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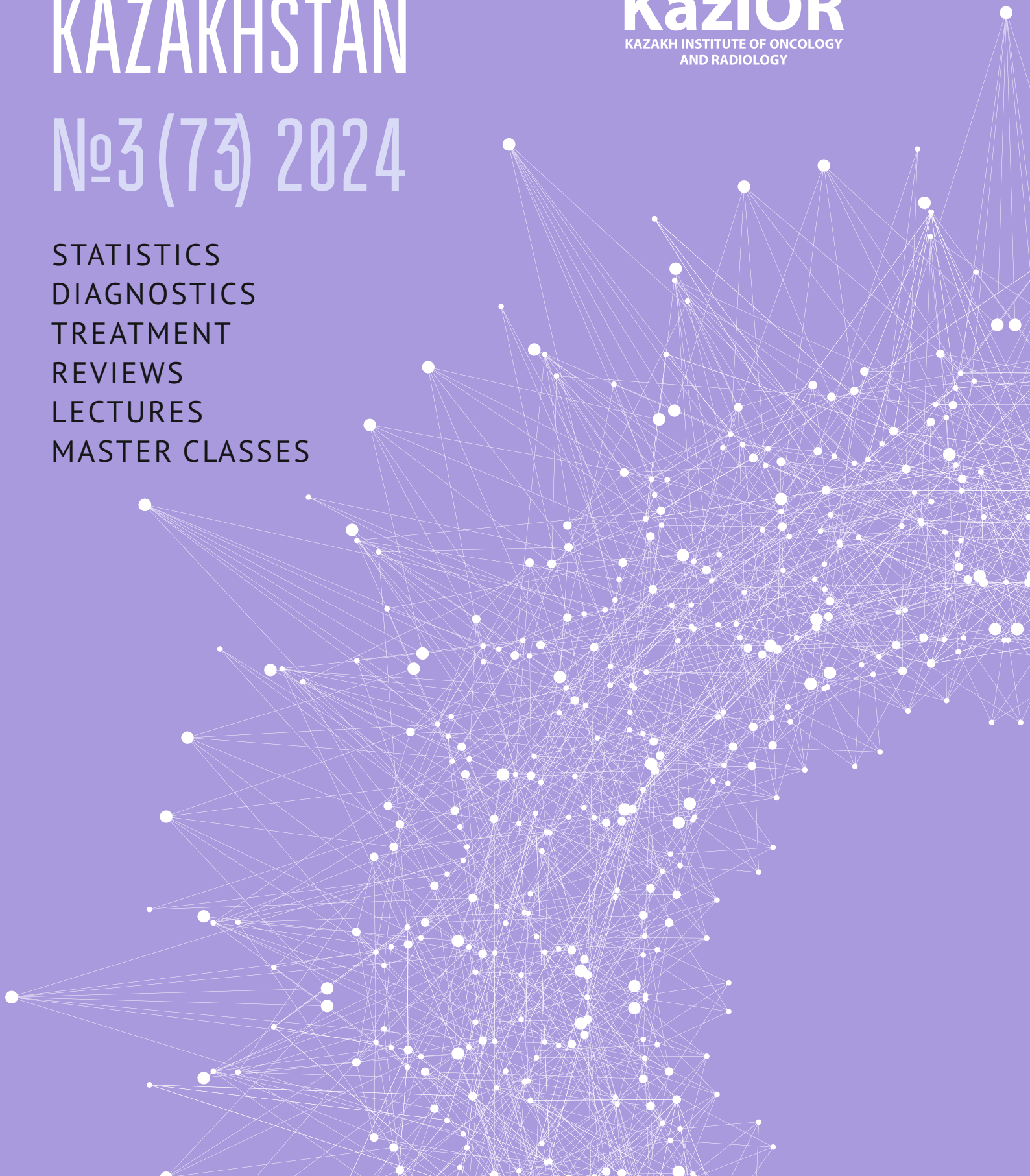

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Contents

Dear readers!

The summer months have flown by, with a series of international scientific conferences, intense clinical and scientific-pedagogical activity have passed – and we meet again on the pages of our journal. The third issue was compiled during the summer holidays, but this did not affect the activity of the authors and editorial colleagues in any way!

The third issue offers the results of interesting studies, various clinical cases, and reviews of the epidemiological situation.

Firstly, we are pleased to announce that after the hacker attacks, the journal platform was updated, and now you can submit an article and read the updated requirements for scientific publications at https://ojs.oncojournal.kz/index.php/oncol-and-radiol-of-kazakhstan.

Besides, we consulted with the Clarivate Analytics agency on the assessment process and criteria for selecting our journal for indexing in Web of Science. Through our joint efforts, high-quality articles, and high citation rates of our authors, we can apply for inclusion in the Web of Science database collection of high-quality journals.

We encourage authors to carefully study all changes and submit correctly prepared articles. This will significantly reduce the time for technical editing and increase the chance of being published in our next issue.

The Journal's table of contents contains the titles of the articles that you can find on our pages.

Thank you for staying with us!

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

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ASSESSMENT OF THE EFFECTS OF RADIATION ON THE STABILITY OF THE GENOME OF THE POPULATION FROM THE TERRITORIES ADJACENT TO THE SOURCE OF POLLUTION

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ABSTRACT

Relevance: *The increasing introduction of new mutagenic factors into the human environment increases the frequency of hereditary human diseases associated with exposure to environmental mutagens. In the case of radiation exposure, the problem arises of the need to identify risk groups of people with hypersensitivity since the effect of radiation on the body, in addition to direct effects on its functional subsystems, induces or activates protective systems (repair, adaptation). If the DNA repair system is damaged, the risk of induction of mutation frequency increases. The above highlights the relevance of the research topic and the results obtained.*

The study aimed to *assess the impact of radiation pollution on the stability of the genome and human health, considering the long-term genetic consequences.*

Materials and methods: *Field and laboratory methods were used, such as creating a system of sites for sampling environmental objects, human peripheral blood samples, methods for measuring the radiation activity of objects, and cytogenetic and molecular genetic methods.*

Results: *Gamma activity measurements showed that the radiation level in the surveyed territory of the landfill and adjacent settlements was 0.6 to 0.14 mSv/h. Of particular importance in this regard is the study of the mechanisms of individual sensitivity to radiation and the role of the DNA repair system. Molecular genetic studies of the DNA of blood cells and cytogenetic analyses of people living in the zone of influence of the radioactive waste landfill revealed the spread of several mutant genotypes, which indicates the likelihood of an increased risk of environmental diseases in persons with pronounced genome instability.*

Conclusion: *The radiation level on the territory of the landfill and adjacent settlements was 0.6 to 0.14 mSv/h. The analysis of the dis-tribution of people by genotypes in the examined groups showed an increase in the frequency of heterozygous alleles of the XRCC1 repair gene to 35% compared with the control group (10%), and the frequency of homozygous alleles for the Trp/Trp allele does not exceed the control level (3%). In turn, for the XRCC3 gene, there is a slight excess in the frequency of heterozygotes, and the homozygous Thr/Met allele remains at the control level – 21% compared with the control of 2%.*

Keywords: *mutagens, radiation, environment, genes, hereditary diseases, genome.*

Introduction: Remote genetic consequences of radiation factors pose a real danger to biota humans and are important for environmental protection and human health. Knowledge of the mechanisms of radiation exposure is associated with individual radiosensitivity of organisms and the activity of the DNA damage reparation system (repair). In this regard, the increased frequency of human diseases associated with environmental mutagens determines the need to identify risk groups of people with increased sensitivity to radiation exposure. In addition to direct exposure, radiation also has an indirect effect on the body, particularly through protective systems, which in most cases leads to disruptions in the structure and function of the DNA molecule [1]. If the reparation systems do not work properly, the risk of mutation increases sharply [2]. The above emphasizes the relevance of the research topic and the results obtained.

The study aimed to assess the impact of radiation pollution on the stability of the genome and human health, considering the long–term genetic consequences.

Materials and methods: The types of radiation sources are given in Tables 1-4: these are settlements adjacent to the radioactive waste disposal site and located, taking into account the wind rose, on the leeward side, mainly in the Munaylinsky district and partially in the Tupkaragansky district, from whose territories soil, plant and water samples were taken (Figure 1).

The names of the surveyed settlements are also provided in Tables 1-4. The locations with elevated radiation levels are indicated in the description of the results of radioecological studies.

The studies of radioactivity of soil and vegetation samples were carried out by the gamma spectrometric method using the Multirad-gamma device (TD Avtomatika, Smolensk, Russian Federation) MKS-OTA No. 1935 (VA.17-

04-46889 dated September 15, 2023) and laboratory studies - molecular genetic analysis of DNA by the RAPD and ISSR methods on human peripheral blood samples [3]. The selected soil and plant samples in rural areas of the Munayli district of the Mangistau region were examined by the gamma spectrometric method in the radiological laboratory of the branch of the RSE on the Right of Economic Management "National Center of Expertise" of the State Public Enterprise of the Ministry of Health of the Republic of Kazakhstan for the Mangistau region following the Order of the Minister of Health of the Republic of Kazakhstan dated August 2, 2022 No. KR DSM-71 "On approval of the research procedure." Water samples were analyzed using the radiometric method on the UMF-2000 radiometer No. 1169, verification certificate No. A.17-04-46969 dated September 11, 2023, and also in the radiological laboratory of the branch of the RSE on the Right of Economic Management "National Center for Expertise" of the Ministry of Health of the Republic of Kazakhstan in the Mangistau region. Blood samples were taken from 60 residents of settlements adjacent to the landfill (38 women and 22 men). The control group consisted of 55 Almaty region residents with no contact with radiation. Genomic DNA was isolated from peripheral blood samples using a genomic DNA purification kit (GeneJET, Thermo Fisher Scientific, USA). Quantitative and qualitative assessment of the isolated DNA was performed using spectrophotometry (NanoDrop One, Thermo Scientific, USA) and agarose gel electrophoresis. Then, specific primers for the genes XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XRCC3 Thr241Met were synthesized. The primers were synthesized on an automatic synthesizer ASM-800 (RF). The synthesized primers were tested in test reactions of PCR genotyping. The finished lyophilized primers were stored in freezers (-20°C) for PCR analysis. The polymerase chain reaction methods included restriction fragment length polymorphism (PCR-RFLP) and gel electrophoresis.

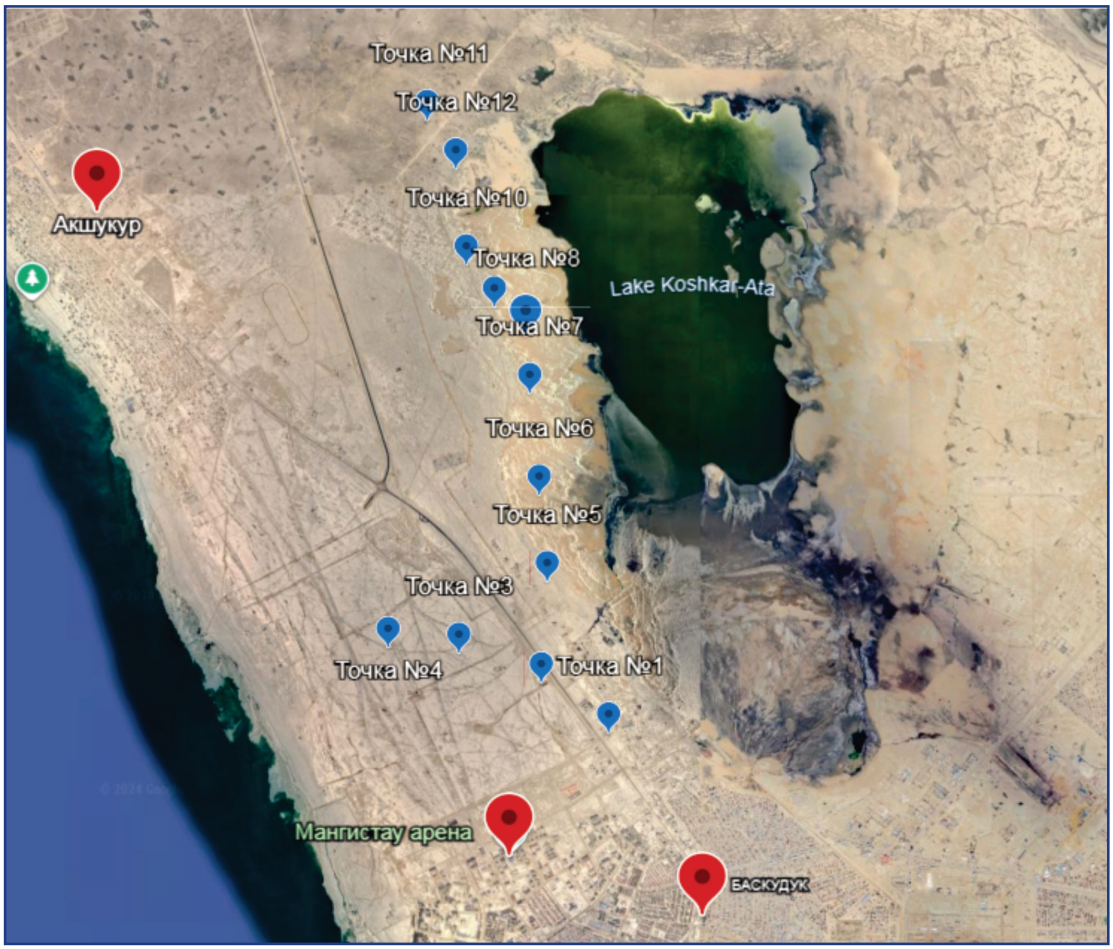


Figure 1 – Overview map of the current state of the tailings storage facility

Results: Below are the results of radiological studies of the total radioactivity of soil, plant, and water samples (tables 1-4).

Tables 1-4 indicate the sampling points of soil, water, and plants and the results of the determination of the level of radiation activity.

Table 1 – Specific effective (total) activity of soil from the solid waste landfill

No. of samples	Sample description	Sampling point	Cs-137	Ra-226	Th-232	K-40	Sr-90
11	Soil	Solid waste landfill	1.2±1.1	23.4±3.9	10.5±2.5	382±74	-*

*Note: * – the activity was below the device sensitivity*

Table 2 – Specific effective (total) activity of soil with plants from the flour terminal area

No. of samples	Sample description	Sampling point	Cs-137	Ra-226	Th-232	K-40	Sr-90
10	Soil with plants	From the flour terminal area	<5.9	<8.8	<20	820±230	-*

*Note: * – the activity was below the device sensitivity*

Table 3 – Total effective activity of drinking water

No. of samples	Sample description	Sampling point	Activity indicators, Bq/L	Detected value	Permissible value
4	Decentralized drinking water	Mangistau region, rural area – 1	Total alpha activity	0.044±0.012	0.2
			Total beta activity	0.062±0.014	1.0

Table 3 – Total effective activity of sea water

No. of samples	Sample description	Sampling point	Activity indicators, Bq/L	Detected value	Permissible value
7	Sea water from the channel, entrance to MAEK, point 1	Mangistau region, coastal sea zones	Total alpha activity	0.15±0.034	not rated
			Total beta activity	0.09±0.018	not rated

Site No. 1: Akshukyr Village. Coordinates: N 43° 0′ 46.089″, E 51° 0′ 5.311″. The elevation of the region is 7 meters. Ground radiation level: 65 nanosieverts per hour.

Site No. 2: Baskudyk Village, Biotope 1. The elevation of the region is 15 meters. Coordinates: N 43° 0′ 41.960″, E 51° 0′ 12.232″. Ground radiation level: 67 nanosieverts per hour. The radiation level at the sampling site is 103 nanosieverts per hour.

Site No. 3: Mangystau-1 Village. Site No. 4. Coordinates: N 40° 0′ 42.529″, E 51° 17′ 707″. The elevation above sea level is 10 meters.

Site No. 4: Mangystau-5 settlement, coordinates: N 43° 0′ 41.649″, E 51° 0′ 17.797″. The elevation of the region is 14 meters. Radiation level: 68 nanosieverts per hour.

Site No. 5: Mangistau Nuclear Power Complex – Chemical and Hydrometallurgical Plant (CHMP) located in the southern region of Aktau. The radiation level in the water samples from the discharge channel of the Mangystau Nuclear Power Engineering Plant is 0.08-0.09 mSv/h. Unusually high levels of gamma radiation were recorded near CHMP and the Aktau Foundry Limited Liability Partnership (LLP). The absolute maximum recorded is 1.98 μSv/h near CHMP [4]. Numerous investigations have demonstrated that the levels of radionuclides in environmental components collected from identical locations in areas surrounding the contamination source (radioactive waste disposal site) conform to sanitary and hygienic norms. The data about the buildup of radionuclides in plant samples aligns with the documented total alpha and beta activity in the assessed villages around the dump. The study area exhibits a negligible background radiation level, with an average environmental radiation dosage of 0.12 μSv/h. The peak measurement of 1.98 μSv/h was documented at site No. 5.

According to the results from the radiological survey of the area, essential preparatory work was conducted for molecular genetic research to evaluate the effects of radiation exposure on public health [5].

Blood samples from 60 individuals residing near the test location were utilized to assess the condition of the body's repair mechanisms in the Mangystau region occupants. The polymorphisms of the XRCC1 Arg194Trp (rs1799782), XRCC1 Arg399Gln (rs25487), and XRCC3 Trp241Met (rs861539) genes were examined. Table 5 presents the exact primers for the examined repair genes, including the sequences of the primers and the endonucleases utilized for analysis. A commercial GeneJET kit (ThermoScientific, USA) was employed for DNA isolation. A qualitative evaluation of the extracted DNA was conducted by agarose gel electrophoresis (Figure 2).

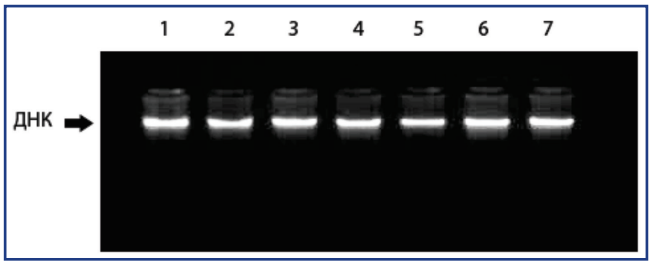


Figure 2 - Electrophoregram of DNA isolated from human peripheral blood: 1-7 - genomic DNA samples

Figure 2 illustrates the electrophoregrams of various DNA samples, showing that the electrophoretic analysis confirmed the isolated DNA's high quality and absence of degradation throughout the isolation procedure.

Table 5 presents the sequences of specific primers for the analyzed genes, the name of the restriction endonuclease used in restriction analysis, and the corresponding fragment sizes.

The diversity of the XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XRCC3 Thr241Met repair genes was examined in individuals residing in places adjacent to radiation-contaminated sites to assess the condition of the body's repair mechanisms. The polymorphism induction of the XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XRCC3 Thr241Met genes was assessed using the PCR-PDRF method. The DNA repair gene polymorphism frequently influences individual susceptibility to environmental stressors, such as radiation.

Table 5 - Primers used and conditions for amplification, restriction, and target products of XRCC1 and XRCC3 repair genes

Gene	Primers	PCR conditions	Restriction enzyme	Restriction products (polynucleotides)
XRCC1 Arg399Gln	(F) 5′-CAA GTA CAG CCA GGT CCT AG-3′ (R) 5′-CCT TCC CTC ATC TGG AGT AC-3′	40 cycles: 94°C - 15 s 55°C - 30 s 72°C - 45 s	NciI	Arg/Arg: 89+59 Arg/Gln: 248+159+89 Gln/Gln: 248
XRCC1 Arg194Trp	(F) 5′-GCC CCG TCC CAG GTA-3′ (R) 5′-AGC CCC AAG ACC CTT T-3′	40 cycles: 94°C – 15 s 57°C – 45 s 72°C – 45 s	PvuII	Arg/Arg: 490 Arg/Trp: 490+294+196 Trp/Trp: 294+196
XRCC3 Met241Thr	(F) 5'-GCC TGG TGG TGG TCA TCG ACT C-3' (R) 5'-ACA GGG GGG CTC CTC TGG AAG GCA CTG CTC AGC TCA CGC ACC-3'	40 cycles: 94°C - 15 s 60°C – 30 s 72°C – 45 s	NcoI	Thr/Thr: 136 Thr/Met: 136+97+39 Met/Met: 97+39

Note: M is a molecular DNA marker. Heterozygotes for XRCC3 241Thr/Met - 1-3, 5, 7-15; homozygotes for mutant allele XRCC3 241 Met/Met - 4

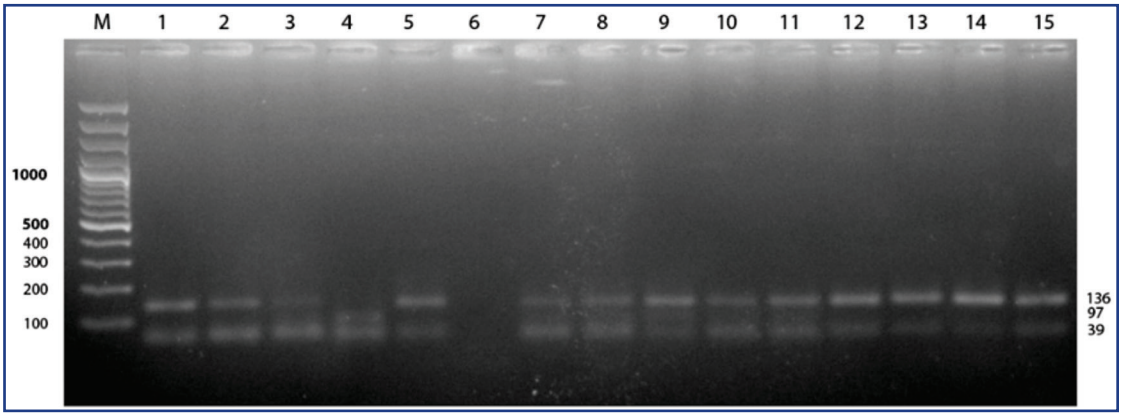
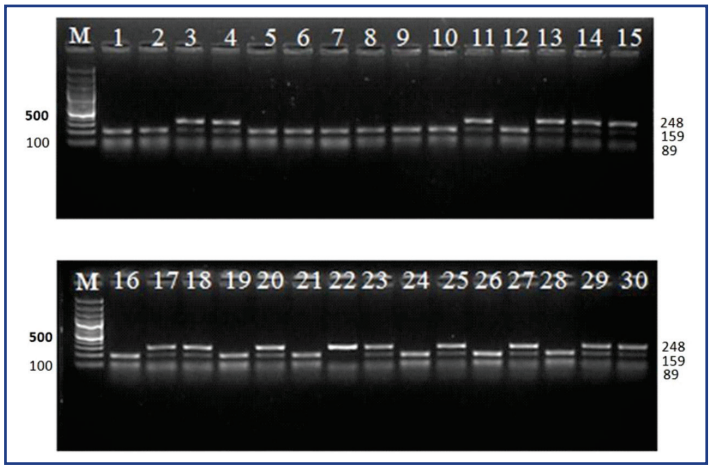


Figure 3 - Electrophoregram of restriction products at the 241Thr/Met polymorphic site of the XRCC3 gene

Figure 3 illustrates the outcomes of the electrophoretic analysis. The genotypic distribution of DNA repair genes - XRCC1 (Arg194Trp) and XRCC3 (Thr241Met) was assessed. For the XRCC1 gene (Arg194Trp): homozygous genotype 194Arg/Arg – 44.8%, heterozygous genotype 194Arg/Trp – 48.3%, and homozygous mutant genotype 194Trp/Trp – 6.9%. The XRCC3 (Thr241Met) gene analysis showed no presence of the homozygous genotype 241Thr/Thr, while the heterozygous genotype 241Thr/Met was observed at a frequency of 73.4%. The homozygous genotype for the 241 Thr/Thr mutant allele constitutes 26.6%.

Figure 4 displays the findings of electrophoretic analysis of restriction products following PCR-PDXRF analysis.



Note: M - molecular DNA marker; homozygous Arg/Arg (89+159) - 1, 2, 5-10, 12, 16, 19, 21, 24, 26 and 28; heterozygous Arg/Gln (248+159+89) - 3, 4, 11, 13-15, 17, 18, 20, 23, 25, 27, 29 and 30; homozygous Gln/Gln (248) - 22

Figure 4 – Electropherogram of restriction products at the polymorphism site of the XRCC1 gene - Arg399Gln

The allele frequencies and genotypes of the studied polymorphic markers in the human samples adhered to the Hardy-Weinberg equilibrium (p>0.05). For the XRCC1 gene, the Arg194Trp variant in the control group exhibits $\chi2=0.243$, p=0.622; in the "case" group, $\chi2=0.398$, p=0.427. For the XRCC3 gene, Trp241Met exhibits $\chi2=3.491$ in the control group (p=0.062) and $\chi2=0.203$ in the case group (p=0.382).

The subsequent analysis focused on the distribution of genotypes for the XRCC1 Arg194Trp and XRCC3 Trp241Met genes in the studied (Mangistau region) and control (Almaty region) groups. The distribution is represented as the percentage of individuals with a specific genotype within the group (Table 6).

The analysis of genotype distribution demonstrated that in the study group for the XRCC1 gene, the frequency of Arg/Arg homozygotes was 62%, Arg/Trp heterozygotes constituted 35%, and Trp/Trp minor allele homozygotes accounted for 3%. In contrast, the control group exhibited frequencies of 90%, 10%, and 0%, respectively. The distribution of donors by genotypes for the XRCC3 gene was observed as follows: Thr/Thr – 77%, Thr/Met – 21%, Met/Met – 2% in the study group, and 67%, 33%, and 0%, respectively, in the control group. The data indicates that there are no people with homozygous genotypes for the minor alleles of both genes (XRCC1 Trp/Trp and XRCC3 Met/Met) among the examined population in the Almaty region. It may result from an inadequate sample size for the study.

