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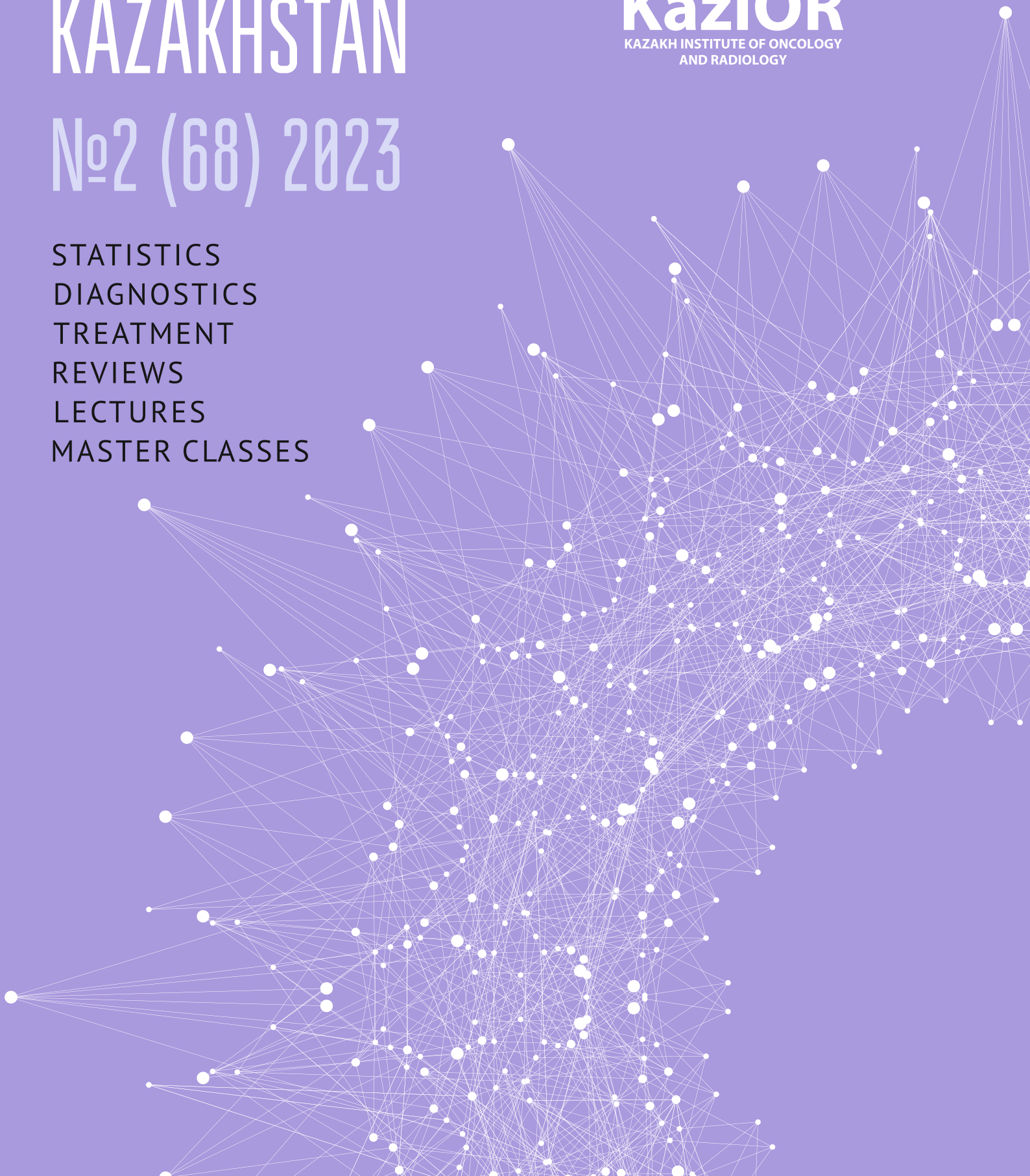

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Contents

Dear readers!

Let's welcome mid-summer – and the next issue of the "Oncology and Radiology of Kazakhstan" journal!

We are pleased to announce that due to the well-coordinated work of the editorial board and reviewers and thanks to your publications, our Journal remains on the Committee for Quality Assurance in the Sphere of Education and Science MES RK list. Your scientific findings, clinical cases, and practical experience meet the MES RK requirements for improving the quality of publications. One requirement we meet is an increased number of articles from authors not affiliated with the editorial office. Several articles on this issue were prepared in collaboration with our colleagues from regional cancer care institutions and neighboring countries.

International experience in applying pediatric early warning signs (PEWS) for critical conditions in oncological children will be of interest to pediatric oncologists.

Articles on the results of joint targeted programs on the study of genetic mutations in benign and malignant breast diseases, double-stranded breaks and repairs in acute leukemia, and the analysis of cervical cancer incidence and mortality in Almaty in 2005-2022, as a result of screening programs introduction, are noteworthy.

The prognostic value of liquid biopsy in CRC is analyzed, and the effectiveness of neoadjuvant chemotherapy in breast cancer is assessed.

The description of developing and implementing a quality control program on a linear accelerator is relevant in the context of providing Kazakhstani regional dispensaries with new high-tech equipment.

The prospects for improving the diagnostics of advanced non-small cell lung cancer by introducing ROS1 testing in Kazakhstan and using DWI capacity in prostate cancer diagnosing are encouraging.

We wish our readers and authors great success, new creative ideas, and inspiration for new research!

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

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DEVELOPING AND IMPLEMENTING THE QUALITY CONTROL PROGRAM ON A LINEAR ACCELERATOR

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ABSTRACT

Relevance: *The article deals with modern problems in the field of ensuring the quality of services provided on linear accelerators from the point of view of the regulatory framework, as well as from the point of view of the frequency of control procedures. The scientific novelty lies in elaborating a linear accelerator quality control program with detailed procedure descriptions and testing frequency recommendations.*

The study aimed to *develop and test a set of simple methods for controlling the linear accelerator's mechanical and dosimetric parameters, which would meet the minimum requirements for high-tech radiation therapy following IAEA and AAPM international recommendations.*

Methods: *In developing the quality control program for the TrueBeamSTx linear accelerator (Varian, USA) installed at the Almaty Oncological Center (AOC, Kazakhstan), we relied on the recommendations of the International Atomic Energy Agency (IAEA) and the American Association of Physicists in Medicine (AAPM), taking into account that intensity-modulated radiotherapy (IMRT, VMAT), stereotactic radiosurgery and stereotactic radiotherapy (SRS, SRT), using image-guided radiation therapy (IGRT) will be performed on the accelerator, which imposes more stringent requirements for control of both mechanical and dosimetry characteristics.*

Results: *Over three years of operation, the TrueBeamSTx accelerator shows good stability of mechanical and dosimetric characteristics, verified using systematic tests according to the quality control program developed by the authors of this article. The IAEA/WHO mail dose monitoring program using radiophotoluminescent detectors, implemented in 2019-2022, showed high dosimetric measurements and calculations accuracy of 0.1-1.7%, at a tolerance of 5%.*

Conclusion: *A quality control program for a high-energy linear accelerator has been developed; the results obtained for all characteristics correspond to the permissible values. The effective and safe use of radiotherapy requires the development of a quality control program for all radiotherapy equipment specifically for each institution and independent verification of the implementation of this program.*

Keywords: *radiation therapy, linear accelerator, quality control, dosimetric equipment.*

Introduction: One of the most important components of the radiotherapy quality assurance program is the control of the physical and technical parameters of the equipment used. According to the generally accepted recommendations of the International Commission on Radiation Units and Measurements (ICRU) [1], in radiation therapy, the dose delivered to the patient should be within ± 5% of the prescribed dose. Each stage of radiation therapy must be performed with an error of less than 5%.

The dosimetric and mechanical characteristics of the radiation device must ensure the accurate implementation of the calculated dosimetric plan for radiation treatment for each patient. A quality control program is required for each radiotherapy device to ensure periodic monitoring of the mechanical and dosimetric characteristics of the device that affect the accuracy of dose delivery to the focus. There are many valid international recommendations for periodic monitoring of radiation therapy devices' mechanical and dosimetric characteristics, including linear accelerators [2, 3]. However, they are just recommendations that must be adapted to the specific device and institution that conducts radiation therapy, the radiation treatment methods used, and the available dosimetric and other auxiliary equipment. The quality control program is based on the data obtained during the beam apparatus acceptance and preparation for clinical operation (commissioning). This data is specific for each type of apparatus and dosimetric planning system. Developing a quality control program is among the most important responsibilities of medical physicists in a radiation therapy department.

Gaps in the existing regulatory framework of providing oncological care to patients in the Republic of Kazakhstan were identified, and ways to correct them were described in terms of ensuring the quality provision of high-tech radiation therapy services at linear accelerators. Effective and safe delivery of radiotherapy requires the development of a quality control program for all types of radiotherapy equipment specific to each institution and independent verification of the implementation of this program.

The study aimed to develop and test a set of simple methods for controlling the linear accelerator's mechanical and dosimetric parameters, which would meet

the minimum requirements for high-tech radiation therapy following IAEA and AAPM international recommendations.

Materials and methods: When developing a quality control program for the TrueBeamSTx linear accelerator (Varian, CA, USA) installed in the Almaty Cancer Center (Kazakhstan), we relied on the recommendations of the International Atomic Energy Agency (IAEA) [2] and the American Society of Medical Physicists (American Association of Medical Physicists). Physicists in Medicine, AAPM) [3-5], taking into account that the accelerator will perform radiation therapy with intensity modulation (IMRT, VMAT), stereotactic radiosurgery, and stereotactic radiotherapy (SRS, SRT) using image guidance (IGRT), which imposes more stringent requirements for the control of both mechanical and dosimetric characteristics. Dosimetry equipment from IBA- Dosimetry (Schwarzenbrück, Germany), as well as phantoms and accessories supplied with the accelerator and quality control plans embedded in the accelerator software, allow performing many, but not all, of the necessary tests, so some additional equipment such as Iso-Align device (CIVCO, USA) and RTQA2 radiochromic film (Gafchromic, NJ, USA).

The protocols of all dosimetric and mechanical tests are kept according to the quality control program developed by the authors of this article and approved by the head of the AOC. Statistics are kept of all measurements taken with an analysis of deviations from the baseline data.

Results: In creating a quality control program, the methods for performing some tests had to be developed independently since sufficiently detailed information was not always available in the literature. We set the frequency of tests in such a way as to provide the necessary control procedures in a short time due to the large therapeutic load of the device, as well as taking into account the available dosimetric equipment. So, it is necessary to check several characteristics of the accelerator daily before the start of medical work, such as the accuracy of the light field dimensions, the accuracy of lasers and the optical rangefinder, the constancy of the radiation output of each beam (the TrueBeamSTx accelerator has six photon beams: 4, 6, 10, 15 MV and beams 6 and 10 MV with high dose rate without equalizing filter). The Machine Performance Check (MPC) program included in the TrueBeam accelerator software, using a special IsoCal phantom, allows you to check the main geometric and radiation characteristics in 30 minutes.

Over three years of operation, the TrueBeamSTx accelerator shows good mechanical and dosimetric stability, verified using systematic tests according to the quality control program developed in the Radiation Therapy Department of the AOC. Participation in the IAEA/WHO mail dose monitoring program using radiophotoluminescent detectors in 2019-2022. showed high dosimetric measurements and calculations accuracy of 0.1 -1.7%, at a tolerance of 5% [6] (Table 1).

Table 1 – Results of daily monitoring of geometric and radiation characteristics according to the Machine Performance Check (MPC) program for the period 2019-2022

Characteristic	Tolerance for MRS	Average actual value
Gantry position	0.3°	0.23
Collimator position	0.5°	0.13
The position of the petals of a multi-leaf collimator	0.5 mm	0.25
Treatment table position longitudinal transverse vertical turn	 0.7mm 0.7mm 1.9 mm 0.4°	 0.17mm 0.12 mm 0.07 mm 0.06°
Radiation output constancy	2%	0.65%
Beam uniformity	2%	0.35%
Isocenter position of MV imaging Position of the isocenter of KV imaging	0.5 mm 0.5 mm	0.19 mm 0.23 mm

After several months of daily MRS performance, we were convinced of the stability of all controlled characteristics and reduced the frequency of this test to three times a week. However, since it is unacceptable to rely on only one method of control, weekly, we check the mechanical and dosimetric characteristics using the StarTrack detector array, control the constancy of the radiation output, energy, symmetry, and uniformity of the beams, as well as the accuracy of lasers, rangefinder, light field dimensions.

We perform monthly verification of the radiation yield of photon beams by taking measurements using an ionization chamber in a water phantom according to the IAEA dosimetric protocol TRS-398 [7]. The beam is calibrated if the dose rate deviation at the maximum depth exceeds 1% of the required value (1 cGy per 1 monitor unit).

Dose distributions and beam profiles are monitored quarterly on a beam scanning system with a large water phantom Blue Phantom 2. Quarterly, the coincidence of the radiation and mechanical isocenters of the accelerator is checked using radiochromic film RTQA2, Ashland (Starshot test). The analysis is carried out using the IsoCheck program. The discrepancy is always less than 1 mm, which meets the stereotaxis tolerance.

The annual control also includes checking the stability of the dependence of the radiation output on the field size (output factors), coefficients of all dynamic wedges, linearity, and constancy of output of monitor units. Over three years of operation of the TrueBeamSTx accelerator, our measurements have shown the high stability of these characteristics (Table 2).

Table 2 – Stability of dosimetric characteristics of photon beams of the TrueBeamSTx accelerator for 2019-2022

Characteristic	Dose at the reference point	Beam energy (quality index)	Radiation output coefficients	Dynamic wedge coefficients
Discrepancy with base data	0.1-0.9%	0.1-0.6%	0.1 -0.8%	0-0.5%
Tolerance	1 %	1%	2%	2%

Intensity-modulated radiation therapy requires high patient positioning accuracy, which is achieved using the IGRT technique. The TrueBeamSTx accelerator has kilovolt X-ray (imaging, fluoroscopy, and cone beam computed tomography) and megavoltage (portal imaging) imaging systems. Portal dosimetry using the EPID megavoltage imaging system is also used to verify intensity-modulated dosimetric treatment plans. Therefore, the accuracy of imaging systems requires systematic monitoring. Varian accelerators have calibration programs for all modes of visualization systems (PVA Calibration). These calibrations are performed monthly after the calibration of the radiation output (absolute dosimetry). However, because stereotaxic therapy requires higher accuracy, we began to calibrate and verify the isocenter weekly (i.e., checking if the imaging system isocenter matches the accelerator isocenter accurately enough). The weekly discrepancy does not exceed 0.2 cm; after calibration and verification, it does not exceed 0.02 cm. Since stereotaxic radiosurgery requires alignment of the imaging isocenters and the device within 1 mm, we perform additional calibration and verification before each SRS session.

The accuracy of the treatment table movement through the images is checked weekly using a cubic plastic phantom with a contrasting ball in the center (Cubic Phantom). Positioning correction based on CBCT images is performed with an accuracy of less than 1 mm.

Based on the recommendations of AARM [4], we developed tests to control megavoltage and kilovoltage imaging systems using phantoms CatPhan 604, Las Vegas phantom, and Leeds TOR 18FG, performed twice a year. Controlled characteristics include scaling, spatial resolution, contrast, image uniformity and noise, and consistency of Hounsfield units for CBCT images.

The quality control program also includes tests for the multileaf collimator (MLC). These are weekly checks of petal positioning accuracy and position reproducibility in static mode (test plans are available in the accelerator software), as well as tests to check the MLC in dynamic mode, which are carried out according to the plans and analysis methods developed by Varian for all types of MLC. Once a year, the conformity of the light and radiation fields created by the MLC is checked using radiochromic film RTQA2, and the dosimetric gap and the transmittance of the MLC are measured.

Measurements of dosimetric characteristics are carried out after performing checks on mechanical parameters. Most mechanical tests (checking the position of the isocenter, the accuracy of the gantry, collimator, and treatment table movements, the position of the collimator shutters, optical rangefinder readings, etc.) are conveniently and quickly performed using the Iso-Align device, CIRS (multipurpose device for precise alignment).

Since quarterly and yearly measurements take a long time, we take them in the evenings and on weekends so as not to stop the patient's treatment process.

Discussion: Systematic testing of the performance of the radiotherapy machine is essential to ensure the accuracy and effectiveness of radiotherapy. This is a complex consisting of daily, weekly, monthly, quarterly, and annual checks, and they should be carried out by physicists and engineers of the radiation therapy department, as established by the "Standard for the Provision of Oncological Care to the Population of the Republic of Kazakhstan," paragraph 2, p. 79 [8], which is in line with international practice. This is a necessary and obligatory aspect of the use of medical particle accelerators, for which a license is issued by the Committee for Nuclear and Energy Supervision and Control of the Republic of Kazakhstan (RK) ("Handling devices and installations generating ionizing radiation"). Unfortunately, at present, permission to conduct operations to control the quality of the operation of sources of ionizing radiation, as well as instruments, equipment, and installations containing such sources or generating ionizing radiation, is issued by a license for the provision of services in the field of the use of atomic energy. This is done by analogy with the control of operational parameters of X-ray diagnostic devices, the annual conduct of which is regulated by the "Sanitary and epidemiological requirements for radiation-hazardous objects" [9], without taking into account the difference in quality control for X-ray diagnostic devices and medical accelerators. If it is sufficient for X-ray diagnostics to monitor the performance once a year, this may not be

enough for radiotherapy devices. Due to this approach, the quality control program implemented by the physicists and engineers of the clinic is not taken into account when issuing licenses. It is necessary to make adjustments to the regulations of the Ministry of Health of the Republic of Kazakhstan and the Committee for Nuclear and Energy Supervision and Control of the Ministry of Energy of the Republic of Kazakhstan and include the Quality Control Program in the set of documents for issuing a license to handle devices and installations that generate ionizing radiation. Unfortunately, not all radiation therapy departments of medical institutions of the Republic of Kazakhstan have and implement quality control programs that include all the necessary aspects and meet the current requirements. We believe independent control could be carried out by an expert group of qualified specialists, physicists, and engineers, approved by the Ministry of Health of the Republic of Kazakhstan. The experts included in this group would systematically conduct such checks and assist hospital professionals in establishing quality control programs and developing test methods to improve radiotherapy delivery accuracy. To ensure the quality and safety of radiotherapy, it is very important to independently control the performance of dosimetric measurements and other procedures included in the quality control program of the radiotherapy device [10].

Conclusion: We have developed a quality control program for a high-energy linear accelerator, the results of which correspond to the permissible values in all characteristics. For the effective and safe use of radiotherapy, it is necessary to develop a quality control program for all types of radiotherapy equipment specific to each institution and independently verify the implementation of this program.

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АҢДАТПА

СЫЗЫҚТЫҚ ҮДЕТКІШТІҢ САПАСЫН БАҚЫЛАУ БАҒДАРЛАМАСЫН ҚҰРУ ЖӘНЕ ОРЫНДАУ

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Өзектілігі: *Мақалада көрсетілетін қызметтердің сапасын қамтамасыз ету саласындағы заманауи проблемалар нормативтік-құқықтық база тұрғысынан қарастырылған, сондай-ақ сызықтық үдеткіштерде-тексеру процедураларының жиілігі бойынша бақылау. Ғылыми жаңалық процедуралардың өзін егжей-тегжейлі сипаттайтын және сынақтардың жиілігі бойынша ұсыныстары бар желілік үдеткіштің сапасын бақылау бағдарламасын әзірлеуде жатыр.*

Зерттеудің мақсаты *– құрылғының механикалық және дозиметриялық параметрлерін бақылаудың қарапайым әдістерінің кешенін әзірлеу және сынау, бірақ олар халықаралық ұсынымдарға сәйкес жоғары технологиялық сәулелік терапияға қойылатын минималды талаптарға жауап береді. Атом энергиясы жөніндегі халықаралық агенттік (МАГАТЭ) және Американдық медициналық физиктер қоғамы (AAPM).*

Әдістері: *Алматыдағы онкологиялық орталықта (Қазақстан) орнатылған TrueBeamSTx сызықтық үдеткішінің (Varian, АҚШ) сапасын бақылау бағдарламасын жасау кезінде біз МАГАТЭ және AAPM ұсыныстарына сүйендік. Үдеткіш интенсивтік модуляцияланған сәулелік терапияны (IMRT, VMAT), стереотактикалық радиохирургияны және кескінді басқаратын стереотаксикалық сәулелік терапияны (SRS, SRT) орындайды.*

Механикалық және дозиметриялық сипаттамаларды бақылауға қатаң талаптар қойылады.

Нәтижелер: *Үш жылдық жұмыс кезеңінде TrueBeamSTx үдеткіші механикалық және дозиметриялық сипаттамалардың жақсы тұрақтылығын көрсетеді, ол мақала авторлары әзірлеген жүйелі сынақтар арқылы тексерілді. Сапасын бақылау бағдарламасы 2019-2022 жж. радиофотолюминесцентті детекторларды пайдалана отырып, МАГАТЭ/ӘДҰ пошта дозасын бақылау бағдарламасына қатысу. дозиметриялық өлшеулер мен есептеулердің жоғары дәлдігін көрсетті: 0,1-1,7% рұқсат етілген 5%.*

Қорытынды: *Жоғары энергиялық сызықтық үдеткішке сапасын бақылау бағдарламасы әзірленді; барлық сипаттамалар бойынша алынған нәтижелер рұқсат етілген мәндерге сәйкес келеді. Сәулелік терапияны тиімді және қауіпсіз қолдану үшін сәулелік терапия жабдықтарының барлық түрлерінің сапасын бақылау бағдарламасын әзірлеу қажет. әрбір мекемеге тән, сондай-ақ осы бағдарламаның орындалуын тәуелсіз тексеру*

Түйін сөздер: *сәулелік терапия, сызықтық үдеткіш, сапаны бақылау, дозиметриялық жабдықтар.*

АННОТАЦИЯ

СОЗДАНИЕ И ВЫПОЛНЕНИЕ ПРОГРАММЫ КОНТРОЛЯ КАЧЕСТВА ЛИНЕЙНОГО УСКОРИТЕЛЯ

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Актуальность: *В статье рассматриваются современные проблемы в области обеспечения качества проводимых услуг на линейных ускорителях с точки зрения нормативно-правовой базы, а также с точки зрения частоты проведения процедур контроля. Научная новизна заключается в разработке программы контроля качества линейного ускорителя с подробным описанием самих процедур и с рекомендациями по частоте проведения тестов.*

Цель исследования *– разработка и апробация набора достаточно простых методик контроля механических и дозиметрических параметров аппарата, которые, тем не менее, соответствовали бы минимальным требованиям для проведения высокотехнологичной лучевой терапии согласно международным рекомендациям Международного агентства по атомной энергии (МАГАТЭ) и Американского общества медицинских физиков (AAPM).*

Методы: *При разработке программы контроля качества для линейного ускорителя TrueBeamSTx (Varian, США), установленного в Алматинском онкологическом центре (Казахстан), мы опирались на рекомендации МАГАТЭ и AAPM с учетом того, что на ускорителе будет выполняться лучевая терапия с модуляцией интенсивности (IMRT, VMAT), стереотаксическая радиохирургия и стереотаксическая лучевая терапия (SRS, SRT) с использованием контроля по изображениям (IGRT), что предъявляет более жесткие требования к контролю как механических, так и дозиметрических характеристик.*

Результаты: *За трехлетний период эксплуатации ускоритель TrueBeamSTx показывает хорошую стабильность механических и дозиметрических характеристик, что проверяется с помощью систематических тестов по разработанной авторами статьи программе контроля качества. Участие в программе почтового контроля доз МАГАТЭ/ВОЗ с помощью радиофотолюминесцентных детекторов в 2019-2022 гг. показало высокую точность дозиметрических измерений и расчетов: 0,1-1,7% при допуске 5%.*

Заключение: *Была разработана программа контроля качества для высокоэнергетического линейного ускорителя; полученные результаты по всем характеристикам соответствуют допустимым значениям. Для эффективного и безопасного использования лучевой терапии необходима разработка программы контроля качества, для всех видов оборудования лучевой терапии конкретно для каждого учреждения, а также независимая проверка выполнения этой программы.*

Ключевые слова: *лучевая терапия, линейный ускоритель, контроль качества, дозиметрическое оборудование.*

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CERVICAL CANCER INCIDENCE AND MORTALITY IN ALMATY IN 2005-2022

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ABSTRACT

Relevance: *In Kazakhstan, the standardized incidence rate of cervical cancer for 2022 was 19 per 100,000 women, and the mortality rate was 5.9 per 100,000 female population. The overall survival of cervical cancer in the Republic of Kazakhstan for 2022 was 59.6% (95% CI: 50.7-54.2). Since 2008, in Kazakhstan, there has been a National Screening Program for cervical cancer for women from 30 to 70 years old with an interval of 4 years. Almaty is the largest city in Kazakhstan, with a high incidence and mortality from all types of cancer.*

The study aimed to *analyze the cervical cancer incidence and mortality in Almaty in 2005-2022.*

Methods: *Epidemiological analysis of cervical cancer incidence in Almaty for 2005-2022 was provided with analyzing reporting forms of documentation. Statistical processing was carried out using the SPSS v. 23.0 software.*

Results: *Over the past 18 years (2005 to 2022), there has been an increase in the incidence rate from 16 to 18.3 per 100,000 female population and a consistently high mortality rate, which was 6.6 per 100,000 female population in 2022. In 2005, 108 women with cervi-cal cancer were identified, of which 70% were patients with the first and second stages. In 2022, 198 cases of cervical cancer were regis-tered, where the first stage accounts for 56.5%. In recent years, there has been an increase in the frequency of registration of new cases of cervical cancer starting from 30-34 years old, with a noticeable increase up to 40-44 years old.*

Conclusion: *The results of this epidemiological study of cervical cancer incidence and mortality in Almaty indicate the need to improve and intensify screening among women of reproductive age, and introduce a vaccination and screening program using HPV testing.*

Keywords: *cervical cancer, incidence, mortality, Almaty.*

Introduction: To date, cervical cancer is among socially significant problems worldwide and one of the leading causes of mortality among socially active women aged 40-50 years in developing countries. According to Globocan 2020, malignant neoplasms (MNs) of the cervix rank fourth among female cancer and seventh among all cancers. In 2020, 604,000 new cases of cervical cancer were identified. More than 85% of cervical cancer cases are detected in developing countries, and a third are diagnosed at an advanced stage [1]. The existing primary prevention methods impact the dynamics of cervical cancer development; there is a global downward tendency, though some countries still demonstrate increasing morbidity from cervical MNs [1].

In Kazakhstan, cervical cancer is the most common malignant tumor, second oncological disease in women, and fifth among all MNs. The National Cancer Registry reports an increase in morbidity and consistently high mortality from this pathology despite the implemented screening program [2-5].

The National Screening Program for cervical cancer has been implemented in Kazakhstan since 2008 under the Order of the Minister of Health of the Republic of Kazakhstan (RK) No. 607, dated October 15, 2007, "On improving preventive examinations of certain categories of the adult population." This screening program utilizes the Bethesda system of detecting and evaluating cervical cytology in Papanicolaou smears [5]. In 2008, women aged 35-60 years were subject to screening. However, since 2011 the age range was expanded from 30 to 60 years, and liquid cytology was also introduced. Noteworthy, at the initial stage of the cervical cancer screening program implementation, the focus was on public coverage, not the screening quality. Target coverage of cervical cancer screening in the regions of Kazakhstan reached 72% [5]. According to the Order of the Minister of Health of the RK dated January 10, 2014, No. 16 "On amendments and additions to the Order of the Ministry of Health of the RK dated August 12, 2011, No. 540 "On approval of the Regulations on the activities of healthcare organizations providing oncological care to the population of the Republic of Kazakhstan," an average prognostic coverage of the target group is to be at least 70%. However, according to the Ministry of Health of the RK report for 2015, the target coverage of cervical cancer screening in the RK was about 50%. This indicated the lack of popularity of cervical cancer screening among the population [6].

Considering this indicator, the Ministry of Health, together with "Kazakh Institute of Oncology and Radiology"

JSC, initiated an audit of the existing screening program by WHO Impact Mission experts. The review resulted in updating the screening program to increase screening coverage and treatment of precancerous pathologies [7]. The National Screening Program for Cervical Cancer in the RK now provides for a free cytological examination every four years of all women aged 30 to 70 [7, 8].

Despite an intensive implementation and improvement of cervical cancer screening, early diagnostics of cervical cancer remains an issue in the RK due to the conceptually outdated screening methods. Many countries have proven the effectiveness of HPV tests as a screening tool for cervical cancer.

Almaty is the biggest city in Kazakhstan, with a population of over 2 million. Women aged 30 to 60 accomplish more than 20% of the city population. As of 2023, 48 primary health care polyclinics carry out cervical cancer screening in Almaty. The "Almaty Oncological Center" MSE on REM monitors the screening program implementation.

The chosen screening strategy shall be medically, socially, and economically efficient [9]. The screening program analysis and assessment are the main tasks of public health to evaluate the screening effectiveness and the relevance of financial investments and optimize the health care resource planning.

The study aimed to analyze the cervical cancer morbidity and mortality in Almaty in 2005-2022.

Materials and Methods: The dynamics and structure of morbidity and mortality from cervical cancer in Almaty over the past 18 years (2005-2022) were analyzed using the main accounting and reporting forms of documents. The object of the study was 2,462 women first diagnosed with cervical cancer in 2005-2022.

The materials for epidemiological analysis included:

1. International Classification of Diseases, revision 10 (ICD-10), by localization;

2. Updated official reports of regional oncological dispensaries – "Report on MNs" (registration form No. 7) in the RK territory in 2005-2022;

3. Medical records of patients first diagnosed with MNs (registration form No. 090/U);

4. Data of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan on the size, sex, and age composition of the population by oblasts and regions of the RK for 2005-2022;

5. Form No. 030-6/U "Control card of dispensary observation";

6. Data from the National Cancer Register (Electronic Register of Cancer Patients) on MNs and cervical cancer;

7. Data from the National Center for Healthy Lifestyle Formation reports on the results of screening surveys of the RK population target groups in 2005-2022.

The epidemiological study of morbidity and mortality from cervical cancer in the RK utilized the descriptive and analytical methods of modern cancer epidemiology [10]. The cervical cancer morbidity and mortality indicators were calculated using generally accepted sanitary statistics methodology. The morbidity presented in absolute figures shows the number of cases registered per 100,000 female population in a year. The population distribution is standardized by the World Standard (World) to eliminate age differences in the compared populations. The IARC-recommended methodology [11] was used to calculate standardized indicators.

Results: Crude intensive morbidity of cervical cancer shows an increase in detecting this disease in 2005-2022 (Figure 1). The morbidity amounted to 16 per 100,000 females in 2005 vs. 18.3 per 100,000 females in 2022. A peak morbidity of 28.7 per 100,000 females was registered in 2017. The National Cancer Register reported 198 cases of cervical cancer in 2022 in Almaty.

A sharp increase in cervical cancer morbidity was associated with increased detection due to the introduction of screening.

The mortality from cervical cancer increased in the analyzed period from 42 deaths registered in 2005 (the mortality rate – 5.5 per 100,000 females) to 72 deaths in 2022 (the mortality rate – 7.2 per 100,000 females) (Figure 1).

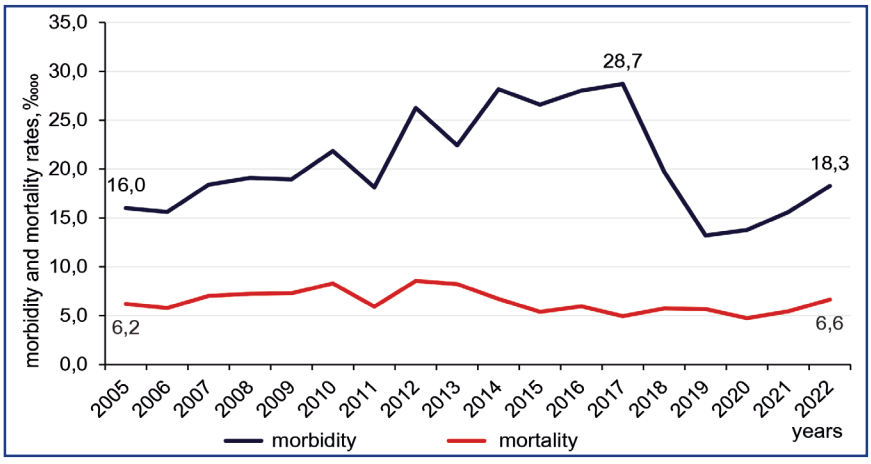

Figure 1 – Trends in intensive morbidity and mortality from cervical neoplasms per 100,000 females in 2005-2022

Age-dependent indicators of new cervical cancer cases showed that the number of cases registered at a younger age increased in 2022 vs. 2005 (Figure 2). The peak morbidity shift towards cervical cancer rejuvenation confirms the need to improve and strengthen screening among young and middle-aged women.

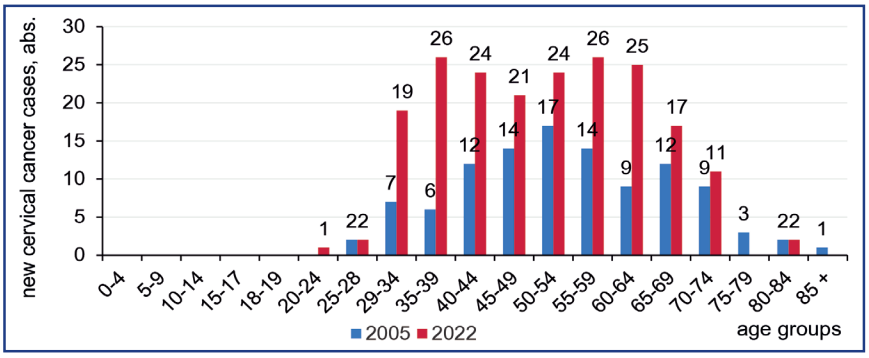

Figure 2 – New cervical cancer cases, by age, 2005 vs. 2022, abs.

Cervical cancer statistics by stage indicated an increase in early detection from 2005 to 2022 (Figures 3, 4). Thus, out of 108 women registered with cervical cancer in 2005, 70% had stage I-II of the disease. In 2022, 85.4% of 198 new cases were registered at stage I-II.

Noteworthy, till 2017, stages I and II were accounted together. Since 2017, they have been separated in the National Cancer Registry. In 2022, stage I accounted for 56.5% of identified cases. A notable fourfold decrease in stage III cervical cancer detection was not accompanied by similar dynamics in advanced stage IV cancer detection.

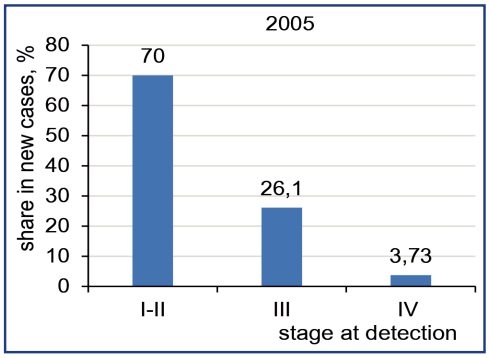

Figure 3 – Shares of stages I-II, III, and IV in new cervical cancer cases registered in Almaty, 2005 (%)

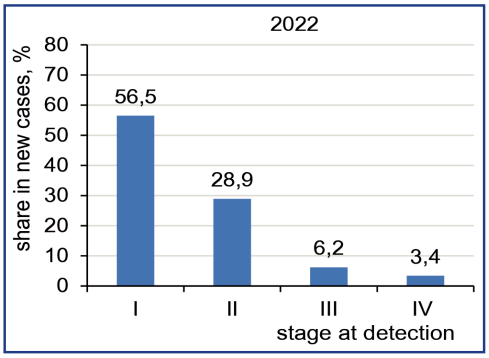

Figure 4 – Shares of stages I-IV in new cervical cancer cases registered in Almaty, 2022 (%)

Table 1 presents the main statistical indicators characterizing the state of oncological care for cervical cancer neoplasms in Almaty. In 2022, the number of new cases achieved 198, an increase of 54.4% vs. 2005. 93.2% of cases were morphologically confirmed in 2022. According to the Cancer Register for 2022, 56.5% of cases were detected at early stages, 81% – during preventive examinations. Early detection of cervical cancer notably increased in 2022 compared to 2005 due to effective screening. Nevertheless, one-year mortality remained high, at 4.32% in 2022.

The percentage of patients who required radical treatment was also high. In 2022, 93.2% of cases required radical treatment; one patient refused specialized treatment.

The number of patients on record increased in 2022 to 2,353; 68.7% were registered for five years and more.

