidity Index (CCI). Complications of the postoperative period (90 days from the date of surgical intervention) were evaluated according to the Clavien-Dindo classification. The correlation between the indicators of CCI and postoperative complications was performed.*

Results: *All patients were divided into 2 groups by CCI equal to 2.5. The statistical analysis directly correlated this value with Grade I-II complications ($\chi 2=13.610$; $p<0.001$). The most significant correlation revealed during the multifactorial logistic regression analysis of preoperative parameters was established between diabetes mellitus and the incidence of postoperative infectious complications (HR – 2.84; 95% CI: 2.59-3.12; $p<0.001$).*

Conclusion: *The expediency of using CCI to identify a group of patients with a high probability of complications was emphasized. Comprehensive assessment of perioperative risk, chronological age as an isolated factor is not a contraindication for surgical treatment of prostate cancer in men over 70 years of age.*

Keywords: *prostate cancer, radical prostatectomy, comorbidity, Charlson Comorbidity Index (CCI), catheter-associated urinary tract infection, perioperative complications, Clavien-Dindo classification.*

Introduction: The broad experience accumulated to date in performing radical prostatectomy (RPE) in high-risk patients has significantly reduced the frequency of perioperative complications, which, along with satisfactory long-term therapy, results in low local progression and the likelihood of metastasis in prostate cancer makes surgery a successful and widely used method of treating this pathology [1].

However, the problem of choosing surgical tactics among elderly patients (over 70 years old), who, according to various sources, account for up to 50% of patients operated on for prostate cancer, remains unresolved. This issue is particularly acute in patients with a high probability of disease progression. On the one hand, increasing the predicted life expectancy in the male population requires a more radical approach from specialists. On the other hand, age, the presence of concomitant diseases, and, accordingly, the risk of perioperative complications may push the surgical intervention into the background.

Several evaluation scales and indices capable of predicting the development of postoperative complications have been developed and are actively used. Despite the lack of consensus on their reliability and effectiveness, the Charlson Comorbidity Index (CCI) today is the most common [2].

The study aimed to determine the safety criteria for performing RPE in patients over 70 years of age with high-risk prostate cancer.

Materials and Methods: A total of 163 patients who underwent open RPE for high-risk prostate cancer between September 2018 and July 2021 were included in the study. Patients with a previous history of prostate surgery or receiving neoadjuvant therapy were excluded from the study. The mean patient age was 66.2±2.1 (54-76) years, and the mean prostate-specific antigen (PSA) level at biopsy was 13.8±4.2 ng/dl (3.6-46.4). All patients underwent radical prostatectomy with extended pelvic lymphadenectomy. Surgical interventions were performed by one surgical team.

All patients were divided into two groups according to age. Group I comprised 91 (55.9%) patients below 70, while Group II included 72 (44.1%) patients over 70 years.

During the preoperative examination, the following concomitant diseases were identified: chronic coronary heart disease in 11 (6.7%) patients, history of previous myocardial infarction in 8 (4.9%) patients, type 2 diabetes mellitus in 22 (13.5%) patients and chronic obstructive pulmonary disease (COPD) in 7 (4.3%) patients. In some cases, a combination of two or more concomitant pathologies was noted in the same patient. Thus, in 5 (3.1%) cases, a history of diabetes mellitus and a previous myocardial infarction were noted. Chronic coronary heart disease as the second concomitant pathology was observed in 11 (6.7%) patients. Patients with concomitant cardiovascular diseases were examined following the recommendations of the European Society of Cardiology and the European Association of Anesthesiologists (ESC/ESA) [3]. One hundred

twenty-one (74.2%) patients did not have any concomitant diseases, of which 75 (82.4%) patients were included in Group I and 46 (63.9%) – in Group II.

The preoperative physical status of all patients was assessed according to the American Society of Anesthesiologists (ASA) classification by a multidisciplinary team. In some cases, the decision on the possibility of surgical intervention was made after the prescribed therapy.

The Charlson Comorbidity Index was developed in 1987 by Charlson and colleagues to classify comorbid conditions that may influence mortality risk [4]. In our study, the high risk of progression and the likelihood of local prevalence of the process of the presence of cancer were taken into account as risk factors.

Complications of the postoperative period (90 days from the date of surgical intervention) were evaluated according to the Clavien-Dindo classification, initiated in 1992 and updated in subsequent years [5]. All complications were evaluated as «minor» (Grade I-II) and «major» (Grade III-IV). Complications associated with Grade V were not included in the study.

The diagnosis and treatment of catheter-associated urinary tract infections (CAUTI) that occurred in several patients were performed following the standards of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Central Disease of Control/ National Healthcare Safety Network (CDC/NHSN) [6]. While in the hospital, all patients were prevented from thromboembolic complications according to generally accepted protocols.

In order to carry out statistical processing, all data on patients and postoperative complications that occurred within 90 days after RPE were entered into the database. Statistical analysis of the results was performed using SPSS 18.0 for Windows software block (SPSS Inc, Chicago, IL, US). The correlation between the CCI value and postoperative complications was analyzed with the calculation of the Pearson coefficient χ^2. Differences with a significance level of 95 were considered statistically significant (*p<0,05*).

Results: The characteristics of patients in the preoperative period are presented in Table 1. The average age of patients in groups I and II was 62.7±0.4 (54-70) and 71.8±0.2 (71-76) years, respectively (*p<0.001*).

Table 1 – Characteristics of patients in the preoperative period by age groups

Parameters	Group I	Group II	P
PSA*, ng/ml	20,9±0,9 (8,74-49,3)	22,4±0,6 (9,67-32,1)	0.178
Prostate volume, ml	56,8±3,9 (20-155)	48,9±3,8 (25-113)	0.159
BMI**, kg/m^2	28,2 (25,5-32,7)	26,3 (24,3-35,1)	0.078
ASA*** classification			0.124
ASA I	10,3%	7,1%	
ASA II	73,3%	71,7%	
ASA III	16,4%	21,2%	
CCI****	2,1±0,05(2-4)	2,5±0,07 (2-4)	0.012
Gleason score (biopsy)			0.010
6	55 (60,4%)	23 (31,9%)	
7	27 (29,7%)	42 (58,3%)	
≥8	9 (9,9%)	7 (9,7%)	
Clinical stage, T			0.142
2a	1 (1,1%)	6 (8,3%)	
2b	14 (15,4%)	12 (16,7%)	
2c	20 (22,0%)	12 (16,7%)	
3a	30 (33,0%)	27 (37,5%)	
3b	26 (28,6%)	(20,8%)	

*Notes: *PSA – Prostate specific antigen; **BMI – Body mass index; *** ASA – American Society of Anesthesiologists; **** CCI – Charlson Comorbidity Index*

The above data shows no significant differences between the study groups concerning the total PSA index (*p=0.178*). However, a significant difference between the compared groups was revealed in the Gleason score (*p=0.010*). Patients in Group I had a higher BMI compared to Group II. However, this difference had no statistically significant confirmation (*p=0,078*).

The postoperative complications were diagnosed in 56 (34.3%) patients. In 52 (31.9%) cases, complications were classified as Grade III according to the Clavien-Dindo classification, and Grade III-IV complications were noted in 4 (2.4%) patients. In 23 (14.1%) cases, one patient had two or three complications at a time.

The main complication graded as I-II was lymphorrhea, diagnosed in 16 (9.8%) patients. Five patients underwent percutaneous lymphocele drainage, regarded as a Grade III-IV complication.

Other complications associated with Grade I-II were urethrovesical anastomosis leakage, hematuria, pneumonia, and lower extremity deep vein thrombosis. They were diagnosed in 6 (3.7%), 7 (4.3%), 4 (2.5%) and 3 (1.8%) patients respectively. In 15 (9.2%) patients in the postoperative period, the presence of CAUTI was diagnosed.

Acute coronary syndrome developed in 5 (3.1%), gastrointestinal bleeding - in 1 (0.6%) and hemorrhagic stroke – in 2 (1.2%) patients. These patients required continued treatment in the intensive care unit.

The performed correlation analysis between Grade I-II complications and age groups did not demonstrate a significant relationship (χ^2=0.472; *p=0.492*). A similar analysis for Grade III-IV complications also revealed no significant correlation (χ2=1,050; *p=0.306*).

In the next stage, all patients were divided into 2 groups by CCI index equal to 2.5. The statistical analysis di-

rectly correlated this value with Grade I-II complications ($\chi 2 = 13.610$; $p<0.001$).

Similar results were obtained compared to Grade III-IV complications ($\chi 2 = 12.515$; $p<0.001$). Moreover, the most significant correlation revealed during the multifactorial logistic regression analysis of preoperative parameters was established between diabetes mellitus and the incidence of postoperative infectious complications (HR 2.84; 95% CI, 2.59-3.12; $p <0.001$).

Discussion: Demographic changes in populations over 65 years require a review of the decision-making process for the treatment of many diseases, including prostate cancer in elderly patients. Until recently, the age over 70 years was considered a relative limitation for the implementation of RPE due to the generally low life expectancy of patients of this age group and, accordingly, the lack of advantages of such aggressive therapy as well as high rates of complications and mortality, today the issue of treatment of elderly patients with this pathology requires a radical revision.

The introduction into clinical practice of modern diagnosis and preoperative preparation methods At the same time, a high risk of postoperative complications tasks the surgeon to ensure the expediency of surgical intervention and determine the type of surgery considering risk factors such as age, cardiovascular, respiratory, endocrine and other concomitant diseases.

One of the most valuable studies was performed by Begg and colleagues, where the authors analyzed the rates of postoperative and late urinary complications in men undergoing prostatectomy. In the structure of complications of the early postoperative period among elderly patients, cardiac (5.5%), respiratory (11%), vascular (4.7%), surgical (6.6%), and infectious complications (0.8-2%) should be distinguished, as well as an increase in the 30-day mortality rate. The frequency of complications increases in proportion to the age of patients. The incidence of at least one complication among patients subjected to RPE aged 65-69, 70-74, and over 75 years was 28%, 31% and 35%, respectively [7]. The authors emphasized that the rate of complications is significantly reduced if the procedure is performed in a high-volume hospital and by a surgeon who performs a high number of such procedures.

At the same time, the question of the «leading» role in the development of postoperative complications of risk factors such as age or the presence of concomitant diseases is still debatable. A limited number of papers have been published on the study of the role of concomitant diseases in the development of perioperative complications in patients undergoing RPE, and they all differ according to the principle of distribution of patients according to age groups, by the number and types of concomitant pathologies accepted for consideration.

In order to determine the risk factors for the development of postoperative complications in the studied cohort of patients, we conducted a study of 163 patients who underwent RPE in connection with prostate cancer and also performed a correlation analysis of the following factors as age, preoperative morbidity (CCI) and the severity of early postoperative complications (Clavien-Dindo classification). The structure of early postoperative complications is presented as follows: complications directly associated with surgery, neurological, cardiorespiratory, and infectious complications.

Lymphocele development should be highlighted among postoperative surgical complications. The development of this complication is associated with extended pelvic lymphadenectomy and undoubtedly increases the duration of hospitalization, which, in turn, is an unfavorable risk factor for developing nosocomial infection.

In our study, lymphorrhea was diagnosed in 16 (9.8%) patients. It is noteworthy that prolonged lymphorrhea was diagnosed in 10 patients in Group I and 6 patients in Group II. This complication has been classified as a Grade III complication. Subsequently, 5 (31.3%) patients needed percutaneous drainage of the formed lymphocele. Three of these patients belonged to Group II.

Routine microbiological urine analysis on Day 7 after surgery revealed a positive result in 21 (12.9%) of 163 patients. However, in 9 cases, the uropathogen was detected in a concentration not exceeding 10^5 CFU/ml. This condition meets the criteria of asymptomatic CAUTI and does not require antibacterial therapy. In 12 patients, the diagnosis of symptomatic CAUTI was made along with the clinical condition and the positive urine culture ($\geq 10^5$ CFU/ml). During microbiological examination of urine, the following uropathogens were isolated as a monoculture in 12 patients: *E.coli* (4 cases), *Klebsiella pneumonia* (3 cases), *Pseudomonas aeruginosa* (1 case) and *Staph. epidermidis* (1 case). In other cases, the infection was polymicrobial. All cases of postoperative UTI developed without it in the preoperative period. It should be noted that 7 patients in this group suffered from diabetes mellitus. The leakage of ureterovesical anastomosis was diagnosed in 2 patients; one of them had hematuria, which required irrigation of the bladder and prolongation of bladder catheterization. The remaining patients were bacteriologically negative.

As stated above, the duration of urine catheter use is the main risk factor for developing CAUTI and bacteriuria. In our study, the leakage of urethrovesical anastomosis in the early postoperative period in 11 (6.7%) patients required a prolongation of bladder catheterization. Bacteriuria was diagnosed in 5 (45.5%) of 11 patients. Two of them belonged to Group I of the study.

In the remaining patients, the results of microbiological analyses were negative (no growth was detected), *and Candida albicans with CFU of* less than 1000 were isolated in three cases. This group of patients was not treated.

Nosocomial pneumonia is the second most common hospital infection after urinary tract infections. According to various studies, the risk of developing nosocomial pneumonia ranges from 0.3 to 20% or higher, depending on the department's profile, the epidemiological situation in the medical institution, and patients' clinical and individual characteristics. In intensive care units, nosocomial pneumonia accounts for 27-47% of the total number of infectious complications, and mortality is equal to 30-70%. Risk factors for the occurrence of hospital-acquired pneumonia are pulmonary diseases, including COPD, age (over 60 years), smoking, obesity, the nature and duration of surgery and anesthesia [8].

In our study, the incidence of nosocomial pneumonia was 2.5%. Two of the 4 patients belonged to Group II. COPD was diagnosed in one patient from Group II; the other was diagnosed with diabetes mellitus. In Group I, one

patient had a history of COPD, while the other had no concomitant diseases. Therapy and dynamic control of pneumonia followed the generally accepted clinical recommendations, considering the findings of physical examination, radiology, and laboratory tests [9].

In five patients, the early postoperative period was complicated by the development of acute coronary syndrome; one of the patients was subsequently diagnosed with myocardial infarction. Hemorrhagic stroke was diagnosed in one patient. The patients were transferred to the intensive care unit and discharged from the hospital on Days 13 and 18, respectively.

In order to calculate the probability of postoperative complications, specialists have proposed several tests and scales, but there is no consensus on their prognostic significance. In addition, the role of the age factor is still debatable. Even though age is closely associated with high rates of complications in the early postoperative period, we suggested that age alone is not a contraindication to surgical intervention in patients with high-risk prostate cancer.

In several studies comparing the prognostic role of age and CCI in the development of postoperative complications and an increase in mortality rates, CCI was identified as a more significant predictor of an increase in morbidity and mortality than age [10].

Similar data was obtained in our study. We found no differences in the frequency of complications in the early postoperative period between the two age groups. However, higher CCI was an independent risk factor for complications. This highlights the potential value of CCI in risk stratification for patients undergoing surgery for prostate cancer. At the same time, it should be noted that type 2 diabetes mellitus was established as a main risk factor for infectious complications in the early postoperative period (HR 2.84; 95% CI, 2.59–3.12; *p <0,001*).

CCI can be used with a greater degree of reliability to calculate the risk of postoperative complications in prostate surgery and accordingly be used as an argument when deciding whether surgery is necessary. Undoubtedly, patients over 70 years of age, having a higher risk of perioperative complications, with a satisfactory physical status and the absence of concomitant diseases, have every chance to undergo surgery well. However, in the presence of at least one of the concomitant diseases listed in CCI, the risk of postoperative complications increases significantly. Persons under 70 years of age who have one or more of the concomitant diseases indicated in the CCI index may also have a high probability of developing complications.

Thus, in the treatment of prostate cancer in patients with a high CCI index, it is mandatory to conduct evaluation tests in the preoperative period, discuss their results, and, accordingly, determine the prognosis of the course of the next postoperative period.

Conclusion: The obtained results did not demonstrate a correlation between age and the development of complications in the 90-day postoperative period. The expediency of using CCI to identify a group of patients with a high probability of complications was emphasized. High rates were independent risk factors for complications, which underlines the potential usefulness of this scale in risk stratification. Thus, subject to a comprehensive assessment of perioperative risk, chronological age as an isolated factor is not a contraindication to radical surgical treatment of prostate cancer in men over 70 years of age.

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АҢДАТПА

ҚУЫҚ АСТЫ БЕЗІНІҢ ҚАТЕРЛІ ІСІГІ БАР ЕГДЕ ЖАСТАҒЫ ЕМДЕЛУШІЛЕРДЕ ОПЕРАЦИЯДАН КЕЙІНГІ АСҚЫНУЛАРҒА ЧАРЛЬСОН ІЛЕСПЕЛІ АУРУЛАР ИНДЕКСІНІҢ ӘСЕРІ

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Өзектілігі: *Бүгінгі күні тәуекел дәрежесі жоғары емделушілерде радикалды простатэктомияны (РП) жүргізудің мол тәжірибесі операциядан кейінгі асқынулардың жиілігін айтарлықтай төмендетті. 70 жастан асқан науқастарда асқынулардың ықтималдығын бағалау үшін қауіп факторларын және ұпайларды бағалайтын зерттеулер маңызды.*

Зерттеудің мақсаты *қуық асты безінің қатерлі ісігімен ауыратын 70 жастан асқан емделушілерде ЖП жүргізудің қауіпсіздік критерийлерін анықтау болды.*

Әдістері: *Зерттеуге 2018 жылдың қыркүйегінен 2021 жылдың шілдесіне дейін жоғары қауіпті қуық асты безінің қатерлі ісігі бойынша ашық RP өткен 163 пациент қамтылды. Операциядан кейінгі асқынулардың қаупі Чарльсонның қатар жүретін ауру индексі (CCI) көмегімен есептелді. Операциядан кейінгі кезеңдегі асқынулар (операция жасалған күннен бастап 90 күн) Клавиен-Диндо классификациясы бойынша бағаланды. CCI ұпайлары мен операциядан кейінгі асқынулар арасында корреляция анықталды.*

Нәтижелері: *Барлық науқастар СКИ 2,5 коэффициенті бойынша 2 топқа бөлінді. Статистикалық талдау бұл мәнді I-II дәрежелі асқынулармен тікелей байланыстырды (χ2=13,610; p<0,001). Операция алдындағы параметрлердің көп нұсқалы логистикалық регрессиялық талдауы арқылы анықталған ең маңызды корреляция қант диабеті мен операциядан кейінгі инфекциялық асқынулардың жиілігі арасында анықталды (OR – 2,84; 95% CI: 2,59-3,12; p<0,001).*

Қорытынды: *Асқыну ықтималдығы жоғары пациенттер тобын анықтау үшін CCI қолданудың орындылығына баса назар аударылады. Операциядан кейінгі қауіпті кешенді бағалау, оқшауланған фактор ретінде хронологиялық жас 70 жастан асқан ерлерде простата обырын хирургиялық емдеуге қарсы көрсетілім болып табылмайды.*

Түйінді сөздер: *қуық асты безінің қатерлі ісігі, радикалды простатэктомия (РП), ілеспелі ауру, Чарльсон ілеспелі ауру индексі (CCI), катетермен байланысты зәр шығару жолдарының инфекциясы, операциядан кейінгі асқынулар, Клавиен-Диндо классификациясы.*

ВЛИЯНИЕ ИНДЕКСА КОМОРБИДНОСТИ ЧАРЛСОНА НА ПОСЛЕОПЕРАЦИОННЫЕ ОСЛОЖНЕНИЯ У ПОЖИЛЫХ ПАЦИЕНТОВ С РАКОМ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ ВЫСОКОГО РИСКА

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Актуальность: *К настоящему времени накопленный богатый опыт выполнения радикальной простатэктомии (РПЭ) у пациентов высокого риска позволил существенно снизить частоту периоперационных осложнений. Важны исследования, оценивающие факторы риска и шкалы для оценки вероятности осложнений у пациентов старше 70 лет.*

Целью *исследования было определение критериев безопасности выполнения РПЭ у пациентов старше 70 лет с раком предстательной железы высокого риска.*

Методы: *в исследование были включены 163 пациента, перенесших открытую РПЭ по поводу рака предстательной железы высокого риска с сентября 2018 г. по июль 2021 г. Риск послеоперационных осложнений рассчитывали с помощью индекса коморбидности Чарлсона (CCI). Осложнения послеоперационного периода (90 дней от даты оперативного вмешательства) оценивали по классификации Clavien-Dindo. Выявлена корреляция между показателями CCI и послеоперационными осложнениями.*

Результаты: *Все пациенты были разделены на 2 группы по коэффициенту CCI, равному 2,5. Статистический анализ напрямую коррелировал это значение с осложнениями I-II степени (χ2=13,610; p<0,001). Наиболее значимая корреляция, выявленная при многофакторном логистическом регрессионном анализе предоперационных показателей, установлена между сахарным диабетом и частотой послеоперационных инфекционных осложнений (ОР – 2,84; 95% ДИ: 2,59-3,12; p<0,001).*

Заключение: *Подчеркнута целесообразность использования CCI для выявления группы пациентов с высокой вероятностью осложнений. Комплексная оценка периоперационного риска, хронологический возраст как изолированный фактор не является противопоказанием к хирургическому лечению рака предстательной железы у мужчин старше 70 лет.*

Ключевые слова: *рак предстательной железы, радикальная простатэктомия (РПЭ), коморбидность, индекс коморбидности Чарлсона (CCI), катетер-ассоциированная инфекция мочевыводящих путей, периоперационные осложнения, классификация Clavien-Dindo.*

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APPLICATION OF LUNG CANCER CT ARTIFICIAL INTELLIGENCE TECHNOLOGY IN LOW-DOSE COMPUTED TOMOGRAPHY FOR EARLY DETECTION OF LUNG CANCER

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ABSTRACT

Relevance: *In recent years, there has been an increase in the use of artificial intelligence (AI) technology in chest low-dose computed tomography (LDCT), which has attracted considerable attention. LDCT scans are widely used for early detection and monitoring of lung diseases, making the accurate analysis of these scans crucial for effective diagnosis and treatment.*

The study aimed to *evaluate the diagnostic effectiveness of an AI system in clinical practice by comparing its sensitivity in detecting pulmonary nodules and differentiating between benign and malignant processes with radiologists. Additionally, it aimed to provide a theoretical basis for the clinical application of AI in LDCT.*

Methods: *The study is based on a retrospective analysis of LDCT scans performed in a pilot lung cancer screening project. High-resolution tomography followed standardized low-dose scanning protocols, and experienced radiologists and an expert with many years of practice interpreted the results. Modern deep learning frameworks (TensorFlow, PyTorch) were applied for data analysis and nodule segmentation.*

Results: *The study results demonstrated that the deep learning model detected pulmonary nodules with a sensitivity of 63.4% (95% CI: 54.0-72.8%) and a specificity of 81.6% (95% CI: 79.8-83.4%), consistent with previous studies findings.*

Conclusion: *Like previous published studies, this study demonstrates that AI can enhance the LDCT interpretation process. However, despite the obtained diagnostic value, it requires further refinement for full implementation in clinical practice.*

Keywords: *artificial intelligence (AI), low-dose computed tomography (LDCT), lung cancer.*

Introduction: Lung cancer is the second most common type of malignant tumor in men and women (after prostate and breast cancer, respectively) and a leading cause of cancer mortality worldwide. According to the World Health Organization (WHO), in 2020, there were 2.2 million new cases of lung cancer and 1.8 million deaths from this burden [1].

Lung cancer is an urgent health problem both throughout the world and in the Republic of Kazakhstan, as it ranks second in morbidity and the main cause of mortality from malignant neoplasms. In 2021, 3,615 new cases of lung cancer and 2,086 deaths were registered in Kazakhstan [2].

Early lung cancer diagnostics is critical for successful treatment and improvement of overall survival rates. According to the literature, low-dose computed tomography (LDCT) is an effective lung cancer screening method. It makes it possible to find cancer at an early stage, resulting in a decrease in mortality from this pathology [3-6]. LDCT screening requires the interpretation of a large number of images. It can be a time-consuming process subject to variability depending on the radiologist's experience. Artificial intelligence (AI) can improve the accuracy and efficiency of lung cancer screening using LDCT by automating image analysis and providing decision-making support to radiologists [7], as well as reducing the time to interpret LDCT images.

Over the past 10 years, significant advances have been made in using AI technology for early lung cancer diagnostics using LDCT. Several studies have demonstrated that AI algorithms can accurately identify and classify lung nodes on CT scans. It greatly improves and is critical for the early diagnostics of lung cancer. Besides increasing lung cancer detection in the early stages, AI can also increase the efficiency of LDCT screening [7-9].

Despite the promising results of the AI models developed in lung cancer screening, aspects still need to be studied. The AI algorithms developed should be improved with more diverse data sets to increase generalizability in different populations, for example, for Central Asians to validate based on the results obtained.

The study aimed to evaluate the diagnostic effectiveness of an AI system in clinical practice by comparing its sensitivity in detecting pulmonary nodules and differentiating between benign and malignant processes with radiologists. Additionally, it aimed to provide a theoretical basis for the clinical application of AI in LDCT.

Materials and methods:

Materials: The data of LDCT studies conducted as part of a pilot project for lung cancer screening from June 1, 2018, to September 31, 2023, in the cities of Almaty, Ust-Kamenogorsk, and the Almaty region were studied retrospectively.

Scanning was performed at the з of Oncology and Radiology (KazIOR) and the East Kazakhstan Regional Multidisciplinary Center for Oncology and Surgery. Computed tomography scanners with a different number of detectors (from 64 to 128) and a slice thickness of not more than 1.25 mm were used for scanning. All scanners had a low-dose scanning protocol: voltage 120 kV, current strength 10-40 mA. The effective dose for the patient did not exceed 1 mSv according to the order on preventive examinations of the population in Kazakhstan [10]. Segmentation, annotation, and interpretation of LDCT scans were performed by 4 radiologists with more than 6 years of experience (Figure 1). The results of LDCT studies were retrospectively analyzed by an invited expert with 30 years of experience in reading computed tomography examinations of the lungs to determine the number of "true" nodes. Lung nodules were classified according to the Lung Imaging Reporting and Data System (Lung-RADS 1.1).

The deep learning model was developed by IT specialists of KazIOR using special deep learning frameworks and sources (libraries) (TensorFlow, PyTorch) (Figure 1).

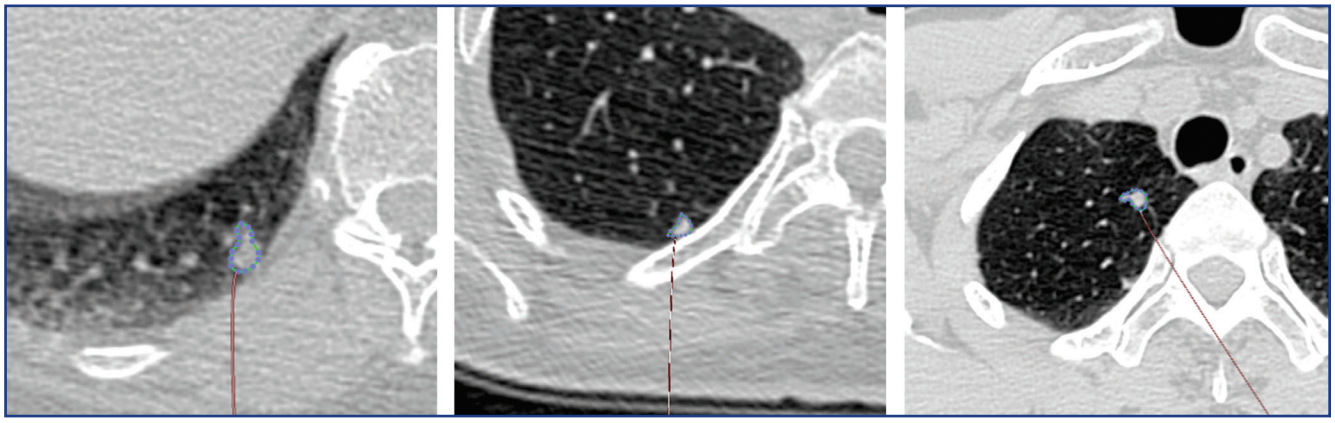

Figure 1 – Segmentation of pulmonary nodule contours on LDCT scans of the patient LDCT0266 performed as part of a pilot lung cancer screening project

Methods:

Data pre-processing:

LDCT obtaining and anonymization.

Extracting regions of interest (ROIs) containing lung nodes from LDCT scans and creating fragments of 2D or 3D images.

Annotations for regions of interest containing nodules in the lungs.

Model development:

Selecting and implementing deep learning architectures for pulmonary nodule diagnostics.

Creating learning models using the annotated CT scans.

Hyperparameter tuning to optimize model performance.

Model assessment:

Assessing the AI model performance using a control set of CT scans and diagnostic value data.

Statistical analysis:

The results were statistically analyzed using appropriate tests (t-tests, chi-squared) and modeling methods (logistic regression). Cohen's Kappa coefficient was used to study the degree of agreement between radiologists and the AI model.