Table 6 – Distribution of the XRCC1 and XRCC3 gene genotypes in the examined groups

Genes	Genotypes	"Case" group, people (%)	"Control" group, people (%)	χ^2	P
		N=60	N=55		
XRCC1 Arg194Trp	Arg/Arg	62%	90%	20.728	0.000
	Arg/Trp	35%	10%		
	Trp/Trp	3%	0		
XRCC3 Trp241Met	Thr/Thr	77%	67%	4.849	0.089
	Thr/Met	21%	33%		
	Met/Met	2%	0		

Discussion: A mutation in the genes of the DNA repair mechanism has significant implications for both the individual cell and the organism overall [5]. Microsatellite polymorphism in repair genes is correlated with increased radiosensitivity and some malignancies. Specifically, variation in this gene influences the risk of lung cancer [6]. The significant function of this gene is further underscored by the observation that homozygous mutations in XRCC1 when inactivated, result in embryonic lethality in mice. Polymorphism in this gene has been conclusively demonstrated to cause substantial deficiencies in DNA repair mechanisms, which markedly elevates the risk of early-onset carcinoma of the colon when combined with urban living. Mutations in this gene present a specific hazard to smokers and individuals with continuous radiation exposure [6]. The classification of surveyed groups into categories to assess the actual risk of radiation exposure to the population will be conducted via a questionnaire after the project, under the Work Schedule in 2025.

Moreover, single nucleotide polymorphisms (SNPs) in DNA repair genes might influence the efficacy of transcription and translation processes and predisposition to various diseases. Consequently, the analysis and identification of the distribution of DNA repair genes by genotypes is critically significant [7, 8].

Generally, the study indicates that radiation risk assessment relies on diversity in individual radiosensitivity [9, 10]. International scientists assert that the threshold dose for assessment of the acute effects of radiation exposure is 0.2 Gy. Consequently, when evaluating the findings regarding the potential effects of radiation on the human body in the study area, at lower doses, the sole radiation effects are stochastic (delayed) effects [11, 12]—oncological and hereditary diseases observed within the population of the study area. Nonetheless, disparities exist in evaluating outcomes attributable to the interaction of dosage functions [13]. Numerous research studies have thoroughly examined hyperradiosensitivity to low radiation doses following in vitro irradiation of cells with charged particles and its correlation with adaptive response and induced radioresistance [14]. All knowledge regarding the long-term consequences of human exposure to low doses of radiation has been derived either by extrapolating experimental data from animals or direct radiation-epidemiological studies. The primary origin of the latter is acute, singular exposure to elevated doses resulting from nuclear catastrophes (Hiroshima and Nagasaki, Chornobyl, Fukushima, etc.) [15-17]. The quantitative parameter "probability of stochastic effects from low doses of radiation" is defined by multiple significant radiobiological factors; however, due to insufficient specific data, these effects have not been accurately established and continue to be contentious. The results can inform the implementation of strategies to enhance the region's environmental quality and the population's health.

The influence of detrimental environmental factors in ecologically unfavorable regions on the human body can be assessed through clinical examination, incorporating both quantitative and qualitative assessments of minor developmental anomalies, which also stem from alterations in the overall genetic equilibrium of the body. Consequently, evaluating the genetic impacts of external factors on human somatic cells may serve as a valuable adjunct to observing clinical outcomes.

Conclusion: A genomic study of persons residing in regions with significantly elevated gamma radiation levels (sites 1-5) demonstrated the development of mutations characterized by the amplification of DNA repair genes, resulting in gene polymorphism among those exposed to radiation.

The analysis of genotype distribution among the studied groups showed an increase in the frequency of hete-

rozygous alleles of the XRCC1 repair gene to 35%, in contrast to the control group's 10%, while the frequency of homozygous alleles for the *Trp/Trp allele remained at or below the control level of 3%. For the XRCC3 gene, there is a marginal increase in the frequency of heterozygotes (21%) relative to the control, whereas the homozygous Thr/Met allele persists at the control level (2%).*

The findings of this study align with existing literature regarding the genetic impacts of radiation exposure on the human genome in instances of nuclear power plant accidents and nuclear weapons testing. Upon completion of the design study, these results can be utilized to evaluate the actual risk for the specific population under investigation.

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АҢДАТПА

ЛАСТАНУ КӨЗІНЕ ІРГЕЛЕС АУМАҚТАРДАН ПОПУЛЯЦИЯ ГЕНОМЫНЫҢ ТҰРАҚТЫЛЫҒЫНА РАДИАЦИЯНЫҢ ӘСЕР ЕТУ ЗАРДАБЫН БАҒАЛАУ

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Өзектілігі: *адамның тіршілік ету ортасына жаңа мутагендік факторлардың көбеюі қоршаған орта мутагендерінің әсеріне байланысты адамның тұқым қуалайтын ауырлататын ауруларының жиілігінің артуына әкеледі. Радиациялық әсер ету жағдайында сезімталдығы жоғары адамдардың тәуекел топтарын анықтау қажеттілігі туындайды, өйткені радиацияның ағзаға әсері, оның функционалды ішкі жүйелеріне тікелей әсер етуден басқа, қорғаныс жүйелерін индукциялайды немесе белсендіреді (репарация, бейімделу). ДНҚ репарация жүйесі зақымдалған кезде мутация жиілігін индукциялау қаупі артады. Жоғарыда айтылғандар зерттеу тақырыбының және алынған нәтижелердің өзектілігін көрсетеді.*

Зерттеудің мақсаты *– созылмалы генетикалық әсерлерді ескере отырып, қоршаған ортаның радиациялық ластануының геномның тұрақтылығы мен адам денсаулығына әсерін бағалау.*

Әдістері: *далалық және зертханалық әдістерді қолданды: қоршаған орта объектілерінің сынамаларын алу үшін алаңдар жүйесін құру; адамның перифериялық қанының үлгілері, объектілердің радиациялық белсенділігін өлшеу әдістері, цитогенетикалық және молекулалық-генетикалық әдістер.*

Нәтижелері: *гамма-белсенділікті өлшеу полигонның зерттелген аумағының және оған іргелес елді мекендердің радиация деңгейі 0,6-0,14 мкЗв/сағ шегінде екенін көрсетті. Қан жасушаларының ДНҚ молекулалық-генетикалық зерттеулері және радиоактивті қалдықтар полигонының әсер ету аймағында тұратын адамдардың цитогенетикалық талдаулары бірнеше мутантты генотиптердің таралуын анықтады, бұл геномның айқын тұрақсыздығы бар адамдарда экологиялық аурулардың даму қаупінің жоғарылау ықтималдығын көрсетеді.*

Қорытынды: *полигон аумағындағы және оған іргелес елді мекендердегі радиация деңгейі 0,6-0,14 мкЗв/сағ шегінде. Зерттелген топтардағы адамдардың генотиптік таралуын талдау XRCC1 репарация генінің гетерозиготалы аллельдерінің жиілігінің бақылау*

тобымен (10%) салыстырғанда 35%-ға дейін жоғарылағанын көрсетті, ал Trp/Trp аллелі бойынша гомозиготалы аллельдердің жиілігі бақылау деңгейінен (3%) аспайды. Өз кезегінде, XRCC3 гені үшін гетерозиготалар жиілігінің шамалы асып кетуі байқалады, Thr/Met гомозиготалы аллель бақылау деңгейінде қалады – 21% бақылаумен салыстырғанда – 2%.

Түйінді сөздер: *мутагендер, радиация, қоршаған орта, гендер, тұқым қуалайтын аурулар, геном.*

АННОТАЦИЯ

ОЦЕНКА ПОСЛЕДСТВИЙ ВЛИЯНИЯ РАДИАЦИИ НА УСТОЙЧИВОСТЬ ГЕНОМА НАСЕЛЕНИЯ ТЕРРИТОРИЙ, ПРИЛЕГАЮЩИХ К ИСТОЧНИКУ ЗАГРЯЗНЕНИЯ

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Актуальность: *Всё возрастающее введение в среду обитания человека новых мутагенных факторов приводит к увеличению частоты наследственно-отягощенных заболеваний человека, связанных с воздействием мутагенов окружающей среды. В случае радиационного воздействия встает проблема необходимости выявления групп риска людей с повышенной чувствительностью, так как влияние радиации на организм, помимо прямого воздействия на его функциональные подсистемы, индуцирует или активирует защитные системы (репарацию, адаптацию). При повреждении системы репарации ДНК возрастает риск индукции частоты мутации. Вышеизложенное подчеркивает актуальность темы исследования и полученных результатов.*

Цель исследования *– оценка воздействия радиационного загрязнения окружающей среды на стабильность генома и здоровье человека с учетом отдаленных генетических последствий.*

Материалы и методы: *Использовались полевые и лабораторные методы: создание системы площадок для взятия проб объектов окружающей среды, образцы периферической крови человека, методики измерения радиационной активности объектов, цитогенетические и молекулярно-генетические методы.*

Результаты: *Измерения гамма-активности показали, что уровень радиации обследованной территории полигона и прилегающих населенных пунктов находится в пределах 0,6-0,14 мкЗв/ч. Особое значение в этом отношении имеет изучение механизмов индивидуальной чувствительности к радиации и роли системы репарации ДНК. Молекулярно-генетические исследования ДНК клеток крови и цитогенетические анализы людей, проживающих в зоне влияния полигона радиоактивных отходов, выявили распространение нескольких мутантных генотипов, что свидетельствует о вероятности повышении риска экологических заболеваний у лиц с выраженной нестабильностью генома.*

Заключение: *Уровень радиации на территории полигона и прилегающих населенных пунктов находится в пределах 0,6-0,14 мкЗв/ч. Анализ распределения людей по генотипам в обследованных группах показал увеличение частоты гетерозиготных аллелей гена репарации XRCC1 до 35% по сравнению с контрольной группой (10%), а частота гомозиготных аллелей по аллелю Trp/Trp не превышает уровень контроля (3%). В свою очередь, для гена XRCC3 отмечается незначительное превышение частоты гетерозигот по сравнению с контролем – 21%, а гомозиготный аллель Thr/Met остается на уровне контроля – 2%.*

Ключевые слова: *мутагены, радиация, окружающая среда, гены, наследственные заболевания, геном.*

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MEDICAL-DEMOGRAPHIC SITUATION AND THE STATE OF HEALTH OF THE ADULT POPULATION IN CONNECTION WITH DISEASES OF NEOPLASMS IN THE ALMATY REGION OF KAZAKHSTAN

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ABSTRACT

Relevance: *Various aspects of the state of public health in connection with malignant neoplasms, as well as the issues of improving the system of providing cancer care to the population, are the subject of many years of research by the authors. Concerns and increased attention to cancer are features of modern healthcare. Worldwide, there is an increase in the incidence of non-communicable chronic diseases associated primarily with the growth of the socio-economic well-being of countries, an increase in life expectancy, and preventive measures aimed at identifying cancer.*

The study aimed to *assess the incidence of malignant neoplasms in the southern region of the Almaty region to improve mortality indicators and five-year survival rates.*

Methods: *an analysis of data from annual medical reporting forms No. 7 on patients and diseases with malignant neoplasms in the Almaty region (the form approved by the Ministry of Health of the Republic of Kazakhstan for 2018-2022), annual regional statistical collections of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan for 2018-2022, and the collections "Health of the population of the Republic of Kazakhstan and activities of healthcare organizations" of the Ministry of Health of the Republic of Kazakhstan.*

Results: *High cancer incidence in Kazakhstan, including the Almaty region, owes mainly to lung and stomach cancers in men and breast and cervical cancers in women.*

The incidence in Kazakhstan and the Almaty region is decreasing, but the target has not been achieved yet.

Cancer mortality remains stable in the country and is decreasing in the Almaty region. The mortality structure is dominated by lung cancer, followed by stomach cancer the 2nd, breast cancer the 3rd, and esophageal cancer the 4th.

Conclusion: *The reduction in mortality is primarily due to the introduction of screening programs, improved early detection of malignant neoplasms, and increased treatment effectiveness. However, the mortality indicator remains high.*

The conducted epidemiological study of cancer incidence and mortality in the Almaty region evidences the need to improve screenings, introduce new forms of screening for stomach and lung cancers, activate screening programs, and enhance preventive and awareness-building outreach among the population.

Keywords: *public health, medical and demographic situation, incidence, mortality, malignant neo-plasms, prevention.*

Introduction: Cancer mortality remains high according to the new GLOBOCAN report on the global burden of cancer in 2022 by world region and human development level, on April 4, 2024 (Table 1). There were an estimated 20.0 million new cases and 9.7 million deaths from cancer worldwide in 2022 for both sexes. Almost half of all cases (49.2%) and the majority (56.1%) of cancer deaths worldwide in 2022 are estimated to have occurred in Asia, where 59.2% of the world's population lives. The burden of cancer mortality in the African and Asian regions is disproportionately more significant than the corresponding incidence burden. This reflects the respective distribution of cancer types along with comparatively higher case-fatality rates in these continents, partly due to late diagnosis. Europe has a disproportionately high cancer incidence and mortality, given that the continent accounts for one-fifth of the world's cancer cases (22.4%) and cancer deaths (20.4%) but accounts for less than 10% of the world's population (9.6%) [9].

The Government of the Republic of Kazakhstan is developing measures to improve the country's medical and demographic situation. The Comprehensive Cancer Plan for 2023-2027 can be noted among them. Implementing the Comprehensive Plan activities is envisaged for 5 years in 5 main areas: prevention and management of risk factors, highly effective early diagnosis, development of specialized treatment, palliative care and rehabilitation, and development of human resources and science [1]. Kazakhstan continues to have an unfavorable medical and demographic situation characterized by a decline in the natural population due to high mortality rates. At the same

time, one of the leading medical and demographic problems today is the increase in mortality from cancer among the adult population. Cancer is a general term for a large group of diseases that can affect any organ. Other terms are also used to describe them: malignant tumors and neoplasms. Cancer occurs due to the transformation of normal cells into atypical cells, during which a precancerous lesion turns into a malignant tumor [2]. There are three categories of harmful factors:

– physical carcinogens (alpha, beta, gamma, and X-ray radiation, proton and neutron fluxes, ultraviolet radiation, radon, mechanical injuries);

– chemical carcinogens (arsenic, lead, nickel, chromium, mercury, cadmium);

– biological carcinogens (viruses, bacteria, or parasites).

Table 1 – Cancer incidence, mortality, and total population in some countries for 2022, abs. figures

Country	Average annual population	Incidence	Mortality
Sweden	10 218 972	91 444	25 569
Italy	60 262 779	436 242	199 706
France	65 584 514	483 568	190 612
Belgium	11 668 276	81 132	29 005
Germany	83 883 587	605 805	253 170
Netherlands	17 211 499	168 070	49 790
Spain	46 719 147	372 121	115 590
Portugal	10 140 568	81 251	33 762
Kazakhstan	19 205 039	36 225	20 686

Risk factors for cancer include chronic infections, especially in developing countries. Carcinogenic infections such as Helicobacter pylori, Human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus are responsible for about 15% of cancer cases diagnosed in 2012. Hepatitis B and C viruses and carcinogenic HPV types increase the risk of liver and cervical cancer, respectively. HIV infection significantly increases the risk of cancer, such as cervical cancer. Another fundamental factor in the development of cancer is age. With age, the incidence of cancer rises sharply due to the layering of various risk factors. The accumulation of risk factors, impaired apoptosis, and decreased immunity become more pronounced as a person ages. Smoking, including e-cigarettes, drinking alcoholic beverages, surrogates, synthetic drugs, poor nutrition, and physical inactivity have been and remain the main risk factors for cancer development in the world.

One of the clinical signs of cancer is metastasis or rapid formation of atypical cells that grow beyond their tissues and are capable of developing into nearby tissues and are carried to other organs with the flow of biological fluids. Metastasis is often one of the leading causes of cancer mortality [2]. Malignant neoplasms (MN) consistently occupy second place in the structure of the population of Kazakhstan seeking medical care - 15.7% according to statistics, the opinion of many authors, and official statistics. MN mortality ranks second after circulatory system diseases. The share of MN in the structure of overall mortality of the population consistently exceeds 50%, and the high level of incidence with temporary loss of ability to work and disability due to MN additionally emphasizes the social significance of this disease [3]. 56% of those affected are people of working age. 30-50% of cancers can be avoided by reducing the influence of risk factors and carrying out primary prevention. In addition, the burden of cancer can be reduced by early detection and management of patients who develop cancer. With timely diagnosis and adequate treatment, there is a high chance of curing many types of cancer. Unfortunately, the existing system of medical institutions does not fully meet the population's needs in terms of volume, accessibility, and quality of specialized medical care, primarily at the primary level.

Various aspects of public health status regarding MNs and improving the system of providing oncological care have been studied for many years [4]. A wide range of examinations used to diagnose MNs include laboratory, immunological, ultrasound, X-ray, endoscopic methods, magnetic resonance imaging (MRI), computed tomography with and without contrast enhancement, and positron emission tomography (PET).Most modern methods of research provide timely diagnosis and prevention of cancer. Organizational issues of attracting the population to screenings and other research methods for early diagnostics of MNs and increasing patient responsibility for their health remain open.

The study aimed to assess the incidence of malignant neoplasms in the southern region of the Almaty region, with the hopeful goal of improving mortality indicators and significantly enhancing five-year survival rates.

Materials and Methods: The analysis of data from medical reporting forms No. 7 on patients with MNs in the Almaty region, annual regional statistical digests of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan, digests "Health of the population of the Republic of Kazakhstan and activities of health care organizations" of the Ministry of Health of the Republic of Kazakhstan was carried out [3, 5, 6].

Results: Cardiovascular and oncological diseases caused 71% of deaths in the European Region, according to the World Health Organization (WHO) [7, 8]. According to WHO forecasts, the incidence and mortality from MNs in 2020 worldwide increased by 1.5-2 times [9]. The increase

in incidence is mainly due to lung cancer and stomach cancer in men and breast and cervical cancer in women.

Mortality from cancer in Kazakhstan ranks second in the structure of population mortality. Every year, about 13,000 people die from cancer, 42% of whom are people of working age. Almost half of primary patients are diagnosed with stage III-IV disease, which indicates low oncological alertness of medical workers and the population.

In 2018, malignant neoplasm incidence in the Republic of Kazakhstan was 229.5 per 100,000, while this indicator in the Almaty region was 154.4 per 100,000 (Figure 1, Table 2). In 2022, the MN incidence rate decreased to 221.9 nationwide and 123.3 in the Almaty region. The southern part of the Almaty region includes 9 rural areas with 1,506,000 people [3]. Today, MN incidence is decreasing.

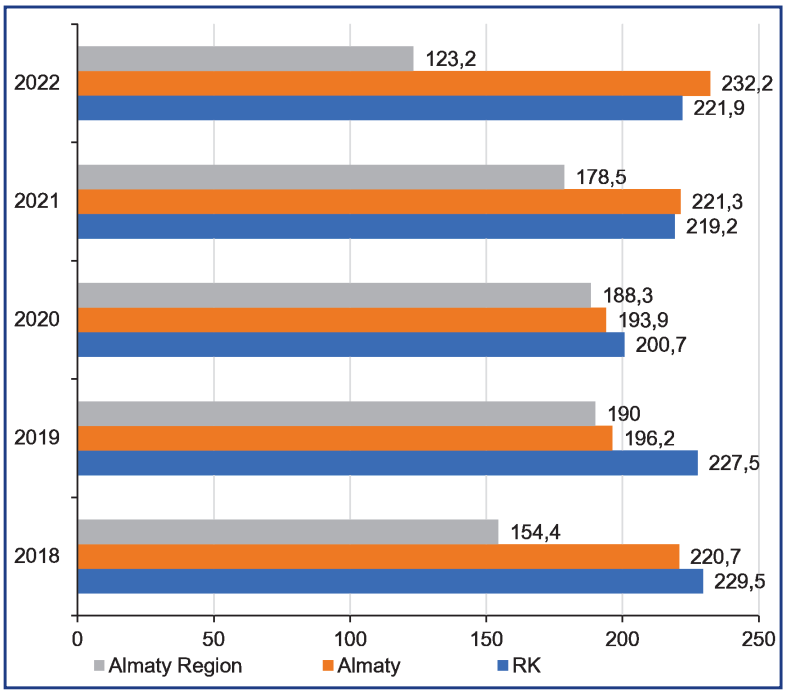

Figure 1 – MN incidence in Kazakhstan and the Almaty Region compared with the figures for RK and the city of Almaty, 2018-2022.

Table 2 – MN incidence in the Republic of Kazakhstan, Almaty, and Almaty Region, 2018-2022

Region	Urban population									
	Abs.					Per 100 000 population				
	2018	2019	2020	2021	2022	2018	2019	2020	2021	2022
the Republic of Kazakhstan	24340	24798	22379	24928	26849	229.5	227.5	200.7	219.2	221.9
Almaty	4035	3760	3833	4482	4950	220.7	196.2	193.9	221.3	232.2
Almaty Region	712	858	857	820	299	154.4	190.0	188.3	178.5	123.3

The MN structure in women is dominated by breast cancer (C50), accounting for 23.0% of all localizations, followed by skin neoplasms (C44, C46.0) with a share of about 11%, and cervical cancer (C53), with 8.6% (table 3). In the structure of gynecological cancers, cervical cancer ranks first, ahead of uterine cancer and ovarian cancer.

In men, lung cancer (C33-34) ranks first, with a share of 18.0%, followed by stomach cancer (C16), with 11.3%, and skin neoplasms (C44, C46.0), with 9.2%.

The nationwide mortality from MNs is decreasing slowly, from 78.6 per 100,000 people in 2018 to 66.4 in 2022. In the Almaty region, the mortality from MNs has also decreased. The figures for the Almaty region in Figure 2 do not consider the 2019 territorial changes and the establishment of the Zhetysu region in 2022.

Over the past five years, one-year mortality from cancer in the republic fluctuated from 7.0 to 7.9%, with the lowest figure in 2021 and the highest in 2018. In general, positive dynamics are observed. In the Almaty region, the one-year mortality rate fluctuated from 7.2 to 7.8%, with a minimum value in 2021 and a maximum value in 2020 (Figure 3).

In the structure of mortality from malignant neoplasms in both sexes in the republic, lung cancer ranks first (16.5%), stomach cancer ranks second (11.5%), breast cancer ranks third (8.5%), and esophageal cancer ranks fourth (5.8%) [10]. In the structure of mortality from malignant neoplasms in both sexes in the Almaty region, a similar picture is observed: lung cancer ranks first (14.4%), stomach cancer ranks second (12.2%), breast cancer ranks third (8.8%), and rectal cancer ranks fourth (4.9%) (Figure 4).

Early diagnosis of oncological diseases of stages 0-I for 2020 amounted to 25.5% of the total structure of new cases of malignant neoplasms. Five-year survival rate at the end of 2020 was 54.0% (2019 - 52.5%). Analysis of the implementation of target indicators in the region revealed a slight decrease in mortality from oncological pathology in 2021, with an indicator of 48.7 per 100,000 population against 58.0 per 100,000 population in 2020. There is an increase in the proportion of stage I-II malignant neoplasms of the cervix – 90.7% in 2020, while in 2021, this indicator was 87.4% [12].

Table 3 – MN incidence structure in the Almaty Region, 2021-2022

No	Localization of malignant neoplasms	Sex	Code according to the ICD, X revision	Total cases, 2021	Total, 2022
01	**All malignant neoplasms, including,**	**f**	**C00-C97**	**15400**	**16688**
02		**m**		**20727**	**22389**
03	Lips	m	C00	83	84
04		f		36	34
05	Tongue, oral cavity, and oropharynx, kaposi's sarcoma of the palate	m	C01-C06, C09, C10, C46.2	328	283
06		f		192	200
07	Salivary gland (except minor salivary glands)	m	C07-C08	79	69
08		f		64	67
09	Nasopharynx	m	C11	54	54
10		f		22	34
11	Larynx	m	C12, C13, C14	119	103
12		f		50	48
13	Esophagus	m	C15	654	639
14		f		476	469
15	Stomach	m	C16	1693	1895
16		f		883	1020
17	Colon	m	C18	776	886
18		f		910	1054
19	Rectum, rectosigmoid junction, anus (anus) and anal canal	m	C19-C21	856	920
20		f		748	793
21	Liver and intrahepatic bile ducts	m	C22	583	602
22		f		316	401
23	Pancreas	m	C25	576	552
24		f		552	623
25	Larynx	n	C32	325	334
26		f		40	36
27	Trachea, bronchi, lung	m	C33-C34	2806	3014
28		f		809	911
29	Bones and articular cartilages	m	C40-C41	71	90
30		f		72	91
31	Connective and other soft tissue	m	C45, C46.1, C47,C49	213	194
32		f		226	216
33	Skin melanoma	m	C43	144	125
34		f		216	211
35	Other skin neoplasms	m	C44, C46.0	1352	1537
36		f		2203	2461
37	Female mammary gland	f	C50	5021	5171
38	Cervix	f	C53	1804	1934
39	Uterine body	f	C54	1240	1315
40	Ovary	f	C56	1249	1201
41	Prostate gland	m	C61	1169	1465
42	Testicle	m	C62	122	133

Note: the localizations of malignant neoplasms ranking first in the incidence structure are marked red.