Table 1 – Main statistical indicators for cervical cancer

Indicator	2005 г.	2022 г.
Number of new cases	108.0	198.0
Morbidity per 100,000 population (crude intensive)	16.0	18.3
Early detection (stages I and II), % of all registered cases	70.0	85.4
Early detection during preventive examinations (stages I and II), % of all new cases	30.5	81.0
Less than one-year survival among those registered in the previous year (one-year mortality, %)	4.5	4.3
Radical treatment provided (% of all new cases)	62.6	65.8
Deaths from cancer	39.0	42.0
Mortality per 100,000 population (crude intensive)	6.2	6.6
Patients registered as of the year-end	971	2353
Of them, those registered for five years and more	597	1618

Discussion: Globocan 2020 reports about 600,000 new cases of cervical cancer registered annually in the world [1]. To date, mortality from this disease remains relatively high despite the primary and secondary prevention programs and new approaches to cervical cancer treatment and diagnostics.

Cervical cancer is a visually localized tumor process with real opportunities for early diagnosis. Morbidity and mortality from cervical cancer have fallen by half in developed countries thanks to successfully organized screening. Still, a more significant decrease is expected when vaccination among girls against HPV is included in the national immunization calendar [12-15].

Increased cervical cancer morbidity in developing countries, high mortality, and one-year mortality indicate gaps in cervical cancer primary and secondary prevention, including in Kazakhstan.

In Almaty, cervical cancer ranks third in female cancer morbidity. Over the past 18 years (2005-2022), 3169 new cervical cancer cases were registered, and 984 women died from this disease. A significant share of new cases affects women of reproductive age.

The increase in cervical cancer mortality in Almaty and the RK is associated with better detection due to the introduction of cervical cancer screening.

Despite the screening aimed at early detection, the mortality from cervical cancer remains consistently high. It amounted to 6.6% in 2020 vs. 6.2% in 2005. The morbidity and mortality rates were similar in developed countries with successful screening programs before they introduced effective screening [16, 17].

In recent years, more new cervical cancer cases have been registered in patients over 30-34 years, with a noticeable increase to 40-44 years. In 2022, peak cervical cancer morbidity shifted to 40-44 years compared to 50-54 years in 2005.

The cervical cancer distribution analysis shows a noticeable increase in early detection. A twofold increase in this disease registration is due to the national screening program for cervical cancer. However, despite cytological tests during screening, late detection of cervical cancer remains at the same level. High one-year mortality and low five-year survival of patients with cervical cancer indicate actual neglect of the tumor process and imperfect actions on early detection.

Conclusion: The conducted epidemiological study of cervical cancer morbidity and mortality in Almaty evidences the need to improve and strengthen screening activities among women of reproductive age and introduce HPV vaccination and HPV tests at screening.

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АҢДАТПА

2005-2022 ЖЫЛДАРДАҒЫ АЛМАТЫ ҚАЛАСЫНДАҒЫ ЖАТЫР МОЙНЫ ОБЫРЫМЕН СЫРҚАТТАНУШЫЛЫҚ ЖӘНЕ ӨЛІМ-ЖІТІМ

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Өзектілігі: *Қазақстан Республикасында (ҚР) 2022 жылға арналған жатыр мойны обырының (ҚК) стандартталған сырқаттанушылық көрсеткіші 100 000 әйелге шаққанда 19-ды құрады, өлім-жітім деңгейі 100 000 әйел халыққа шаққанда 5,9 болды. 2022 жылға Қазақстан Республикасында жатыр мойны обырының жалпы өмір сүру деңгейі 59,6%-ды құрады (95% СИ: 50,7-54,2). 2008 жылдан бастап Қазақстан Республикасында жатыр мойны обырының Ұлттық скринингтік бағдарламасы жұмыс істейді, ол 30 жастан 70 жасқа дейінгі әйелдер арасында 4 жыл аралықпен жүргізіледі. Бүгінгі күнде Алматы қаласы, Қазақстан Республикасындағы қатерлі ісік ауруы мен өлім-жітім деңгейі жоғары қала болып қала береді.*

Зерттеудің мақсаты *– Алматы қаласы бойынша 2005-2022 жж. жатыр мойны обырынан сырқаттанушылық пен өлім-жітім динамикасын талдау.*

Әдістері: *Құжаттаманың негізгі есепке алу және есептілік нысандарын пайдалана отырып, 2005-2020 жылдар аралығында Алматы қаласы бойынша жатыр мойны обырынан сырқаттанушылық пен өлім-жітім динамикасы мен құрылымына талдау жүргізілді. Статистикалық өңдеу SPSS23.0 көмегімен жүзеге асырылады*

Нәтижелері: *Соңғы 18 жылда аурушаңдық деңгейі 100 000 әйелге шаққанда 16-дан 18,3-ке дейін өсуі және өлім-жітімнің тұрақты жоғары деңгейі байқалды, ол 2022 жылы 100 000 әйелге шаққанда 6,6 құрады. 2005 жылы жатыр мойны обырына шалдыққан 108 әйел анықталды, оның 70%-ы бірінші және екінші сатыдағы науқастар. 2022 жылы жатыр мойыны обырының 198 жағдайы тіркелді, оның бірінші сатысы 56,5% құрайды.Соңғы жылдары 30-34 жастан бастап айтарлықтай байқалатын жатыр мойны обырының жаңа жағдайларының тіркелу жиілігінің артуы байқалады. 40-44 жасқа дейін өседі. 2022 жылы жатыр мойны обырының 2005 жылмен салыстырғанда ең жоғары деңгейі «50-54 жастан» 40-44 жас тобына ауысты.*

Қорытынды: *Қазақстандағы жатыр мойны обырынан болатын аурушаңдық пен өлім-жітім көрсеткіштерін эпидемиологиялық зерттеу нәтижелері скринингті жақсарту, репродуктивті жастағы әйелдер арасында оны белсендіру, сондай-ақ HPV-ге тестілеуді қолдана отырып, вакцинация және скринингтік бағдарламаны енгізу қажеттілігін көрсетеді.*

Түйінді сөздер: *жатыр мойны обыры, аурушаңдық, өлім-жітім, Алматы.*

АННОТАЦИЯ

ПОКАЗАТЕЛИ ЗАБОЛЕВАЕМОСТИ И СМЕРТНОСТИ ОТ РАКА ШЕЙКИ МАТКИ В ГОРОДЕ АЛМАТЫ ЗА 2005-2022 гг.

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Актуальность: *В Республике Казахстан (РК) показатель стандартизованной заболеваемости раком шейки матки (РШМ) за 2022 г. составил 19 на 100 000 женщин, показатель смертности - 5,9 на 100 000 женского населения. Показатель общей выживаемости РШМ в РК за 2022 г. соответствовал 59,6% (95% ДИ:50,7-54,2). В РК с 2008 г. существует Национальная скрининговая программа РШМ, которая охватывает женщин в возрасте 30-70 лет и проводится с интервалом в 4 года. На сегодняшний день г. Алматы остается крупнейшим городом РК с высоким уровнем заболеваемости и смертности от всех видов рака.*

Цель исследования *– анализ динамики заболеваемости и смертности от РШМ в г. Алматы за 2005-2022 гг.*

Методы: *Анализ динамики и структуры заболеваемости и смертности от РШМ в г. Алматы с 2005 по 2022 гг. проведен с использованием основных форм учетно-отчетной документации. Были проанализированы сравнительные данные. Статистическая обработка проведена с помощью программного обеспечения SPSS v. 23.0.*

Результаты: *За последние 18 лет в г. Алматы отмечается рост показателя заболеваемости с 16 до 18,3 на 100 000 женского населения и стабильно высокий показатель смертности, который в 2022 г. составил 6,6 на 100 000 женского населения. В доскрининговом периоде в 2005 г. РШМ был обнаружен у 131 женщины, из них 70% составили пациентки с первой и второй стадией заболевания. В 2022 г. было зарегистрировано 198 случаев РШМ, причём на долю I-II стадии пришлось 85,4%.*

За последние годы отмечается увеличение частоты регистрации новых случаев РШМ, начиная с возраста 30-34 лет, с заметным ростом до 40-44 лет. В 2022 г. пик заболеваемости РШМ по сравнению с 2005 г. сместился с возраста 50-54 года на возрастную группу 40-44 года.

***Заключение:** Проведенное эпидемиологическое исследование заболеваемости и смертности от РШМ в г. Алматы свидетельствуют о необходимости совершенствования скрининга, его активизации среди женщин репродуктивного возраста, а также внедрения программы вакцинации и скрининга с использованием тестирования на ВПЧ.*

***Ключевые слова:** рак шейки матки (РШМ), заболеваемость, смертность, г. Алматы.*

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OPTIMIZATION OF MOLECULAR GENETIC DIAGNOSTICS OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER BY INTRODUCING ROS1 TESTING IN THE REPUBLIC OF KAZAKHSTAN

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ABSTRACT

Relevance: *Currently, molecular diagnosis in NSCLC in Kazakhstan includes detection of EGFR, ALK driver mutations status, and PD-L1-status, but not ROS1, what limits the access of patients with this driver mutation to vital therapy.*

The study aimed to *optimize the methods of molecular genetic diagnosis of patients with NSCLC by introducing ROS1 testing in the Republic of Kazakhstan.*

Methods: *The biopsy and surgical material of non-small cell lung cancer (NSCLC) fixed in 10% buffered formalin was studied. After the initial morphological diagnosis of adenocarcinoma, EGFR, and ALK mutation status determination, EGFR and ALK-negative tumor assays were sent for further determination of ROS1 mutation status. First, we performed immunohistochemistry (IHC) using the Ventana BenchMark Ultra platform using the ROS1 antibody (SP283) and the OptiView DAB Detection Kit imaging system. After that, samples with positive and doubtful IHC results were sent for reverse transcriptase polymerase chain reaction (RT-PCR) to confirm the ROS1 mutation status.*

Results: *A total of 99 tumor samples from patients with EGFR-negative and ALK-negative lung adenocarcinoma were studied by IHC from January 01 to September 30, 2022. The results of IHC staining were assessed as 0 (negative) – 59 samples, 1+ (negative) – 25 samples, 2+ (doubtful) – 12 samples, 3+ (positive) – 3 samples. Cases with ≥70% immunostaining were considered positive. Samples with an IHC stain score of 2+ (doubtful), 3+ (positive), and a few samples of 1+ were sent for confirmation by PCR.*

Overall, 22 samples were tested using RT-PCR, and results were considered as follows:1 (4%) – positive, 13 (59%) – negative, 8 (37%) – invalid.

Conclusion: *A large proportion of positive and equivocal results were obtained when determining ROS1 mutation status using IHC, and a large proportion of invalid results during subsequent RT-PCR testing. Choosing methods for nationwide ROS1 implementation, one should evaluate the economics of the methods to be implemented and compare them with a standard validated FISH method.*

Keywords: *ROS1 molecular genetic diagnostics, lung cancer (LC), non-small cell lung cancer (NSCLC), immunohistochemistry (IHC), reverse transcriptase polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH).*

Introduction: Lung cancer (LC) ranks second in incidence after breast cancer and first in cancer mortality in both sexes in the Republic of Kazakhstan (RK) over the past decades. LC incidence in men shares 20% of all cancer cases, significantly higher than in women. In 2021, 3615 new trachea, bronchi, and lung cancer cases were detected. The proportion of cases diagnosed at stages I-II was only 28%, while the proportion of advanced forms (stage IV) of trachea, bronchi, and lung cancer was 27.1 %. The LC survival rate depends on the stage of the disease at diagnosis and remains relatively low. In 2021, one-year mortality from LC in the Republic of Kazakhstan was 43.3%. In Kazakhstan, in 2021, 2,086 men and women died from LC, more than from breast, rectal, and prostate cancers combined [1]. According to Globocan estimates, in 2020 in the Republic of Kazakhstan, the primary incidence of LC was 21.8 per 100,000 population (4642 new cases), and the mortality rate was 16.7 per 100,000 population, which corresponds to 17% of all deaths from cancer [2]. The literature reports that non-small cell lung cancer (NSCLC) accounts for 80-90% of all cases of LC, while the incidence of small cell lung cancer (SCLC) has been declining over the past two decades in many countries [3]. Depending on the histological structure, NSCLC is subdivided into adenocarcinoma (most common subtype, 40-50% of NSCLC), squamous cell carcinoma (25-40% of NSCLC), large cell carcinoma (3-5% of NSCLC), adenos-

quamous (2-3% of NSCLC), and sarcomatoid (2-3% NSCLC) carcinomas [4, 5].

Fig. 1 shows the algorithm for testing patients with advanced NSCLC adopted in Kazakhstan [6].

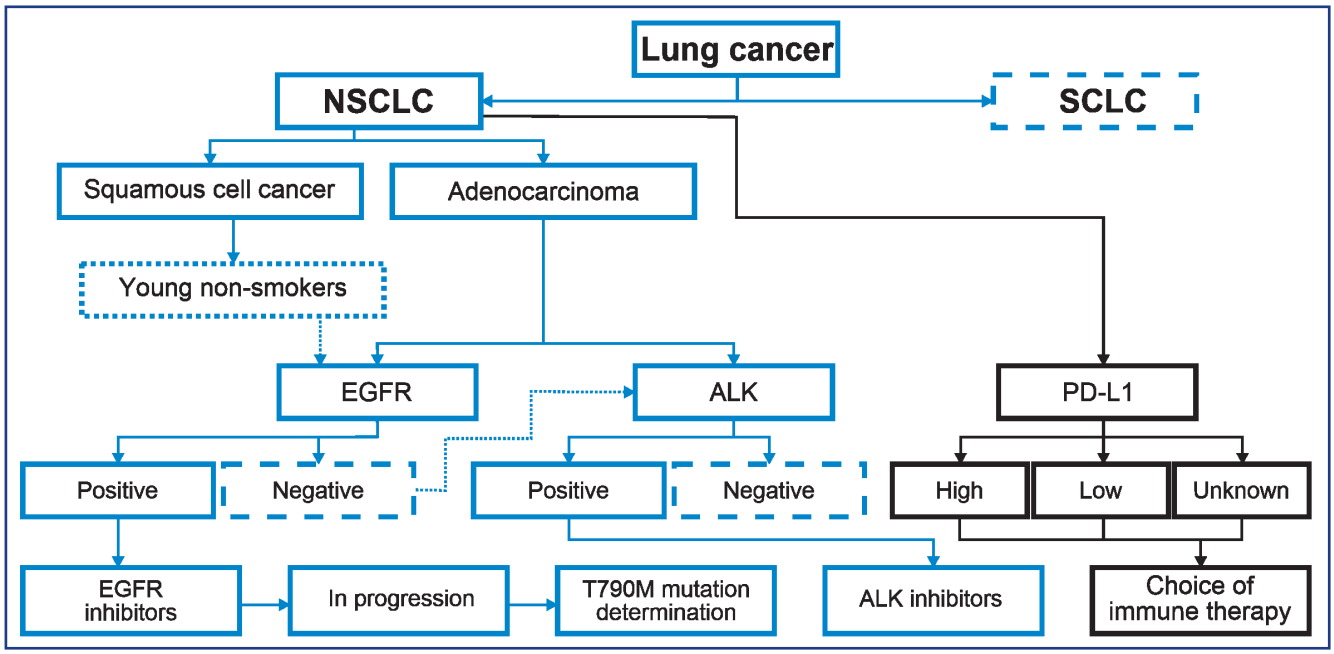

Figure 1 – Algorithm for testing patients with advanced NSCLC in Kazakhstan

Morphological diagnostics is followed by testing for biomarkers. Cancer subtype identification based on biomarker testing enables to identify patients with a high or lower probability of response to therapy to provide individualized treatment [7, 8]. Currently, the US and most European countries do mandatory testing for EGFR, ALK, and ROS1 translocation mutations, including testing for EGFR T790M mutations in disease relapse [9, 10]. Testing for ROS1 mutations was included in the updated protocol for diagnosing and treating LC in the Republic of Kazakhstan [6]. Molecular genetic tests required by the Comprehensive Cancer Control Plan for 2023-2025 in NSCLC include the detection of EGFR, ALK mutations, and PD-L1 status [11]. The project includes the determination of T790M in the progression of EGFR-positive NSCLC (liquid biopsy). Unfortunately, ROS1 mutation testing was not included in the current and previous comprehensive plans to combat oncological diseases [11, 12]. According to the Center for Morphological Studies of Kazakh Institute of Oncology and Radiology JSC (KazIOR JSC), in 2020, 1658 out of 3240 patients with newly diagnosed LC had NSCLC (adenocarcinoma), and 1161 were sampled for testing. In total, 932 patients were tested for EGFR mutation, and 167 (17.9%) were positive; 753 were tested for ALK (38 (5%) positive); 825 were tested for PD-L1 (320 (39%) positive).

ROS1 (ROS Proto-Oncogene 1) is a tyrosine kinase receptor. In NSCLC, ROS1 gene translocation leads to the formation of several oncogenic ROS1 fusion proteins with constitutive kinase activity, CD74-ROS1 the most common. ROS1 translocations are rarely combined with other oncogenic driver mutations, such as ALK translocations and activating EGFR mutations in NSCLC [13, 14]. The reported prevalence of ROS1-positive NSCLC is 1.6% in North America, about 2% in Europe, and 2.3% in Asia [15]. No data on the ROS1 mutation prevalence is currently available in Kazakhstan.

International guidelines recommend testing all patients with advanced adenocarcinoma of the lung for ROS1 mutation, regardless of the clinical symptoms [9, 10, 16]. ROS1 translocations can be detected using several methods: fluorescence in situ hybridization (FISH), RNA-based next-generation sequencing (NGS), or reverse transcriptase polymerase chain reaction (RT-PCR) [16].

FISH is a research-proven method to detect ROS1 gene translocations [9, 10, 16]. Immunohistochemistry (IHC) screening for ROS1 translocation in NSCLC may be preferable to FISH or molecular diagnostics under certain conditions due to a relatively low incidence of these mutations. However, interpreting ROS1 IHC is challenging since about one-third of tumors with no ROS1 mutation can present low-intensity spotted staining [16].

IHC can be used for prescreening; FISH or PCR is required to confirm the diagnosis [10, 16]. NGS is becoming an alternative molecular test for screening or confirming

the presence of gene fusion [16]. However, today, in most countries, NGS is not a routine practice due to its high cost, the need to accumulate multiple samples in one cycle, as well as the availability of sophisticated diagnostic equipment and well-trained personnel [17].

In this study, the ROS1 status of adenocarcinoma patients negative for EGFR, ALK mutations were determined using an alternative ROS1 diagnostic method – IHC followed by RT-PCR – due to the unavailability of FISH for ROS1 at KazIOR JSC during the project implementation.

The study aimed to optimize the methods of molecular genetic diagnosis of patients with NSCLC by introducing ROS1 testing in the Republic of Kazakhstan.

Materials and Methods: The biopsy and surgical samples of NSCLC fixed in 10% buffered formalin were studied. The tissue pieces were subjected to standard processing in a tissue processor and placed into paraffin (FFPE blocks). After initial morphological diagnostics of adenocarcinoma and testing for EGFR and ALK mutations, tumor assays negative for EGFR and ALK mutations were further tested for ROS1 mutations. Paraffin slices 3-4 μm thick were prepared on adhesive glass. First, we performed IHC analysis using the Ventana BenchMark Ultra platform using the ROS1 antibody (SP283) and the OptiView DAB Detection Kit imaging system. After that, IHC-positive or doubtful samples were subjected to RT-PCR to confirm ROS1 mutation status. RT-PCR utilized an AmoyDx ROS1 gene fusion detection kit according to the manufacturer's instructions.

The ROS1 oncogene encodes an orphan receptor tyrosine kinase associated with anaplastic lymphoma kinase (ALK) along with the insulin receptors. ALK and ROS1 synthesize the related tyrosine kinases, whose ATP-binding domains are 77% identical in amino acid composition [18]. Translocation leads to the fusion of the ROS1 part, including the entire tyrosine kinase domain, with 1 of 12 different partner proteins [19].

IHC detects known oncogenic mutations by mutation-specific antibodies in a tissue sample. The antibodies bind with an enzyme or fluorescent dye, which allows to identify the mutation-positive samples with a microscope [19].

To diagnose ROS1 translocations, we used VENTANA ROS1 (SP384) Rabbit Monoclonal Primary Antibody following the published recommendations [19]. IHC diagnostic assays to detect ROS1 utilized a BenchMark Ultra (Ventana) platform with a monoclonal antibody to ROS1 (SP284, Ventana) and the OptiView DAB Detection Kit. The assessments were made using a Leica DM1000 optical microscope. The cytoplasmic staining of type II non-tumor pneumocytes served as an internal positive control. The intensity of cytoplasmic staining of tumor cells was assessed at a magnification of 4 (x4): 0 (negative), 1+ (negative), 2+ (doubtful), and 3+ (positive). The case was considered positive at intensive staining of at least 70% of tumor cells.

RT-PCR was to confirm positive or equivocal ROS1 IHC results. This highly specific method detects the fusion of tumor RNA genes and does not detect alternative fusion partners [19].

The study was performed on a Tanlong Real-time PCR System amplifier with the following reagents in accordance with the manufacturer's instructions: Invitrogen, DNase I, and PureLinktm FEPE (Thermo Fisher Scientific, USA) – for RNA/DNA isolation, NanoDrop 2000 (Thermo Fisher Scientific, USA) – for checking the RNA/cDNA concentration by spectrophotometry, ROS1 Gene Fusions Detection Kit (AmoyDx, China) – for amplification and detection of the results.

PCR results were interpreted according to the manufacturer's instructions for the FAM and HEX/VIC detection channels:

1) For NTC: the Ct FAM values of reaction mixture 1-4 and the Ct HEX/VIC values of reaction mixture four shall be ≥31. If not, the results were considered invalid. According to the recommendation of the manufacturer, the sample should be retested.

2) For positive control: the Ct FAM values of reaction mixtures 1-4 and the Ct HEX/VIC values of reaction mixture four should be <24. If not, the result is invalid. According to the recommendation of the manufacturer, the sample should be retested.

3) Assay for the reference gene (HEX/VIC signal) in reaction mixture 4 for each sample:

a) HEX / VIC значение Ct должно быть ≤20. The HEX/VIC value of Ct should be ≤20.

b) If the HEX/VIC value of Ct is >20, it indicates the RNA degradation or precision reaction of PCR inhibitors. According to the manufacturer's recommendation, the sample should be retested or re-extracted RNA, as there could be false negative results.

4) Analysis for each sample: Ct FAM value of reaction mixtures 1-4 for each sample was recorded:

a) If the Ct FAM value of the reaction mixture 1-4 is ≥30, the sample was identified as negative (ROS1 fusion not detected) or LOD (detection limit) of the set below.

b) If any Ct FAM value of the reaction mixture 1-4 is <30, the sample was identified as positive (ROS1 fusion gene detected).

Fig. 2 shows a simplified algorithm for testing patients with NSCLC adenocarcinoma applied in this study.

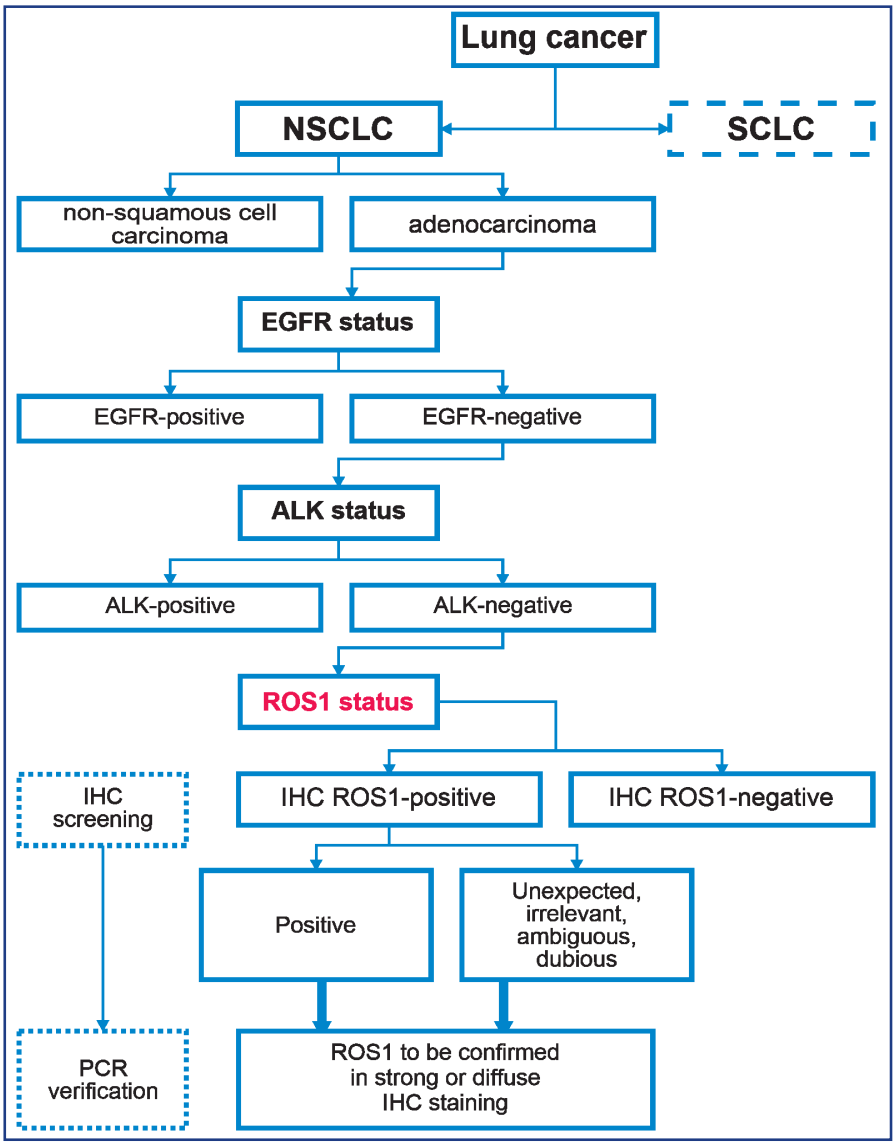

Figure 2 – Algorithm for testing patients with NSCLC adenocarcinoma

Results: A total of 99 tumor samples from patients with EGFR-negative and ALK-negative lung adenocarcinoma were studied by IHC from January 01 to September 30, 2022. The results of IHC staining were assessed as 0 (negative) – 59 samples, 1+ (negative) – 25 samples, 2+ (doubtful) – 12 samples, and 3+ (positive) – 3 samples. Cases with ≥70% immunostaining were considered positive. Samples with an IHC stain score of 2+ (doubtful), 3+ (positive), and a few samples of 1+ were sent for confirmation by PCR.

Overall, 22 samples were tested using RT-PCR at KazIOR JSC Center for Molecular Genetic Studies, and the results were considered as follows:1 (4%) – positive, 13 (59%) – negative, 8 (37%) -– invalid.

Discussion: In IHC, a large proportion of samples – 15 out of 99 samples (15%) – were found positive or equivocal. The IHC results interpretation was problematic due to many positive or equivocal results. This required additional consultations to interpret the obtained data. In some cases, heterogeneous sample staining required a FISH test to assess the tumor sites with bright and moderate staining. The aim was to identify the tumor's intrinsic heterogenicity or attribute the result to the preliminary preparation of the material.

According to RT-PCR results, 1 (4%) of 22 samples was positive, 13 (59%) – negative, and 8 (37%) were invalid. Unfortunately, a large share of invalid samples (37%) suggested a low quality of RNA isolated from FFPE blocks and inappropriate quality of the samples for PCR. The obtained results require further research for accurate conclusions.

N.I. Lindeman et al. report an IHC sensitivity of 96% (95% CI: 71-99%) and specificity of 94% (95% CI: 89-96%) compared to FISH when using D4D6 antibodies with a staining intensity of at least 2+ (as determined by studies). Due to poor IHC specificity (there is no unified assessment of IHC results, and each laboratory selects its limit for staining intensity), the authors also report

difficulties interpreting the staining intensity. However, due to IHC's high sensitivity, the tumor samples without ROS1 staining could be interpreted as negative for ROS1 translocations [16].

In a similar study, 34 111 (30.6%) samples demonstrated an immune reaction to ROS1 in IHC. However, a later FISH test revealed only 5 ROS1-positive tumors out of 34 [20]. Out of 60 samples studied by Shan L. et al., 16 (26.7%), 13 (21.7%), and 20 (33.3%) cases were found ROS1-positive by IHC, FISH, or RT-PCR, respectively [21].

In a study by T.A. Boyle et al., 33 samples were IHC-assessed for ROS1 translocations, and only six samples had a high expression of ROS1 protein. Five of them were also positive for ROS1 gene translocation in a FISH test. Twenty-seven lung cancer biopsy samples negative for ROS1 translocation in genetic testing had low or absent ROS1 protein expression. The authors proposed IHC as a practical and cost-effective ROS1 gene translocations screening method in lung cancer [22].

Although ROS1 mutations are relatively rare and found in 2-3% of lung adenocarcinomas [13-15], tumors with structural translocations involving the ROS1 gene can be successfully treated with targeted drugs. In phase I clinical trial involving 50 patients with NSCLC, a ROS1 translocation found by FISH or RT-PCR predicted a response to targeted inhibition with crizotinib of 72% and a median progression-free survival of 19.2 months [23]. Based on this study, in 2016, FDA expanded the use of crizotinib in NSCLC patients with ROS1 translocations. In a European multicenter retrospective study, 32 NSCLC patients with ROS1 translocation treated with crizotinib demonstrated an ORR of 80% and a median relapse-free survival of 9.1 months [24].

Conclusion: In this study, IHC delivered many positive or equivocal results (15 out of 99) when determining ROS1 mutation status, and subsequent RT-PCR testing revealed a large proportion of invalid results. Choosing a ROS1 detection method for nationwide use shall consider the economic component of proposed methods and compare the results with a standard validated FISH method.

In Kazakhstan, patients with lung cancer have limited access to vital molecular diagnostics to determine ROS1 mutations. Hence, it is necessary to introduce the ROS1 test based on a recommended, approved, and reliable methodology to provide personalized, targeted therapy.

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АҢДАТПА

ҚАЗАҚСТАН РЕСПУБЛИКАСЫНДА ROS1 ТЕСТІЛЕУІН ЕНГІЗУ АРҚЫЛЫ ҰСАҚ ЖАСУШАЛЫ ЕМЕС ӨКПЕНІҢ ҚАТЕРЛІ ІСІГІ БАР НАУҚАСТАРДЫ МОЛЕКУЛАЛЫҚ-ГЕНЕТИКАЛЫҚ ДИАГНОСТИКАЛАУ ӘДІСТЕРІН ОҢТАЙЛАНДЫРУ

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Өзектілігі: *Қазіргі уақытта Қазақстанда ұсақ жасушалы емес өкпенің қатерлі ісігінің (ҰЖЕӨҚІ) молекулярлық диагностикасы EGFR, ALK-дағы драйверлік мутациялардың мәртебесін және PD-L1 мәртебесін, бірақ та ROS1 емес, анықтауды қамтиды, ол осы драйверлік мутацияға оң нәтиже берген пациенттердің өмірлік маңызды терапияны алу мүмкіндігін шектейді.*

Зерттеудің мақсаты *– Қазақстан Республикасында ROS1 тестілеуін енгізу арқылы ҰЖЕӨҚІ бар науқастардың молекулалық-генетикалық диагностикасының әдістерін оңтайландыру.*

Әдістері: *ҰЖЕӨҚІ бар науқастардың 10% буферленген формалинге салынған биопсиялық және операциялық материалы зерттелді. Аденокарциноманың бастапқы патологиялық диагностикасынан кейін, EGFR және ALK мутациясының күйін анықтағаннан кейін, EGFR және ALK теріс мәртебесі бар ісік үлгілері ROS1 мутациясының мәртебесін әрі қарай анықтау үшін жіберілді. Определение статуса мутации ROS1 мутациясының мәртебесін анықтау екі әдіспен жүргізілді: Бірінші әдіс – Ventana BenchMark Ultra платформасында ROS1 антиденесін (SP283) және OptiView DAB Detection Kit визуализация жүйесін пайдалана отырып, иммуногистохимиялық талдау (ИГХ). ИГХ нәтижелері бойынша оң және күмәнді нәтижелері бар үлгілер ROS1 мутациясының мәртебесін растау сияқты екінші әдіс үшін кері транскриптазасы бар полимеразды тізбекті реакцияға (КТ-ПТР) жіберілді.*

Нәтижелері: *01.01.2022 бастап 30.09.2022 дейін ИГХ әдісімен EGFR-теріс және ALK-теріс өкпе аденокарциномасы бар науқастардан алынған жалпы 99 ісік үлгілері зерттелді. ИГХ-бояу нәтижелері былайша бағаланды: 0 (теріс) – 59 үлгі, 1+ (теріс) – 25 үлгі, 2+ (күмәнді) – 12 үлгі, 3+ (оң) – 3 үлгі. ≥70% иммундық бояуы бар жағдайлар оң деп саналды. 2+ (күмәнді), 3+ (оң) және 1+ бірнеше үлгілері ИГХ бояуын бағалауы бар үлгілер ПТР-тестілеумен растауға жіберілді.*

КТ-ПТР бойынша барлығы 22 үлгі тексерілді, нәтижесі келесідей бағаланды: 1 (4%) – оң, 13 (59%) – теріс, 8 (37%) – сәйкес емес.

Қорытынды: *ИГХ арқылы ROS1 мутациясының мәртебесін анықтау көптеген оң және күмәнді нәтижелерге әкелді, ал кейінгі КТ-ПТР тестілеуі кезінде сәйкес емес нәтижелердің үлкен бөлігі орын алды. Әрі қарай елдік деңгейде талдау жүргізу үшін ROS1 анықтау әдісін таңдаған кезде, енгізілетін әдістердің экономикалық шығындық құрамын бағалау керек, сондай-ақ FISH стандартты валидацияланған әдістememен салыстыру қажет.*

Түйінді сөздер: *ROS1 молекулалық-генетикалық диагностикасы, өкпенің қатерлі ісігі, ұсақ жасушалы емес өкпенің қатерлі ісігі (ҰЖЕӨҚІ), иммуногистохимия (ИГХ), кері транскриптазасы бар полимеразды тізбекті реакция (КТ-ПТР), in situ флуоресценттті гибридизациясы (FISH).*

АННОТАЦИЯ

ОПТИМИЗАЦИЯ МЕТОДОВ МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКОЙ ДИАГНОСТИКИ ПАЦИЕНТОВ С РАСПРОСТРАНЕННЫМ НЕМЕЛКОКЛЕТОЧНЫМ РАКОМ ЛЕГКОГО ПУТЕМ ВНЕДРЕНИЯ ТЕСТИРОВАНИЯ ROS1 В РЕСПУБЛИКЕ КАЗАХСТАН

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Актуальность: *В настоящее время молекулярная диагностика немелкоклеточного рака легкого (НМРЛ) в Казахстане включает определение статуса драйверных мутаций EGFR, ALK и статуса PD-L1, но не ROS1, что ограничивает возможности получения жизненно важной терапии пациентами с положительным результатов на эту драйверную мутацию.*

Цель исследования *– оптимизация методов молекулярно-генетической диагностики пациентов с НМРЛ путем внедрения тестирования ROS1 в Республике Казахстан.*

Методы: *Исследовался биопсийный и операционный материал пациентов с НМРЛ, фиксированный в 10%-ном забуференном формалине. После первоначальной морфологической диагностики аденокарциномы, определения статуса мутаций EGFR и ALK образцы*

опухоли с отрицательным статусом EGFR и ALK отбирались для дальнейшего выявления статуса мутации ROS1. Определение статуса мутации ROS1 проводилось двумя методами: первый метод – иммуногистохимический анализ (ИГХ) на платформе Ventana BenchMark Ultra с использованием антитела ROS1 (SP283) и системы визуализации OptiView DAB Detection Kit. По результатам ИГХ образцы с положительными и сомнительными результатами направлялись на полимеразную цепную реакцию с обратной транскриптазой (ОТ-ПЦР), чтобы подтвердить статус мутации ROS1 – второй метод.

Результаты: *С 01.01.2022 по 30.09.2022 гг. всего методом ИГХ исследовано 99 образцов опухолей пациентов с EGFR-отрицательной и ALK-отрицательной аденокарциномой легкого. Результаты ИГХ-окрашивания расценивали как: 0 (отрицательно) – 59 образцов, 1+ (отрицательно) – 25 образцов, 2+ (сомнительно) – 12 образцов, 3+ (положительно) – 3 образца. Случаи с ≥70% иммуноокрашивания считались положительными. Образцы с оценкой окрашивания ИГХ 2+ (сомнительно), 3+ (положительно) и несколько образцов 1+ были отправлены на подтверждение ПЦР-тестированием.*

Всего с помощью ОТ-ПЦР было протестировано 22 образца; результаты расценены следующим образом: 1 (4%) – положительный, 13 (59%) – отрицательный, 8 (37%) – невалидный.