According to international requirements, the statistical significance of findings was checked using the p-value and confidence intervals. The statistical processing results were considered statistically significant at $p < 0.05$ obtained using the Monte Carlo method. All data obtained during the study were statistically processed. The data was statistically processed using SPSS software version 21.0 and Microsoft Office Excel.

The study was approved by the local ethics committee of the Kazakh Institute of Oncology and Radiology JSC (Almaty, Kazakhstan).

Results: The study analyzed LDCT scans of 1,500 lung cancer screening program participants. Our deep learning model for lung cancer screening demonstrated a sensitivity of 63.4% (95% CI: 54.0-72.8%) and a specificity of 81.6% (95% CI: 79.883.4%) when detecting lung nodules by LDCT. The Lung Cancer CT model was trained on a dataset of annotated CT scans and tested on a reference dataset of 1,000 CT scans. Then, we analyzed the efficiency of the deep learning model, comparing it with the work of radiologists with different levels of experience.

The data in Figure 2 demonstrate that the proposed model, trained to find lung nodules, successfully identified a lung nodule by indicating its location using labels. It illustrates the potential of AI in the automatic detection and diagnostics of pulmonary pathologies.

However, it should be noted that it is always necessary to consider possible limitations and potential er-

rors when interpreting the results based on AI systems. In this case, despite the successful diagnostics of the mass, there may be situations where the AI mistakenly identifies pleural adhesions at the apices of the lungs (Figure 3) as lung nodules or has limited capabilities to find subpleural nodules.

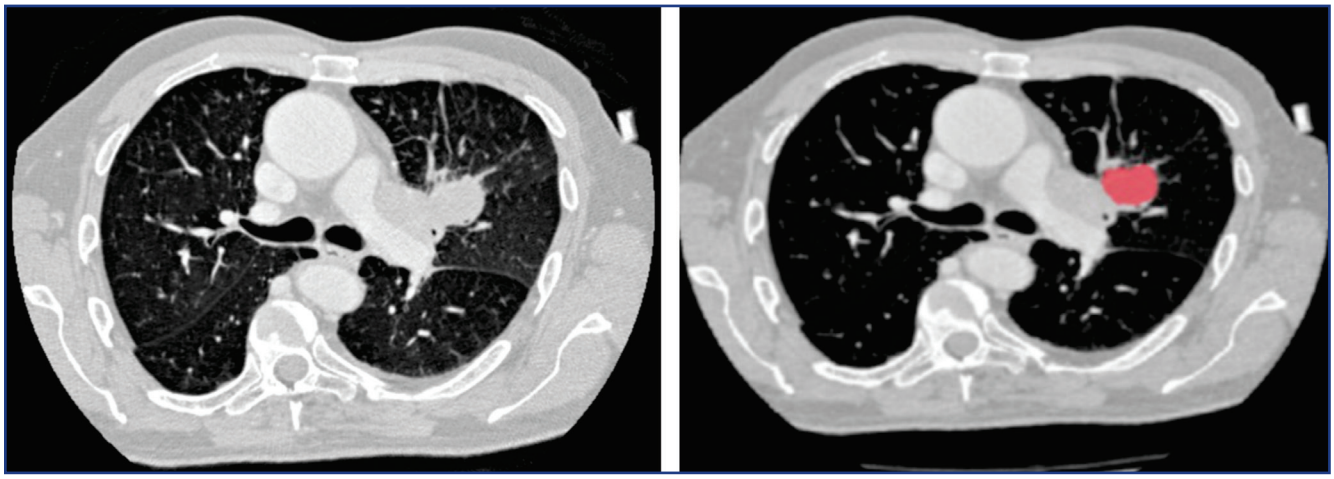

Figure 2 – LDCT image of the central neoplasm S1/2 in the upper lobe of the left lung of the patient LDCT0286 performed as part of the pilot project on lung cancer screening

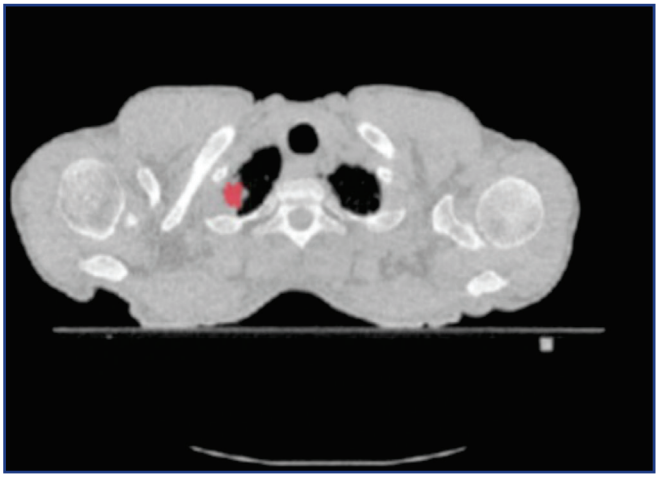

Figure 3 – Pleural adhesions at the apices of the lungs that the AI mistakenly identified as lung nodules, patient images LDCT1106 performed as part of the pilot lung cancer screening project

The AI model's performance was similar to radiologists with less than 5 years of experience, with a sensitivity of 67.1% and a specificity of 83.8%. More experienced radiologists showed higher accuracy in diagnostics of pulmonary nodules, with a sensitivity of 94.2% and a specificity of 98.8%. However, radiologists needed three times more time to interpret LDCT than AI technologies.

It was also found that the deep learning model improves the radiologists' work by increasing the volume of interpreted LDCT studies within the same time interval by 38%.

However, it should be noted that the AI model showed lower sensitivity (40%) and specificity (82%) during detecting subpleural nodules of different sizes. When the model's performance was analyzed for the size and location of the lung nodules, it was found that the AI showed better results in detecting parenchymal lung nodules in patients with larger lung nodules (> 10 mm in diameter) compared to smaller nodules (< 10 mm in diameter) with a sensitivity of 83.3% and 67.8%, respectively.

Discussion: Our study assessed the efficiency of the deep learning model in lung cancer screening using LDCT. The model achieved a sensitivity of 63.4% and a specificity of 81.6% in detecting pulmonary nodules, and it is consistent with previous studies that reported sensitivity from 63% to 96% and specificity from 60% to 98% [11-14]. It was also found that the AI model performance is similar to that of radiologists with less than 5 years of experience, indicating its potential for development.

This is consistent with previous studies that reported that experienced radiologists have higher sensitivity and specificity than less experienced physicians [15-17]. However, the fact that radiologists in both groups spent

more time interpreting the results than the AI model suggests that the AI model may be a more efficient and reliable alternative to manual CT interpretation, especially for less experienced radiologists.

Despite the promising results of AI use in lung cancer screening, our study identified several significant limitations that need to be considered in the clinical application of AI:

Low accuracy in detecting subpleural nodules: In this study, AI demonstrated a significantly lower sensitivity (40%) and specificity (82%) in detecting subpleural nodules, especially those of a small diameter (<10 mm). This limits the model's effectiveness in detecting neoplasms in hard-to-interpret areas, which may lead to the omission of potentially malignant neoplasms.

Error in classifying pulmonary structures: In some cases, AI mistakenly interprets pleural adhesions, especially in the apices of the lungs and vessels, and degenerative changes in vertebral elements as pulmonary nodules. It can lead to false positives, increasing the burden on doctors.

Limited ability to interpret complex cases: Although AI-based technology can significantly improve the diagnostics of pulmonary nodules, its capabilities in complex clinical cases, such as multifocal or diffuse pulmonary parenchymal lesions and central lung neoplasms, remain limited.

The study showed the need to further refine the Lung Cancer CT model to detect subpleural nodules. This may require including additional characteristics of the elements or a large amount of data.

Despite the limitations in detecting subpleural lesions, our study suggests that the AI model could be useful for lung cancer screening with LDCT. The Lung Cancer CT model improved the performance of radiologists with less than 5 years of experience and increased the total volume of LDCT scans interpreted by radiologists. AI technology certainly has the potential to improve the efficiency and accuracy of lung cancer screening using LDCT [16-18]. However, further study is required to test the model's performance on larger, more diverse data sets.

Although many AI models are developed and tested today, there is still a need to find the most optimal models for automatic detection and differentiation of pulmonary nodules on LDCT scans. Our results suggest that such a model could be useful in lung cancer screening with LDCT, especially for less experienced radiologists, and could increase the amount of CT data processed. However, further improvements are needed to increase its sensitivity and specificity, especially when smaller and subpleural lesions are found. Further study is needed to test the model's performance with a larger sample.

Conclusion: In this study, the Lung Cancer CT model has proven the potential of AI models in lung cancer screening. Despite technological limitations in detecting subpleural nodules and small-diameter lung nodules, the model could become a valuable tool for improving the overall efficacy of screening programs. However, further improvement and validation are required to realize the full potential of AI models in lung cancer screening.

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АҢДАТПА

ӨКПЕ ҚАТЕРЛІ ІСІГІН ЕРТЕ ДИАГНОСТИКАЛАУ ҮШІН АЗ ДОЗАЛЫ КОМПЬЮТЕРЛІК ТОМОГРАФИЯДА LUNG CANCER CT ЖАСАНДЫ ИНТЕЛЛЕКТ ТЕХНОЛОГИЯСЫН ҚОЛДАНУ

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Өзектілігі: *Соңғы жылдары өкпенің аз дозалы компьютерлік томографиясын (АДКТ) жасағанда жасанды интеллект (ЖИ) технологиясын қолдану айтарлықтай артқандықтан оған деген назар да артып келеді. АДКТ өкпе ауруларын ерте анықтау және бақылау үшін кеңінен қолданылады, ал тиімді диагностика мен емдеу үшін зерттеуді нақты талдау өте маңызды.*

Зерттеудің мақсаты *– өкпе түйіндерін анықтау сезімталдығын және қатерлі мен қатерсіз үдерістерді ажыратудағы жасанды интеллект (ЖИ) жүйесінің диагностикалық тиімділігін клиникалық тәжірибеде бағалау, оны радиолог дәрігерлердің нәтижесімен салыстыру, сондай-ақ клиникалық қолдануға теориялық негіз ұсыну.*

Әдістері: *Зерттеу өкпе қатерлі ісігін скринингтеу бойынша пилоттық жоба аясында орындалған АДКТ сканларын ретроспективті талдауға негізделген. Ажыратылымы жоғары томографтарда аз дозалы стандартталған сканерлеу хаттамалары қолданылып, нәтижелерді тәжірибелі радиологтар мен көпжылдық тәжірибесі бар сарапшы интерпретациялады. Деректерді талдау және түйіндерді сегментациялау үшін заманауи терең оқыту платформалары (TensorFlow, PyTorch) қолданылды.*

Нәтижелері: *Біз жүргізген зерттеу нәтижесі бойынша өкпедегі түйіндерді анықтауға арнап әзірленген Lung Cancer CT терең оқыту моделінің өкпе түйіндерін анықтауда сезімталдығы 63,4% (95% СИ: 54,0-72,8%) және арнайылығы 81,6% (95% СИ: 79,8-83,4%) екенін көрсетті.*

Қорытынды: *Аталмыш зерттеу жұмысы осыған дейінгі зерттеулерде көрсетілген ақпаратты растай отырып, ЖИ АДКТ талдауын жақсарта алатынын көрсетті. Алайда өкпе түйіндерін ерте анықтаудағы АДКТ сезімталдығы мен арнайылық көрсеткіштеріне қарамастан, ЖИ оларды анықтау үшін қосымша жетілдірулер мен дайындықты қажет етеді.*

Түйінді сөздер: *жасанды интеллект (ЖИ), аз дозалы компьютерлік томография (АДКТ), өкпе обыры.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ ТЕХНОЛОГИИ ИСКУССТВЕННОГО ИНТЕЛЛЕКТА LUNG CANCER CT ПРИ НИЗКОДОЗНОЙ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ ДЛЯ РАННЕЙ ДИАГНОСТИКИ РАКА ЛЕГКОГО

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Актуальность: *В последние годы отмечается рост применения технологии искусственного интеллекта (ИИ) при выполнении низкодозной компьютерной томографии (НДКТ) легких, что, в свою очередь, привлекает значительное внимание. НДКТ широко используется для раннего выявления и мониторинга заболеваний легких, а точный анализ исследований имеет важное значение для эффективной диагностики и лечения.*

Цель исследования *– оценить диагностическую эффективность ИИ-системы в клиническом применении, сравнивая чувствительность к обнаружению легочных узлов и дифференциацию доброкачественных и злокачественных процессов с помощью ИИ и врачей-радиологов, с предоставлением теоретической основы для клинического использования.*

Методы: *Исследование основано на ретроспективном анализе НДКТ исследований, выполненных в рамках пилотного проекта по скринингу рака легкого. Использованы стандартизированные протоколы низкодозного сканирования на томографах с высоким*

разрешением, а интерпретация результатов проводилась опытными радиологами и экспертом с многолетним стажем. Для анализа данных и сегментации узлов применялись современные фреймворки глубокого обучения (TensorFlow, PyTorch).

Результаты: *Результаты исследования показали, что модель глубокого обучения Lung Cancer CT, созданная для определения легочных узлов, обладает чувствительностью 63,4% (95% ДИ: 54,0-72,8%) и специфичностью 81,6% (95% ДИ: 79,8-83,4%).*

Заключение: *ИИ может улучшить процесс интерпретации НДКТ, однако, несмотря на полученные значения диагностической ценности, все еще требует дополнительной доработки для полного применения в практике.*

Ключевые слова: *искусственный интеллект (ИИ), низкодозная компьютерная томография (НДКТ), рак легкого.*

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FIRST EXPERIENCE WITH VATS BRONCHOPLASTIC LOBECTOMY

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ABSTRACT

Relevance: *Surgical treatment for lung cancer is the primary radical approach in antitumor therapy, utilized as a standalone method and as part of a combined strategy. Radical surgical intervention typically involves anatomical lung resection accompanied by lymph node dissection. Modern oncological surgery increasingly emphasizes organ- and function-preserving procedures that maintain oncological efficacy. Video-assisted thoracoscopic surgery (VATS) presents an alternative to traditional open methods, although it is technically more challenging and generally more expensive. Nonetheless, its advantages – such as reduced postoperative pain, shorter duration of pleural drainage, better preservation of lung function, decreased length of hospital stay, and quicker return to normal activities—continue to motivate the surgical community to adopt minimally invasive techniques. This report highlights the first observation of a VATS lobectomy with bronchoplasty.*

The study aimed to *demonstrate the feasibility of minimally invasive bronchoplastic lobectomy as an alternative to pneumonectomy and traditional thoracotomy lobectomy with bronchoplasty.*

Methods: *This paper details a case of video-assisted thoracoscopic surgery performed on a patient with non-small cell lung cancer (NSCLC), along with the technical specifics of the surgical procedure.*

Results: *The article presents short-term outcomes of the VATS bronchoplastic lobectomy, showcasing the effectiveness of this surgical approach.*

Conclusion: *For the first time in Kazakhstan, we successfully performed a thoracoscopic bronchoplastic lobectomy. Based on our experience and insights from international colleagues, we believe this intervention is safe and effective for patients with centrally located lung tumors.*

Keywords: *Video-assisted thoracoscopic surgery (VATS), bronchoplasty, non-small cell lung cancer (NSCLC), sleeve resection, lobectomy.*

Introduction: Improvement of organ-preserving operations is currently one of the priorities of modern oncosurgery. Cancer treatment relies on the functional and oncological adequacy of such operations. In the case of central lung tumors, reconstructive plastic surgery is the only life-saving alternative to pneumonectomy. Bronchoplasty was first performed in 1947 to remove a benign tumor [1, 2]. Later, in 1959, the first bronchoplastic surgery was performed to remove a bronchial carcinoma [1, 3]. In 2002, L. Santambrogio et al. performed the world's first thoracoscopic bronchoplastic lobectomy [4, 5].

With the development and implementation of minimally invasive techniques worldwide, the number of articles on thoracoscopic bronchoplastic surgeries was growing [6,7]. Experience in performing such operations, modern tools and equipment, and the development of anesthesia are the main reasons for expanding indications for the most complex procedures with VATS appliances [8, 1]. The possibility of using lobectomy with bronchoplasty and angioplasty as an alternative to pneumonectomy makes it admissible to perform these operations with acceptable immediate and long-term outcomes, non-inferior to those after pneumonectomy [9].

The study aimed to demonstrate the feasibility of minimally invasive bronchoplastic lobectomy as an alternative to pneumonectomy and traditional thoracotomy lobectomy with bronchoplasty.

Methods: This paper details a case of video-assisted thoracoscopic surgery performed on a patient with non-small cell lung cancer (NSCLC), along with the technical specifics of the surgical procedure.

Patient information: Patient S., 68 years old. On 07/30/2024, he applied to the Kazakh Research Institute of Oncology and Radiology (KazIOR), complaining of shortness of breath in slight physical activity, general weakness, and periodic heart pain. From the anamnesis: The patient's condition worsened in June 2024, so he visited a pulmonologist who prescribed CT (computed tomography). Due to moderately severe COPD of category B, the patient is subject to regular medical check-ups by a pulmonologist. The patient receives regular treatment. A cardiologist who consulted the patient diagnosed CHD (coronary heart disease), effort angina, FC 2, and arterial hypertension stage 1, risk level 4.

Clinical findings: The general condition of the patient was relatively satisfactory. ECOG scale was – 0-1 points. The Karnofsky scale was - 90-80 points. The CCI index was 5 points.

Diagnostics: Prior to referring to KazIOR, the patient was examined at the cancer care dispensary of the residence place.

Computed tomography (CT) of the chest organs from 07/03/2024 Conclusion: Formation of the upper lobe of the right lung with involvement of the upper left bronchus and development of lymphogenic carcinomatosis rightward? Pulmonary emphysema.

The district oncology dispensary oncologist consulted the patient on 07/10/2024 and recommended additional examination.

Fiberoptic bronchoscopy as of 07/17/2024: C-r of the upper lobe bronchus rightward.

Biopsy. Histology report as of 07/29/2024: Non-small cell lung carcinoma, G2. The contrast-enhanced CT scan of the chest organs as of 07/17/2024. Formation of the upper lobe of the right lung with involvement of the upper left bronchus and development of lymphogenic carcinomatosis rightward? Pulmonary emphysema. The contrast-enhanced CT scan of the abdominal organs as of 07/17/2024: Single liver cyst. Right kidney concretion.

The contrast-enhanced CT scan of the brain as of 07/17/2024: Microangiopathy. No formations have been detected. The ultrasound scan of the peripheral lymph nodes as of 07/17/2024: A single lymph node of the supraclavicular region rightward (reactive changes?). Age-related changes in the axillary lymph nodes. EGDS as of 07/17/2024: gastroduodenitis, inactive. Spirography as of 07/26/2024: Moderate to severe obstruction.

The KazIOR interdisciplinary team prescribed neoadjuvant polychemotherapy according to the cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 scheme. The patient underwent follow-up control examinations after 2 courses of neoadjuvant polychemotherapy.

The contrast-enhanced CT scan of the chest organs as of 09/16/2024. Conclusion: CT image of the condition after PCT regarding the central Cr of the upper lobe of the right lung. Pulmonary emphysema (Figure 1). According to a video bronchoscopy from 10/01/2024: On examination, the segmental bronchi of the upper lobe of the right lung B1,2 were obturated by an exophytic formation, irregular shape, the surface was uneven and looked loose. The infiltrative component of the formation along the lateral wall was spread to the upper lobe bronchus with a wide transition to its mouth. The interlobular spur was without features. The middle lobe and lower lobe bronchi were intact. The content of the bronchi was mucous in small amounts (Figure 2). A comprehensive examination with an assessment of the tumor spread and functional operability did not reveal any contraindications. Physical status according to ASA II. Ryabov IIB anesthetic risk.

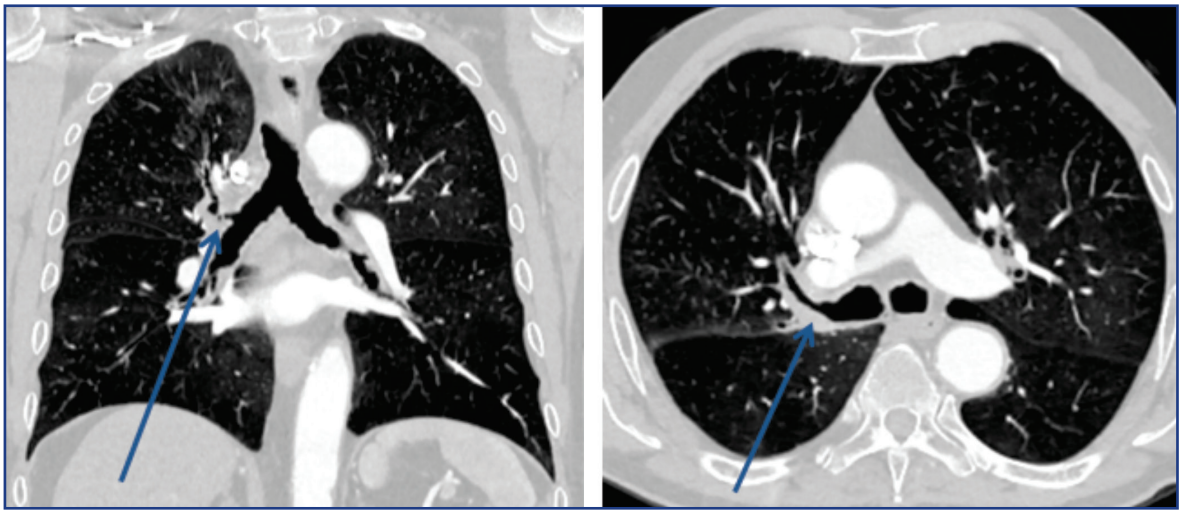

Figure 1 – Computed tomography of patient S., 68 years old. Formation of the root of the upper lobe of the right lung with infiltrative narrowing of the lumen. Signs of pulmonary emphysema

Treatment: The patient was admitted to the hospital for surgery on a scheduled basis. On 10/03/2024, the patient underwent surgery in the scope of VATS rightward, upper lobectomy of the lung with circular resection of the main and intermediate bronchi, bronchial anastomosis, and lymph node dissection. The surgical intervention was performed under combined anesthesia with separate intubation of the bronchi and single-lung ventilation. In the 5th intercostal space, a mini-access of 4-5 cm was made; in the 7th intercostal space along the posterior axillary line, a 10 mm thoracic portal for a video camera was installed. After revision and determination of the absence of signs of metastases, mobilization of bronchial and vascular structures was carried out with parallel systematic lymph node dissection, and interlobular fissures were dissociated. After suturing and crossing all vascular structures of the root of the upper lobe of the right lung, the mobilized intermediate and right main bronchi were circularly crossed, and the upper lobectomy was performed (Figure 3). The macro preparation is indicated in the snapshot (Figure 4). Subsequently, the bronchial resection margin has been referred for further express histology examination. After confirmation of R0 resection, an anastomosis was performed between the right main and intermediate bronchi with a blanket suture of a 4/0 monofilament thread (Figure 5a, 5b). After completion of the bronchial anastomosis, a water test for sufficiency and a control bronchoscopy were performed (Figure 5c). The draining was carried out through the thoracic portal in the 7th intercostal space along the posterior axillary line to the pleural cavity cupula with one drain. The operation took 390 minutes; the intraoperative blood loss was about 30-40 ml.

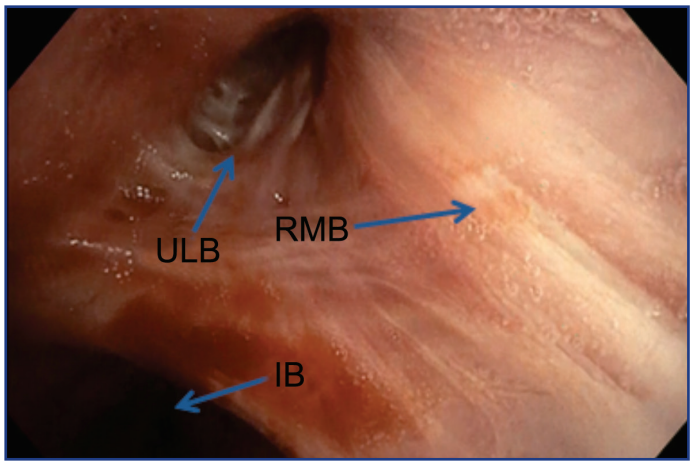

Figure 2 – Preoperative video bronchoscopy of patient S., 68 years old. The arrows indicate ULB (upper lobar bronchus), IB (intermediate bronchus), RMB (right main bronchus)

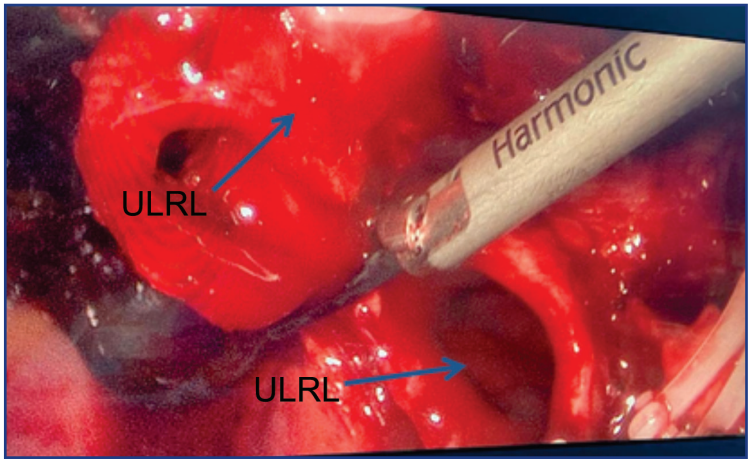

Figure 3 – Stage of circular bronchial crossing. The arrows indicate RMB (right main bronchus), ULRL (upper lobe of the right lung)

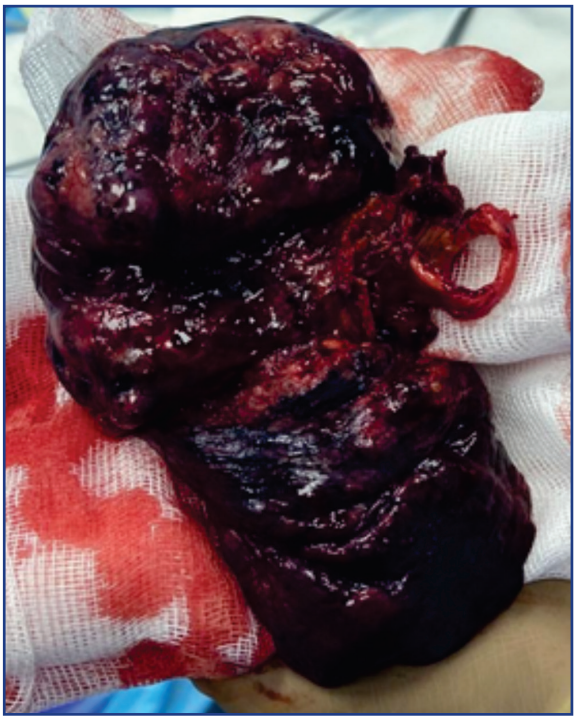

Figure 4 – Macropreparation of the upper lobe of the right lung

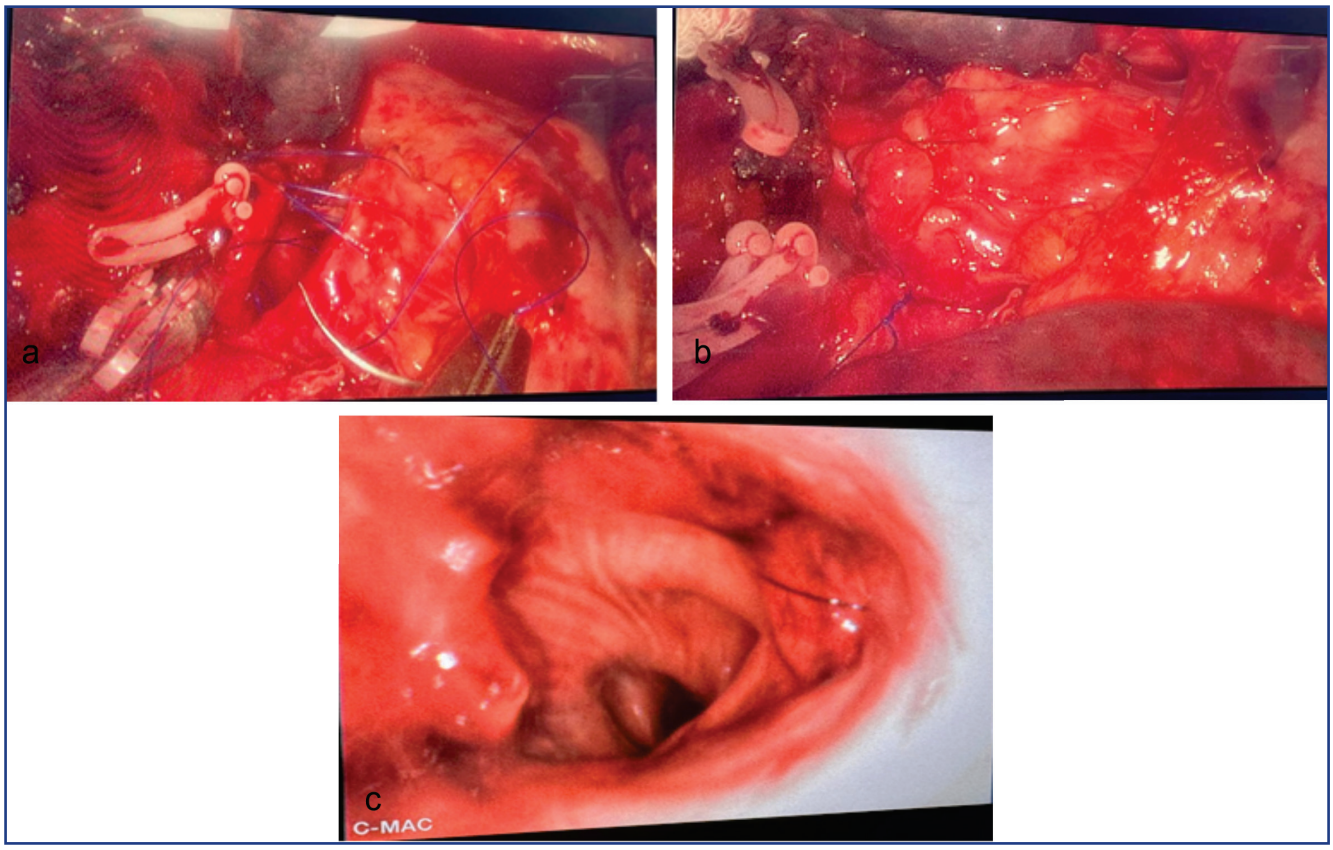

Figure 5 – Stages of applying a circular intrabronchial anastomosis
Notes: a – anastomosis between the intermediate and right main bronchi with a blanket suture of a 4/0 monofilament thread; b – completed anastomosis; c – bronchoscopic image after surgery

Results: The postoperative period proceeded without complications, and the draining lasted 6 days due to exudation. The bronchoscopic control examination was conducted on Day 7 after surgery (Figure 6). The patient was discharged on Day 10 after surgery. Scheduled histology reported a basaloid variant of squamous cell carcinoma of the lung upper lobe, 2.5 cm in the largest dimension, with invasion into the adjacent peribranchial lymph node. The bronchus resection margin was outside the tumor. No metastases were found in 21 removed lymph nodes.