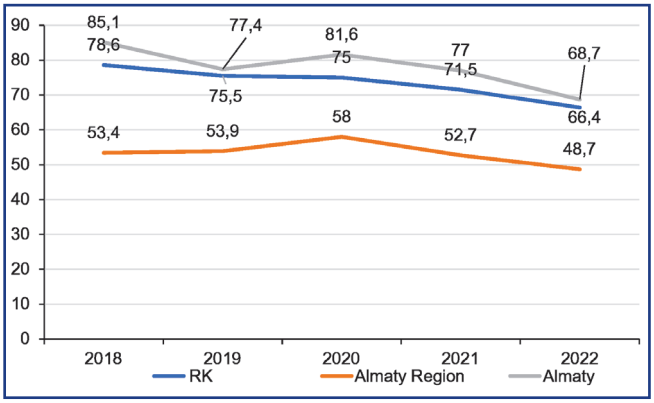

Figure 2 - Mortality from MNs in the Almaty region compared with the figures for RK and the city of Almaty, 2018-2022

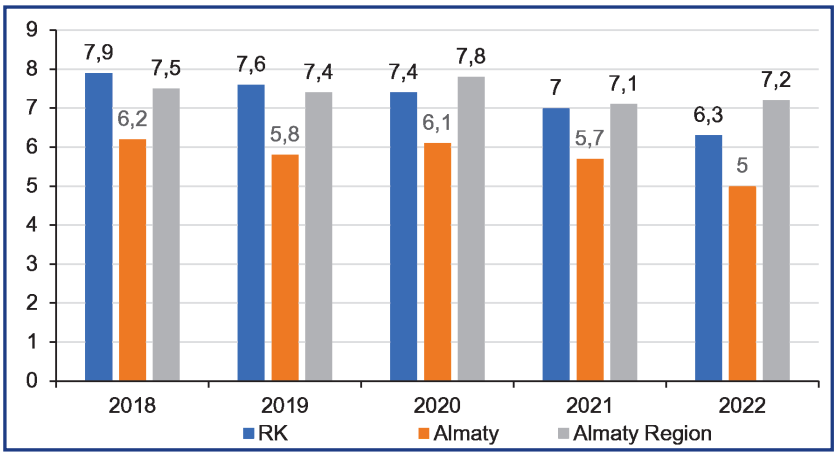

Figure 3 - One-year mortality from MNs in the Almaty Region compared with the figures for RK and the city of Almaty, 2018-2022

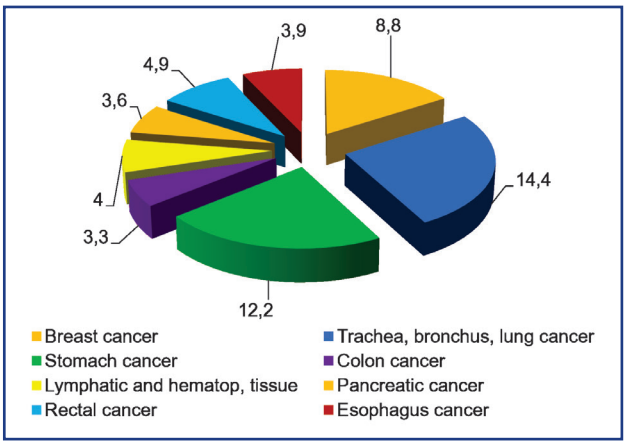

Figure 4 – MN mortality structure in the Almaty region, 2018-2022

Discussion: Some features of modern healthcare are cancer alertness and increased attention to cancer diseases. All over the world, there is an improvement in the detection of malignant neoplasms, primarily due to the growth of countries' socio-economic well-being, an increase in life expectancy, and the implementation of preventive measures to identify cancer diseases.

Most of the cancer diseases encountered in Kazakhstan can be diagnosed at early stages (tumors of the mammary gland, skin, cervix, esophagus, stomach, liver, colon and rectum, prostate gland) by conducting screening programs. Accordingly, a decrease in mortality from tumors of this localization can become a reserve for reducing overall mortality from cancer diseases [13].

Timely and early diagnosis of cancer diseases can significantly improve treatment outcomes and increase patient survival. To further enhance the prevention of oncological diseases in the republic, early diagnostic (screening) programs have been introduced, the availability of high-tech diagnostic and treatment methods with scientifically proven effectiveness has been increased, and a modern system of rehabilitation and palliative care for cancer patients has been introduced [14].

Conclusion: The reduction in mortality is primarily due to the introduction of screening programs, improved early detection of malignant neoplasms, and increased treatment effectiveness. However, the mortality indicator remains high. Following the introduction of screening as an indicator of the work of primary health care, the coverage of the population with screening programs is improving. However, it is necessary to constantly monitor the correctness of the screening programs, the adequacy of the interpretation of the results by medical personnel, and reliable information about the screening results for patients. Conducting targeted on-the-job training for medical personnel who routinely or occasionally conduct screening activities is essential. The methodological recommendations developed by the Kazakh Institute of Oncology and Radiology should become a reference guide for doctors and nurses in contact with the risk group for malignant neoplasms. Conducting educational work among students of secondary schools, colleges, and higher educational institutions should be mandatory and systematic. Resuming preventive examinations among employees of large

industries and public and private organizations is relevant. Educational videos calling for responsibility for their health and timely medical examinations should appear more often on social networks. However, due to the active implementation of an integrated model of oncological care with increased supervision of primary health care organizations by the oncological service, the work of district curators has improved significantly. Managing the oncological situation regarding neoplasm incidence is only possible with a comprehensive approach, including work with all objects of influence: patients, general practitioners (or physicians), and oncologists.

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АНДАТПА

ҚАЗАҚСТАН РЕСПУБЛИКАСЫНЫҢ АЛМАТЫ ОБЛЫСЫ БОЙЫНША ІСІК АУРУЛАРЫНА БАЙЛАНЫСТЫ МЕДИ-ЦИНАЛЫҚ-ДЕМОГРАФИЯЛЫҚ ЖАҒДАЙ МЕН ЕРЕСЕК ХАЛЫҚТЫҢ ДЕНСАУЛЫҚ ЖАҒДАЙЫ

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Өзектілігі: *Аллогендік гемопоэтикалық дің жасушаларын трансплантациялау (АГЖТ) әдісі болып табылады жоғары мамандандырылған көмек көрсету, науқастарға, онкологиялық және гематологиялық аурулармен, ауыр аралас бастапқы иммунодефицитами, сондай-ақ басқа да туа біткен және тұқым қуалаушылық аурулары өтетін зақымданған қан түзетін және иммундық жүйелер.*

Зерттеудің мақсаты *– аллогенді АГЖТ жүргізген нәтижелерді және жынысы, кондиционерлеу режимі, донордың үй-лесімділігі, АГЖТ жүргізген кездегі негізгі аурудың мәртебесі сияқты факторлардың жоғары қауіпті топтардың онкоге-матологиялық аурулары бар науқастардың өмір сүру көрсеткіштеріне ықтимал әсерін зерттеу.*

Әдістері: *Алматы облысы бойынша қатерлі ісіктері бар науқастар мен аурулар туралы № 7 жылдық медициналық есеп нысандарының деректеріне талдау 2018-2022 жылдар (Қазақстан Республикасы Денсаулық сақтау министрлігі бекіткен нысан), ҚР Ұлттық статистика бюросының жыл сайынғы өңірлік статистикалық жинақтары. Қазақстан Рес-публикасы Стратегиялық жоспарлау және реформалар агенттігі, Қазақстан Республикасы Денсаулық сақтау ми-нистрлігінің «Қазақстан Республикасы халқының денсаулығы және денсаулық сақтау ұйымдарының қызметі» жинақтары 2018-2022 жылдар.*

Нәтижелері: *Алматы облысында және республикада онкологиялық аурулардың жоғары деңгейін негізінен ерлерде өкпе және асқазан обыры, әйелдерде сүт безі мен жатыр мойны обыры құрайды. Алматы облысында және жалпы Респуб-лика бойынша онкологиялық аурулар көрсеткішінің төмендеу үрдісі байқалады. Алайда, мақсатты көрсеткішке қол жет-кізілген жоқ. Республика бойынша онкологиялық аурулардан болатын өлім-жітім деңгейі іс жүзінде тұрақты, ал Алматы облысында төмендеу байқалады. Өлім құрылымында бірінші орында өкпе ісігі, екінші орында асқазан ісігі, үшінші орында сүт безі обыры, төртінші орында өңеш ісігі.*

Қорытынды: *Өлім-жітім деңгейін төмендетудегі табыс скринингтік бағдарламаларды енгізу, қатерлі ісік ауруын ер-те сатысында диагностикалауды жақсарту және емдеудің тиімділігіне байланысты, бірақ өлім-жітім деңгейі әлі де жоғары болып отыр. Алматы облысында онкологиялық аурулардан болатын аурушаңдық пен өлім-жітімді эпидемиологи-ялық зерттеу скринингтік тексеруді жақсарту, асқазан және өкпе обырын анықтау үшін скринингтің жаңа нысандарын енгізу, скринингті күшейту, сондай-ақ халық арасында профилактикалық және ағарту жұмыстарын күшейту қажеттігін көрсетеді.*

Түйінді сөздер: *халықтың денсаулығы, медициналық-демографиялық жағдайы, аурушаңдық, өлім-жітім, қатерлі ісіктер, алдын алу.*

АННОТАЦИЯ

МЕДИКО-ДЕМОГРАФИЧЕСКАЯ СИТУАЦИЯ И СОСТОЯНИЕ ЗДОРОВЬЯ ВЗРОСЛОГО НАСЕЛЕНИЯ В СВЯЗИ С БОЛЕЗНЯМИ НОВООБРАЗОВАНИЙ В АЛМАТИНСКОЙ ОБЛАСТИ РЕСПУБЛИКИ КАЗАХСТАН

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Актуальность: *Онконастороженность и повышенное внимание к онкологическим заболеваниям – одна из особенностей современного здравоохранения. Во всем мире отмечается улучшение выявляемости злокачественных новообразований (ЗНО), связанное, прежде всего, с ростом социально-экономического благополучия стран, увеличением продолжительности жизни, проведением профилактических мероприятий, направленных на выявление онкологических заболеваний.*

Цель исследования *– оценка заболеваемости злокачественными новообразованиями в Алматинской области для улучшения индикаторов смертности и пятилетней выживаемости.*

Методы исследования: *Проведен анализ данных из ежегодных медицинских отчетных форм №7 о больных и болезнях ЗНО по Алматинской области (форма, утвержденная Министерством здравоохранения РК за 2018-2022 годы), ежегодные региональные*

статистические сборники Бюро Национальной статистики Агентства по стратегическому планированию и реформам Республики Казахстан за 2018-2022 годы, сборники «Здоровье населения РК и деятельность организаций здравоохранения» Министерства Здравоохранения Республики Казахстан.

***Результаты:** Высокий уровень заболеваемости ЗНО по Алматинской области и по Республике в основном достигается за счет рака легкого и рака желудка у мужчин и рака молочной железы и шейки матки у женщин.*

Отмечается тенденция к снижению показателей заболеваемости ЗНО по Алматинской области и по Республике в целом. Тем не менее целевой индикатор не достигнут.

Смертность от ЗНО по Республике остается практически стабильной, при этом по Алматинской области наблюдается снижение. В структуре смертности первое место занимает рак легкого, второе – рак желудка, третье – рак молочной железы, четвертое – рак пищевода.

***Заключение:** Успехи по снижению показателя смертности обусловлены внедрением скрининговых программ, усовершенствованием диагностики ЗНО на ранних стадиях и эффективностью лечения, однако показатель смертности все еще остается высоким.*

Проведенное эпидемиологическое исследование заболеваемости и смертности от ЗНО в Алматинской области свидетельствует о необходимости совершенствования скрининга, внедрения новых форм скрининга для выявления рака желудка и легкого, активизации скрининга, а также усиления профилактической и просветительской работы среди населения.

***Ключевые слова:** здоровье населения, медико-демографическая ситуация, заболеваемость, смертность, злокачественные новообразования (ЗНО), профилактика.*

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RESULTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN AT THE CLINIC OF THE SCIENTIFIC CENTER OF PEDIATRICS AND PEDIATRIC SURGERY

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ABSTRACT

Relevance: *Hematopoietic stem cell transplantation (HSCT) is a method of providing highly specialized care to patients with various oncological and hematological diseases, primary immunodeficiencies, as well as other congenital and hereditary diseases affecting the hematopoietic and immune systems. In Kazakhstan, HSCT has been performed for pediatric patients since 2012 at the Scientific Center of Pediatrics and Pediatric Surgery (SCPPS, Almaty, Kazakhstan). The article presents the experience of conducting allogeneic HSCT in children with oncohematological pathology at SCPPS.*

The study aimed to *analyze the results of allo-HSCT and the possible influence of factors such as gender, conditioning regimen, donor compatibility, and status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT in order to improve the treatment results and quality of life of patients with high-risk oncohematological diseases.*

Methods: *Retrospective analysis of observational data on 53 patients after HSCT, carried out at the Scientific Center of Pediatrics and Pediatric Surgery from 2012 to 2020. Patient survival was assessed according to Kaplan-Meier, and static processing was carried out using the SPSS Statistic program.*

Results: *In our study, 39.6% of patients were diagnosed with acute lymphoblastic leukemia (ALL, n=21), 28.85% of patients (n=15) with acute myeloblastic leukemia (AML), for aplastic anemia alloHSCT was performed in 20.75% of cases (n=11), in 9.46% (n=5) alloHSCT was performed for myelodysplastic syndrome (MDS), of which three patients (60%) had juvenile myelomonocytic leukemia (JMML). According to the results of the study, when performing allo-HSCT, the overall survival rate of patients with ALL after from a matched related donor was 63.6%, while when performing HSCT in the earliest stages from the onset of the disease, survival rates were significantly higher (83.3%). The effectiveness of HSCT was also influenced by treatment before transplantation and the presence of a fully matched related donor. In aplastic anemia, the time from the start of therapy is a significant factor.*

Conclusion: *HSCT is an important and necessary stage of therapy for oncological and hematological diseases of high-risk groups in the early stages and in case of relapses of diseases. When HSCT was performed in the earliest period from the onset of the disease, survival rates were significantly higher (83.3%) compared to those with HSCT performed during the 3rd remission. Also, it was shown that the success of HSCT depends on previous therapy. HSCT in children with aplastic anemia should be performed early from the onset of the disease with minimal hematological load to HSCT, which guarantees engraftment.*

Keywords: *hematopoietic stem cell transplantation, children, acute leukemia, oncohematological diseases.*

Introduction: In the past 30 years, treating pediatric patients with leukemia and other oncohematological disorders in the Republic of Kazakhstan has experienced substantial transformations. Since 1993, the protocols of international cooperative groups have been implemented throughout the country, notably including the protocol for treating acute lymphoblastic leukemia established by the German cooperative group BFM. Simultaneously, the treatment program for pediatric oncohematological diseases progressively included more sophisticated and contemporary chemotherapy methods.

The implementation of standardized chemotherapy protocols and the improvement of adjunctive therapies have enhanced the prognosis of leukemia and other oncohematological disorders in Kazakhstan, resulting in a substantial rise in pediatric survival rates. Nonetheless, despite the advancements in the treatment of acute leukemias, few patients exhibited inadequate response to conventional chemotherapy and experienced disease relapses, requiring a novel, more rigorous, intensive therapeutic intervention.

In 2012, the establishment of a hematopoietic stem cell transplantation (HSCT) department at the Scientific Center of Pediatrics and Pediatric Surgery (SCPPS) in Almaty, Kazakhstan, marked a new phase in the advancement of the children's oncohematology service in the Republic of Kazakhstan.

HSCT is a method for delivering specialized treatment to infants suffering from diverse oncological and hematological disorders, severe combined primary immunodeficiencies, and other congenital and hereditary diseases that include impairment of the hematopoietic and immune systems. Bone marrow transplantation as a therapeutic approach is advancing rapidly and is increasing-

ly employed in pediatric treatment. In the United States, more than 1,000 pediatric hematopoietic stem cell transplants have been conducted yearly during the previous decade. HSCT encompasses pre-transplant immunosuppressive and myeloablative therapies and a comprehensive array of adjunctive treatments designed to optimize safety during the post-transplant phase. The transplantation method is continually being improved to accommodate more patients, including children. This article discusses the experience of HSCT in pediatric patients with oncohematological disorders at the SCPPS.

The study aimed to analyze the results of allo-HSCT and the possible influence of factors such as gender, conditioning regimen, donor compatibility, and status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT in order to improve the treatment results and quality of life of patients with high-risk oncohematological diseases.

Materials and Methods: We retrospectively analyzed observational data on 53 patients after HSCT treated at SCPPS from 2012 to 2020.

We analyzed medical records of 53 allo-HSCTs (two patients required two repeated allo-HSCTs) performed at the SCPPS clinic. The study included all patients who underwent allo-HSCT at SCPPS. The assessed factors were the patient gender and age, nosological form and period of the disease, presence of concomitant infection, duration of therapy before HSCT, donor characteristics, transplant engraftment time, complications, and overall survival. We analyzed the possible influence of such factors as gender, conditioning regimen, donor compatibility, and the status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT. Today, different centers actively study the influence of the above factors on HSCT outcomes in children. The accumulation of such data can serve as a basis for developing unified diagnostic and therapeutic approaches [2].

Patient survival was assessed using the Kaplan-Meier method; statistical processing was performed using the SPSS Statistics program (IBM SPSS, USA).

Results: Allo-HSCT was performed for 53 children with various oncohematological diseases treated at the SCPPS clinic from 2012 to 2020.

Allo-HSCT was performed for the following nosologies: 21 acute lymphoblastic leukemia cases (39% of all cases); of them, 42.8% (n=9) of allo-HSCTs were performed during the 2nd remission, and 33.3% (n=7) during the 3rd remission, which, according to global data, significantly reduces the effectiveness of the treatment [3].

28.85% (n= 15) were children with acute myeloid leukemia; of them, 20% (n= 3) underwent HSCT after the FLAI protocol therapy in a state of incomplete hematologic remission, and 73.3% (n=11) underwent HSCT during the second or third remission.

Allo-HSCT was performed on 20.75% (n=11) of children with aplastic anemia. Of them, 54.5% (n=6) had a very severe form, and 45.5% (n=5) had a severe form.

In 9.46% (n=5) of cases, allo-HSCT was performed for myelodysplastic syndrome, including three patients (60%) with juvenile myelomonocytic leukemia.

In one case (1.9%), allo-HSCT was performed on a patient with primary severe combined immunodeficiency (Table 1).

Table 1 – Structure of diseases for which allogeneic hematopoietic stem cell transplantation was performed

Diagnosis	No. of patients, n (%)	Nosological form/period of the disease, n (%)	
Acute lymphoblastic leukemia	21 (39.6)	1st remission	5 (23.8)
		2nd remission	9 (42.9)
		3rd remission	7 (33.3)
Acute myeloid leukemia	15 (28.85)	1st remission	1 (6.7)
		≥2nd remission	11 (73.3)
		not in remission	3 (20)
Aplastic anemia	11 (20.75)	Severe	6 (54.5)
		Very severe	5 (45.5)
Myelodysplastic syndrome	9 (9.46)	Juvenile myelomonocytic leukemia	3 (60)
Primary immunodeficiency	1 (1.9)	Primary severe combined immunodeficiency	1 (1.9)

56.6% of patients (n=30) had a concurrent diagnosis of viral hepatitis before HSCT; all were carriers of cytomegalovirus (CMV) infection (Figure 1).

Considering the distribution by age, most patients (46.15%) were elder children, including 10 to 15 years (35.8%, n=19) and above 15 years (11.3%, n=6). Children of 3 to 7 years accounted for 20.8% (n=11), below 3 years – 18.9% (n=10), and 7 to 10 years – 13.2% (n=7). The median age was 4.7 years. The gender ratio was nearly equal: 47.2% (n = 25) of boys vs. 52.8% of girls.

In 64.1% of cases (n=34), the HSCs were sourced from matched siblings (matched sibling donors (MSD) – 10/10 siblings), in 5.7% (n=3) from matched unrelated donors (matched unrelated donors (MUD)), in 28.3% (n=15) from partially matched related donors (haploidentical parents), and in 1.9% (n=1) from a matched family donor 10/10 (MFD) (Figure 2).

60.4% (n=32) of donors were males, and 39.6% (n=21) were females. The mean age of MSD donors was 10 years (n=34), MUD donors were 29 years (n=3), and one MFD donor was 43 years old. At the same time, the median age of donors for haploidentical HSCT was 35 years (Figure 3).

In transplantations from matched donors (MD), 89.5% (n=34) of hematopoietic stem cells (HSCs) originated from bone marrow, whereas 10.5% (n=4) were derived from peripheral blood HSCs.

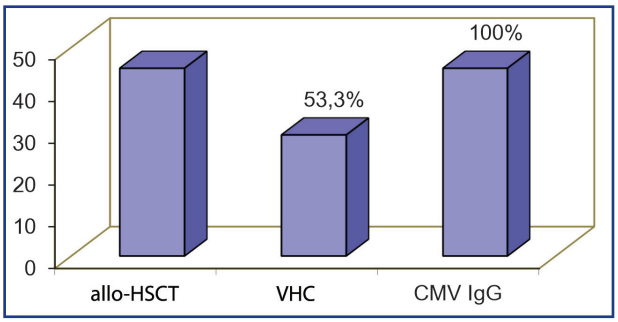

Figure 1 – Concurrent viral infections.

Notes: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; VHC, viral hepatitis C; CMV IgG, cytomegalovirus immunoglobulin.

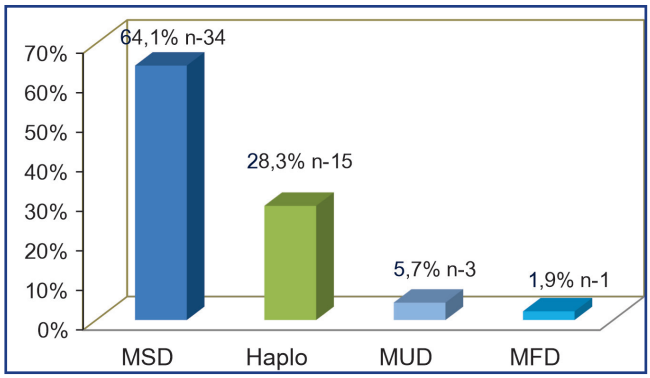

Figure 2 – Structure of HSC donors

Notes to Figures 3-5: HSCs, hematopoietic stem cells; MSD, matched sibling donors; Haplo, partially matched donor (parents); MUD, matched unrelated donors; MFD, matched family donor 10/10.

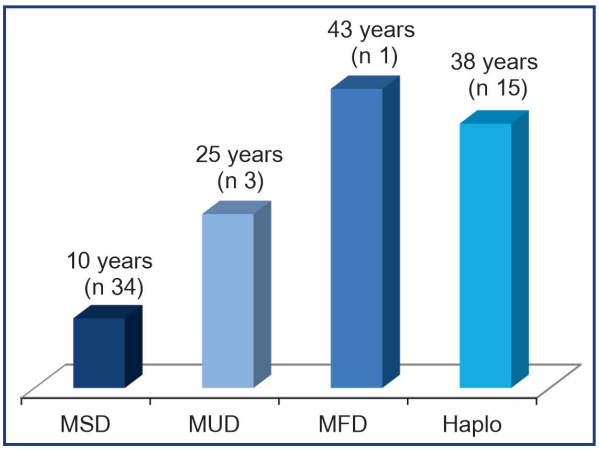

Figure 3 – Median age of HSC donors for allo-HSCT

In haploidentical HSCT, αβ/CD19-depleted peripheral blood-derived HSCs were utilized in 66.7% of cases (n=10), whereas in 33.3% of cases (n=5) HSCs were isolated from bone marrow (Figure 4).

Engraftment was evaluated by neutrophil count (absolute count >500-1000) and platelet count (>20x10^9/l). On average, engraftment of hematopoietic stem cells in peripheral circulation occurred by +15 days and in bone marrow by +30 days following hematopoietic stem cell transplantation. Engraftment in bone marrow hematopoietic stem cell transplantation from matched sibling donors occurred on average by +22 days (range 14-35 days). In bone marrow haploidentical HSCT, engraftment was achieved by day +38, while in haploidentical HSCT with αβ/CD19 depletion, it was attained by day +15 (Figure 5).

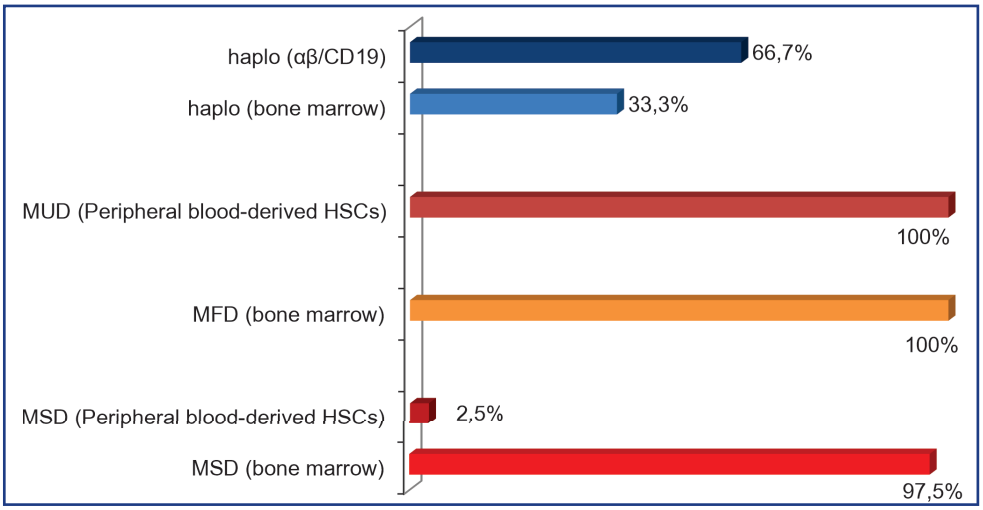

Figure 4 – Characteristics of HSC sources for allo-HSCT

During the engraftment phase, CMV activated in 37.7% (n=20) of patients, Epstein-Barr virus – in 7.5% (n=4), and herpes simplex virus – in 5.7% (n=3). After HSCT, all patients (100%) exhibited a varied reduction in B- and T-cell components of immunity and disruption of cell subpopulation ratios (Figure 6).

The mortality rate from CMV in the early post-transplant interval was 5.7% (n=3).

Acute graft-versus-host disease (GVHD) is critical for survival and treatment efficacy prognosis. In our study, grade I-II GVHD occurred in 9.4% of cases (n=5), and chronic GVHD also manifested in 9.4% of cases (n=5). A case has been reported where acute GVHD coexisted with microangiopathic damage syndrome during GVHD treatment with concurrent CMV activation.