Заключение: *При определении статуса мутации ROS1 с помощью ИГХ было получено большое количество положительных и сомнительных результатов, а при последующем тестировании ОТ-ПЦР – большая доля невалидных результатов. В дальнейшем при выборе методики обнаружения ROS1 для проведения анализов на страновом уровне необходимо оценить экономическую затратную составляющую внедряемых методов, а также сравнить со стандартной валидированной методикой FISH.*

Ключевые слова: *молекулярно-генетическая диагностика ROS1, рак легкого (РЛ), немелкоклеточный рак легкого (НМРЛ), иммуногистохимия (ИГХ), полимеразная цепная реакция с обратной транскриптазой (ОТ-ПЦР), флуоресцентная гибридизация in situ (FISH).*

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DNA DOUBLE-STRANDED BREAKS AND REPAIRS IN ACUTE LEUKEMIA

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ABSTRACT

Relevance: *Errors in the damage repair system, such as double-stranded DNA breaks, can lead to mutations that will be passed on to subsequent generations of cells, and some of these mutations may have oncogenic potential.*

The study aimed to *evaluate the number of double-stranded breaks and DNA repairs of peripheral blood lymphocytes in a group of conditionally healthy children and in patients diagnosed with acute leukemia (AL) to develop a method for predicting the outcome of the disease and determining the effectiveness of therapy.*

Methods: *Peripheral blood lymphocytes were studied: a) 38 conditionally healthy children (control group); b) 100 patients diagnosed with acute leukemia (AL); c) 14 children with relapse of the disease. We examine double-stranded DNA breaks/repairs using the Aklides system (MEDIPAN, Germany), consisting of a fluorescent analyzer and the AKLIDES Nuk software.*

Results: *In patients with T-lymphoblastic leukemia, both at admission and the end of Day 7 at the hospital, the number of 53BPI repair foci was, on average, three times higher than the number of DNA damages. In most cases, the ratio of breaks/repairs indicators during treatment did not change among patients with B-line leukemia. Double-stranded DNA breaks prevailed over repairs, with the newly established disease on the 7th, 15th Day, and 3rd month of treatment.*

Conclusion: *The level of lymphocyte DNA damage in patients with B-ALL was higher than expected. In addition, the ratio of double-strand breaks to repairs remained unchanged at all stages of therapy in patients with B-ALL. The changes we suggest in these patients can be observed during and/or after maintenance therapy. Monitoring double-strand breaks/reparations was the initial step in developing a method of predicting the disease outcome and determining the therapy efficacy. The results obtained are of direct interest and require further research.*

Keywords: *double-stranded breaks, DNA repair, acute leukemia, lymphocytes, immunofluorescence.*

Introduction: Among the main types of deoxyribonucleic acid (DNA) damage, double-stranded breaks (DSB) are the most severe form. The double-stranded breaks (DSB) are formed either due to a direct rupture of two complementary sites - so-called "direct" DSB, or formed from other lesions, from single-stranded breaks, as a result of repair disorders during the work of relevant repair enzymes.

Reparation is the body's response to DNA damage. Two following mechanisms can restore the double-stranded breaks:

a) Non-homologous reunion of the DNA ends, in which the damaged chain ends are connected directly;

b) Homologous recombination, in the presence of the DNA fragment identically intact in the nucleotide sequence [1].

However, DNA repair may not be fully effective, and in addition, in some cases, DNA damage repair leads to errors and, as a result, to the occurrence of mutations.

The p53 transcription factor, also known as the "genome guardian," plays a crucial role in ensuring the stability of the genetic apparatus [2]. The p53 protein marks the sites of double-stranded breaks and activates the transcription of genes responsible for repair mechanisms. In turn, to start the DNA repair, the p53 protein binds with the phosphorylated form of H2AX histone (denoted as – γH2AX). A separate γH2AX focus represents each double-stranded break. The presence of standard physiological repair mechanisms leads to successful repair and a decrease in the γH2AX foci [3, 4].

The large amounts of double-stranded breaks and other types of DNA damage initiate an apoptosis program. However, programmed cell death is an exceptional case of maintaining homeostasis (the balance between newly formed and dying cells) since the triggering of apoptosis is possible only if the DNA damage in the nucleus is irreversible and cannot be corrected by the repair system [5].

Thus, the main pathway of the DNA repair system can be presented as the DNA damage → p53 expression → DNA repair/apoptosis (in a condition that threatens the cell life) [6]. The quantitative determination of the DNA breaks and repairs are carried out using flow cytometry, confocal microscopy, and indirect immunofluorescence analysis (IIF). We used the method of indirect immunofluorescence in the current study. The IIF method is based on the detection of a) the H2AX protein, which is formed when double-stranded DNA breaks appear in phosphorylated form; b) the p53-binding protein 1, also known as 53BP1, involved in signal transmission to repair the DNA double-stranded break.

The study aimed to evaluate the number of double-stranded breaks and DNA repairs of peripheral blood lymphocytes in a group of conditionally healthy children

and in patients diagnosed with acute leukemia (AL) to develop a method for predicting the outcome of the disease and determining the effectiveness of therapy.

Materials and methods: The peripheral blood lymphocytes were the material for the study. The following groups of children have been studied:

Group 1 (n=38, median age – 9.7 years) – control (conditionally healthy children);

Group 2 (n=100, median age – 8 years) – patients with AL: acute lymphoblastic leukemia (ALL) = 82, acute myeloid leukemia (AML) = 17, AL of mixed linearity = 1.

Group 3 – (n=14, median age 9.7 years) – children with AL relapse.

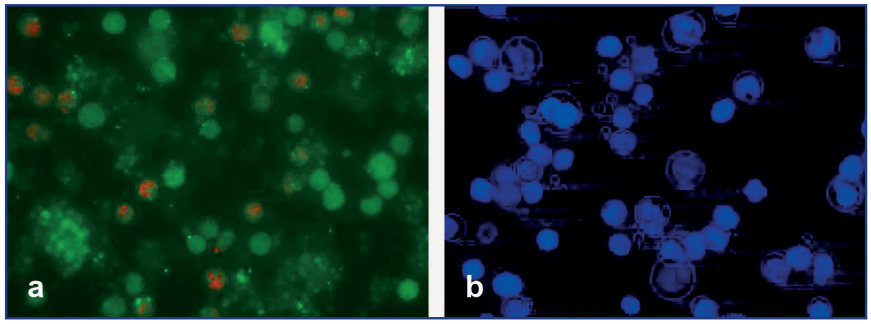
Inclusion criteria: children aged 0 to 18 with primary AL and recurrent AL who were diagnosed and treated at the Scientific Center for Pediatrics and Pediatric Surgery (Almaty, Kazakhstan).

Exclusion criteria: persons over 18 years old; children with severe cytopenia.

The data collection period was from January 2022 to March 2023. The inpatient stay was eight months with ALL and 4-5 months with AML.

The study of double-stranded breaks/DNA repairs was carried out with the application of the Aklides system (MEDIPAN, Germany), consisting of a fluorescence analyzer and AKLIDES Nuk software. The quantitative determination of the double-stranded DNA breaks and repair of lymphocytes in patients with acute leukemia was performed for the first time in Kazakhstan. The commercial AKLIDES Nuk Human Lymphocyte Complete Combi kits were used within the study frames. The method is based on binding specific antibodies with the γH2AX protein component. The second stage of the analysis was to bind the 53BPI-specific antibodies with the initially formed complex. A fluorescence signal displayed the focus of rupture and repair. A green glow in the FITC channel was observed at the rupture focus, and a red glow in the APC channel was observed at the repair center (Figure 1a). The DAPI channel based on autofocus and counterstaining was used to detect the cell nuclei (Figure 1b). The Aklides system has selected cells of the same morphology and typical rounded shape. The calculation of double-stranded breaks/repairs was carried out per 100 lymphocytes. The final result was displayed as reports (Single Report). As stated, the Aklides digital system has been fully standardized and supported the analysis of objects of only specific shapes and sizes. However, the tumor cells are morphologically different when compared with normal cells. In this regard, it is advisable to introduce changes to the sample parameters for subsequent studies of leukemic cells.

The statistical analysis was performed using SPSS Statistics software, version 23.0, for Windows.



a) Viewing the image in simultaneous FITC and APC modes
b) Automatic focus on cells in the DAPI channel
Figure 1 – An example of indirect immunofluorescence assay for the quantitative determination of phosphorylated γH2AX and 5ZBP1 protein in lymphocytes

Results: Table 1 presents the quantification of double-stranded breaks and DNA repair in the control group. The children in the control group's age corresponded to the studied patients' age.

Based on data from Table 1, in the group of children aged 0 to 5 years old, the number of cells with breaks prevailed over the number of cells with repairs, while the total number of repairs was detected. The total number of ruptures and reparations was approximately equal in the age group of 5-10 years old. More double-stranded breaks than repairs were found for the third group of children over ten years old. The elevation of DNA damage with age may be due to the influence of external environmental factors and various biochemical processes of the body.

Table 1 – Indicators of the ratios of breaks/repairs of lymphocyte DNA (LP) in patients of the control group (arithmetic mean M±m)

Age, years	Cells with ruptures and repairs of LP (FITC/APC)	Total number of ruptures and reparations of LP (FITC/APC)	Number of ruptures and reparations per 1 cell
0-5 years old	43±5/38±4*	122±6/131±8*	1/1
5-10 years old	51±4/35±6 (p≤0,05)	109±10/104±9*	1/1
Over 10 years old	48±5/34±6*	114±11/96±8*	1/1

*Note: * - the result is unreliable*

Diagram 1 shows the distribution of the number of patients depending on the AL immunological variant.

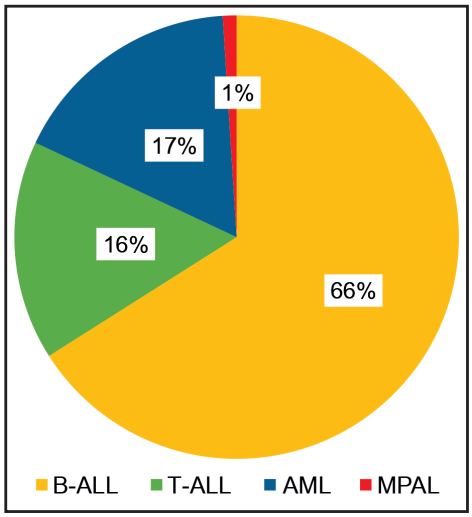


Diagram 1 – Number of patients by AL variants

The distribution of AL variants was as follows: "Acute B-lymphoblastic leukemia" (B-ALL) was identified in 66 patients, comprising 66% of the total number of patients. Among patients with B-ALL, the pro-B1 variant was detected in 9 children (14%), B2-38 (58%), B3-16 (24%), and B4-3 (4%). The diagnosis of *"acute myeloid leukemia"* was established in 17 patients (17%), including 11 (65%) - with AML M1-M2, 3 (18%) - M3, 1 (6%) - M4-M5 and 2 (11%) - M7. Besides, 16 people (16%) were admitted with acute T-lymphoblastic leukemia (T-ALL), ten children (62%) with the T3-cortical immunological variant, and 6 (38%) with T-non-cortical leukemia. Besides, one case of mixed linearity AL (B+myelo) classified as mixed-phenotype acute leukemia (MPAL) has been revealed.

The distribution of patients by age and linear identity of primary AL is presented in Table 2.

According to Table 2, B-ALL was more often detected in children aged 5-10 years old, 45% (n=30). Among children over 10 years old, AML was diagnosed in 42% (n=7).

Table 2 – Distribution of patients with AL by age and immunological variant of the disease

AL variant	Number of patients, abs., (%)		
	0-5 years old	5-10 years old	Over 10 years old
Acute lymphoblastic leukemia	19 (29%)	30 (45%)	17 (26%)
T-acute lymphoblastic leukemia	4 (25%)	7 (44%)	5 (31%)
Acute myeloid leukemia	5 (29%)	5 (29%)	7 (42%)
Acute leukemia of mixed phenotype	1 (100%)	-	-

The number of breaks and DNA repairs of peripheral blood lymphocytes among patients with newly diagnosed AL is presented in Table 3.

Table 3 – Indicators of double-stranded breaks/repairs in patients with primary AL (arithmetic mean M±m)

AL variant	Cells with ruptures and repairs (FITC/APC)	Total number of ruptures and reparations of LP (FITC/APC)	Number of ruptures and reparations per 1 cell
ALL B2	41±3/31±4 (p≤0,05)	95±8/109±7*	1/1
ALL B1	73±5/38±3 (p≤0,01)	186±9/209±8 (p≤0,05)	2/2
ALL B3	29±4/22±5*	52±5/38±4* (p≤0,05)	1/1
ALL B4	20±3/17±3*	59±4/14±3 (p≤0,01)	1/1
ALL T3-cortical	24±4/41±5 (p≤0,05)	53±5/143±9 (p≤0,01)	1/1
ALL T-non-cortical	25±2/44±4 (p≤0,01)	55±7/194±11 (p≤0,01)	1/2
AML M1-M2	34±5/24±4*	62±5/60±7*	1/1
AML M3	60±5/52±4*	153±6/117±8 (p≤0,01)	1/1
AML M4-M5	67±6/2±1 (p≤0,001)	165±10/2±1 (p≤0,001)	2/1
AML M7	34±5/38±3*	76±4/91±6 (p≤0,05)	1/1
MPAL (B+myelo)	84±7/12±3 (p≤0,01)	239±11/42±7 (p≤0,001)	2/1

*Note: * - the result is unreliable*

According to Table 3, in the patient with biphenotypic acute leukemia, the repair has declined by 5.7 times. The prognosis for biphenotypic leukemia is worse than acute lymphoblastic or myeloid leukemia. However, the patient tolerated the polychemotherapy relatively well, and following the therapy, the child's condition stabilized. The average number of ruptures in cortical (n=53) and non-cortical (n=55) variants is approximately equal for the group of patients with T-ALL. At the same time, the number of repairs in patients with T3-cortical ALL (n=143) and T-non-cortical ALL (n=194) was significantly more significant than the number of ruptures themselves. Among patients with AML in M1-M2, the minimum damage has been detected – 62 ruptures, and the maximum in M4-M5 – 165 per 100 lymphocytes. For the latter, it is worth highlighting that the reparation has been reduced by 82 times. For the group of patients with AML, the average number of reparations in M1-M2 composed 60; in M3, it made a total of 117. Among AML, only in M7 were more reparations (n=91) than ruptures (n=76). The prognosis for AML M7 is highly unfavorable.

In patients with B-linear AL, the average number of double-stranded breaks in pro-B1 was the maximum of -186, the minimum in pre-B3 - 52. The average number of cell repair foci in patients with B-ALL has been distributed in B1 – 209, B2 – 109, and B3 – 38. The level of repairs for B4-ALL was the lowest compared to other B-ALL variants. At the same time, the clinically mature cell B4-ALL was characterized by a high proliferative index, which in turn was reflected in a poor outcome.

The number of breaks and DNA repairs of peripheral blood lymphocytes among patients with recurrent AL is presented in Table 4. In the "relapses" group, three patients had a recurrence of AL less than a year after the start of treatment.

Table 4 – Indicators of double-stranded breaks/reparations in patients with recurrence of AL (arithmetic mean M±m)

AL variant	Number of cells with ruptures and repairs (FITC/APC)	Total number of ruptures and reparations of LP (FITC/APC)	Number of ruptures and reparations per 1 cell
Recurrence of ALL B2	36±5/20±5 (p≤0,05)	74±6/60±3 (p≤0,05	1/1
Recurrence of ALL B4-mature cell type	45±7/0 (p≤0,001)	45±4/0 (p≤0,001)	1/0
Relapse of AML M1-M2	29±4/20±3*	50±5/30±3 (p≤0,01)	1/1

*Note: * - the result is unreliable*

As seen from Table 4, among patients with recurrence of the disease, regardless of the variant of AL, the double-stranded breaks prevailed over repairs. Most patients who relapsed the disease were with B2 standard (N = 11). Recurrence of M1-M2 AML was detected in two children, and B4-mature cell ALL was revealed in one child. The repair was utterly absent in B4-ALL, and despite the therapy, the patient died.

The results of counting the number of breaks and DNA repairs of peripheral blood lymphocytes during treatment are presented in Table 5. In patients with ALL, by the treatment protocol at the induction stage, the first seven days included taking glucocorticoid prednisolone. At the same time, for AML, the course introduced the cytotoxic drugs group. The following points for calculating the breaks/repairs were Day 15 and 3rd Month.

In some patients, starting from Day 15th, severe cytopenia was noted due to chemotherapy. In blood samples with a leukocyte concentration of less than 2×10^9/L, the Aklides system did not count the breaks/repairs due to a considerable distance between the cells recorded on the carrier's slot. In addition, the morphological changes in cells, shape, and size have been revealed against the background of taking cytotoxic drugs. It could stem from the developed tumor lysis syndrome, primarily observed in children with hyperleukocytosis. We assume that when cells were isolated from peripheral blood in a specific density gradient, the blasts could be subsequently analyzed in addition to lymphocytes.

According to Table 5, among patients with B-lymphoblastic leukemia, in most cases, the ratio of breaks/repairs rates did not change during treatment. The double-stranded DNA breaks prevailed over repairs at the newly detected AL and on Day 7, 15th Day, and 3rd month of treatment. According to the observations of specialists [7], the B-cell ALL is considered a more favorable option than T-ALL in terms of prognosis. A curious fact is that a positive response to chemotherapy accompanied the reduced repair of lymphocytes in patients with B-ALL. No changes have been registered in patients with T-ALL on Day 7 of prophase. Also, more repairs (n=7) have been detected than ruptures (n=4). However, on the 15th Day of polychemotherapy (n=6) and the 3rd Month (n=3), more patients with ruptures were recorded than with repairs, n=3 and n=2, respectively. Among patients with AML, on Day 7 of therapy - the double-stranded breaks (n=8) prevailed, while on the 15th Day (n=5) and on the 3rd month – the repairs were increased (n=4).

Table 5 – Dynamics of double-stranded breaks/repair ratios during therapy

Day of therapy	Number of patients (n)		
	AL variant	b>r*	r>b*
Day 7	B-ALL	22	15
	T-ALL	4	7
	AML	8	4
Day 15	B-ALL	18	12
	T-ALL	6	3
	AML	4	5
3rd month	B-ALL	22	13
	T-ALL	3	2
	AML	2	4

Note: b – double-stranded breaks; r – repair

Discussion: For many cases of leukemia, lymphoma, or sarcoma, the first events of carcinogenesis are most often the translocations that activate or form the oncogene [8]. Unrepaired damage increases due to inherited mutations in DNA repair genes in replicating somatic cells [9]. The patient with M4-M5 AML had 169 ruptures and two repairs. FISH study revealed a rearrangement of the mixed-lineage leukemia (MLL) gene. These results coincide with published data. The lymphocyte repair in patients with T-ALL of pro-T1, pre-T2, and mature-T4 variants was 1.3 times higher than in patients with cortical T3-ALL. The doctors reported no significant clinical differences; however, patients with T-noncortical ALL variant initially had a worse response to chemotherapy than patients with T-cortical ALL.

Overall, patients with T-lymphoblastic leukemia had fewer double-stranded breaks. At the same time, in almost all patients with this immunological AL variant, both at the time of admission and at the end of Day 7 of prophase, the number of repair foci was, on average, three times higher than the DNA damage. Thus, prednisolone did not play a significant role in changing the nature of ratios of the double-stranded breaks and DNA repair. The obtained results corresponded with clinical signs of the relevant AL variant. By the end of Day 7 of prophase, in most cases, no regression of hyperplastic syndrome was noted, and a high number of blasts in the complete blood count remained. At the same time, cytotoxic drugs increased double-stranded DNA damage and improved the disease's clinical picture. The results of the reparative ability of lymphocytes in patients with T-ALL are debatable. High repair rates could be one of the reasons for poor response to chemotherapy. The repair shall correct the DNA damage, reducing the likelihood of mutations and, therefore, the emergence of the tumor substrate [10, 11]. The results are consistent with the data published by Trenner A. et al., who consider the repair mechanism one of the main resistance factors to chemotherapy [12].

Only a few studies consider double-stranded breaks and DNA repair in patients with acute leukemia. In the available literature, the double-stranded DNA damage and repair were investigated under "in vitro" conditions [3, 13]. In our study, we monitored ruptures/repairs in patients with AL before and after exposure to several anticancer drugs.

Conclusion: The level of lymphocyte DNA damage in patients with B-ALL was higher than expected. In addition, the ratio of double-strand breaks to repairs remained unchanged at all stages of therapy in patients with B-ALL. The changes we suggest in these patients can be observed during and/or after maintenance therapy. Monitoring double-strand breaks/reparations was the initial step in developing a method of predicting the disease outcome and determining the therapy efficacy. The results obtained are of direct interest and require further research.

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АНДАТПА

ЖЕДЕЛ ЛЕЙКОЗ КЕЗІНДЕГІ ДНҚ ҚОСТІЗБЕКТІ ҮЗІЛІСТЕРІ МЕН РЕПАРАЦИЯСЫ

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Өзектілігі: *ДНҚ-ның қос тізбекті үзілістері сияқты зақымдануды қалпына келтіру жүйесіндегі қателер жасушалардың кейінгі ұрпақтарына берілетін мутацияларға әкелуі мүмкін және мұндай мутациялардың кейбіреулері онкогендік потенциалға ие болуы мүмкін.*

Зерттеудің мақсаты *– шартты түрде сау балалар тобындағы және "жедел лейкоз" (ЖЛ) диагнозы қойылған пациенттердің перифериялық қан лимфоциттерінің қос тізбекті үзілістері және ДНҚ репарациясының санын салыстырмалы талдау және оны аурудың нәтижесін болжау мен емнің тиімділігін анықтау әдісін әзірлеу үшін қолдану.*

Әдістері: *тікелей емес иммунофлуоресцентті талдау әдісі флуоресцентті анализатор мен Aklides nuk бағдарламалық қамтамасыз етуден тұратын Aklides (Medipan, Германия) жүйесінде өткізілді. Әдіс арқылы перифериялық қан лимфоциттері зерт-*

телді: а)шартты түрде сау 38 бала (бақылау тобы); б) жедел лейкоз (ЖЛ) диагнозы қойылған 100 науқас; в) аурудың қайталануы бар 14 науқас.

Нәтижелері: *Т-лимфобластикалық лейкозбен ауыратын науқастарда емнің басында және ауруханаға жатқызудың 7-ші күні 53BP1 репарация ошақтарының саны ДНҚ зақымдану санынан орта есеппен 3 есе жоғары болды. В-бағытты лейкозбен ауыратын науқастар арасында көп жағдайда емдеу кезінде ДНҚ қостізбекті үзілісі/репарациясы көрсеткіштерінің арақатынасы өзгерген жоқ. ДНҚ-ның қостізбекті үзілістері ауру алғаш анықталған сәтте, емдеудің 7-ші, 15-ші күні, 3-ші айында да репарациядан басым болды.*

Қорытынды: *B-ALL бар емделушілерде лимфоциттердің ДНҚ зақымдану деңгейі күтілгеннен жоғары болды. Сонымен қатар, екі тізбекті үзілістердің жөндеуге қатынасы B-ALL бар емделушілерде терапияның барлық кезеңдерінде өзгеріссіз қалды. Бұл емделушілерде біз ұсынып отырған өзгерістер демеуші терапия сатысында және/немесе оны аяқтағаннан кейін байқалуы мүмкін. Екі қатарлы үзілістердің/репарациялардың мониторингі аурудың нәтижесін болжау және терапияның тиімділігін анықтау әдісін әзірлеудің бастапқы қадамы болды. Алынған нәтижелер тікелей қызығушылық тудырады және қосымша зерттеулерді қажет етеді.*

Түйінді сөздер: *ДНҚ қостізбекті үзілістері, ДНҚ репарациясы, жедел лейкоз, лимфоциттер, иммунофлуоресценция.*

АННОТАЦИЯ

ДВУЦЕПОЧЕЧНЫЕ РАЗРЫВЫ И РЕПАРАЦИИ ДНК ПРИ ОСТРЫХ ЛЕЙКОЗАХ

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Актуальность: *Ошибки в системе репарации повреждений, таких как двуцепочечные разрывы ДНК, могут привести к возникновению мутаций, которые передадутся последующим поколениям клеток. Некоторые из таких мутаций могут об-ладать онкогенным потенциалом.*

Цель исследования *– анализ количества двуцепочечных разрывов и репараций ДНК лимфоцитов периферической крови в группе условно здоровых детей и у пациентов с диагнозом «острый лейкоз» (ОЛ) для оценки степени повреждения ДНК.*

Методы: *Лимфоциты периферической крови были взяты у: а) 38 условно здоровых детей (контрольная группа); б)100 пациентов с диагнозом ОЛ; в) 14 детей с рецидивом заболевания были исследованы методом непрямого иммунофлуорес-центного анализа (НИФ) и исследованы с помощью системы Aklides (MEDIPAN, Германия), состоящей из флюоресцентно-го анализатора и программного обеспечения AKLIDES Nuk.*

Результаты: *У пациентов с Т-лимфобластным лейкозом как на момент поступления, так и на конец 7-го дня госпита-лизации количество репарационных очагов 53BP1 в среднем в 3 раза превышало количество повреждений ДНК. Среди паци-ентов с В-линейными лейкозами в большинстве случаев отношения показателей разрывов/репараций в ходе лечения не из-менились. Двуцепочечные разрывы ДНК преобладали над репарациями, как при впервые установленном заболевании, так и на 7-й, 15-й день, 3-й месяц лечения.*

Заключение: *Уровень повреждений ДНК лимфоцитов у пациентов с В-ОЛЛ оказался выше ожидаемого. Кроме того, на всех этапах терапии больных В-ОЛЛ отношение двуцепочечных разрывов к репарациям сохранилось. Предполагаемые нами изменения у данных пациентов могут наблюдаться на этапе поддерживающей терапии и/или после ее окончания. Монито-ринг двуцепочечных разрывов/репараций являлся первоначальным этапом для разработки метода прогнозирования исхода заболевания и определения эффективности терапии. Полученные результаты вызывают непосредственный интерес, и требует дальнейших исследований.*

Ключевые слова: *двуцепочечные разрывы, репарация ДНК, острый лейкоз (ОЛ), лимфоциты, иммунофлюоресценция.*

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QUANTIFICATION OF DNA DOUBLE-STRAND BREAKS IN BENIGN AND MALIGNANT BREAST DISEASES

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ABSTRACT

Relevance: *Double-strand DNA breaks are the most dangerous DNA damage. Analysis of foci of phosphorylated histone protein H2AX (γH2AX) is currently the most sensitive method for detecting DNA double-strand breaks. This protein modification can become a biomarker of cellular stress, especially in diagnosing and monitoring neoplastic diseases. In this study, we used novel pattern recognition algorithms on the AKLIDES® platform to automatically analyze immunofluorescent images of γH2AX foci and compare the results with visual scores. The γH2AX foci formation on peripheral blood mononuclear cells of women with breast cancer or benign breast tumors was studied.*

The study aimed to *quantify DNA double-strand breaks in peripheral blood lymphocytes in women with breast cancer and benign breast masses to identify a possible biomarker.*

Methods: *γ-H2AX foci in lymphocytes were analyzed using the automated AKLIDES system in patients with breast cancer (n=29) and benign breast tumors (n=24).*

Results: *When comparing the parameters of the main and control groups in the channel of ruptures "FITC," a statistically significant difference was found in the parameters "Foci diameter" (p=0.0382), "Foci intensity means" (p=0.0166), "Colocalisation" (p=0.0486). In the repair channel "APC," significant differences were found in the parameters "Nuclei intensity" (p=0.0166) and "Foci intensity means" (p=0.0118).*

Conclusion: *The revealed changes of DNA double-strand breaks along the FITC break channels and APC repair between the main and control groups can possibly serve as a breast cancer diagnostic marker.*

Keywords: *DNA double-strand breaks, H2AX histone protein, breast cancer.*

Introduction: Breast cancer is the most commonly diagnosed invasive cancer among women worldwide and the number one cause of female cancer deaths [1].

H2AX histone undergoes phosphorylation in response to DNA double-strand breaks (DSBs), which are part of the oncogenic process. Eukaryotic cells have developed a set of complex signaling networks that detect these DNA damages, organize cell cycle checkpoints, and eventually lead to their repair to prevent the catastrophic consequences of persistent DNA double-strand breaks. Together, these signaling networks constitute a response to DNA damage [2, 3]. Double-strand breaks are one of the first procedures that occur during the formation and progression of cancer due to endogenous and exogenous factors. The H2AX histone variant is phosphorylated on serine 139 due to double-strand breaks, while gamma-H2AX is formatted due to genome instability [4, 5]. There are two main DSB repair pathways, namely non-homologous end joining and homologous recombination; the pathway choice is partially controlled by post-translational histone modifications, including ubiquitination [6, 7]. Thus, activated components of the DNA damage and repair pathway can be used as cancer biomarkers, with H2AX being the most sensitive. Thus, measurements of H2AX levels can help detect precancerous lesions or cancer at an early stage [8-10]. Immunofluorescent staining with anti-γH2AX antibody provides visualization of these nuclear foci that have been found and correlates with the amount of DSB [11, 12].

Fluorescent microscopy allows for a rapid and standardized γH2AX assay and a quick assessment of DNA damage in clinical practice. The platform, called AKLIDES (Medipan, Germany), allows not only fully automated screening evaluation of antinuclear immunofluorescent antibodies [13] but also conducts a computational analysis of γ-H2AX foci, which has now been successfully validated by several independent study groups [14-18].

The study aimed to quantify DNA double-strand breaks in peripheral blood lymphocytes in women with breast cancer and benign breast masses to identify a possible biomarker.

Materials and Methods: This prospective cohort study involved two groups of female patients: the main group of 29 patients with primary verified breast cancer and 24 controls with a histologically verified benign breast tumor. The study was performed at the Medical Center and Scientific-and-Practical Center of West Kazakhstan Marat Ospanov Medical University (Aktobe, the Republic of Kazakhstan). Each participant submitted written informed consent. The project was approved by

the local Commission on Bioethics (Minutes No. 57 of Jan. 17, 2020).

In the main group (29 patients with breast cancer), the average age was 56.10±12.23 years. By disease stage, 25 (86.2%) had stage II disease, and four (13.8%) had stage III. By tumor immune histochemistry, 3 (10.3%) had Luminal type A, 21 (72.4%) had Luminal type B, four (13.8%) had a triple-negative tumor, and one (3.4%) patient had a HER+ cancer.

In the controls, 24 patients had a verified «Mammary Gland Benign Neoplasia» (BI-RADS M2); their average age was 43.08 ± 10.12 years.

The study object was peripheral venous blood in a volume of 10 ml (EDTA tube) containing mononuclear cells. γ-H2AX foci in lymphocytes were analyzed using the γ-H2AX immunofluorescent staining kit (AKLIDES Nuk Human Lymphocyte Complete, Medipan) following the manufacturer's instructions.

The AKLIDES system is based on a motorized inverse fluorescence microscope combined with various hardware and software modules to fully automate image acquisition, analysis, and evaluation. In each sample, we analyzed 80-100 cells at least. DNA double-strand breaks in γ-H2AX were assessed by 12 parameters in the AKLIDES automated system tear channel (FITC) and the repair channel (ARC):

1. Foci diameter;
2. Nuclei intensity;
3. Nuclei with foci;
4. Foci overall;
5. Foci intensity means%
6. Clusters;
7. Foci mean;
8. Foci mean + clusters;
9. Clusters positive cells;
10. Clusters of low intensity;
11. Damaged cells;
12. Colocalization.

Statistical analysis included comparisons of two groups on numerical variables using the nonparametric Mann-Whitney method. The statistical significance of group differences for binary and categorical parameters was determined using Pearson's Chi-square method.

The statistical significance level was fixed at 0.05. Statistical data was processed using the Statistica 10 and SAS JMP 11 application packages.

Results: Analysis of the results of the AKLIDES automated system showed that the average number of cells counted in the main group of patients with breast cancer (113) and in the control group (108) corresponded to the minimum number (100) of cells required for the study.

Tables 1-2 present the results of the analysis of foci of γ-H2AX in the control and main groups (stage 1) according to the rupture channel (FITC) and the repair channel (APC).

Table 1 - Comparison of parameters in the main (breast cancer) and control groups according to the FITC gap channel (Average value ± standard deviation)

Parameter	Group		p-value
	Breast cancer (n=29)	Control (n=24)	
Foci diameter	7.34±0.68	7.00±0.52	0.0382
Nuclei intensity	35.95±10.84	39.13±10.25	0.1921
Nuclei with foci	55.66±37.00	58.25±31.50	0.5918
Foci overall	167.17±219.72	141.67±119.92	0.7342
Foci intensity means	69.88±17.97	81.83±19.28	0.0166
Clusters	0.24±0.79	0.12±0.45	0.5477
Foci mean	1.45±1.58	1.29±1.10	0.9005
Foci mean + clusters	1.46±1.59	1.30±1.10	0.8863
Clusters positive cells	51.13±29.87	53.22±27.89	0.8025
Clusters of low intensity	2.45±1.81	2.10±1.40	0.5554
Damaged cells	72.46±27.92	74.27±23.13	0.8442
Colocalization	18.62±19.12	9.71±13.69	0.0486

It was found that three parameters differed statistically significantly between the two compared groups in the FITC discontinuity channel. A statistical difference was found for the "Foci diameter" parameter, which in the main group was higher than the control group parameter (p=0.0382), and for the "Foci intensity means," this parameter was lower in the main group than in the control group (p=0.0166). The parameter "Colocalization" in the main group was higher than in the control group (p=0.0486) (Figures 1-3).

Two statistically significant parameters were identified when comparing the parameters in the main and control groups on the APC repair channel. Thus, significant differences were found for the parameter "Nuclei intensity," which in the main group was lower than in the control group (p=0.0166), and the parameter "Foci intensity means" in the main group was lower than in the control group (p=0.0118) (Figures 4-5).

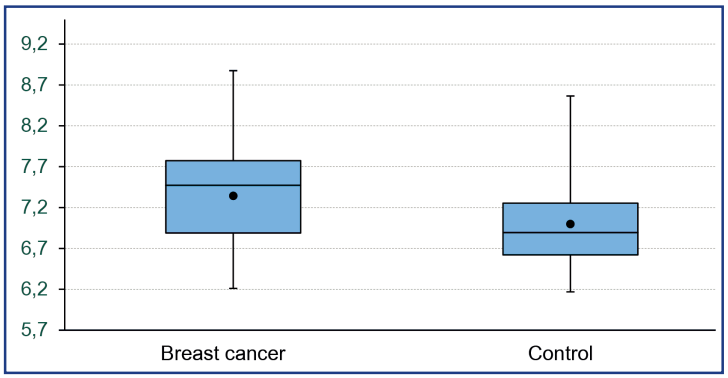

Figure 1 - Comparison of the parameter "Foci diameter" in the main and control groups

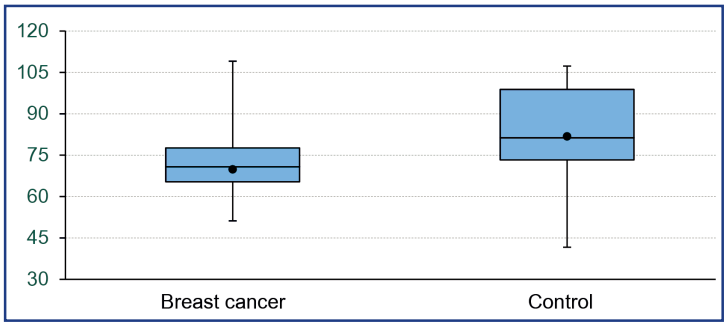

Figure 2 - Comparison of the parameter "Foci intensity means" in the main and control groups

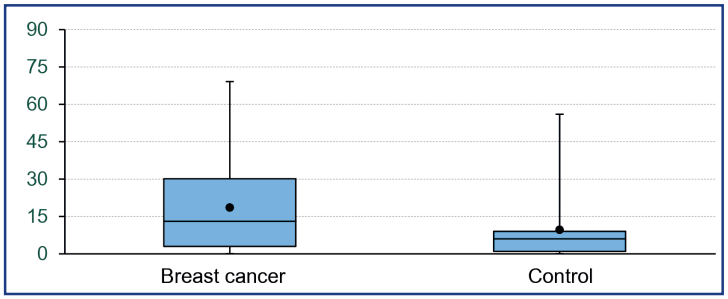

Figure 3 - Comparison of the parameter "Colocalization" in the main and control groups

Table 2 - Comparison of parameters in the main (breast cancer) and control groups on the APC repair channel (Average value ± standard deviation)

Parameter	Group		p-value
	Breast cancer (n=29)	Control (n=24)	
Nuclei intensity	455.23±286.58	738.93±512.67	0.0166
Nuclei with foci	76.79±25.57	76.04±20.51	0.7749
Foci overall	288.10±251.77	217.88±141.48	0.5494
Foci diameter	0.56±0.05	0.54±0.03	0.0830
Foci intensity means	302.94±81.62	369.91±109.65	0.0118
Clusters	49.34±80.94	46.50±100.59	0.9712
Foci mean	2.81±2.96	2.00±1.28	0.7750
Foci mean + clusters	8.05±13.26	6.68±11.43	0.9715
Clusters positive cells	70.38±23.74	69.99±17.44	0.6551
Clusters of low intensity	3.17±2.83	2.28±1.18	0.2918
Damaged cells	81.74±16.52	79.40±10.93	0.1333

Next, we decided to identify significant factors influencing the development of breast cancer. We have obtained the results of statistical one-factor forecasting of the target parameter of breast cancer development "BC (+)" for quantitative and binary factors.