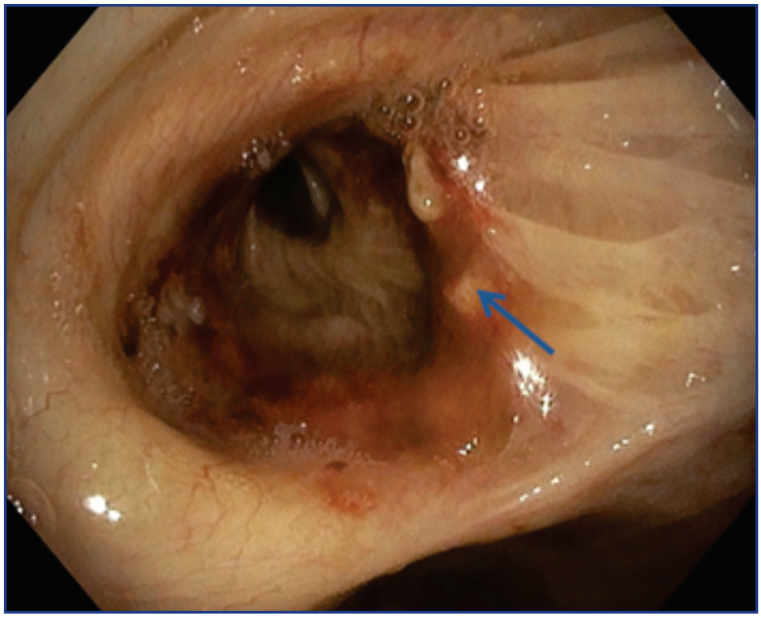

Figure 6 – Bronchoscopic image on Day 7 after surgery. The arrow indicates the anastomosis zone

The timeline of the clinical case described above is presented in Table 1.

Table 1 – The clinical case timeline of VATS surgery of the bronchoplastic lung lobectomy.

Stages of examinations, treatment	Timeline
Laboratory and instrumental examinations at the primary level	July 2024
KazIOR Interdisciplinary Team	08/12/2024
1st course of neoadjuvant polychemotherapy	08/13/2024
2nd course of neoadjuvant polychemotherapy	09/03/2024
Surgical treatment	10/03/2024
Patient discharge	10/13/2024

Discussion: From the technical point of view, the performance of minimally invasive bronchoplastic surgeries is undoubtedly a challenging surgical intervention. Patients planned for this volume of surgery require careful selection. In addition to the technical special aspects of the operation, the medical facility has to be supplied with all necessary equipment, and the medical personnel should be ready for the peculiarities of the surgical intervention. It is especially known that patients with concomitant pathologies such as COPD, diabetes mellitus, diseases requiring treatment with steroid drugs, etc., have a higher risk of bronchial anastomosis failure [10]. However, despite the presence of COPD in the observed patient S., it did not cause problems with the anastomosis.

Conclusion: Bronchoplastic surgery has proven highly efficient and safe in treating patients with centrally located lung tumors. It preserves a significant volume of lung tissue and ensures positive functional and oncological outcomes. The successful outcomes of these interventions confirm them as an important component of modern surgical interventions for lung cancer. The experience gained, and the introduction of advanced technologies minimize the risks of complications and improve patients' quality of life.

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АҢДАТПА

VATS БРОНХОПЛАСТИКАЛЫҚ ЛОБЭКТОМИЯНЫ ЖҮРГІЗУДІҢ АЛҒАШҚЫ ТӘЖІРИБЕСІ

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Өзектілігі: *өкпенің қатерлі ісігін хирургиялық емдеу тәуелсіз нұсқада да, кешенді және аралас емдеуде де ісікке қарсы терапияның негізгі радикалды әдісі болып табылады. Радикалды хирургиялық емдеу дегеніміз лимфодиссекциямен қоса өкпенің анатомиялық резекциясы болып табылады. Қазіргі заманғы онкохирургия онкологиялық радикализмді қадағалаумен аязаны - және функционалдылықты сақтайтын операцияларды орындауға ұмтылуда. Видеоассистирленген торакоскопиялық хирургия (VATS) ашық дәстүрлі әдістерге балама болып табылады, бірақ техникалық жағынан қиынырақ және материалдық жағынан шығындылау. Дегенмен, келесі артықшылықтарға ие: операциядан кейінгі ауырсынуды азайту, плевраны дренаждау уақытын қысқарту, өкпе функциясын жақсырақ сақтау, стационарда аз болу, сондай-ақ науқастың әдеттегі өмір әрекеттеріне тезірек оралуы, хирургиялық қауымдастықты минимнвазивті әдістерді қолдануға көбірек сендіруде. Біз VATS тәсілімен бронхопластикалық лобэктомия операциясының алғашқы бақылауын береміз.*

Зерттеудің мақсаты *– пневмонэктомияға және бронхопластикамен дәстүрлі торакотомиялық лобэктомияға балама ретінде минимнвазивті бронхопластикалық лобэктомия жасау мүмкіндігін көрсету.*

Әдістері: *бұл жұмыста өкпенің ұсақ жасушалы емес қатерлі ісігі (ӨҰЖЕҚІ) бар науқасты бейнеторакоскопиялық хирургиялық емдеу жағдайы және операцияның техникалық ерекшеліктері сипатталған.*

Нәтижелері: *мақалада VATS бронхопластикалық лобэктомиясының ең жақын нәтижелері келтірілген, хирургиялық араласудың осы әдісінің тиімділігі көрсетілген.*

Қорытынды: *қазіргі уақытта біз Қазақстанда алғаш рет торакоскопиялық бронхопластикалық лобэктомия операциясын жасадық. Өз тәжірибеміздің және шетелдік әріптестеріміздің тәжірибесін біле отырып, біз мұндай араласуды орталық өкпе ісіктері бар науқастар үшін жеткілікті қауіпсіз және тиімді әдіс деп санай аламыз.*

Түйінді сөздер: *VATS, бронхопластика, ӨҰЖЕҚІ, sleeve резекциясы, лобэктомия.*

АННОТАЦИЯ

ПЕРВЫЙ ОПЫТ ПРОВЕДЕНИЯ VATS БРОНХОПЛАСТИЧЕСКОЙ ЛОБЭКТОМИИ

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Актуальность: *Хирургическое лечение рака лёгкого является основным радикальным методом противоопухолевой терапии, как в самостоятельном варианте, так и в комплексном и комбинированном лечении. Радикальным хирургическим лечением определяется анатомическая резекция легкого с лимфодиссекцией. Современная онкохирургия всё более стремится к выполнению органо- и функционально сохраняющих операций, при этом с сопоставимым онкологическим радикализмом. Видеоассистированная торакоскопическая хирургия (VATS) – альтернатива открытым традиционным методам, но сложнее технически и материально затратнее. Однако имея такие преимущества как: уменьшение послеоперационной боли, сокращение времени плеврального дренирования, лучшее сохранение легочной функции, меньшее пребывание в стационаре, а также более ускоренное возвращение больного к обычной его деятельности, всё более убеждают хирургическое сообщество к применению миниинвазивных методик. Нами приводится первое наблюдение операции VATS лобэктомии с бронхопластикой.*

Цель исследования *– продемонстрировать возможность проведения миниинвазивной бронхопластической лобэктомии как альтернативу пневмонэктомии и традиционной торакотомной лобэктомии с бронхопластикой.*

Методы: *В данной работе описан случай видеоторакоскопического хирургического лечения пациента с немелкоклеточным раком легкого (НМРЛ) и техническими особенностями проведения операции.*

Результаты: *В статье приведены ближайшие результаты VATS бронхопластической лобэктомии, показана эффективность данного метода хирургического вмешательства.*

Заключение: *на настоящий момент нами впервые в Казахстане самостоятельно проведена торакоскопическая бронхопластическая лобэктомия. Имея собственный опыт и зная опыт зарубежных коллег, можем считать такой вид вмешательства достаточно безопасным и эффективным для больных с центральными опухолями лёгких.*

Ключевые слова: *VATS, бронхопластика, НМРЛ, sleeve резекция, лобэктомия.*

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CRYOTHERAPY FOR BASAL CELL SKIN CANCER

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ABSTRACT

Relevance: *Basal cell skin cancer is the most common type of skin cancer, accounting for about 80% of all cases. Given its benign course, early treatment of basal cell skin cancer (at stages 1 and 2) is an important point. These stages typically have a high cure rate, and one of the key goals of treatment is to minimize exposure with good cosmetic results.*

The study aimed to *provide an overview and analysis of cryotherapy as a treatment option for basal cell skin cancer (BCSC), including assessing its effectiveness and safety.*

Methods: *The study included patients of 18 years and older, both sexes, with BCSC stage I and II, who underwent cryotherapy as the main treatment.*

Results: *Between 2017 and 2023, the Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan) performed cryotherapy on 983 patients with BCSC stages I and II.*

Conclusion: *Cryotherapy is an effective method for treating BCSC in the early stages of the disease, providing a good cosmetic result and minimal complications.*

Our 983 patients who received cryotherapy had a local response to treatment, manifested by partial or complete disappearance of the tumor.

Cryotherapy has been successfully used in patients aged 18 years and older, regardless of gender and the presence of concomitant diseases.

Absolute standardized morbidity and mortality rates were calculated using the world standard (World).

Keywords: *basal cell skin cancer, cryotherapy, treatment outcome.*

Introduction: Basal cell carcinoma of the skin (BCSC) is one of the most common malignant skin tumors, representing a significant medical and social problem. According to the World Health Organization, BCSC cases are constantly increasing, especially in countries with high ultraviolet radiation levels. In 2022, 3221 new cases of basal cell cancer were registered in the Republic of Kazakhstan, which is 83% of all skin tumors [1]. In 2023, the number of cases increased to 3998, i.e., an increase of 19% compared to the previous year.

Given the increasing epidemiological status of skin cancer and the importance of developing effective treatments, cryotherapy, a procedure based on the use of low temperatures to destroy tumor cells, is gaining more attention as an alternative treatment for BCSC.

Several methods used currently to treat basal cell carcinoma include cryosurgery, classical open surgery, radiotherapy, photodynamic therapy, and therapy with such topical medicines as 5-fluorouracil and imiquimod (imidazoquinolinone amine, a synthetic immunomodulator that stimulates the elimination of such cytokines as IFN-alpha, IL-6, and TNF-alpha). Each therapeutic or surgical option has specific indications, side effects, advantages, and disadvantages [2, 3, 4, 5, 6].

We studied data collected between 2017 and 2023 at the Kazakh Institute of Oncology and Radiology (KazIOR, Almaty, Kazakhstan), where cryotherapy was performed on 983 patients with BCSC stages I and II. This paper presents the results of a cryotherapy efficacy and safety analysis and its implications for cancer treatment. The collected data emphasize the possibility of using this method in oncological institutions of the Republic of Kazakhstan and its potential to improve the quality of life of patients.

The study aimed to provide an overview and analysis of cryotherapy as a treatment option for basal cell skin cancer (BCSC), including assessing its effectiveness and safety.

Materials and methods: In 2017-2023, cryotherapy was performed at KazIOR for 983 patients with a preliminarily cytologically confirmed diagnosis of BCSC, of which 612 (62%) were women and 371 (38%) were men.

Cryotherapy was conducted using a Cryo-S Electric II device (Metrum Cryoflex, Poland) and a probe with a diameter of 5 and 20 mm, depending on the size of the skin tumor (Figures 1-3). The refrigerant was carbon dioxide (CO_2) at -74 degrees and above. Usually, one cryotherapy session included 6-12 applications and lasted 15 seconds to 3 minutes.

Results: From 2017 to 2023, 983 patients underwent cryotherapy at KazIOR. 934 (95%) of the total number of patients had basal cell carcinoma of the skin, and 49 (5%) had metatypical cancer. In the first four years, 43 procedures were performed per year. However, since 2021, there has been a sharp increase in the number of procedures performed. It amounted to an increase of up to 83% compared to previous years (Figure 4).

Figure 1 – Cryo-S Electric II device (Metrum Cryoflex, Poland)

Figure 2 – Probes with a diameter of 5 and 20 mm

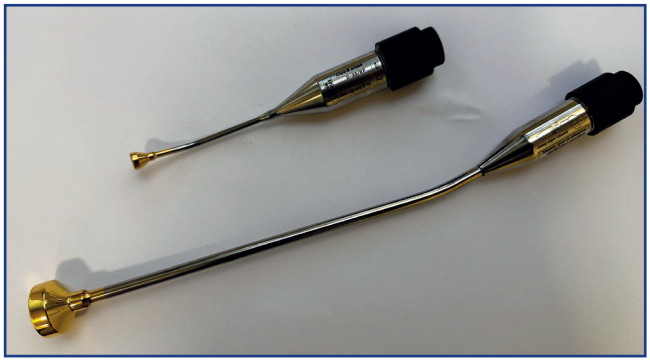

Figure 3 – Probes with a diameter of 5 and 20 mm

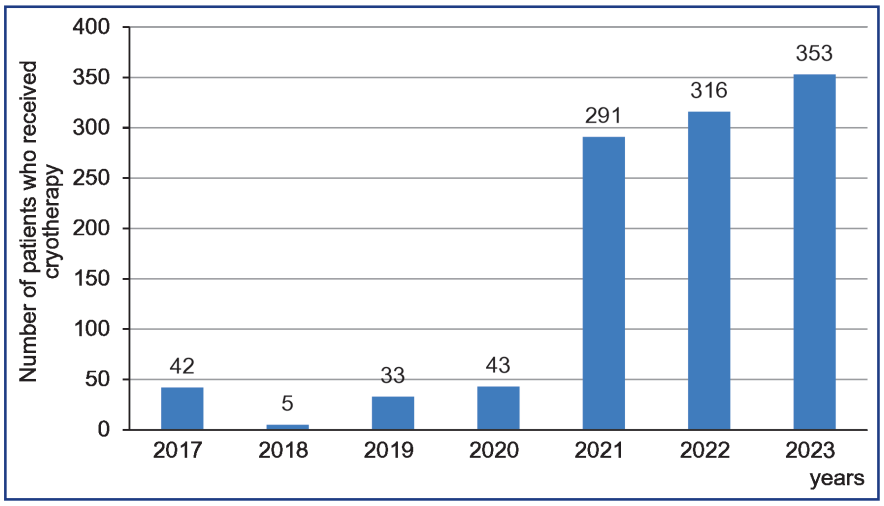

Figure 4 – Distribution of patients who received cryotherapy by years (absolute number)

From 2017 to 2023, the number of women who received cryotherapy exceeded the number of men by 25-51% in all age groups, except for the 50-59 age group, where there were 4% more men (Figure 5).

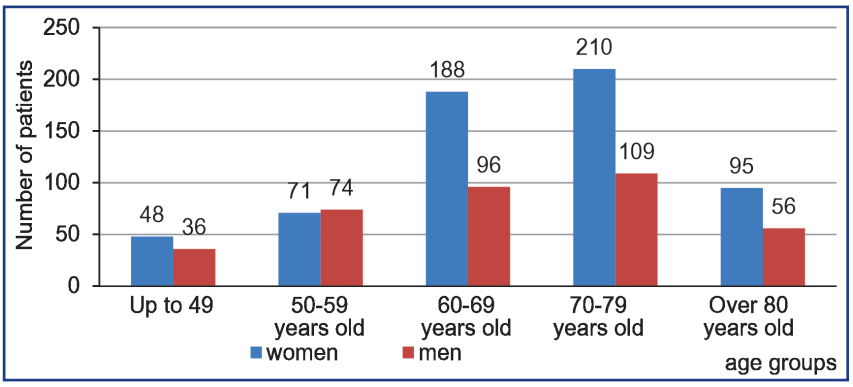

Figure 5 – Total number of patients who received cryotherapy in 2017-2023 by gender and age groups (absolute number)

97% of the patients who received cryotherapy for BCSC were stage I patients, while 3% were stage II patients (Figure 6).

In terms of localization, cryotherapy was performed for facial skin cancer in 72% of patients, for the scalp in 10.0%, for the trunk in 7.2%, for the ear in 5.0%, and the rest of locations in 5.3% of patients (Figure 7). The therapy was performed for the first time in 836 (85%) patients, of whom 43 (4.3%) relapsed after previous surgical interventions and radiation therapy. Repeated cryotherapy was performed in 147 (15%) patients. Of these, 30 patients were prescribed repeated sessions of cryotherapy for relapses after cryotherapy, 6 patients were prescribed a course of radiation therapy, and 5 patients were prescribed surgery.

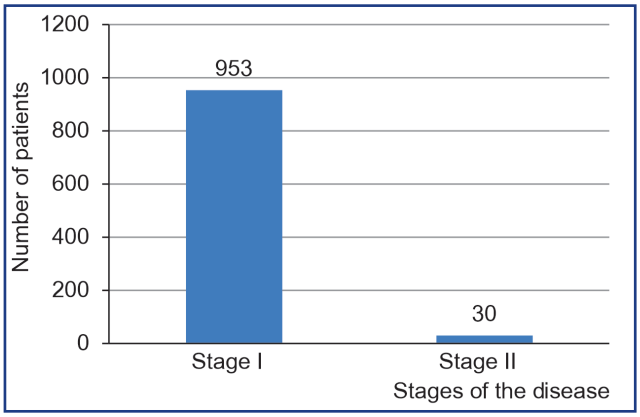

Figure 6 – Distribution of patients who received cryotherapy in 2017-2023, depending on the disease stage (absolute number).

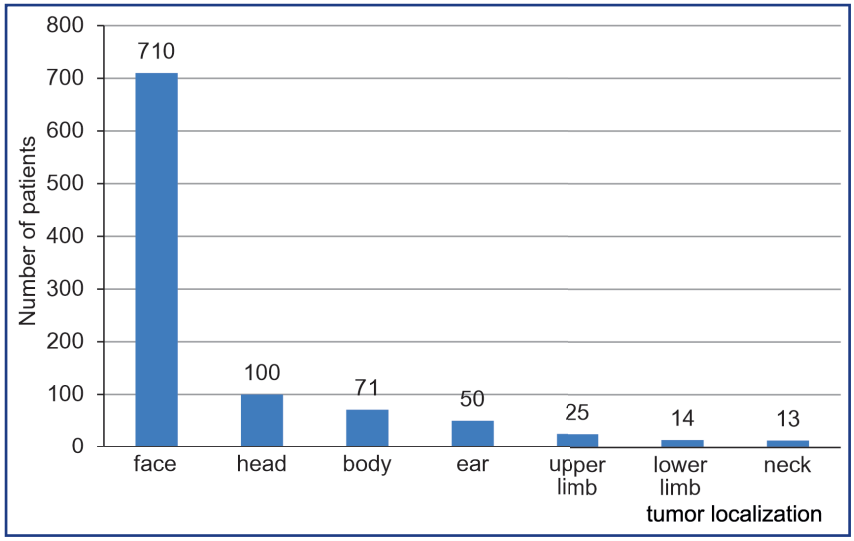

Figure 7 – Distribution of patients depending on the skin tumor location (absolute number)

As a result of treatment, 69 (7%) patients had a relapse successfully treated with radiation therapy in 6 patients, excision of the skin tumor in 4 patients, and repeated sessions of cryotherapy in 30 patients.

After cryotherapy, hyperpigmentation was observed mainly in dark-skinned patients, while skin hypopigmentation was recorded in light-skinned patients. In 30% of cases, a hypertrophic scar in the form of a convex stripe occurred. It resolves on its own in 6-8 months.

Data from other studies also confirm that cryotherapy is efficient at stage I of the disease and delivers high cure rates and minimal recurrence [7, 8]. Cryosurgical procedures showed good results in a study involving 91 patients with T2 and T3 tumors: 82 (94.4%) out of 86 patients with T2 stage BCSC achieved a cure. Relapses in 4 patients were also successfully treated. As for T3 tumors, cryosurgery has only been used in selected cases for strict indications. One of the five patients in this group experienced a surgically resolved recurrence. These findings highlight the need for an individualized approach to treating more complex forms of this disease [2].

Below, there are cases of treatment using cryotherapy performed in our clinic.

Case 1: Patient K, born in 1939, diagnosis: Skin cancer in the infraorbital region on the right StII (T2NoMo),

cytological conclusion - basal cell carcinoma of the skin in the infraorbital region on the right. She underwent 2 sessions of cryotherapy with the Cryo-S Electric II device at an interval of a month at KazIOR in October-November 2021 (Figures 8-11).

Case 2: Patient G., born in 1946, diagnosis: Skin cancer in the wing of the nose and the bridge of the nose on the right StII (T2NoMo), cytological conclusion - basal cell carcinoma of the skin on the nose on the right. He underwent 4 cryotherapy sessions with the Cryo-S Electric II device with a month interval at KazIOR in 2022 (Figures 12, 13).

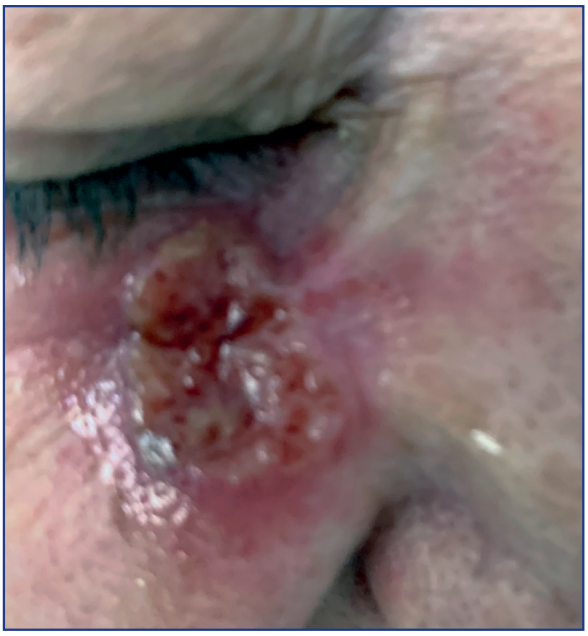

Figure 8 – Skin tumor in the infraorbital region on the right, condition before treatment

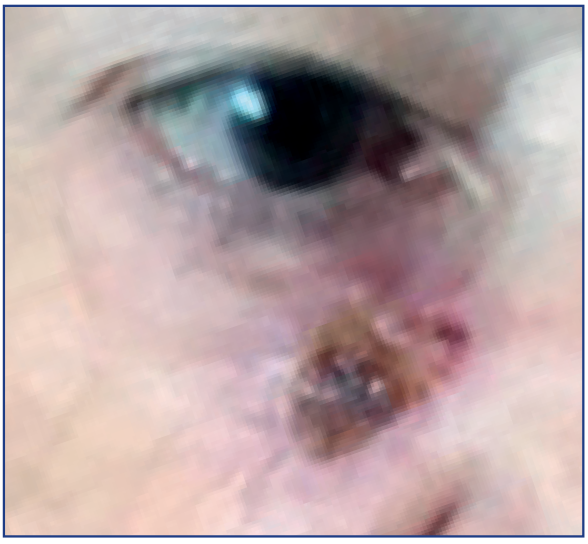

Figure 9 – Condition in 4 weeks after 1 cryotherapy session

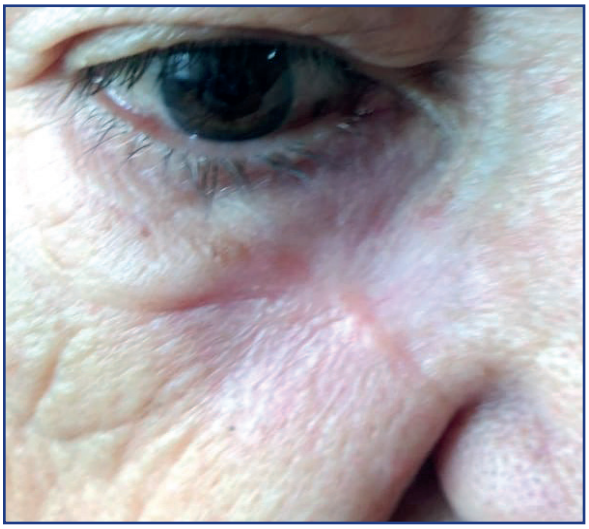

Figure 10 – Condition in 8 weeks after cryotherapy

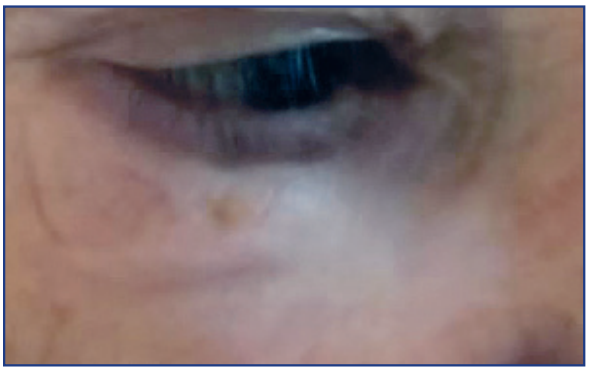

Figure 11 – Condition in 3 years after cryotherapy

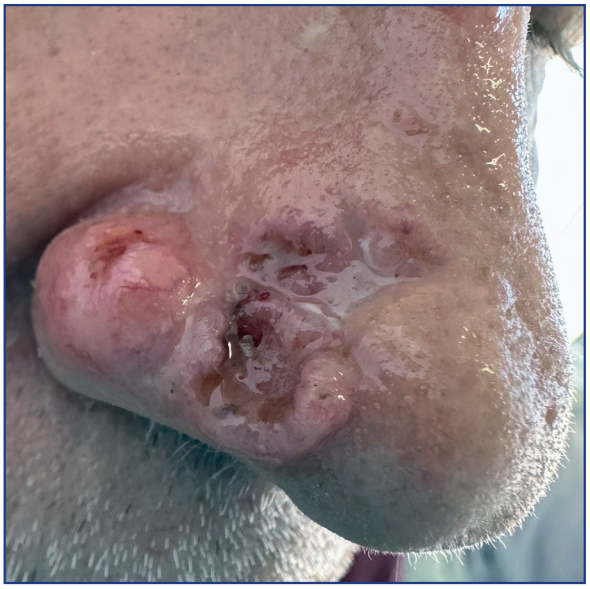

Figure 12 – Skin tumor of the wing and bridge of the nose on the right, condition before treatment

Discussion:

Main characteristics of the patients

97% were at stage I of the disease, and only 3% were at stage II. The peak of the age group was observed in

the range of 60-79 years; 40% were women, and 21% were men in this group. Besides, 72% of tumors were localized on the skin of the face.