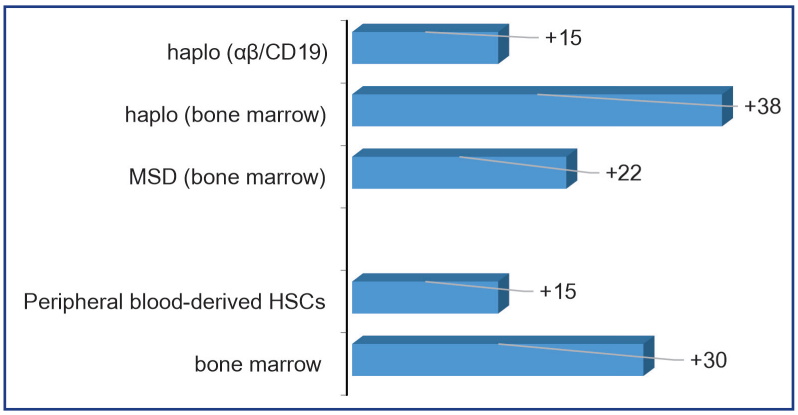

Figure 5 – Engraftment of the graft

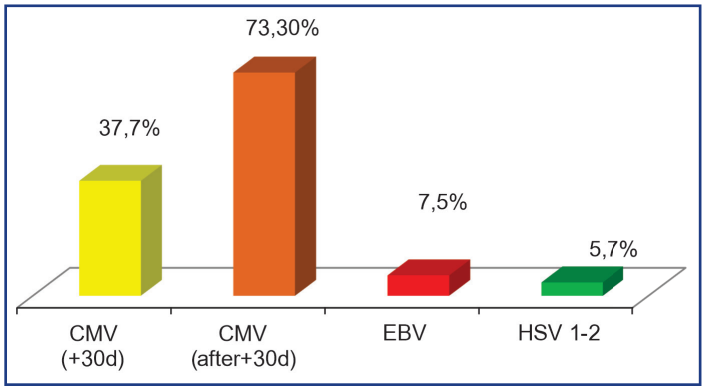

Figure 6 - Activation of viral infection after graft engraftment

Notes: CMV – cytomegalovirus infection; EBV – Epstein-Barr virus; HSV – herpes simplex virus

Recurrences of AL (n=36) post-allo-HSCT were documented in 47.2% of cases (n=17). A patient experiencing a recurrence underwent a second transplantation.

The overall survival percentage of patients following allo-HSCT from a matched donor was 55.2% (n=21), whereas from a related matched donor, it was 57.1% (n=20).

The survival rate of patients with severe and supersevere aplastic anemia was 63.6% (n= 7/11).

The overall survival rate for patients with ALL receiving transplants from matched-related donors was 63.6% (n=7). It was observed during the categorization of patients based on the interval between the onset of the disease and HSCT that the cohort of children who received HSCT at an earlier disease stage (n=6) exhibited a survival rate of 83.3%, whereas those in the third remission undergoing HSCT (n=5) demonstrated a survival rate of merely 40%.

Discussion: HSCT is essential in managing patients with oncohematological diseases since it can markedly increase patient survival rates. HSCT is a necessary stage of therapy for high-risk oncohematological disorders in their early stages, as well as for disease relapses. Still, HSCT efficacy depends on many parameters, including the disease type, conditioning regimens, complications like GVHD, infections, etc. The success of HSCT is contingent upon prior therapy, which must be systematic, comprehensive, adhere to contemporary standard guidelines, and be administered promptly. The authors previously disclosed the initial findings of the allo-HSCT trial involving 42 patients with oncohematological disorders [4]. Prior research revealed higher post-transplantation mortality, which could be due to more inclusive candidate selection criteria for allo-HSCT. This provides foundations for the study of the determinants influencing the success and efficacy of allo-HSCT in pediatric patients.

Furthermore, overall survival rates were not considered. The study's findings indicate that the overall survival rate for patients with ALL receiving transplants from matched related donors was 63.6% with allo-HSCT. In contrast, those undergoing HSCT at the earliest stages of the disease exhibited significantly higher survival rates of 83.3% compared to patients who received transplants during the third remission. To ensure successful graft engraftment, HSCT in pediatric patients with aplastic anemia should be conducted promptly after the disease onset, with minimal hematological burden.

Conclusion: The present study was a retrospective analysis of risk factors influencing the efficacy of allo-HSCT in pediatric patients. In the future, the rise in HSC transplantation necessitates comprehensive studies that consider new factors, an expanded patient pool that has undergone allo HSCT, and the creation of risk assessment

scales for the disease. Generally, it is important to acknowledge that children necessitating HSC transplantation differ markedly from adults in several aspects. It renders the application of calculated disease risk indices from adults to infants unfeasible [5, 6]. A specific approach is required, preferably coordinated among various centers [7]. Future plans include enhancing HSCT technology in pediatric patients through diverse conditioning regimens, incorporating immunotherapy, including bridge therapy, increasing transplantation volume based on indications, and advancing unrelated HSCT and haploidentical transplantation. It is imperative to prioritize the implementation of molecular genetic diagnostics for pediatric oncohematological diseases in our country to stratify risk groups and ascertain minimal residual disease, utilizing next-generation sequencing technologies. The challenges of implementing and augmenting the number of HSCTs in children within the Republic of Kazakhstan are pertinent and require additional efforts to guarantee a tailored treatment approach, thereby enhancing survival rates, prolonging life expectancy, and mitigating the risk of adverse and severe treatment complications in pediatric patients.

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АҢДАТПА

ПЕДИАТРИЯ ЖӘНЕ БАЛАЛАР ХИРУРГИЯСЫ ҒЫЛЫМИ ОРТАЛЫҒЫНЫҢ КЛИНИКАСЫНДА БАЛАЛАРҒА АЛЛОГЕНДІК ГЕМОПОЭТИКАЛЫҚ ДІҢ ЖАСУШАЛАРЫН ТРАНСПЛАНТАЦИЯЛАУ НӘТИЖЕЛЕРІ

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Өзектілігі: *Өмір сүруді жақсарту үшін аллогендік гемопоэтикалық дің жасушаларын трансплантациялау нәтижелерін және жынысы, кондиция режимі, донорлық үйлесімділік, АГЖТ кезіндегі негізгі аурудың статусы сияқты факторлардың АГЖТ кейін пациенттердің өмір сүру көрсеткіштеріне ықтимал әсерін зерттеу. жоғары қауіпті онкогематологиялық аурулары бар науқастардың нәтижелері мен өмір сүру сапасы.*

Қазақстан Республикасында педиатрия және балалар хирургиясы ғылыми орталығының базасында 2012 жылы педиатриялық науқастарда гемопоэтикалық дің жасушаларын трансплантациялау қолданыла бастады. Мақалада онкогематологиялық патологиясы бар балаларда балалар мен балаларды күту ғылыми орталығының жағдайында аллогенді АГЖТ жүргізу тәжірибесі берілген.

Әдістері: *2012 жылдан 2020 жылға дейін Балалар мен балаларға арналған ғылыми орталықта жүргізілген АГЖТ кейін 53 науқастың бақылау деректеріне ретроспективті талдау.*

Зерттеудің мақсаты *– АГЖТ нәтижелерін және жынысы, кондициялық режимі, донорлық үйлесімділігі, АГЖТ кезіндегі негізгі аурудың жағдайы сияқты факторлардың қауіпті топтағы онкогематологиялық аурулары бар науқастардың өмір сүру көрсеткіштеріне ықтимал әсерін зерттеу. Пациенттің өмір сүруі Каплан-Майер бойынша бағаланды, статикалық өңдеу SPSS Statistic бағдарламасы арқылы жүзеге асырылды.*

Нәтижелері: *Біздің зерттеуімізде науқастардың 39,6% -ында жедел лимфобластикалық лейкоз (БАРЛЫҚ n=21), жедел миелобластикалық лейкозбен (ЖМЛ) 28,85% (n=15) пациенттер диагнозы қойылды, апластикалық анемия үшін аллоHSCT 20,75% жағдайда орындалды (n =11), 9,46% (n =5) миелодиспластикалық синдромға (MDS) АГЖТ жасалды, оның ішінде үш пациентте (60%) кәмелет-*

ке толмаған миеломоноцитарлық лейкоз (JMML) болды. Зерттеу нәтижелеріне сәйкес, алло- АГЖТ жүргізген кезде, үйлесімді туыстық донордан ALL бар науқастардың жалпы өмір сүру деңгейі 63,6% құрады, ал аурудың басталуынан бастап ең ерте кезеңде АГЖТ жасағанда, өмір сүру деңгейі айтарлықтай болды. жоғары (83,3%). АГЖТ тиімділігіне трансплантацияға дейінгі емдеу және толық үйлесімді донордың болуы да әсер етті. Апластикалық анемияда терапияның басталу уақыты маңызды фактор болып табылады.

Қорытынды: *АГЖТ ерте кезеңдерінде және аурулардың қайталануы жағдайында жоғары тәуекел топтарының онкологиялық және гематологиялық ауруларын емдеудің қажетті кезеңі болып табылады. АГЖТ оң нәтиже алдыңғы терапияға байланысты, яғни. емдеу бағдарламалық, толық көлемде, заманауи стандартты хаттамаларға сәйкес және уақытылы жүргізілуі керек. Қазақстан Республикасында балаларда жүргізілетін ЖҚТК енгізу және санын арттыру мәселелері өзекті болып табылады және өмір сүру ұзақтығын, күтілетін өмір сүру ұзақтығын жақсартуға, педиатриялық ауруларда қажетсіз және қауіпті асқынулардың даму қаупін азайтуға жекелендірілген тәсілді қамтамасыз ету үшін одан әрі күш салуды талап етеді.*

Түйін сөздер: *гемопоэтикалық дің жасушаларын трансплантациялау, балалар, жедел лейкоз, онкогематологиялық аурулар.*

АННОТАЦИЯ

РЕЗУЛЬТАТЫ АЛЛОГЕННОЙ ТРАНСПЛАНТАЦИИ ГЕ-МОПОЭТИЧЕСКИХ СТВОЛОВЫХ КЛЕТОК У ДЕТЕЙ В КЛИНИКЕ НАУЧНОГО ЦЕНТРА ПЕДИАТРИИ И ДЕТСКОЙ ХИРУРГИИ

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Актуальность: *Трансплантация гемопоэтических стволовых клеток (ТГСК) является методом оказания высокоспециализированной помощи пациентам, с онкологическими и гематологическими заболеваниями, тяжелыми комбинированными первичными иммунодефицитами, а также другими врожденными и наследственными болезнями, протекающими с поражением кроветворной и иммунной систем.*

Цель исследования *– изучить результаты проведенных аллоТГСК и возможное влияние таких факторов, как пол, режим кондиционирования, совместимость донора, статус основного заболевания на момент проведения ТГСК на показатели выживаемости пациентов с онкогематологическими заболеваниями групп высокого риска.*

Методы: *Ретроспективный анализ данных наблюдений за 53 пациентами с онкогематологической патологией после ТГСК в условиях Научного Центра педиатрии и детской хирургии г. Алматы с 2021-2020 гг. Выживаемость пациентов оценивали по методу Каплана-Майера, статическая обработку проводили с помощью программы SPSS Statistics.*

Результаты: *Результаты проведенных аллоТГСК были оценены у 39,6% пациентов с острым лимфобластным лейкозом (n=21), у 28,85% пациентов (n=15) с острым миелобластным лейкозом, при апластической анемии в 20,75% случаев (n=11), в 9,46% (n=5) при миелодиспластическом синдроме, из них трое пациентов (60%) с ювенильным миеломоноцитарным лейкозом.*

Общая выживаемость пациентов с острым лимфобластным лейкозом при проведении аллоТГСК от совместимого родственного донора составила 63,6%, при этом показатели выживаемости при проведении ТГСК в наиболее ранние сроки от начала заболевания были значительно выше (83,3%). Так же на эффективность ТГСК влияли лечение до трансплантации, наличие полностью совместимого родственного донора. При апластической анемии значимым фактором являлось время от начала терапии.

Заключение: *ТГСК является необходимым этапом терапии при онкогематологических заболеваниях групп высокого риска в ранние сроки и при рецидивах заболеваний. Положительный результат ТГСК зависит от ранее проводившейся терапии, т.е. лечение должно быть программным, осуществляться в полном объёме, в соответствии с современными стандартными протоколами и своевременным. В детской практике необходим специализированный подход, в идеале гармонизированный между различными трансплантационными центрами. Вопросы увеличения количества проводимых ТГСК у детей требуют дальнейшего изучения для улучшения выживаемости, продолжительности жизни, снижения риска развития нежелательных осложнений у пациентов детского возраста.*

Ключевые слова: *трансплантация гемопоэтических стволовых клеток (ТГСК), дети, острый лейкоз, онкогематологические заболевания.*

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THE POSSIBILITIES OF QUANTITATIVE ASSESSMENT OF SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF THYROID DISEASES

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ABSTRACT

Relevance: *The main pathologies of the thyroid gland (TG) include hyperthyroidism, hypothyroidism, nodular goiter, autoimmune diseases (AIT), and cancer. An increase in morbidity from TG pathologies in the Republic of Kazakhstan requires more efficient diagnostic and treatment methods.*

The study aimed to *determine the diagnostic value of SPECT with sodium pertechnetate (99mTc) quantitative parameters in TG pathologies.*

Methods: *The study involved 112 patients. SPECT assessment of the TG was carried out using a Philips Forte gamma camera and a radionuclide drug – 99mTc. A boxplot diagram was used for statistical analysis of the results, with which the data was visualized, as well as SPSS software ver-sion 21.0 and Microsoft Office Excel.*

Results: *Of the 112 patients, 96 (85.7%) were women, and 16 (14.3%) were men. The participants were aged from 10 to 89 years, with a mean age of 50.9 years. The median administered activity of the 99mTc was 160 MBq. The analysis showed that the largest proportion of patients with SPECT studies of the TG were in the age group over 55 years (37.5%). Regarding the distribution of TG nodules, 47 (42%) patients had nodular formations, including 25 (53.2%) "hot," 20 (42.6%) "cold," and 2 (4.3%) "warm." Classification of thyroid diseases in patients with nodular formation showed that 13 (27.7%) suffered from diffuse goiter, 19 (40.4%) had nodular goiter, 12 (25.5%) had AIT, and 3 (6.4%) patients had cancer. Analysis of the distribution of radiopharmaceutical accumulation in the TG depending on the diagnosis showed that the median accumulation of radiopharmaceuticals in cancer was 0.6, in AIT – 1.15, and in diffuse and nodular goiter – approximately 1.5 and 1.7, respectively.*

Conclusion: *Our study confirms the importance of quantitative SPECT parameters for understanding the various manifestations and pathological processes in the TG. Future research may improve diagnostic and treatment strategies for this disease by further exploring the relationship be-tween these parameters and various forms of TGC.*

Keywords: *Thyroid gland, node, single-photon emission computed tomography (SPECT), radiopharmaceuticals, radiopharmaceutical accumulation, quantitative assessment.*

Introduction: Thyroid gland (TG) disorders are the conditions that impact the TG function, size, and structure. The TG disorders primarily include hyperthyroidism, hypothyroidism, TG nodules, autoimmune diseases, and thyroid cancer. Worldwide, approximately 200 million persons have been diagnosed with TG disorder. The prevalence rate of hyperthyroidism ranges from 0.2% to 1.3%, while the prevalence rate of hypothyroidism ranges from 1% to 2%. And the proportion of palpable TG nodules ranges from 4% to 7% [1]. Besides, there is a constant increase in thyroid cancer, according to the International Agency for Research on Cancer. For example, the number of newly diagnosed thyroid cancer cases increased by 1.4 times (from 586,202 to 821,214) from 2020 to 2022 [2, 3].

In the Republic of Kazakhstan, the incidence of TG disorders has also increased. Kh.I. Kudabayeva et al. report that foci of endemic goiter have been registered in 11 regions [4]. The share of thyroid cancer in the structure of oncological morbidity is 1-3% and is in the 17th place [5].

New diagnostic methods appear with the development of science and technology in medicine. Ultrasonic scanning (Ultrasound) is still the main TG examination method [6]. The ultrasound is sensitive to TG nodules in 19-67% of cases but has a limited capacity to differentiate benign and malignant neoplasms. Fine-needle aspiration puncture biopsy (TAPB) is a mandatory part of the examination to assess nodular neoplasms [7]. High sensitivity and specificity are the strengths of this method. Scintigraphy or single-photon emission computed tomography (SPECT) is used to visualize the TG functional activity. This method allows for assessing the TG function and determining the number, location, and types of foci. Scintigraphy or SPECT before TAPB is recommended to sort out patients with non-functioning "cold" nodules.

The study aimed to determine the diagnostic value of SPECT with sodium pertechnetate (^{99m}Tc) quantitative parameters in TG pathologies.

Materials and methods: The data for this retrospective study were collected from 112 patients who underwent TG examination from 2016 to 2023 in the Department of Radiology and Nuclear Medicine of the Kazakh Research Institute of Oncology and Radiology (Almaty, Kazakhstan). The collected data included the SPECT, US, and TAPB results, data on the therapy performed, and the results of the postoperative histological examination.

The SPECT study was conducted under the recommendations of the European Society of Nuclear Medicine (EANM) for TG scintigraphy and SPECT [8]. The patients who had undergone TG examinations had a referral from a physician. Patients received detailed information about the study while making an appointment and preparing for it. Pregnancy and breastfeeding were contraindications for the study.

The thyroid SPECT was performed using a Philips Forte gamma camera equipped with a high-energy collimator or a pinhole collimator centered on a photopeak with an energy of 140 keV. A radioactive pharmaceutical ^{99m}Tc was used for the study. The activity dose was calculated individually for each patient at 1-1.5 MBq/kg b.w. The syringe with the product was measured on an immersion dosing device and directly with a gamma camera before and after administration to calculate the administered dose. The study was conducted 10-15 minutes after administering ^{99m}Tc in the supine position with the patient's head thrown back. The image was obtained in 3 minutes per the standard gamma camera examination protocol. Parameters such as thyroid size, uniformity of radioactive pharmaceutical (RPh) uptake, and local foci of increased or decreased accumulation of RPh were evaluated as a result of the scanning. Nodules in the thyroid indicate that a focal formation has formed. Nodular formations of the thyroid were classified depending on the degree of RPh accumulation. Nodular formations were classified according to the adopted standard, as: "cold" – not accumulating RPh, "warm" – with the accumulation of RPh equivalent to the thyroid tissues, and "hot" (autonomous) – with the accumulation above the accumulation of thyroid tissues. Two nuclear medicine doctors from the Radiology and Nuclear Medicine Department of the Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan) interpreted the study results.

Statistical analysis of the results was conducted with the help of a boxplot, and such parameters as median, arithmetic mean, and standard deviation were used. All data obtained during the study were statistically processed. Statistical data processing was conducted using SPSS software version 21.0 and Microsoft Office Excel.

Results: 112 thyroid SPECT studies with ^{99m}Tc were performed in the Department of Radiology and Nuclear Medicine of the Kazakh Research Institute of Oncology and Radiology from 2016 to 2023. Demographic variables such as gender, age, and ethnicity were collected during the study (Table 1).

Table 1 – Demographic characteristics of the study participants

Category	Subgroup	Absolute Parameter	Percentage Parameter
Gender	Men	16	14.3%
	Women	96	85.7%
Age	0-24	5	4.5%
	25-34	17	15.2%
	35-44	23	20.5%
	45-54	25	22.3%
	55<	42	37.5%
Ethnic group	Kazakhs	63	56.25%
	Russians	31	27.69%
	Dungans	2	1.79%
	Ukrainians	1	0.89%
	Koreans	2	1.79%
	Uyghurs	3	2.68%
	Tatars	4	3.57%
	Kurds	1	0.89%
	Azerbaijanis	1	0.89%
	Kirgiz	1	0.89%

As seen from Table 1, most patients were women, 96 out of 112 (85.7%). The ages of the patients ranged from 10 to 89 years. The group over 55 prevailed in the age range of 42 persons (37.5%). The mean age of all patients was 50.9 years, 44.8 years in men and 51.4 years in women. The Kazakhs were the largest among the patients based on ethnic group, accounting for 56.25%.

The median of the introduced RPh activity during the study was 99mT – 160 MBq (60-260 MBq). The distribution of RPh accumulation in the thyroid, depending on gender, was visualized using boxplot analysis. As a result, the minimum value of RPh accumulation in women and men was the same - 0.1, and the maximum value was 13.8 and 9.1, respectively. The median in the first group, that is, in women, was 1.2; in the second group, it was less by 33.3% (0.8). The lower and upper quartiles in women were 0.6 and 2.3, respectively, and 0.4 and 1.6 in men (Figure 1).

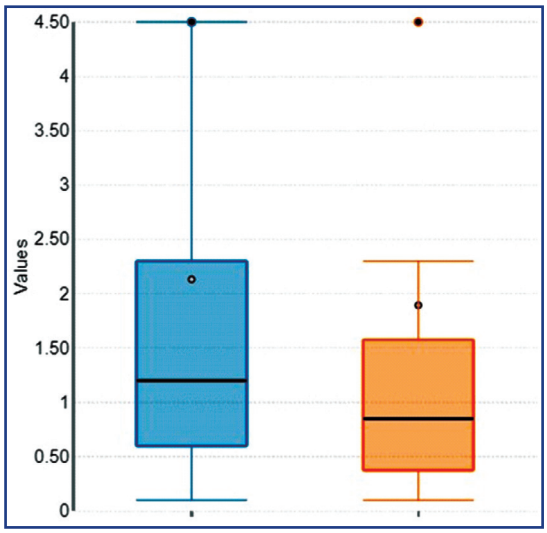


Figure 1 – Accumulation of RPh ^{99m}Tc in the thyroid in men and women

Table 2 – Distribution of TG nodules depending on the accumulation of ^{99m}Tc

Group	Category	Absolute parameter	Percentage Indicator
Presence of nodules	Present	47	41.96%
	Absent	65	58.04%
Classification of Nodules	Hot	25	53.2%
	Warm	2	4.3%
	Cold	20	42.6%
Nodule locations	Left lobe	15	31.9%
	Right lobe	25	53.2%
	Isthmus	3	6.4%
	Left/Right Lobes	4	8.5%

Nodular formations were found during the examination of the thyroid gland. The characteristics of the found TG nodules are presented in Table 2.

Table 2 shows that nodules were found in 47 (42%) patients, of which 25 (53.2%) were "hot," 2 (4.3%) nodules were "warm," and 20 (42.6%) nodules were "cold." More than half of the nodules were located in the right lobe, at 25 (53.2%), and only 15 (31.9%) were in the left lobe. The nodule's location in the isthmus was 6.4% and 8.5% in both lobes.

The nodules were categorized by visual qualitative assessment for the RPh accumulation degree (Figure 2).

Patients with nodular formations were classified into 4 groups according to TG disorder: diffuse goiter, nodular goiter, autoimmune thyroiditis (AIT), and thyroid cancer (Table 3).

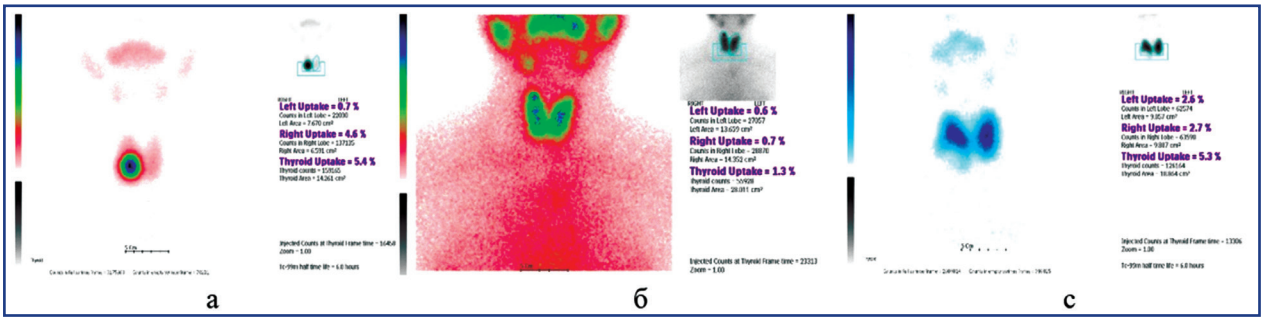


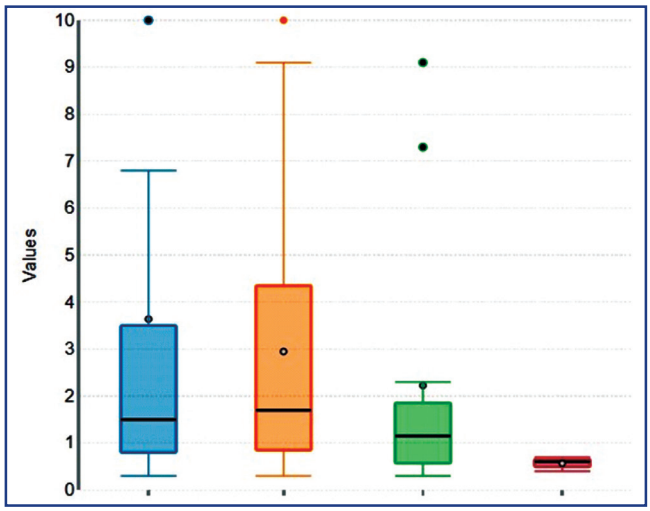
Figure 2 – Images of the thyroid: a) "hot" nodule, b) "warm" nodule, c) "cold" nodule

Table 3 – Classification of TG nodular formations

Group of disorders	Absolute parameter	Percentage parameter
Diffuse goiter	13	27.7%
Nodular goiter	19	40.4%
Autoimmune thyroiditis	12	25.5%
Thyroid cancer	3	6.4%

The number of patients with thyroid cancer was 6.4%, and the number with diffuse goiter and AIT were approximately the same, 27.7% and 25.5%, respectively, and the largest part of patients was with nodular goiter, 40.4% (Table 3).

The distribution of RPh accumulation in the thyroid, depending on the disorder, can be seen in Figure 3 and Table 4.



Note: Y-axis – values; Diagrams (from left to right): diffuse goiter, nodular goiter, autoimmune thyroiditis, thyroid cancer

Figure 3 – RPh accumulation in the thyroid under diagnosis

Table 4 – Summary data

Group	Number	Min.	Q1	Median	Q3	Max.	Medium value	Standard deviation
Diffuse goiter	13	0.3	0.8	1.5	3.5	13.8	3.6385	4.6543
Nodular goiter	19	0.3	0.85	1.7	4.35	10.2	2.9474	2.8899
Autoimmune thyroiditis	12	0.3	0.575	1.15	1.85	9.1	2.225	2.8794
Thyroid cancer	3	0.4	0.5	0.6	0.65	0.7	0.5667	0.1528

Analysis of quantitative SPECT parameters showed that the median RPh accumulation in thyroid cancer was 0.6 (mean value was 0.7). In contrast, this parameter was 2 times higher (1.15) in AIT. And the median RPh accumulations were approximately the same – 1.5 and 1.7, respectively, in diffuse and nodular goiter (Figure 3).