Table 3 presents the TOP-12 list of risk factors for the "BC(+)" parameter.

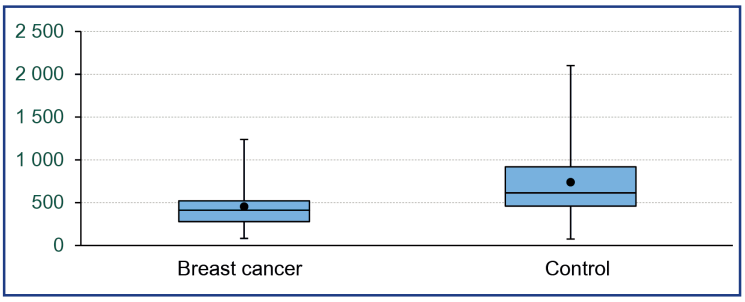

Figure 4 - Comparison of the parameter "Nuclei intensity" in the main and control groups

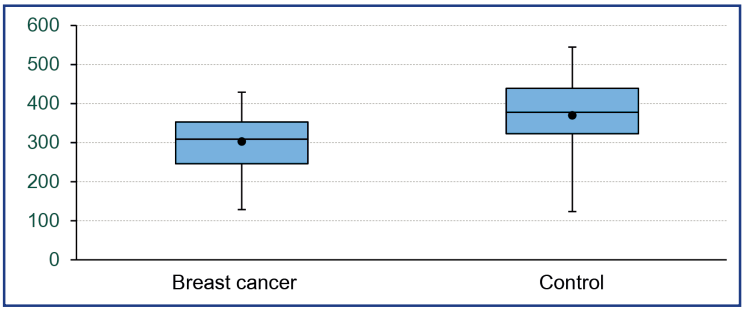

Figure 5 - Comparison of the parameter "Foci intensity means" in the main and control groups

Table 3 - TOP-12 key factors influencing the risk of developing breast cancer

Factor	BC(+): frequency (risk, %)		Risk change, % (95% CI)	Relative risk (95% CI)	p-value
	Factor: No	Factor: Yes			
Age ≥48.0 years old	5 (23.8%)	24 (75.0%)	51.2 (27.6; 74.8)	3.15 (1.43; 6.95)	0.0003
Foci intensity means (Stage 1) <341.6	8 (32.0%)	21 (75.0%)	43.0 (18.7; 67.3)	2.34 (1.27; 4.31)	0.0017
Foci intensity means (Stage 1) <77.8	7 (31.8%)	22 (71.0%)	39.1 (14.0; 64.3)	2.23 (1.16; 4.28)	0.0048
Nuclei intensity (Stage 1) <574.8	6 (30.0%)	23 (69.7%)	39.7 (14.2; 65.2)	2.32 (1.15; 4.71)	0.0049
Foci diameter (Stage 1) ≥0.5	21 (46.7%)	8 (100.0%)	53.3 (38.8; 67.9)	2.14 (1.57; 2.93)	0.0052
Nucleus diameter (Stage 1) ≥7.5	15 (41.7%)	14 (82.4%)	40.7 (16.4; 64.9)	1.98 (1.27; 3.08)	0.0055
Percentage of damaged cells (Stage 1) ≥89.3	19 (45.2%)	10 (90.9%)	45.7 (23.0; 68.4)	2.01 (1.37; 2.94)	0.0068
Colocalization (Stage 1) ≥9.0	11 (39.3%)	18 (72.0%)	32.7 (7.5; 58.0)	1.83 (1.09; 3.09)	0.0169
Foci diameter (Stage 1) ≥0.5	9 (37.5%)	20 (69.0%)	31.5 (5.8; 57.1)	1.84 (1.04; 3.26)	0.0220
Nuclei intensity (Stage 1) <35.6	12 (41.4%)	17 (70.8%)	29.5 (3.9; 55.0)	1.71 (1.03; 2.83)	0.0320
Percentage of nuclei with foci in low-intensity clusters (Stage 1) ≥87.3	15 (44.1%)	14 (73.7%)	29.6 (3.7; 55.5)	1.67 (1.05; 2.66)	0.0381

Based on univariate forecasting, it can be concluded that 12 factors have a statistical significance of influencing the risk of developing "BC +" with a range of risk levels from 69.0% to 100.0%. The leading statistically significant factors for the development of breast cancer with a risk of 75.0% to 81.0% are "Age ≥48.0 years old" and "Foci intensity means (Stage 1) <341.6". At the end of the list of statistically significant factors are "Percentage of nuclei with foci in low-intensity clusters (Stage 1) ≥87.3", "Nuclei intensity (Stage 1) <35.6," and "Foci diameter (Stage 1) ≥0.5", which increase the risk level from 69.0% to 73.7%.

Table 4 and Figure 6 present the results of the analysis performed by POC on the channels of FITC breaks and APC repair of the target parameter "Foci intensity means" to determine the sensitivity and specificity of the technique.

Table 4 – Prognostic parameters for the target parameter "Foci intensity means" for the FITC break channel and the APC repair channel

Parameter	Value	
	through the FITC break channel	through the APC repair channel
Cutoff point	341.6	77.83
Area Under Receiver Operating Characteristic (AuROC)	0.70	0.69
Sensitivity	72.41%	75.86%
Specificity	70.83%	62.50%
Efficiency	71.62%	69.18%

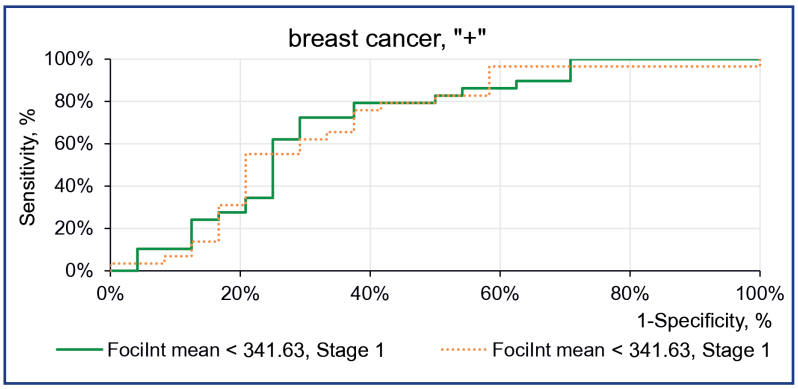

Figure 6 – Prognostic parameters for the target parameter "Foci intensity means" for the channel of FITC breaks and APC repair

During the study, 2 out of 29 main group patients died. In one patient, the cause of death was the progression of the tumor process, and the second died of covid-associated pneumonia. One-year survival was 93%.

In our study, when analyzing foci of γ-H2AX in patients with breast cancer in the channel of FITC ruptures, the parameters " Foci diameter " and " Colocalization " turned out to be higher than in patients with benign tumors, while the parameter " Foci intensity means " was lower than in the control group. In the APC repair channel, the parameters "Nuclei intensity" and "Foci intensity means" in patients with breast cancer were lower than in patients with benign tumors. The revealed changes in the parameters for the FITC rupture channel and the APC repair channel suggest that the main and control groups differ, which may serve as a diagnostic marker for the detection of breast cancer.

Discussion: DNA damage and genomic stability are well-known factors associated with the transition of normal tissues to precancerous and then to malignant states. γ-H2AX, a marker of genomic instability, may be a marker of cancer formation and progression [19].

The most common method for analyzing DNA double-strand break foci, visual assessment of immunofluorescently labeled γ-H2AX foci, is time-consuming. In addition, it is not standardized and is characterized by high intra- and inter-laboratory variability in estimates [18].

We developed a pilot study design to test the possibility of detecting double-strand breaks represented by γ-H2AX foci in human blood using automated fluorescence microscopy and the automated AKLIDES system in patients with breast cancer. We analyzed γH2AX foci on peripheral blood mononuclear cells (lymphocytes) in 29 patients with newly verified breast cancer and 24 control women with a verified benign disease of the mammary glands.

A study by B. Wang et al. reported a high positive frequency of γ-H2AX in tumor cells compared to normal breast tissues in the same patients with breast cancer. The significant difference in tumor and adjacent healthy tissues demonstrates that γ-H2AX can help improve the efficiency of early diagnosis [20].

However, these studies were performed in tissues, and in most cases, the collection of tumor samples is a complex medical procedure, especially when repeated samples are required. Therefore, clinicians often have to turn to safer and less invasive procedures that can be routinely used in the clinic to assess response to therapy, with the potential for reproducible results. In this regard, we used a safer method for detecting foci of γ-H2AX in peripheral blood mononuclear cells in patients with breast cancer using the automated AKLIDES system.

Our analysis of γH2AX foci showed a statistically significant difference in the main and control groups. Thus, in the channel of breaks "FITC," the parameter "Foci diameter" was slightly higher than in the control group (p=0.0382). The parameter "Colocalisation" in the main group was higher than in the control group (p=0.0486). The parameter "Foci intensity means" was lower in the breast cancer group (p=0.0166) (Table 1). In the "APC" repair channel, the parameter "Nuclei intensity" in the main group was lower than in the control group (p = 0.0166). The parameter "Foci intensity means" in the channel of ruptures and repair was lower in the main group than in the control group (p=0.0118) (Table 2).

In the literature we studied, no study was found to quantify DNA double-strand breaks in cancer patients with benign neoplasms.

We found published studies on mobile phones' potential genotoxic radiofrequency effects on human peripheral blood mononuclear cells in vitro measured using the automated AKLIDES system [21].

Studies have also been conducted on the analysis

of foci of γ -H2AX on the automated AKLIDES system in athletes during rest after exercise. The parameters were the analysis of the diameter of γ-H2AX foci and the number of γ-H2AX foci per affected cell [21].

There is experience in using the automated system AKLIDES in Kazakhstan for the diagnosis of systemic autoimmune diseases, where antinuclear antibodies, cytoplasmic antineutrophil antibodies, and perinuclear antineutrophil antibodies were studied in patients with rheumatoid diseases [22].

As a pilot project, our study had some limitations and limits, including:

1) the lack of a standard study methodology;

2) we have not conducted a study of long-term results;

3) the lack of standard reference parameters to interpret the results and make conclusions.

DNA DSBs are a personalized response of the body to certain risk factors so that they can vary individually, and this can create barriers to population-based validation. Like any other biomarker, γH2AX has biological variability, which could be predictable and cyclic [24].

The lack of experimental standardization of the γH2AX assay leads to wide heterogeneity of the results obtained and problems with their interpretation, making it difficult to use γH2AX as a routine biomarker in population studies. Further research is needed to standardize the results, with a strict organization of the research and individual training of personnel [24].

Z. Zhang [26] states, "Laboratory medicine is aimed at providing tests for clinical decision-making." The result of using a predictive biomarker in this pilot study will serve as the basis for a larger study using γH2AX lesions in breast cancer patients to develop methods for the real-time detection of neoplasms.

Conclusion: An increase in the parameters "Foci diameter" (p=0.0382), "Foci intensity means" (p = 0.0166), and "Colocalisation" (p=0.0486) was found in the breast cancer group in the "FITC" channel of ruptures. In the "APC" repair channel, the parameters "Nuclei intensity" (p=0.0166) and "Foci intensity means" (p=0.0118) in the breast cancer group were lower than in the control group.

The detected changes in the parameters of DNA double-strand breaks along the "FITC" break and "APC" repair channels between the main and control groups can possibly serve as a breast cancer diagnostic marker.

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АНДАТПА

СҮТ БЕЗІНІҢ ҚАТЕРСІЗ ЖӘНЕ ҚАТЕРЛІ ІСІК АУРУЛАРЫНДА ДНҚ ҚОС ТІЗБЕКТІ ҮЗІЛІСТЕРІН САНДЫҚ АНЫҚТАУ

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Өзектілігі: *ДНҚ зақымдануының ең қауіпті түрі – ДНҚ қос тізбекті үзілуі. Фосфорланған гистон ақуызының H2AX (γH2AX) ошақтарын талдау қазіргі уақытта ДНҚ қос тізбекті үзілістерін анықтаудың ең сезімтал әдісі болып табылады. Бұл ақуыз модификациясы жасушалық стресстің жеке биомаркеріне айналуы мүмкін, әсіресе ісік ауруларының диагностикасы мен мониторингінде. Бұл зерттеуде біз γH2AX ошақтарының иммунофлуоресцентті кескіндерін автоматты түрде талдау және нәтижелерді көрнекі ұпайлармен салыстыру үшін AKLIDES® платформасында жаңа үлгіні тану алгоритмдерін қолдандық. Сүт безінің қатерлі ісігі бар науқастар мен сүт безінің қатерсіз ісігі бар әйелдердің шеткергі қан мононуклеарлы жасушаларында γH2AX ошақтарының түзілуі зерттелді.*

Зерттеудің мақсаты: *мүмкін болатын биомаркерді анықтау үшін сүт безі қатерлі ісігі және сүт безінің қатерсіз ауруы бар әйелдердегі шеткергі қан лимфоциттеріндегі ДНҚ қос тізбекті үзілістерін сандық түрде анықтау.*

Әдістері: *Сүт безінің қатерлі ісігі (n=29) және сүт безінің қатерсіз ісіктері (n=24) бар науқастарда автоматтандырылған AKLIDES жүйесін қолдану арқылы лимфоциттерде γ-H2AX ошақтарын талдау.*

Нәтижелер: *«FITC» үзілу арнасындағы негізгі және бақылау топтарының көрсеткіштерін салыстыру кезінде «Орташа өзек диаметрі» (p=0,0382), «Барлық ошақтар үшін орташа қарқындылық мәні» (p=0,0166), «Екі арнадағы қабаттасатын ошақтардың саны» (p=0,0486) көрсеткіштерінде статистикалық маңызды айырмашылық анықталды. «APC» жөндеу арнасында «Люминесценция қарқындылығы жоғары ядролар» (p=0,0166) және «Барлық ошақтар үшін орташа қарқындылық мәні» (p=0,0118) көрсеткішкерде айтарлықтай айырмашылықтар анықталды.*

Қорытынды: *Негізгі және бақылау топтары арасындағы FITC үзіліс және «APC» жөндеу арналары бойынша ДНҚ қос тізбекті үзілу жылдамдығының анықталған өзгерістері сүт безі обырын анықтау үшін диагностикалық маркер ретінде қызмет етуі мүмкін.*

Түйінді сөздер: *ДНҚ қос тізбекті үзілуі, H2AX гистон протеині, сүт безі қатерлі ісігі.*

ABSTRACT

КОЛИЧЕСТВЕННАЯ ОЦЕНКА ДВУЦЕПОЧЕЧНЫХ РАЗРЫВОВ ДНК ПРИ ДОБРОКАЧЕСТВЕННЫХ И ЗЛОКАЧЕСТВЕННЫХ ЗАБОЛЕВАНИЯХ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Актуальность: *Наиболее опасным типом повреждений ДНК являются двуцепочечные разрывы ДНК. Анализ очагов фосфорилированного гистонового белка H2AX (γH2AX) в настоящее время является наиболее чувствительным методом обнаружения двуцепочечных разрывов ДНК (ДЦР). Эта модификация белка может стать индивидуальным биомаркером клеточного стресса, особенно при диагностике и мониторинге неопластических заболеваний. В этом исследовании нами были использованы новые алгоритмы распознавания образов на платформе AKLIDES® для автоматического анализа иммунофлуоресцентных изображений фокусов γH2AX и сравнения результатов с визуальными оценками. Изучено формирование очагов γH2AX на мононуклеарных клетках периферической крови женщин с раком молочной железы (РМЖ) и доброкаче-ственными образованиями молочных желез.*

Цель исследования *– провести количественную оценку двуцепочечных разрывов ДНК в лимфоцитах периферической крови у женщин с раком молочной железы и доброкачественными образованиями молочных желез для определения возможного биомаркера.*

Методы: *Проведение анализа очагов γ-H2AX в лимфоцитах на автоматизированной системе AKLIDES у женщин с РМЖ (n=29) и доброкачественными образованиями молочных желез (n=24).*

Результаты: *При сравнении показателей основной и контрольной групп в канале разрывов «FITC» обнаружена статистически значимая разница показателей «Средний диаметр ядра» (p=0,0382), «Среднее значение интенсивности для всех очагов» (p=0,0166), «Количество перекрывающихся очагов в двух каналах» (p=0,0486). В канале репарации «APC» выявлены достоверные различия показателей «Ядра с повышенной интенсивностью свечения» (p=0,0166) и «Среднее значение интенсивности для всех очагов» (p=0,0118).*

Заключение: *Выявленные изменения показателей двуцепочечных разрывов ДНК по каналам разрывов FITC и репарации APC между основной и контрольной группами, возможно, могут служить биомаркером для выявления РМЖ.*

Ключевые слова: *двуцепочечные разрывы ДНК, гистоновый белок H2AX, рак молочной железы (РМЖ).*

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DWI CAPACITY IN PROSTATE CANCER DIAGNOSING

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ABSTRACT

Relevance: *Prostate cancer is one of the leading causes of cancer deaths in men worldwide. Transrectal ultrasound-guided (TRUS) prostate biopsy is the most important diagnostic step, without which a definitive diagnosis cannot be made. Despite this, TRUS-guided prostate biopsy has a high rate of false negatives and is often accompanied by various clinical complications. Multiparametric MRI (mpMRI) is now widely used in routine urological and oncological practice. An element of mpMRI is diffusion-weighted imaging (DWI), which is successfully used in detecting and localizing clinically significant prostate cancer.*

The study aimed to *evaluate the DWI capacity in diagnosing prostate cancer.*

Methods: *52 patients, 48-86 years old, with suspected prostate cancer, underwent mpMRI. DWI sequences obtained using T2-weighted imaging (T2WI) were compared with each other and compared with the anatomical structure of the prostate. Suspicious prostate cancer sites were marked as regions of interest, for which an apparent diffusion coefficient (ADC) was calculated. A 12-point TRUS-guided biopsy confirmed the presence or absence of prostate cancer.*

Results: *When analyzing quantitative measurements, ADC showed low values for cancer in the cen-tral gland (transitional zone and central zone) – 0.610±0.157×10^{-3} mm^2/s, p=0.0001, and for cancer in the peripheral zone – 0.651±0.228×10^{-3} mm^2/s, p=0.0004, compared to normal tissue. It was found that the highest sensitivity value (87.5%) is typical for ADC central gland, and the lower value for ADC peripheral zone is 75%. The highest specificity value (90.9%) was observed in ADC peripheral zone, and a lower value in ADC central gland – was 84.1%.*

Conclusion: *DWI is an effective non-invasive method for detecting and localizing prostate cancer, providing a qualitative (visual) and quantitative assessment of prostate cancer.*

Keywords: *prostate cancer, multiparametric magnetic resonance imaging (mpMRI), transrectal ultrasound (TRUS), diffusion-weighted imaging (DWI).*

Introduction: Prostate cancer has a high prevalence and is one of the main causes of death of men from oncological diseases worldwide [1]. The problem of early diagnosis of prostate cancer is associated not only with the late treatment of patients but also with the insufficient accuracy of traditional diagnostic methods. The complexity of visualization of tumor foci in the prostate gland (PG) remains an urgent task, despite the modern development of prostate imaging methods. Ultrasound-guided transrectal biopsy of the prostate (TRUS) is the most important diagnostic step, without which it is impossible to make a final diagnosis. Despite this, TRUS-guided prostate biopsy has a high false-negative rate [2] and is often accompanied by various clinical complications [3]. Multiparametric MRI (mpMRI) is widely used in everyday urological and oncological practice. One of the elements of multiparametric MRI is diffusion-weighted imaging (DWI) [4, 5], which is successfully used in the detection and localization of clinically significant prostate cancer [6].

The study aimed to evaluate the DWI capacity in diagnosing prostate cancer.

Materials and methods:

Patients. The study protocol was developed based on the Sunkar Diagnostic and Treatment Center in Almaty, Kazakhstan. We selected 52 prostate cancer suspects aged 48-86 years. The inclusion criteria for the study were: an elevated PSA level and the patient's ability to give informed consent. The exclusion criteria were: contraindications for MRI and inability to decide and/or sign an informed consent sheet.

The mean age of the patients was 65.5 years (interquartile interval: 60.0-71.75), the mean PSA level was 9.5 (interquartile interval: 6.3-9.8 ng/mL), the mean prostate volume was 47, 5 (interquartile interval: 26.75-53.75). All patients underwent TRUS-guided biopsy. Prostate cancer was diagnosed in 8 patients; of them, four (7.7%) had a Gleason score of 7, two (3.8%) scored 8, one (1.9%) scored 6, and another one (1.9%) scored 9 (Table 1).

Table 1 – Characteristics of the study patients

	All (n=52)	Healthy controls, n=44	Prostate cancer patients, n=8	Significance
Age, average [IQR]	65.5 [60.0-71.75]	65.2 [58.25-71.0]	67.3 [63.0-72.0]	p=0.19
PSA (ng/ml), average [IQR]	9.5 [6.3-9.8]	8.1 [6.2-9.5]	17.2 [8.0-17.5]	p=0.08
Prostate volume on MRI (ml), average [IQR]	47.5 [26.75-53.75]	46.1 [25.25-61.0]	55.6 [37.75-53.75]	p=0.23

Table 1 (continued)

Gleason score	Value (%)
Gleason 6 (3 + 3)	1 (12.5%)
Gleason 7 (3 + 4)	4 (50.0%)
Gleason 7 (4 + 3)	0
Gleason 8 (4 + 4)	2 (25.0%)
Gleason 9 (4 + 5)	1 (12.5%)
Localization	n (%)
Cancer in the peripheral zone	3 (37.5%)
Cancer in the central gland	4 (50.0%)
Cancer in the central gland and peripheral zone	1 (12.5%)

Notes: n – number, PSA – prostate-specific antigen, IQR - interquartile range

MRI study protocol. mpMRI was performed on a 3T scanner (Signa Architect, GE, USA) with a surface coil. The data collection protocol included the following sequences:

1. Axial T2-weighted turbo spin echo sequence with fast relaxation T2WI frFSE (TR/TE – 4249/102.7 ms, slice thickness – 4 mm, gap – 0.5 mm, matrix – 352x288 mm, rotation angle (FLIP) – 111°, the number of averages (NEX) – 1, scan time – 2:52 min);

2. Sagittal T2-weighted turbo spin echo sequence with periodically rotated overlapping parallel lines with improved T2WI Propeller reconstruction (TR/TE – 10490/86.0 ms, slice thickness – 4 mm, gap – 0.4 mm, matrix – 320x320 mm, FLIP – 160°, NEX – 2.05, scan time – 5:53 min);

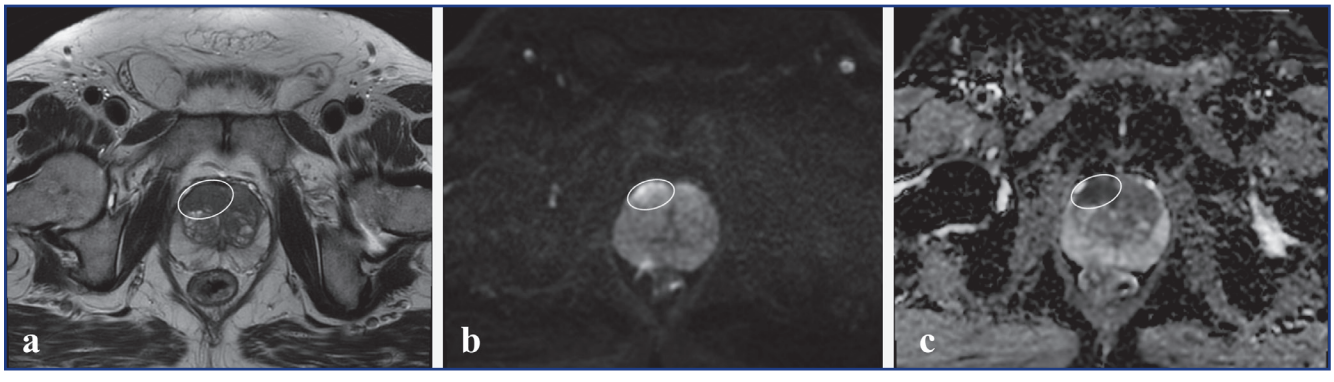
3. Axial T1-weighted turbo spin echo sequence with fat suppression T1WI FSEFS (TR / TE – 751/9.2 ms, slice thickness – 4 mm, gap – 0.5 mm, matrix – 384x224 mm, FLIP – 111°, NEX – 1, scan time – 3:59 min);

4. Coronal T2-weighted turbo spin echo sequence with fast relaxation T2WI frFSE (TR/TE – 5253/102.0 ms, slice thickness – 4 mm, gap – 0.5 mm, matrix – 412x320 mm, FLIP – 160°, NEX – 2, scan time – 4:55 min);

5. Coronal T1-weighted sequence of turbo spin echo T2WI FSE (TR/TE – 693/8.5 ms, slice thickness – 4 mm, gap – 0.5 mm, matrix – 320x320 mm, FLIP – 111°, NEX – 0.5, scan time – 1:55 min);

6. Diffusion-weighted sequence using a single DWI echo-planar sequence (TR/TE – 5400/75.3 ms, slice thickness – 4 mm, gap – 0.5 mm, matrix – 120x120 mm, 3*b*-values – 50, 600, 1000 s/mm^2, FLIP – 90°, NEX – 2, scan time – 3:57 min).

ADC Quantitative Maps. The anatomical structure of the prostate obtained using T2-weighted imaging (T2WI) was compared with DWI data and a map of the measured diffusion coefficient (apparent diffusion coefficient, ADC) obtained from DWI. Regions of interest were manually marked corresponding to cancer-suspicious sites in the central gland (central/transitional zones) and the peripheral zone of the prostate. The remaining sections of the prostate's central/transitional and peripheral zones were considered healthy areas (Figure 1). The average diffusion coefficient on the ADC was measured using the software Volume Viewer (GE, USA) at the workstation (GE) in the regions of interest.



Picture 1 - Education in the central gland prostate: a – T2, b – DWI, c – ADC; white ellipsoid – prostate formation

Pathology. A TRUS-guided 12-point biopsy confirmed the presence or absence of prostate cancer.

Statistical analysis. Microsoft Excel and the IBM SPSS Statistics package served as a tool for the statistical processing of the obtained data. We used Student's t-test to evaluate differences in clinical scores and ADC values between normal tissue and cancerous lesions. Combined data on the results of diagnostic tests and data on the presence of prostate cancer confirmed by biopsy

and the results of association statistics: Fischer's Exact test and odds ratio were used. We calculated the ADC sensitivity and specificity in prostate cancer diagnostics. ADC ROC curve analysis was performed, and the area under the curve (AUC) was calculated.

Results: When analyzing quantitative measurements, ADC showed low values for cancer in the central gland (transition zone and central zone) – 0.610±0.157 (mean value ± SD)×10^{-3} mm^2/s, p=0.0001 and for cancer in the peripheral zone – 0.651±0.228 (mean value ± SD)×10^{-3} mm^2/s, p=0.0004, compared with normal tissue (table 2).

Table 2 – DWI values: ADC in the peripheral zone and central gland (transitional/central zones)

Values (10^{-3} mm^2/s)	Normal tissue	Prostate cancer	Average difference	Significance
Peripheral zone	1.279±0.457	0.651±0.228	-0.628	0.0004
Central gland	0.885±0.173	0.610±0.157	0.610	0.0001

Note: Data are presented as mean value ± standard deviation

When the ADC value in the identified cases of prostate cancer is correlated with the Gleason scale, lower ADC values (0.375×10^{-3} mm^2/s and 0.498×10^{-3} mm^2/s) correspond to the sum of Gleason scores of 9 and 8 (Table 3), which indicates a proportional relationship between ADC values and tumor aggressiveness.

Table 3 – ADC correlation with the Gleason score in post-biopsy patients

Central gland ADC (10^{-3} mm^2/s)	**Peripheral zone** ADC (10^{-3} mm^2/s)	**Gleason score**
0.685	0.692	7(3+4)
0.550	0.550	7(3+4)
0.570	0.590	7(3+4)
0.498	0.498	8(4+4)
0.912	0.935	7(3+4)
0.626	1.044	6(3+3)
0.665	0.525	8(4+4)
0.375	0.375	9(4+5)

Table 4 presents the combined data on the results of diagnostic tests and data on biopsy-confirmed prostate cancer, as well as the results of association statistics: Fischer's Exact test and odds ratio. Based on the analysis results, a statistically significant relationship/dependence was revealed between the diagnostic ability of the ADC of the central gland and the peripheral zone to correctly determine the presence of prostate cancer in patients. Fischer's Exact test statistic was considered significant at p<0.001.

Table 4 – Baseline test results vs. biopsy-confirmed prostate cancer and association statistics

Diagnostic tests	prostate cancer		Fischer's Exact test (FET)	Odds ratio
	+	–		
Diagnosis of ADC (central gland)				
Below 0.700×10^{-3} mm^2/s	7	7	FET=0.00018, p<0.001	37.000
Over 0.700×10^{-3} mm^2/s	1	37		
ADC diagnostics (peripheral zone)				
Below 0.700×10^{-3} mm^2/s	6	4	FET=0.00025, p<0.001	30.000
Over 0.700×10^{-3} mm^2/s	2	40		

The obtained results indicate that the ADCs of the central gland below the threshold of 0.700×10^{-3} mm^2/s increase the chance of clinical verification of prostate cancer by 37 times, and the peripheral zone ADC values below 0.700×10^{-3} mm^2/s increase the prostate cancer probability 30 times.

Table 5 presents the ADC sensitivity and specificity in diagnosing prostate cancer. The highest sensitivity of 87.5% was typical for the central gland's ADC, and the peripheral zone's ADC had a lower sensitivity of 75%. ADC of the peripheral zone had the highest specificity of 90.9%, and the ADC of the central gland had a lower specificity of 84.1%.

Table 5 – ADC sensitivity and specificity in prostate cancer diagnosing

Diagnostic tests	Sensitivity	Specificity
ADC (central and transitory zone)	0.875	0.841
ADC (peripheral zone)	0.750	0.909

Along with determining sensitivity and specificity values, plots of sensitivity versus specificity were plotted. Figure 2 shows the ROC curves of the diagnostic ability of the logistic regression model for adenocarcinoma verification.

The constructed curves for the central gland and the peripheral zone ADCs mostly located in the upper left corner of the graph, indicating acceptable diagnostic properties of the tests.

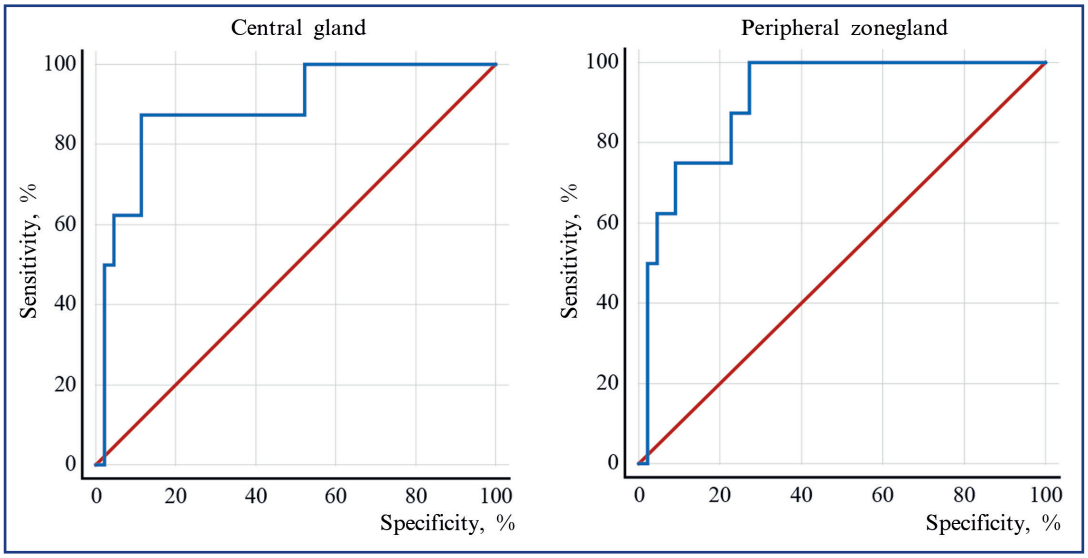


Figure 2 – ROC curves of diagnostic ability of the logistic regression model of prostate cancer verification

At the final stage, the area under the ROC curves was estimated (Table 6).

Table 6 – Area under the ROC curve

Diagnostic tests	Area [CI]	Asymptotic Significance
ADC (central gland)	0.889 [0.733÷1.000]	p=0.001
ADC (peripheral zone)	0.909 [0.820÷0.998]	p<0.001

In the study, ADC showed high diagnostic accuracy, with an area of -0.909 for the peripheral zone and -0.889 for the central gland. Both tests are characterized by high (excellent) quality predictive accuracy.

Discussion: Diffusion is a physiological process of random thermal movement of water molecules in tissues. Visualization of the DWI image is determined by the difference in the speed of movement of water molecules in different biological tissues, and this movement is inversely proportional to the cellularity of the tissue and the integrity of the cell membrane. Therefore, diffusion capacity is retained in normal tissue, resulting in low signal intensity on DWI. Tumor formation destroys the normal tissue structure and has a higher cell density than normal tissue. Therefore, in the cancerous tissue, the movement of water molecules is limited, resulting in high signal intensity on DWI. In addition, using DWI, differences in the movement of water molecules are qualitatively assessed by the relative intensity of the tissue signal but can also be assessed quantitatively by calculating the ADC [7].

In everyday clinical practice, an MRI of the prostate is performed using 1.5- or 3 T-tomographs using a multichannel surface coil for the trunk or endorectal coil. The endorectal coil increases the signal-to-noise ratio (SNR) of an MR image, but high examination cost, patient discomfort, and susceptibility artifacts limit its use [5]. DWI is usually performed in the axial plane using single or multiple EPI planar echo imaging. In particular, single EPI is sensitive to motion and susceptibility artifacts to any metal inserts in the body or air in the rectum. For DWI of the prostate, B values from 50 to 1400 s/mm^2 on a 1.5 T tomograph and from 1000 to 2000 s/mm^2 on a 3 T tomograph are commonly used [5]. In our study, we performed DWI on a 3 T MRI using a single echo-planar sequence and a surface coil.

In earlier studies, using a 1.5 T tomograph, ADC values in normal prostate tissues were as follows: in the peripheral zone of the prostate – 1.0-1.9×10^{-3} mm^2/s; in the central gland of the prostate (central and transient zone) – 0.9-1.7×10^{-3} mm^2/s. When using a 3.0 T tomograph, the ADC values in normal tissues of the prostate were as follows: in the peripheral zone of the prostate – 0.8-2.6×10^{-3} mm^2/s; in the central gland of the prostate (central and transient zone) – 0.8-2.2×10^{-3} mm^2/s. ADC values tended to be higher in the peripheral zone than in the central gland and higher with the 3.0 T scanner than the 1.5 T scanner [7].

The values of ADC in malignant lesions of the prostate using a 1.5 T tomograph were as follows: in the pe-

ripheral zone – 0.6-1.4×10^{-3} mm^2/s; in the central gland – 0.9-1.1×10^{-3} mm^2/s; when using a 3.0 T tomograph: in the peripheral zone – 0.6-1.6×10^{-3} mm^2/s, in the central gland – 0.8-1.6×10^{-3} mm^2/s. Therefore, the ADC values in the peripheral zone and the central gland were almost identical but tended to increase when using a 3.0 T tomograph. In addition, in all studies conducted, ADC values in malignant lesions of the peripheral zone and central gland were lower than the normal prostate's corresponding areas. Moreover, at higher b values, ADC values in normal and cancerous tissues tended to decrease [7].

In our study using a 3.0 T tomograph, in normal tissues of the prostate, there was also an increase in the ADC value in the peripheral zone (1.279±0.457×10^{-3} mm^2/s, mean ± SD) compared with the central gland (0.885.25±0.173×10^{-3} mm^2/s, mean ± SD). ADC values in cancer-suspicious areas were lower compared to normal prostate tissue both in the peripheral zone (0.651±0.228×10^{-3} mm^2/s, mean ± SD) and in the central gland (0.610±0.157×10^{-3} mm^2/s, mean ± SD).