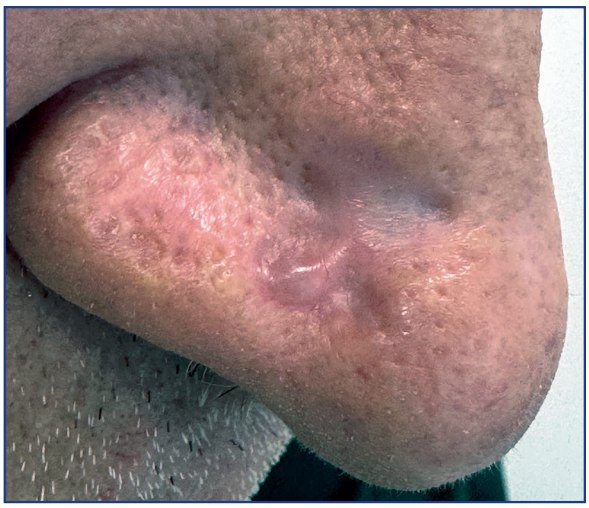

Figure 13 – Condition in 2 years after cryotherapy

Safety and complications

After cryotherapy, 80% of patients experienced localized edema with lymphatic discharge during the first week. It varied depending on the location of the tumor. The most common manifestations were blisters on the neck, limbs, and trunk skin and swelling of half of the face, eyelids, and auricle. A crust formed in 20% of patients immediately after the procedure.

A dry crust was formed in the second week after treatment. It was rejected on its own in 2-3 weeks, leaving an atrophic scar. It is important to note that the healing process proceeded without the need for ointments and solutions, indicating good tolerability and efficiency of the method. This natural recovery process highlights the benefits of cryotherapy as a less invasive approach to treating basal cell carcinoma of the skin.

Clinical and practical aspects

Cryotherapy is an effective treatment for patients with stage I and II BCSC, especially those with comorbidities. This method is characterized by accessibility, low cost, rapid implementation, and good tolerability, making it the treatment of choice for many patients. In addition, cryotherapy provides good cosmetic results, and it is especially important for patients whose tumors are localized on visible areas of the skin.

Advantages and limitations

Cryotherapy shows good cure results, especially in Stages I and II of BCSC, making it a reliable choice for treatment.

The method is low in trauma, and it reduces the risk of complications. It allows patients to recover faster and does not impair the quality of life.

Cryotherapy is a safe procedure, especially for patients with concomitant diseases, as it avoids serious surgical interventions and associated risks.

Conclusion As a result of the study of cryotherapy as a method intended to treat basal cell carcinoma of the skin in patients with Stages I and II of the disease, we came to the following conclusions:

Cryotherapy has shown its high efficiency in the early stages of BCSC, providing a good cosmetic result and minimal complications.

A significant response was expressed regarding the partial or complete disappearance of tumors in patients who underwent cryotherapy.

Cryotherapy has been successfully used as the primary treatment for our cohort of patients with BCSC, confirming its safety and efficacy.

Our results also show that cryotherapy can be successfully used in patients aged 18 years and older, regardless of gender and the presence of comorbidities.

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АҢДАТПА

БАЗАЛЬДЫ ЖАСУШАЛЫҚ ТЕРІ РАГИНА КРИОТЕРАПИЯ

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Анықтама: *Базальды жасушалы тері қатерлі ісігі тері қатерлі ісігінің ең таралған түрі болып табылады, барлық жағдайлардың шамамен 80% құрайды. Терінің базальды жасушалық қатерлі ісігін ерте кезеңде емдеу (1 және 2), оның жақсы ағымын ескере отырып, маңызды сәт болып табылады. Бұл кезеңдер әдетте жоғары емдеу жылдамдығына ие және емдеудің негізгі мақсаттарының бірі жақсы косметикалық нәтижелермен әсер етуді азайту болып табылады.*

Зерттеудің мақсаты *– оның тиімділігі мен қауіпсіздігін бағалауды қоса алғанда, базальды жасушалық тері обырын (BCSC) емдеу нұсқасы ретінде криотерапияны шолу және талдау.*

Әдістері: *Зерттеуге негізгі емдеу әдісі ретінде криотерапиядан өткен екі жыныстағы 18 жастан асқан, БКК I және II сатылары бар пациенттер қатысты.*

Абсолютті стандартталған аурушаңдық пен өлім-жітім көрсеткіштері әлемдік стандартты (Әлемдік) пайдалана отырып есептелді.

Нәтижелері: *2017-2023 жылдар аралығында Қазақ Ұлттық онкология және радиология ғылыми-зерттеу институты (Алматы, Қазақстан) базальды жасушалық карциноманың (БЦК) I және II сатысымен ауыратын 983 науқасқа криотерапия жүргізді.*

Қорытынды: *Криотерапия - бұл жақсы косметикалық нәтиже және асқынулардың ең аз санын қамтамасыз ететін аурудың ерте кезеңдерінде БКК емдеудің тиімді әдісі.*

Криотерапиядан өткен 983 пациентіміз ісіктің ішінара немесе толық жойылуымен көрінетін емдеуге жергілікті жауап берді.

Криотерапия жынысына және қатар жүретін аурулардың болуына қарамастан 18 жастан асқан науқастарда сәтті қолданылды.

Түйінді сөздер: *базальды жасушалы тері ісігі, криотерапия, емдеу нәтижесі.*

АННОТАЦИЯ

КРИОТЕРАПИЯ БАЗАЛЬНОКЛЕТОЧНОГО РАКА КОЖИ

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Актуальность: *Базальноклеточный рак кожи является наиболее часто встречающимся типом рака кожи, составляя около 80% всех случаев. Лечение базальноклеточного рака кожи на ранних стадиях (1 и 2), учитывая его доброкачественное течение, является важным моментом. На этих стадиях обычно достигается высокий процент излечиваемости, и одной из ключевых целей лечения является минимизация воздействия с хорошим косметическим результатом.*

Цель исследования *– предоставление обзора и анализа криотерапии в качестве метода лечения базальноклеточного рака кожи (БКРК), включая оценку ее эффективности и безопасности.*

Методы: *Для исследования были включены пациенты с I и II стадиями БКРК, возраст от 18 лет и старше, обоих полов, которым проведена криотерапия как основной метод лечения.*

Абсолютные стандартизованные показатели заболеваемости и смертности рассчитаны с применением мирового стандарта (World).

Результаты: *В период с 2017 по 2023 год в Казахском Национальном Исследовательском Институте Онкологии и Радиологии (Алматы, Казахстан) была проведена криотерапия у 983 пациентов, страдающих базальноклеточным раком (БКРК) I и II стадий.*

Заключение: *Криотерапия является эффективным методом лечения БКРК на ранних стадиях заболевания, обеспечивая хороший косметический результат и минимальное количество осложнений.*

У наших 983 пациентов, получивших криотерапию, наблюдался локальный ответ на лечение, выражающийся в частичном или полном исчезновении опухоли.

Криотерапия успешно применена у пациентов в возрасте от 18 лет и старше, независимо от пола и наличия сопутствующих заболеваний.

Ключевые слова: *базальноклеточный рак кожи (БКРК), криотерапия, результат лечения.*

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Authors' input: *contribution to the concept, study design, execution and interpretation of the study, preparation of the manuscript – D. Tuleuova.*

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IMMEDIATE RESULTS OF SURGICAL TREATMENT OF STAGE III FACIAL SKIN CANCER: A CLINICAL CASE

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ABSTRACT

Relevance: *Most cases of skin cancer are widespread on continents with predominantly fair-skinned populations and high levels of ultraviolet radiation exposure, such as Australia and New Zealand. In Kazakhstan, as well as throughout the world, there is an increasing trend in the incidence of skin cancer. In 2023, 4,481 new cases of this disease were registered, of which 85% were basal cell carcinoma. Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan) utilizes various methods, including surgical excision, which remains the main treatment method, as well as radiation therapy, electrochemotherapy, and cryotherapy.*

The study aimed to *describe a case of surgical treatment of a patient under local anesthesia with stage III basal cell skin cancer of the zygomatic region on the left, accompanied by clinical bleeding and pain.*

Methods: *The article describes a case of surgical treatment of skin cancer under local infiltration anesthesia.*

Results: *The postoperative period proceeded without complications. The cosmetic result was assessed as satisfactory. The patient did not experience difficulties with facial movements, and no sensory disturbances were observed. The patient was discharged home with recommendations to consult a radiologist considering the tumor histotype to decide on the possibility of a postoperative course of radiation therapy.*

Conclusion: *The presented case demonstrates the possibility of performing surgery for stage II-III skin cancer with complete closure of the defect under local anesthesia. This may be an alternative to general anesthesia in patients with concomitant diseases and a high risk of complications. The method can be used in the absence of tumor invasion into the bone to avoid the difficulties associated with general anesthesia.*

Keywords: *Squamous cell carcinoma, clinical case, surgical treatment.*

Introduction: Most skin cancers are prevalent on continents with predominantly white populations and high levels of exposure to ultraviolet radiation, such as Australia and New Zealand. At the same time, mortality rates from the disease remain high on continents with fewer light-skinned people. One of the reasons for the higher mortality rates in such regions as Asia is the lack of awareness of the population about the prevention of skin cancer and the importance of early diagnostics of the disease [1].

There is a trend towards an increase in the incidence of skin cancer in the world and Kazakhstan, with 3998 new cases of this disease reported in 2022. Of them, 85% were basal cell carcinoma [2]. In 2023, the number of cases increased to 4,481. Its frequency is related to exposure to ultraviolet radiation. BCC is often asymptomatic until such signs as tumor enlargement, bleeding, or growth into underlying tissues occur. Despite the rarity of metastasis, the disease can cause significant local destruction.

A comprehensive approach to diagnostics includes medical history, visual examination, and dermatoscopy with cytological or histological examination. In terms of treatment, the Kazakh Institute of Oncology and Radiology JSC (KazIOR, Almaty, Kazakhstan) uses various methods, including surgical excision, which remains the main treatment, as well as radiation therapy, electrochemotherapy, and cryotherapy. These methods can be used depending on the disease stage, the tumor location, and the patient's condition.

The study aimed to describe a case of surgical treatment of a patient under local anesthesia with stage III basal cell skin cancer of the zygomatic region on the left, accompanied by clinical bleeding and pain.

Methods: The article describes a case of surgical treatment of skin cancer under local infiltration anesthesia. The patient has provided a signed informed consent form to the manipulations and the use of his/her treatment results for scientific research, educational, scientific, and advertising purposes.

Clinical case:

Patient's information: Patient S., male, 79 years old. In 2022, this patient developed a tumor-like formation on the skin of the zygomatic region on the left. After an injury in 2024, he notes a gradual increase in dynamics. He went to the oncology center in Taldykorgan, where a smear was made from his skin tumor of the zygomatic region on the left. Cytological study No. 4354/4 as of 05.08.2022: squamous cell carcinoma. The patient did not visit a doctor or receive any treatment. Due to increased pain and bleeding during contact in August 2024, he went to the KazIOR clinic. Considering the disease history and status localis, the patient was recommended surgery at the KazIOR Center for Bone and Soft Tissue Tumors.

On 26.09.2024, this patient was discussed at a meeting of the KazIOR multidisciplinary group (MDG). The Concilium recommended surgical treatment in the amount of excision of

the skin tumor of the zygomatic region on the left under general anesthesia.

Clinical data: The patient was hospitalized on 30.09.2024 in the Center for Bone and Soft Tissue Tumors with a clinical diagnosis of "Malignant tumor of the skin in the zygomatic region on the left, stage III (T3N0M0)".

Complaints upon admission: a tumor-like formation on the skin of the zygomatic region on the left, bleeding on contact, painful.

General condition: satisfactory. Under the Karnofsky scale – 80%. ECOG – 1. BP: 120/80 mmHg, Pulse: 78/min. Temperature 36.6°C. Consciousness was clear, adequacy was preserved. Breathing was vesicular; the respiratory rate was 16/min, with no wheezing. Heart sounds were muffled; the rhythm was correct. The tongue was moist. The abdomen was soft, symmetrical, not swollen, painless. There were no peritoneal symptoms. Urination was independent. Peristalsis was active. Defecation was independent.

Locally: a 5.0x4.0 cm exophytic formation on the skin of the zygomatic region on the left protruding 1.5 cm above the skin level, covered with a black crust with ulceration in the center, covered with fibrinous plaque, bleeding on contact, immobile, with pronounced tenderness during palpation (see Figure 1).

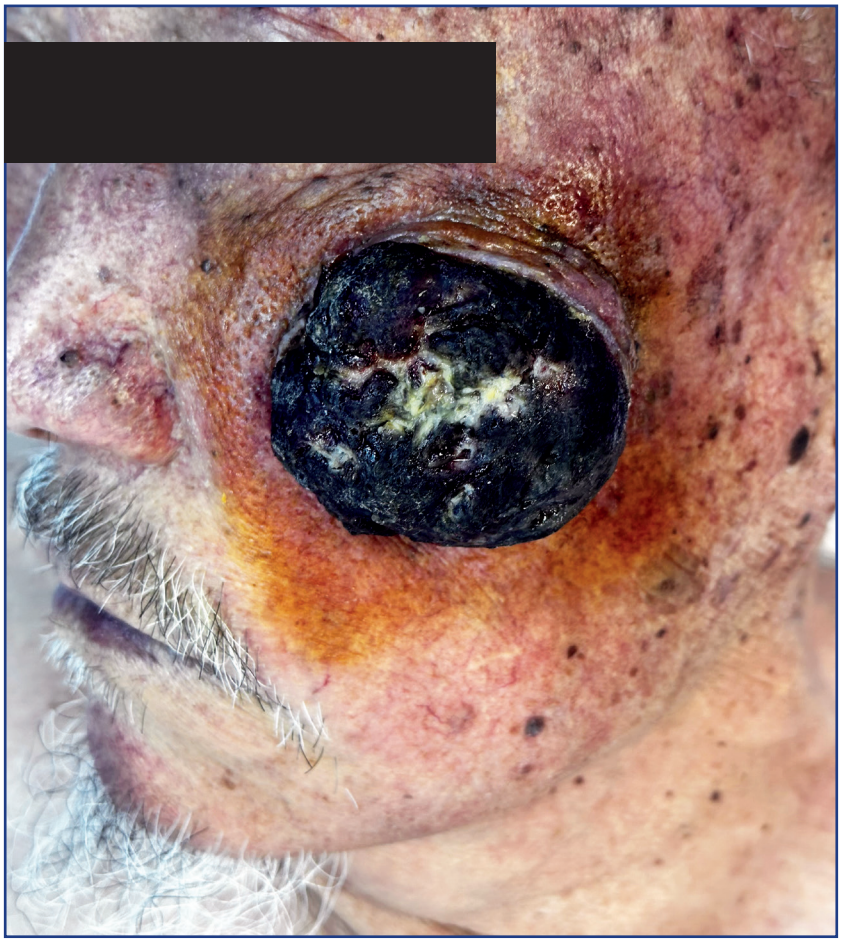

Figure 1 – A 5.0x4.0 cm skin tumor, bulging by 1.5 cm, at the admission of patient S.

Laboratory data

Blood ELISA for viral hepatitis B as of 12.09.2024 was negative.

Blood ELISA for viral hepatitis C as of 12.09.2024 was negative.

HIV results as of 12.09.2024 were negative.

RW results as of 24.09.2024 were negative. Complete Blood Count as of 24.09.2024: WBC – $8.81x10^9$/l, RBC – $5.26x10^{12}$/l, HGB – 156 g/L, PLT – $242x10^9$/l.

Blood biochemistry as of 24.09.2024: ALT– 14.17ME/l, AST – 17.57 ME/l, GLUC – 4.36 mmol/L, creatinine – 124.75 mmol/L, urea – 5.84 mol/L, total protein – 74.20g/L, total bilirubin – 24.0 mol/L.

Clinical Urine Analysis as of 05.09.2024: color – straw yellow, transparency – transparent, relative density – 1,017, leukocytes – 0 in the field of view, pH reaction – 5.

Coagulogram as of 24.09.2024: PTT – 16.8 sec., INR – 1.53, PTI – 68% sec, APTT – 49.50 sec., fibrinogen – 4.17 g/L.

Elevated INR and PTI values were most likely associated with concomitant pathology of the cardiovascular system.

Instrumental studies:

Computed tomography of the chest as of 24.09.2024 Impression: CT picture of interstitial fibrosis in both lungs, probably of a post-inflammatory nature. Adenopathy of the mediastinal lymph nodes. Effusion in the pleural cavities. Pulmonary emphysema. Solid nodules in the right lung. Cardiomegaly.

ECG as of 16.09.2024 Findings: Atrial fibrillation, heart rate – 115 beats per minute. Complete block of the right bundle branch. Ventricular extrasystole. Left ventricular hypertrophy.

Echocardiography as of 03.09.2024 Findings: Ejection fraction of the left ventricular 30 %, dilation of the right atrium, left atrium, and right ventricular. Dilation of the ascending portion of the aorta. Hypertrophy of the interventricular septum and left ventricular posterior wall. The aortic valve and mitral valve flaps were hardened with calcifications. Diffuse hypokinesis of the left ventricular walls. The contractile function of the left ventricular was reduced. Tricuspid regurgitation 3+ mitral insufficiency 3+ pulmonary regurgitation + aortic regurgitation 1.5+. Pulmonary hypertension of the 1st degree.

Fiberoptic gastroduodenoscopy as of 19.09.2024: Chronic gastroduodenitis. Remission.

Doppler ultrasonography of lower extremity veins as of 23.09.2024: Varicose veins of the short saphenous vein basin on both sides. No thrombosis was found.

Consultation:

On 16.09.2024, a cardiologist at the Cardiology Center of the Research Institute of Cardiology and Internal Medicine (Almaty, Kazakhstan) consulted the patient and diagnosed a Coronary heart disease, exertional angina FCII. Ischemic cardiomyopathy. Atrial fibrillation, permanent form. EHRA II, Grade 2 HAS-BLED, Grade 4 CHA2DS2-Vas. SP (???) of ICD implantation as of 05.2023: Arterial hypertension stage 3, risk 4. Dyscirculatory encephalopathy. Chronic heart failure (with preserved ejection fraction– 59%) FC III, according to NYHA. Surgical treatment was possible against the background of therapy.

The patient was discussed with the Head of the Resuscitation and Intensive Care Unit on 01.10.2024 for preoperative purposes. It was established, taking into account the clinical and laboratory data, the patient's somatic state and decompensation of concomitant pathology, and the physical status according to ASA IV, that the patient had an extremely high risk of developing life-threatening complications in the intraoperative period. Anesthesia support was possible only for vital indications absent during the examination. In this regard, it was recommended to consider alternative methods to treat the underlying disease.

On 01.10.2024, the patient was re-evaluated by the MDG at the KazIOR Center for Bone and Soft Tissue Tumors. It was found that the history of the disease, the location and size of the tumor, the presence of pain and bleeding, and the cytological conclusion that the anesthetic risk exceeds the surgical risk were taken into account. It was decided that surgical treatment under local anesthesia should be performed in this regard.

Treatment: Scheduled surgical treatment was conducted on 02.10.2024 in the volume of: Excision of a skin tumor of the zygomatic region on the left side. Plastic surgery of the defect with a skin-fat flap from the parotid region and the lateral surface of the neck on the left. Drainage.

Intraoperatively: Excision of the skin tumor of the zygomatic region on the left with resection of the periosteum was performed after premedication with Trimeperidine, a negative intradermal test for Novocain 0.5%, 0.1 mL, and 4-fold treatment of the surgical field with iodine-povidone, under local infiltration anesthesia with a solution of Novocain 0.5%, 40.0 mL, 1.0 cm away from the tumor edges. It resulted in a 7.0 x 6.5 cm deep defect with bone denudation. The bone was not affected. The wound was treated with 3% hydrogen peroxide and a furacilinum solution (Figure 2).

Given the defect's size and the absence of the periosteum, closure of the defect with a free skin flap was impossible due to the risk of non-engraftment of the flap. Therefore, it was decided to close the defect with a rotational skin-fat flap from the parotid region and the lateral surface of the neck on the left. Then, a skin-fat flap was cut out and separated under local anesthesia with a solution of 0.5% Novocain, 70 mL, and moved to the defect of the zygomatic region on the left. Blood loss was about 10.0 mL. Hemostasis of the wound was performed. Nodal sutures were applied to the wound in layers, leaving a drainage tube through a counteropening. The wound was treated with iodine and alcohol, followed by aseptic dressings (Figure 3).

The operation lasted for 80 minutes, and it was without complications.

Results:

Postoperative test results:

Biochemical blood test as of 03.10.2024: ALT – 10.67 U/L, AST – 23.54 U/L, bilirubin (total) – 36.03 μmol/L, glucose (blood sugar) – 4.43 mmol/L, creatinine – 77.83 mmol/L, urea – 5.16 mmol/L.

Clinical Urine Analysis as of 03.10.2024: amount – 50 mL, ketones – negative, color – straw yellow, transparency – cloudy, specific gravity – 1.015 AU/mL, pH level ≥9 AU/mL, nitrites – positive in the field of vision, leukocytes – 1+ C g/d, calcium (total) in urine ≤1 mmol/L, microalbumin – 150 mg/L, creatinine – 8.80 mmol/L, albumin/creatinine ratio – 3.4-33.9.

Coagulogram as of 03.10.2024: PTT – 18.6 sec., PTI – 61%, INR – 1.71, TPO – 1.63, TT – 12.7 sec., APTT – 36.00 sec., ethanol test (in blood plasma by manual method) – negative.

Complete Blood Count as of 03.10.2024: hematocrit (HCT) – 0.436 L/L, hemoglobin (HGB) – 150 g/L, leukocytes (WBC) – 9.99 10^3/μL, platelets (PLT) – 235.6 10^3/μL, erythrocytes (RBC) – 5.00 10^6/μL.

Histological report as of 17.10.2024: squamous cell keratinizing skin cancer, 5 cm in the largest dimension, with invasion to the hypodermis.

The INR and PTI values remain slightly elevated.

The postoperative period proceeded without complications, the patient's state was satisfactory, and the pain syndrome was relieved. Antibiotic therapy was conducted 2 times a day for 5 days. Dressings were made daily; the sutures were consistent, and the wound healed with primary tension. The drainage tube was removed on the 7th day.

Cosmetic result: There was moderate swelling of the lower eyelid on the left during the first days after the operation. It went away on its own within a week. The cosmetic result was assessed as satisfactory.

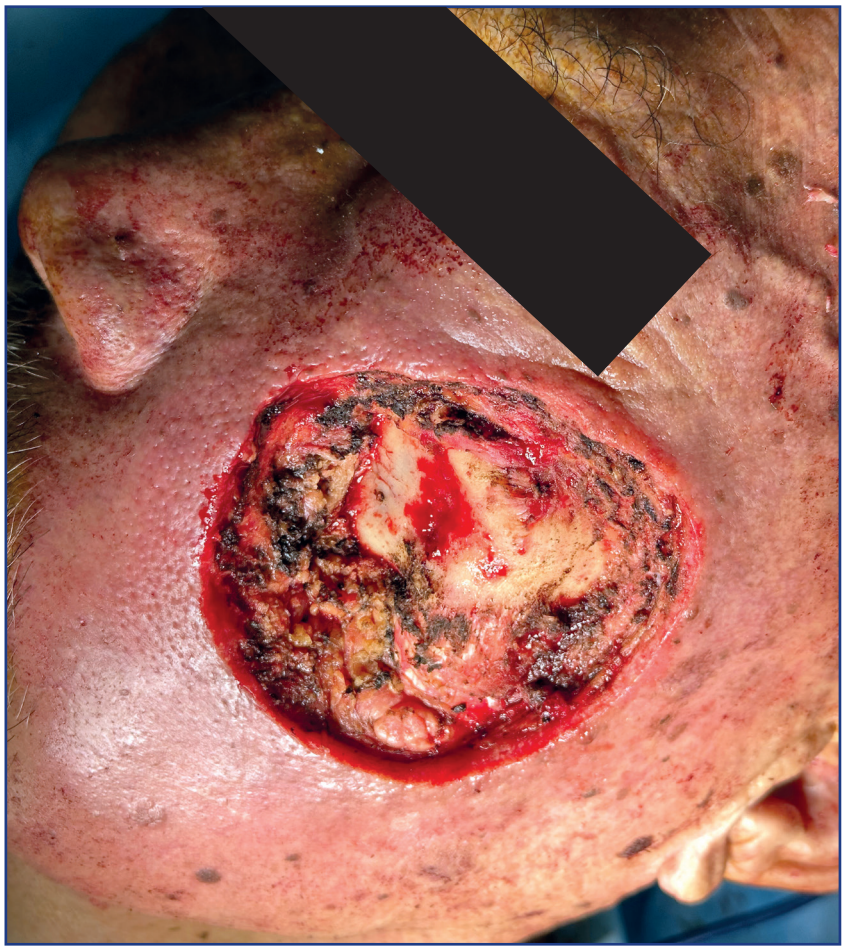

Figure 2 – View of patient S. after excision of a skin tumor: defect of the zygomatic region on the left

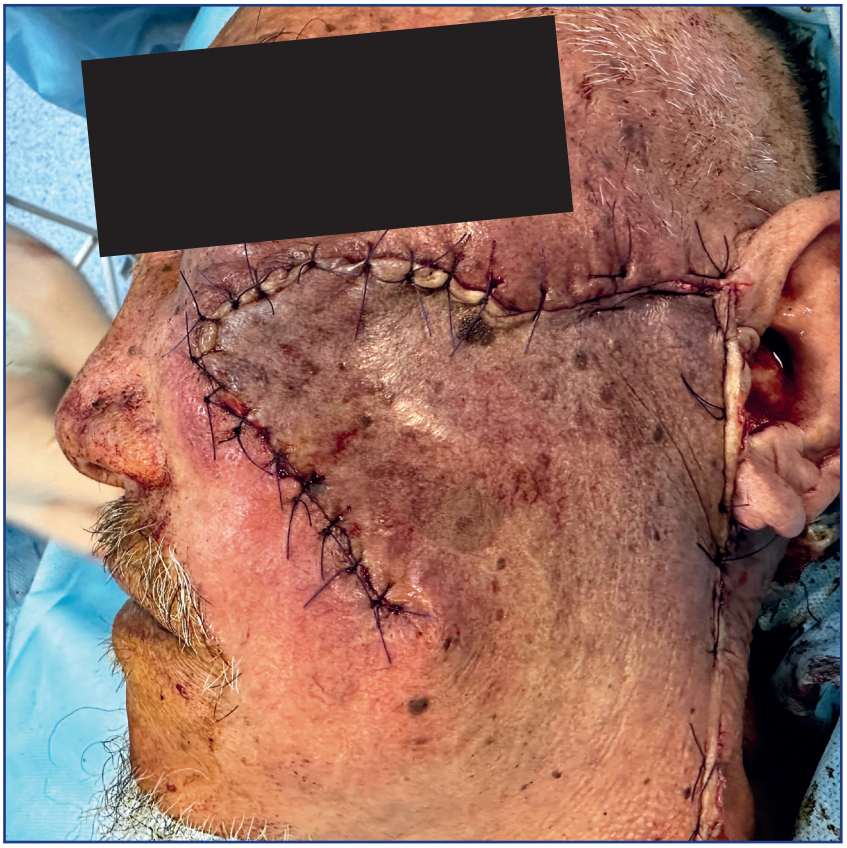

Figure 3 – Postoperative view of the wound in patient S.

Functional results: The patient did not experience facial movement difficulties; no sensory disturbances were observed.

The patient was discharged with recommendations: given the histotype of the tumor, it is required to consult a radiologist to decide on the possibility of a postoperative course of radiation therapy (Figure 4).