Discussion: We studied thyroid SPECT data from 2016 to 2023 as part of our study performed in the Department of Radiology and Nuclear Medicine of KazRIOR. During 112 thyroid studies, it was found that 85.7% (96) of participants were females, while males accounted for 14.3% (16). In the studies by G.B. Morand et al. [9], N. Bilen et al. [10], and C. Gong et al. [11], an average of 78% of patients were females. According to GLOBOCAN, females are also more affected by breast cancer; i.e., in 2022, the women-to-men ratio was 2.98 [3]. The gender imbalance in our study probably reflects the high incidence of TG disorder in the female population. There are several reasons for the explanation of this difference. The estrogenic environment and the cyclic nature of hormonal changes in women are strong stimulators of thyroid dysfunction in women. The fact that TG disorders are the most common endocrine factors affecting women of reproductive age is of paramount importance [12-15].

Analysis of the age distribution of patients allows us to see that thyroid studies with SPECT were conducted in a wide age range - from 10 to 89 years. In our studies, most patients were aged 35 to 44 years or above 55 years. In the study by N. Kwong et al., nodular TG disorders in patients of the oldest group (>70) increased by 0.7 [16]. Thyroid cancer was found oftener in the age group above 55, according to the 2022 GCO observation [3]. It may indicate an increased need for such diagnostics at an older age.

Several key aspects should be discussed regarding the study's results on the distribution of RPh accumulation in thyroid tissue depending on gender. First, it is noticeable that the minimum RPh accumulation in women and men is the same, at 0.1. It indicates a similarity in the initial levels of thyroid activity in both genders. Second, the differences become more pronounced in the maximum value analysis: in women, the maximum value is 13.8 vs. 9.1 in men. This indicates various pathological processes or metabolic characteristics related to thyroid activity in different genders. The third important observation concerns the median. The median value of the RPh accumulation in women is 1.2, while this value in men is lower by 33.3% and is 0.8. It indicates potential differences in the distribution of thyroid activity between the genders.

Thus, the study results highlight potential differences in thyroid activity between men and women. It may have clinical implications in assessing thyroid function and possible pathological processes. Further studies may focus on identifying the causes of these differences and their clinical implications for understanding TG disorders.

The study of the characteristics of TG nodules provides valuable information about the various manifestations of this disease. It is noted that 42% of patients were found to have nodules, and many of them were classified as "hot," which is 53.2% of the nodules found. In previous studies, the proportion of hot TG nodules found during SPECT ranged from 8-72% [17-21]. Many authors in their research papers concluded that the "cold nodules" are mostly ma-

lignant, while the "hot nodules" are benign based on the comparison of the preoperative study results of SPECT and histology [22]. However, several studies show that it is not always the case, and 11.5% of hot nodules turn out to be malignant, while the rate for cold nodules is only 5-8%, and it was 25% in some studies. Radionuclide diagnostics is limited in differentiating benign tumors from malignant ones.

Analysis of the distribution of nodules by thyroid lobes showed a higher frequency of localization in the left lobe (53.2%). However, the location of the nodules, depending on the pole, is more significant, according to the works of other authors [23,24].

Classifying TG disorders among patients with nodular formations helps better understand their clinical manifestations. It was found that nodular goiter (40.%) and diffuse goiter (27.7%) were the most common TG disorders in the cohort of patients in our study.

The thyroid gland increases evenly in diffuse goiter, one or more nodular formations are observed in the thyroid in nodular goiter, and their simultaneous combination is noted in diffuse-nodular goiter. Interestingly, the median of the RPh accumulation in these two cases does not differ much. At the same time, the RPh accumulation rate was lower than in diffuse goiter in patients with AIT but twice as high as in thyroid cancer.

US is widely used as a primary examination method for TG disorders. However, the US capabilities may be limited in the differential diagnosis of benign and malignant nodules [25,26]. Usually, TAPB is the "gold standard" for the differential diagnostics of thyroid lesions [27,28], and SPECT is used to diagnose thyroid goiter in certain cases. This method can help determine the goiter's size, shape, activity, and spread. Their combined use is important for this reason [29]

Quantitative SPECT/CT is considered useful for risk stratification of functional TG disorders. It becomes obvious from the quantitative SPECT data analysis that the RPh accumulation level in thyroid cancer was noticeably lower than in other groups. It may be due to a decrease in the ability of the thyroid gland to concentrate iodine in some types of malignant neoplasms [30]. Due to the similarity of technetium and iodine in terms of physical and chemical properties, technetium uptake is also reduced [28].

This figure doubled with AIT, reaching 1.15. The median indicators of RPh accumulation were approximately equal in diffuse and nodular goiter and amounted to 1.5 and 1.7, respectively.

The work by H. Lee et al. showed that the quantitative parameters of SPECT/CT were the highest in diffuse goiter and lower in the euthyroid state, but this parameter was the lowest in thyroiditis ($p<0.0001$). The work demonstrated that the quantitative assessment of SPECT/CT is more accurate than the qualitative assessment of the RPh accumulation, so it is considered the main method [31]. In the work of H.J. Kim et al., the percentage of RPh uptake was also more significant in detecting euthyroidism and made it possible to distinguish destructive thyroiditis from a euthyroid state [32].

Thus, the results of our study showed that the quantitative parameters of SPECT are informative in the differentiation of thyroid cancer from other thyroid pathologies. However, the method has a lower diagnostic accuracy in the differential diagnostics between non-oncological thyroid pathologies. Further studies may deepen the understanding of the relationship between the quantitative parameters of SPECT and various thyroid pathologies. It will help to develop more effective strategies for the diagnostics and treatment of TG disorders.

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АҢДАТПА

ҚАЛҚАНША БЕЗІНІҢ АУРУЛАРЫН ДИАГНОСТИКАЛАУДА БІР ФОТОНДЫ ЭМИССИЯЛЫҚ КОМПЬЮТЕРЛІК ТОМОГРАФИЯНЫҢ САНДЫҚ БАҒАЛАУЫҢ МҮМКІНДІКТЕРІ

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Өзектілігі: *Қалқанша безінің негізгі патологияларына гипертиреоз, гипотиреоз, түйінді зоб, аутоиммунды аурулар және қатерлі ісік жатады. Қазақстан Республикасында диагностика мен емдеудің негұрлым тиімді әдістерін талап ететін ҚБ ауруымен ауыратын науқастар санының артуы байқалады.*

Зерттеудің мақсаты *– ҚБ-нің патологиясын зерттеу кезінде натрий пертехнетатын (99mTc) қолданып БФЭКТ-ның сандық параметрлерінің диагностикалық мәнін анықтау болып табылады.*

Әдістері: *Зерттеу барысында 112 науқастың деректері қамтылды. ҚБ-дің сцинтиграфиясы Philips Forte гамма камерасы және радионуклидті препарат – 99mTc көмегімен жүргізілді. Нәтижелердің статистикалық талдауы кезінде, boxplot диаг-*

раммасы көмегімен деректер визуализацияланды және SPSS-тің 21.0 нұсқасы мен Microsoft Office Excel бағдарламалық құралы пайдаланылды.

Нәтижелері: *112 науқастардың 96 (85,7%) әйелдер, 16 (14,3%) ер адамдар болды. Зерттеу жүргізілген науқастардың жасы 10-нан 89 жас аралығында болды, ал орташа жасы 50,9 құрады. Енгізілген радиофармдәрмектің (РФД) 99mTc-дің белсенділігінің медианасы 160 МБк құрады.*

Талдау ҚБ-інің БФЭКТ-лық зерттеуінен өткен науқастардың үлкен үлесі 55 жастан асқан (37,5%) жас тобы екенін көрсетті. ҚБ-інің түйіндерінің таралуына келетін болсақ, 47 (42%) пациентте түйінді түзілімдер болды, оның ішінде 25 (53,2%) «ыстық», 20 (42,6%) «суық» және 2 (4,3%) – «жылы» болды.

ҚБ-нің Түйінді формациясы бар науқастардың жіктелуінде: 13 (27,7%) диффузды зобпен, 19 (40,4%) – түйінді зобпен, 12 (25,5%) – аутоиммунды тиреоидитпен (АИТ) және 3 (6,4%) – қатерлі ісікпен ауырғанын көрсетті.

Диагнозға байланысты ҚБ-де РФД-тің жинақталуының таралуын талдау кезінде, препараттың жинақталу медианасы қатерлі ісік кезінде 0,6, АИТ-те – 1,15, ал диффузды және түйінді зобта сәйкесінше 1,5 және 1,7-ні құрайтыны анықталды.

Қорытынды: *Біздің зерттеуіміз ҚБ-дегі әртүрлі білінулер мен патологиялық процестерді түсіну үшін БФЭКТ сандық параметрлерінің маңыздылығын растайды.*

Түйінді сөздер: *қалқанша безі, түйін, бір фотонды эмиссиялық компьютерлік томография (БФЭКТ), радиофармдәрі (РФД), РФД-тің жинақталуының, сандық бағалау.*

ABSTRACT

ВОЗМОЖНОСТИ КОЛИЧЕСТВЕННОЙ ОЦЕНКИ ОДНОФОТОННОЙ ЭМИССИОННОЙ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ В ДИАГНОСТИКЕ ЗАБОЛЕВАНИЙ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Актуальность: *Основные патологии щитовидной железы (ЩЖ) включают гипертиреоз, гипотиреоз, узловой зоб, аутоиммунные заболевания (АИТ) и рак. В Республике Казахстан наблюдается увеличение заболеваемости ЩЖ, требующее более эффективных методов диагностики и лечения.*

Цель исследования *– определение диагностической ценности количественных параметров однофотонной эмиссионной компьютерной томографии с натрия пертехнетатом (99mTc) при патологиях щитовидной железы.*

Методы: *Материалы для исследования включали данные 112 пациентов. Количественная оценка ОФЭКТ ЩЖ проводилась с использованием гамма-камеры Philips Forte и радионуклидного препарата 99mTc. Для статистического анализа результатов использовали программное обеспечение SPSS версии 21.0 и Microsoft Office Excel, а также диаграммы boxplot для визуализации данных.*

Результаты: *В исследование было включено 112 пациентов, в т.ч. 96 (85,7%) женщин и 16 (14,3%) мужчин. Возраст участников находился в диапазоне от 10 до 89 лет, средний возраст составил 50,9 лет. Медиана введенной активности радиофармпрепарата (РФП) 99mTc составила 160 МБк .*

Анализ показал, что большинство пациентов (37,5%) были старше 55 лет. Что касается распределения узлов ЩЖ, то у 47 (42%) пациентов были выявлены узловые образования, среди которых 25 (53,2%) были «горячими», 20 (42,6%) – «холодными» и 2 (4,3%) – «теплыми».

Классификация заболеваний ЩЖ у пациентов с узловым образованием показала, что 13 (27,7%) страдали диффузным зобом, 19 (40,4%) – узловым зобом, 12 (25,5%) – АИТ и 3 (6,4%) – раком ЩЖ.

Анализ распределения накопления РФП в ЩЖ в зависимости от диагноза показал, что медиана накопления РФП при раке составила 0,6, при АИТ – 1,15, а при диффузном и узловом зобе – примерно 1,5 и 1,7, соответственно.

Заключение: *Наше исследование подтверждает важность количественных параметров ОФЭКТ для понимания разнообразных проявлений и патологических процессов в ЩЖ. Дальнейшие исследования могут улучшить стратегии диагностики и лечения этого заболевания, глубже изучив связь между этими параметрами и различными формами заболеваний ЩЖ.*

Ключевые слова: *щитовидная железа (ЩЖ), узел, однофотонная эмиссионная компьютерная томография (ОФЭКТ), радиофармпрепараты (РФП), накопление РФП, количественная оценка.*

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ENDOSCOPIC BOUGIENAGE OF BENIGN ESOPHAGEAL STRICTURES USING A BOUGIE CAP

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ABSTRACT

Relevance: *Esophageal stricture is a narrowing of the lumen of the esophageal tube caused by the proliferation of connective tissue in its wall. This condition can develop against the background of esophagitis, peptic ulcers, chemical burns of the esophagus, and iatrogenic causes. Cicatricial changs of the esophagus occupy the second place among diseases of this organ after esophagitis and are formed in 70-80% of patients with postburn strictures.*

The study aimed to *analyze the results of endoscopic treatment of benign esophageal stenosis using distal Bougie Cap caps and evaluate the effectiveness of this new device in the short term of use for treatment purposes.*

Methods: *The authors have retrospectively analyzed the first results of using Bougie Cap distal caps in the endoscopic treatment of benign esophageal stenosis in Kazakhstan. From 2022 to 2023, 81 bougie sessions with steel caps were performed in 55 patients with esophageal stenosis in the endo-scopic department of the National Research Oncology Center (Astana, Kazakhstan).*

Results: *The leading causes of esophageal stenosis were chemical burns (60% of patients), stenosis after radiation therapy (25.4%), and strictures of esophageal anastomosis (14.6%). The stenoses were short, up to 3.0 cm, in 37 patients (67.2%), extended – in 15 patients (27.2%), subtotal – in 2 patients (3.6%), and only one patient (1.8%) had a stenosis of 17 cm. The bougienage outcome was good in all patients with short stenoses, satisfactory – in patients with stenoses up to 9 cm, and unsatisfactory – in patients with subtotal and total stenoses. The number of sessions was 3 to 11. Three patients with total and subtotal stenosis were denied a bougienage due to a tortuous stenosis with a high risk of perforation, and a percutaneous gastrostomy was installed.*

Conclusion: *Endoscopic bougienage with distal caps of the Bougie Cap is a safe method of bougienage of benign esophageal strictures since the cap is transparent, and an endoscopist visually supervises the bougienage. During the three years of using distal caps to dilate esophageal stenosis, not a single case of perforation was registered in our department. Therefore, we recommend this method as the safest and most predictable method of bougienage, both in outpatient practice and in the hospitals in the republic.*

Keywords: *stenosis, stricture, bougienage, dilatation, esophagus.*

Introduction: Esophageal stricture is a narrowing of the esophageal tube's lumen due to the proliferation of connective tissue in its wall. This condition can develop against the background of esophagitis, peptic ulcers, chemical burns of the esophagus, and iatrogenic causes. It is accompanied by symptoms such as dysphagia (swallowing problem), belching, sore throat and retrosternal pain, and weight loss. Esophagoscopy and radiography of the esophagus are used to diagnose strictures. Treatment options include balloon dilation of the stricture, bougienage, esophagoplasty, etc. [1, 2]. Cicatricial changes in the esophagus occupy the second place among esophageal diseases after esophagitis and occur in 70-80% of patients with post-burn strictures. The prevalence of such pathologies is gradually increasing, especially among children and young people. In modern abdominal surgery, developing effective methods for treating cicatricial strictures of the esophagus and preventing disruption of normal digestive function remains an urgent problem.

Benign scar strictures can occur after inflammatory diseases of the esophagus, damage to the organ wall with aggressive agents, or surgical interventions on the esophagus, e.g., application of anastomosis [3, 4].

Endoscopic classification of esophageal constrictions by Gallinger:

Degree I – esophageal stenosis up to 9-11 mm;

Degree II – esophageal stenosis up to 6-8 mm;

Degree III – esophageal stenosis up to 3-5 mm;

Degree IV – esophageal stenosis up to 1-2 mm or a complete obliteration [5].

In addition, the patient's medical history, the presence of a causal factor of stenosis, the duration of stenosis, and the degree of dysphagia are clarified during the initial consultation. Violation of the passage of food into the esophagus (dysphagia) is the most common manifestation of the disease. There are four degrees of dysphagia:

Degree I – violation of the passage of solid food through the esophagus;

Degree II – difficulty in semi-fluid food intake;

Degree III – difficulty in fluid intake;

Degree IV – complete esophageal obstruction.

A distal bougienage cap enables visual assessment of the esophageal opening dilation. An endoscopist can observe changes in tissue tension through the transparent wall of the cap and avoid unwanted sprains. In addition, using fewer tools reduces the procedure time. [6,7]. Caps are made in different sizes: 10, 12, 14, and 16 mm for both standard and ultrathin endoscopes (Figure 1). There are three holes in the distal part of the cap. Two of them are designed to suck out air and water, and one central hole is designed to insert guide wires.

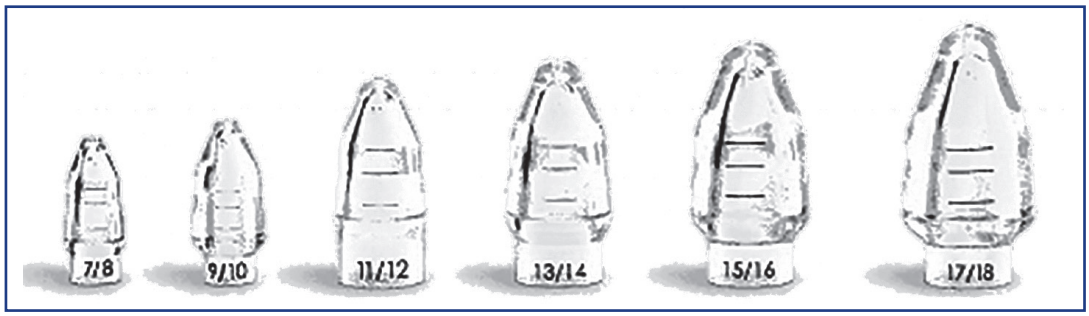

Figure 1 – Types and sizes of endoscope distal caps for bougienage

There was no need for patient sedation during the bougienage. This is because the procedure time is comparable to conventional elective gastroscopy and is accompanied by mild discomfort without pronounced pain. Successful bougienage with a distal may be visually confirmed during the procedure through a transparent distal cap; therefore, documentary (radiographic) confirmation is unnecessary. For monitoring, it is enough to ask the patient to drink a glass of water, and patients and doctors will recognize the clinical effectiveness of the bougienage procedure based on the feeling of free passage of water from the esophagus into the stomach cavity (Figure 2).

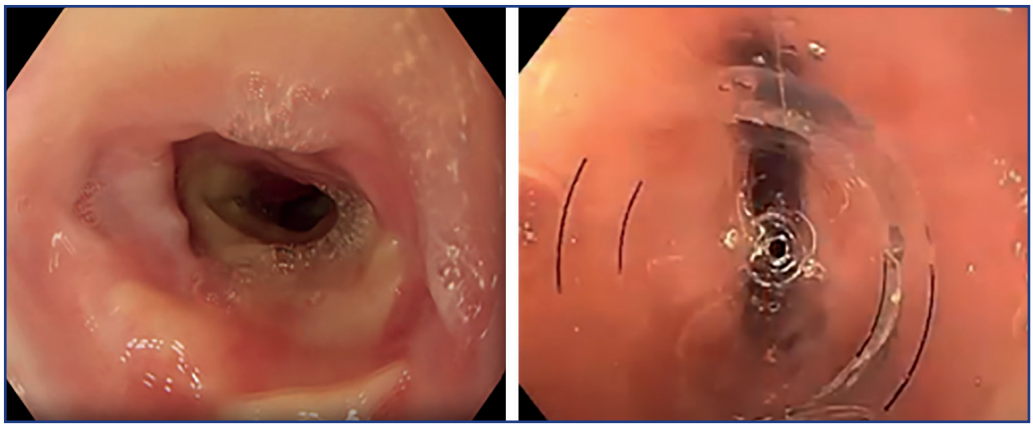

Figure 2 – Endoscopic view of bougienage with a distal cap. Bougienage is visually controlled through a transparent polymer cap.

Since the opening of the endoscopic department of the National Scientific Cancer Center (Astana, Kazakhstan) in 2019, we have been engaged in esophageal dilation on an ongoing basis for both malignant and benign diseases. Patients with benign esophageal stricture usually predominate and comprise the lion's share of stenotic patients. Since 2022, we have primarily used distal Bougie Caps for esophageal dilation and have stopped using polymer bougies along the guide wire.

The study aimed to analyze the results of endoscopic treatment of benign esophageal stenosis using distal Bougie Cap caps and evaluate the effectiveness of this new device in the short term of use for treatment purposes.

Materials and methods: From 2019 to 2022, the NSCC endoscopy department, for benign strictures of the esophagus, used polymer bougies for bougienage along the guide wire. After purchasing new distal Bougie Caps for the first time, polymer bougies were no longer used since bougienage with polymer bougies along the guide wire did not allow direct visual endoscopic control during the stricture bougienage process, which carries excellent risks of esophageal perforation or creating a false passage in the esophageal wall. While using polymer bougies along the guide wire, two cases of unintentional esophageal perforation were reported by the NSCC department and subsequently managed by emergency surgery. Later, we stopped using polymer bougies. From 2022 to 2023, the NSCC endoscopy department only performed 81 bougienage sessions with distal caps in 55 esophageal stenotic patients. The persistent clinical effect of bougienage with distal caps was achieved on average for 7-8 sessions, and no further bougienage was required. Subsequently, during the dynamic monitoring, 1-2-3 months after the last bougienage session, the esophageal lumen retained a width of 10-14 mm, which caused no dysphagia in patients. The presented review describes a retrospective analysis of the first and most successful Kazakh experience of endoscopic treatment of benign esophageal strictures using a new device. While using distal caps, our department reported no cases of esophageal perforation, which indicates the safety of this device compared to bougienage with polymer bougies.

According to Table 1, men accounted for 70.9%, and only 29.1% of patients were women. By age, 43.6% of patients were 18-44 years old (Group 1), 41.9% were 45-59 years old (Group 2), and 14.5% were of other ages.

Table 1 – Distribution of patients by gender and age

Пол пациентов	Возраст пациентов, абс. (%)				
	18-44	45-59	60-74	75-90	90+
Мужчины	15 (27.3)	19 (34.6)	3 (5.4)	2 (3.6)	0
Женщины	9 (16.3)	4 (7.3)	2 (3.6)	1 (1.8)	0

Results: Before bougienage, all patients underwent a contrast-enhanced X-ray examination of the esophagus to determine the narrowing zone, the severity of stenosis, the extent of stenosis, the shape of the stenosed lumen of the esophagus, and the degree of stenosis according to Gallinger (1999) [5].

Most often, patients came with the 3rd or 4th degree of esophageal stenosis and with the 3rd degree of dysphagia. In patients with short stenoses, bougienage sessions were performed on an outpatient basis, mostly without sedation, since bougienage corresponds to a routine gastroscopy procedure in time and severity of discomfort. In patients with prolonged, subtotal, and total stenosis, the first bougienage sessions were conducted on an inpatient basis and under general sedation due to the high risk of esophageal perforation. Further, if the first bougienage sessions are thriving and there is no perforation, repeated sessions were performed on an outpatient basis and under sedation at the patient's request.

Table 2 – Characteristics of stenosis in patients

Cause of stenosis	Extent of stenosis			
	Short (<3.0 cm)	Extended (4-9 cm)	Subtotal (10-15 cm)	Total (>16 cm)
Post-burn stenosis	18	12	2	1
Postradiation stenosis	11	3		
Anastomotic strictures	8			

According to Table 2, the main causes of esophageal stenosis were chemical burns – in 33 patients (60% of the total number of patients), post-radiation stenosis – in 14 patients (25.4%), and strictures of esophageal anastomosis – in 8 patients (14.6%). Most stenoses were short, extending up to 3.0 cm in 37 patients (67.2%). Extended stenoses were found in 15 patients (27.2%), subtotal stenosis up to 15 cm– in 2 patients (3.6%), and only one patient (1.8%) had a 17 cm stenosis.

In all patients with short stenoses, good results of bougienage were reported; patients with extended stenoses up to 9 cm had satisfactory results, and patients with subtotal and total stenoses had unsatisfactory results. The number of sessions varied from 3 to 11. Three patients with total and subtotal stenosis were burred from bougienage due to the presence of a tortuous course of stenosis, which is accompanied by a high risk of perforation, and they underwent percutaneous gastrostomy placement.

Discussion: The Bougie Cap is a relatively new device for treating esophageal and gastric stenoses. The first international publication on the use of this device dates back to 2018, and the first video on the use of this distal cap for bougienage dates back to 2017. A few publications on the experience of using this device are probably because the caps for bougienage are designed for single use and are pretty expensive, making the procedure more expensive than reusable polymer bougies. The foreign literature describes the experience of using caps for bougienage of post-radiation stricture, eosinophilic esophagitis, and cicatricial stricture of the esophagus. In contrast, no case describes the experience of using bougienage with this device in malignant stricture [8, 9]. As for Kazakhstan, the NSCC endoscopy department was one of the first in the country to use this device in 2022. The device has already been used for benign esophageal stricture and malignant esophageal stenosis [10]. In such a short time, the experience of using this cap for bougienage has already been accumulated. The safety of this device is achieved due to the possibility of visual inspection through its transparent wall directly during the bougienage process. The endoscopist visually monitors the direct pointing of the cone-shaped part of the cap at the mouth of the stricture and controls the stretching of scar tissue. Most importantly, the bougienage is not carried out blindly, and there is no risk of false passage. Our experience using the distal cap for bougienage suggests its clinical effectiveness in treating esophageal strictures.

Conclusion: Endoscopic bougienage with distal caps is a safe method for benign esophageal strictures since the cap is transparent and bougienage is performed under the visual supervision of an endoscopist. During the three years of using distal caps to expand esophageal stenosis, our department reported no cases of perforation; therefore, we recommend this method as the safest and most predictable option of bougienage in outpatient practice and hospitals of the republic.