However, ADC values can often be the same in normal and cancerous tissues. Some studies have reported limitations in differentiating normal tissue from malignant lesions. In particular, the use of ADC threshold values of 1.67×10^{-3} mm^2/s for the peripheral zone and 1.61×10^{-3} mm^2/s for the central gland on a 1.5 T tomograph gives good results in detecting prostate cancer with sensitivity and specificity of 94% and 91% for the peripheral zone and 90% and 84% for the central gland. The use of the ADC threshold value of 1.35×10^{-3} mm^2/s demonstrates the sensitivity and specificity of ADC in detecting prostate cancer – 88% and 96%, respectively, both in the peripheral zone and the central gland [7]. Therefore, differences in magnetic field strength affect the accuracy of prostate cancer diagnosis. In addition, ADC measurement is particularly useful for improving the detection of central cancer (central and transient zone), as there are significant differences in ADC values in central cancer, stromal hyperplasia, and glandular hyperplasia [5, 8].

In our study, we used ADC threshold values for the peripheral zone and central gland – 0.700×10^{-3} mm^2/s, while the sensitivity and specificity of prostate cancer diagnosis for the peripheral zone were 75% and 90.9%, respectively, and for the central gland – 87.5% and 84.1%, respectively. The results obtained are comparatively lower than previous studies, which is more likely due to the low threshold value of ADC and the small number of patients.

In recent studies, prostate cancer detection sensitivity on T2WI was 54-96%, with a specificity of 21-91%, but the results varied between studies. The low specificity of T2WI has also been reported. DWI has a relatively high specificity, and when DWI is combined with T2WI, sensitivity and area under the ROC curve increase [7, 8].

Our study compared T2WI and DWI, followed by the ADC measurement in cancer-suspicious prostate areas, and showed high diagnostic accuracy, with a ROC curve area of 0.909 for the peripheral zone and 0.889 for the central gland.

Compared to T2WI and DCE, DWI is the most effective and the only sequence for detecting prostate cancer [5]. The combination of DWI and T2WI – biparametric MRI (bpMRI) – increases the sensitivity of diagnosing prostate cancer of both the central gland and the peripheral zone [9-14]. However, bpMRI provides a lower prostate cancer diagnosing accuracy compared to the combined use of T2WI, DWI, and DCE (mpMRI) [10, 14].

Higher *b*-values may increase diffusion weighting, contrast-to-noise ratio (CNR), and theoretically better prostate cancer detection. The disadvantages are the frequent appearance of motion and susceptibility artifacts and a reduced SNR [7]. Koo et al. compared b=1000 s/mm^2 and b=2000 s/mm^2 and reported that b=1000 s/mm^2 had a higher ADC sensitivity in detecting prostate cancer, but the specificity at b=1000 s/mm^2 was lower compared to b=2000 s/mm^2 [15]. After qualitatively evaluating the DWI image, Rosenkrantz et al. and Ueno et al. showed that b=2000 s/mm^2 is preferable for diagnosing prostate cancer compared to b=1000 s/mm^2 [16, 17]. When evaluating ADC maps in the diagnosis of prostate cancer, Rosenkrantz et al. found no significant difference between b=1000 s/mm^2 and b=2000 s/mm^2 [16]. In a qualitative DWI image analysis, Manenti et al. reported a higher sensitivity of b=2000 s/mm^2 than b=1000 s/mm^2 in diagnosing prostate cancer for less and more experienced radiologists. In their opinion, images with a value of b=1000 s/mm^2 cannot suppress benign prostate tissue and sometimes hide tumor lesions. Regarding the quantification of ADC maps, a higher diagnostic accuracy was obtained at b=2000 s/mm^2 compared to b=1000 s/mm^2, although this was not statistically significant [18].

In our study using a 3 T tomograph, we applied b = 50, 600, and 1000 s/mm^2 and obtained a good SNR and a few motion or susceptibility artifacts. At the same time, the signal intensity in the cancerous areas on DWI was increased, while in the surrounding normal areas, it decreased (Fig. 1).

Assessment of tumor aggressiveness with ADC is currently an area of clinical application of DWI that is attracting much attention. According to some authors, ADC can serve as a potential marker of PCa aggressiveness and a prognostic indicator [7]. Several investigators have reported that ADC can detect high-risk cancers with a Gleason score of ≥7 [19, 20]. While previous studies have shown the importance of using ADC with a high b value for differentiating a non-cancerous lesion from prostate cancer, in the study by Barbieri et al., these parameters were found to provide little additional information when correlating high and low grade formation. They reported that ADC values differ between high-grade and low-grade prostate cancer, but given the large overlap in ADC values between high- and low-grade

prostate cancer, non-invasive diagnosis of individual patients using DWI in clinical practice is not yet possible [21].

We correlated the ADC value in identified cases of prostate cancer with the Gleason score and found that lower ADC values (0.375×10^{-3} mm^2/s and 0.498×10^{-3} mm^2/s) to the Gleason scores of 9 and 8, indicating a proportional relationship between the ADC value and the tumor aggressiveness.

Our study demonstrates high diagnostic accuracy DWI using a 3.0 T tomograph, with *b*-values = 50, 600, 1000 s/mm^2, ADC threshold for the peripheral zone and central gland – 0.700×10^{-3} mm^2/s in the diagnosis of prostate cancer.

Conclusion: DWI is an effective non-invasive method for diagnosing and localizing prostate cancer, providing a qualitative (visual) and quantitative assessment of prostate cancer.

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АНДАТПА

ҚУЫҚ АСТЫ БЕЗІНІҢ ҚАТЕРЛІ ІСІГІН ДИАГНОСТИКАЛАУДАҒЫ DWI-дың МҮМКІНДІКТЕРІ

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Өзектілігі: *Қуық асты безінің қатерлі ісігі бүкіл әлем бойынша ерлер арасындағы қатерлі ісік өлімінің негізгі себептерінің бірі болып табылады. УДЗ жетекшілігімен қуық асты безінің трансректалды биопсиясы диагностикалық маңызды қадам болып табылады, онсыз соңғы диагнозды қою мүмкін емес. Осыған қарамастан, УДЗ басқаратын қуық асты безінің биопсиясы жоғары жалған-теріс көрсеткішке ие және жиі әртүрлі клиникалық асқынулармен байланысты. Көппараметрлі МРТ қазіргі уақытта күнделікті урологиялық және онкологиялық тәжірибеде белсенді түрде қолданылады. Көппараметрлі МРТ элементтерінің бірі простата безінің клиникалық маңызды обырын анықтауда және локализациялауда сәтті қолданылған диффузиялық өлшенген бейнелеу (DWI) болып табылады.*

Зерттеудің мақсаты *– қуық асты безінің қатерлі ісігін диагностикалауда DWI мүмкіндіктерін бағалау.*

Әдістері: *48-86 жас аралығындағы қуық асты безінің обырына күдікті 52 пациентке көппараметрлік МРТ, соның ішінде DWI жүргізілді. Алынған T2WI, DWI реттілігі бір-бірімен және қуық асты безінің анатомиялық құрылымына сәйкес салыстырылды. Қуық асты безінің қатерлі ісігінің күдікті жерлері қызығушылық аймақтары ретінде (ROI) белгіленді, олар үшін өлшенетін диффузия коэф-*

фициенті (ADC) есептелді. Қуық асты безінің қатерлі ісігінің болуы немесе болмауы ультрадыбыстық бақылаудағы 12 нүктелі трансректалды биопсияның көмегімен расталды.

Нәтижелері: *сандық өлшемдерді талдау кезінде, қалыпты тінмен салыстырғанда, ADC орталық бездегі қатерлі ісік (өтпелі аймақ және орталық аймақ) үшін төмен мәндерді көрсетті – 0,610±0,157×10^{-3} мм^2/с, p=0,0001 және перифериялық аймақтағы ісік үшін – 0,651±0,228×10^{-3} мм^2/с, p=0.0004. Сезімталдықтың ең жоғары мәні (87,5%) ADC орталық без үшін, ал төменгі мән ADC перифериялық аймақ үшін 75% болатыны анықталды. Ең жоғары ерекшелік мәні (90,9%) ADC перифериялық аймақ, ал төменгі мән ADC орталық без – 84,1% болды.*

Қорытынды: *DWI – қуық асты безінің қатерлі ісігін анықтау, локализациялау, қуық асты безінің қатерлі ісігінің сапалық (визуалды) және сандық бағалауын қамтамасыз ететін пайдалы инвазивті емес әдіс.*

Түйінді сөздер: *мультипараметрлік магнитті-резонанстық томография, трансректалды ультрадыбыстық зерттеу, диффузиялық өлшенген бейнелеу (DWI).*

АННОТАЦИЯ

ВОЗМОЖНОСТИ DWI В ДИАГНОСТИКЕ РАКА ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

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Актуальность: *Рак предстательной железы (РПЖ) является одной из главных причин смертности мужчин от онкологических заболеваний во всем мире. Трансректальная биопсия предстательной железы (ПЖ) под контролем ультразвукового исследования (ТРУЗИ) является важнейшим диагностическим этапом, без которого невозможно поставить окончательный диагноз. Несмотря на это, биопсия ПЖ под контролем ТРУЗИ имеет высокий уровень ложно-отрицательных результатов и часто сопровождается различными клиническими осложнениями. Мультипараметрическая МРТ (мпМРТ) в настоящее время активно применяется в повседневной урологической и онкологической практике. Одним из элементов мультипараметрической МРТ является диффузионно-взвешенная визуализация (DWI), которая успешно используется в выявлении и локализации клинически значимого РПЖ.*

Цель исследования *– оценить возможности DWI в диагностике рака предстательной железы.*

Методы: *52 пациентам в возрасте 48-86 лет с подозрением на РПЖ была проведена мпМРТ. DWI последовательности, полученные при помощи Т2-взвешенной визуализации (T2WI), были сопоставлены между собой и сравнены с анатомическим строением ПЖ. Подозрительные на рак участки ПЖ были отмечены как области интереса, для которых рассчитывали измеряемый коэффициент диффузии (apparent diffusion coefficient, ADC). Наличие или отсутствие РПЖ было подтверждено путем проведения 12-точечной биопсии под контролем ТРУЗИ.*

Результаты: *При анализе количественных измерений ADC показала низкие значения при раке в центральной железе (переходная зона и центральная зона) – 0,610±0,157×10^{-3} мм^2/с, p=0,0001 и при раке в периферической зоне – 0,651±0,228×10^{-3} мм^2/с, p=0,0004, по сравнению с нормальной тканью. Установлено, что наибольшее значение чувствительности (87,5%) характерно для ADC центральной железы, а меньшее значение для ADC периферической зоны – 75%. Наибольшее значение специфичности (90,9%) наблюдалось у ADC периферической зоны, а меньшее значение у ADC центральной железы – 84,1%.*

Заключение: *DWI – эффективный неинвазивный метод диагностики и локализации РПЖ, обеспечивающий качественную (визуальную) и количественную оценку РПЖ.*

Ключевые слова: *рак предстательной железы (РПЖ), мультипараметрическая магнитно-резонансная томография (мпМРТ), трансректальное ультразвуковое исследование (ТРУЗИ), диффузионно-взвешенная визуализация (DWI).*

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THE ROLE OF CLINICAL-HEMATOLOGICAL AND CYTOGENETIC CHARACTERISTICS IN THE PROGRAM THERAPY OF B-CELL LEUKEMIA IN CHILDREN IN THE REPUBLIC OF KAZAKHSTAN

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ABSTRACT

Relevance: *The study of immunological and molecular genetic characteristics of leukemia in children and the influence of biological features of the tumor population of acute B-cell lymphoblastic leukemia (B-ALL) on the effectiveness of therapy is particularly relevant for the Republic of Kazakhstan.*

The study aimed to *evaluate the effectiveness of modern program chemotherapy in children depending on the biological characteristics of B-cell leukemias.*

Methods: *The study analyzed the data of 154 children aged six months to 15 years with primary B-ALL on inpatient treatment at the Scientific Center of Pediatrics and Pediatric Surgery JSC (Almaty, the Republic of Kazakhstan) in 2016-2018. When determining events, we were guided by the criteria of the protocols of the ALL-BFM group.*

Results: *The age groups most exposed to B-ALL were 3-7 years old (43.5%), reflecting the so-called infant peak. In the clinical picture of this type of ALL, intoxication syndrome accompanying the period of manifestation was present in 75.3% of patients. The clinical polymorphism of the debut period determined the most diverse list of diagnoses of "masks." Damage to organs and systems, in the form of liver failure, was detected in 41 (26.6%) children, with the development of respiratory failure in 12 (7.8%), cardiovascular failure in 5 patients (3.2%), acute kidney injury in 3 (1.9%), CNS damage in 5 (3.2%) patients. With B-ALL, the distribution of immunological variants was determined as follows: B1 – 9 (5.8%), B2 – 123 (79.8%), B3 – 18 (11,7%), B4 – 4 (2,6%) and leukemia of B-cell lymphoma was noted in one (0.6%) patient. From the group of quantitative anomalies, hyperploidy was detected in 12 (7.8%) cases. Among qualitative anomalies, t(12;21) (p13;q22) was determined in 6 (3.9%) patients and was a favorable prognostic factor (remission was recorded). Trisomy of chromosome 21 with Down syndrome in 3 (1.9%) patients with combined anomalies (isochromosome 7, trisomy 4, 6, 15, 17, translocation t(9; 22) (q34;q11) was detected in 1.3%. Translocations t(1;19)(q23;p13.3) in 5.8% and del 9-chromosome defect in 3.2% of cases.*

Conclusion: *The response to therapy and long-term prognosis are largely determined by biological factors such as cytogenetic features of the tumor, sensitivity to prednisone, as well as the degree of aggressiveness, which manifests itself in the form of pronounced symptoms of lymphoproliferation and hyperleukocytosis. The research has shown the high efficiency of modern ALL-BFM program therapy in children.*

Keywords: *children, acute B-cell lymphoblastic leukemia, blast cells, immunophenotyping, cytogenetic study.*

Introduction: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer [1]. ALL means a heterogeneous group of hematological malignancies characterized by abnormal proliferation of immature lymphoid cells. It is the most commonly diagnosed childhood cancer, with an almost 80% cure rate. Despite favorable survival rates in pediatric population, some patients develop resistance to therapy, relapse of the disease, and clonal evolution of cells, which determines a poor prognosis of the disease.

Leukemia is caused by abnormal changes in the lymphoid lineage of blood cells that can affect the bone marrow, blood, and extramedullary sites, causing bone and joint pain, fatigue and weakness, swollen lymph nodes, pale skin, easy bleeding or bruising, fever, or infection.

The currently used classification system for hemoblastoses is based on a combined analysis of clinical and biological data (cytology, immunophenotype, and cell cytogenetics) [2, 3]. ALL can be classified into acute B-cell lymphoblastic leukemia (B-ALL) (85% of cases) and T-ALL types. An oncological lineage of mature B cells indicates a rapidly growing Burkitt's lymphoma or acute leukemia from B cell progenitors [4].

Recent advances in molecular biology and new technologies resulted in a significantly better understanding of ALL pathophysiology. In some patients, environmental risk factors interacted with hereditary genetic susceptibility. Chromosomal and genetic anomalies play a significant role in the pathological differentiation and proliferation of lymphoid precursor cells. New findings

in molecular genetics, pharmacology, and related fields shall change the B-ALL diagnostics and treatment [5]. The intensive development of next-generation sequencing in the last decade has expanded the study of genomic changes. New technologies allowed detecting molecular changes such as point mutations and characterizing epigenetic or proteomic profiles. Newly researched subtypes of this disease are characterized by genetic changes, including changes in chromosomes, sequence mutations, and changes in the number of DNA copies. These genetic abnormalities are used as diagnostic, prognostic, and predictive disease biomarkers.

Next-generation sequencing during leukemogenesis has proven the B-ALL heterogeneity. This emphasizes the diversity of the pathogenesis of a malignant clone, predetermines the nature of the clinical course of the tumor, differences in susceptibility or resistance to chemotherapy, and opens up prospects for targeted treatment [6].

Thus, the pronounced heterogeneity of the studied pathology attaches great importance to diagnosing molecular genetic changes in patients for the prognosis of the tumor process [7]. The analysis of these studies is important for understanding the theoretical foundations of the development of leukemia, optimizing the results of tumor pathology chemotherapy by establishing a linear affiliation, the stage of cell maturity, accurately determining the variant of leukemia, and stratifying into program risk groups [8, 9].

Materials and Methods: A retrospective analysis of the case histories of 154 children aged six months to 15 years with primary B-ALL who were hospitalized at the Scientific Center of Pediatrics and Pediatric Surgery JSC (Almaty, Kazakhstan) in 2016-2018 was carried out. The analysis of clinical and laboratory data and the dependence of the response to therapy on the level of leukocytosis, lymphoproliferative syndrome (LPS), cytogenetic changes, and completeness of the response to the cytoreduction phase with prednisolone was performed. The effectiveness of specialized therapy was measured by 5-year event-free survival (EFS) and overall survival (OS) calculated using the Kaplan-Meier method. The therapy results were assessed by the number of patients who achieved complete remission and are in complete long-term remission, as well as by the number of induction deaths and deaths in remission. The minimum follow-up period for the entire group of patients with ALL was 23 months.

Results: The age and gender analysis of patients showed the boys-to-girls ratio in the B-ALL group of 1.16:1 (53.8%, n=83: 46.1%, n=71). Most children with B-ALL were 3-7 years old (43.5%, n=67) or below three years (22.7%, n=35). This corresponds to the so-called infant peak noted by other researchers [10, 11]. Children of the older age groups, 7-10 and 10-15 years old, accounted for 15.6%, respectively. The nationality analysis revealed a significant predominance of children of Kazakh nationality – 77.9%. Representatives of Slavic peoples were second in terms of incidence and accounted for 20.8% of cases.

Clinically, in 75.3% of patients with B-ALL, the intoxication syndrome during the period of manifestation was manifested by weakness, lethargy, hypodynamia, asthenia, fever from subfebrile to febrile values, sweating, and weight loss. The disease manifestation was due to the multiplication and accumulation of blast cells. Exceeding the conditional threshold limit (more than 1000 billion) of blast cells leads to the depletion of the body's compensatory capabilities depending on the degree of hematopoiesis suppression and the intensity of manifestations outside the bone marrow [10, 11]. This was confirmed by the length of the period from the onset of the first symptoms to the diagnosis (Figure 1).

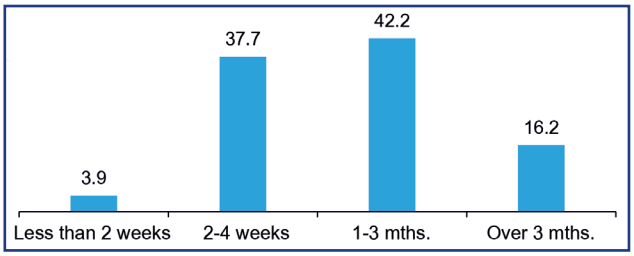

Figure 1 - Duration of the disease before diagnosis in children with B-ALL (%)

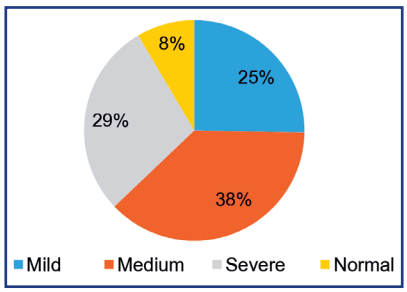

Figure 2 - Anemia levels in children with B-ALL (%)

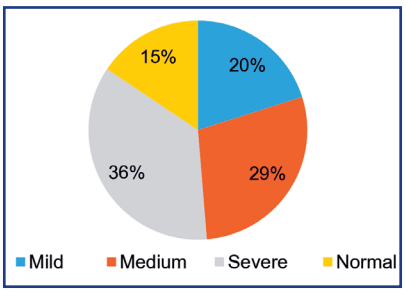

Figure 3 - Thrombocytopenia levels in children with B-ALL (%)

The severity of the anemic syndrome is shown in Figure 2. In 75% of cases, hemorrhagic syndrome of varying severity was observed due to thrombocytopenia (Figure 3).

The level of leukocytes in the blood was normal in 30 (5%) cases; =14), leukocytosis over 100x10^9/l – in 4.5% (n=7), leukopenia – in 26.6% (n=41) of patients. Blastemia, regardless of the total number of leukocytes, was observed in 87% of patients.

The analysis of EFS and OS in all five groups (Figures 4-8) showed high survival rates in children in groups with leukocytosis up to 50 thousand cells per µl (OS – 85.6±5.5, EFS – 83.3±5.8), as well as with normal (OS – 74.5±6.3, EFS – 74.5±6.3) and low levels of leukocytes (OS – 85.4±5.5, EFS – 82.1±6.2), and a significantly lower survival rate, especially EFS, in children with initial hyperleukocytosis (OS – 42.9±18.7, EFS – 28.6±17.1). At the same time, this statistically unreliable indicator difference was most likely due to a statistically unrepresentative sample of patient groups.

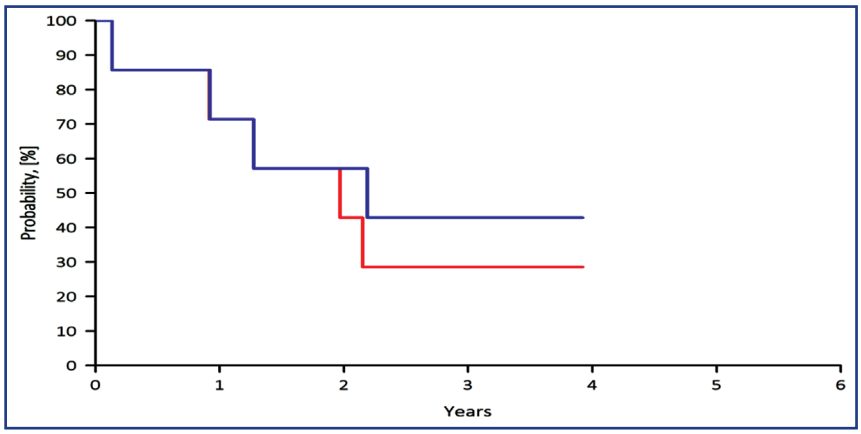

Figure 4 – EFS and OS of children with hyperleukocytosis (over 100,000/L)
(n=7, OS – 42.9±18.7%, EFS – 28.6±17.1%)

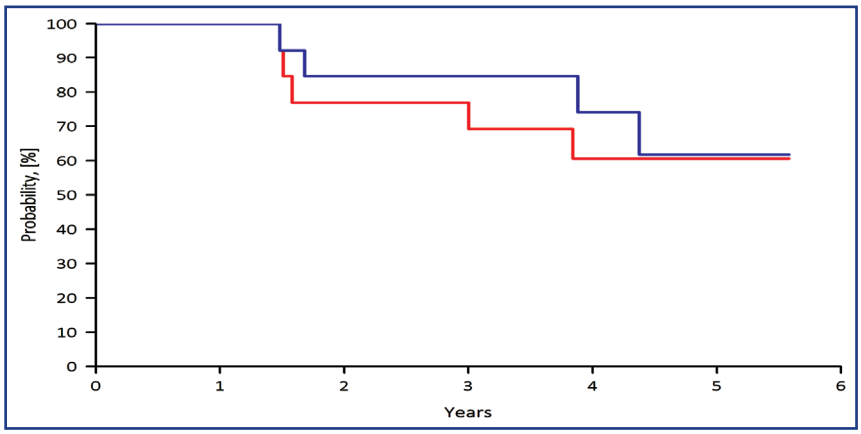

Figure 5 - EFS and OS of children with hyperleukocytosis (50-99,900/L)
(n=13, OS – 61.7±15.7%, EFS – 60.6±13.8%)

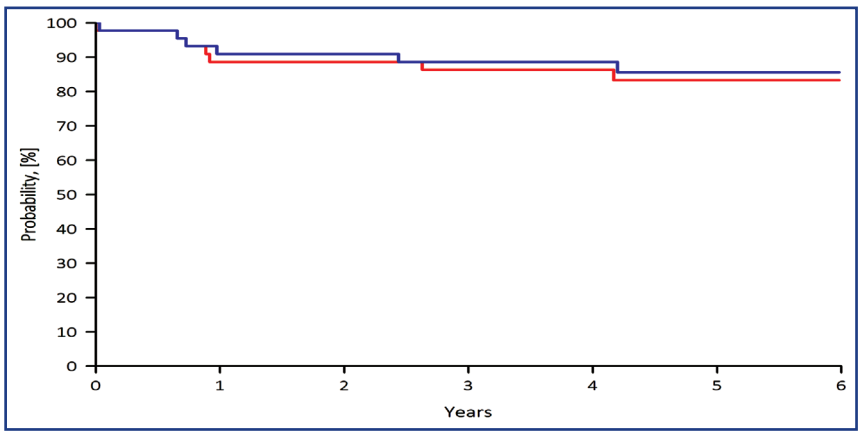

Figure 6 – EFS and OS of children with leukocytosis (up to 49,9000/L)
(n=45, OS – 85.6±5.5%, EFS – 83.3±5.8%)

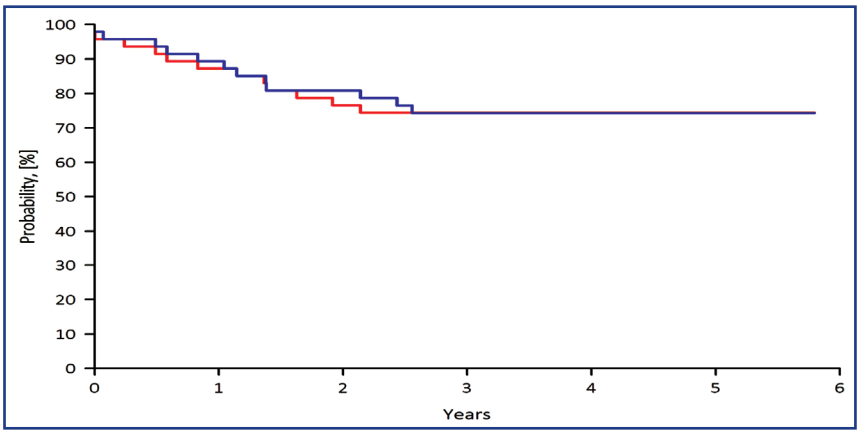

Figure 7 - EFS and OS in children with normal leukocyte levels
(n=47, OS – 74.5±6.3%, EFS – 74.5±6.3%)

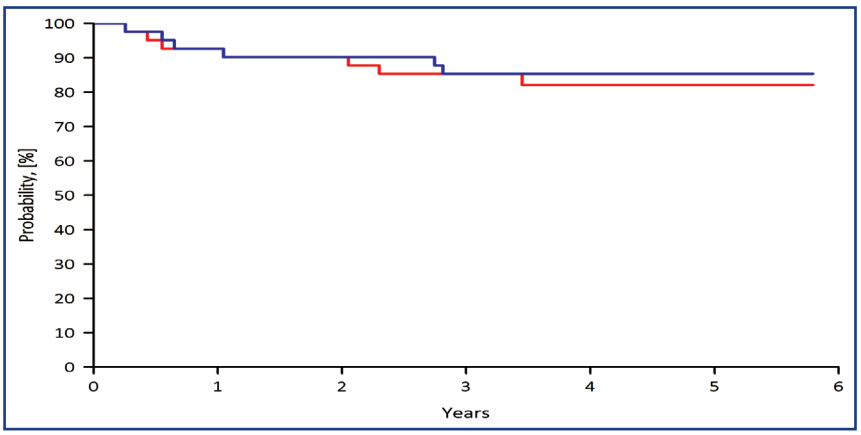

Figure 8 - EFS and OS in children with leukopenia
(n=41, OS – 85.4±5.5%, EFS – 82.1±6.2%)

LPS, one of the typical symptoms of this disease in children, was determined in 75.3% of cases. A comparison of survival rates showed a relatively worse survival prognosis in children with various manifestations of hyperplastic syndrome (Fig. 9 & 10).

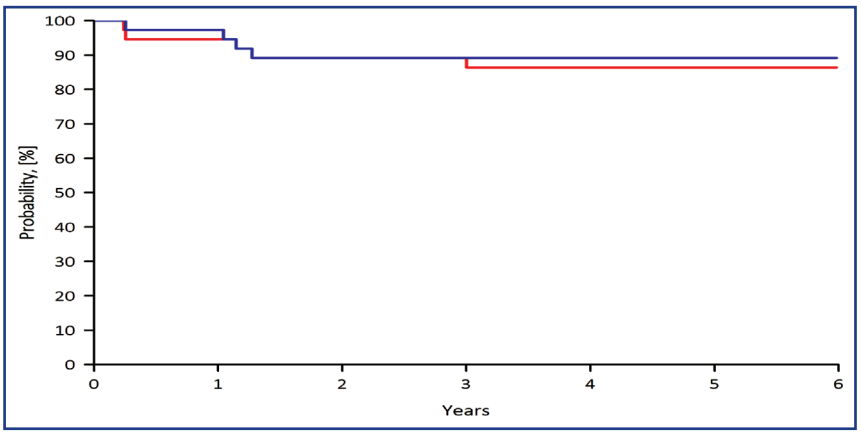

Figure 9 – EFS and OS in children without LPS
(n=37, OS – 89.2±5.1%, EFS – 86.4±5.6%)

Various mask diagnoses manifested clinically in the debut period (such as SARS, pneumonia, tonsillitis, otitis media, infectious mononucleosis, arthritis, mumps, lymphadenitis, stomatitis, hepatitis, and cholecystitis) challenged the diagnosis.

The cytomorphological study revealed the following B-ALL variants: L1 – 41 (26.7%), L1-L2 – two cases (1.3%), L2 – 107 (69.5%), and L3 – four cases (2.6%).

In our study, in all cases of B-linear leukemia, blast cells expressed CD19 and/or CD79a and/or cytoplasmic

CD22 and stem cell marker CD34, as well as differentiation clusters CD33 and CD41. In total, the B-ALL immunological variants determined by a set of line-associated markers of the differentiation stage included B1 in nine cases (5.8%), B2 – 123 (79.8%), B3 – 18 (11.7%), and B4 – in 3 cases (1.9%). Leukemization of B-cell lymphoma was noted in one (0.6%) patient.

At present, cytogenetic and molecular genetic studies are widely used to diagnose blood cancers. The cytometric DNA index is a quantitative indicator of chromosomal anomalies in tumor cells. Chromosomal translocations that determine ALL subvariants usually occur first, followed by point mutations and deletions acquired due to clonal evolution. A cytogenetic study of bone marrow blast cells revealed chromosomal anomalies in 58 (37.6%) patients. See Table 1 for cytogenetic test results and the most common chromosomal anomalies detected in the study participants.

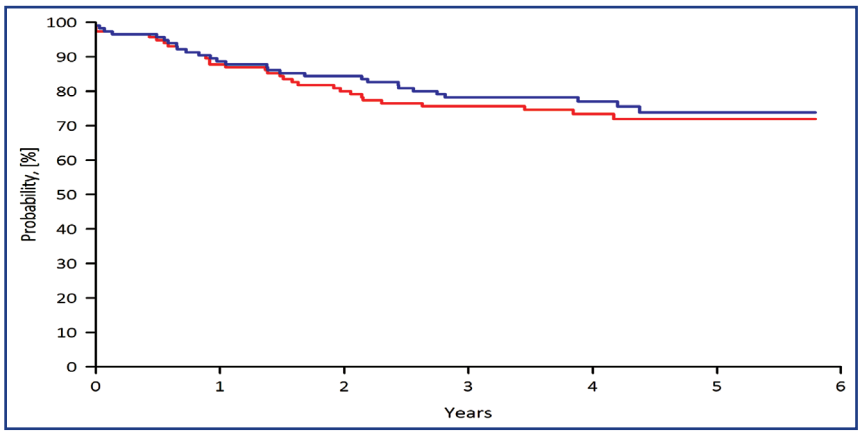

Figure 10 – EFS and OS in children with HFRS
(n=116, OS – 73.9±4.4%, EFS – 72.0±4.3%)

Table 1 – Chromosomal anomalies in patients with B-ALL

Anomalies	Number of patients (abs. /%)	Concomitant anomalies
Translocation t(12; 21)(p13; q22)	6/3.9%	+ ETV / RUNX 1 - 4, + RTV / RUNX ! - 1
Hyperploid karyotype	12/7.8%	
C - MYC	2/1.3%	+t(8;14)(q24;q32) – 1
MLL	5/3.2%	
Translocation t(1;19)(q23;p13)	9/5.8%	
Translocation t(9;22)(q34;q11)	2/1.3%	(+ t (7;12)(q36;p13), chromosome 12 monosomy – 1)
Trisomy of 21st chromosome	3/1.9%	(+ additional isochromosome 7,
Deletion of chromosome 9	5/3.2%	(+ t(4;11)(q21;q23) t(5;12) (q33; p13) – 1, + monosomy of chromosome 20 – 1, + monosomy of chromosome 7 – 1, + t (9;22) (q34 ;q11) – 1)
Single cases of anomalies	+ concomitant anomalies	
Translocation t(14;15)(q32;q11)		
Translocation t(9;17)(p13;p12)		
Translocation t(1;19)(q23;p13)	isochromosome 9	
Translocation t(2;11)(p21;q23)MDS	trisomy 8	
Trisomy of 7th chromosome	isochromosome 7	
Karyotype 45, xx	monosomy on chromosome 20	
Translocation t(4;11)(q21;q23)	extra X chromosome	48 XY, + der (4)
Karyotype 45, XY	Translocation t(12;13) (p13;q12)	
Karyotype 46, XY	Translocation t(12;20) (q13;p11.2)	add (22 q) ETV 6/ RUNX 1
The (1;18)(q10;q10) translocation in 60% of cells	Translocation t(1;18;22) was detected in 10% of cells	
Translocation t(3;6)(p21;q15).		
Translocation t(8;11)(p11;p15)		
Translocation (t(8;14), t(8;22),	Duplication of the q-arm of the 1st chromosome	
Rob (14;14) (q10:q10)		

Among quantitative anomalies, hyperploidy (additional chromosomes 4,10,17) was detected in 12 (7.8%) cases. All these patients showed an early response to therapy and preserved remission to date; no relapses were recorded.

Translocations mean the exchange of genetic material between chromosomes [4, 10]. The most common examples of such translocations are t(12;21)(p13; q22) with the TEL-AML hybrid gene and t(9;22) translocation with the BCR-ABL chimeric gene. In B-ALL, chromosomal rearrangements t(8;14)(q24.1;q32) transfer the MYC oncogene under the control of regulatory elements in the IGH locus [10].

The identified translocations from the group of qualitative anomalies were distributed among patients inhomogeneously (Table 1). Thus, in our study, t(12;21) translocation detected in 6 (3.9%) patients was a favorable prognostic factor. All six patients were in remission during treatment.

Three (1.9%) patients with a hereditary burden (Down's syndrome) had a trisomy of 21st chromosome with concomitant anomalies including an additional isochromosome 7 and trisomy 4, 6, 15, and 17.

The Philadelphia chromosome t(9;22)(q34;q11) was found in two (1.3%) patients.

In our study, nine (5.8%) patients had a t(1;19)(q23;p13.3) translocation. In children with ALL, this cytogenetic marker is associated with a high risk of recurrence with CNS damage. This group of patients achieved remission and preserved it to the present. One patient died during consolidating therapy from infectious complications.

A deletion of chromosome 9 was registered in 5 (3.2%) cases. One patient died from a relapse; another was continuing polychemotherapy at the time of the study. The group of single random rearrangements, also presented in Table 1, includes changes with no diagnostic value and those requiring further study of their significance for treatment and prognosis.

In recent decades, the introduction of chemotherapy protocols for ALL in children resulted in a significantly higher curability of many patients. Traditional chemotherapy consists of four important phases: remission induction, consolidation, reinduction (delayed intensification), and continuation (maintenance). Steroids, vincristine, L-asparaginase, cytarabine, methotrexate, and 6-mercaptopurine are prescribed based on stratified risk classification. Multidrug pediatric chemotherapy for ALL is performed in various combinations and sequences depending on the treatment protocol. An analysis of the association between the initial clinical and laboratory data and long-term treatment outcomes brought the researchers to the idea of biological heterogeneity of the disease and possible identification of initial characteristics of the so-called risk groups of patients characterized by different probabilities of remission against similar therapy. This induced the concept of risk-adapted therapy when the therapy intensity and toxicity should correspond to the risk group. In other words, patients with a favorable prognostic baseline should receive the least toxic therapy and not be at risk of developing severe complications due to high doses or a combination of chemotherapy drugs. In contrast, patients with initially unfavorable forms of the disease should receive high-dose therapy, increasing the chances for recovery [2, 6].

The risk profiling of patients for different therapy protocols takes into account such initial parameters as initial leukocytosis, blast cell immunophenotype, and early response to therapy. This grouping is also used to assess complex parameters such as the specific genotype of leukemic cells and the kinetics of the disappearance of the residual tumor population. Therefore, modern diagnostics shall include cyto- and molecular-genetic testing [14].