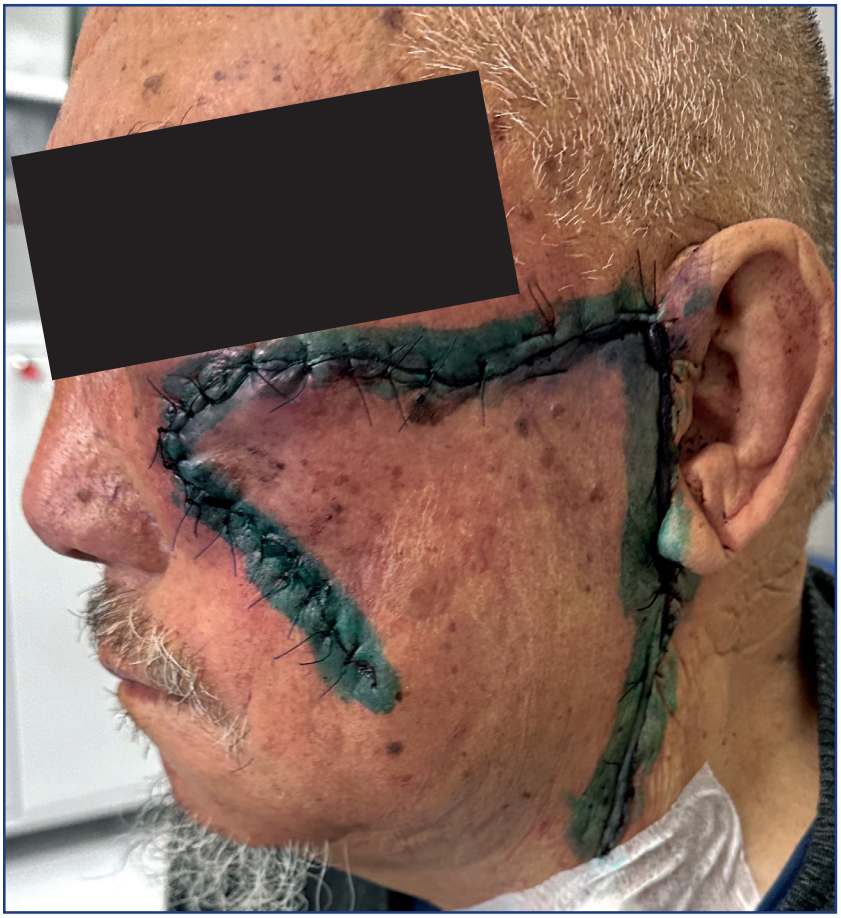

Figure 4 – The state of the wound in patient S. on the 7th day after surgery, at the time of discharge

Discussion: Surgical treatment of skin cancer at stages II-IV usually requires the use of general anesthesia because the surgeries at these stages can be more complex and extensive. Various plastic surgery methods are required to close surgical defects and restore functionality and aesthetics. However, the patient had contraindications to general anesthesia from the cardiovascular system, and they made its use unsafe in this clinical case. Therefore, it was decided to operate under local infiltration anesthesia.

The surgery involved closing the defect using a rotational skin-fat flap taken from the parotid region and the lateral surface of the neck on the left. Although this method is usually performed under general anesthesia, we have successfully performed the intervention under local anesthesia. Rotational skin-fat flap is a widely used technique in oncological practice, providing high functional and aesthetic results.

Conclusion: Surgical treatment of stage III skin cancer under local anesthesia in a patient with severe concomitant diseases made it possible to radically remove the tumor, relieving pain and bleeding, especially in situations when radiation therapy is impossible. Using a rotational skin-fat flap ensured complete defect closure with a good cosmetic result. This case demonstrates that local anesthesia can be a safe and effective alternative to general anesthesia, especially in patients with contraindications, and can serve as a guide for oncologists when choosing treatment methods in clinical practice.

This case demonstrates the possibility of performing operations for stage II-III skin cancer with complete closure of the defect under local anesthesia. It can be an alternative to general anesthesia in patients with comorbidities and a high risk of complications. The method can be used without tumor growth into the bone, avoiding the difficulties associated with general anesthesia.

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АҢДАТПА

БЕТ ТЕРІСІНІҢ ҚАТЕРЛІ ІСІГІНІҢ III САТЫСЫН ХИРУРГИЯЛЫҚ ЕМДЕУДІҢ ШҰҒЫЛ НӘТИЖЕЛЕРІ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Аннотация: *Тері қатерлі ісігінің көпшілігі Австралия мен Жаңа Зеландия сияқты популяциясы ақшыл терісі басым және ультракүлгін сәулеленудің жоғары деңгейі бар континенттерде кең таралған. Бүкіл әлемде сияқты Қазақстанда да тері ісігімен сырқаттанушылықтың өсу үрдісі байқалады. 2023 жылы бұл аурудың 4 481 жаңа жағдайы тіркелді, оның 85% базальды жасушалық карцинома Қазақ онкология және радиология ғылыми-зерттеу институты (Алматы, Қазақстан) әртүрлі әдістерді қолданады, оның ішінде негізгі емдеу әдісі болып қала береді, сонымен қатар сәулелік терапия, электрохимиотерапия және криотерапия.*

Зерттеудің мақсаты *– клиникалық қан кетумен және ауырсынумен жүретін сол жақтағы зигоматикалық аймақтың базальды жасушалы тері обыры III сатысы бар науқасты жергілікті анестезиямен хирургиялық емдеу жағдайының сипаттамасы.*

Әдістері: *Мақалада тері ісігін жергілікті инфильтрациялық анестезиямен хирургиялық емдеу жағдайы сипатталған.*

Нәтижелері: *Операциядан кейінгі кезең асқынусыз өтті. Косметикалық нәтиже қанағаттанарлық деп бағаланды. Науқаста бет қимылдары қиындаған жоқ, сенсорлық бұзылыстар байқалған жоқ. Пациент ұсыныстармен үйге шығарылды: ісіктің гистотипін ескере отырып, сәулелік терапияның операциядан кейінгі курсын жүргізу мүмкіндігін шешу үшін радиологпен кеңесу қажет.*

Қорытынды: *Бұл жағдай жергілікті анестезиямен ақауды толық жабу арқылы II-III сатыдағы тері ісігіне операциялар жасау мүмкіндігін көрсетеді. Бұл қатар жүретін аурулары бар және асқыну қаупі жоғары науқастарда жалпы анестезияға балама болуы мүмкін. Бұл әдіс жалпы анестезияға байланысты қиындықтарды болдырмайтын сүйекке ісік инвазиясы болмаған кезде қолданылуы мүмкін.*

Түйінді сөздер: *Скамозды жасушалық карцинома, клиникалық жағдай, хирургиялық емдеу.*

АННОТАЦИЯ

НЕПОСРЕДСТВЕННЫЕ РЕЗУЛЬТАТЫ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ РАКА КОЖИ ЛИЦА III СТАДИИ ЗАБОЛЕВАНИЯ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Большинство случаев рака кожи широко распространены на континентах, где преобладает светлокожее население и наблюдаются высокие уровни воздействия ультрафиолетового излучения, например, в Австралии и Новой Зеландии. В Казахстане, как и во всем мире, наблюдается тенденция к росту заболеваемости раком кожи. В 2023 году было зарегистрировано 4481 новых случаев этого заболевания, из которых 85% составила базальноклеточная карцинома в АО «Казахский научно-исследовательский институт онкологии и радиологии» (Алматы, Казахстан) применяются разные методы, включая хирургическое иссечение, которое остаётся основным способом лечения, а также лучевую терапию, электрохимиотерапию и криотерапию.*

Цель исследования *– описание случая хирургического лечения пациента под местной анестезией с базальноклеточным раком кожи скуловой области слева III стадией, сопровождающейся клиникой кровотечения и болевым синдромом.*

Методы: *В статье описан случай хирургического лечения рака кожи под местной инфильтрационной анестезией.*

Результаты: *Послеоперационный период протекал без осложнений. Косметический результат оценён как удовлетворительный. Пациент не испытывал трудностей с движением лица, нарушения чувствительности не наблюдались. Пациент выписан домой с рекомендациями: учитывая гистотип опухоли необходимо консультации радиолога для решения вопроса о возможности проведения послеоперационного курса лучевой терапии.*

Заключение: *Данный случай демонстрирует возможность выполнения операций при раке кожи II-III стадии с полным закрытием дефекта под местной анестезией. Это может стать альтернативой общей анестезии у пациентов с сопутствующими заболеваниями и высоким риском осложнений. Метод может быть применён при отсутствии прорастания опухоли в кость, что позволяет избежать сложностей, связанных с общей анестезией.*

Ключевые слова: *плоскоклеточная карцинома, клинический случай, хирургическое лечение.*

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NEW BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF THERAPEUTIC APPROACHES TO GASTRIC CANCER: A LITERATURE REVIEW

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АННОТАЦИЯ

Relevance: *Gastric cancer is a heterogeneous disease whose development is associated with both genetic and acquired somatic mutations. Identifying optimal diagnostic markers for gastric cancer with high sensitivity and specificity can significantly improve patient survival rates and contribute to the advancement of personalized medicine. By integrating clinical data and comprehensive genomic analysis, the identification of biomarkers can dramatically enhance the accuracy of diagnosis, dis-ease progression prediction, recurrence risk assessment, and treatment response. This work discusses promising biological markers that may be used to diagnose gastric cancer early and predict the effec-tiveness of various treatment methods, potentially revolutionizing patient care.*

The study aimed to *analyze current scientific literature to identify new and recently developed bi-omarkers for diagnostic and prognostic value concerning malignant stomach tumors.*

Methods: *In this review, we comprehensively searched electronic medical literature in the PubMed and Google Scholar databases. The search utilized keywords: "biomarker," "gastric cancer," "early detection," "diagnosis," and "prognosis." We included full-text publications in English and Russian, which are available for open access. We focused on the role of biomarkers in early diagnosis and prognosis of gastric cancer, published in the last ten years. We excluded case reports, correspond-ence, letters, and studies not conducted on humans from the review, as these did not meet our criteria for inclusion.*

Results: *The analysis revealed an insufficient accuracy of existing biomarkers for gastric cancer di-agnosis and prognosis. Within the modern approach to disease classification framework, a new mo-lecular type was proposed: tumors infected with the Epstein-Barr virus, tumors with microsatellite instability, genomically stable tumors, and chromosomally unstable tumors.*

Conclusion: *Current research on gastric cancer focuses on identifying and validating new non-invasive biomarkers. Further studies are necessary to enhance sensitivity and broaden the application of these biomarkers for early diagnosis and predicting treatment efficacy.*

Keywords: *Biomarker, gastric cancer, early detection, diagnosis, prognosis.*

Introduction: Despite advances in medicine, food preservation techniques, and Helicobacter pylori treatment, gastric cancer remains the fifth most common cancer and the fourth leading cause of cancer deaths worldwide as of 2020 [1]. The prevalence of gastric cancer shows significant geographic variations, with men being twice as likely to be affected as women. According to recent data, the highest incidence rates are observed in East Asia and Central and Eastern Europe, where 87% of all new cases worldwide are concentrated. At the same time, Africa and North America have a significantly lower prevalence of gastric cancer [2].

One approach to reducing the burden of gastric cancer is early diagnosis. Although upper gastrointestinal endoscopy is recognized as the "gold standard" for screening, early tumor detection requires methods with higher accuracy, sensitivity, and specificity. Since many patients are asymptomatic at the initial stages of the disease and there are currently no effective screening methods for the early detection of gastric cancer, the diagnosis is often made at a late stage, which leads to a poor prognosis and low survival [3].

A more accessible and cost-effective method shall be developed to implement a large-scale screening program for gastric cancer in a healthy population.

In recent decades, serological tumor markers have traditionally been used to diagnose cancer in specific patient groups, as well as to monitor cancer progression.

Oncological biomarkers, also known as tumor markers, are specific molecules whose presence indicates the presence and development of malignant neoplasms. These biomarkers play a crucial role in cancer diagnostics, allowing physicians to detect the disease at an early stage and in planning personalized therapy, which increases the effectiveness of treatment [4]. In short, we are talking about objectively measurable characteristics used as indicators of normal body functioning, pathological processes, or response to therapy. Their use is steadily expanding due to genetic analysis and molecular therapy progress.

There are no biomarkers with sufficient accuracy and specificity for diagnosing gastric cancer in clinical practice. Such markers are relevant at all stages of the disease to optimize its course. This paper summarizes current achievements and approaches to developing gastric cancer biomarkers that can potentially be used for early diagnosis, accurate prediction of treatment effectiveness, and molecular classification of the tumor.

The study aimed to analyze current scientific literature to identify new and recently developed biomarkers for diagnostic and prognostic value concerning malignant stomach tumors.

Materials and Methods: In this review, we comprehensively searched electronic medical literature in the PubMed and Google Scholar databases. The search utilized keywords: "biomarker," "gastric cancer," "early detection," "diagnosis," and "prognosis." We included full-text publications in English and Russian, which are available for open access. We focused on the role of biomarkers in early diagnosis and prognosis of gastric cancer, published in the last ten years. We excluded case reports, correspondence, letters, and studies not conducted on humans from the review, as these did not meet our criteria for inclusion.

Results: Modern medicine increasingly relies on non-invasive biomarkers to diagnose malignant neoplasms promptly and monitor their progression. In clinical practice, tumor markers are commonly employed for the early detection of gastric cancer. The most widely used markers include carcinoembryonic antigen (CEA), carbohydrate antigens such as CA19-9, CA72-4, CA125, CA24-2, and CA50, along with pepsinogen and α-fetoprotein (AFP) [5]. However, these serological biomarkers often exhibit low specificity and sensitivity, and none serve as a specific or personalized marker for gastric cancer diagnosis [6]. This issue will be revisited later.

T. Li highlights the potential of 'liquid biopsy' as an innovative diagnostic approach for gastric cancer. This method involves detecting circulating tumor cells, tumor DNA or RNA fragments, exosomes, and atypical platelets in biological fluids like blood and urine, enabling early disease detection [7]. Despite its promise, the American Society of Clinical Oncology (ASCO), in a recent review, concluded that current evidence is insufficient to establish its clinical relevance and efficacy for gastric cancer diagnosis [8]. Similarly, guidelines from the European Society for Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (NCCN) recommend liquid biopsy only when tumor tissue sampling is unfeasible or the available material is inadequate for analysis [9].

Advancements in high-throughput technologies have significantly improved the understanding of the molecular mechanisms underlying gastric adenocarcinoma. This progress has resulted in a molecular classification system that distinguishes four subtypes based on distinct genomic characteristics.

The Cancer Genome Atlas (TCGA) project has refined this classification, stratifying gastric cancer based on genetic and epigenetic alterations. This molecular stratification enhances understanding of the disease progression mechanisms and is a foundation for developing targeted therapies [10].

– **Epstein-Barr virus-infected tumors:** These tumors are characterized by the presence of a viral agent, the Epstein-Barr virus, in the tumor cells, which may affect the immune response and disease progression.

– **Tumors with microsatellite instability (MSI):** These tumors show a high frequency of mutations in short repetitive DNA sequences called microsatellites. Microsatellite instability is associated with certain cancers and may serve as a marker for immunotherapy.

– **Genomically stable (GS) tumors:** This group includes tumors with no microsatellite instability (MSI) or chromosomal instability (CIN). The diverse molecular characteristics of these tumors make their classification particularly challenging.

– **Chromosomally unstable (CIN)** tumors are characterized by instability in the number and structure of chromosomes, resulting in aneuploidy and other genetic abnormalities. CIN may be associated with an aggressive disease course and poor survival rates.

The Asian Cancer Research Group (ACRG) classifies gastric cancer based on MSI (microsatellite instability) and MSS (microsatellite stable) markers. Tumors exhibiting microsatellite mutations are categorized as MSI, while MSS tumors are further divided into three subtypes:

* MSS/EMT: Tumours demonstrating epithelial-mesenchymal transition.

* MSS/TP53+: Tumours with an active TP53 gene mutation.

* MSS/TP53-: Tumours with absence of TP53 gene activity [11, 12].

This new classification has provided the foundation for several clinical trials to identify effective therapeutic strategies that combine immune checkpoint inhibitors with molecularly targeted therapies. Early results from these studies are highly promising [13]. Nevertheless, early disease detection remains critical, underscoring the importance of ongoing research to discover novel biological markers or genetic signatures associated with the pathology.

According to a systematic review by H.Shimada, although some circulating tumor antigens have long been used in routine clinical practice, their efficacy in the early diagnosis of gastric cancer remains questionable due to the high frequency of false-positive and false-negative results [14, 15]. CEA, CA19-9, and CA72-4 are widely used as

standard markers in diagnostics, disease prognosis determination, treatment efficacy monitoring, and gastric cancer recurrence detection [16]. In cancer diagnostics, both CEA and CA 19-9 levels can serve as valuable prognostic markers to assess the extent of the tumor process and the presence of distant metastases [17]. Despite particular possibilities, these methods do not have sufficient accuracy and selectivity for screening programs for the early detection of gastric cancer [18].

According to T. Matsuoka and M. Yashiro, the CA72-4 indicator has greater sensitivity and accuracy than CEA. However, the number of studies evaluating its effectiveness in screening tests for gastric cancer is limited [4].

F. Feng et al. have found that tumor markers such as AFP and CA125 have low sensitivity in the early diagnosis of gastric cancer [19]. In addition, CA50 has limited diagnostic value [20].

In their search for ways to enhance the accuracy of gastric cancer diagnosis through the combined analysis of several serological tumor markers, S. Ning et al. demonstrated that simultaneous detection of CEA, CA19-9, and CA72-4 along with thymidine kinase 1 (TK1) –a biomarker of cell proliferation – markedly improves the sensitivity and specificity of gastric cancer detection compared to the utilization of individual biomarkers [21].

A recent study by Li J. proposed a diagnostic model for early detection of gastric cancer. The model is based on the levels of CEA, CA72-4, and three inflammatory cytokines: tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8. In a validation study, the model demonstrated high performance in differentiating between healthy subjects, individuals with atypical gastric mucosal hyperplasia, patients with early-stage GC, and patients with advanced-stage GC [22].

In a study of gastric cancer in 2015, M. Kanda and Y. Kodera discovered an elevated expression of several genes, including xpg, interferon-induced transmembrane protein 1 (iftim1), matrix metalloproteinase-9 (mmp-9), pituitary tumor transforming gene-1 (pttg1), and stc1. These genes show potential as biomarkers for early disease detection [23].

This review also emphasizes promising directions for searching gastric cancer biomarkers based on different molecular genetic characteristics (Table 1). These biomarkers have been classified depending on their roles in early disease diagnosis, recurrence prediction, and chemotherapy efficacy assessment.

Kazakhstani scientists have also studied DNA double-strand breaks with repair activity, such as γ-H2AX and 53BP1, as biomarkers in gastric cancer [46]. These markers have clinical significance and can be used as diagnostic tools in personalized medicine.

Gastric cancer biomarkers play an important role in personalized treatment, allowing for a more accurate therapy selection and prediction of outcomes. However, many of them are in the clinical trial stage. In the future, biomarkers may be integrated into clinical practice, helping doctors improve treatment outcomes and choose the most effective therapies while minimizing side effects.

Biomarker-based prognosis will help identify patients at high risk of recurrence and tailor individualized therapeutic efficacy, which is of great importance in determining survival and quality of life for patients with gastric cancer. A study by D. Wu et al. found increased serum levels of IFNGR1, TNFRSF19L, GHR, SLAMF8, FR-beta, and integrin alpha 5 proteins in patients with gastric cancer. This discovery indicates the prospect of using these proteins as novel biomarkers for early detection and prediction of the disease course of gastric cancer [47].

According to W. Hou et al., the level of CD44 protein expression can serve as an independent prognostic marker for gastric cancer. This protein correlates with immune infiltration in tumor tissue and shows increased activity in patients with this disease [48].

Prof X. Zhou et al. found that the presence of piR-1245 in gastric juice could serve as a promising biological marker for diagnosing and prognosis of gastric cancer [49].

A study by J. Ji et al. demonstrated increased expression of KK-LC-1 in gastric cancer patient tissues compared to normal tissues. In addition, a correlation between higher KK-LC-1 expression and more prolonged survival of gastric cancer patients was established. These results indicate the potential value of KK-LC-1 as a biomarker to predict favorable outcomes in patients with gastric cancer [50].

CircERBB2 concentrations in preoperative plasma samples can be considered a non-invasive prognostic biomarker for gastric cancer. In addition, monitoring postoperative circERBB2 plasma concentrations may help detect gastric cancer recurrence [51].

Recent studies in China have shown a strong correlation between high levels of COMMD10 gene expression and unfavorable prognosis for gastrointestinal cancer patients. The functional activity of COMMD10 is associated with the modification of N6-methylamino adenosine (m6A) mRNA and plays a vital role in gastric cancer's immune tumor infiltration processes [52].

The study by W. Gu et al. found a correlation between the level of ITGB1 gene expression and the activity of the Wnt/β-catenin signaling pathway in gastric cancer. Data analysis from TCGA-STAD/ACRG/GSE15459 cohorts showed a positive association between ITGB1 expression and factors inhibiting the immune response and a negative association with factors activating the immune response. Thus, ITGB1 affects the prognosis of patients with gastric cancer and plays a crucial role in suppressing the immune response [53].

Table 1 – Topical issues of molecular markers application in diagnostics, prognosis of the course, and response to therapy of gastric cancer (adapted from the article [4])

Biological marker	Change	Clinical goal	Detection method	Reference
Genes associated with metastasis				
Growth factors				
HER2 - Gene encoding a receptor associated with cell growth.	Overexpression	Diagnostic / prognostic	Tissue	[24]
FGFR – Fibroblast growth factor involved in cell proliferation and differentiation.				[25]
PI3K/Akt/mTOR (PIK3CA) - Gene encoding a subunit involved in a signal transduction pathway that promotes cell growth.				[26]
MET - Gene encoding a receptor associated with growth and metastasis.				[27]
VEGF (VEGF-2) - Vasoendothelial growth factor involved in angiogenesis.				[28]
VEGF-D) - Vasoendothelial growth factor involved in angiogenesis.				[29]
Cell cycle regulation				
TP53 - Gene encoding a protein involved in cell cycle control.	Mutation	Diagnostic	Tissue	[30]
Adhesion molecule				
E-cadherin (CDH1) - Adhesion molecule involved in intercellular communication.	Mutation/epigenetic alteration	Diagnostic / prognostic	Tissue/Blood	[31]
Immune checkpoint				
PD-L1 - An immune checkpoint that regulates the immune response.	Mutation	Prognostic / therapeutic	Tissue	[32]
Epigenetic alterations				
CDH1, CHFR, DAPK, GSTP1, p15, p16, RARβ, RASSF1A, RUNX3, TFPI2 - Groups of gene methylation changes associated with cancer.	Hypermethylation	Diagnostics	Tissue	[33]
Genetic polymorphism				
IL1-β, IL-1RN, CD44	SNP	Prognostic	Tissue	[34]
TP53, SYNE1, CSMD3, LRP1B, CDH1, PIK3CA, ARID1A, PKHD, KRAS, JAK2, CD274, PDCD1LG2 - Variations in DNA affecting disease susceptibility.	Copy number variations/ mutations	Diagnostic/prognostic/ therapeutic	Tissue	[35]
Circulating tumor cells				
CD44, N-cadherin, vimentin - Cells released into the blood from the tumor.	Overexpression	Diagnostic/therapeutic	Blood	[36]
pan-CK, E-cadherin	Reduced expression	EMT process	Blood	[37]
EE2 - Estrogen, which can influence tumor growth.	Overexpression	Therapeutic	Blood	[38]
Gastrin specific biomarker				
ADAM23, GDNF, MINT25, MLF1, PRDM5, RORA - Genes associated with gastric cancer.	Hypermethylation	Diagnostic	Gastric lavage	[39]
BARHL2 - Genes associated with gastric cancer.	Hypermethylation	Diagnostic/therapeutic	Gastric lavage/juice	[40]
PVT1	Regulated	Diagnostic / prognostic	Gastric juice	[41]
miR-421, miR-21, miR-106a, miR-129 - MicroRNAs involved in gene regulation.	Regulated	Diagnostic	Gastric juice	[42]
KagA	Regulated	Diagnostic	Tissue	[43]
VAK	Regulated	Diagnostic	Tissue	[44]
Gastrokin 1 - Protein associated with the regulation of digestive processes.	Deactivation	Prognostic	Tissue	[45]

Discussion: The current review discusses the most commonly used cancer markers, including CEA and CA, such as CA19-9, CA72-4, CA125, CA24-2, CA50, pepsinogen, and AFP. According to ASCO, ESMO, and NCCN guidelines, liquid biopsy is acceptable only when tumor tissue sampling is impossible, or the obtained sample is insufficient for analysis.

It should be noted that modern scientific literature offers a classification of gastric cancer based on the TCGA project, which is based on the analysis of genetic and epigenetic alterations.

Although several researchers have confirmed the effectiveness of standard serological methods of oncomarker diagnosis in detecting and assessing the risk of gastric cancer recurrence, the limited specificity and sensitivity of these molecular markers do not allow their use for early diagnosis of the disease.

This review article presents promising research directions for gastric cancer biomarkers based on different molecular genetic characteristics. A classification of these biomarkers according to their function in early diagnosis of the disease, prediction of recur-

rence, and evaluation of chemotherapy efficacy is performed.

Biomarkers of gastric cancer play an essential role in diagnostics, predicting the outcome of the disease, monitoring its course, and developing more effective treatment methods. Due to the often asymptomatic course of gastric cancer in its early stages, its diagnostics are a significant challenge. Biomarkers offer new opportunities to improve the accuracy of diagnostics and timely detection of this disease.

In the future, new molecular markers may significantly change the approach to treating and monitoring gastric cancer, providing more personalized treatment strategies.

Conclusion: Gastric cancer remains one of the leading causes of mortality from malignant neoplasms worldwide, primarily due to late diagnosis when therapeutic options are limited. Current biomarkers used for diagnosis and prognosis exhibit inadequate sensitivity and specificity. Diagnosis often relies solely on invasive procedures like upper gastrointestinal endoscopy. Consequently, ongoing research in gastric cancer is directed toward identifying and validating non-invasive biomarkers secreted by tumor tissues into body fluids. However, many of these biomarkers are detected only in advanced stages of the disease, rendering them unsuitable for early diagnosis. Further studies are necessary to enhance sensitivity and broaden the application of these biomarkers for early diagnosis and predicting treatment efficacy.

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АҢДАТПА

АСҚАЗАН ОБЫРЫНА ТЕРАПЕВТІК ТӘСІЛДЕРДІ ЕРТЕ АНЫҚТАУ МЕН БОЛЖАУҒА АРНАЛҒАН ЖАҢА БИОМАРКЕРЛЕР: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Асқазан обыры гетерогенді ауру болып табылады, оның дамуы генетикалық және жүре пайда болған соматикалық мутациялардың әсерімен байланысты.*

Асқазан обырына арналған жоғары сезімталдығы мен ерекшелігі бар оңтайлы диагностикалық маркерлерді бөлу пациенттердің өмір сүру көрсеткіштерін арттыруға мүмкіндік береді және дербес медицинаның дамуына ықпал ететін болады. Клиникалық деректерді біріктіру және геномды кешенді талдау негізінде биомаркерлерді сәйкестендіру диагностиканың нақтылығын, аурудың ағымын болжауды, қайталану қаупін және терапияға реакцияны айтарлықтай жақсартуы мүмкін. Бұл жұмыста асқазан обырын ерте диагностикалау және әртүрлі емдеу әдістерінің тиімділігін болжау үшін пайдаланылуы мүмкін перспективалық биологиялық маркерлер қарастырылады.

Зерттеудің мақсаты *– асқазанның қатерлі ісіктеріне қатысты диагностикалық және болжамдық құндылығы бар жаңа және таяуда әзірленген биомаркерлерді анықтау мақсатында қазіргі заманғы ғылыми әдебиетке талдау жүргізу.*

Әдістері: *Осы шолуда PubMed және Google Scholar дерекқорларын пайдалана отырып, медициналық әдебиетте электрондық іздеу пайдаланылды. Іздестіру «биомаркер», «асқазан обыры», «ерте анықтау», «диагностика», «болжам» деген негізгі сөздер бойынша жүргізілді. Шолуға ағылшын және орыс тіліндегі ашық қолжетімді, асқазан обыры ағымын ерте диагностикалау мен болжауда биомаркерлердің рөлін зерттеуге арналған толық мәтінді жарияланымдар енгізілді. Олар соңғы он жылда жарияланды. Адамдарда жүргізілмеген жеке бақылаулар, хат алмасу, хаттар мен зерттеулер туралы есептер шолуға енгізілмеген.*

Нәтижелері: *Жүргізілген зерттеулер барысында асқазан обыры ағымын диагностикалау және болжау үшін қолда бар биомаркерлердің жеткіліксіз дәлдігі бар екені анықталды. Ауруды жіктеудің қазіргі заманғы тәсілі шеңберінде жаңа молекулалық түр ұсынылды: Эпштейн-Барр (EBV) вирусын жұқтырған ісіктер, микрожүйе тұрақсыздығы бар ісіктер (MSI), геномдық тұрақты ісіктер (GS) және хромосомдық тұрақсыз ісіктер (CIN).*

Қорытынды: *Асқазан обырын зерттеу жаңа инвазивті емес биомаркерлерді іздеуге және тексеруге бағытталған. Сезімталдықты арттыру және биомаркерлерді қолдану саласын кеңейту үшін ерте диагностикалау және емдеу тиімділігін болжау мақсатында қосымша зерттеулер қажет.*

Түйінді сөздер: *биомаркер, асқазан обыры, ерте анықтау, диагностика, болжам.*

АННОТАЦИЯ

НОВЫЕ БИОМАРКЕРЫ ДЛЯ РАННЕГО ВЫЯВЛЕНИЯ И ПРОГНОЗИРОВАНИЯ ТЕРАПЕВТИЧЕСКИХ ПОДХОДОВ К РАКУ ЖЕЛУДКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак желудка представляет собой гетерогенное заболевание, развитие которого связано с воздействием как генетических, так и приобретенных соматических мутаций.*

Выделение оптимальных диагностических маркеров для рака желудка с высокой чувствительностью и специфичностью позволит повысить показатели выживаемости пациентов и будет способствовать развитию персонализированной медицины. Идентификация биомаркеров на основе интеграции клинических данных и комплексного анализа генома может существенно улучшить точность диагностики, прогнозирования течения заболевания, риска рецидива и реакции на терапию. В данной работе рассматриваются перспективные биологические маркеры, которые могут быть использованы для ранней диагностики рака желудка и предсказания эффективности различных методов лечения.