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АҢДАТПА

BOUGIE CAP КӨМЕГІМЕН ӨҢЕШТІҢ ҚАТЕРСІЗ СТРИКТУРАЛАРЫН ЭНДОСКОПИЯЛЫҚ СҮМБІЛЕУ

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Өзектілігі: *Өңештің стриктурасы – өңеш түтігінің қабырғасындағы дәнекер тіннің көбеюінен болатын саңылаудың тарылуы. Өңештегі цикатриялық өзгерістер осы органның аурулары арасында эзофагиттен кейін екінші орынды алады және күйіктен кейінгі стриктурасы бар науқастардың 70-80% құрайды.*

Зерттеудің мақсаты *– дистальды Bougie Caps көмегімен өңештің қатерсіз стеноздарын эндоскопиялық емдеу нәтижелерін талдау және осы жаңа құрылғыны емдік мақсатта пайдаланудың қысқа мерзіміндегі тиімділігін бағалау.*

Әдістері: *Қазақстанда өңештің қатерсіз стриктурасын эндоскопиялық емдеуде дистальды Буги қақпағын алғаш рет қолдану тәжірибесінің деректеріне ретроспективті талдау жасалды. 2022-2023 жылдар аралығында Ұлттық ғылыми онкология орталығының (Астана, Қазақстан) эндоскопиялық бөлімшесінде өңеш стенозы бар 55 науқасқа дистальды қалпақшалармен бугиенаждың 81 сеансы өткізілді.*

Нәтижелері: *Өңеш стенозының негізгі себептері химиялық күйік (пациенттердің 60%), сәулелік терапиядан кейінгі стеноз (25,4%) және өңеш анастомозының тарылуы (14,6%) болды. 37 науқаста (67,2%) қысқа стеноздар 3,0 см-ге дейін, 15 науқаста (27,2%) ұзартылған стеноздар, 2 науқаста (3,6%) – ұзындығы 15 см-ге дейінгі субтотальды стеноздар, бір науқаста (1,8%), стеноз 17 см-ді құрады, қысқа стенозы бар науқастардың барлығында бугиенаждың жақсы нәтижелері, 9 см-ге дейінгі стенозы бар науқастарда қанағаттанарлықсыз нәтижелер, субтотальды және жалпы стенозы бар науқастарда байқалды. Сеанстардың саны 3-тен 11-ге дейін болды. Толық және субтотальды стенозы бар үш науқас перфорация қаупі жоғары стеноздың бұралмалы ағымының болуына байланысты бугиенаждан бас тартылды және перкутандық гастростомия орнатылды.*

Қорытынды: *Bougie Cap дистальды қақпақтарымен эндоскопиялық сүмбілеу өңештің қатерсіз стриктураларын сүмбілеудің қауіпсіз әдісі болып табылады, өйткені қақпақ мөлдір және сүмбілеу эндоскопистің көзбен бақылауымен жүзеге асырылады. Өңеш стенозын кеңейту үшін дистальды қақпақтарды қолданудың үш жылдық кезеңінде біздің бөлімшеде перфорацияның бірде-бір жағдайы тіркелген жоқ, сондықтан біз бұл әдісті амбулаториялық тәжірибеде де, Республиканың стационарларында да сүмбілеудің ең қауіпсіз және болжамды әдісі ретінде ұсынамыз.*

Түйінді сөздер: *стеноз, стриктура, сүмбілеу, өңештің кеңеюі.*

АННОТАЦИЯ

ENDOSCOPIC BOUGIENAGE OF BENIGN ESOPHAGEAL STRICTURES USING A BOUGIE CAP

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Актуальность: *Стриктура пищевода представляет собой сужение просвета пищеводной трубки, вызванное разрастанием соединительной ткани в ее стенке. Рубцовые изменения пищевода занимают второе место среди заболеваний данного органа после эзофагита и формируются у 70-80% пациентов с постожоговыми стриктурами.*

Цель исследования *– проанализировать результаты эндоскопического лечения доброкачественных стенозов пищевода с использованием дистальных колпачков Bougie Cap и оценить эффективность этого нового девайса в краткосрочном периоде использования в лечебных целях.*

Методы: *Проведен ретроспективный анализ данных опыта первого применения дистальных колпачков Bougie Cap в эндоскопическом лечении доброкачественных стриктур пищевода в Казахстане. С 2022 по 2023 год в эндоскопическом отделении Национального научного онкологического центра (Астана, Казахстан) проведен 81 сеанс бужирования дистальными колпачками 55 пациентам со стенозом пищевода.*

Результаты: *Основной причиной стеноза пищевода послужили химические ожоги (60% пациентов), стеноз после лучевой терапии (25,4%) и стриктуры пищеводного анастомоза (14,6%). У 37 пациентов (67,2%) стенозы были короткими – до 3,0 см, у 15 паци-*

ентов (27,2%) установлены протяженные стенозы, у 2 (3,6%) – субтотальный стеноз длиной до 15 см, и у одного пациента (1,8%) стеноз составлял 17 см. Хорошие результаты бужирования зафиксированы у всех пациентов с короткими стенозами, удовлетворительные – у пациентов со стенозами до 9 см, неудовлетворительные – у пациентов с субтотальными и тотальными стенозами. Количество сеансов – от 3 до 11. Трем пациентам с тотальным и субтотальным стенозом было отказано в бужировании из-за наличия извитого хода стеноза с высоким риском перфорации, и была установлена перкутанная гастростома.

Заключение: *Эндоскопическое бужирование дистальными колпачками Bougie Cap является безопасным методом бужирования доброкачественных стриктур пищевода, поскольку колпачок прозрачный, а бужирование проводится под визуальным наблюдением эндоскописта. За трехлетний период использования дистальных колпачков для расширения стеноза пищевода в нашем отделении не было зарегистрировано ни одного случая перфорации, поэтому мы рекомендуем этот метод как самый безопасный и предсказуемый метод бужирования как в амбулаторной практике, так и в стационарах республики.*

Ключевые слова: *стеноз, стриктура, бужирование, дилатация пищевода.*

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ROLE OF MicroRNAs 223, 155, AND 17~92 IN THE REGULATION OF MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS) IN THE PATHOGENESIS OF OBESITY-ASSOCIATED BREAST CANCER

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ABSTRACT

Relevance: *Breast cancer (BC) is a pressing global health dilemma due to its high prevalence worldwide. According to the World Health Organization (WHO), more than 2.3 million cases of BC occur each year, and BC is the first leading cause of female cancer deaths globally. Evidence indicates that obesity increases the risk of developing BC, and myeloid-derived suppressor cells (MDSCs) play a significant role in the pathogenesis of both BC and obesity. The primary function of MDSCs is tissue repair and wound healing, which helps prevent uncontrolled inflammation and maintain homeostasis as part of the immune response. However, MDSCs can be reprogrammed by pathological processes due to longterm tissue damage caused by chronic inflammation and cancer, leading to their prolonged expansion and enhanced immunosuppressive activity. The pathological process of obesity-associated and MDSC-associated BC progression remains poorly understood at the molecular level. There is considerable interest in studying microRNAs due to their regulatory roles in various biological processes in different cell types. Recent studies have begun to unravel the crosstalk between microRNAs and MDSCs in cancer.*

The study aimed to *provide summarized data to reveal the mechanisms by which microRNAs influence the activity of MDSC and the course of obesity-associated BC.*

Methods: *We conducted a comprehensive literature search on the web and in Medline (PubMed) u Google Scholar databases until June 7, 2024, in the areas «breast cancer» and/or «obesity» and/or «MDSC» and/or «microRNA.» Based on the literature analysis, microRNA-223, -155, and -1792 were selected as the most significant objects.*

Results: *This review presents data on the expression dynamics of major signal microRNAs (microRNA-223, -155, and -17~92), focusing on their roles in the pathogenesis of BC, obesity, and MDSC regulation; we also summarized and discussed the regulation of MDSCs in the obesity-associated BC by microRNA-223, -155, and -17~92.*

Conclusion: *Based on the literature data analysis, miR-223, -155, and -17~92 may be promising diagnostic and therapeutic cancer biomarkers, including BC, associated with pathological metabolic disorders and impaired functional activity of MDSC.*

Keywords: *microRNA, breast cancer, obesity, myeloid-derived suppressor cells (MDSC).*

Introduction: Breast cancer (BC) is a pressing global health dilemma due to its high prevalence worldwide. Breast cancer ranks first in the world in terms of incidence in women, affecting women of any age after puberty, and the incidence rate increases with age. For example, during post-menopause, BC is the first leading cause of female cancer deaths globally, accounting for 23% of all cancer deaths [1]. It is also important to note that 0.5–1% of all breast cancer cases occur in male patients [2]. In addition, data obtained to date indicate that there is a risk of developing breast cancer in people diagnosed with obesity [3]. According to the World Health Organization, 2.3 million women were diagnosed with BC in 2022, with more than 670,000 deaths worldwide [2]. According to the Ministry of Health of the Republic of Kazakhstan (MoH RK), in Kazakhstan, breast cancer is diagnosed annually in an average of 5,000 patients and up to 1,200 deaths [4]. At the same time, according to statistics from the Ministry of Health of the Republic of Kazakhstan, at the beginning of 2024, more than 16 thousand people (10,392 women; 5,841 men) with a confirmed diagnosis of obesity were registered at the dispensary [5].

Breast cancer is a complex disease characterized by a high degree of heterogeneity. Its classification is based on its histological stratification, mainly depending on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (ERBB2/HER2) [6]. The pathogenesis of obesity and breast cancer involves common factors: insulin-like growth factor-I, sex hormones, and cytokines produced by adipocytes.

These factors are related to the endo- and paracrine dysregulation of adipose tissue observed in obesity. Moreover, when neoplastic cells penetrate stromal compartments rich in adipose tissue, adipocytes function as endocrine cells, forming a tolerogenic tumor microenvironment that promotes tumor development and progression. The adipocyte activity is associated with the risk of developing cancer and the percentage of deaths from it in obese people [3].

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of immature myeloid cells with an impaired ability to differentiate into monocytes, macrophages, granulocytes, and dendritic cells. MDSC are defined by the phenotype CD11b+Gr1+ and Lin-HLA-DR-CD33+ in mice and CD11b+CD14+CD33+ in humans. The primary function of MDSC is to prevent uncontrolled inflammation and maintain immune homeostasis [7]. However, MDSC reprogramming occurs through pathological processes such as long-term tissue damage caused by chronic inflammation, cancer, extensive tissue damage, or chronic infections, leading to long-term expansion and enhanced immunosuppressive function of MDSCs. Obesity induces chronic inflammation through cytokines, chemokines, and adipokines, stimulating the immunosuppressive activity of MDSCs. In addition, some of these soluble mediators contribute to the progression of malignancies [8]. In addition, MDSC is also associated with a poor prognosis of BC. The proportion of MDSC in the peripheral blood of patients with breast cancer is significantly higher compared to healthy people, and the level of MDSC positively correlates with the proportion of metastases [9].

Despite the available data, the molecular mechanisms of MDSC regulation in the pathological process of obesity-related breast cancer remain poorly understood. In this regard, there is currently significant interest in studying microRNAs due to their regulatory function in various biological processes occurring in multiple types of cells. More than 2,500 microRNAs have been identified in humans, which act as critical mediators of transcriptional and post-transcriptional gene regulation, thereby maintaining cellular balance and functional activity of cells. Over the past two decades, miRNAs have been involved in the pathogenesis of several human diseases, including breast cancer and obesity [10].

The study aimed to provide summarized data to reveal the mechanisms by which microRNAs influence the activity of MDSC and the course of obesity-associated BC.

Materials and Methods: We analyzed scientific papers in the Medline (PubMed) and Google Scholar databases to search for research results on the role of microRNAs in regulating MDSC and the pathogenesis of obesity-related breast cancer. The search terms used were "breast cancer," "obesity," "MDSC," and "microRNA." We analyzed data sources in databases – 186; other sources - 3. As a result of an analysis of the literature in three main areas, the most significant research objects were selected - microRNA-223, -155, and -17~92; data from studies on microRNA data were included in the review (n = 88). After excluding sources with duplicate data and checking the quality of studies, the evaluation included 47 sources from databases and three sources containing statistical data on the prevalence of diseases. Search is limited to June 7, 2024.

Results:

Characteristics of microRNA

MicroRNAs are characterized as small, non-coding RNA molecules that regulate gene expression by inhibiting protein translation and promoting the breakdown of messenger RNA (mRNA). Since their discovery, miRNAs have been characterized in large numbers, and advances have been made in understanding their functions and applications in research and clinical practice [10].

The biogenesis of microRNAs is generally considered a multistage process that begins in the nucleus and ends in the cytoplasm. The first stage is characterized by the transcription of microRNAs predominantly by RNA polymerase II, mapping, splicing, and polyadenylation. The result of these processes is the formation of primary microRNA molecules (pri-microRNA), characterized by one or more hairpin structures [11]. Pri-miRNA is then processed in the nucleus by RNase and its cofactor DGCR8 into microRNA precursors - pre-miRNAs, consisting of 70-100 nucleotides, which are then transported into the cytoplasm using exportin-5 through nuclear pores [12]. In the cytoplasm, RNase converts pre-microRNA into a double-stranded RNA duplex consisting of a microRNA strand and its complementary sequence. Helicase enzymes unwind this duplex into a single-stranded mature miRNA, which is then incorporated into the RNA-inducible silencing complex (RISC) containing the Ago-2 protein [13]. This inclusion directs the RISC complex to the 3' untranslated region (3'UTR) of the target mRNA, resulting in cleavage of the mRNA in the case of high sequence homology or inhibition of translation, the latter mechanism more common in mammals. Subsequently, mature miRNAs play a crucial role in post-transcriptional gene silencing by binding to RISC and partially complementary sequence motifs in target mRNAs, predominantly located in the 3'UTR region [14].

Since a single miRNA can target several hundred mRNAs, dysregulation of miRNA expression can affect multiple transcripts and significantly impact signaling pathways associated with various pathological processes. The complex incorporation of miRNAs into cellular regulatory networks may represent an Achilles' heel, where dysregulation of a small subset of miRNAs can significantly alter gene expression patterns and potentially lead to cell transformation [15].

Usually, microRNAs act as important feedback components, ensuring the stability of essential biological processes through their buffering effect. By modulating

protein synthesis, microRNAs increase the accuracy of gene expression, ensuring the maintenance of proteins at a physiologically optimal level [15].

Although many aspects of miRNA function are not fully understood, miRNAs play critical roles in biological processes, including stem cell division, cell proliferation, cell cycle progression, apoptosis, differentiation, and metabolism. These functions are also involved in cancer pathogenesis, making miRNAs promising targets for therapy [15].

MicroRNA-223

One of the essential signaling microRNAs is microRNA-223, first discovered in 2003 using quantitative polymerase chain reaction [16]. This microRNA is located in the q12 locus of the X chromosome, is highly conserved, and is believed to play a potential role in significant physiological changes in the body [17]. The miR-223 has been shown to act as an oncogene in several cancers, including T-cell acute lymphoblastic leukemia, leukemia, breast, gastric, liver, and prostate cancers. Still, it is a tumor suppressor in acute myeloid leukemia and cervical and small-cell cancers. Lung cancer [18-21]. MicroRNA-223 plays a vital role in processes such as proliferation and invasion of cancer cells [17]. Proliferation and invasion of breast cancer cells are enhanced after the transfer of miR-223 into cells [22]. Another study showed that ectopic expression of miR-223 can inhibit the invasion, migration, growth, and proliferation of breast cancer cells [23]. In 2021, T. Du et al. found that the transcription level of miR-223 was significantly higher in breast cancer cells than in normal breast cells. In addition, they found that transfection of miR-223 inhibitor into cells significantly suppressed miR-223 expression. When miR-223 was inhibited, the carcinogenic activity of tumor cells was markedly reduced while the apoptosis rate increased. The miR-223 may be essential in breast cancer cell proliferation, metastasis, and invasion [17].

In addition to its role in carcinogenesis, miR-223 is a crucial regulator of MDSC maturation/differentiation and their functional activity [24]. It has been shown that miR-223 is predominantly expressed in hematopoietic tissues, and its expression is also bone marrow-specific. In contrast, the expression of miR-223 in bone marrow cells is limited to myeloid cell lines. MicroRNA-223 was subsequently found to be an essential modulator of myeloid differentiation in humans. In a model of granulocyte differentiation, it was shown that overexpression of miR-223 increases the number of cells transitioning to a granulocyte-specific cell lineage.

In contrast, the knockdown of miR-223 has the opposite effect. Further analysis of miR-223 expression revealed an exciting regulatory loop involving two known regulatory proteins, CCAAT enhancer binding protein (C/EBP) and nuclear factor I A (NFI-A). Notably, these two transcription factors compete for binding to the miR-223 promoter. In this case, the NFI-A factor ensures weak expression of microRNA-223 before the differentiation process begins. During differentiation, the transcription factor C/EBP, which induces higher expression of microRNA-223, replaces the transcription factor and suppresses the post-transcriptional expression of NFI-A. The microRNA-223 enters an autoregulatory feedback loop, controlling its expression and enhancing granulocyte differentiation [25].

The role of miR-223 in obesity as a regulator of developing myeloid cells into macrophages in adipose tissue is limited. The microRNA-223 regulates the polarization of adipose tissue-resident macrophages by targeting the transcription factor Pknox1, which, in turn, leads to the suppression of nuclear factor kappa B (NF-κB) and N-terminal kinase c- Jun (JNK) and stimulates the response of adipocytes to insulin stimulation [26, 27]. Increased expression of miR-223 in subcutaneous adipose tissue in obesity has also been reported. Moreover, miR-223 expression has been shown to increase in obesity not only in subcutaneous adipose tissue but also in white adipose tissue in obesity [28].

We can conclude that miR-223 plays an essential role in the pathogenesis of breast cancer and obesity and the functional activity of MDSCs. This demonstrates the importance of clinical studies of this miRNA in regulating cellular functions and metabolism.

MicroRNA-155

MicroRNA-155 is processed from the primary transcript of the B-cell integration cluster (BIC) located on chromosome 21. It was first identified as a promoter of inflammation and activation of expressed oncogenic microRNAs in many human cancers. MicroRNA-155 is predominantly expressed in the thymus and spleen and is an essential biomarker for various diseases. T.C. Ivkovic et al. found that miR-155 overexpression regulates several cancer-related pathways involved in uncontrolled cell growth, invasion, migration, stemness, and angiogenesis [29]. MicroRNA-155 has also been shown to be one of the critical regulators of inflammation and immune response. A study by Li L. and colleagues showed that microRNA-155 is actively involved in the expansion of MDSC in both granulocyte subpopulations and monocytes. They found that high levels of microRNA-155 expression characterized bone marrow MDSCs and spleen MDSCs from tumor-inoculated mice. The effect of miR-155 on MDSCs is associated with STAT3 activation. Moreover, miR-155 deficiency in macrophages and MDSCs has been shown to promote tumor growth by enhancing the immunosuppressive functions of these cells [30].

The miR-155 was first identified as an oncogenic miRNA. The role of this miRNA in carcinogenesis and disease progression has been demonstrated in various hematological malignancies and solid tumors. For example, increased expression of microRNA-155 is characteristic of breast cancer, oral cavity, liver, lung, pancreas, and prostate cancers [31-36]. However, there is some evidence

that expression of miR-155 by cancer cells is associated with improved overall survival in patients with several types of cancer, including breast cancer, colorectal cancer, and melanomas [37–39]. Thus, conducting a retrospective analysis, J. Wang et al. showed a correlation between increased levels of microRNA-155 expression and favorable antitumor immune infiltration and prognosis of patients with breast cancer. There are conflicting reports regarding the role of miR-155 in the development and progression of breast cancer. For example, it has been demonstrated that the expression level of miR-155 in breast cancer is associated with high-grade, advanced-stage metastasis and invasion [40]. However, in a large case series of triple-negative breast cancer (TNBC), it was found that high expression of miR-155 was associated with the homologous recombination repair process by influencing the RAD51 recombinase, and, as a consequence, was associated with better overall survival of patients [37].

In addition to being identified as an oncogenic miRNA and a regulator of the immune response, miR-155 regulates the development and maintenance of obesity through its effects on adipogenic and inflammatory processes. First, miR-155 has been demonstrated to alter adipocyte differentiation toward white rather than brown adipose tissue [41]. Secondly, miR-155 has been shown to target RNAs that control lipolysis, the dysregulation of which may affect the energy storage process in adipocytes [42]. The miR-155 plays an essential role in adipose tissue accumulation by stimulating pro-inflammatory factors. E. Karkeni et al. demonstrated that overexpression of miR-155 in adipocytes leads to increased secretion of various chemokines that promote the recruitment of leukocytes into adipose tissue and the development of inflammation [43]. The effects of microRNA-155 listed above aggravate the course of obesity.

MiR-155 is a multifunctional miRNA involved in carcinogenesis, immune response, and metabolic processes associated with obesity.

MicroRNA 17~92

In 2004, a new gene called chromosome 13 open reading frame 25 (C13orf25) was discovered in cells from 70 lymphoma patients. This gene contains an 800-nucleotide transcript of the miR-17~92 cluster, encoding six microRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1. The miR-17~92 cluster and its two paralogues encode a total of 15 different miRNAs, conventionally divided based on primer sequence similarity into four families: the miR-17 family, the miR-18 family, the miR-19 family, and the miR-92 family. The miR-17 family includes 6 miRNAs: miR-17-5p, miR-20a-5p, miR-20b-5p, miR-93-5p, miR-106a-5p and miR-106b-5p based on the AAAGUG nucleotide sequence. The miRNA-18 family includes 2 microRNAs with the nucleotide sequence AAGGUG. MicroRNA-19a-3p and microRNA-19b-3p are members of the miRNA-19 family with the nucleotide sequence GUGCAA. The miR-92 family consists of three miRNAs: miR-92a-3p, miR-25-3p, and miR-363-3p, with the nucleotide sequence AUUGCA [44].

It has been previously demonstrated that miRNA-17-5p and miRNA-20a regulate the suppressive potential of MDSCs by regulating STAT3 expression. Moreover, transfection with miRNA-17-5p or miRNA-20a significantly reduces the production of reactive oxygen species (ROS) and H2O2, which STAT3 regulates. A decrease in the expression of these miRNAs under the influence of tumor-associated factors and suppression of antigen-specific CD4+ and CD8+ T-cell response as a result of ectopic expression of miRNA-17-5p or miRNA-20a in MDSCs were also shown [45]. In addition to regulating the immune response, the miRNA-17~92 cluster plays a significant role in oncogenic processes. Amplification of the genomic locus miRNA-17~92 is observed in malignant neoplasms of the hematopoiesis: breast cancer, lung cancer, colon cancer, prostate cancer, pancreas cancer, thyroid cancer, bladder cancer, stomach cancer, liver cancer, and lymphoma [44, 46]. Members of the miRNA-17~92 cluster with different maturation levels play various roles in cancer pathogenesis [44]. High levels of expression of mature miRNA-20a are characteristic of leukemia and breast cancer cells. Moreover, increased expression of miRNA-17~92 is observed in TNBC, while decreased expression of this cluster is described in estrogen receptor-positive breast cancer (ERBC) [47]. It was also shown that ectopic expression of miRNA-17~92 suppresses cell proliferation in ERBC while it promotes tumor cell growth and invasion in TNBC [44].

Few studies describe the role of the microRNA-17~92 cluster in the pathogenesis of obesity. To date, limited data have been obtained on the role of microRNA-18a in the development of fatty tissue. However, miR-18a has been shown to play a significant role in the polarization of macrophages toward the pro-inflammatory M1 lineage in adipose tissue. Overexpression of this miRNA in obesity may promote increased production of pro-inflammatory cytokines (e.g., interleukins 1β and 6) and exacerbate adipose tissue dysfunction despite adequate estrogen levels. Interestingly, microRNA-18a also affects the regulation of ER1 expression in tumor cells [48]. It was also previously shown that high levels of expression of this microRNA are associated with increased proliferation and worse prognosis in ERBC. A significant correlation between ER1 mRNA levels and miR-18a concentrations in subcutaneous adipose tissue was found only in premenopausal women, suggesting that miRNAs may partially mediate menopause-associated changes in adipose tissue [49]. The microRNA-17~92 cluster plays a multifaceted role in immune regulation, tumorigenesis, and possibly metabolic processes.

Discussion: Inflammation associated with obesity is known to contribute not only to the initiation but also to the progression and angiogenesis of breast cancer. The

inflammatory process that occurs due to current or progressive obesity leads to disturbances in cellular metabolism and hormonal metabolism. All these processes are widely regulated by the action of microRNAs, which may represent potential biomarkers influencing the pathogenesis of breast cancer [3]. In breast cancer, there is also an abnormality in the expression profiles of microRNAs that are involved in disease progression. In breast cancer, tumor and tumor-infiltrating cells secrete abundant amounts of microRNAs through the extracellular transport of vesicles, which act as messengers between cells in the tumor microenvironment and other organs and tissues [17]. However, a complete picture of the influence of these microRNAs on the pathological process of obesity-associated breast cancer is still missing.

We summarized the available literature data on the role of miR-223, -155, and the miR-17~92 cluster in the pathogenesis of breast cancer and obesity. These microRNAs regulate a wide range of biological processes in various cell types. They are involved in oncogenesis and progression of multiple types of cancer, including breast cancer. In particular, miR-155 and miR-223 regulate multiple processes in cancer cells, such as proliferation, invasion, stemness, and angiogenesis [17-23, 31-40]. The expression level of these miRNAs may be associated with various characteristics of cancer, such as the grade of malignancy and the presence of metastases. The microRNA-17~92 cluster also plays a vital role in cancer pathogenesis. Multiple members of this cluster, including microRNA-18a, influence pro-inflammatory processes and the regulation of gene expression in cancer cells. The expression of miR-17~92 may have different effects depending on the cancer type, highlighting the importance of studying the specific mechanisms of action of miRNAs in other tumor types [44–47]. In addition, there is evidence that microRNA-223, -155, and the microRNA-17~92 cluster also affect the development of adipose tissue and are involved in the aggravation of obesity-induced inflammation [28, 43, 48].

MicroRNAs secreted in adipose tissue influence the development and progression of obesity-induced breast cancer and may also influence MDSC activity. The role of MDSCs in the development of obesity-mediated breast cancer has previously been demonstrated [50]. Obesity, the number of MDSCs, and their immunosuppressive activity significantly increase, which, in turn, contributes to the progression of cancer [50]. MicroRNAs-223, -155, and -17~92 are involved in the expansion of the MDSC pool, and an increase in their functional activity is a crucial regulator of MDSC maturation/differentiation [24, 30, 45].

We assume that miR-223, -155, and -17~92 can be classified not only as new candidates for the role of diagnostic and prognostic indicators but also as potential therapeutic targets in new treatment strategies, especially for clinically aggressive breast cancer associated with obesity. Modulating the expression of microRNA-223, -155, and -17~92 by inhibiting their transcription or a direct blockade can be a promising method for treating and preventing breast cancer combined with obesity.