In our study, the following risk groups were identified according to the BFM group protocols [15]: standard risk – 140 (90.9%) children and high risk – 14 (9%) patients. Early response to therapy was assessed on Day 8 of prednisolone monotherapy by reducing blast cells in the peripheral blood. The absolute number of blast cells was below 1,000 in 136 (88.3%), over 1,000 – in 12 (7.8%) patients, and unknown in 6 (3.9%) children. Patients with less than 1,000 blasts/1 μL formed a group of good response (prednisone good response, PGR) (Figure 11), with more than 1,000 blasts/1 μL – a group of poor response (prednisone poor response, PPR) (Figure 12).

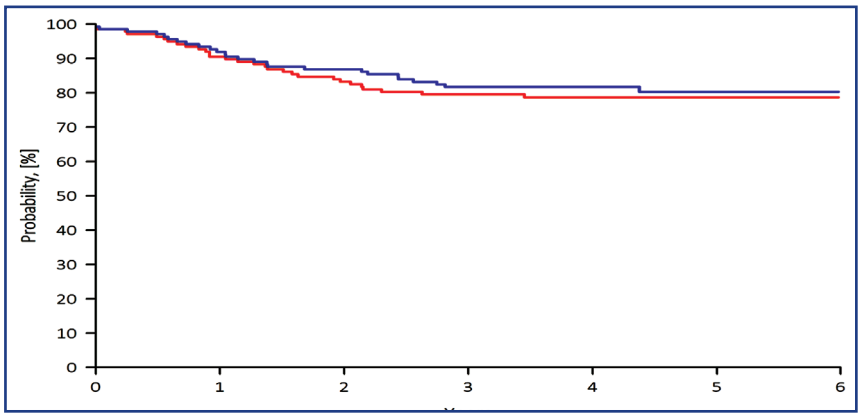

Figure 11 – EFS and OS in patients with a good response to prednisolone (n=136, OS – 80.3±3.5%, EFS – 78.7±3.5%)

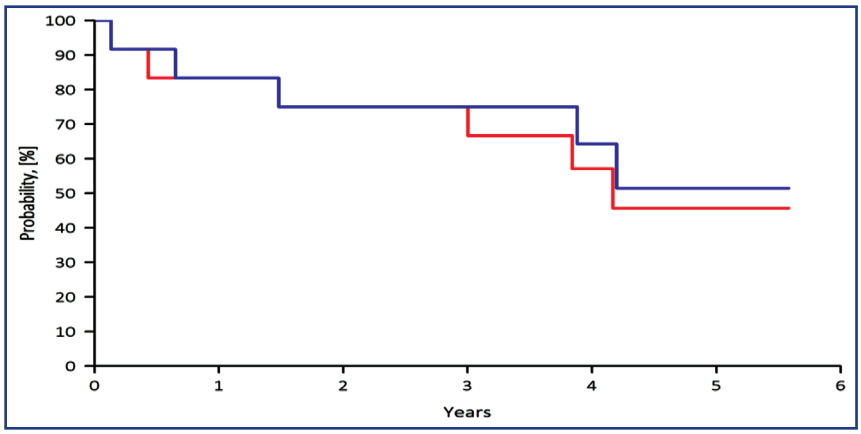

Figure 12 – EFS and OS in patients with poor response to prednisone (n=12, OS – 51.4±16.3%, EFS – 45.7±15.5%)

In the protocols used, early response is assessed by the number of blasts in the bone marrow on Days 15 and 33 of induction. On Day 15 of the protocol, 46 (29.9%) patients had an "empty" bone marrow on the myelogram, 69 (44.8%) had a remission, 32 (20.8%) did not achieve remission, and the result was unknown in 7 (4.5%) patients. On Day 33 of the protocol, remission was achieved in 140 (90.9%) patients, not achieved in 11 (7.1%), and the result was unknown in 3 (1.9%) patients. Regardless of the evaluation criteria, a good early response (PGR or M1 status at Day 15) allows distinguishing a group with a 5-year EFS >80% (Figure 13), while a poor early response (PPR or M3 status at Day 15) defines a group with a 5-year EFS around 40%.

Remission status after 4-6 weeks of therapy is also a major prognostic factor. The probability of long-term EFS in patients who have not achieved remission by this time does not exceed 30% [6].

The analysis of treatment outcomes under the BFM program in 154 patients showed death in induction in 2 (1.3%) patients and death from complications in remission in 15 (9.7%) patients. Relapses were the main cause of therapy failure in 4 (2.6%) patients. Remission continues in 133 (86.4%) patients.

Discussion: In our study, as in other research [10, 11], the age peak incidence of B-ALL was at 3 to 7 years.

The debut in most children has an acute onset and is characterized by heterogeneous clinical symptoms [10]. Diagnosing is often difficult at the initial stages of the disease since the disease is manifested by blast infiltration into internal organs and systems, with no characteristic changes in blood tests [12].

In most children, B-ALL is manifested by vivid clinical symptoms ahead of hemogram data, and this is one of the most important reasons for the late diagnosis of this malignant disease. Many sources emphasize the absence of a single clinical sign characteristic of acute leukemia and its subvariants [11, 12]. Consequently, this disease's polymorphic clinical picture requires oncological awareness of the doctors of all specialties. They should study the anamnestic and clinical data and the appropriate laboratory tests and refer such patients to a pediatric hematologist.

Immunophenotyping of lymphoblasts revealed the prognostic significance of certain markers' expression in various ALL types. Thus, according to published data [8], the CD34 expression on leukemic cells in the B variant had a favorable prognostic value. In contrast, in the T variant, it was associated with a poor prognosis.

The described bone marrow cytogenetic and molecular genetic tests are necessary to classify pediatric hematological malignancies. All children with leukemia shall undergo a cytogenetic test before protocol treatment, which reveals clonal chromosomal anomalies in 80-90% of cases. Most common molecular genetic changes in ALL include quantitative and structural anomalies, such as translocations, inversions, deletions, duplications, and point mutations [2, 10]. The most justified was the targeted identification of quantitative anomalies represented by hyperploidy (7.8% of cases). Among the structural chromosomal anomalies, the t(12; 21)(p13; q22) translocation, a favorable prognostic factor, was the most frequent. The detection of the Philadelphia chromosome and trisomy of the 21st chromosome, as well as the t(1; 19)(q23; p13.3) translocation, is associated with an extremely unfavorable course of ALL. This study's results align with the general trends [13, 14].

Modern pediatric polychemotherapy programs resulted in the successful treatment of childhood B-ALL [15]. In this study, remission was observed in 93.2% of B-ALL patients.

The identification of new biomarkers, and therefore a better understanding of the molecular basis of ALL, may improve the monitoring of the course of this disease. An in-depth identification of genetic aberrations in this neoplasm is crucial for assessing the prognosis of the disease and introducing molecular targeted therapy to improve response to treatment and better survival. A more accurate prognosis calculation will allow more effective treatment of all types with fewer side effects. A deep under-

standing of the full spectrum of genetic defects opens the door to the potential targeting of therapy and precision medicine in childhood.

Conclusion: This study confirmed the high efficiency of modern program therapy for ALL children. An analysis of the results of program therapy for B-ALL in 154 patients showed remission in 93.2% of patients and five-year event-free survival in 86.4% of patients.

At the same time, the response to therapy and long-term prognosis is largely determined by such biological factors as the cytogenetic features of the tumor, as well as the degree of aggressiveness manifested in the form of symptoms of lymphoproliferation and hyperleukocytosis.

Research continues to develop new monoclonal antibodies and cellular immunotherapy, but at the moment, they are effective only in some patients. New research is needed using targeted therapies to treat first-line disease.

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АҢДАТПА

ҚАЗАҚСТАН РЕСПУБЛИКАСЫНДАҒЫ БАЛАЛАРДАҒЫ В-ЖАСУШАЛЫҚ ЛЕЙКОЗДАРДЫҢ БАҒДАРЛАМАЛЫҚ ТЕРАПИЯСЫНДАҒЫ КЛИНИКАЛЫҚ-ГЕМАТОЛОГИЯЛЫҚ ЖӘНЕ ЦИТОГЕНЕТИКАЛЫҚ СИПАТТАМАЛАРДЫҢ РӨЛІ

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Өзектілігі: *Балалардағы лейкоздардың иммунологиялық және молекулалық-генетикалық сипаттамаларын және жедел в-сызықты лимфобластикалық лейкоздың (в-ОЛЛ) ісік популяциясының биологиялық ерекшеліктерінің терапияның нәтижелілігіне әсерін зерттеу Қазақстан Республикасы үшін аса өзекті болып табылады.*

Зерттеудің мақсаты *– В-жасушалы жедел лейкоздардың биологиялық сипаттамасына байланысты балалардағы заманауи бағдарламалық химиотерапияның тиімділігін бағалау.*

Әдістері: *Зерттеу барысында 2016-2018 жылдары "Педиатрия және балалар хирургиясы ғылыми орталығы" АҚ (Алматы, Қазақстан Республикасы) стационарлық емдеуде болған 6 айдан 15 жасқа дейінгі бастапқы В-ОЛЛ бар 154 баланың деректері талданды.*

Нәтижелері: *Ең көп зардап шеккен жас топтары 3-7 жаста (43,5%) болды, бұл нәресте шыңы деп аталады. Барлық типтегі клиникалық көріністе манифестация кезеңімен бірге жүретін интоксикация синдромы пациенттердің 75,3% - ында болды. Дебюттік кезеңнің клиникалық полиморфизмі "маскалар"диагноздарының әртүрлі тізімін анықтады. Бауыр жеткіліксіздігі түріндегі органдар мен жүйелердің зақымдануы 41 (26,6%) балада, тыныс алу жеткіліксіздігінің дамуымен 12 (7,8%), 5 науқаста жүрек-қантамыр жеткіліксіздігімен (3,2%), 3 науқаста ОПП (1,9%), 5 (3,2%) науқаста ОЖЖ зақымдануы анықталды.*

Барлық иммунологиялық нұсқалардың таралуы анықталды мынадай түрде: В1 – 9 (5,8%), В2 – 123 (79,8%), В3-18 (11,7%), В4-3 (1,9%). Сүйек кемігін цитогенетикалық зерттеу кезінде 12(7,8%) жағдайда гиперплоидия анықталды, 6(3,9%) пациенттерде t (12;21) (p13;q22) транслокациясы анықталды және қолайлы болжамдық фактор болды (ремиссия тіркелген).Трисомия 21 хромосома 3 (1,9%) науқастарда байқалды, балалардың 1,3% - Кост сүйек кемігін зерттеу кезінде біріктірілген ауытқулар анықталды(изохромосома 7, трисомия 4, 6, 15, 17, транслокация t(9; 22) (q34;q11), t(1;19)(q23;p13.3) транслокациялары 5,8%, del 9p – 3,2% жағдайда болды.

Қорытынды: *Терапияға жауап және ұзақ мерзімді болжам көбінесе ісіктің цитогенетикалық ерекшеліктері, преднизолонға сезімталдық, сондай-ақ лимфопролиферация мен гиперлейкоцитоздың айқын белгілері ретінде көрінетін агрессивтілік дәрежесі сияқты биологиялық факторлармен анықталады. Зерттеу балалардағы заманауи ALL-BFM бағдарламалық терапиясының жоғары тиімділігін көрсетті.*

Түйінді сөздер: *балалар, жедел в-жасушалық лимфобластикалық лейкемия, бласт жасушалары, иммунофенотиптеу, цитогенетикалық зерттеу.*

АННОТАЦИЯ

РОЛЬ КЛИНИКО-ГЕМАТОЛОГИЧЕСКИХ И ЦИТОГЕНЕТИЧЕСКИХ ХАРАКТЕРИСТИК В ПРОГРАММНОЙ ТЕРАПИИ В-КЛЕТОЧНЫХ ЛЕЙКОЗОВ У ДЕТЕЙ В РЕСПУБЛИКЕ КАЗАХСТАН

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Актуальность: *Изучение иммунологических и молекулярно-генетических характеристик лейкозов у детей и влияния биологических особенностей опухолевой популяции острого В-линейного лимфобластного лейкоза (В-ОЛЛ) на результатив-ность терапии представляется особо актуальным для Республики Казахстан.*

Цель исследования *– оценить эффективность современной программной химиотерапии у детей в зависимости от био-логической характеристики В-линейных лейкозов.*

Методы: *В ходе исследования были проанализированы данные 154 детей в возрасте от 6 месяцев до 15 лет с первич-ными В-ОЛЛ, находившихся на стационарном лечении в АО «Научный центр педиатрии и детской хирургии» (Алматы, Республика Казахстан) в 2016-2018 гг. При определении событий руководствовались критериями протоколов группы ALL-BFM.*

Результаты: *Большинство пациентов с В-ОЛЛ относились к возрастной группе 3-7 лет (43,5%), что отражает "мла-денческий пик" согласно протоколам BFM. Интоксикационный синдром, сопутствовавший периоду манифестации, при-сутствовал у 75,3% больных. Клинический полиморфизм дебютного периода определял самый разнообразный перечень диа-гнозов-«масок». Поражение органов и систем в виде печеночной недостаточности выявлено у 41 (26,6%) ребенка, дыха-тельной недостаточности – у 12 (7,8%) детей, сердечно-сосудистой недостаточности – у 5 больных (3,2%), ОПП – у 3 (1,9%), поражение ЦНС – у 5 (3,2%) больных. При иммунофе-нотипировании бластных клеток определялись следующие варианты: В1 – 9 (5,8%), В2 – 123 (79,9%), В3 – 18 (11,7%), В4 – 4 (2,6%). При цитогенетическом исследовании костного мозга в 12 (7,8%) случаях была выявлена гиперпло-идия, транслокация t(12;21)(p13;q22) определена у 6 (3,9%) пациентов и являлась благоприятным прогностическим факто-ром (зафиксирована ремиссия). Трисомия 21 хромосомы наблюдалась у 3 (1,9%) больных, у 1,3% детей при исследовании костного мозга выявлены сочетанные аномалии (изохромосома 7, трисомия 4, 6, 15, 17, транслокация t(9; 22)(q34;q11). Транслокации t(1;19)(q23;p13.3) имелись в 5,8%, del 9p – в 3,2% случаев.*

Заключение: *Ответ на терапию и долгосрочный прогноз во многом определяются такими биологическими факторами, как цито-генетические особенности опухоли, чувствительность к преднизолону, а также степень агрессивности, которая проявляется в виде выраженных симптомов лимфопролиферации и гиперлейкоцитоза. Проведенное исследование показало высокую эффективность совре-менной программной ALL-BFM терапии у детей.*

Ключевые слова: *дети, острый В-клеточный лимфобластный лейкоз (В-ОЛЛ), бластные клетки, иммунофенотипирование, цитоге-нетическое исследование.*

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EVALUATION OF THE EFFECTIVENESS OF NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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ABSTRACT

Relevance: *Breast cancer is the most common cancer among women. Modern treatment of locally advanced breast cancer requires a multidisciplinary approach, including local treatment: surgical and radiotherapy, systemic treatment, and a wide range of medications. The importance of systemic therapy is to improve relapse-free survival based on the control of micrometastases with the potential to spread throughout the body.*

Systemic therapy for operable breast cancer includes adjuvant therapy and neoadjuvant therapy. Hormone therapy, chemotherapy, and targeted therapy represent systemic therapy, which can be prescribed individually or in combination.

For the most effective breast cancer treatment, tumors are classified into subtypes depending on the expression of biological markers. The presence of expression of the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and the rate at which tumor cells divide are determined by determining the Ki67.

It is known that neoadjuvant chemotherapy (NCT) has clinical significance in locally advanced and inoperable breast cancer. NCT increases the frequency of organ-preserving operations and the overall survival rate when a complete pathomorphological regression of the tumor (pCR) is achieved.

The study aimed to *conduct a literature review of previously published publications on the effectiveness and expediency of neoadju-vant chemotherapy for breast cancer.*

Methods: *The search and analysis of scientific publications were carried out in the databases Web of Science, Pubmed, and Scopus for ten years, from 2013 to 2023. According to the search, about 3000 articles were found, and 39 sources were left during the selection according to the inclusion and exclusion criteria*

Results: *Efficiency of NCT depending on different immunophenotypes in breast cancer patients was established. Tumor response was assessed according to RECIST criteria. A complete pathological response was observed more often in more aggressive subtypes of breast cancer – Her2-positive and triple-negative cancer. The relationship between pCR and long-term outcomes – OS and DFS have also been estab-lished.*

Conclusion: *Neoadjuvant chemotherapy is a systemic treatment of breast cancer, the main purpose of which is to reduce the size of the tumor for the possibility of performing organ-preserving surgery, as well as to increase the overall and relapse-free survival rates. NCT allows for evaluating the effectiveness of therapy in vivo and using alternative treatment regimens without tu-mor response to the therapy.*

Keywords: *breast cancer, neoadjuvant chemotherapy.*

Introduction: Modern treatment for locally advanced breast cancer (BC) requires a multidisciplinary approach which includes local (surgery and radiotherapy) and systemic therapy with a wide range of medications. Systemic therapy is important for improving relapse-free survival (RFS) by controlling micro metastases prone to spread throughout the body.

Systemic therapy for operable BC includes adjuvant therapy after surgery and neoadjuvant therapy before surgery. These treatment methods are equally effective in improving RFS when similar drugs and evidence-based regimens are based [1]. Systemic therapy might include hormone therapy, chemotherapy, and targeted therapy, which can be prescribed individually or in combination.

For the most effective BC treatment, tumors are classified into subtypes by the expression of biological markers, such as the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67, which is a tumor's proliferation index. The presence or absence of these receptors identifies five immunophenotypes of tumors, presented in Table 1.

Table 1 – Breast cancer (BC) classification by phenotype based on tumor biological features [2, 3]

BC classification by immunophenotype	Presence of receptor expression
Luminal A	ER (+) and/or PR (+), HER2 (-), Ki 67 <20%
Luminal B, HER2 negative	ER (+) and/or PR (+), HER2 (-), Ki 67 >20%,
Luminal B, HER2 positive	ER (+) and/or PR (+), HER2 (+), Ki 67 any
Triple-negative	ER (-), PR (-), HER2 (-)
HER2 positive (non-luminal)	ER (-), PR (-), HER2 (+)

Neoadjuvant chemotherapy (NCT) has a known clinical significance in locally advanced and inoperable BC [4]. NCT can transform an inoperable breast tumor without distant metastases into an operable one, leading to a slight increase (7% to 12%) in the share of organ-preserving operations [5-6]. Studies have shown that patients who present complete pathomorphological regression of the tumor (pCR) after NCT have more prolonged overall survival (OS) and RFS, especially with triple-negative and HER2-positive BC [7-9]. NCT aims to increase the share of organ-preserving operations and support choosing adequate adjuvant therapy in the future. The regimen choice aims to achieve the maximum antitumor effect in accordance with cancer etiopathogenesis.

The study aimed to conduct a literature review of previously published publications on the effectiveness and practicality of neoadjuvant chemotherapy for breast cancer.

Materials and methods: The search and analysis of scientific publications were carried out in the databases Web of Science, Pubmed, and Scopus for ten years, from 2013 to 2023. The keywords searched included "breast cancer" and "neoadjuvant chemotherapy." The criteria for including the source in the literature review were: reports on randomized and cohort studies conducted on large populations, meta-analyses, systematic reviews, and full versions of articles. The analysis should have included articles describing isolated cases, reports from conferences, abstracts, and papers without citations published in journals with dubious reputations. According to the search, about 3000 articles were found, and 39 sources were left during the selection according to the inclusion and exclusion criteria. The agreement of the author's opinions on the selected articles was 98%.

Results:

Criteria of tumor response to therapy.

The modern criteria for the tumor response to therapy are the RECIST criteria. These criteria are based on a one-dimensional measurement of tumors, as described in Schwartz L.H. et al. [10]. RECIST adopted a simplified measurement method using the sum of the longest diameters of the target lesions. In contrast, previous WHO criteria used the sum of the two longest diameters measured perpendicular to each other. RECIST designers believe these criteria should be updated and adapted to remain relevant [11]. In 2009, RECIST 1.1 was published, according to which the complete response (CR) is the disappearance of all target lesions and regression of any pathological lymph nodes (both target and non-target) to <10 mm. The partial answer (PR) is a reduction in the sum of the diameters of the foci by at least 30%. Disease progression (PD) is an increase of 20% or more in the sum of the diameters of the main foci (>5 mm), as well as the appearance of one or more new foci; unconditional progression of non–target foci. Disease stabilization (SD) means all other cases [12-13].

Modern clinical assessment methods include breast physical examination and imaging using mammography and ultrasound. Physical examination is often insufficient to assess the localized BC response to NCT. Therefore, such methods as two-dimensional and three-dimensional mammography, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET), as well as their combinations (PET-CT, PET-MRI), are essential to assess the treatment efficacy [14-18].

Tumor microscopy is a key diagnostic tool for accurately measuring tumor size. This method provides the most objective assessment of the true sizes of a neoplasm. The tumor size is determined by carefully comparing clinical examination and microscopy results. If a breast tumor is a distinct mass outside the point of origin, its size can be easily estimated using visualization and macroscopy. However, an accurate measurement may be challenging at a tumor location in an ill-defined area of genetic instability and with intra-tumor diffuse fibrosis. In addition, the detection and precise measurement of small malignancies detected by advanced imaging may pose a problem if they are not visible during a general examination of the sample. This is because a surgical sample submitted to a pathology laboratory may differ greatly from the in vivo form observed by the surgeon and radiologist due to the mammary gland tissue elasticity [19, 20].

Several authors have earlier classified tumor response to therapy by the generosity of changes in the tumor. E.g., I.D. Miller and S. Payne (Miller-Payne classification) identified five grades of pathomorphism in response to treatment; the grades are characterized in Table 2. This classification assesses the cell structure of postoperative material and compares the results with the tumor structure before treatment. The assessment of pathological response after NCT has recently become an important independent prognostic factor. A complete pathomorphological response (pCR) is the endpoint of efficiency determination, characterized by a complete absence of tumor cells in postoperative material [4].

Table 2 – Miller-Payne therapeutic pathomorphosis grading system [3]

Degree of pathomorphosis	Characteristic changes in a tumor
I	Subtle changes in individual tumor cells without reducing their number.
II	A slight reduction in cells (≤ 30% of the tumor)
III	Tumor cells lose 30 to 90% in number.
IV	Marked disappearance of invasive cells. Only widely dispersed small nests of cells are detected (>90% of cell losses)
V(pCR)	No tumor cells in sectional cuts from the primary tumor location.

The US Food and Drug Administration (FDA) established a CTNeoBC working group tasked to analyze the results of 12 combined randomized controlled trials of NCT in BC [21-22]. The group concluded that the most significant association between pCR and the long-term outcome was observed in more aggressive BC subtypes. pCR was defined as the absence of malignant cells in the residual primary tumor or regional lymph nodes. The best pCR of 50.3% was achieved in patients with non-luminal HER2-positive BC against the background of treatment with a monoclonal antibody to the HER2 receptor – trastuzumab. Without trastuzumab, pCR with this type of tumor amounted to 30.2%. In triple-negative BC, pCR after NCT was also frequent, reaching 33.6%. In stage III luminal HER2-negative BC, pCR was 16.2% [16]. With hormone-sensitive tumors, pCR values were lower in luminal type A tumors (6.4%) and higher in luminal type B tumors (11-22%) [23-28].

The results were similar in the I-SPY 2 study, where stage II or III BC cases were randomized for different variants of standard neoadjuvant therapy. The pCR was lowest in luminal HER2-negative BC (17.4%) and achieved 68% in a non-luminal HER2-positive tumor [29-31].

Three-year event-free survival achieved 95% in patients with pCR and 78% without pCR (95% confidence interval (CI): 0.12, 0.31). Similarly, 3-year RFS amounted to 95% in patients with pCR versus 81% without pCR (CI 95%: 0,13, 0,34) [32-34].

A meta-analysis confirmed no differences in outcomes between adjuvant and neoadjuvant therapy when the same drugs are used [35]. Breast preservation frequency after NCT is higher than after adjuvant therapy. However, patients receiving NCT had a higher incidence of local relapses [36]. NCT standard regimen includes anthracyclines followed by taxane [37]. Adding carboplatin to the standard regimen may be effective for patients with triple-negative RBC , especially with the BRCA1/2 mutation [30, 38, 39].

Discussion: NCT is systemic therapy for BC performed before the main surgical treatment. NCT targets to:

1. Reduce tumor volume: NCT can reduce the size of the tumor focus and make surgical removal of the formation possible.

2. Reduce the risk of relapse: NCT can reduce the likelihood of BC recurrence after complex treatment.

3. Evaluate the treatment efficacy: NCT results can indicate the efficacy of the selected chemotherapy by assessing the tumor pathomorphosis.

NCT regimens for BC may vary depending on many factors, including the tumor size, immunophenotype, disease stage, hormonal status, the patient's age, and general health.

NCT can include a single drug or a combination of chemotherapy drugs. Usually, drug combinations such as anthracyclines (doxorubicin) and taxanes (paclitaxel or docetaxel) are used for NCT. Other drugs, such as cyclophosphamide and fluorouracil, can also be included in combination. NCT is performed for several months before surgery. Usually, 3 to 8 courses are carried out, depending on the patient's response to treatment.

NCT has been proven effective depending on different BC immunophenotypes. The tumor response evaluated according to RECIST criteria showed that pCR was more frequent in more aggressive BC subtypes such as Her-2+ and triple-negative. The relationship between pCR and long-term outcomes such as OS and RFS has also been established.

Conclusion: NCT is currently the routine treatment for BC. The former main target of NCT was to reduce the tumor size (also known as stage reduction) to allow for breast-preserving surgery and possibly exclude axillary dissection in patients who opposed extended surgery. However, the current role of NCT has expanded to include patients with early stages of operable BC, such as stages II and III (T1-4N0-3M0). NCT improves cosmetic results and reduces postoperative complications, such as secondary lymphocytosis of the upper extremities. Clinical trials evaluating neoadjuvant and adjuvant chemotherapy showed no difference in BC treatment long-term effects with either approach.

NCT allows for assessing the therapeutic efficacy in vivo and applying alternative treatment regimens for tumor resistance to therapy. The endpoint, the response to chemotherapy, is a significant prognostic risk factor for relapse, especially in triple-negative and HER2-positive BC. The above advantages are the reason for the widespread introduction of NCT.

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНДЕ НЕОАДЪЮВАНТТЫ ХИМИОТЕРАПИЯНЫҢ ТИІМДІЛІГІН БАҒАЛАУ

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Өзектілігі: *Сүт безі қатерлі ісігі (СБҚІ) – әйелдер арасында ең көп тараған қатерлі ісік. Жергілікті таралған СБҚ ісігін заманауи емі көпсалалы, оның бірі – жергілікті ягни хирургиялық және сәулелік терапияны қолдану арқылы болса, екіншісі дәрі-дәрмектердің кең спектрін қамтитын жүйелі ем. Жүйелік терапияның маңыздылығы бүкіл денеге таралу әлеуеті бар микрометастаздарды бақылауға негізделген рецидивсіз өмір сүруді жақсарту болып табылады.*

Жүйелік терапия адъювантты терапия мен неоадъювантты терапияны қамтиды. Гормондық терапия, химиотерапия және таргетті терапия жүйелік терапия ретінде қолданылады, оларды жекелей немесе басқа әдістермен бірге тағайындауға болады.

СБҚІ тиімді емдеу үшін биологиялық маркерлердің экспрессиясына сәйкес ісіктерді кіші түрлерге жіктеу қолданыла-ды. Эстроген рецепторының (ER), прогестерон рецепторының (PR), адамның эпидермиялық өсу факторы рецепторының 2 (HER2) экспрессиясының болуы және Ki67 индексін анықтау арқылы ісік жасушаларының бөліну жылдамдығы анықтала-ды.

Неоадъювантты химиотерапияның (НХТ) жергілікті дамыған және сүт безі қатерлі ісігінің оталық емес түрінде клиникалық маңызы бар екені белгілі. НХТ ағзаны сақтау операцияларының жиілігін арттырады, сонымен қатар ісіктің толық патоморфологиялық регрессиясына (pCR) жеткенде жалпы өмір сүруді арттырады.

Зерттеудің мақсаты *– сүт безі қатерлі ісігінің неоадъювантты химиотерапиясының тиімділігі мен орындылығы ту-ралы бұрын жарияланған басылымдарға әдеби шолу жасау.*

Әдістері: *ғылыми жарияланымдарды іздеу және талдау web of Science, Pubmed, Scopus дерекқорларында 10 жыл, ягни 2013 жылдан бастап жүргізілді. Іздеу нәтижесінде 3000-ға жуық мақала қамтылды, сәйкес іріктеу кезінде қосу және алып тастау критерийі 39 дерекқоз қалдырылды.*

Нәтижелері: *Сүт безі обыры бар науқастарда әртүрлі иммунофенотиптерге байланысты НХТ қолдану тиімділігі анықталды. Ісік реакциясы RECIST критерийлері бойынша бағаланды. Патологиялық толық жауап сүт безі қатерлі ісігінің агрессивті түрлерінде, ягни HER2 оң және үштік негативті қатерлі ісігінде жиі байқалатыны анықталды. pCR мен ұзақ мерзімді нәтижелер, оның ішінде жалпы өміршендік пен асқынусыз өміршенділік арасындағы байланыс бар екені расталды.*

Қорытынды: *Неоадъювантты химиотерапия – бұл сүт безі обырын жүйелі емдеу. Оның негізгі мақсаты ісік мөлшерін азайтып, зақымдалған ағзаны сақтайтын операцияны орындау мумкіндігі, сондай-ақ жалпы және асқынусыз өмір сүру деңгейін арттыру болып табылады. НХТ артықшылығы- емнің in vivo тиімділігін бағалау және сәйкесінше ісіктің емге жауабы болмаған жағдайда, емдеудің балама режимдерін қолдану.*

Түйінді сөздер: *сүт безі қатерлі ісігі, неоадъювантты химиотерапия.*

АННОТАЦИЯ

ОЦЕНКА ЭФФЕКТИВНОСТИ НЕОАДЪЮВАНТНОЙ ХИМИОТЕРАПИИ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Актуальность: *Рак молочной железы (РМЖ) является самым распространенным онкологическим заболеванием среди женщин. Современное лечение местнораспространенного РМЖ требует мультидисциплинарного подхода, которое включает в себя местную, то есть хирургическую и лучевую терапию, а также системное лечение, включающее широкий спектр лекарственных препаратов. Важность системной терапии состоит в улучшении безрецидивной выживаемости (БРВ), основанной на контроле микрометастазов с потенциалом распространения по всему организму.*

Системная терапия операбельного РМЖ включают адъювантную терапию и неоадъювантную терапию. В качестве системной терапии используют гормональную терапию, химиотерапию и таргетную терапию.

Для наиболее эффективного лечения РМЖ используется классификация опухолей на подтипы, в соответствии с экспрессией биологических маркеров. Определяются наличие экспрессии рецептора эстрогена (ER), рецептора прогестерона (PR), рецептора

эпидермального фактора роста человека 2 (HER2) и скорость, с которой делятся опухолевые клетки, посредством определения индекса Ki67.

Неоадъювантная химиотерапия (НХТ) имеет клиническое значение при местнораспро-страненном и неоперабельном РМЖ. НХТ увеличивает частоту органосохраняющих операций (ОСО), а также увеличивает общую выживаемость (ОВ) при достижении полного патоморфологического регресса опухоли (pCR).

***Цель исследования** – оценить эффективность неоадъювантной химиотерапии рака молочной железы.*

***Методы:** Поиск и анализ научных публикаций проведен в базах данных Web of Science, Pubmed, Scopus в период 10 лет, с 2013 года. В результате поиска было найдено около 3000 статей, в ходе отбора согласно критерий включения и исключения оставлено 39 ис-точников.*

***Результаты:** Установлена эффективность применения НХТ в зависимости от различного иммунофенотипа у пациентов РМЖ. Ответ опухоли был оценен согласно критериям RECIST. Выявлено, что патологический полный ответ чаще наблюдался при более агрес-сивных подтипах РМЖ – Her2-позитивном и тройном негативном раке. Также установлена взаимосвязь между pCR и отдаленными исходами – ОВ и БРВ.*

***Заключение:** НХМ – это системное лечение РМЖ, основной целью которого является уменьшение размера опухоли для возможности выполнения ОСО, а также увеличение показа-телей ОВ и БРВ. Преимуществом НХТ является оценка эффективности терапии in vivo и, соответственно, применение альтернативных схем лечения при отсутствии ответа опухоли на проводимую терапию.*

***Ключевые слова:** рак молочной железы (РМЖ), неоадъювантная химиотерапия (НХТ).*

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ENDOCRINE TOXICITY OF IMMUNE CHECKPOINT INHIBITORS IN CLINICAL PRACTICE

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ABSTRACT

Relevance: *Immunological control points significantly changed cancer therapy worldwide after registering a new class of inhibitor drugs. Based on clinical studies, this type of treatment was associated with better survival in sensitive patients than cytostatic therapy. Checkpoint inhibitors exert their effect by regulating the immune response to malignant cells, blocking the usual inhibitory pathways of T-cell regulation. The receptors of cytotoxic T-lymphocytic antigen-4 (CTLA-4) and programmed cell death protein (PD-1) or its associated ligand (PD-L-1) are the target of inhibitors. CTLA-4 acts at an early stage of triggering an antigenic response, and PD-1 and PD-L-1 act by modulating interaction with peripheral tissue*

However, treatment with checkpoint inhibitors (ICTs) is accompanied by a wide range of immune mediated adverse events associated with the activation of the immune system. Despite the positive effect on survival, side effects with endocrine effects were noted in about 10% of patients.

The study aimed to *assess the incidence of immune mediated adverse events from the thyroid gland in clinical practice in patients with different localization of malignant tumors in the first and subsequent lines of therapy with checkpoint inhibitors.*

Methods: *The study utilized anamnestic, laboratory, and instrumental tests. Laboratory analysis included determining the blood levels of TSH, T3, T4, ACTH, and cortisol. Data analysis was carried out using the Microsoft Excel program.*

Results: *The frequency of development of immune mediated thyroiditis against the background of therapy with blockers of control points of the immune pathway in our observation was 29%. The debut of thyroid disorders was diagnosed in the first 12-16 weeks of therapy, beginning with hyperthyroidism against the background of thyroid destruction, followed by a transition to persistent hypothyroidism after 1-3 months.*

Conclusion: *When analyzing the safety profile of ICTs in patients in our study, immune mediated adverse reactions did not differ in frequency and spectrum from world practice. The spec-trum of toxicity did not depend on the localization of the tumor. Early diagnosis of thyroid lesions necessary for optimal and effective treatment can be carried out using laboratory tests. Knowing the timing of the development of adverse events during ICT therapy allows timely diagnosing and correcting complications from the thyroid to continue effective therapy.*

Keywords: *immune mediated endocrinopathy, immunotherapy, checkpoint inhibitors (ICTs).*

Introduction: The emergence of such highly effective drugs as checkpoint target blockers has increased the duration of the recurrence-free period but posed new challenges to oncologists and endocrinologists [1]. The thyroid gland is most frequently affected by tumor therapy with drugs that inhibit immune signal transduction checkpoints due to the peculiarities of the immune status of this organ [1, 2]. It has been confirmed that normal thyroid tissue expresses PD-L1 and PD-L2 proteins [3]. Immune checkpoint inhibitors (ICT) can increase the level of pre-existing antibodies [2] and, in addition, reduce immune tolerance even in normal thyroid tissue, leading to the development of thyroiditis [3, 4]. Endocrine tissue does not regenerate and has a very small volume, so immune destruction has great consequences for the secretion of major hormones [5]. The development of clinically significant immune mediated adverse reactions may require discontinuing antitumor therapy and prescription of immunosuppressants, so early diagnosis and timely therapy of complications serve as important criteria for successful antitumor therapy [6].

Registration of a new class of ICT inhibitor drugs has significantly changed the approach to cancer therapy worldwide. In clinical trials, the survival rate of patients susceptible to this type of treatment increased compared to cytostatic therapy.

ICTs regulate the immune response to malignant cells by blocking regular inhibitory pathways of T-cell regulation [7].

The PD-1 glycoprotein was first identified in 1992 by a group of Japanese researchers who subsequently recognized its key role in T-cell activity regulation.

PD-L1 (B7-H1) was identified in 2000 by two independent groups in lymphoid tissue, including T-cells, APCs, dendritic cells, macrophages/monocytes, and B cells. PD-L1 is also found in non-lymphoid cells such as vascular endothelial cells, thyroid cells, muscle cells, hepatocytes, placental cells, mesenchymal stem cells, and pancreatic islet cells [8]. The following year PD-L2 was identified [9].

However, ICT treatment is accompanied by a wide range of immune-mediated adverse events (imAE) associated with the activation of the immune system.

Endocrine-mediated side effects occur in approximately 10% of patients [5]. These include hypophysitis, thyroid dysfunction, insulin deficiency, diabetes mellitus, and primary adrenal insufficiency. Diabetes mellitus and primary adrenal insufficiency are rare endocrine pathologies associated with therapy with control point target blockers but can be fatal if not detected and treated in time [10]. Hypophysitis leading to central adrenal insufficiency is particularly associated with anti-CTLA-4 therapy, whereas thyroid dysfunction is often associated with anti-PD-1 therapy [11].