Цель исследования *– провести анализ современной научной литературы с целью выявления новых и недавно разработанных биомаркеров, обладающих диагностической и прогностической ценностью в отношении злокачественных новообразований желудка.*

Методы: *В настоящем обзоре был использован электронный поиск в медицинской литературе с использованием баз данных PubMed и Google Scholar. Поиск осуществлялся по ключевым словам: «биомаркер», «рак желудка», «раннее выявление», «диагностика», «прогноз». В обзор были включены полнотекстовые публикации на английском и русском языках, доступные в открытом доступе, посвященные исследованию роли биомаркеров в ранней диагностике и прогнозировании течения рака желудка. Опубликованы они были за последние десять лет. Отчеты о единичных наблюдениях, переписка, письма и исследования, не проводившиеся на людях, в обзор не включались.*

Результаты: *В ходе проведенных исследований было выявлено, что существующие биомаркеры для диагностики и прогнозирования течения рака желудка обладают недостаточной точностью. В рамках современного подхода к классификации заболевания был предложен новый молекулярный тип: опухоли, инфицированные вирусом Эпштейна-Барра, опухоли с нестабильностью микроспутников, геномно-стабильные опухоли и хромосомно-нестабильные опухоли.*

Заключение: *Современные исследования рака желудка направлены на поиск и проверку новых неинвазивных биомаркеров. Для повышения чувствительности и расширения области применения биомаркеров в целях ранней диагностики и прогнозирования эффективности лечения необходимы дополнительные исследования.*

Ключевые слова: *биомаркер, рак желудка, раннее выявление, диагностика, прогноз.*

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THE ROLE OF MONOCLONAL B-CELL LYMPHOCYTOSIS IN PREDICTING LYMPHOPROLIFERATIVE DISEASES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Monoclonal B-cell lymphocytosis (MBL), introduced by the World Health Organization in 2017 to classify certain types of blood diseases, opens up new perspectives in classification but also raises issues that require further study. MBCL studies are essential for improving diagnosis and monitoring, which can contribute to the early detection and prevention of chronic lymphocytic leukemia (CLL).*

The study aimed to *evaluate the immunophenotypic aspects of monoclonal B-cell lymphocytosis and the risk of progression to chronic lymphocytic leukemia.*

Methods: *A review of scientific publications examined the causes of MBL and its association with CLL, emphasizing immunophenotypic aspects of these conditions. The literature survey provided information on factors associated with the progression of MBL to CLL, including biomarkers and clinical characteristics, allowing a more comprehensive assessment of the risk of leukemia in patients with MBL.*

Results: *Numerous studies regarding the association between MBL and CLL were analyzed. The analysis showed that MBL often precedes the development of CLL, with MBL clones being detectable years before clinical diagnosis. This supports the hypothesis that MBL may be an early biomarker for detecting developmental risk.*

Various studies emphasize significant ethnic and geographic differences in the prevalence and progression of MBL and CLL. These differences may be related to epigenetic factors, immunoglobulin rearrangements, and other genetic features. Understanding these differences is essential for more accurate diagnostic and prognostic approaches that consider individual and patient population characteristics.

Conclusion: *The analysis shows that further investigation of the association between MBL and CLL and the introduction of screening programs for early detection of MBL can significantly improve the prognosis and health of patients in Kazakhstan.*

The review results emphasize the importance of early diagnosis and an individualized approach to treatment. This will help prevent MBL progression to CLL and improve our country's medical care quality.

Keywords: *monoclonal B-cell lymphocytosis (MBL), chronic lymphocytic leukemia, immunophenotype, risk of development, flow cytometry.*

Introduction: In recent years, the widespread use of 10 color (multicolor) blood cell measurement panels, thanks to advances in flow cytometry, has made it possible to detect in healthy individuals deficient levels of monoclonal B-lymphocytes in the blood that are immunophenotypically similar to chronic lymphocytic leukemia cells. As a result, general practitioners and even specialists who do not specialize in hematology may encounter patients who have a slight increase in the number of lymphocytes in the blood consisting of abnormal B-cell clones but who lack the diagnostic criteria for chronic lymphocytic leukemia (CLL) [1, 2].

The term 'monoclonal B-cell lymphocytosis (MBL)' was introduced by the World Health Organisation in 2017 to describe certain conditions in the field of oncohematology. It has improved understanding chronic lymphocytic leukemia (CLL) and raised new unanswered questions [3].

MBL is defined by peripheral blood monoclonal B-cell concentration of less than 5×109/L without evidence of lymphoproliferative diseases such as lymphadenopathy, organomegaly, or extramedullary lesions [4].

In approximately 75% of cases, the immunophenotypic profile of clonal B-cell expansion overlaps with the immunophenotypic profile of CLL with co-expression of CD19, CD5, CD23, and low levels (dim) of CD20 and surface immunoglobulins with light chain restriction ('CLL-like'). Other cases may co-express CD19 and CD5 but with bright CD20 and no CD23 ('atypical CLL-type'), while others are CD5-negative, with moderate

to bright expression of surface immunoglobulins ('non-CLL-type') [2-4].

In addition to the immunophenotypic profile, a key distinction is based on B-cell count, which further stratifies the category of MBL into low count ($<0.5\times10^9$/L) or high count ($\geq0.5\times10^9$/L) MBL. Data from a meta-analysis collecting information from MBL series worldwide clearly documented a bimodal distribution of MBL cases based on absolute B-cell count [5]. In cases detected in population-based screening studies, the number of clonal B cells ranged from 0.1 to 10 B cells per μL (with a median of 1 cell per μL), while in cases of MBL detected by routine examination for lymphocytosis, the mean number of B cells was 2.9×10^9/L and ranged from 0.5 to 5.0×10^9/L. Very few cases were intermediate, maintaining the threshold currently accepted.

This distinction is not trivial, given that the clinical and biological features and risk of progression to full-blown CLL significantly differ between the two conditions.

In general, MBL occurs more frequently with age. It was insignificant before age 40 and present in about 10% of all individuals over this age, reaching a maximum of >50% among those over 90 [6-8].

Therefore, these findings support the importance of studying MBL, as its prevalence increases with age and may indicate a pre-existing stage of serious diseases such as CLL. A more in-depth analysis of MBL can improve diagnostic and monitoring methods, leading to earlier detection and potential prevention of disease development. Also, a detailed study of the immunophenotypic characteristics of MBCL will give hematologists additional tools to effectively monitor patients' conditions, increasing the likelihood of accurate prediction and the development of targeted therapies.

The study aimed to evaluate the immunophenotypic aspects of monoclonal B-cell lymphocytosis and the risk of progression to chronic lymphocytic leukemia.

Materials and Methods: A review of scientific publications examined the causes of MBL and its association with CLL, emphasizing immunophenotypic aspects of these conditions. The review covered actual studies published in peer-reviewed scientific journals since 2010.

The review compared Immunophenotypic profiles of monoclonal B cells identified in patients with MBL and CLL using data from large meta-analyses and review studies conducted in different regions worldwide.

The literature survey provided information on factors associated with the progression of MBL to CLL, including biomarkers and clinical characteristics, allowing a more comprehensive assessment of the risk of leukemia in patients with MBL.

Source inclusion criteria:

– Publications containing empirical data on MBL and CLL.

– Articles published in peer-reviewed scientific journals since 2010.

– Work performed on hematological samples.

Source exclusion criteria:

– Research is based only on specific evidence or case reports without statistical analysis.

– Publications without access to the full text or published in journals without scientific peer review.

– Articles that are not in clinical medicine, immunology, or hematology.

Results: High-grade MBL has the highest prevalence among first-degree relatives of CLL patients and, unlike low-grade MBL, has IGHV mutations with a repertoire similar to CLL, indicating a biological link. However, in both types of MBL, cytogenetic changes associated with CLL are noted, including del (13q), +12, and del (17p), although at lower levels, suggesting that these changes occur early in clonal evolution and are not prognostically significant in the absence of B-cell lymphocytosis [9, 10]. We know that almost all clinical cases of CLL are preceded by the MBL phase. High-grade MBL progresses to CLL at a rate of 1-2% per year, with the number of clonal B-cells at presentation being the most significant risk factor. This is in contrast to MBL with low lymphocyte counts, which proceeds without overt lymphocytosis and does not require clinical monitoring of progression. In addition, there are cases of MBL with a different phenotype from CLL that are thought to be associated with marginal zone lymphoma. Given that CLL-like cells can be found in patients without lymph node enlargement (<1.5 cm) who have undergone lymphadenectomy for reasons not related to lymphoproliferative diseases, a third category has been proposed to describe this phenomenon – the 'nodal equivalent of MBL,' which is different from full-fledged small cystic lymphoma [11, 12].

Flow cytometry is the primary method to detect the MBL because it accurately identifies and differentiates phenotypes. MBL is classified into three phenotypes - CLL/SLL, atypical CLL/SLL, and non-CLL/SLL - based on specific markers on the surface of the cells. These markers include CD5, CD19, CD20, and CD23, as well as immunoglobulins, either light chains or complete chains (consisting of light and heavy chains). The distinction between these phenotypes is crucial since each can be associated with developing different types of malignant lymphocyte neoplasms [12-15].

Table 1 presents the markers for the three MBL phenotypes. Marker expression is indicated as follows: (+) for the presence of expression (weak, moderate, or bright), (–)

for its absence, and 'not allowed' for cases where the data are not applicable. Fluorescent probes determine expression by binding to marker proteins on cells. Flow cytometry, preferably using 6-8 different fluorescent probes, can detect this binding by analyzing about 5 million cells from the patient's blood. The table also shows the percentage of cases of each MBL phenotype that can progress to malignancies [4].

Table 1 – Markers of three MBL phenotypes on flow cytometry [4, 12-15]

MBL phenotype	CD5	CD19	CD20	CD23	Immunoglobulin light chains	Percentage with phenotype	Potential malignant complication
CLL / SLL MLB	+	+	+ (dim)	+	Ig with a light chain, either +, + (dim), or –	68-75%	CLL/ SLL
Atypical CLL / SLL MLB	+	+	+ (bright)	- or +	Full Ig, either + (moderate), or + (bright)	~15%	Mantle cell lymphoma, follicular lymphoma
Not- CLL/ SLL MLB	or – or + (dim)	+	+	N/A	Light chain Ig, ei-ther + (moderate) or + (bright)	~14%	Lymphoma of the mar-ginal zone of the spleen, lymphoma of the spleen/leukemia unclassified

Cases of non-CLL/SLL MBL where monoclonal B-cells do not express CD5, CD23, CD10, or CD103 but show high expression of CD79b and immunoglobulin light chains are generally classified as marginal zone monoclonal B-cell lymphocytosis (CBL-MZ). This designation applies because normal B cells in this area also express these markers. People with CBL-MZ often have very high levels of B-cells in their blood (>4.0x10^9/L, usually 3.0x10^9/L to 37.1x10^9/L) [13]. These cases constitute a significant proportion among non-CLL/non-SML MBL. These patients are also often found to have monoclonal IgM gammopathy, which means high levels of one type of IgM antibody. It is similar to Waldenstrom's macroglobulinemia and IgM monoclonal gammopathy, which are of uncertain significance. Such patients are more likely to develop malignant diseases, such as B-cell lymphomas of the marginal spleen zone, indeterminate lymphomas/leukemias of the spleen, hairy cell leukemia, and, possibly, Waldenstrom's macroglobulinemia [4, 12-15].

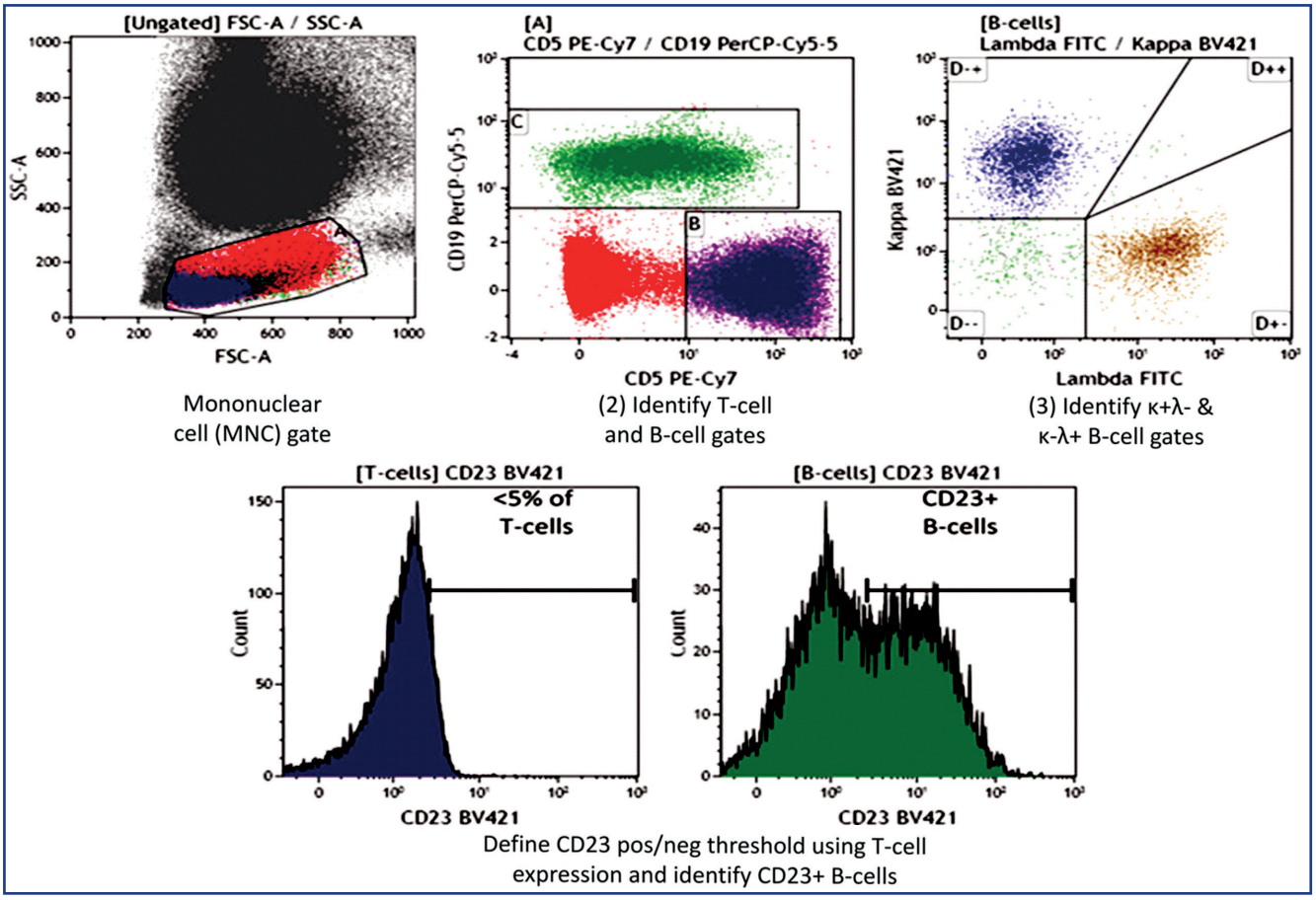

Figure 1 – Reproducible diagnosis of chronic lymphocytic leukemia using flow cytometry: European Research Initiative on CLL (ERIC) and European Society for Clinical Cell Analysis (ESCCA) Harmonization Project [19]

In 34 cases, the clinical, cytological, immunological, and genetic features of non-CLL MBL were described. As previously reported, the current cases have immunological and genetic similarities with marginal zone lymphoma (MZL). They may be associated with a new suspected condition, marginal zone clonal B-cell lymphocytosis (CBL-MZ). In addition, in some cases, similarities have been observed with diffuse lymphoma of the red pulp of the spleen (DLRPS). As a result, according to the literature, non-CLL MBL (associated with CBL-MZ) may be a precancerous condition leading to MZL and DLRPS [16, 17].

MBL is defined by fewer than 5×9 clonal B-cells in the peripheral blood in the absence of lymphadenopathy, enlarged spleen or liver, and symptoms of B-CCL. These symptoms include unintentional weight loss, fatigue with a score of 2 or higher on the Eastern Cooperative Oncology Group (ECOG) scale, prolonged fever, and night sweats with no signs of infection. In contrast, CLL, the most common lymphoid malignant tumor, is diagnosed at a B-cell count greater than 5×10^9/L [18].

Table 1 shows that MBL can be classified into three types based on the immunophenotypic characteristics of abnormal peripheral lymphoid cells: *CLL, atypical CLL, and non-CLL type*. Advances in flow cytometry have made it possible to detect deficient levels of clonal B-cells, especially in healthy older adults.

For a more detailed understanding and clarification of the differences between these conditions, it is essential to consider the immunophenotypic characteristics of abnormal peripheral lymphoid cells for different types of MBL with specific biomarkers that will aid in diagnostics in clinical and diagnostic laboratories. *CLL* with immunophenotype CD19+, CD5+, CD23+, CD20dim (low expression), kappa or lambda surface immunoglobulins usually (+) (sIg), white blood cell count: marked elevation: $\geq5\times10^9$/L. CLL is a heterogeneous disease, and its course can range from long-term survival to rapid progression. This disease is associated with a pronounced clonic B-cell expansion [18].

Atypical CLL with immunophenotype CD19+, CD5+, CD23-/dim (low), CD20+ (bright expression), kappa or lambda surface immunoglobulins usually (moderate to bright expression), white blood cell count: significant increase, may range from 5×10^9/L to higher values. Atypical CLL shows altered immunophenotypic profiles compared to classic CLL, including bright CD20 expression and moderate to bright sIg expression [19].

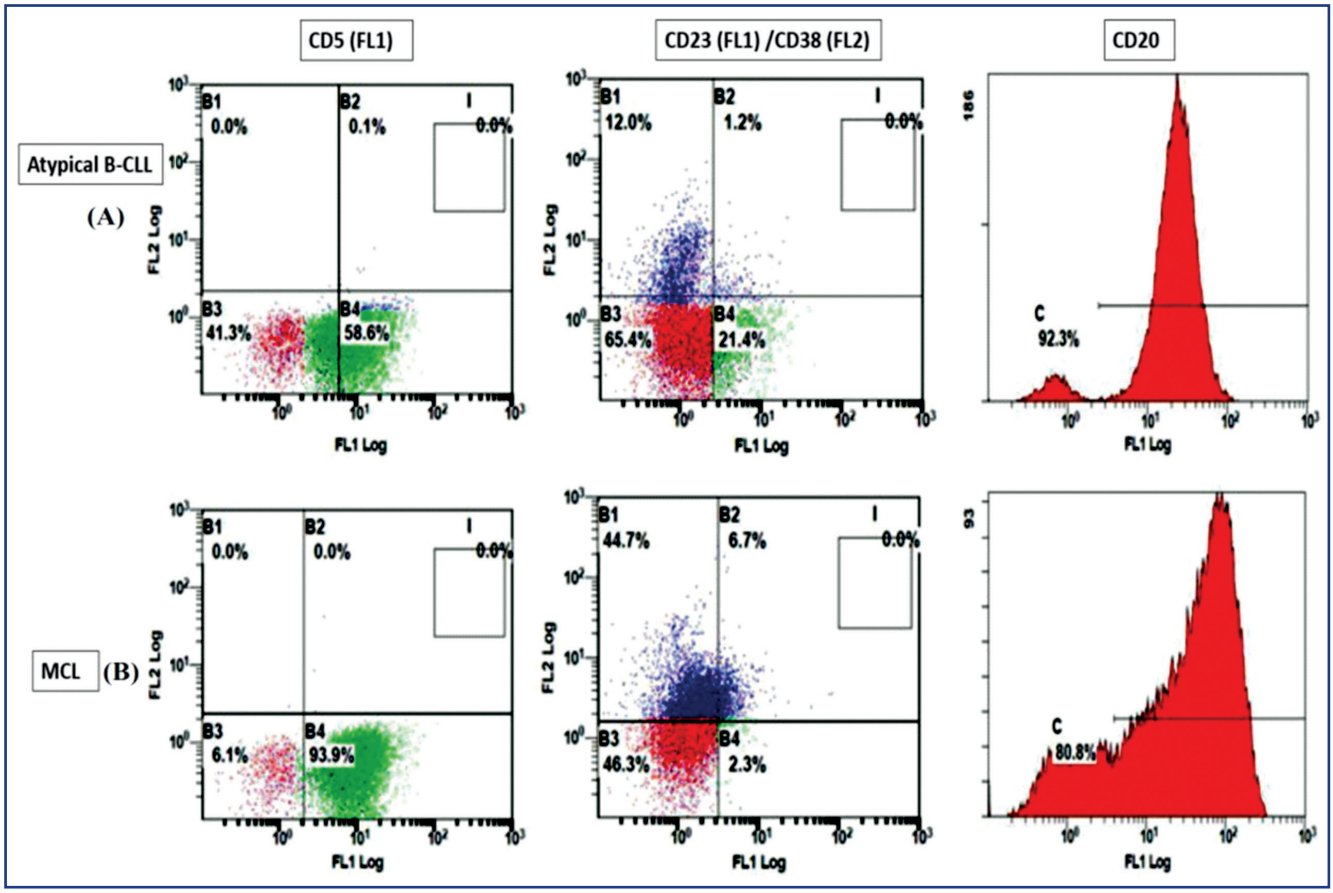

Figure 2 – Immunophenotypic assay for CD5, CD23, CD38 expression, and CD20 histogram in atypical (A) B-CLL and (B) MBL. Patients with MBL were found to have high expression of the CD5 marker, although patients with atypical B-CLL had lower levels of this marker. In patients with atypical B-CLL, CD23 expression was lower, but in patients with MBL, this marker was rarely expressed. In almost all patients with atypical B-CLL and MBL, CD38 expression was negative and positive, respectively. Both groups expressed CD20 without significant differences [20]

Non-CLL type with immunophenotype CD19+, CD5+, CD23-/dim (low), CD20+ (bright expression), kappa or lambda surface immunoglobulins (moderate to bright expression), white blood cell count may be normal or slightly elevated depending on the specific type of lymphoma or leukemia that is not CLL. This type includes various forms of lymphoma or leukemia that do not meet the criteria for CLL and may exhibit different immunophenotypic profiles [21].

In 2019, a team of scientists investigated the presence of CLL clones decades before a diagnostics of CLL, using the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) to analyze pre-diagnostic peripheral blood samples obtained during visits between 1992 and 2014 from healthy individuals who were subsequently diagnosed with CLL between 2001 and 2019. They assessed clonal CLL DNA by minimal residual disease (MRD) analysis according to EuroMRD guidelines.4. A total of 247 individuals diagnosed with CLL, registered after participation in CCHS or CGPS between 1992 and 2014, were identified. A total of 22 of these patients underwent immunoglobulin heavy chain variable region (IGHV) mutational status analysis performed at the Department of Haematology at Rigshospitalet (Copenhagen, Denmark) from 2001 to 2017 at the time of CLL diagnosis and had a >5-year latency period from participation in CCHS or CGPS to CLL diagnostics. The study was manually supplemented with eight cases of individuals who either had an IGHV mutational status established at Rigshospitalet and a <5-year latency period (two cases) or IGHV mutational status established at Rigshospitalet in 2018 and 2019 and a >10-year latency period (six cases). A total of 10 patients were excluded either due to a lack of sufficient complete blood DNA material in the biobanks or due to misdiagnosis of CLL (patients with small lymphocytic lymphoma). In addition, three patients were excluded due to technically insufficient analysis. The final cohort consisted of samples from 17 patients [22, 23].

In another randomized trial, patients with CLL were divided into three epigenetic subtypes (epitypes) with high prognostic significance. These studies have shown that the intermediate epitype is particularly common in patients with rearrangements 3-21 and high-risk immunoglobulin lambdas variable (IGLVs), which affects their outcomes. This study used a combined strategy to create an epigenetic and light chain immunoglobulin (ELCLV3-21) signature to classify 219 individuals with MBL. The high-risk signature of ELCLV3-21 made it possible to identify individuals with MBL who had a high probability of disease progression (39.9% at 5 years and 71.1% at 10 years). ELCLV3-21 improved the accuracy of predicting time to treatment in patients with MBL compared to other established prognostic measures, including the International Prognostic Index for CLL (c-statistic 0.767 vs. 0.668). A comparison of ELCLV3-21 risk groups among patients with MBL and a cohort of 226 CLL patients showed that high-risk individuals with ELCLV3-21 and MBL had a significant reduction in time to treatment (P = 0.003) and a decrease in overall survival (P = 0.03) compared to low-risk ELCLV3-21 and CLL patients. These results highlight the effectiveness of the ELCLV3-21 approach in identifying patients with a high likelihood of an adverse clinical outcome. They may provide a more accurate classification of individuals with small B-cell clones [24].

In a cross-sectional study, A.C. Rawstron et al. studied individuals at least 45 years of age who were HIV-1 seronegative from an established cohort of Ugandan populations from whom whole blood samples were taken. Also, in the UK, blood samples were collected from people of the same age and sex who did not have cancer and had average blood test results. Flow cytometry was used to determine the presence of MBL in the specimens, according to standard diagnostic criteria. Comparisons were made between the proportion of cases with an MBL phenotype characteristic of CLL and CD5-negative MBL and differences in the absolute number of monoclonal B-cells between the two cohorts. Between January 15 and December 18, 2012, samples were collected from 302 volunteers from Uganda and 302 from the United Kingdom, matching age and gender. The overall prevalence of MBL was higher in participants from Uganda (42 cases, 14%) than in the UK cohort (25 cases, 8%; p=0.038). The CLL MBL phenotype was identified in three (1%) participants from Uganda and 21 (7%) participants from the United Kingdom (p=0.00021). All three participants from Uganda had absolute monoclonal B-cell counts below one cell per μL. In comparison, 21 participants from the UK had an average absolute number of circulating tumor cells of 4.6 (interquartile range 2 - 12) cells per μL. The prevalence of CD5-negative MBL was higher in the Ugandan cohort (41 cases (14%), of which two (5%) also had the MBL phenotype, CLL) than in the UK cohort (six cases (2%), of which two (33%) also had the MBL phenotype, CLL; p<0.0001). However, the median absolute number of B-cells was similar (227 cells per μL (interquartile range 152-345) in the Ugandan cohort versus 135 cells per μL (interquartile range 105-177) in the UK cohort; p=0.13) [25].

CLL is much less common in Asians than in Caucasians. In the previous stage of CLL development, known as the MBL phenotype CLL (CLL-like MBL), the likelihood of progression to CLL is low. MBL is classified as high or low based on the number of clonal B-cells in the peripheral blood. Patients with high levels of MBL have a higher risk of progression to CLL than patients with low MBL.

Unlike Caucasian populations, in which MBL is quite common, Asian populations, including Japanese, have a lower incidence of MBL. The exact reasons for the ethnic differences in the prevalence of CLL and MBL remain unknown but may be related to the lower incidence of MBL and the slower progression of CLL-like MBL in Asians.

Therefore, studying the prevalence of MBL among Asian populations may help to understand these ethnic differences and the mechanisms of CLL development.

This study was conducted among descendants of Japanese immigrants living abroad, including the city of São Paulo in Brazil. It involved 258 healthy Japanese adults over 40, mostly without racial mixing. The study used highly sensitive multiparametric flow cytometry (MFC) to analyze clonal B-cells in peripheral blood. The study found a low incidence of MBL, which precedes CLL, among the descendants of Japanese immigrants living abroad. Patients with high MBL levels were rare; low MBL levels were more common, but the risk of progression to CLL was low. This supports the assumption of a lower incidence of MBL and a slow progression to CLL in the descendants of Japanese immigrants living abroad. These results may help to understand better ethnic differences in the development of CLL and its previous conditions, as well as shed light on the mechanisms of the development of this type of leukemia [26].

This review considers research on MBL and its relationship to CLL. Studies conducted in different populations have shown significant differences in the prevalence and progression of MBL and chronic lymphocytic leukemia (CLL). These differences are revealed not only between ethnic groups but also between patients with different epigenetic profiles. In particular, a combined strategy to create an epigenetic and light chain immunoglobulin (ELCLV3-21) signature has demonstrated high prognostic significance. It allows you to identify people with MBL who have a high probability of disease progression, which improves the accuracy of predicting the time to therapy compared to other prognostic indicators.

A study in Uganda and the United Kingdom found significant differences in the prevalence of MBL between the two populations. These results highlight the importance of considering ethnic and geographic factors when studying MBL and CLL, as they can significantly influence the prevalence and phenotypic characteristics of the disease.