Conclusion: This review summarizes data indicating that miR-223, -155, and -1792 may be promising targets for developing new approaches to treating and preventing breast cancer associated with obesity. Further studies of microRNAs in the pathogenesis of breast cancer associated with pathological metabolic disorders and regulation of the functional activity of immune suppressor cells are necessary. Understanding the role of signaling microRNAs in tumorigenesis and other pathological processes may open new perspectives for personalized medicine and the development of innovative therapeutic strategies.

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АҢДАТПА

СЕМІЗДІКПЕН БАЙЛАНЫСТЫ СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ПАТОГЕНЕЗІНДЕГІ МИЕЛОИДТЫ СУПРЕССОРЛЫҚ ЖАСУШАЛАРДЫҢ (MDSC) БЕЛСЕНДІЛІГІН РЕТТЕУДЕГІ 223, 155 ЖӘНЕ 17~92 МИКРОРНҚ-ЛАРДЫҢ РӨЛІ

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Өзектілігі: *Сүт безінің қатерлі ісігі (СБІ) бүкіл әлемде таралуының жоғары болуына байланысты өзекті жаһандық денсаулық мәселесі болып табылады. Дүниежүзілік денсаулық сақтау ұйымының (ДДСҰ) мәліметтері бойынша, жыл сайын 2,3 миллионнан астам адамнан СБІ анықталады, сондай-ақ бүкіл әлемде әйелдердің қатерлі ісік ауруымен өлімінің басты себепшісі болып табылады. Семіздік сүт безі қатерлі ісігінің даму қаупін арттыратыны белгілі және миелоидты супрессорлық жасушалар (MDSC) сүт безі қатерлі ісігінің де, семіздіктің де патогенезінде маңызды рөл атқарады. MDSC-тің негізгі функциясы тіндерді қалпына келтіру және жараларды емдеу болып табылады, ол бақыланбайтын қабынудың алдын алуға және иммундық гомеостазды сақтауға көмектеседі. Дегенмен, созылмалы қабынудың ұзаруы MDSC-дің кеңеюіне және иммуносупрессиялық белсенділігінің жоғарылауына әкеледі. Семіздік кезіндегі сүт безі қатерлі ісігінің дамуының патологиялық процесі және осы процесте индукцияланған MDSC рөлі молекулалық деңгейде әлі де аз зерттелген. Соңғы жылдары дүниежүзілік ғылыми қоғамдастықта микроРНҚ-ны зерттеуге олардың әртүрлі жасуша типтерінің әртүрлі биологиялық процестеріндегі реттеуші рөліне байланысты үлкен қызығушылық пайда болды. Соңғы онжылдықта жүргізілген зерттеулер онкологиялық аурулардағы микроРНҚ және MDSC арасында өзара байланыстың болуын көрсетті.*

Зерттеудің мақсаты *– семіздікпен байланысты сүт безі қатерлі ісігінің даумуына және MDSC белсенділігіне микроРНҚ әсер ету механизмдерін ашу үшін мәліметтерді жинақтау.*

Әдістері: *Бұл жұмыс бойынша 2024 жылдың 7 маусымына дейінгі интернетте, Medline (PubMed) және Google Scholar дерекқорларындағы мәліметтерден «сүт безі ісігі» және/немесе «семіздік» және/немесе «MDSC» және/немесе «микроРНҚ» салаларындағы әдебиеттерге жан-жақтылы іздеу жүргіздік. Әдебиеттерді талдау нәтижесінде ең маңызды нысандар ретінде микроРНҚ-223, -155 және -17~92 таңдалды.*

Нәтижелері: *Шолуда негізгі сигналдық микроРНҚ-лардың (микроРНҚ-223, -155 және -17~92) экспрессиясының динамикасы, сондай-ақ олардың сүт безі қатерлі ісігінің, семіздіктің патогенезіндегі және MDSC белсенділігін реттеудегі рөлі туралы қазіргі уақытта қолда бар деректер ұсынылды. Сондай-ақ, микроРНҚ деректері арқылы семіздікпен байланысты сүт безі ісігі кезінде MDSC жасушасының екі бағытты реттелуі бойнша мәліметтер қортыланды.*

Қорытынды: *Әдебиет деректерін талдау нәтижелері бойынша микроРНҚ -223, -155 және -17~92 патологиялық метаболикалық бұзылулармен және MDSC функционалдық белсенділігінің бұзылуымен байланысты қатерлі ісіктің оның ішінде сүт безі ісігінің перспективалы диагностикалық және емдік биомаркерлері болуы мүмкін.*

Түйінді сөздер: *микроРНҚ, сүт безі қатерлі ісігі, семіздік, миелоидты супрессорлық жасушалар.*

ABSTRACT

РОЛЬ МИКРОРНК 223, 155 И 17~92 В РЕГУЛЯЦИИ АКТИВНОСТИ МИЕЛОИДНЫХ СУПРЕССОРНЫХ КЛЕТОК (MDSC) В ПАТОГЕНЕЗЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ, СВЯЗАННОМ С ОЖИРЕНИЕМ

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Актуальность: *Рак молочной железы (РМЖ) является глобальной проблемой здравоохранения из-за его высокой распространенности во всем мире. По данным Всемирной организации здравоохранения, ежегодно регистрируется более 2,3 миллиона случаев РМЖ, который является главной причиной смертности женщин от рака во всем мире. Известно, что ожирение увеличивает риск развития РМЖ, а миелоидные супрессорные клетки (MDSC) играют значительную роль в патогенезе как РМЖ, так и ожирения. Основная функция MDSC – восстановление тканей и заживление ран, что помогает предотвратить неконтролируемое воспаление и поддерживать иммунный гомеостаз. Однако хроническое воспаление и рост неопластических клеток приводят к длительной экспансии и усилению иммуносупрессорной активности MDSC. Патологический процесс прогрессии РМЖ при ожирении и роль индуцированных MDSC на молекулярном уровне в этом процессе остается малоизученными. В последние*

годы в мировом научном сообществе существует значительный интерес к изучению микроРНК в связи с их регуляторной ролью в различных биологических процессах различных типов клеток. Исследования, проведенные за последнюю декаду, показали наличие взаимодействия между микроРНК и MDSC при онкологических заболеваниях.

***Цель исследования** – обобщение имеющихся данных для раскрытия механизмов влияния микроРНК на активность MDSC и на течение РМЖ, связанного с ожирением.*

***Методы:** Проведен комплексный поиск литературы в интернете и в базах данных Medline (PubMed) и Google Scholar до 7 июня 2024 г. по направлениям «рак молочной железы» и/или «ожирение» и/или «MDSC» и/или «микроРНК». По результатам анализа были выбраны наиболее значимые объекты исследования – микроРНК-223, -155 и -17~92.*

***Результаты:** В обзоре представлены имеющиеся на сегодняшний день данные о динамике экспрессии основных сигнальных микроРНК (микроРНК-223, -155 и -17~92) и их роли в патогенезе РМЖ, ожирении и регуляции активности MDSC, а также двунаправленной регуляции MDSC при РМЖ, связанном с ожирением, посредствам данных микроРНК.*

***Заключение:** Основываясь на результатах анализа литературных данных, микроРНК-223, -155 и -17~92 могут быть многообещающими диагностическими и терапевтическими биомаркерами онкологических заболеваний, в том числе и РМЖ, связанных с патологическими метаболическими нарушениями и нарушением функциональной активности MDSC.*

***Ключевые слова:** микроРНК, рак молочной железы, ожирение, миелоидные супрессорные клетки (MDSC).*

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SIMULTANEOUS SURGICAL MANAGEMENT OF HEART DISEASES AND KIDNEY CANCER: A CASE SERIES

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ABSTRACT

Relevance: *Renal cell carcinoma (RCC), the most common type of kidney cancer, poses a significant health burden worldwide. Despite advancements in diagnostic techniques and treatment modalities, RCC remains a formidable challenge due to its heterogeneous nature, varied clinical presentations, and complex molecular landscape. Understanding the intricacies of RCC is crucial for improving patient outcomes, optimizing therapeutic strategies, and advancing personalized medicine approaches.*

The study aimed to *investigate the feasibility and outcomes of simultaneous surgeries in patients with kidney cancers and heart diseases, aiming to address the current centralization of specialized care.*

Methods: *The authors evaluated and analyzed five cases of simultaneous surgeries performed at the National Scientific Medical Center (Astana, Kazakhstan) from January 2012 to December 2023. Each case provides unique insights into the diagnostic challenges, treatment dilemmas, and long-term outcomes associated with RCC.*

Results: *From January 2012 to December 2023, we evaluated and analyzed 5 cases of simultaneous surgeries at the National Scientific Medical Center, Astana. Each case offers unique insights into the diagnostic challenges, treatment dilemmas, and long-term outcomes associated with RCC.*

Conclusion: *Simultaneous surgeries for RCC and concomitant diseases represent a viable approach to optimize patient care and streamline treatment. These cases demonstrate the successful management of RCC alongside various comorbidities, highlighting the importance of multidisciplinary collaboration and careful surgical planning. By addressing multiple conditions in a single procedure, simultaneous surgeries offer a promising strategy to improve outcomes and enhance patient satisfaction in managing RCC.*

Keywords: *kidney, cancer, heart, ischemic, aortic valve, simultaneous surgery.*

Introduction: Kidney cancer ranks sixth among male cancers and accounts for 5% of all cancer cases. It is also the tenth most prevalent malignancy in women and the source of 3% of malignancies [1]. The lungs, liver, brain, bone, and adrenal glands are the organs most commonly afflicted, and it has a significant propensity to spread. Early detection of RCC is essential for patient treatment and decreasing death rates. Nevertheless, the best methods and techniques for screening have not yet been determined.

Selecting the most effective therapy strategy is essential to enhancing the prognosis of RCC patients [1]. There have been documented cases of late metastases from RCC in the literature, occurring even decades following the initial tumor's potentially curative surgical resection; around one in three RCC patients eventually develop distant metastases [2].

Localized Kidney cancer is potentially curable by surgery alone (i.e., stage I–III), though recurrence is seen in 3%–30% depending on the stage. It has been estimated that 4–10% of individuals undergoing nephrectomy to treat cancer have a direct extension of RCC into the inferior vena cava (IVC). Kidney cancer often coexists with other medical conditions, presenting challenges in treatment planning. Tumor thrombi can extend into the right atrium in 0.3–1% of patients with RCC [3].

The study aimed to investigate the feasibility and outcomes of simultaneous surgeries in patients with kidney cancers and heart diseases, aiming to address the current centralization of specialized care.

Moreover, by publishing this article, we want to emphasize the possibility of performing simultaneous surgery, which should be a part of the daily surgical plan in hospitals to benefit our patients.

Materials and Methods: The study was conducted at the National Scientific Medical Center in Astana, Kazakhstan, from January 2012 to July 2023. A total of 5 simultaneous surgeries were performed during this timeframe. The retrospective analysis involved thoroughly examining the patient's medical records to ascertain crucial data points, including the type of surgical procedure, operation duration, intraoperative complications, intensive care unit (ICU) stay, and postoperative recovery period. Survival analysis was conducted using the Kaplan-Meier method, with the date of surgical intervention as the starting point and the date of death or the last observation as the endpoint. This statistical approach facilitated the estimation of cumulative survival probabilities over the designated follow-up period.

Ethical approval for this retrospective study was obtained from the institutional review board of the National Scientific Medical Center, Astana, ensuring adherence to ethical standards and patient confidentiality protocols. Data analysis was conducted using appropriate statistical software, and descriptive statistics were employed to

summarize patient characteristics, surgical outcomes, and long-term survival probabilities.

Results: Simultaneous surgeries for kidney conditions and heart diseases resulted in successful outcomes across all five cases. Before the surgery, the radiologic diagnosis of kidney cancer was based on computed tomography of the abdominal segment with intravenous contrast. The date of hospitalization, date of surgery, type of simultaneous surgeries performed, duration of the operation, intraoperative complications, transfusions, and amount of bleeding are shown below in Table 1. Table 2 contains post-op data about ICU length of stay, any complications, histology results, and date of discharge. Each patient underwent complex procedures addressing RCC and accompanying medical conditions, with satisfactory postoperative courses and no significant complications.

Table 1 – Major case findings

Case no.	Date of hospitalization (1) and date of surgery (2)	Type of surgery	CPB or Off-pump	Duration of surgery (minutes)	Intraoperative complications	Blood transfusions	Intraoperative bleeding (mL)
1	1. 22.01.2012 2. 25.01.2012	1. CABG – 4 vessels, AVP with biological prosthesis 2. Laparoscopic radical right nephroureterectomy	CPB	470	Bleeding	During surgery: FFP – 1800 mL; RBC – 750 mL Day 1 post-op: ен67FFP – 1200 mL; RBC – 670 mL; Platelet – 250 mL; Cryoprecipitate – 40 mL.	1000
2	1. 15.01.2020 2. 21.01.2020	1. CABG – 3 vessels, 2. Laparoscopic radical left nephroureterectomy	CPB	330	No	FFP – 4 doses	250
3	1. 09.09.2020 2. 14.09.2020	1. CABG – 1 vessel 2. Open radical right nephroureterectomy	Off-pump	220	No	RBC – 2 doses	100
4	1. 08.02.2023 2. 20.02.2023	1. Suture annuloplasty of the tricuspid valve Right atrial myxomectomy 2. Laparoscopic radical right nephroureterectomy	CPB	310	No	Before surgery – 2 doses of RBC After surgery – 3 doses of RBC	30
5	1. 26.06.2023 2. 29.06.2023	1. CABG – 3 vessels 2. Laparoscopic left radical nephroureterectomy with resection of the left ureter orifice.	CPB	390	No	RBC – 1 dose	250

Notes: CBP – cardiopulmonary bypass; CABG – coronary artery bypass grafting; AVP – aortic valve prosthesis; FFP – fresh frozen plasma; RBC – red blood cells

Table 2 – Major post-op findings

Case no.	ICU stay (days)	Postoperative complications	Histology results	Date of discharge
1	3	No	Renal cell carcinoma	01.02.2012
2	4	No	Renal cell carcinoma	29.01.2020
3	4	No	Renal cell carcinoma	25.09.2020
4	3	No	Renal cell carcinoma	01.03.2023
5	5	Acute renal failure of mixed origin (prerenal, renal tubulointerstitial nephritis) stage 2 according to KDIGO (2012) Oliguria. Chronic pyelonephritis, latent course.	Carbuncle of the kidney. Purulent ureteritis, paranephritis.	10.07.2023

Case 1

A 61-year-old male with clinical stage I right kidney cancer and ischemic heart disease (IHD) undergoes coronary artery bypass grafting (CABG) and aortic valve replacement alongside laparoscopic right-sided radical nephrectomy. Despite the complexity of the procedure and aortic valve stenosis, the operation was completed successfully in 470 minutes. The intraoperative bleeding was successfully managed by transfusion of plasma and red blood cell components. The patient spent 3 days in the ICU and then discharged 7 days post-op, without any postoperative complications, highlighting the feasibility of addressing multiple conditions in a single surgery.

Case 2

A 70-year-old man with stage 1 left kidney cancer and severe coronary artery disease underwent simultaneous CABG and left-sided laparoscopic nephroureterectomy. The duration of the operation was 330 minutes, and despite the patient's elderly age, the postoperative course was uneventful, and the patient was discharged without issues, emphasizing the safety of concurrent interventions in elderly patients with comorbidities. Following histological examination, the patient was diagnosed with cancer of the left kidney pT1M0N0, StI, R0.

Case 3

A 68-year-old woman diagnosed with stage I right kidney cancer and coronary artery disease undergoes internal mammary artery bypass surgery and right-sided radical nephroureterectomy simultaneously. Due to utilizing the off-pump technique, the operation time was shortened to 220 minutes. However, due to a tumor >10 cm, the patient has proposed a laparotomy. The patient was discharged without any postoperative complications, underscoring the feasibility of simultaneous surgeries even in elderly female patients. The postoperative diagnosis was cancer of the right kidney pT2N0M0, St II.

Case 4

A 60-year-old man diagnosed with stage 3 right kidney carcinoma presents with a concomitant myxoma in the right atrium and tricuspid insufficiency grade 2. Simultaneous procedures include tricuspid valve annuloplasty, myomectomy, and laparoscopic radical nephroureterectomy. Due to preoperative anemia, the patient received 2 doses of RBC pre-op and 3 doses during the operation. The operation lasted 310 minutes, and he was discharged without postoperative complications, showcasing the safety and efficacy of combined surgeries. The postoperative diagnosis was cancer of the left kidney pT3aN0M0 StIII.

Case 5

A 67-year-old man was admitted to the hospital with suspected cancer of the left kidney and IHD. Simultaneous surgery was performed without complications. However, in the postoperative period, the patient developed acute renal failure of mixed origin (prerenal, tubulointerstitial renal nephritis) stage 2, according to KDIGO (2012). Oliguria. The patient had 4 hemodialysis sessions, and despite this, the patient was discharged in satisfactory condition. Histologic examination revealed a carbuncle of the left kidney. This case was included in the analysis since the patient was initially suspected of kidney cancer and managed for cancer.

Discussion: The simultaneous surgeries in this case series highlight the complexity of managing renal cell carcinoma (RCC) alongside concomitant diseases. These cases underscore the importance of a multidisciplinary approach to treatment and the need for careful preoperative evaluation and planning to ensure optimal outcomes for patients with RCC and comorbid conditions.

In one case series, the authors discuss the role of cytoreductive nephrectomy following immunotherapy-based treatment in metastatic RCC. While the focus of their study differs from ours, it emphasizes the evolving landscape of RCC management and the importance of considering various treatment modalities in different clinical scenarios [4]. Another study explores rare metastatic sites of RCC, further highlighting the diverse presentations and challenges encountered in managing advanced disease [5].

Furthermore, the cases presented in our series align with findings from previous literature regarding the epidemiology and risk factors associated with RCC. Paglino et al. [1] provide insights into RCC's epidemiology and molecular epidemiology, emphasizing the importance of understanding the underlying mechanisms driving tumor development and progression.

The management of patients with heart disease and renal cancer presents a dilemma for physicians. Namely, which one to treat first. Both conditions carry high risks for patients. Given the elderly age of the patients and many comorbidities, performing surgery in 2 stages may entail a high risk of complications and mortality. A simultaneous surgery can reduce risks since a patient can decide long for the next surgery, resulting in a worsening condition and disease progression. A simultaneous surgery allows for avoiding tumor progression in the interstage period by performing early radical intervention on neoplasms and reducing the hospital stay.

Simultaneous operations have several benefits: shorter hospital stay, a single postoperative recovery period, lower stress level, and time-saving for the patient because preoperative preparation will be required only once. However, simultaneous operations also carry risks and disadvantages that should be discussed with the patient: increased surgery duration, prolonged anesthesia time, higher risk of bleeding, and wound infection.

Consequently, there may be additional requirements for the patient's health. Another disadvantage includes the fact that the area of surgical intervention becomes bigger, which may lead to increased pain after surgery and subsequently require more analgesics. We will have to consider all these criteria while preparing for the operation.

Kazakhstan is a developing country with a large rural population. Early detection of both diseases is currently problematic. The case series by Setia and Kedan [6] showcases the utility of point-of-care ultrasound in detecting RCC in the ambulatory setting, highlighting the importance of early diagnosis and intervention. This aligns with the principle of early detection and timely treatment emphasized in our cases, as prompt recognition of RCC allows for timely surgical intervention and improved outcomes.

The case report by Filomena et al. [3] parallels one of the presented cases of simultaneous surgical management of RCC and severe coronary artery disease with atrial thrombotic extension. Their experience underscores the feasibility and safety of concurrently addressing multiple conditions, further supporting our case series findings.

This year, in another case series [7], simultaneous surgeries for coexisting cardiac and non-cardiac pathologies were evaluated in terms of the feasibility of treatment. The paper above included a wide variety of diseases, such as benign and malignant tumors of the abdomen and thorax with concomitant heart pathologies. Compared to the other paper, this article focuses on the safety of simultaneous surgery on the heart and kidney without any major complications.

Since cardiopulmonary bypass (CPB), used in heart operations, can cause acute kidney injury (AKI) in 18.2 to 30% of patients [8], one of the major challenges for surgeons and anesthesiologists is preventing and managing AKI as a possible complication. In this paper, one out of five reviewed patients developed postoperative AKI, which eventually required hemodialysis. Fortunately, the patient's kidney function recovered. A cardiac surgeon should always be aware of AKI when using CBP in surgery. In simultaneous surgery for the heart and kidney, the possibility of AKI should always be considered in preoperative assessment and preparation. Simultaneous surgeries require great preparation and a multimodal approach to ensure it is safe and beneficial for the patient.

The presented case series contributes to the growing literature on managing RCC with concomitant heart diseases. By highlighting the feasibility and outcomes of simultaneous surgeries in complex clinical scenarios, this study emphasizes the importance of tailored treatment approaches and collaborative care in optimizing outcomes

for patients with RCC and heart diseases. Further research and collaboration are warranted to refine treatment strategies and improve patient outcomes in this challenging patient population.

Conclusion: The presented cases demonstrate successful simultaneous interventions and favorable postoperative courses, proving the feasibility and safety of simultaneous surgeries for RCC and concomitant diseases. Despite complex procedures and multiple comorbidities, all patients had favorable postoperative outcomes, underscoring the importance of multidisciplinary collaboration and meticulous surgical planning in optimizing patient care for RCC and accompanying medical conditions.

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АҢДАТПА

ЖҮРЕК АУРУЛАРЫ МЕН БҮЙРЕК ҚАТЕРЛІ ІСІГІН БІР МЕЗГІЛДЕ ХИРУРГИЯЛЫҚ ЕМДЕУ: КЛИНИКАЛЫҚ ЖАҒДАЙЛАР СЕРИЯСЫ

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Өзектілігі: *Бүйрек қатерлі ісігінің ең көп таралған түрі болып табылатын бүйрек жасушалы карциномасы (БЖК) бүкіл әлемде денсаулыққа айтарлықтай ауыртпалық түсіреді. Диагностикалық әдістер мен емдеу әдістеріндегі жетістіктерге қарамастан, БЖК гетерогенді табиғатына, әртүрлі клиникалық көріністеріне және күрделі молекулалық ландшафтына байланысты күрделі мәселе болып қала береді. БЖК күрделілігін түсіну пациенттердің нәтижелерін жақсарту, терапевтік стратегияларды оңтайландыру және жекелендірілген медицина тәсілдерін ілгерілету үшін өте маңызды.*

Зерттеудің мақсаты *– бұл жағдайлық зерттеу мамандандырылған көмектің қазіргі орталықтандырылуын шешуге бағытталған бүйрек ісігі және жүрек аурулары бар науқастарға бір мезгілде хирургиялық араласудың мүмкіндігі мен нәтижелерін зерттейді.*

Әдістері: *2012 жылдың қаңтарынан 2023 жылдың желтоқсанына дейін біз Астана қаласында Ұлттық Ғылыми Медициналық Орталықта бір мезгілде жасалған оталардың 5 жағдайын бағалап, талдадық. Әрбір жағдай диагностикалық қиындықтарға, емдеу дилеммаларына және БЖК-мен байланысты ұзақ мерзімді нәтижелерге бірегей түсінік береді.*

Нәтижелері: *5 науқастың 1-інде операция кезінде, 1-інде операциядан кейінгі кезеңде асқынулар болған. Барлық науқастар қанағаттанарлық жағдайда шығарылды.*

Қорытынды: *БЖК және жүрек ауруларына бір мезгілде жасалатын операциялар пациенттерге күтім көрсетуді оңтайландыру және емдеуді жеңілдетудің тиімді әдісі болып табылады. Бұл жағдайлар пәнаралық ынтымақтастық пен мұқият хирургиялық жоспарлаудың маңыздылығымен қатар, әртүрлі ілеспелі аурулармен бірге БЖК-ның сәтті басқарылуын көрсетеді. Бір процедурада бірнеше жағдайды қарастыратын бір мезгілде жасалатын операциялар нәтижелерді жақсартудың және пациенттердің БЖК-ның еміне қанағаттануының перспективалы стратегиясы болып табылады.*

Түйінді сөздер: *бүйрек, қатерлі ісік, жүрек, жүрек ишемиясы, қолқа қақпақшасы, симультанды ота.*

АННОТАЦИЯ

ОДНОВРЕМЕННОЕ ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ ЗАБОЛЕВАНИЙ СЕРДЦА И РАКА ПОЧКИ: СЕРИЯ СЛУЧАЕВ

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Актуальность: *Почечно-клеточный рак (ПКР), наиболее распространенный тип рака почки, представляет серьезную угрозу для здоровья во всем мире. Несмотря на достижения в диагностических методах и методах лечения, ПКР остается серьезной проблемой из-за его гетерогенной природы, разнообразных клинических проявлений и сложного молекулярного ландшафта. Понимание тонкостей ПКР имеет решающее значение для улучшения результатов лечения пациентов, оптимизации терапевтических стратегий и продвижения подходов персонализированной медицины.*

Цель исследования: *в этом тематическом исследовании рассматриваются возможности и результаты одновременных операций у пациентов с раком почки и заболеваниями сердца, направленные на решение проблемы нынешней централизации специализированной помощи.*

Методы: *В период с января 2012 по декабрь 2023 года мы оценили и проанализировали 5 случаев одновременных операций в Национальном научном медицинском центре в Астане. Каждый случай дает уникальную информацию о диагностических трудностях, дилеммах лечения и отдаленных результатах, связанных с ПКР.*

Результаты: *Из 5 пациентов у 1 возникло интраоперационное осложнение и у 1 возникло осложнение в послеоперационном периоде. Все пациенты выписаны в удовлетворительном состоянии.*

Заключение: *Симультанные операции по поводу ПКР и заболеваний сердца представляют собой эффективный подход к оптимизации ухода за пациентами и рационализации лечения. Эти случаи демонстрируют успешное ведение ПКР наряду с различными сопутствующими заболеваниями, подчеркивая важность междисциплинарного сотрудничества и тщательного планирования операции. Одновременные операции, направленные на устранение нескольких состояний в рамках одной процедуры, являются многообещающей стратегией улучшения результатов и повышения удовлетворенности пациентов с ПКР.*

Ключевые слова: *рак, почки, сердце, ишемическая болезнь сердца, аортальный клапан, одномоментные операции.*

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THE RESULTS OF THE COMPLEX THERAPY OF HEMOBLASTOSES WITH COVID-19: SINGLE-CENTER EXPERIENCE AT THE CVI-1 DEPARTMENT OF THE NATIONAL RESEARCH ONCOLOGY CENTER (ASTANA, KAZAKHSTAN)

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ABSTRACT

Relevance: *The SARS-Cov2 pandemia caused an unparalleled health crisis that directly affected the course and treatment of patients with hemoblastosis. Hematologists faced an extraordinarily challenging situation due to the administered chemotherapy along with the treatment of the concomitant infectious pathology of coronavirus infection (CVI). However, there were no clear recommendations and approved protocols for diagnosis and treatment for this category of patients for the described period. Patients with hematological malignancies are generally more susceptible to infections due to immunosuppression caused by their disease and the deteriorating effect of treatment on the immune system.*

The study aimed to *investigate and analyze the impact of the SARS-Cov-2 viral infection on mortality from oncohematological diseases.*

Methods: *Data for the retrospective cohort study was obtained from patient electronic medical records. CVI was confirmed by a positive PCR test for SARS-Cov-2 RNA and chest computed tomography. All patients underwent a determination of the disease status at the time of admission to the department. Further, the therapy performed was estimated, and a descriptive analysis of the treatment results was carried out.*

Results: *From July 2020 to July 2021, 56 patients with hemoblastosis and hematopoietic depression with concomitant CVI were treated in the CVI-1 department of the National Research Oncology Center (Astana, Kazakhstan). During this period, 2 patients died, and the mortality rate was 3.6%, while at the specialized hematology department, the mortality rate in 2020 amounted to 2.9% (26 deaths per 904 patients).*

Conclusion: *Our department's results conclude that without systemic antitumor therapy for hemoblastosis and achieving remission, the treatment of infectious complications will be ineffective. SARS-CoV-2 infection during or after systemic anticancer therapy does not dramatically affect mortality from COVID-19.*

Keywords: *hemoblastosis, COVID-19, prognosis, oncohematology, mortality, myeloma, leukemia.*

Introduction: The COVID-19 pandemia caused an unparalleled health crisis that directly affected the course and treatment of patients with hemoblastosis. Hematologists faced an extraordinarily challenging situation due to the administered chemotherapy along with the treatment of concomitant infectious pathology of coronavirus infection (CVI). However, there were no clear recommendations and approved protocols for diagnosis and treatment for this category of patients for the described period [1-4].