Yamauchi et al. study [2] analyzed five consecutive cases of thyroid dysfunction associated with Nivolumab therapy. All patients developed thyrotoxicosis within four weeks of the first Nivolumab administration and normalized within four weeks of initiation in three of five patients. Two patients discontinued therapy with Nivolumab because of concomitant adverse events.

Most endocrinopathies exhibit nonspecific symptoms, which creates a diagnostic challenge. The most common side effect of ICT is fatigue. Because of this, symptoms may be overlooked or attributed to other causes. Diagnosis is also complicated by the extensive use of corticosteroids, antiemetics (together with ICT), and episodes of severe disease secondary to immunosuppression, which complicates diagnostic testing [5].

Our study investigated the frequency of endocrinopathies when using ICT in patients with different localization of the malignant tumor and compared the incidence of thyroid imAE in real clinical practice with research data and medical statistics.

All data was obtained from the medical records of patients who received Pembrolizumab and Nivolumab at the Republican Clinical Oncology Dispensary named after Prof. M.Z. Sigal of the Ministry of Health of Tajikistan from May 2019 to May 2021. Data are current as of March 1, 2022.

The study aimed to assess the incidence of immune-mediated adverse events from the thyroid gland in clinical practice in patients with different localization of malignant tumors in the first and subsequent lines of therapy with checkpoint inhibitors.

Materials and Methods: The study utilized anamnestic, laboratory, and instrumental tests. Laboratory analysis included determining the blood levels of TSH, T3, T4, ACTH, and cortisol. Data analysis was carried out using the Microsoft Excel program.

Before treatment, all patients underwent a comprehensive examination, including collecting their complaints and anamnesis, objective examination, CT/MRI of the thorax and abdomen or whole-body PET-CT, ultrasound of the neck organs, and endocrine system functionality assessment by blood serum hormone indices. Other methods (ultrasound, scintigraphy, consultation with an Endocrinologist, etc.) were used when examining patients with thyroid dysfunction.

The therapy efficacy was evaluated every six courses of treatment or when clinical signs of progression appeared. The maximum number of immunotherapy courses was 35 injections. Response to treatment was assessed using iRECIST 1.1 criteria.

A total of 55 patients aged 24 to 79 were enrolled (the mean age was 55.9%); 13 (23.6%) were above 65. The men-women ratio was close to one – 25 and 30 (45.4% and 54.6%, respectively).

Distribution of patients by diagnosis was as follows: head and neck squamous cell cancer – 11, urothelial cancer – 7, clear cell renal adenocarcinoma – 2, squamous cell cervical cancer – 4, melanoma – 14, small cell lung cancer – 1, ovarian cancer (in the framework of the RCT) – 7, lung squamous cell cancer (in the framework of the RCT) – 9.

ICT therapy was administered in a mono regimen to 36 patients; the other 19 received ICT with chemotherapy (ChT) in the Etoposide + Cisplatin or Paclitaxel + Carboplatin regimens. ChT was administered in cycles, 4 to 6 courses, as per the clinical guidelines.

The median hospital stay was one day. The median follow-up of patients was 13.5 months (1 to 27 months of follow-up). The median follow-up period after imAE development was 90 days.

Results: Sixteen (29%) patients in the study developed immune-mediated endocrinopathies. Patients in the ICT + ChT group had thyroid disorders, and one developed immune-mediated hypophysitis. The results are reflected in Table 1.

Table 1 - Development of endocrinopathies against the background of systemic antitumor therapy in the study

imAE	Endocrine disorders in the ICT group (all) (n)	Endocrine disorders in the ICT+ ChT group (all) (n)	Endocrine disorders in the ICT group (3rd-4th de-gree) (n)	Endocrine dis-orders in the ICT+ ChT group (3-4 de-grees) (n)	Total
Hypothyroidism	7	6	0	0	13
Hyperthyroidism	2	0	0	0	2
Hypophysitis	0	1	0	1	1
Total	9	7	0	1	16

In two patients, a moderate degree of hyperthyroidism developed at 12 weeks of ICT therapy, which required medication correction. The clinical picture manifested as tachycardia, unstable hemodynamics, and required therapy with β-blockers.

Secondary adrenal insufficiency in one case was due to 3rd-degree hypophysitis with a pronounced clinical picture (hypotension, unstable hemodynamics, electrolyte disturbances) combined with 2nd-degree hypothyroidism. The patient required hospitalization.

Hypothyroidism was noted in most cases (81.2%).

Patients mainly complained of weakness and fatigue in the study (Table 2).

Table 2 - Complaints against the background of ICT therapy in the study

Symptoms and Signs	Men (n)	Women (n)
Headache	0	0
Fatigue or weakness	3	4
Vision impairment	0	0
Tachycardia	1	1
Total	4	5

In most patients, hypothyroidism was asymptomatic or had manifestations of a mild degree and did not require medical correction. A moderate degree of hypothyroidism developed in 2 patients with a clinical picture in the form of weakness and fatigue, and after consultation with an Endocrinologist, the patients were prescribed L-thyroxine replacement therapy.

When analyzing complications in patients treated at the Republican Clinical Oncology Dispensary named after Prof. M.Z. Sigal of the Ministry of Health of Tajikistan, the median time to development of imAE was approximately the same – 12 weeks (CI 95% 1-5), which corresponds to the literature data [4]. The results are reflected in Table 3.

Table 3 - Duration of immune-mediated endocrinopathies against the background of ICT therapy in comparison with literature data [4]

The drug	Number of patients (n)	Time to the beginning of the imAE (weeks)		Time until the end of the imAE (weeks)	
		literature data	own data	literature data	own data
Pembrolizumab	10	12-16	17	48	59
Nivolumab	6	12-16	12	38	28

The main difference was the time to resolve the phenomenon: a short and rapid course was noted with Nivolumab (average time – 38 vs. 48 weeks).

The average percentage of thyroid function abnormalities against anti-PD-1 monotherapy amounts to 10% [7] and does not affect the subsequent immunotherapy. No imAE registered in our patients required cancellation of anti-PD-1 therapy.

Takeaways:

1. The frequency of immune-mediated thyroiditis against the background of therapy with immune checkpoint blockers in our study was 29%.

2. The debut of thyroid disorders was diagnosed in the first 12-16 weeks of therapy, beginning with hyperthyroidism against the background of thyroid destruction, followed by a transition to persistent hypothyroidism in 1-3 months.

3. Analysis of the ICT safety profile demonstrated the expected spectrum of adverse reactions.

Discussion: Typically, hypothyroidism begins with a transient phase, which may be asymptomatic or manifested by nonspecific symptoms similar to those of the underlying disease – weakness, weight loss, tachycardia, changes in hair and nails [1, 12], followed by persistent subclinical or overt hypothyroidism. On this basis, a spectrum of complaints was defined for subsequent analysis.

When interpreting the laboratory results, one should consider the possibility of secondary thyroid lesions due to hypophysitis [1, 4, 5].

Hypophysitis occurred infrequently in the study – in 1.8% of cases, which correlates with the data of other authors: max frequency is from 1.2% to 0.9% [12]. A sensitive and specific indicator of hypophysitis is an enlargement of the pituitary gland on radiographs, which can precede the clinical diagnosis of hypophysitis by several weeks.

A multidisciplinary team of physicians is recommended to provide optimal treatment and maintain quality of life. An endocrinologist will be of value to this team.

Thyroid function should be monitored before and during systemic antitumor therapy.

Regular laboratory screening of thyroid function with tests is recommended at baseline, before each dose of immunotherapy, every 6-12 weeks for the first six months after completion of treatment. Expansion of the examination scope is required if abnormalities or an increase in symptoms are detected.

Treatment of endocrine disorders is independent of the immune inhibitor that causes these events.

Conclusion: When analyzing the safety profile of ICT in patients in our study, immune-mediated adverse reactions did not differ in frequency and spectrum from world practice. The spectrum of toxicity did not depend on the localization of the tumor. Early diagnosis of thyroid lesions necessary for optimal and effective treatment can be carried out using laboratory tests.

Knowing the timing of the development of adverse events during ICT therapy allows timely diagnosing and correcting complications from the thyroid to continue effective therapy.

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АҢДАТПА

КЛИНИКАЛЫҚ ТӘЖІРИБЕДЕ ИММУНДЫҚ БАҚЫЛАУ НҮКТЕСІ ИНГИБИТОРЛАРЫНЫҢ ЭНДОКРИНДІК УЫТТЫЛЫҒЫ

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Өзектілігі: *ингибиторлық препараттардың жаңа класын тіркеуге байланысты иммунологиялық бақылау нүктелері бүкіл әлемде қатерлі ісік терапиясы айтарлықтай өзгерді. Клиникалық зерттеулерге сүйене отырып, емдеудің осы түріне сезімтал науқастарда цитостатикалық терапиямен салыстырғанда өмір сүрудің жоғарылауы дәлелденді. Бақылау нүктесінің ингибиторлары өздерінің әсерін қатерлі жасушаларға иммундық реакцияны реттеу, Т-жасушаларын реттеудің әдеттегі тежеу жолдарын блоктау арқылы көрсетеді. Цитотоксикалық т-лимфоцитарлық антиген-4 (CTLA-4) және бағдарламаланған жасуша өлімі ақуызының (PD-1) немесе онымен байланысты лигандтың (PD-L-1) рецепторлары ингибиторлардың нысаны болып табылады. CTLA-4 антигендік реакцияны бастаудың ерте сатысында әрекет етеді, ал PD-1 және PD-L-1 перифериялық тінмен өзара әрекеттесуді модуляциялау арқылы әрекет етеді.*

Алайда, бақылау нүктесінің ингибиторларымен (акт) емдеу иммундық жүйенің белсендірілуіне байланысты иммундық жанама жағымсыз құбылыстардың (ион) кең спектрімен бірге жүреді. Өмір сүруге оң әсер еткеніне қарамастан, пациенттердің шамамен 10% -. эндокриндік әсерлері бар жаңама әсерлер байқалды.

Зерттеудің мақсаты *– Бақылау нүктесінің ингибиторларымен емдеудің бірінші және кейінгі желілерінде қатерлі ісіктердің әртүрлі локализациясы бар емделушілерде клиникалық тәжірибе жағдайында қалқанша безінің иммундық-делдалдық жағымсыз құбылыстарының даму жиілігін бағалау.*

Әдістер: *Жұмыс анамнездік, зертханалық және аспаптық зерттеу әдістерін қолдану арқылы орындалды. Зертханалық талдау қандағы TSH, T3, T4, ACTH, кортизол деңгейін анықтауды қамтиды. Мәліметтерді талдау Microsoft Excel бағдарламасы арқылы жүргізілді.*

Нәтижелер: *иммундық жолдың бақылау нүктелерін блокаторлармен емдеу аясында иммундық тиреоидиттің даму жиілігі біздің бақылауымызда 29% құрады. Қалқанша безінің бұзылуының дебюті терапияның алғашқы 12-16 аптасында диагноз қойылды, қалқанша безінің бұзылуы аясында гипертиреоздан басталды, содан кейін 1-3 айдан кейін тұрақты гипотиреозға көшті.*

Қорытынды: *Біздің зерттеуімізде пациенттердегі АКТ қауіпсіздік профилін талдау кезінде иммундық әсер ететін жағымсыз реакциялар жиілігі мен спектрі бойынша әлемдік тәжірибеден ерекшеленбеді. Уыттылық спектрі ісіктің локализациясына байланысты емес. Оңтайлы және тиімді емдеу үшін қалқанша безінің зақымдануын ерте диагностикалау қажет, оны зертханалық зерттеулер арқылы жүзеге асыруға болады. АКТ терапиясы кезінде қолайсыз құбылыстардың даму уақытын білу қалқанша безінің терапиясынан болатын асқынуларды уақтылы диагностикалауға және түзетуге мүмкіндік береді және тиімді терапияны жалғастыруға мүмкіндік береді.*

Түйін сөздер: *иммундық эндокринопатия, иммунотерапия, бақылау нүктесінің ингибиторлары (акт).*

АННОТАЦИЯ

ЭНДОКРИННАЯ ТОКСИЧНОСТЬ ИНГИБИТОРОВ ИММУННЫХ КОНТРОЛЬНЫХ ТОЧЕК В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Актуальность: *В связи с регистрацией нового класса препаратов-ингибиторов иммунных контрольных точек (ИКТ) существенно изменилась терапия рака во всем мире. На основе клинических исследований было доказано увеличение выживаемости по сравнению с цитостатической терапией у пациентов, чувствительных к этому виду лечения. Ингибиторы контрольных точек проявляют свой*

эффект, регулируя иммунный ответ на злокачественные клетки, блокируя обычные тормозные пути регуляции Т-клеток. Рецепторы цитотоксического Т-лимфоцитарного антигена-4 (CTLA-4) и белка запрограммированной гибели клеток (PD-1) или связанного с ним лиганда (PD-L-1) являются мишенью ингибиторов. CTLA-4 действует на ранней стадии запуска антигенного ответа, а PD-1 и PD-L-1 действуют, модулируя взаимодействие с периферической тканью

Однако применение ИКТ сопровождается широким спектром иммуно-опосредованных нежелательных явлений, связанных с активацией иммунной системы. Несмотря на положительное влияние на выживаемость, были отмечены побочные эффекты с эндокринными эффектами примерно у 10% пациентов.

***Цель исследования** – оценить частоту развития иммунноопосредованных нежелательных явлений со стороны щитовидной железы в условиях клинической практики у пациентов с со злокачественными опухолями различной локализации в первой и последующих линиях терапии ИКТ.*

***Методы:** Работа выполнена с использованием анамнестических, лабораторных и инструментальных методов исследования. Лабораторный анализ включал определение уровней ТТГ, Т3,Т4, АКТГ и кортизола в крови. Анализ данных проводился с помощью программы Microsoft Excel.*

***Результаты:** Частота развития иммуноопосредованного тиреоидита на фоне терапии ИКТ в нашем наблюдении составила 29%. Дебют нарушений щитовидной железы диагностировался в первые 12-16 недель терапии, начинался с гипертиреоза на фоне деструкции щитовидной железы с последующим переходом в стойкий гипотиреоз через 1-3 мес.*

***Заключение:** При анализе профиля безопасности ИКТ у пациентов в нашем исследовании иммуноопосредованные нежелательные реакции не отличались по частоте и спектру от мировой практики. Спектр токсичности не зависел от локализации опухоли.*

Для оптимального и эффективного лечения необходима ранняя диагностика поражений щитовидной железы, которую возможно проводить методом лабораторного анализа.

Знание сроков развития нежелательных явлений во время терапии ИКТ позволяет своевременно диагностировать и корректировать осложнения со стороны щитовидной железы и продолжать эффективную терапию.

***Ключевые слова:** иммуноопосредованная эндокринопатия, иммунотерапия, ингибиторы контрольных точек (ИКТ).*

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THE PROSPECTS AND CHALLENGES OF CRISPR/CAS9 GENE EDITING IN CANCER THERAPY: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Cancer remains one of the leading causes of death in Kazakhstan, and CRISPR/Cas9 offers possible solutions to treat it. Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) is a system bacteria use to cleave foreign in-vaders. This system has been considered promising for cancer therapeutics by allowing researchers to edit cancer cell genes.*

The system requires more trials, so it is essential to raise awareness of this technique for stu-dents and potential investors and highlight the current challenges that could be research opportuni-ties for researchers.

The study aimed to *analyze and provide up-to-date information from reputable scientific journals on the current use of the CRISPR/Cas9 system in cancer therapeutics for medical students and researchers. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics.*

Methods: *The scientific literature and databases (PubMed and the Nature Journal) were searched and analyzed using the CRISPR/Cas9 system in cancer therapy.*

Results: *The results of this research indicate that scientists should focus on improving the types and structure of the Cas protein as well as the delivery methods, including the non-viral deliv-ery methods (liposome-based particles, hybrid vectors, gold nanoparticles, and extracellular vesicles) to contribute to improving the current status of cancer therapeutics.*

Conclusion: *CRISPR/Cas9 is an important technique that is still fraught with challenges and should be turned into research opportunities. The current challenges include the form and structure of the Cas nuclease, the types of engineering (in vivo vs. ex vivo), and the varieties of delivery methods. Each delivery method type has pros and cons and requires further research. In particular, future studies should focus on non-viral vectors, such as liposome-based particles, extracellular vesi-cles, hybrid vesicles, and gold nanoparticles.*

Keywords: *CRISPR, Cas9, cancer, oncology, delivery vectors, nanoparticles.*

Introduction: Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) is a system used by bacteria to cleave foreign invaders. The system has been considered promising for cancer therapeutics by allowing researchers to edit cancer cell genes. The CRISPR/Cas9 gene editing system is essential in current cancer research and therapy because it offers possible cancer treatment solutions and is simple and easy to design [1].

One of the goals of this research paper was to analyze and provide the current information from reputable scientific journals about the current status of the use of the CRISPR/Cas9 system in cancer therapeutics for medical students, researchers, and everyone interested in the current progress in the field of genetic engineering and cancer treatment. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics. The results of this literature review should offer an overview of the current challenges that scientists could utilize for their future research, meaning that this literature review aims to provide a concise review of the current challenges, prospective solutions, their advantages, and disadvantages, which researchers could use to inform their future studies.

The CRISPR/Cas9 gene editing system is a cost-effective and efficient tool. Although there are areas for improvement, these challenges offer new avenues for studies for researchers who seek to discover novel cancer therapy techniques, thereby making a significant contribution to the field of genetic engineering and molecular biology. This literature review highlights the most significant aspects that need further research and enhancement to improve CRISPR/Cas9 system-based cancer therapy. The results of this future research will significantly contribute to cancer therapeutics. They may save lives, so addressing the challenges of implementing the CRISPR/Cas9 system for cancer treatment is essential.

The study aimed to analyze and provide information from reputable scientific journals about the current status of using the CRISPR/Cas9 system in cancer therapeutics for medical students and researchers. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics.

Materials and Methods: The scientific literature and databases, including PubMed and the famous and reputable Nature Journal, were searched and analyzed using the CRISPR/Cas9 system in cancer therapy. The articles' references were also examined for relevance and analyzed for additional material. The criteria for choosing the scientific articles included relevance to the given research questions and topic as well as the time of publication. Based on

the gathered literature, the articles were selected based on their exigence, relevance to the topic under study, and novelty. Finally, the articles were examined and utilized to find new information to answer the research questions posed in this article, namely, "To what extent and how successfully can the CRISPR-Cas9 gene editing system be applied in cancer therapeutics? What challenges do scientists face in the clinical application of CRISPR/Cas9 gene editing technology in cancer therapeutics that could be transformed into research opportunities?"

Results:

The CRISPR/Cas9 gene editing in cancer therapy. The CRISPR/Cas9 gene editing system has been utilized to enhance T-cell therapy using two types of DNA repair: nonhomologous end-joining repair and homologous recombination repair. The former has been employed to remove molecules, such as PD-1, which inhibit the function of T cells in targeting cancer cells [1]. Furthermore, editing based on homologous recombination repair of DNA has been used to insert a specialized CAR gene (chimeric antigen receptor) into the TCR alpha chain of T cells, thereby increasing their efficiency [1]. This modified version of T cells is reportedly more efficient than the T-cells produced in the usual way [2]. Both types of engineering require more trials and appear effective in therapy.

Furthermore, CRISPR/Cas9 has been used to improve the side effects of chimeric antigen receptor (CAR) T cells for treating solid cancer. Previously, chimeric antigen receptor T cells have been successfully utilized for blood cancer treatment [3]. These T cells are genetically modified to recognize the antigens on target cancer cells. Apart from being used in blood cancer research, they have also been the subject of research as a possible treatment for solid cancers. However, the treatment of solid cancer cells with T cells has proved more difficult compared with the treatment of blood cancer. The significant challenges have been the heterogeneous nature or the absence of a sufficient number of antigens on the solid cancer cells, most of which are located within the cells, making it hard for the T cells to recognize them [3]. These challenges have been addressed using the CRISPR/Cas9 gene editing tool.

CRISPR/Cas9 has efficiently alleviated some aspects of utilizing genetically engineered T cells in solid cancer therapeutics by neutralizing the negative consequences of cytokine release and rejecting graft T cells. Specifically, the system has been used to silence HLA-I and TCR of graft T cells to minimize the organism's rejection of such cells [3]. It means that it has allowed the possibility of utilizing graft T cells in cancer treatment without causing distress to the organism. In addition, CRISPR/Cas9 has also been used to modify cytokine cells and prevent autoimmune reactions, which could hurdle cancer therapeutics [3]. Nevertheless, some aspects of the therapeutics still need further research.

Apart from T cell therapy, the development of CRISPR/Cas9 has prompted new genetic engineering approaches, including the regulation of transcription, editing of single bases, and cleavage of messenger RNA [4]. For example, DCas9, a modified version of Cas9, shows the potential to regulate transcription [5]. This modified version differs from the regular one in being more specific and having less off-target effects. It regulates transcription by loading activating, repressing domains or epigenetic modification enzymes [6]. However, the process is complicated and may result in errors, leading to multiple proteins possibly being affected by the intervention. In this regard, the specificity of the tool and the off-target effects require further research.

The challenges with the implementation of CRISPR/Cas9 in clinical settings. The two types of engineering include in vivo and ex vivo, and in vivo, genetic engineering should be prioritized over ex vivo engineering. One of the reasons for this is that ex vivo genetic engineering of T cells poses several challenges for researchers. First, genetically modified T cells are costly [1]. In addition, the process involves complex procedures, making it challenging to implement in practice [1]. While it could be wise to continue researching both types of engineering, researchers should also focus on improving the methods of in vivo genetic engineering. For example, experiments involving mice have shown promise in modifying T cells in vivo using polymeric Nano carriers loaded with CAR genes [7]. Such experiments must be replicated since the in vivo delivery method appears more advantageous in enhancing delivery efficiency.

Researchers should also focus on enhancing the CRISPR/Cas9 system, including the forms it delivers. One challenge concerns the CRISPR/Cas9 system's bacterial nature and the presence of immunity against it in some people [8, 9]. Some people have previously been infected with the Cas protein derived from the bacteria. As a result, these people have immunity against the nuclease derived from these bacteria. It would eliminate the protease from their organisms and the inability to introduce any changes to the organism's genome [1]. Future studies could focus on alternative ways to deliver the system, including its delivery in mRNA. However, such delivery methods have yet to be researched and carried out on a wide scale and remain a possible avenue for future research [1].

There is a need to research the delivery methods (and vectors) of genetically engineered T cells into cancer cells. Nanoparticles based on lipids or polymers, adeno- and lentiviruses have been utilized to deliver CRISPR-edited T cells into solid tumors; however, none of the delivery methods have proven to target the tumor cells specifically [10, 11]. In addition, although the methods may deliver the cells into some parts of the tumor, it is difficult to ensure a sufficient concentration of the cells in the target tissues [3]. The delivery methods are said to be one of the most significant challenges with applying T cells engineered by CRISPR/Cas9 in solid cancer therapeutics.

Viruses are one of the delivery vectors, and viral delivery methods suffer from packaging problems. Scientists note that new viral vectors with a low ability to produce an immune response or non-viral vectors with higher specificity are needed [1]. The viral method of delivery may be unsafe for the host organism. Apart from safety issues, the difficulty lies in packing the nuclease into the virus [12]. Although shorter variants of the nuclease introduced into several viral particles have been studied, researchers could focus on further enhancing the safety and packaging of the material into viral particles in future studies [12].

Furthermore, non-viral delivery methods are more advantageous in several ways than viral methods. Firstly, the viral vectors suffer from packaging problems in that only short nucleases can be packaged into the viruses. By contrast, the non-viral CRISPR delivery vectors do not have packaging issues because the CRISPR/Cas9 systems can be delivered in various forms in non-viral vectors (these include mRNA, ribonucleoprotein (RNP), and plasmid DNA) [1]. In other words, non-viral vectors are not limited in the number of particles that can be packaged into them. Secondly, viruses are known to cause immune reactions in the host organism. By contrast, the non-viral vectors are supposed to cause less severe reactions from the host. Researchers claim that non-viral vectors are easy to design [1, 12]. Non-viral vector materials could include micelles, liposomes, and other nanoparticles [12]. Several studies have described the delivery targeting the molecules that can enter the cell membrane, including the cell-penetrating peptide and delivery to the cell's nucleus [12]. Nevertheless, scientists acknowledge that few or an insufficient number of trials have been conducted using non-viral vectors for CRISPR delivery.

Non-viral and hybrid vectors for the delivery of CRISPR/Cas9. One of the encouraging methods of delivery is liposome-based nanoparticles. Liposome-based nanoparticles comprise cholesterol, phospholipids, and other components [13]. The method is particularly suitable for the delivery of drugs to the liver because it is the leading site of lipid processing; however, the disadvantage of this method is that the drugs accumulate in the liver and may not reach other organs in the required amounts. In addition, there have been concerns about the immunogenicity of such vectors. Although some of these vectors could be prone to causing an immune reaction, scientists have utilized peptides and introduced modifications into non-viral vectors to avoid immune responses. As a result of the addition of proteins on the surface of the non-viral vectors, the vectors could withstand or avoid the immune system reaction of the host organism.

In addition, biofilms and extracellular vesicles, such as exosomes, have been introduced into non-viral vectors to avoid immune response. Extracellular vesicles, including micro vesicles and exosomes, participate in cell signaling, transporting the signaling molecules or genetic material from inside the cell to other cells [14]. Exosomes are membrane-bound vesicles arising from multivesicular bodies in organelles [15]. These vesicles transport biomolecules inside the cell and can transport almost any substance within the cell. Such vesicles can deliver the CRISPR/Cas9 system with high specificity. The method seems effective since the vesicles retain the host organism's proteins on their surfaces, minimizing the risk of developing immune reactions [16]. Because the surface of such vesicles closely resembles that of the host cells, these cells will likely be recognized by the host as its cells, thereby reducing the likelihood of rejection by the host organism. In addition, the specificity of such vesicles can be improved by adding particular molecules on their surfaces (aptamers or antibodies) [14]. For example, extracellular vesicles covered with Chimeric antigen receptors (CARs) have been used to target B cell cancer [17].

Furthermore, hybrids of different vectors could be utilized to minimize each vector's side effects and enhance them. For example, exosomes hybridized with AAV (adeno-associated virus) or liposomes could be used. The presence of the exosome should protect the vector from being recognized by the host's immune system [18]. Such hybrid vectors have been used in experiments involving mice with immunity against the introduced virus. The results indicated that the exosome-protected virus did not cause immune reactions [19]. In addition, experiments have involved the introduction of such vectors into various tissues, such as nerve cells, particularly those in the inner ear [20, 21]. It means that the hybrid vectors can be safely introduced into different types of tissue, and the result is that they do not cause any severe immune reactions. However, the vectors have yet to be widely applied in CRISPR/Cas9 research, so this remains an opportunity for future studies.

Gold nanoparticles also promise to deliver gene drugs into tumor cells, though they should be further researched. Gold nanoparticles are a suitable drug delivery method because they are non-toxic, do not cause severe reactions, are stable, can inhibit bacteria, and can be modified to deliver substances into the cells [22]. Specifically, ligands can be added onto the gold nanoparticles for better recognition of cancer cells. For example, Wang et al. [23] have successfully introduced the CRISPR/Cas9 system into skin cancer cells using nanoparticles and liposomes. To deliver the plasmids to the cancer cells, they coated the gold nanoparticles with genetic material with positively charged liposomes [23]. These particles enter cancer cells and can release the drug when exposed to a laser; as a result of the intervention, the target gene (Plk-1) is knocked out, and the tumor is inhibited [23].

However, despite the successful experiment, scientists still claim that the challenge with gold nanoparticles lies in the accurate and efficient release of drugs at the target site, which will require further research [22]. Apart from previously discussed lasers, different stimuli have been studied concerning triggering the release of drugs

into the target cells. These have included internal and external stimuli [22]. However, the nanoparticles should be further modified to allow for a more efficient release of drugs into the target cells, which could be the focus of future studies.

Discussion: Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) gene editing tool is a promising technique for cancer therapeutics. As many researchers have pointed out, its advantage lies in its efficiency and ease of design. It offers a possible solution to the treatment of cancer, which is why researchers in molecular biology need to direct their attention to the study of the current challenges associated with the implementation of the technique in clinical settings. The challenges have included the structure of the Cas protein and different ways of delivering it into cancerous cells. The research results show that non-viral delivery methods have fewer disadvantages, as they have greater packaging efficiency.

Furthermore, non-viral delivery vectors circumvent the immune reactions that could result from introducing viral vectors. Different modifications and ligands can be introduced on the surface of non-viral vectors to improve their recognition by the host and the specificity of some non-viral vectors. The study also indicates a need for investments in gold nanoparticle experiments, which possess several benefits in delivering CRISPR into the cells, including their high packaging efficiency and antimicrobial properties. However, the vector might be costly and will require investments.

Conclusion: This research paper has examined and highlighted several challenges, including the form and structure of the Cas nuclease, the types of engineering (in vivo vs. ex vivo), and the varieties of delivery methods. Different delivery methods appear efficient, including non-viral vectors, such as liposome-based particles, extracellular vesicles, hybrid vesicles, and gold nanoparticles. The delivery methods outlined in this research paper need further studies, and their side effects should be mitigated. Therefore, the delivery methods should be the focus of future studies.

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АҢДАТПА

ҚАТЕРЛІ ІСІК ТЕРАПИЯСЫНДА CRISPR/CAS9 ГЕНДІ ӨҢДЕУ ТЕХНОЛОГИЯСЫН ҚОЛДАНУДЫҢ ПЕРСПЕКТИВАЛАРЫ МЕН МӘСЕЛЕЛЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Қатерлі ісік Қазақстандағы өлімнің негізгі себептерінің бірі болып қала береді және CRISPR/Cas9 оны емдеудің ықтимал шешімдерін ұсынады. Кластерленген, тұрақты интервалды қысқа палиндромдық қайталанулар/CRISPR-байланысты протеин 9 (CRISPR/Cas9) – бөгде басқыншыларды жою үшін пайдаланатын жүйелі бактериялар. Бұл жүйе зерттеушілерге қатерлі ісік жасушаларының гендерін өңдеуге мүмкіндік беру арқылы қатерлі ісік терапиясы үшін перспективалы болып саналды.*

Жүйе көбірек сынақтарды қажет етеді, сондықтан студенттер мен әлеуетті инвесторлар үшін осы әдістеме туралы хабардар болу маңызды, сонымен қатар зерттеушілер үшін зерттеу мүмкіндіктері болуы мүмкін ағымдағы қиындықтарды атап өту маңызды.

Зерттеудің мақсаты *– зерттеу медициналық студенттер мен зерттеушілер үшін қатерлі ісік терапиясында CRISPR/Cas9 жүйесін қолданудың ағымдағы жағдайы туралы беделді ғылыми журналдардан ағымдағы ақпаратты талдауға және ұсынуға бағытталған. Бұл зерттеу жұмысы сондай-ақ Crispr/Cas9-ды онкологиялық ауруларды емдеуге арналған клиникалық жағдайларда енгізуге байланысты қиындықтарды көрсетеді.*

Әдістері: *Ғылыми әдебиеттер мен мәліметтер қорынан зерттеулер. (PubMed дерекқоры, Nature ғылыми журналы).*

Нәтижелері: *бұл зерттеу нәтижелері ғалымдардың Cas протеинінің түрлері мен құрылымын, сондай-ақ жеткізу әдістерін, соның ішінде вирустық емес жеткізу әдістерін (липосома негізіндегі бөлшектер, гибридті векторлар, алтын нанобөлшектері және жасушадан тыс) жақсартуға назар аударуы керек екенін көрсетеді. везикулалар) қатерлі ісік терапиясының қазіргі жағдайын жақсартуға ықпал ету.*

Қорытынды: *CRISPR/Cas9 - бұл әлі де қиындықтарға толы маңызды әдіс, оны зерттеу мүмкіндіктеріне айналдыру керек. Ағымдағы қиындықтарға Cas нуклеазасының нысаны мен құрылымы, инженерия түрлері (in vivo және ex vivo) және жеткізу әдістерінің сорттары кіреді. Жеткізу әдісінің әр түрінің өзіндік артықшылықтары мен кемшіліктері бар және одан әрі зерттеуді қажет етеді. Атап айтқанда, липосома негізіндегі бөлшектер, жасушадан тыс көпіршіктер, гибридті везикулалар және алтын нанобөлшектері сияқты вирустық емес векторлар болашақ зерттеулердің назарында болуы керек.*

Түйінді сөздер: *CRISPR, Cas9, қатерлі ісік, онкология, жеткізу векторлары, нанобөлшектер.*

АННОТАЦИЯ

ПЕРСПЕКТИВЫ И ПРОБЛЕМЫ РЕДАКТИРОВАНИЯ ГЕНОВ CRISPR/CAS9 В ТЕРАПИИ РАКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак остается одной из ведущих причин смертности в Казахстане, и CRISPR/Cas9 предлагает возможные решения для его лечения. Кластеризованные, регулярно чередующиеся короткие палиндромные повторы / CRISPR-ассоциированный белок 9 (CRISPR/Cas9) – это система, которую бактерии используют для расщепления чужеродных захватчиков. Система была признана многообещающей в отношении терапии рака, поскольку позволяет исследователям редактировать гены раковых клеток.*

Данная система требует дополнительных испытаний, поэтому важно повысить осведомленность студентов и потенциальных инвесторов об этой методике, а также привлечь внимание к текущим проблемам, которые могут стать исследовательскими возможностями.

Цель исследования *– проанализировать и предоставить актуальную информацию из авторитетных научных журналов о текущем статусе использования системы CRISPR/Cas9 в терапии рака студентам-медикам и исследователям. В этом исследовательском документе также освещаются проблемы, связанные с внедрением Crispr/Cas9 в клинических условиях для лечения рака.*

Методы: *Проведено исследование по научной литературе и базам данных (база данных PubMed, научный журнал Nature).*

Результаты: *Полученные результаты указывают, что ученым следует сосредоточиться на улучшении типов и структуры белка Cas, а также методов доставки, включая невирусные методы доставки (частицы на основе липосом, гибридные векторы, наночастицы золота и внеклеточные везикулы), чтобы способствовать улучшению текущего состояния средств для лечения рака.*

Заключение: *CRISPR / Cas9 – важный метод, который все еще сопряжен с трудностями, которые следует превратить в возможности для исследований. Текущие проблемы включают форму и структуру Cas-нуклеазы, типы инженерии (in vivo против ex vivo) и разнообразие методов доставки. Каждый вид способа доставки имеет свои плюсы и минусы и требует дальнейшего изучения. В частности, невирусные векторы, такие как частицы на основе липосом, внеклеточные везикулы, гибридные везикулы и наночастицы золота, должны быть в центре будущих исследований.*

Ключевые слова: *CRISPR, Cas9, рак, онкология, векторы доставки, наночастицы.*

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INTERNATIONAL EXPERIENCE IN APPLYING THE SYSTEM OF PEDIATRIC EARLY WARNING SIGNS OF CRITICAL CONDITIONS IN ONCOLOGICAL CHILDREN: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Oncological diseases remain the main cause of death in children, increasing the need for intensive care. Hospitalized children suffering from oncological diseases are at high risk for sudden deterioration of their condition, both for the underlying disease and due to infectious complications and the toxic effects of medications. This review highlights information on the Pediatric Early Warning Signs (PEWS) system in oncological patients to detect clinical deterioration promptly.*

The study aimed to *analyze international literature on using pediatric early warning signs (PEWS) for clinical deterioration in pediatric oncology.*

Methods: *Current literature on using the PEWS of clinical deterioration in pediatric oncology was studied.*

Results: *The published data show the critical role of using the PEWS system in cancer patients for early detection of deterioration of the condition with subsequent provision of emergency medical care.*

Conclusion: *The analysis of international experience has shown that using the PEWS system in children with oncological diseases is an effective method of early recognition of signs of clinical deterioration, which, in turn, allows the timely initiation of complex intensive therapy.*

Keywords: *oncology, hematology, PEWS, clinical deterioration, children, intensive care.*

Introduction: Pediatric oncology studies tumors and develops practical recommendations for prevention, diagnosis, and complex therapy. Approximately 10% of all pediatric cancer patients have a genetic predisposition to cancer [1].

Due to the opportunity of obtaining high-quality medical services, more than 80% of pediatric cancer patients are cured in high-income countries. Pediatric cancer patients in low- and middle-income countries are cured in less than 30% of cases [2]. A modern approach to therapy in pediatric oncology is the creation of interdisciplinary teams with the participation of pediatric hematologists, oncologists, infection control specialists, anesthesiologists, resuscitators, transfusiologists, pediatricians, pediatric surgeons, neurosurgeons, vascular surgeons, neurologists, gynecologists, endocrinologists and other specialists necessary for patients at different stages of the path to recovery [3].