Discussion:

This review examines modern approaches to diagnostics and classification of MBL in detail, emphasizing the importance of flow cytometry in identifying and differentiating its phenotypes.

Studies of MBL and its progression to CLL and other lymphoproliferative diseases suggest that different biomarkers and phenotypes play a crucial role in predicting risk. The review presents data from the MBL, demonstrating heterogeneity with different profiles. The number of clonal B-cells in the peripheral blood is one of the most significant risk factors. A low MBL level, at which the number of clonal B-cells is less than 0.5×10^9/L, can remain stable for a long time. At the same time, high-grade (HC) CLL type MBL (>0.5×10^9/L clonal B-cells) can progress from a precancerous state to true CLL [11]. The prediction of lymphoproliferative diseases such as CLL is based on analyzing these clonal populations and their characteristics. MBL is defined as a circulating population of monoclonal B-cells below 5×10^9/L (5,000/μL) persisting for at least three months in otherwise asymptomatic individuals [9, 10].

MBL phenotypes, as determined by flow cytometry, also play an essential role in predicting the risk of progression to CLL and other lymphoproliferative diseases. There are three types of MBCL: CLL-type, atypical CLL-type and non-CLL-type. Each of these types has its own unique immunological and clinical characteristics. The expression of the CD5, CD19, CD20, and CD23 markers characterizes the CLL-like phenotype. This phenotype has the most significant risk of progression to CLL, an atypical CLL-like phenotype expressing CD5, CD19, and CD20 markers but not CD23. The risk of progression to CLL is lower than that of the CLL-like phenotype but higher than that of the non-CLL phenotype; the non-CLL phenotype does not express the CD5 marker but expresses CD19 and CD20. Associated with marginal zone lymphoma and has the lowest risk of progression to CLL. Determination of immunoglobulin light and heavy chains on the surface of B-cells may help in predicting the risk of progression. Kappa and lambda light chains and their ratio and expression level may indicate clonality and possible disease progression [13-15, 18-21].

Mutations in the Immunoglobulin Heavy Variable (IGHV) genes are an essential prognostic factor in MBL. The presence of mutated or unmutated IGHV genes may indicate a different risk of progression to CLL. Unmutated IGHV genes are associated with a more aggressive course of the disease and a higher risk of progression [18, 19].

Cytogenetic changes such as del(13q), +12, and del(17p) are often found in patients with MBL and may be significant for prognosis. The detection of del(13q) is usually associated with a favorable prognosis, del+12 may be associated with an intermediate prognosis, del(17p) is associated with a more aggressive course of the disease and a worse prognosis and is often found in patients with CLL [9, 11].

Conclusion: The present study confirms the importance of different types of MBL differentiation for accurate diagnostics and prognosis. High-grade MBL, which has a higher probability of progression to CLL, requires closer monitoring. The detection of cytogenetic alterations such as del(13q), +12, del(11q), and del(17p) early in clonal evolution emphasizes the need for early detection and surveillance.

In contrast, MBL with low lymphocyte content proceeds more benignly and does not require as intensive monitoring as MBL with high content. Differences in the expression of surface markers between MBL phenotypes, such as CD5, CD23, CD10, CD103, CD79b, and immunoglobulin light chains, are critical to their classification and determination of progression risk.

The next stage of our study will be to examine archival material from the last 15 years. We plan to determine the number of patients with CLL, identify cases of genetic predisposition and MBL, and estimate clonality. Our experience will also show how many patients with CLL had MBL and what types of clonality were found.

Further studies are needed to understand better the molecular mechanisms underlying the progression of MBL to CLL and to develop better strategies to predict and prevent this progression. Clinicians must be aware of the differences between types of MBL and utilize appropriate diagnostic and monitoring techniques to ensure the best patient outcomes.

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АҢДАТПА

ЛИМФОПРОЛИФЕРАТИВТІ АУРУЛАРДЫ БОЛЖАУДАҒЫ МОНОКЛОНАЛДЫ В ЖАСУШАЛЫ ЛИМФОЦИТОЗДЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Дүниежүзілік денсаулық сақтау ұйымы 2017 жылы қан ауруларының кейбір түрлерін жіктеу үшін енгізген моноклоналды в-жасушалы лимфоцитоз (МБКЛ) жіктеудің жаңа перспективаларын ашады, сонымен қатар қосымша зерттеуді қажет ететін мәселелерді көтереді. МБКЛ зерттеулері диагностика мен бақылауды жақсарту үшін өте маңызды, бұл созылмалы лимфоцитарлық лейкемияны (ХЛЛ) ерте анықтауға және алдын алуға көмектеседі.*

Зерттеудің мақсаты: *моноклоналды В жасушалы лимфоцитоздың иммунофенотиптік аспектілерін және созылмалы лимфоцитарлы лейкозға айналу қаупін бағалау.*

Әдістері: *Ғылыми жарияланымдарды талдау барысында MBL себептері және оның cll-мен байланысы қарастырылып, осы жағдайлардың иммунофенотиптік аспектілеріне назар аударылды. Әдеби деректерді зерттеу MBL-дің CLL-ге өтуіне байланысты факторлар, соның ішінде биомаркерлер Мен клиникалық сипаттамалар туралы ақпарат берді, бұл MBL бар науқастарда лейкоздың даму қаупін толық бағалауға мүмкіндік берді.*

Нәтижелері: *MBL мен CLL арасындағы байланысқа қатысты көптеген зерттеулер талданды. Талдау көрсеткендей, MBL көбінесе CLL дамуынан бұрын пайда болады, MBL клондары клиникалық диагноздан бірнеше жыл бұрын анықталуы мүмкін. Бұл MBL даму қаупін анықтау үшін ерте биомаркер бола алады деген гипотезаны қолдайды.*

Әр түрлі зерттеулер MBL және CLL таралуы мен дамуындағы айтарлықтай этникалық және географиялық айырмашылықтарды көрсетеді. Бұл айырмашылықтар эпигенетикалық факторларға, иммуноглобулиннің өзгеруіне және басқа генетикалық ерекшеліктерге байланысты болуы мүмкін. Бұл айырмашылықтарды түсіну пациенттердің жеке және популяциялық ерекшеліктерін ескеретін дәлірек диагностикалық және болжамды тәсілдерді әзірлеу үшін маңызды.

Қорытынды: *Жүргізілген талдау MBL мен CL арасындағы байланысты одан әрі зерделеу, сондай-ақ MBL ерте анықтау үшін скринингтік бағдарламаларды енгізу Қазақстандағы пациенттердің болжамы мен денсаулығын айтарлықтай жақсарта алатынын көрсетеді.*

Шолу нәтижелері ерте диагностиканың және емдеуге жеке көзқарастың маңыздылығын көрсетеді. Бұл MBL-дің CLL-ге өтуіне жол бермейді және біздің елдегі денсаулық сақтау сапасын жақсартады.

Түйін сөздер: *Моноклоналды в жасушалы лимфоцитоз, созылмалы лимфоцитарлық лейкемия, иммунофенотип, даму қаупі, ағындық цитометрия.*

АННОТАЦИЯ

РОЛЬ МОНОКЛОНАЛЬНОГО В-КЛЕТОЧНОГО ЛИМФОЦИТОЗА В ПРОГНОЗИРОВАНИИ ЛИМФОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Моноклональный В-клеточный лимфоцитоз (МБКЛ), введенный Всемирной организацией здравоохранения в 2017 году для классификации некоторых видов заболеваний крови, открывает новые перспективы в классификации, но также поднимает вопросы, требующие дальнейшего изучения. Исследования МБКЛ имеют важное значение для улучшения диагностики и мониторинга, что может способствовать раннему выявлению и предотвращению развития хронического лимфоцитарного лейкоза (ХЛЛ).*

Цель исследования *– оценить иммунофенотипические аспекты моноклонального В-клеточного лимфоцитоза и риск прогрессирования в хронический лимфоцитарный лейкоз.*

Методы: *В ходе анализа научных публикаций были рассмотрены причины возникновения МБКЛ и его связь с ХЛЛ, акцентируя внимание на иммунофенотипических аспектах данных состояний. Исследование литературных данных предоставило информацию о факторах, связанных с прогрессированием МБКЛ в ХЛЛ, включая биомаркеры и клинические характеристики, что позволило более полно оценить риск развития лейкоза у пациентов с МБКЛ.*

Результаты: *Были проанализированы многочисленные исследования, касающиеся связи между МБКЛ и ХЛЛ. Анализ показал, что МБКЛ часто предшествует развитию ХЛЛ, причем клоны МБКЛ могут быть обнаружены за годы до клинического*

диагноза. Это подтверждает гипотезу о том, что МБКЛ может служить ранним биомаркером для выявления риска развития.

Различные исследования подчеркивают значительные этнические и географические различия в распространенности и прогрессировании МБКЛ и ХЛЛ. Эти различия могут быть связаны с эпигенетическими факторами, иммуноглобулиновыми перестройками и другими генетическими особенностями. Понимание этих различий важно для разработки более точных диагностических и прогностических подходов, которые учитывают индивидуальные и популяционные особенности пациентов.

***Заключение:** Проведенный анализ показывает, что дальнейшее изучение связи между МБКЛ и ХЛЛ, а также внедрение программ скрининга для раннего выявления МБКЛ могут существенно улучшить прогноз и здоровье пациентов в Казахстане.*

Результаты обзора подчеркивают важность ранней диагностики и индивидуального подхода к лечению. Это поможет предотвратить прогрессирование МБКЛ в ХЛЛ и повысить качество медицинского обслуживания в нашей стране.

***Ключевые слова:** моноклональный В-клеточный лимфоцитоз, хронический лимфоцитарный лейкоз, иммунофенотип, риск развития, проточная цитометрия.*

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PERSPECTIVES OF USING THE EXTRACELLULAR NEUTROPHIL TRAP LEVELS IN COLORECTAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *This literature review evaluates an alternative type of neutrophil immune response – the ability for NETosis or forming neutrophil extracellular traps (NETs). NETs influence the processes of carcinogenesis and cancer metastasis and play a role in the formation of tumor microenvironment and tumor-associated inflammation. The study of netosis has provided a deeper understanding of the mechanisms of intercellular interactions of the tumor microenvironment. NETs can also potentially become prognostic markers and predictors of complications of antitumor treatment of various cancers, including colorectal cancer (CRC).*

The study aimed to *summarize and systematize the current information on NETs and the impact of this phenomenon on the course of CRC and metastasis, as well as identify potential clinical points for using this marker in oncological practice.*

Methods: *The articles were searched and selected in Pubmed, Web of Science, Scopus, and RSCI databases by keywords among articles published in the past 10 years.*

Results: *NETs play an important role in the immune response to tumor niches and the metastasis of various solid tumors. There are data on the possibility of using NETs as a prognostic marker in various oncologic diseases. Experimental and clinical studies showed a potential relationship between NET levels and chemotherapy resistance and the impact of chemotherapy on the incidence of various complications. Chemotherapy with 5-Fluorouracil, according to the results of experimental studies, significantly increases the formation of NETs. The influence on the mechanism of NET release showed limited clinical efficacy of chemotherapy in CRC patients with PIK3CA mutation.*

The phenomenon of NETs is still poorly understood, and more studies are needed to widely implement this indicator into routine practice; however, research in this direction has the potential to have broad prospects for clinical application.

Conclusion: *Advances in immunology and the discovery of the netosis process have led to a deeper understanding of the mechanisms of interactions in the tumor microenvironment. Studying this process may make it possible to control or predict cancer progression and complications of antitumor treatment.*

Keywords: *neutrophil extracellular traps (NETs), netosis, colorectal cancer (CRC), oncology, immunology, biomarkers.*

Introduction: Colorectal cancer (CRC) is among the leading nosologies in the structure of cancer incidence worldwide and in Kazakhstan. CRC ranks 3rd-4th in prevalence, counting for 10% of all detected malignant neoplasms, and 2nd in mortality worldwide (ceding only to breast cancer and lung cancer in these indicators) [1, 2].

In metastasis, tumor cells exhibit certain characteristics, including increased expression of cell adhesion molecules, chemokine receptors, and strengthening of cytoskeletal changes that promote migration in response to chemotactic signals to distant organs [3].

According to the literature, up to 25% of all tumors could result from chronic inflammation, likely to generate chemoattractants that promote tumor cell proliferation, adhesion, and migration. Neutrophils play a key role in the immune response process and, according to some studies, accumulate in the pre-metastatic organs in increased numbers [4, 5].

Apart from the well-known phagocytosis mechanism, neutrophils can form sticky, web-like structures from decondensed chromatin filaments, containing an abundance of histones and proteins from neutrophil granules called the neutrophil extracellular traps (NETs). Studies suggest that NETs play a role in carcinogenesis and cancer metastasis [6].

For example, D. Lin et al. showed a connection between the formation of NETs in the vessels of the microcirculatory bed under the influence of systemic inflammation with the subsequent capture of cancer cells in the process of netosis in both the liver and lungs [7]. Intravascular neutrophil extracellular traps can increase vascular permeability, promoting the extravasation of immune and tumor cells from blood vessels to organs, thus providing the basis for hematogenous metastasis.

Some studies have also shown that body stress due to surgical treatment can contribute to cancer spread, possibly associated with an inflammatory process [8].

In addition, staining of tissue samples from patients with CRC using immunohistochemical methods revealed the presence of NETs in both the primary tumor and regional affected lymph nodes [9].

Based on these data, it can be assumed that NETs potentially play a role in the provision of proliferative signals and may be involved in colon cancer metastasis.

The study aimed to summarize and systematize the current information on NETs and the impact of this phenomenon on the course of CRC and metastasis, as well as identify potential clinical points for using this marker in oncological practice.

Materials and methods: We searched and selected articles published in the past 10 years using keywords in Pubmed, Web of Science, Scopus, and RSCI databases. We selected and analyzed 50 articles and generalized the relevant data in a review.

Results:

Molecular mechanisms of formation of neutrophil extracellular traps.

The process of NETs formation is known as netosis. Initially, netosis was called a new type of protective neutrophil death, but later, it was found that pathogenic stimulation can also cause viable and rapid production of NETs without affecting neutrophil viability [10].

In a further study of the mechanisms of netosis in order to clarify the mechanism of NETs formation, M. Ravindran et al. suggested two ways of netosis formation:

1) NADPH-oxidase (NOX)-dependent and lytic formation of NETs;

2) NADPH-oxidase (NOX)-independent nonlytic formation of NETs [11].

The first NOX-dependent lytic mechanism of netosis begins with recognizing pathogens or activating various receptors, including Toll-like receptors (TLRs), antibody fragment receptors, complement receptors, and others. Activation of these receptors eventually leads to the formation of reactive oxygen species that can stimulate the PAD4 enzyme, which leads to the decondensation of nuclear chromatin. Besides, the neutrophil granule protein myeloperoxidase promotes the translocation of neutrophil elastase into the nucleus, which promotes chromatin decondensation, nuclear membrane destruction, and chromatin release into the cytosol, where cytosol and granule proteins are attached to the DNA. Ultimately, NETs are released with the membrane destruction followed by neutrophil death [12].

Several studies found that the formation of NETs can occur independently of cell death, which was later specified as *the vital* or *nonlytic* mechanism of netosis. As a rule, this mechanism is characterized by the lack of participation in the NOX pathway and does not lead to oxidant formation (reactive oxygen species, ROS) [13].

The main difference between the lytic and nonlytic mechanisms of netosis is that nonlytic netosis occurs within minutes of stimulation without forming reactive oxygen species, while lytic netosis requires several hours of stimulation and ROS formation. The netosis nonlytic mechanism is activated by bacteria, platelet bacterial products, or complement proteins [10].

In both mechanisms of netosis, the chromatin decondensation and translocation of neutrophil granule elastase occur similarly. However, chromatin "encrusted" by bactericidal proteins is released by rupture of the nuclear envelope rather than by apparent destruction of the nuclear membrane. Nuclear membrane rupture and vesicle-mediated extracellular transport of NETs occur independently of plasma membrane disintegration [14, 15].

Scientists have connected the NETs formation with the pathogenesis of many gastrointestinal tract diseases, including inflammatory bowel disease, liver disease, and acute pancreatitis [16, 17]. Over the years, NETs have been associated with various types of cancer, suspecting their involvement in tumor growth or destruction, depending on the type of cancer, the state of the immune system, or the tumor microenvironment [18-20].

Consequently, NETs and their role in the immune response are also the object of active study in a wide range of nosologies, including cancer diseases.

The role of NETs in the microtumor microenvironment.

The tumor microenvironment is a complex environment that includes an extracellular matrix, microcirculation vessels, inflammatory factors, and immune cells, in which tumor cells proliferate and gain the ability for metastatic growth [21].

One microenvironment component is tumor-infiltrating immune cells such as neutrophils, which are involved in various stages of tumor genesis and can be divided into N1/N2 subtypes according to different functions and phenotypes. In light of the rapid growth of tumors and subsequent local necrosis caused by insufficient blood supply or treatment, a large number of inflammatory factors and damaging molecular patterns are discharged [22]. Neutrophils are mobilized into the tumor microenvironment under the influence of various pro-inflammatory factors, such as the cytokines CXCL1, IL-8/CXCL8, and CXCL12, complement proteins C3a and C5a, and lipid metabolism metabolites LTB4 [23-24]. These pro-inflammatory factors induce the formation of NETs to a certain extent. Besides, damaging molecular factors produced by necrotic cells in the microtumor environment induce TLR activation-dependent netosis. Clinical methods of treatment, such as radiotherapy and chemotherapy, can directly or indirectly induce netosis, which contributes to resistance to therapy [25-26].

NETs networks can promote tumor progression by inhibiting the proliferation, activation, and function of CD8+ T cells and NK cells. In addition, NETs can carry the programmed cell death ligand-1 (PD-L1) from the neutrophils surface, which is involved in immune regulation as an inhibitory component in the immune microenvironment. Based on this, inhibition of netosis can be an addition to immunotherapy. Besides, NETs can promote tumor growth, change the metabolism of tumor cells, and promote tumor metastasis by capturing cancer cells or directly binding to nucleic acid receptors on the tumor cell surface [27, 28].

Summarizing all aforesaid information, NETs play an important role in carcinogenesis and forming the tumor microenvironment, potentially impacting the clinical aspects, such as immunotherapy of malignant tumors.

The role of NETs in the pathogenesis of various types of cancer.

Elevated NETs levels in blood plasma have been observed in patients with various types of cancer, including lung, pancreatic, and bladder cancer [17-20, 29].

According to experimental studies, it was assumed that cancer cells can independently induce the NETs for-

mation, which in turn promotes further adhesion and growth of cancer cells in breast cancer metastases to the lungs. A higher level of netosis was also revealed in breast cancer metastases to the liver, and NETs level in blood serum showed the prognostic value of this indicator as a risk factor for liver metastases in patients with early stages of breast cancer. It was also found that the CCDC25 transmembrane protein of breast cancer cells can recognize distant NETs and attract the tumor cells in response to this [28].

In vitro experiments have shown that NETs can induce invasion and migration of breast cancer cells and subsequent digestion of NETs by DNase I-coated nanoparticles, as well as reduce metastasis of breast cancer cells to the lungs in mice [30].

The NETs formation is observed in pneumonia caused by exposure to smoke or nasal instillation of lipopolysaccharide in animal models. The NETs-related proteases, neutrophil elastase, and matrix metalloproteinase 9 can break down basal laminin and thus promote the growth of "dormant" cancer cells by activating alpha-3 beta-1 integrin signals. NETs can act as a trap to capture the circulating cancer cells in the microcirculatory bed of organs distant from the primary tumor focus. In a mouse model of sepsis, circulating lung carcinoma cells have been reported to be retained by NETs in liver microcirculation vessels and cause metastatic lesions following injection of tumor cells. Besides, treatment with DNase or a neutrophil elastase inhibitor showed a trend towards a reduced risk of cancer metastases spread. The neutrophil subpopulation with high CD16 counts and low CD62 counts has a higher ability to produce NETs, and in patients with squamous cell carcinoma of the head and neck, this subpopulation shows better survival. Another study showed that tumors can release granulocytic colony-stimulating factors into the bloodstream and promote the accumulation of intra-tumoral NETs and tumor growth, stimulating the circulating neutrophils [31].

The blood samples analysis revealed elevated levels of NETs in patients with gastric cancer (GC). The results indicate a higher diagnostic value of NETs compared to such tumor markers as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9).

These data indicate the key role of NETs in the GC carcinogenesis. Another study reported that low-density neutrophils (LDNs) from postoperative lavage generate huge NETs in vitro culture. Moreover, the co-transfer of peritoneal LDNs with human GC cells enhances the peritoneal metastatic spread in vivo [32].

Indicatively, detecting NETs levels at an early stage of tumor development or premetastatic stage can help predict the severity of disease progression, and targeting the impact on NETs with specific inhibitors could potentially help to control the tumor growth and synergized with other antitumor treatments [27, 28, 33, 34].

The role of DNase and PAD4 inhibition on NETs levels in various cancer types.

Given the role of NETs in cancer progression and metastasis, the possibilities of blocking the process of netosis have been studied. The most convenient target for that is the extracellular part of DNA. The use of DNase enzymes led to a decrease in netosis. There is also data on the reduction of lung metastases in mouse models using these drugs [29].

Currently, DNases are applied in a fairly limited number of cases; for example, inhaled forms of DNases are used for cystic fibrosis and help reduce sputum viscosity through NET destruction. The DNase preparations are not recommended for systemic use due to marked toxicity during parenteral use [35].

The potential use of DNase preparations is limited due to a small amount of available data. But despite this, there are studies on the use of DNase in thrombosis associated with cancer [36, 37], and there are data on the successful local use of DNase in cancer, in particular, based on the data obtained by researchers from Spain who used this drug on urothelial bladder cancer cells in vitro [38].

Inhibition of PAD4 in experimental models also demonstrated the interruption of the netosis process. For example, prostaglandin E2 and chlorine inhibit tumor-induced netosis, reducing cancer patients' blood clots [39].

It is worth noting that no drugs would have a selective effect on NETs without affecting the immune system in the form of excessive immunosuppression or immune stimulation, and the issue of developing such drugs remains open.

Involvement of NETs in CRC progression and metastatic spread.

Several studies have confirmed that patients with CRC can excrete elevated levels of NETs in vivo and in vitro, which are mainly scattered in the primary tumor foci and along the CRC tumor margin [9, 40].

Despite the widespread use of chemoradiotherapy and screening programs for early detection of CRC, about half of patients who undergo therapeutic resolution resection develop metastatic disease. Accumulated data suggest that preoperative systemic inflammation may be involved in CRC recurrence after the surgical resection. In addition, several mouse models and human observational studies have demonstrated the potential prognostic value and association of NETs with the progression of CRC. Recurrence and metastasis may be associated with NETs production due to perioperative systemic inflammation, such as sepsis or NETs production in a surgical wound [41].

Several mechanisms have been proposed that can trigger the formation of NETs in the CRC microenvironment. For example, polyphosphate (polyP) expressed by CD68+ mast cells has been shown to stimulate neutrophils to form NETs in CRC ex vivo. Activation of the mutated KRAS gene regulates the oncogenic malignant transformation followed by the proliferation of cancer cells through activation of the RAS/MAPK signaling pathway, which occurs in 40-50% of CRC cases. Malignant cells can secrete exosomes to control the cellular microenvironment, and studies have shown that CRC cells with the KRAS mutation can transfer this mutation to neutrophils via exosomes, which induces neutrophil mobilization and subsequent formation of NETs by increasing interleukin-8 (IL-8) levels both in vivo and in vitro. The production of elevated levels of IL-8 and the formation of NETs may stimulate CRC cell

proliferation and ultimately worsen the course and prognosis in that category of patients [40, 42].

Effect of IL-8 and the microtumor environment on netosis in CRC.

It is known that IL-8, through its CXCR1 and CXCR2 receptors, attracts neutrophils and other myeloid leukocytes to the site of infection. IL-8 acts as a multifaceted chemotactic stimulus used by the tumor to simultaneously induce transmigration and angiogenesis. IL-8 released by tumor cells can also promote their survival and proliferation by activating the autocrine system, promoting the angiogenesis and tumor infiltration of neutrophils.

In some studies, IL-8 has been shown to promote angiogenesis and cancer metastasis by directly stimulating the formation of NETs through activation of the Src, ERK, and p38 signaling pathways. NETs can directly stimulate the TLR9 pathways, affecting cancer progression. The myeloid suppressor cells expressing CXCR1 and CXCR2 are also stimulated by IL-8. This increases the NET levels, which, in turn, can capture the tumor cells [43].

R.F. Rayes et al. found that serum levels of IL-8 and its receptor CXCR2 have been significantly elevated at different stages of CRC compared to normal samples. Secreted IL-8 significantly stimulates proliferation, penetration, and migration and enhances the angiogenesis around the tumor. Moreover, IL-8-stimulated neutrophils secreted by NETs contribute to further invasion and proliferation of CRC [44].

It has been established that the formation of NETs not only enhances the proliferation of CRC cells but also stimulates the process of metastatic spread. NETs promote the adhesion of circulating tumor cells to the hepatic or pulmonary endothelial surface and thus enhance the migration of CRC cells to major vital organs and prognostically significant areas of the body, such as the liver, lungs, and peritoneal cavity. According to population studies, about 25-30% of patients with colon cancer develop concomitant liver metastases, and most of them have a significant elevation of NETs formation [45-49].

NETS are not cytotoxic for CRC cells captured in the liver. However, they can increase their malignant potential by stimulating the tumor production of IL-8, which, in turn, stimulates the formation of even more NETs, creating a vicious cycle provoking the progression of liver metastases [45]. In addition, the NETs-associated cell adhesion molecule 1 (CEACAM1), bound to carcinoembryonic antigen (CEA), has been shown to stimulate the movement of CRC cells to the liver both in vitro and in vivo [46].

Alongside the anatomical and above-mentioned immunological prerequisites for CRC metastasis to the liver, dysregulation of the intestinal microbiota also plays an important role in the progression process. Numerous studies have found a relationship between certain strains of intestinal bacteria (e.g., pks + E. coli and Bacteroides fragilis) and the occurrence of CRC, and intestinal bacteria translocation is commonly observed during the CRC progression. The intestinal microbiota forms the tumor microenvironment through direct contact with immune cells or through its functional metabolites. However, the question of how the intestinal microbiota contributes to CRC metastasis remains controversial. Meanwhile, recent studies have revealed the spread of bacteria from the intestinal lumen to the liver, suggesting intestinal microbiota's role in forming tumor niches. Protumor pre-metastatic niches in the liver are characterized by infiltration of immunosuppressive cells and reinforcement of pro-inflammatory immune responses [47].

Discussion: The study of NETs is one of the promising areas of oncology and immunology, which pushes us to look for clinical points of application for the phenomenon of netosis and the regulation of the activity of this process. Given their role in carcinogenesis and metastasis, NETs may play a role in personalizing treatment based on NETs levels and influence the course of systemic therapy for CRC.

According to the results of experimental studies conducted by L. Basyreva et al. [48], during prolonged incubation of whole blood with free 5-fluorouracil (5-FU) at certain concentrations, the chemotherapy drug has contributed to a significant NETs release (the maximum number of NETs was formed at a concentration of free 5-FU of 0.1 μg/ml during incubation from 2 to 3 hours). The authors considered an increase in the number of NETs combined with an unchanged total number of leukocytes to be a manifestation of vital netosis. The authors suggest that the release of mitochondrial DNA forms NETs, and neutrophils retain the nucleus and remain alive. It is reported that about 3% of the cells could generate more than one NETs from a single cell. In this experimental work, it was also demonstrated that the application of 5-FU coated with composite polymer nanoparticles significantly reduces netosis.

In the studies of Mousset et al. [25, 50], the following hypothesis has been expressed: strategic exposure to NETs is a promising direction for identifying combination therapies that can help counter resistance or increase the effectiveness of chemotherapy, as well as limit the complications caused by that type of treatment. In this experimental work on mouse models, the elevation of renal parameters levels, such as creatinine and urea, was noted during treatment with cisplatin, which may suggest the development of acute kidney injury. In the course of the experimental work, the studied mice showed an increase of the neutrophils levels that form NETs in the kidneys of mice treated with cisplatin, and that NETs targeting not only restored the sensitivity of cancer cells to chemotherapy but also significantly improved the kidney function. According to the authors, these findings are consistent with the results of similar studies and may confirm that the side effects of chemotherapy in the form of acute kidney injury are partially mediated by NETs generated in response to treatment.

In the work of Li Y. et al., the role of NETs in the course of chemotherapy for CRC was studied. These researchers studied treatment using a glutaminase inhibitor (CB-839), which inhibits the NETs formation, and 5-FU chemotherapy in CRC with PIK3CA mutation, which is found in 30% of patients. The researchers chose this molecular type of tumor because, in previous experimental work, the infiltration of the tumor with NETs was significantly lower [49].

The combination of NETs inhibitors and 5-FU induces IL-8 expression in tumor cells, which attracts neutrophils to the tumor niche. This combination also increases the level of reactive oxygen species in neutrophils, inducing the formation of NETs. The NETS-bound cathepsin G (CG) enters the cancer cells via the receptor for advanced glycation end (RAGE), after which CG can break down the sequestration protein 14-3-3ε, releasing the active Bcl-2-associated protein X (Bax), which in turn activates the apoptosis pathway.

Thus, in the context of CRC, NETs have shown a synergizing role in conjunction with antitumor chemotherapy. Thus, A. Mousset et al. mentioned the previous phase 2 clinical trials using this drug regimen, which did not have positive results [51] since the study sample did not have objective answers, despite the positive relationship between the NETs level elevation and prolongation of progression-free survival in tumor biopsies after conducted treatment.

Accordingly, the complexities of converting promising pre-clinical results into successful clinical outcomes highlight the need to consider factors such as patient heterogeneity, tumor-specific characteristics, and sample size.

One of the other clinically relevant treatment-limiting side effects of chemotherapy is chemotherapy-induced peripheral neuropathy. In the course of research conducted by C.Y. Wang et al., mice treated with oxaliplatin chemotherapy have been shown to have NETs accumulation in the dorsal radicular ganglia and extremities, which disrupts the microcirculation. In turn, inhibition of NETs formation successfully counteracted the chemotherapeutic hyperalgesia and restored the peripheral microcirculation [52].

A. Mousset et al. concluded that a combination of control of NETs levels and a targeted effect on their formation in the blood can potentially:

1. Reduce the serious side effects of anticancer therapy in the conditions, such as acute kidney injury, chemotherapy-induced neuropathy, and potentially gastrointestinal complications, all of which may be a reason for discontinuation of systemic therapy;

2. Predict the development of chemoresistance;

3. Reduce the time spent on chemotherapy and influence the effectiveness of treatment [25, 51].

In summary, it should be highlighted that despite the relevance of netosis, this phenomenon is still poorly understood. In order to extend our understanding of the role of NET formation, more experimental studies are necessary. The number and quality of clinical studies of this phenomenon in malignant neoplasms at the moment may not be enough for the widespread introduction of NETs as a marker for the prognosis of the course of cancer or its treatment. However, considering the promising results of the existing work, research in this direction could potentially have broad prospects for clinical application.

Conclusion: The development of immunology and the discovery of the process of netosis made it possible to better understand the mechanisms of intercellular interactions of the tumor microenvironment. A thorough study of each step of this process can help to find the leverages and targets to control and prevent tumor progression. Also, the NETs levels can potentially become the markers for prognosis of the course of cancer and perhaps even be a predictor of complications of antitumor treatment. The future outlook and lack of studies on this phenomenon are considered topical issues in immunology and oncology.

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АҢДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІККЕ ЖАСУШАДАН ТЫС НЕЙТРОФИЛЬДІ ТҰЗАҚ ДЕҢГЕЙЛЕРІН ҚОЛДАНУ КЕЛЕШЕГІ: ӘДЕБИЕТКЕ ШОЛУ

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Сәйкестік: *Бұл жұмыста нейтрофилдердің иммундық реакциясының балама түрі-нетозға қабілеттілік немесе жасушадан тыс «тұзақтардың» пайда болуын (ЖТТ) бағалауға бағытталған зерттеу ұсынылған. ЖТТ қатерлі ісік канцерогенезі мен метастаз процесіне әсер етеді, ісік микроортасының және ісікпен байланысты қабынудың қалыптасуында рөлі атқарады. Нетоз процесінің зерттелуі ісік микроортасының жасушааралық өзара әрекеттесу механизмдерін тереңірек түсінуге мүмкіндік берді. ЖТТ сонымен қатар әртүрлі онкологиялық аурулардың, сондай-ақ әсіресе колоректальды қатерлі ісіктің болжамды белгілері болуы мүмкін, тіпті ісікке қарсы емдеудің асқынуларының болжаушысы болуы мүмкін.*

Зерттеудің мақсаты *– бұл әдебиет шолу ЖТТ бойынша актуальды мәлімет жүйелеуге және жалпылауға, және осы феноменның тоқ және тік ішек обыры ағымына әсер етуіне арналған. Осы маркердің онкологиялық практикада потенциалдық клиникалық қолдануын анықтау үшін жасалынған.*

Әдістері: *Pubmed, Web of Science, Scopus, РИНЦ базаларының ішінен түйін сөздер бойынша ізделу және талдау жасалынды; осы әдебиет шолына кейінгі 10 жылдың көлемінде кірген жұмыстар алынды.*

Нәтижелері: *ЖТТ ісіктік ойықша иммундық реакцияны қалыптастыруда және әртүрлі солидті ісіктердің метастаз беру процесінде маңызды рөл атқарады. ЖТТны әртүрлі онкологиялық ауруларда болжамды маркер ретінде пайдалану мүмкіндігі туралы деректер бар. Сондай-ақ, эксперименттік және клиникалық зерттеулер жүргізілді, олар ЖТТ деңгейлерінің ықтимал байланысын және химиотерапияға төзімділіктің қалыптасуын, сондай-ақ химиотерапияның әртүрлі асқынуларының жиілігіне әсерін көрсетті. Эксперименттік жұмыстардың нәтижелері бойынша 5-фторурацилмен химиотерапиясы ЖТТ түзілуін едәуір арттырады. ЖТТ босату механизміне әсері PIK3CA мутациясы бар колоректальды обыр бар пациенттерде химиотерапия жүргізуде шектеулі клиникалық тиімділікті көрсетті.*

ЖТТ феномені әлі де жақсы зерттелмеген және бұл көрсеткішті күнделікті тәжірибеге енгізу үшін көбірек зерттеулер жүргізу қажет; дегенмен, осы бағыттағы зерттеулер клиникалық қолдану үшін келешекте үлкен нәтижелерге ие болуы мүмкін.

Қорытынды: *Иммунологияның дамуы және нетоз процесінің ашылуы ісік микроортасындағы өзара әрекеттесу механизмдерін тереңірек түсінуге мүмкіндік берді. Бұл процессті зерттеу онкологиялық аурулардың дамуын және ісікке қарсы емдеудің асқынуларын бақылауға немесе болжауға мүмкіндік береді.*

Түйінді сөздер: *жасушадан тыс нейтрофильді тұзақтар, нетоз, колоректальды қатерлі ісік, онкология, иммунология, биомаркерлер.*

АННОТАЦИЯ

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ УРОВНЕЙ ВНЕКЛЕ-ТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК ПРИ КОЛОРЕКТАЛЬНОМ РАКЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *В данной работе представлена оценка возможности альтернативного вида иммунного ответа нейтрофилов – способности к нетозу, или же образованию «внеклеточных ловушек» (ВНЛ). ВНЛ оказывают влияние на процессы канцерогенеза и метастазирования рака, играют роль в формировании опухолевого микроокружения и опухоль-ассоциированного воспаления. Изучение нетоза позволило глубже понять механизмы межклеточных взаимодействий опухолевого микроокружения.ВНЛ также потенциально могут стать маркерами прогноза течения и предикторами осложнений противоопухолевого лечения различных онкологических заболеваний, в том числе колоректального рака (КРР).*

Цель исследования *– обобщение и систематизация актуальной информации по внеклеточным нейтрофильным ловушкам, их влиянию на течение и процесс метастазирования колоректального рака и возможности применения в клинической практике.*

Методы: *Произведен поиск и отбор статей в базах данных Pubmed, Web of Science, Scopus, РИНЦ по ключевым словам исследования; в обзор были включены статьи давностью не более 10 лет.*

Результаты: *ВНЛ играют важную роль в иммунном ответе на опухолевые ниши и процесс метастазирования различных солидных опухолей. Имеются данные о возможномсти использования ВНЛ в качестве прогностического маркера при различных*

онкологических заболеваниях. Экспериментальные и клинические исследования показали потенциальную взаимосвязь уровней ВНЛ и формирования резистентности к химиотерапии, а также влияние химиотерапии на частоту различных осложнений. Химиотерапия 5-Фторурацилом, по результатам экспериментальных работ выраженно повышает образование ВНЛ. Влияние на механизм высвобождения ВНЛ показало ограниченную клиническую эффективность при проведении химиотерапии у пациентов с КРР с мутацией PIK3CA.

Феномен ВНЛ все еще недостаточно изучен, и необходимо проведение большего количества исследований для широкого внедрения этого показателя в рутинную практику, однако исследования в данном направлении потенциально могут иметь широкие перспективы для клинического применения.

***Заключение:** Развитие иммунологии и открытие процесса нетоза позволило глубже понять механизмы взаимодействий в опухолевом микроокружении. Изучение этого процесса может позволить контролировать либо прогнозировать прогрессирование онкологических заболеваний и осложнений противоопухолевого лечения.*

***Ключевые слова:** внеклеточные нейтрофильные ловушки (ВНЛ), нетоз, колоректальный рак (КРР), онкология, иммунология, биомаркеры.*

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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF EPSTEIN-BARR VIRUS AND HUMAN PAPILLOMAVIRUS ASSOCIATED WITH THROAT CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Pharyngeal cancer (PC) is a malignant neoplasm in the oropharynx and nasopharynx associated with Epstein-Barr viruses (EBV) and human papillomavirus (HPV). Both viruses have oncogenic potential, affecting the pathogenesis of PC.*

EBV, which infects more than 90% of the population, can cause various benign and malignant diseases. HPV, especially types 16 and 18, is the main oncogenic factor of oropharyngeal cancer (OPC). The E6 and E7 proteins produced by HPV disrupt the action of tumor suppressors p53 and Rb, which leads to uncontrolled cell proliferation.

EBV activates latent proteins and regulates the immune response, whereas HPV affects cell cycle control by inactivating p53 and Rb. HPV-induced PC has a better prognosis compared to EBV-associated cancer due to higher sensitivity to treatment.

The study aimed to *systematize literature data on assessing the diagnostic and prognostic significance of EBV and HPV associated with PC and improve programs for early diagnosis and primary prevention of head and neck tumors.*

Methods: *Since 2015, a literature review has been conducted on the study's keywords in the PubMed and MedLine databases.*

Results: *Studies show that EBV and HPV are important in the diagnosis and prognosis of PC. The EBV presence in tumor cells can mark a more aggressive course of the disease. However, in some cases, it is associated with better treatment results. Patients with HPV-positive tumors have better prognoses and a more favorable response to treatment compared to HPV-negative cases. Both viruses play an important role in the pathogenesis of PC, and their diagnosis and characterization can significantly affect treatment tactics and prognosis of the outcome of the disease.*

Conclusion: *EBV and HPV play key roles in the pathogenesis of RG, but their mechanisms of action and clinical outcomes differ. EBV is more often associated with nasopharyngeal cancer, and HPV is associated with OPC. The latter is more common in Western countries and has a more favorable prognosis. Future research should focus on developing more effective prevention, diagnosis, and treatment methods for these viruses.*

Keywords: *Epstein-Barr virus (EBV), human papillomavirus (HPV), pharyngeal cancer, diagnostics.*

Introduction: Pharyngeal cancer (PC) applies to malignant neoplasms (MNO) in the oropharynx and nasopharynx. Epstein-Barr virus (EBV) and human papillomavirus (HPV) are the main infectious agents associated with developing these tumors. EBV, a member of the family of herpesviruses, and HPV, a member of the family of papillomaviruses, have different effects on the pathogenesis of PC, but both have a significant oncogenic potential.

These viruses are the most common cause of infectious oncological diseases. HPV and EBV are associated with 38% of all virus-associated STDs [1]. The majority of virus-associated types of cancer develop after a long latent period, which can take from 15 to 40 years [2].

The preferred way of transmission of VEB is airborne. Today, it has become known that organ transplantation and blood transfusion can also contribute to the spread of EBV [2,3].

According to data for 2019, HPV caused 620,000 cases of cancer among women and 70,000 among men. Cervical diseases account for 93% of all HPV-associated STDs in women. In 2022, cervical cancer was the fourth leading cause of cancer and death among women, with 660,000 new cases and approximately 350,000 deaths worldwide [4]. HPV is associated with more than 90% of cases of cervical cancer and about 70% of cases of oropharyngeal cancer (OPC).

According to estimates from the International Agency for Research on Cancer (IARC), 10% of cancer cases worldwide are caused by viral infections [5].

EBV and HPV have been classified as high-risk group 1 (certainly established) human carcinogens. EBV is etiologically associated with Burkitt's lymphoma, extranodal NK/T-cell lymphoma (i.e., nasal type), Hodgkin's lymphoma, nasopharyngeal carcinoma (NA), and lymphoepithelioma-like carcinoma [6].

EBV, first identified in 1964, is associated with several NCDs, including nasopharyngeal carcinoma (NPC). RNG is one of the most common head and neck tumors, espe-

cially in endemic areas such as China, Southeast Asia, and North Africa. EBV causes the transformation of epithelial cells of the nasopharynx through the activation of latent proteins, such as latent membrane protein-1 (latent membrane protein 1, LMP1), which acts as an oncogene, activating the NF-kB and JAK/STAT signaling pathways. These molecular processes lead to a decrease in apoptosis and an increase in cell proliferation and cell migration.

The study aimed to systematize literature data on assessing the diagnostic and prognostic significance of EBV and HPV associated with PC and improve programs for early diagnostics and primary prevention of head and neck tumors.

Materials and methods: A literature review of scientific and clinical studies from PubMed and MedLine databases was conducted under the main keywords and phrases: "Epstein-Barr virus associated with PC," "human papillomavirus associated with PC," "diagnostic and prognostic significance of Epstein-Barr virus and human papillomavirus." Filters were used in the search procedure: publication date from 2015 to the present.

Results: Presumably, a specific combination of the EBV variant and a specific person exists. A eucocyte antigen allows the proliferating epithelial cells to evade immune control [7]. The histological subtypes of nasopharyngeal squamous cell carcinoma (NPC) and the suspected etiological factors vary by geographic region. According to the WHO classification of head and neck tumors, NPCs are classified into 3 main types: keratinizing squamous cell carcinoma (KC), non-keratinizing carcinoma (NKC), and basaloid squamous cell carcinoma. NPC can be divided into differentiated and undifferentiated forms. In endemic areas with high incidence, up to 99.6% of NPC tumors belong to the KC subtype. It is more strongly associated with EBV positivity than other subtypes. In non-endemic areas with low incidence, the prevalence of the NKC subtype is significantly lower, while the prevalence of KC is higher than in endemic regions. [8].

In comparison, in non-endemic areas with low incidence, the prevalence of subtypes (NKC) is significantly lower, whereas the prevalence (KC) is higher than in endemic areas.

High-risk HPV infection is thought to be one of the etiological factors causing NPC in Caucasian people. In one of the studies, patients with HPV-positive and EBV-positive tumors had a significantly higher overall survival rate than patients with EBV/HPV-negative tumors [9, 10].

Previous studies of viral infections in NPCs have mainly reported small and heterogeneous groups of patients treated at 1 or 2 facilities. Thus, data on the predictive value of EBV and HPV in NPCs are limited. This retrospective population-based study aimed to describe the status of EBV and HPV in cases of Finnish NPC and to link them to histopathological subtypes of NPC and patient survival.

There is evidence of a relationship between HPV and oral cavity cancer. According to the results of the study, "Prevalence of HPV-induced oral cavity and OPC in Kazakhstan and its prognostic significance," conducted at Kazakh Research Institute of Oncology and Radiology JSC (Almaty, Kazakhstan), the analysis of HPV incidence among patients with malignant neoplasms of the oral cavity and oropharynx in the Republic of Kazakhstan is of great clinical importance, since the HPV presence in the tumor is a favorable prognostic sign of the course of the disease. The highest survival rates in patients with oropharyngeal and oral malignancies associated with HPV (93%) are explained by a higher response to chemotherapy and radiation therapy compared to patients without HPV (82%). The presence of a high level of p16 protein proliferative activity in oropharyngeal and oral cavity tumors is also associated with HPV infection and can be used as a marker for the diagnostics of HPV-associated tumors at these locations. These results will develop methods for early diagnostics and improve methods for primary prevention of laryngeal cancer.

Discussion: Why does the virus cause cancer? Viral infections are one of the most common causes of infectious cancers, accounting for 12-15% of all cases. HPV and EBV are associated with 38% of all virus-associated malignancies. Most types of cancer associated with viruses develop after a long latency period that can last from 15 to 40 years [2, 11, 12].

Oncogenic viruses include various groups of DNA and RNA viruses, which are important but not always sufficient for the occurrence of all types of malignant tumors [2]. A common feature is that cancer develops only in a few people infected with viruses for a long time and only after many years of chronic infection [4, 13].

Both viruses have different mechanisms of influence on cellular processes. EBV mainly acts through the activation of latent membrane proteins and the regulation of the immune response, whereas HPV alters the control of the cell cycle through the inactivation of p53 and Rb. Studies show that HPV-induced OPC has a better prognosis than cancers associated with EBV or classic risk factors. This is due to the higher sensitivity of HPV-positive tumors to treatment (especially to chemoradiotherapy).

Currently, the main confirmation of the viral nature of tumors is the detection of the virus or its components in tumor cells using monoclonal analysis. This method allows for the confirmation of a chronic infection that precedes malignant transformation and the detection of viral oncogenes that contribute to the start of the tumor process.

Viral carcinogenesis is divided into two main types: direct and indirect. The direct mechanism is that once infected, the virus persists in the cell as an independent genetic element, either as an eposome (as it occurs in herpes viruses) or integrates into the host genome (e.g.,

in retroviruses or hepatitis B virus). It can lead to inactivation of the p53 and pRB genes, genomic instability, increased mutations, changes in telomere length, disruption of cellular polarity, and the formation of miRNA. An indirect mechanism involves chronic inflammation and oxidative stress in normal cells caused by the production of pro-inflammatory cytokines by infected cells (e.g., in hepatitis C virus), resulting in prolonged antigenic stimulation. Viruses can also induce immunosuppression in surrounding tissues by destroying or impairing the function of CD8+ lymphocytes (e.g., in HIV, EBV, or KSHV) [13-15].

HPV belongs to the *Papillomaviridae* family. To date, more than 100 types of these viruses are known to be involved in the development of various diseases. They are divided into two groups: low and high-risk ones. Low-risk subtypes 6 and 11 cause cutaneous and anogenital warts and upper respiratory tract papillomatosis, rarely leading to malignancy. Subtypes 16 and 18 are at high risk and are more likely to be associated with the development of malignant tumors. Type 16 is mainly associated with OPC (up to 95%) and invasive cervical cancer (up to 70%), and type 18 is associated with squamous cell carcinoma of various sites. HPV is transmitted through contact and sexual routes. A characteristic feature of this virus is its ability to persist in the body for a long time without obvious clinical signs.

Antibodies to HPV can be found in 50-60% of infected people. The natural process of HPV-associated tumors usually takes 10 to 30 years from the time of initial infection. The pathogenesis of tumor progression against the background of HPV infection includes changes in the expression of viral oncogenes at different stages of the disease and the accumulation of mutations in the host genome. Clinically, this is manifested by such epithelial changes as CIN-1, CIN-2, and CIN-3. The main oncoproteins are E6 and E7. They must maintain a malignant state as they inactivate the retinoblastoma and p53 genes. This is important because such inactivation increases p16INK4A (cyclin-dependent kinase 2A inhibitor/tumor suppressor 1), a marker of oncogenic HPV infection [13, 16].

A literature review shows significant fluctuations in the HPV incidence in the oral cavity and pharyngeal diseases, which range from 0 to 100% in different studies. For example, a comprehensive analysis of 60 studies conducted in different regions of the world showed that more than 25% of malignant head and neck tumors are associated with HPV infection [16, 17].

EBV associated with RNG (???) is diagnosed by detecting specific antibodies to EBV, such as EBNA1 and VCA. PCR to detect EBV DNA in tumor tissue is also a standard diagnostic method. For HPV associated with laryngeal cancer, PCR detects HPV DNA, and immunohistochemical methods are used to find E6 and E7 proteins [18].

One of the main methods to combat HPV-related diseases is primary prevention in the form of vaccination against this virus.

A nine-valent vaccine was approved in 2014. It covers five additional HPV types (31, 33, 45, 52, and 58). In June 2020, the FDA expanded the indications for the use of this vaccine to allow its use for the prevention of OPC and other head and neck tumors. These indications were approved under an accelerated procedure based on the proven efficacy of the vaccine in preventing anogenital diseases associated with HPV. The vaccine is recommended for women and men aged 9 to 45 years. The World Health Organization states that modern HPV vaccines (types 16/18) can prevent more than 90% of HPV-induced OPC cases[2, 16, 19].

Traditional treatments for head and neck cancer include surgery, radiotherapy, and chemotherapy. However, new approaches have been developed for virus-associated tumors. HPV, including its types 16 and 18, is one of the main causes of cervical, oropharyngeal, anal, vaginal, labia, and penile cancers. The most effective method to reduce morbidity and mortality from these tumors is vaccination. The bivalent Cervarix vaccine, designed to protect against types 16 and 18, and the quadrivalent Gardasil vaccine, which protects against types 16, 18, 6, and 11, are used in medical practice. The main goal of vaccination was to prevent precancerous and cancerous changes in the cervix caused by HPV. In countries where vaccination of adolescent girls was introduced 5-10 years ago (for example, Australia and Denmark), there is a 90% decrease in HPV infection among vaccinated people, as well as a 90% decrease in genital warts and an 85% decrease in the detection rate of CIN2-3. It will take longer for vaccination to reduce the incidence of cervical cancer since the risk of developing this cancer increases 15-20 years after the onset of viral carriage. Nevertheless, the already available data confirm the high efficiency of vaccine prophylaxis [19].

The importance of HPV vaccination for our country can hardly be overestimated. Reduction of the incidence and, accordingly, mortality from such widespread tumors as cervical cancer and OPC is impossible without the use of preventive measures, one of which is vaccination. In the absence of screening programs and early diagnostics of malignant tumors associated with HPV, vaccination is an economically viable method to prevent these diseases in the Republic of Kazakhstan. Oncologists shall make every effort to include the HPV vaccine in the national vaccination schedule.

Conclusion: EBV and HPV play key roles in the pathogenesis of RG, but their mechanisms of action and clinical outcomes differ. EBV is more often associated with nasopharyngeal cancer, and HPV is associated with OPC. The latter is more common in Western countries and has a more favorable prognosis. Future research should focus on developing more effective prevention, diagnosis, and treatment methods for these viruses.

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АҢДАТПА

ЭПШТЕЙН-БАРР ВИРУСЫНЫҢ ЖӘНЕ ЖҰТҚЫНШАҚ ҚАТЕРЛІ ІСІКПЕН БАЙЛАНЫСТЫ АДАМ ПАПИЛЛОМАВИРУСЫНЫҢ ДИАГНОСТИКАЛЫҚ ЖӘНЕ БОЛЖАМДЫҚ МАҢЫЗЫ: ӘДЕБИЕТКЕ ШОЛУ

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Сәйкестік: *Бұл Өзектілігі: Жұтқыншақтың қатерлі ісігі (ЖҚІ) – Эпштейн-Барр (ЭББ) және адам папиллома вирустарымен (АПВ) байланысты ауыз-жұтқыншақ пен мұрын-жұтқыншақ аймағындағы қатерлі ісіктер (МЖҚІ). Екі вирустың да онкогендік потенциалы бар, олар ЖҚІ патогенезіне әсер етеді.*

Халықтың 90% – астамын ЭББ жұқтырған және ол әртүрлі қатерсіз және қатерлі ауруларды тудыруы мүмкін. АПВ, әсіресе 16 және 18 типтері, ауыз-жұтқыншақ қатерлі ісігінің (АЖҚІ) негізгі онкогендік факторы болып табылады. АПВ өндіретін Е6 және Е7 ақуыздары p53 және Rb ісік супрессорларының әсерін бұзады, бұл жасушалардың бақылаусыз көбеюіне әкеледі.

ЭББ жасырын ақуыздарды белсендіреді және иммундық жауапты реттейді, ал АПВ p53 және Rb инактивациясы арқылы жасуша циклін басқаруға әсер етеді. ЭББ байланысты АЖҚІ қарағанда АПВ туындаған АЖҚІ жақсы болжамға емдеуге сезімталдығы жоғары болғандықтан ие болып саналады.

Зерттеудің мақсаты *– бас және мойын ісіктерінің ерте диагностикасы мен бастапқы алдын алу бағдарламаларын жақсарту үшін ЭББ және АПВ байланысты ЖҚІ диагностикалық және болжамдық маңыздылығын бағалау үшін әдебиет деректерін жүйелеу.*

Әдістері: *2015 жылдан бастап PubMed және MedLine дерекқорларында зерттеудің негізгі сөздері бойынша әдеби шолу жүргізілді.*

Нәтижелері: *Зерттеулер ЭББ және АПВ ЖҚІ диагностикасы мен болжауында маңызды екенін көрсетеді. Ісік жасушаларында ЭББ болуы аурудың агрессивті ағымының белгісі бола алады, бірақ кейбір жағдайларда емдеудің жақсы нәтижелерімен де байланысты. Емделушілердегі АПВ оң ісіктері мен АПВ теріс ісіктері жағдайлармен салыстырғанда оң ісіктері жақсы болжамдар және емдеуге қолайлы жауап береді. Екі вирус та ЖҚІ патогенезінде маңызды рөл атқарады және олардың диагностикасы мен сипаттамасы емдеу тактикасына және аурудың нәтижесін болжауға айтарлықтай әсер етуі мүмкін.*

Қорытынды: *ЭБВ және АПВ ЖҚІ патогенезінде шешуші рөл атқарады, бірақ олардың әсер ету механизмдері мен клиникалық нәтижелері әртүрлі. ЭБВ көбінесе МЖҚІ — мен, ал АПВ АЖҚІ-мен байланысты, соңғысы батыс елдерінде жиі кездеседі және қолайлы болжамды көрсетеді. Болашақ зерттеулер осы вирустардың алдын-алу, диагностикалау және емдеудің тиімді әдістерін жасауға бағытталуы керек.*

Түйінді сөздер: *Эпштейн-Барр вирусы (ЭБВ), адам папилломавирусы (АПВ), жұтқыншақ қатерлі ісігі, диагностика.*

АННОТАЦИЯ

ДИАГНОСТИЧЕСКАЯ И ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ВИРУСА ЭПШТЕЙНА-БАРР И ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА, АССОЦИИРОВАННЫХ С РАКОМ ГЛОТКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак глотки (РГ) представляет собой злокачественные новообразования в области ротоглотки и носоглотки, которые имеют связь с вирусами Эпштейна-Барр (ВЭБ) и папилломы человека (ВПЧ). Оба вируса обладают онкогенным потенциалом, влияя на патогенез РГ.*

ВЭБ, которым инфицировано более 90% населения, может вызывать различные доброкачественные и злокачественные заболевания. ВПЧ, особенно типы 16 и 18, является основным онкогенным фактором рака ротоглотки (РРГ). Белки Е6 и Е7, продуцируемые ВПЧ, нарушают действие супрессоров опухолей p53 и Rb, что приводит к бесконтрольной пролиферации клеток.

ВЭБ активизирует латентные белки и регулирует иммунный ответ, тогда как ВПЧ влияет на контроль клеточного цикла через инактивацию p53 и Rb. РРГ, вызванный ВПЧ, имеет лучший прогноз по сравнению с раком, ассоциированным с ВЭБ, из-за более высокой чувствительности к лечению.

Цель исследования *– систематизация данных литературы для оценки диагностической и прогностической значимости ВЭБ и ВПЧ, связанных с РГ, для улучшения программ ранней диагностики и первичной профилактики опухолей головы и шеи.*

Методы: *Проведен литературный обзор по ключевым словам исследования в базах данных PubMed и MedLine с 2015 года.*

Результаты: *Исследования показывают, что ВЭБ и ВПЧ имеют важное значение диагностике и в прогнозировании РГ. Наличие ВЭБ в опухолевых клетках может служить маркером более агрессивного течения болезни, однако в некоторых случаях ассоциируется с лучшими результатами лечения. Пациенты с ВПЧ-положительными опухолями имеют лучшие прогнозы и более благоприятный ответ на лечение по сравнению с ВПЧ-отрицательными случаями. Оба вируса играют важную роль в патогенезе РГ, и их диагностика и характеристика могут существенно повлиять на тактику лечения и прогнозирование исхода заболевания.*

Заключение: *ВЭБ и ВПЧ играют ключевую роль в патогенезе РГ, однако их механизмы действия и клинические исходы различаются. ВЭБ чаще ассоциируется с РНГ, а ВПЧ – с РРГ, причем последний чаще встречается в западных странах и демонстрирует более благоприятный прогноз. Будущие исследования должны быть направлены на разработку более эффективных методов профилактики, диагностики и лечения этих вирусов.*

Ключевые слова: *вирус Эпштейна-Барр (ВЭБ), вирус папилломы человека (ВПЧ), рак глотки, диагностика.*

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