The global burden of pediatric oncology is disproportionately shifting towards low- and middle-income countries. Countries with limited resources account for about 80% of childhood cancer morbidity and about 90% of cancer mortality in children [4]. Hospitalized children suffering from oncological diseases are in a high-risk group since frequent life-threatening complications can deteriorate their conditions. The most common childhood oncological diseases include leukemia, malignant brain tumors, lymphomas, and solid tumors such as neuroblastoma and nephroblastoma [5].

Timely early diagnosis of various complications aimed at improving survival rates in oncological diseases [6-8]. Medical personnel needs clear criteria and algorithms to prevent critical conditions, allowing timely identification and provision of necessary, complete, and urgent care, which is particularly important in hospitals with limited resources [9]. During inpatient treatment, inadequate initial assessment of the general condition, lack of constant monitoring of vital signs, and inadequate therapy lead to undesirable results, partly due to the lack of systems that detect clinical deterioration in patients [10]. As a result, several severity assessment systems have been developed and tested to

improve the identification of patients in the pediatric population with a higher risk who need complex intensive care [11-13].

Pediatric Early Warning Signs (PEWS) system is a tool for the clinical assessment of the patient's condition, taking into account vital signs and symptoms of the oncological patients to detect clinical deterioration promptly [14]. The use and implementation of the PEWS system in children's hospitals showed a decrease in the frequency of cardiopulmonary arrest outside the intensive care unit (ICU), unscheduled transfers to the ICU, and general hospital mortality [15].

The study aimed to analyze international literature on using pediatric early warning signs (PEWS) for clinical deterioration in pediatric oncology.

Materials and methods: We searched using keywords like oncology, hematology, PEWS, clinical deterioration, and children in the databases PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane Library. To compile the review, we studied all publications on this topic in open access, the search depth was ten years, and the original language is English. The analysis included the results of original clinical and comparative studies in pediatric oncology hospitals, as well as case studies in the field of pediatric oncology. The exclusion criteria were abstracts not in English, summaries of materials, and personal messages that did not contain the primary significance.

Results: This review includes 50 studies published over the past ten years evaluating the results of the introduction and impact of PEWS in clinical practice in cancer patients. The parameters used in the PEWS system include neurological problems, heart rate, capillary filling time, respiratory rate, participation of auxiliary muscles, oxygen therapy, and body temperature.

In recent decades, against the background of complex therapy, there has been a noticeable increase in the overall survival of children with hematological diseases. However, some cancer patients need treatment that includes hematopoietic stem cell transplantation, and these patients still represent a group with a higher mortality risk. In addition, we have learned that ventilation and cardiovascular support, along with renal replacement therapy, can benefit pediatric patients with hematological diseases if these procedures are started promptly [16].

In an international multicenter study, Parshuram C.S. et al. conducted a case-control study in hospitalized children with the participation of three clinics from Canada and one from the UK (n=2074 patients). In the case of clinical deterioration, patients experienced either immediate referral to the intensive care unit or urgent hospitalization in the ICU. No events were recorded in the control patients. The overall scores on the Bedside PEWS system were different; the assessment was carried out 24 hours before the event of clinical deterioration. The median (interquartile range) of the leading indicators of Bedside PEWS for 12 hours ending 1 hour before clinical deterioration was 8 (from 5 to 12) in patients receiving treatment and 2 (from 1 to 4) in patients of the control group (P<0.0001). The Area Under Curve Receiver Operator Characteristic (AUCROC) curve (95% confidence interval) was 0.87 (from 0.85 to 0.89). In patients who received treatment, the average scores were 5.3 for 20-24 hours and 8.4 for 0-4 hours before the event (P<0.0001). The AUCROC curve (95% CI) of retrospective nurse evaluations was 0.83 (0.81 to 0.86). Assessment of Bedside PEWS allows us to distinguish "sick" from "healthy" hospitalized patients. These data suggest that the PEWS assessment can help doctors identify children at risk of immediate and actual cardiac arrest [17].

In the following retrospective study, before and after introducing the PEWS tool with an appropriate algorithm for interdisciplinary actions in the department of Hematology, it is reported that barriers between departments that prevented the timely transfer of children with clinical deterioration requiring urgent care were eliminated. The introduction of the PEWS system improved the interaction between multidisciplinary teams, which helped ensure that the necessary assistance was received in the right place and at the right time [18]. Finally, the study mainly focuses on implementing the system itself.

At Kamuzu Central Hospital, a large specialty hospital in Lilongwe, Malawi, with over 15,000 hospitalizations of children per year, the introduction of the PEWS system reduced the inpatient mortality rate in study phases A, B, and C: from Phase A (9.3%) to Phases B (5.7%) and C (6.9%) [19].

In an observational study by Sefton G. et al. before and after the introduction of the PEWS system in a pediatric hospital, the median infant mortality index (PIM2) decreased from 0.60 to 0.44 ($p < 0.001$). For fewer hospitalizations, invasive lung ventilation was required – 62.7% versus 75.2% ($p = 0.015$); its average duration decreased from 4 to 2 days. The average length of stay in the ICU decreased from 5 to 3 days ($p = 0.002$). In addition, there was a slight decrease in mortality ($p= 0.47$) [20].

The study by Agulnik A. et al., introducing the PEWS system in the Pediatric Cancer Hospital in Guatemala (Unidad Nacional de Oncologia Pediatrica), has reduced unplanned ICU transfers. The results of a study published in 2016 show that hospital investments in PEWS can improve the quality of pediatric cancer care, optimize the use of ICU and reduce costs [21].

A 2017 publication highlighting the results after the successful implementation of PEWS in a children's cancer hospital with limited resources in Guatemala reported a significant reduction in unplanned transfers to the

ICU, a decrease in the length of stay in the ICU and a decrease in the frequency of severe sepsis or septic shock when transferring to the ICU [22].

The same author shows that the PEWS assessment largely correlates with the need for unplanned transfer to the ICU in patients with oncology after hematopoietic stem cell transplantation. In addition, it is reported that the PEWS system correctly identified most patients who needed ICU care [23].

According to the St. Jude Research Hospital, patients after hematopoietic cell transplants have a worsening condition requiring ICU transfer. As a rule, critical deterioration is preceded by a long period of abnormal vital signs, which makes it potentially preventable by earlier recognition of the precursors of critical conditions; PEWS appropriately identified hospitalized patients who needed to be transferred to a higher level of treatment [24].

At Alder Hey Children's Hospital, a top-level pediatric facility in Liverpool, United Kingdom, parents of children were invited to participate in semi-structured telephone interviews. Recruitment was conducted in the period from February 2020 to February 2021. There is data on parents' experience and perception of the acceptability of a hospital-wide active electronic system for early warning of complications in children. Parents reacted positively and welcomed the use of new technologies to support the care of their children [25].

Dylan G. et al . described the algorithmic approach to care used in Guatemala and the United States, showing that PEWS improves interdisciplinary communication, expanding the capabilities of medical professionals [26]. PEWS also improves communication between attending physicians and families by enhancing interaction, which once again demonstrates the importance of PEWS for improving the quality of medical care in conditions with both high and limited resources [27].

In turn, there are clinical and organizational risk factors for mortality with deterioration among patients with pediatric oncology. Thus, in Latin America, a multicenter prospective study involving 16 centers registered 553 critical impairments in patients from 11,536 hospitalizations and 119,414 days of hospital stay. Event mortality was 29% but varied greatly by the center (11-79%). In addition, cases with organ dysfunction and high disease severity had higher mortality. According to the researchers, early detection of complications and timely transfer to the ICU can improve the prognosis [28].

After introducing PEWS in 29 pediatric cancer centers in Latin America, an anonymous survey among medical staff showed a high ability to maintain the PEWS system [29].

A qualitative study involving five pediatric oncology centers with limited resources in 4 Latin American countries assessed barriers and factors contributing to introducing an early warning system for complications. The survey involved 71 employees (70% women), including 32 doctors (45%), 32 nurses (45%), and seven administrators (10%). Many obstacles to implementing PEWS have been identified, including insufficient resources and staff resistance to change. In addition, the survey participants highlighted barriers at the level of clinical staff, hospital, and external factors. The survey (research) result showed that many barriers are not unchangeable and can be transformed into factors contributing to the implementation process [30].

The Dutch Children's Oncology Hospital conducted a prospective cohort study, where all national pediatric oncology care is centralized and which is directly connected to a 22-bed general ICU, the results of which may provide additional evidence of the benefits of using the PEWS system in hospitalized patients with pediatric oncology or indicate that PEWS needs optimization (modification) in children with oncological diseases [31].

Discussion: Regular assessment, monitoring, and registration of the vital signs of the child are critical components of monitoring the patient's condition, fundamental for early detection of clinical deterioration and provision of high-quality medical care [32, 33]. Clinical deterioration in a patient not recognized in time becomes a source of the critical condition [34]. It can lead to extended hospitalization, unplanned hospitalization in the ICU, cardiac arrest, or death [35, 36]. Many children who die unexpectedly or whose condition worsens in the hospital have noticeable signs before the severity of their condition is recognized [37]. Untimely recognition of clinical deterioration is an urgent patient safety problem, necessitating the introduction of PEWS systems in the care of children in the hospital [38]. Using PEWS to stratify the risk of clinically deteriorating patients can also help solve the problem of the burden on medical institutions that lack resources [39, 40]. The assessment of the condition is calculated manually or electronically, while each component is evaluated, taking into account its deviation from the norm [41-43]. The data indicate that electronic assessment has advantages over paper assessment [44].

During the night shift, one doctor on duty serves all departments. Given the potential burden of many patients for whom a doctor may be responsible, the PEWS system can provide an objective triage tool to effectively assess the risk of clinical deterioration, leading to more efficient use of resources. However, we should note that many patients do not require interventions after the PEWS assessment. Moreover, it could create an unintended burden on the department's medical staff. There are also contradictory data on the effectiveness of the PEWS system, reflecting the complexity of using and evaluating measurement results [45].

Hospitalized children suffering from oncological diseases are at high risk for sudden deterioration of their condition. However, as access to pediatric cancer therapy expands in resource-constrained settings, there is a need for effective and inexpensive methods to improve the care of cancer patients, as a lack of infrastructure and a shortage of staff can lead to late detection of PEWS.

During the long therapy process, it is necessary to maintain a dialogue between doctors, nursing staff, the child, and his parents. It is paramount for optimizing the care of children with complex diseases and changing medical status. After all, the life of parents whose child needs intensive care in an ICU is turned upside down; many compare it to "riding a roller coaster" [46]. In addition, some parents of children with severe and long-term illnesses become "experts" in vital indicators of their child's health status and can recognize changes in their condition [47]. In addition, there is evidence that parents are reliable partners in expanding care [48].

According to the analyzed publications, many positive results are reported, but there are also contradictory data on using PEWS. In this regard, it is necessary to evaluate the effectiveness in the long term.

Conclusion: The lack of early diagnosis of complications, infections, erroneous interpretation of the observed symptoms, and late referral to specialists – all these factors are crucial concerning the outcome of the disease [49]. Deterioration of the child's condition can develop at any stage of program polychemotherapy [50]. Therefore, special qualification of medical staff is required for timely recognition of early signs of clinical deterioration and provision of comprehensive, intensive care.

Implementing the PEWS assessment system in the Department of Pediatric Hematology/Oncology is feasible. It can contribute to an adequate assessment of the patient's condition by increasing the frequency of collecting vital signs in real time.

We want to emphasize the need for early diagnosis of clinical deterioration before, during, and after program therapy in children with oncological diseases to promptly provide the necessary complex intensive therapy. Thus, unified approaches to early precursors of critical conditions in children with oncological diseases are necessary to prevent critical conditions and reduce adverse disease outcomes.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ БАЛАЛАРДАҒЫ АУЫР ЖАҒДАЙЛАРДЫҢ ЕРТЕ АЛДЫН АЛУДЫҢ ПЕДИАТРИЯЛЫҚ БЕЛГІЛЕРІ ЖҮЙЕСІН ҚОЛДАНУДЫҢ ХАЛЫҚАРАЛЫҚ ТӘЖІРИБЕСІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Онкологиялық аурулар ісік балалар өлімінің басты себебі болып қала береді, нәтижесінде қарқынды терапия жүргізу қажеттілігі артуда. Онкологиялық аурулармен ауыратын ауруханаға жатқызылған балалар негізгі ауру бойынша да, жүқпалы асқынуларға және дәрілік препараттардың уытты әсеріне байланысты да жағдайдың кенеттен нашарлауы бойынша жоғары тәуекел тобына жатады. Бұл шолуда клиникалық нашарлауды уақтылы анықтау мақсатында онкологиялық науқастарда ерте ескертудің педиатриялық белгілері (Pediatric Early Warning Signs, PEWS) жүйесі туралы мәліметтер қамтылған.*

Зерттеудің мақсаты *– балалар онкологиясындағы клиникалық нашарлаудың ерте алдын алудың педиатриялық белгілері жүйесін қолдану туралы өзекті әдеби деректерге шолу.*

Әдістері: *онкологиялық балаларда PEWS жүйесін қолдану бойынша интернет-ресурстарда жарияланған зерттеулерге шолу жасалды.*

Нәтижелері: *жарияланған деректер бойынша онкологиялық науқастарда PEWS жүйесін қолдану маңызды рөл көрсетеді, ол клиникалық жағдайдың нашарлауын ерте анықтау үшін және уақытылы шұғыл медициналық көмек көрсету үшін қажет.*

Қорытынды: *Халықаралық тәжірибеге жүргізілген талдау көрсеткендей онкологиялық аурулары бар балаларда PEWS жүйесін қолдану халықаралық тәжірибеде клиникалық нашарлау белгілерін ерте танудың тиімді әдісін ұсынады, бұл өз кезегінде кешенді қарқынды терапияны уақтылы қосуға мүмкіндік береді.*

Түйінді сөздер: *онкология, гематология, pews, клиникалық нашарлау, балалар, қарқынды терапия.*

АННОТАЦИЯ

МЕЖДУНАРОДНЫЙ ОПЫТ ПРИМЕНЕНИЯ СИСТЕМЫ ПЕДИАТРИЧЕСКИХ ПРИЗНАКОВ РАННЕГО ПРЕДУПРЕЖДЕНИЯ КРИТИЧЕСКИХ СОСТОЯНИЙ У ОНКОЛОГИЧЕСКИХ ДЕТЕЙ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Онкологические заболевания остаются основной причиной смерти у детей, в результате потребность в проведении интенсивной терапии возрастает. Госпитализированные дети, страдающие онкологическими заболеваниями, находятся в группе*

высокого риска по внезапному ухудшению состояния, как по основному заболеванию, так и в связи с инфекционными осложнениями и токсичными действиями лекарственных препаратов. В этом обзоре освещаются сведения по системе педиатрические признаки раннего предупреждения (Pediatric Early Warning Signs, PEWS) у онкологических пациентов, с целью своевременного выявления клинического ухудшения.

***Цель исследования** – изучение актуальных литературных данных о применении системы педиатрических признаков раннего предупреждения клинического ухудшения в детской онкологии.*

***Методы:** Был проведен обзор опубликованных исследований по применению системы PEWS у онкологических детей.*

***Результаты:** Опубликованные данные показывают важную роль использования PEWS у онкологических пациентов для раннего выявления ухудшения состояния с последующим оказанием интенсивной помощи.*

***Заключение:** Проведенный анализ международного опыта показал, что применение системы PEWS у детей с онкологическими заболеваниями является эффективным методом раннего распознавания признаков клинического ухудшения, что, в свою очередь, позволяет своевременно подключить комплексную интенсивную терапию.*

***Ключевые слова:** онкология, гематология, педиатрические признаки раннего предупреждения (Pediatric Early Warning Signs, PEWS), клиническое ухудшение, дети.*

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PROGNOSTIC VALUE OF LIQUID BIOPSY IN CRC: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Liquid biopsy is a modern, quite appropriate, and promising method for diagnosing malignant neoplasms for oncology. The method allows us to determine the level of freely circulating tumor cells – micrometastases, tumor DNA, microRNA, and exosomes in blood plasma- and detect various genetic changes. A literature review of current scientific publications on liquid biopsy techniques, indexed in Medline, PubMed, and Medscape, was carried out as part of the work.*

The study aimed to *review is to assess the prognostic significance of liquid biopsy, to determine the place of the method in current recommendations, and its expediency from the point of view of the practice.*

Methods: *The information search was conducted in the Medline, PubMed, and Medscape databases, with a search depth of 8 years. Data from randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses were analyzed. The review includes full-fledged articles in the public domain and abstracts to obtain complete information on the problem.*

Results: *Liquid biopsy surpasses tissue biopsy in simplicity and speed of research, easy repeatability, and minimal invasiveness, as well as the possibility of dynamic monitoring of progression – the overall clonal transformation of the tumor and the emergence of resistance to treatment.*

The disadvantages of this method are low sensitivity, difficulty in correctly interpreting biomarkers and determining their specificity, and high risk of false positive and false negative results due to dormant tumor cells.

Conclusion: *At present, the Liquid biopsy method is relevant and in demand, but it needs to be tested on a validated sample of the main population, and in order to achieve effective clinical use, significant work needs to be done to standardize both pre-analytical and analytical procedures and generalize them for all components of liquid biopsy.*

Keywords: *Liquid biopsy, colorectal cancer, metastatic colorectal cancer, the validity of methods, tissue biopsy, the value of methods, micrometastases.*

Introduction: Approaches to cancer treatment have improved due to the increased specialists' knowledge about molecular disorders that stimulate tumors, which has led to even more effective targeted therapy development. Due to these achievements, testing molecular biomarkers for the stratification of cancer patients has become mandatory. First, a biopsy is performed – puncture of material from primary tumors for diagnosis pathomorphological confirmation. This approach is convenient for diagnostic purposes but excludes patient monitoring during the disease progression and possible relapse [1].

This approach has some advantages and limitations. The liquid biopsy method allows us to determine the level of freely circulating tumor cells – micrometastases, tumor DNA, microRNA, and exosomes in blood plasma- and detect various genetic changes [2]. All of the above allows us to study the literature and accumulated data on the liquid biopsy method as a diagnostic method from the point of view of prognostic significance, the place of the method in current recommendations, and practical expediency.

The study aimed to review is to assess the prognostic significance of liquid biopsy, to determine the place of the method in current recommendations, and its expediency from the point of view of the practice.

Materials and methods: Medline, PubMed, and Medscape databases were used to search for information. The search depth is eight years (2015-2022). Keywords used for selecting publications: liquid biopsy, colorectal cancer, metastatic colorectal cancer (mCRP), the validity of methods, tissue biopsy, the value of methods, micrometastases.

Type of articles for analysis: randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses. Full-fledged articles in the public domain and abstracts were selected to obtain complete information on the problem.

Information was collected according to the PRISMA 2020 scheme (Figure 1):

As a result of a keyword literature search, 78 sources were found. At the first stage of the analysis, 19 sources were eliminated, some were duplicated, and some did not correspond to the therapeutic area. Of the remaining 59 sources, 42 more were excluded, as they needed to reflect the purpose of the study entirely. As a result, 17 sources were used for this review article.

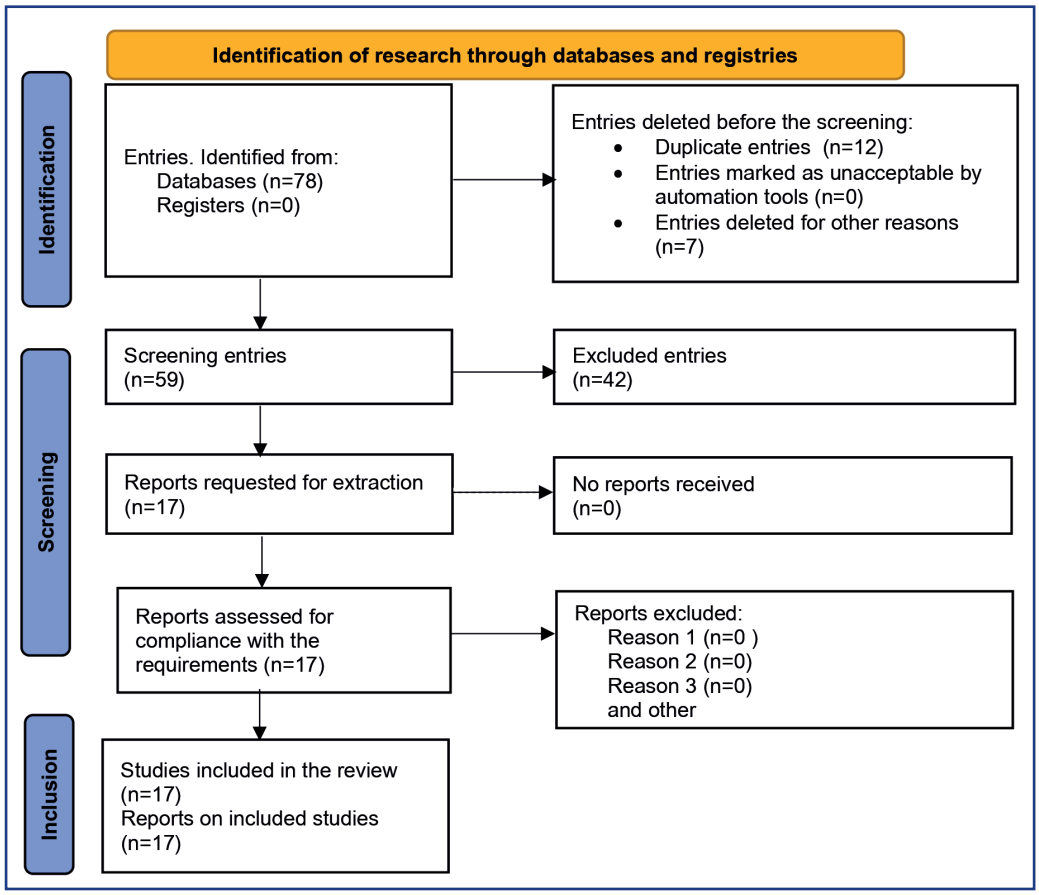

Figure 1 – Collecting information for a literature review

Results: Evaluation of the mutational profile of cancer is usually carried out using a fragment of a primary tumor or metastasis [1]. Obtaining a tissue biopsy requires surgical intervention, which significantly limits the possibility of taking a biopsy. Depending on the tumor's location, tumor tissue's availability may be problematic.

Moreover, heterogeneity within the tumor, especially spatial heterogeneity, can lead to unreliable biomarker detection results, especially when testing a single biopsy area [3-5]. In addition, multiple tumor foci complicate the characterization of the patient's cancer. The availability of tumor samples during long-term treatment of patients may be difficult, and, in addition, testing of archived tumor samples may be suboptimal due to the evolution of the tumor. Since it is necessary to conduct serial monitoring of tumor progression and development in patients, repeated use of tissue biopsy is only sometimes possible.

There is an urgent need to use more accessible materials implying non-invasive or minimally invasive procedures that allow systematic and real-time monitoring of molecular changes in the patient's cancer, including colorectal cancer.

There is some data in the literature studying the inclusion of RAS/BRAF liquid biopsy and the determination of circulating DNA (cDNA) in the work of cancer centers. So, Van't Erve I. et al.. studied liquid biopsies taken from 100 MCC patients to compare digital PCR analysis of cDNA with conventional RAS/BRAF mutation profiling of tumor tissue. The results of a liquid biopsy of tissue DNA and cDNA showed a 93% match, which underlines the potential clinical usefulness of a liquid biopsy for detecting primary resistance to anti-EGFR [6].

Pastor B. et al. found that circulating extracellular DNA (ecDNA) contains circulating tumor cDNA, which can be obtained from serial fluid biopsies, allowing tumor genome analysis throughout treatment. The authors have investigated that ecDNA and mutant cDNA can be potential biomarkers to predict the best treatment outcomes for MCC patients. The authors analyzed longitudinally collected plasma ecDNA from 43 MCC patients, prospectively included in the TEXCAN phase II study, using an advanced real-time IntPlex PCR method based on critical observations of a specific structure and size of the ecDNA. Qualitative mutations (KRAS, NRAS, BRAFV600E) and quantitative (total ecDNA concentration, mutant cDNA concentration, mutant cDNA fraction) parameters correlated with overall survival (OS) and progression-free survival (PFS), and shows that the levels of ecDNA before treatment and mutant

cDNA levels can identify MCC patients who need one or another targeted treatment [7].

In the Poseidon study, published in October 2021, the authors conducted a prospective direct comparison of liquid and standard tissue biopsy (STB) in the exact center. This study was because some patients may have different results from standard molecular tissue studies during the first visit. A liquid biopsy can help circumvent these obstacles. The authors, in natural conditions, included in the study MCC patients with unknown RAS/BRAF status at the time of the first visit. The inclusion criteria were the presence of tumor tissue in the archive and the absence of previous anti-EGFR treatment. At the first visit, a plasma sample was taken from the patients for liquid biopsy and STB. The primary endpoint was comparing the time to the liquid biopsy results (T1) and STB (T2) using the Mann-Whitney U-test. The secondary endpoints were the correspondence between the methods, defined as a total percentage match, and the accuracy of the liquid biopsy in terms of specificity, sensitivity, and positive and negative prognostic value. As a result, the average value of T1 and T2 was 7 and 22 days, respectively ($p < 0.00001$), and the overall percentage correspondence between the liquid biopsy results and STB was 83%. The specificity and sensitivity of liquid biopsy compared with STB were 90% and 80%, respectively, with a positive prognostic value of 94% and a negative 69% for liquid biopsy. The obtained results allowed the authors to conclude that faster execution time, high consistency, and accuracy are the three critical points for introducing liquid biopsy into the routine management of MCC, mainly when the decision on first-line therapy is urgent. The request for biomaterial from the archive of external centers may take a long time [8].

A liquid biopsy is an ideal procedure, primarily confirmed by the impressive developments we have witnessed in recent years (Table 1).

Table 1 – Comparative characteristics of standard tissue and liquid biopsy methods

Standard tissue biopsy	Liquid biopsy
The Gold Standard	High interest among researchers
Availability for histological analysis and stag-ing	Limited ability to perform histological analysis
May be unavailable	Easily available It takes a shorter time to get the result Risk of false results (+/-)
Invasive method Patient dis-comfort (risk of clinical complications)	Minimal invasiveness
Depending on the collection and storage pro-cedures, preserved tissues can represent high-ly variable DNA of different qualities.	New DNA, not modified with preservatives, must follow a strict procedure for collecting, processing, and storing the material to avoid DNA degradation.
High DNA yield, risk of DNA degradation, cross-linking, and the amount of DNA varies depending on sampling methods.	The quantity and quality of DNA depend on the pre-analytical and analytical processes.
The localized analysis does not allow us to characterize the intra- and inter-tumor hetero-geneity (metastasis) characteristic of most tu-mors, especially in the late stages and with multiple tumor localization.	Allows, in principle (if it is possible to isolate and analyze a sufficient amount of DNA to identify both intra- and inter-tumor heterogene-ity and multiplicity of tumor sites.
Not applicable to sequential monitoring.	Applicable to sequential monitoring
Fixed time to get the result.	Sampling of the material can be performed at any time during therapy or observation of the patient.
Dynamic observation of the molecular chang-es of the tumor is impossible.	Dynamic observation of tumor evolution (sig-nificant for the short half-life of circulating tu-mor DNA).

Many authors discuss intra-tumor heterogeneity and its significance in CC. For example, F. Fabbri et al. demonstrated for the first time the possibility of analyzing pure circulating tumor cells (CTC) at the molecular level and avoiding mixing with lymphocytes using the DEPArray platform (Menarini Silicon Biosystem, USA) based on dielectrophoresis as well as the KRAS mismatch between CTC and primary tumor tissue after 100% extraction of uninfected cells and sequencing. In a cohort of 40 patients with metastatic CC, 21 patients had more than three CTC in a 7.5 ml blood sample. An additional analysis of KRAS in 16 patients showed only a 50% correspondence between the assessment of primary tumor tissue and CTC [9].

The RAS CC study using the OncoBEAM™ system (Sysmex Inostics, Germany) showed that the overall consistency of standard and liquid biopsies results was 96.4%. Of 55 patients with a positive RAS mutation in tumor tissue, 53 also had a RAS mutation in ecDNA [10]. With the same analysis, an additional study with a cohort of 236 patients with mCRP showed an 89% correlation of the RAS mutation between tumor biopsy and ecDNA [11]. Another study evaluating the clinical usefulness of ecDNA involving 140 MCC patients showed slightly different results. Only a moderate correspondence (accuracy 72-87%) was observed between plasma samples and tumor tissue, possibly due

to the higher frequency of KRAS mutation in plasma samples [12].

Discussion: Liquid biopsy may be of great practical importance for treating patients. Accurate and continuous molecular characterization of CC is crucial for the correct and timely use of molecular-targeted therapies.

KRAS and NRAS mutations differ significantly between sporadic CC lesions, and the status of these mutations in tumor metastases is unpredictable [13].

Liquid biopsy can detect KRAS mutations in ecDNA in cases where the mutation has not been determined by biopsy of the primary tumor. It may be a fundamental step in choosing therapy since tumor cells with KRAS mutation resist treatment with monoclonal antibodies against EGFR [13]. Achieving effective clinical use of liquid biopsy requires significant efforts to standardize and generalize pre-analytical and analytical procedures for all components of liquid biopsy. Much has already been done in this area. The need for standardization of pre-analytical procedures includes the selection of blood collection tubes, the time between blood collection and plasma treatment, and procedures for extraction/isolation of liquid biopsy components. Standard procedures should be approved accordingly for their characterization and quantification. Moreover, standardization should maximize the yield of liquid biopsy markers.

The liquid biopsy technique can provide a critical clinical understanding of the molecular subtypes of the tumor, especially when the discrepancy of KRAS mutations between primary and recurrent or metastatic tumors after resection can reach about 20% [14].

As mentioned above, the method of liquid biopsies can determine the exact characteristics of cancer heterogeneity (tumors and metastatic sites) and its evolution. In this process, a necessary step is to accumulate data from extensive clinically validated studies to evaluate and demonstrate the effectiveness of several markers detected during liquid biopsy (including exosomes, cDNA) in clinical settings and positive results of choosing therapy options in patients [15]. In addition, the complementarity of several components of liquid biopsy, potentially originating from different populations of tumor cells, has yet to be studied.

In 2020, efforts were made to standardize pre-analytical workflows for liquid biopsy in the context of the Horizon 2020 SPIDIA4P consortium project of the European Union, indicating the existing demand and proven workflow [16].

Conclusion: Morbidity, mortality, age of diagnosis, nonspecific symptoms, and intra-tumor heterogeneity in CC demonstrate that there are still opportunities to improve clinical management and treatment outcomes of patients. A liquid biopsy can be a tool that adds a new perspective to clinical routine and confidence in clinical decision-making.

A standard tissue biopsy is crucial for the pathological evaluation of a tumor during a tumor biopsy and displays the current pathological status of a particular lesion. Liquid biopsy is ideal for the longitudinal monitoring of a common disease by molecular characterization with the additional possibility of understanding the spatial and temporal heterogeneity of the CC [17].

A liquid biopsy can improve diagnosis, prognosis, and treatment response by providing valuable information about a patient's disease to aid clinical decision-making.

The great potential of liquid biopsy in oncology is just beginning to be effectively studied in research. In recent years, impressive data have begun to appear in the literature, highlighting the potential clinical use of liquid biopsy. It tends to develop since many current clinical studies include serial blood collection as a biomaterial for tumor research, determining prognosis, and therapy options. Moreover, the constant improvements in precise and susceptible technologies we have observed in recent years will open up even more opportunities to study several components secreted by tumors simultaneously.

The use of DNA and CTC can offer new methods of diagnosis, prediction, and subsequent response to treatment, and, most importantly, liquid biopsy platforms are aimed at providing the necessary information to improve patient outcomes. However, issues such as pre-analytical variables, the rarity of CTC and cDNA in samples, analytical validity, clinical validation, cost-effectiveness, and regulatory approval must be addressed before clinical use.

Summing up the above, liquid biopsy is an easily repeatable and minimally invasive method that can and should be used to detect early metastases and relapses and determine the characteristics of the tumor phenotype, its heterogeneity, and minimal residual disease.

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АҢДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІК КЕЗІНДЕГІ СҰЙЫҚТЫҚТЫ БИОПСИЯНЫҢ БОЛЖАМДЫҚ МАҢЫЗЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сұйық биопсия (FB) онкология үшін қатерлі ісіктерді диагностикалаудың заманауи, өте өзекті және перспективалы әдісі болып табылады. Бұл әдіс қан плазмасындағы еркін айналымдағы ісік жасушаларының – микрометастаздардың, ісік ДНҚ-ның, микроРНҚ-ның және экзосомалардың деңгейін анықтауға, сондай-ақ әртүрлі генетикалық өзгерістерді анықтауға мүмкіндік береді. Жұмыс шеңберінде Medline, PubMed, Medscape индекстелген сұйық биопсия әдістемелеріне арналған өзекті ғылыми жарияланымдарға әдеби шолу жүргізілді.*

Зерттеудің мақсаты *– сұйық биопсияның болжамды маңыздылығын бағалау, әдістің қазіргі ұсыныстардағы орнын, практика тұрғысынан орындылығын анықтау болып табылады.*

Материалдар мен әдістері: *Ақпаратты іздеу үшін 8 жылдық терең тарихы бар Medline, PubMed, Medscape дерекқорлары пайдаланылды. Рандомизацияланған бақыланатын зерттеулердің, клиникалық зерттеулердің, шолулардың, жүйелі шолулардың және мета-талдаулардың деректері талданды. Шолуға еркін қол жетімді толық мақалалар да, мәселе бойынша толық ақпарат алу үшін дерексіз мақалалар да кірді.*

Ақпаратты өңдеу үшін Excel кестесі пайдаланылды, оның ішінде кейінгі талдау үшін ақпарат бар.

Нәтижелері: *СБ қарапайымдылығы мен зерттеу жылдамдығы, жеңіл қайталануы және төмен инвазивтілігі, сондай-ақ прогрессияны динамикалық бақылау мүмкіндігі ісіктің жалпы клондық трансформациясы және емдеуге төзімділіктің пайда болуы бойынша тіндік биопсиядан асып түседі.*

Бұл әдістің кемшіліктері төмен сезімталдық, биомаркерлерді дұрыс түсіндірудің және олардың ерекшелігін анықтаудың күрделілігі, дормантты ісік жасушаларының болуына байланысты жалған оң және жалған теріс нәтижелердің жоғары қаупі болып саналады.

Қорытынды: *қазіргі уақытта СБ әдісі өзекті және сұранысқа ие, бірақ оны негізгі популяцияға тексерілген үлгіде сынау қажет, ал тиімді клиникалық қолдануға қол жеткізу үшін аналитикалық және аналитикалық процедураларды стандарттаумен оларды сұйық биопсияның барлық компоненттері үшін жалпылау үшін маңызды жұмыс жасалуы керек.*

Түйінді сөздер: *сұйық биопсия, колоректальды қатерлі ісік, метастатикалық колоректальды қатерлі ісік, әдістердің жарамдылығы, тіндік биопсия, әдістердің құндылығы, микрометастаздар.*

АННОТАЦИЯ

ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ЖИДКОСТНОЙ БИОПСИИ ПРИ КРР: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Жидкостная биопсия является современным, достаточно актуальным и перспективным методом диагностики злокачественных новообразований для онкологии. Данный метод в качестве диагностической концепции позволяет определять циркулирующие факторы, производных опухоли, которые в последствии позволят определить прогноз опухоли, и определить тактику ведения.*

Цель исследования *– оценить прогностическую значимость жидкостной биопсии, определить место метода в современных рекомендациях, целесообразность с точки зрения практики.*

Методы: *Был проведен поиск информации в базах данных Medline, PubMed, Medscape. Были проанализированы данные рандомизированных контролируемых исследований, клинических исследований, обзоров, систематических обзоров, и мета-анализов. В обзор вошли как полновесные статьи в свободном доступе, так и абстракты, для возможности получения пол-ной информации по проблеме.*

Результаты: *Жидкостная биопсия превосходит тканевую биопсию по минимальной инвазивности, а соответственно более низком риске осложнений от процедур забора материала, возможности выявления как внутри – так и межопухолевой гетерогенности и множественность участков опухоли, что позволяет наблюдать за опухолью в динамике и мониторировать общую клональную трансформацию опухоли и возможную резистентность к лечению.*

Недостатками данного метода принято считать низкую чувствительность, сложность правильной интерпретации биомаркеров и определения их специфичности, высокий риск ложноположительных и ложноотрицательных результатов из-за присутствия дормантных опухолевых клеток.

Заключение: *В текущее время метод жидкостной биопсии актуален, востребован, но его требуется апробировать на валидированной выборке к основной популяции, а для достижения эффективного клинического использования предстоит выполнить важную работу по стандартизации как преаналитических, так и аналитических процедур и обобщить их для всех компонентов жидкостной биопсии.*

Ключевые слова: *жидкостная биопсия, колоректальный рак, метастатический колоректальный рак (мКРР), валидность методов, тканевая биопсия, ценность методов, микрометастазы.*

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