Patients with hematological malignancies are more susceptible to the virus [5-6] due to the secondary immunodeficiency that appears against the disease and the deteriorating effect of treatment. These patients have a more aggressive course of viral infection [7-9].

According to international experience, patients with COVID-19 were transferred to a hospital for infectious disorders, with chemotherapy being suspended for an indefinite period, which resulted in a detrimental impact on the prognosis [10-11]. Given the spread of CVI in the Republic of Kazakhstan, also among patients with hemoblastoses, the management of the National Research Oncology Center (NROC, Astana, Kazakhstan) proposed to the Ministry of Health of the Republic of Kazakhstan to open a specialized department at NROC for patients with oncohematological diseases and concomitant COVID-19. In July 2020 in Astana, the only infectious disease department in the Republic of Kazakhstan was deployed to receive oncohematological patients with CVI who needed treatment for the underlying disease and concomitant infectious pathology by a multidisciplinary group of hematologists, infectious disease specialists, and resuscitators. In this study, the impact of the COVID-19 virus on the course and prognosis of oncohematological diseases was analyzed by simultaneously prescribing chemotherapy and treating the infectious pathology of COVID-19.

The study aimed to investigate and analyze the impact of the SARS-Cov-2 viral infection on mortality from oncohematological diseases.

Materials and Methods: Patient data were taken from their electronic medical records and analyzed retrospectively. The NROC Local Ethics Committee approved the

study (Minutes No. 18 of 01/25/2023). The study included patients of both sexes over 18 years of age with confirmed oncohematological diseases and concomitant coronavirus infection. Concomitant CVI was confirmed by a positive PCR test for detecting SARS-Cov-2 RNA and chest computed tomography. All patients included in the study were assessed for their disease status at admission to the department (debut/remission/relapse). Descriptive statistics were used to summarize the patient demographic and clinical characteristics. Percentages were calculated; the number and percentage of patients in each category demonstrated the distribution of categorical variables such as gender, diagnosis, and disease status.

Results: For the period from July 2020 to July 2021, 56 patients with hemoblastosis and hematopoietic depression with concomitant CVI were treated in the CVI-1 department of NROC. The patients were aged 18 to 66 years when contracting CVI. The distribution by gender was even: 27 women vs 29 men.

Among 56 patients, there were 9 patients with multiple myeloma (MM), 9 patients with acute lymphoblastic leukemia (ALL), 2 with myelodysplastic syndrome (MDS), 28 with acute myeloid leukemia (AML), 3 with chronic myeloid leukemia (CML), 2 with Hodgkin's lymphoma (HL), 3 with diffuse large B-cell lymphoma (DLBCL). There were 14 patients with "Debut" hemoblastosis (ALL-1; AML-10; MDS-1, DLBCL-1, CML-1); all patients with AML and ALL underwent induction courses of chemotherapy. Regarding the disease status, 14 patients had the onset of hemoblastosis, 35 patients had remission status, and 7 patients had a progression or relapse. In general, responses to the therapy for hemoblastosis were achieved regardless of an infectious pathology and were comparable to patients treated without COVID-19. Complications were similar to post-chemotherapy cycle complications in patients without concomitant CVI and included oral mucositis, febrile neutropenia, probable invasive pulmonary aspergillosis, and bilateral hydrothorax.

Patients were treated for the underlying disease and therapy for concomitant infectious pathology. For CVI therapy, patients received glucocorticoid therapy with dexamethasone, anticoagulant therapy with Enoxaparin sodium or heparin, and oxygen therapy [12].

To assess the impact of COVID-19 on hospital mortality, we compared the mortality rates at the CVI department and our Center's specialized Hematology Department in 2020 (Table 1). This comparison suggests that COVID-19 did not significantly affect hospital mortality among patients with oncohematological diseases treated in the CVI department. However, further investigation with larger patient cohorts and consideration of additional factors like disease stage and specific diagnoses is required to support these findings.

Table 1 – Mortality rates among oncohematological patients at NROC (July 2020 – July 2021)

Department	Sample Size	Mortality Rate
CVI Department (SARS-Cov-2 positive)	56	3.6%
Specialized Hematology Department	904	2.9%

A chi-square test to compare mortality rates between the departments yielded a chi-square value of 0.0865 (df=1, $p<0.05$), indicating no statistically significant difference between the mortality rates in the two departments. Therefore, SARS-CoV-2 infection during or after systemic anticancer therapy does not dramatically affect mortality from COVID-19 in patients with oncohematological diseases.

Discussion: The study shows that patients with blood cancers had a higher mortality rate from coronavirus infection. This prompted the oncology communities in different countries to recommend changing the treatment regimens for cancer patients and, if possible, reducing the risk of infection in hospitals or postponing treatment.

It was evidenced in the study conducted by researchers from the Specialized Oncology Center of Spain (Barcelona) for adult patients with 26 beds: "The Institut Català d'Oncologia-Hospital Duran I Reynals," in the first months of the pandemic (13/12/2020-12/04/2020). They noted that hematological cancer patients have a higher mortality rate compared with non-immunocompromised patients. The inpatient mortality rate was 46%, and only 1 patient out of 12 recovered. There was also a decrease in initial visits by 55% and a delay in chemotherapy courses by 19%. Higher mortality was observed in individuals over 70 years of age and at D-dimer levels ≥900 mcg/L ($p= 0.04$). In conclusion, it was stated that the COVID-19 pandemic is associated with increased mortality in hematological patients [13].

However, accumulated data and analysis of a larger number of patients showed that such results were obtained largely due to the congestion of multidisciplinary hospitals and comorbidities in these patients, which determined the overall severity of the condition. In cases where anti-epidemic measures were correctly organized in a specialized hospital, the coronavirus infection did not dramatically affect the course of the oncological process, and there was no need to change the treatment tactics. Now, oncologists recommend not to postpone cancer treatment in most cases [14].

In July 2020, the Hospital Universitario de Burgos researchers determined that the epidemiological behavior of community-acquired respiratory viruses among cancer patients is similar to the general population's behavior. Cancer patients appear to carry a higher risk of severe events. However, among patients suffering from hematological diseases, no increase in COVID-19 infections was observed [13, 15].

According to the results of complex therapy of patients with hemoblastoses and hematopoietic depressions with infectious pathology in the CVI department of LLP NROC, in the course of treatment, we managed to avoid relapses or progression of the underlying disease, due to the timely start of treatment of the underlying disease.

Moreover, patients with the debut of an oncohematological disease were administered a course of chemotherapy on time since untimely started chemotherapy significantly worsens the prognosis of these patients.

Over the entire period of functioning of the CVI department, 2 patients were deceased, and the mortality rate was 3.6%, while in the specialized hematology department, the mortality rate in 2020 amounted to 2.9%. Patients of oncohematology departments No. 1 and No. 2 received the analogous treatment as the CVI department patients with the same nosologies but without additional treatment for COVID-19 infection.

Conclusion: During the working period (July 2020 - July 2021) of the infectious diseases department established for the treatment of patients with oncohematological diseases based on LLP "NROC," it was determined that there is no need to postpone the treatment of blood cancers (chemotherapy) against the backdrop of COVID-19, as this may worsen treatment prognosis. Furthermore, analysis of the outcomes showed the effectiveness of the early appointment of pathogenetic therapy for coronavirus infection (glucocorticosteroids, anticoagulants, oxygenation), which made it possible to achieve certain success.

Despite the conflicting world data, based on our department's results, it can be concluded that without systemic antitumor therapy for hemoblastosis and achieving remission, the treatment of infectious complications will be ineffective. Finally, contracting SARS-CoV-2 during or after completion of systemic anticancer therapy does not dramatically affect mortality from COVID-19. However, these results are limited due to the small sizes of both groups and require further investigation. Due to typically low survival among hematology patients, collecting a sizable cohort within a single center remains exceptionally challenging.

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АҢДАТПА

COVID-19 КЕЗІНДЕГІ ГЕМОБЛАСТОЗДЫ КЕШЕНДІ ТЕРАПИЯНЫҢ НӘТИЖЕЛЕРІ: «ҰЛТТЫҚ ҒЫЛЫМИ ОНКОЛОГИЯ ОРТАЛЫҒЫ» ЖШС КИ-1 БӨЛІМШЕСІ НЕГІЗІНДЕГІ МОНООРТАЛЫҚ ТӘЖІРИБЕСІ (АСТАНА, ҚАЗАҚСТАН)

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Өзектілігі: *SARS-Cov2 гемобластозбен ауыратын науқастардың ағымы мен еміне тікелей әсер еткен теңдесі жоқ денсаулық дағдарысын тудырды. Гематологтар коронавирустық инфекцияның қатар жүретін жұқпалы патологиясын емдеумен қатар жүргізілген химиотерапияға байланысты төтенше қиын жағдайға тап болды. Алайда, сипатталған кезеңдегі пациенттердің осы санаты үшін диагностика және емдеу бойынша нақты ұсыныстар мен бекітілген хаттамалар болған жоқ. Гематологиялық қатерлі ісіктері бар науқастар, әдетте, аурудан туындаған иммуносупрессияға және емнің иммундық жүйеге әсерінің нашарлауына байланысты инфекцияларға көбірек бейім.*

Зерттеудің мақсаты *– SARS-Cov-2 вирустық инфекциясының онкогематологиялық аурулардан болатын өлімге әсерін зерттеу және талдау.*

Әдістері: *Ретроспективті когортты зерттеу үшін пациенттердің деректері пациенттердің электронды медициналық жазбаларынан алынды. Коронавирустық инфекция COVID-19 РНҚ анықтауға арналған оң ПТР сынағымен, сондай-ақ кеуде қуысының компьютерлік томографиясымен (КТ) расталды. Барлық науқастар бөлімшеге түскен кездегі ауру жағдайын анықтаудан өтті. Әрі қарай жүргізілген терапия бағаланып, емдеу нәтижелеріне сипаттамалық талдау жүргізілді.*

Нәтижелері: *2020 жылдың шілдесі мен 2021 жылдың шілдесі аралығында Ұлттық ғылыми онкология орталығының (Астана, Қазақстан) КИ-1 бөлімшесінде гемобластоз және гемопоэтикалық депрессиямен қатар жүретін КИ бар 56 науқас емделді. Осы кезеңде 2 науқас қайтыс болды, өлім-жітім көрсеткіші 3,6% болса, мамандандырылған гематология бөлімшесінің өлім-жітім көрсеткіші 2020 жылы 2,8% құрады (904 науқастың 26-сы қайтыс болды).*

Қорытынды: *Біздің бөлімше жұмысының нәтижелеріне сүйене отырып, гемобластозды жүйелі ісікке қарсы терапиясыз және ремиссияға қол жеткізбестен, инфекциялық асқынуларды емдеу тиімсіз болады деп қорытынды жасауға болады. Қатерлі ісікке қарсы жүйелі терапия кезінде немесе одан кейін SARS-CoV-2 инфекциясы COVID-19-дан болатын өлімге айтарлықтай әсер етпейді.*

Түйінді сөздер: *гемобластоз, COVID-19, болжам, онкогематология, өлім, миелома, лейкоз.*

АННОТАЦИЯ

РЕЗУЛЬТАТЫ КОМПЛЕКСНОЙ ТЕРАПИИ ГЕМОБЛАСТОЗОВ ПРИ COVID-19: ОПЫТ МОНОЦЕНТРА НА БАЗЕ ОТДЕЛЕНИЯ «КИ-1» ТОО «НАЦИОНАЛЬНЫЙ НАУЧНЫЙ ОНКОЛОГИЧЕСКИЙ ЦЕНТР» (АСТАНА, КАЗАХСТАН)

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Актуальность: *SARS-Cov2 вызвал беспрецедентный кризис здравоохранения, который непосредственно повлиял на течение заболеваний и лечение больных гемобластозами. Гематологи оказались в чрезвычайно сложной ситуации в связи с назначением химиотерапии наряду с лечением сопутствующей инфекционной патологии коронавирусной инфекции. Однако четких рекомендаций и утвержденных протоколов диагностики и лечения данной категории больных в описываемый период не было. Пациенты с гематологическими злокачественными новообразованиями, как правило, более восприимчивы к инфекциям из-за иммуносупрессии, вызванной заболеванием, и усиления воздействия лечения на иммунную систему.*

Цель исследования *– изучить и проанализировать влияние вирусной инфекции SARS-Cov-2 на смертность от онкогематологических заболеваний.*

Методы: *Данные пациентов для ретроспективного когортного исследования были получены из электронных медицинских карт пациентов. Коронавирусная инфекция подтверждена положительным результатом ПЦР-теста на выявление РНК COVID-19, а также компьютерной томографии (КТ) органов грудной клетки. Всем пациентам на момент поступления в отделение проводилось определение статуса заболевания. Далее оценивалась проведенная терапия и проводился описательный анализ результатов лечения.*

Результаты: *За период с июля 2020 г. по июль 2021 г. в отделении КИ-1 Национального научного онкологического центра (Астана, Казахстан) пролечено 56 пациентов с гемобластозами и депрессией кроветворения с сопутствующей КИ. За этот период умерло 2 пациента, летальность составила 3,6%, тогда как летальность специализированного гематологического отделения составила 2,8% в 2020 году (26 смертей на 904 больных).*

Заключение: *По результатам работы нашего отделения можно сделать вывод, что без системной противоопухолевой терапии гемобластозов и достижения ремиссии лечение инфекционных осложнений будет неэффективным. Инфекция SARS-CoV-2 во время или после системной противораковой терапии не оказывает существенного влияния на смертность от COVID-19.*

Ключевые слова: *гемобластоз, COVID-19, прогноз, онкогематология, смертность, миелома, лейкемия.*

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A NEW APPROACH TO THE IMPLEMENTATION AND OPERATION IN BRACHYTHERAPY: COMPREHENSIVE ANALYSIS FOR QUALITY ASSURANCE

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ABSTRACT

Relevance: *The scientific novelty consists in developing a method for estimating dose distributions around the applicator using Gafchromic RTQA2 radiochromic film and a 1 cm thick solid phantom. This technique minimizes deviations between the actual and planned dose distributions around the source. The use of radiochromic film and solid phantoms allows for detailed analysis of dose profiles, which can optimize source positioning and improve treatment accuracy, especially in the context of 3D planning in high-dose brachytherapy.*

The study aimed to *improve the accuracy of dosimetric measurements and the quality of procedure planning in brachytherapy.*

Methods: *Gafchromic RTQA2 radiochromic film and a solid phantom made of polymethylmethacrylate (30×30×1cm³, density 1.05 g/cm³) were used in the study. The doses chosen for analyzing isodose curves around the applicator were 0.6 Gy, 1 Gy, 1.7 Gy, 2 Gy, 2.5 Gy, 3 Gy, and 4 Gy.*

Results: *According to the experiment, the radiochromic film darkens proportionally to the absorbed dose when irradiated. The experimental results show deviations of the measured data from the planned system in the range of 4.2-10.6%. The lower deviation on the second film indicates a more accurate and stable dose distribution in its region, which can be explained by its optimal location relative to the source and reduced scattering and absorption effects.*

Conclusion: *The proposed method combines an Epson Expression 10000XL scanner, a solid phantom with radiochromic film, and ImageJ software to efficiently assess dose distributions around the applicator. The resulting graphs demonstrate how radiation dose correlates with distance through isodose profiles, with RGB channel changes accurately reflecting radiation density. This approach enhances the visualization and validation of dosimetric calculations, making it crucial for improving source positioning and ensuring reliable quality control in brachytherapy through optimized dose modeling.*

Keywords: *Quality control, radiochromic film, dose distribution, isodose.*

Introduction: High-dose-rate brachytherapy using Ir-192 and Co-60 sources is used to treat various types of tumors such as cervical, prostate, breast, head, neck cancers, and others. In 3D brachytherapy, the position of the first source is determined either by X-ray catheters on CT images or by markers on MRI images [1-4]. This is a critical step since the position of each subsequent source is determined relative to the first. Thus, the dose distribution is formed based on the position of the first and subsequent sources, representing the cumulative dose from each source position. There are source positioning and film dosimetry methods used when changing the source. These methods allow for a layer-by-layer assessment of the dose distribution, i.e., the relationship between the distance from the source and the cumulative dose can be determined. Therefore, there is a need to develop a new quality assurance approach to verify the dose distribution. While many studies have focused on determining the initial source positions and ensuring source quality control [5-7], few have considered the dose distribution around the applicator. However, ensuring quality control in high dose rate brachytherapy is equally important.

The study aimed to improve the accuracy of dosimetric measurements and the quality of procedure planning in brachytherapy.

Materials and Methods: Gafchromic RTQA2 radiochromic films and 1 cm thick solid phantoms (2 units) were used for this study. The solid phantoms are 30x30x1 cm^3; they are made of polymethyl methacrylate with a 1.05 g/cm^3 density. The solid phantoms were positioned vertically, one above another, as shown in Figure 1. A transparent applicator was securely fixed on the upper phantom in the center. Then, a CT image of the solid phantom was obtained using computed tomography.

The radiochromic films are located at intervals of 1 cm, corresponding to the solid phantom's thickness. The arrangement diagram is shown in Figure 2. The factory parameters of the film are 25x25 cm. The study used whole films without additional mechanical processing to avoid defects. The total film thickness is a standard 0.23 mm, of which the active layer, according to literary data, is 20 μm [8].

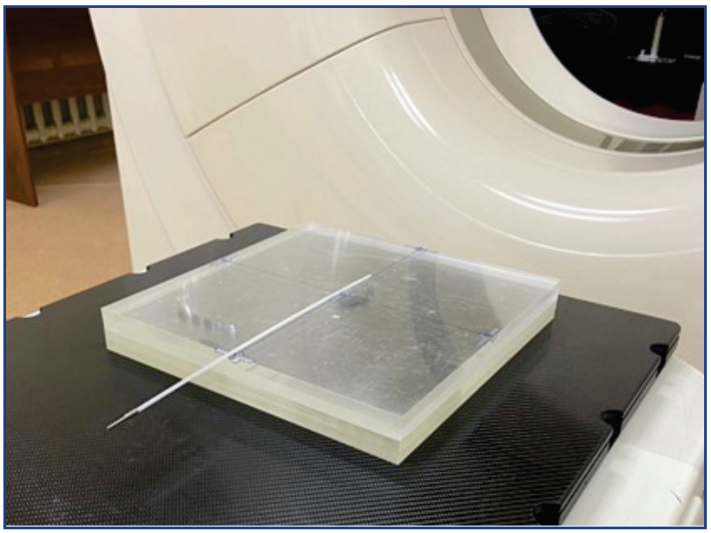

Figure 1 – Two solid phantoms located one above the other

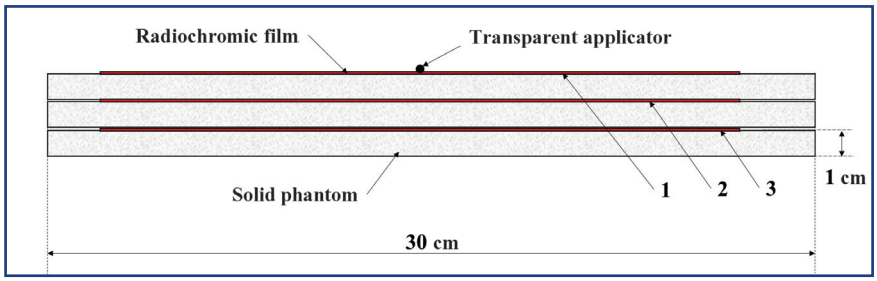

Figure 2 – Layout of the solid phantom, radiochromic film, and transparent applicator (1, 2, 3 – film layout)

After the experiment, the films were scanned at a resolution of 600 dpi using Epson Expression 10000XL equipment. In the planning system, a dose of 200 cGy was set for film #3 (Figure 2). An active length of 10 cm was chosen during planning since this length is often used in the test mode and when determining activity.

The study used the GammaMedPlus device (Medical Systems, California, USA), equipped with an ionizing radiation source Ir-192 with a half-life of 74 days [9, 10].

The open-source program ImageJ [11-14] was used to analyze and process the images. The results of the isodose curve study obtained using the ImageJ program were compared with the data of the Eclipse Brachytherapy planning system (Varian). The quantitative and qualitative characteristics of the dose distribution around the applicator were determined using radiochromic film.

Results:

Exposure to radiation source. The radiation source in the apparatus was recharged on April 16, 2024, with an activity of 10,000 mCi at that time. The experiment was conducted on May 16, 2024, when the source dose rate was 40,700 cGy cm2/h. Figure 4 shows the source downtime as shown in the planning plan during the experiment. The downtime varies at each point, with values automatically calculated by the planning system. The calculations are performed according to the TG-43 protocol established by the American Association of Physicists in Medicine [9]. The sum of the dose curves for this exposure is uniformly distributed along the length of the applicator.

Traditionally, when working with radiochromic films, the method used involved analyzing data exclusively from the red channel of the scanned images. This data was then processed to obtain the dose distribution. However, some methods suggest using all three image channels: red, green, and blue (RGB) [16]. This approach allows for greater accuracy in film dosimetry. Our study used the software to create graphs showing the relationship between distance and color levels in the three channels (Figure 5). The results demonstrate changes in color levels in the isodose profiles from the center of the applicator to its edge. The data for the three films show less dependence on the green and blue channels than the red channel. This suggests that the red channel provides the most reliable and accurate results for estimating the dose distribution using the RTQA2 radiochromic film.

Film analysis. Radiochromic films have high spatial resolution and do not have such disadvantages, making them useful for determining the absolute and relative values of the absorbed radiation dose [15]. The study showed that the radiochromic film darkens after irradiation, and this changing color is directly proportional to the absorbed dose. Figure 4 (1, 2, 3) shows isodose lines corresponding to certain doses obtained after processing using the ImageJ program. Figure 4 (4) shows a dose distribution plan obtained using the Brachytherapy planning system.

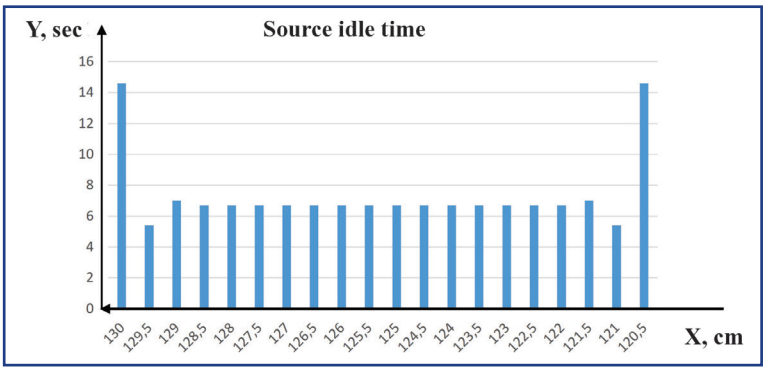

Figure 3 – Exposure time for each point

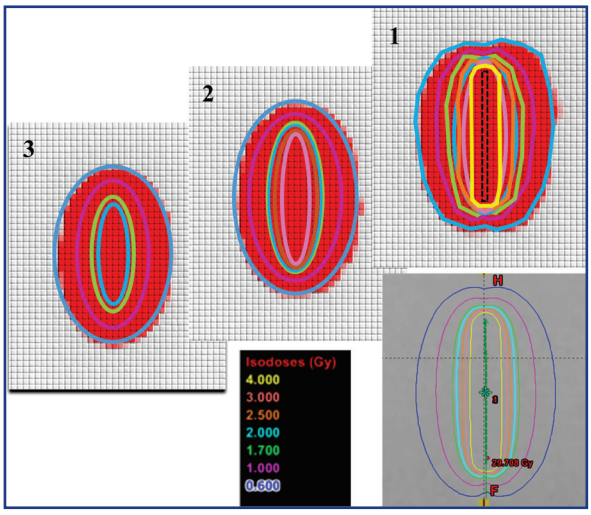

Figure 4 – Film processing results (1, 2, 3) and the Brachytherapy planning system (4)

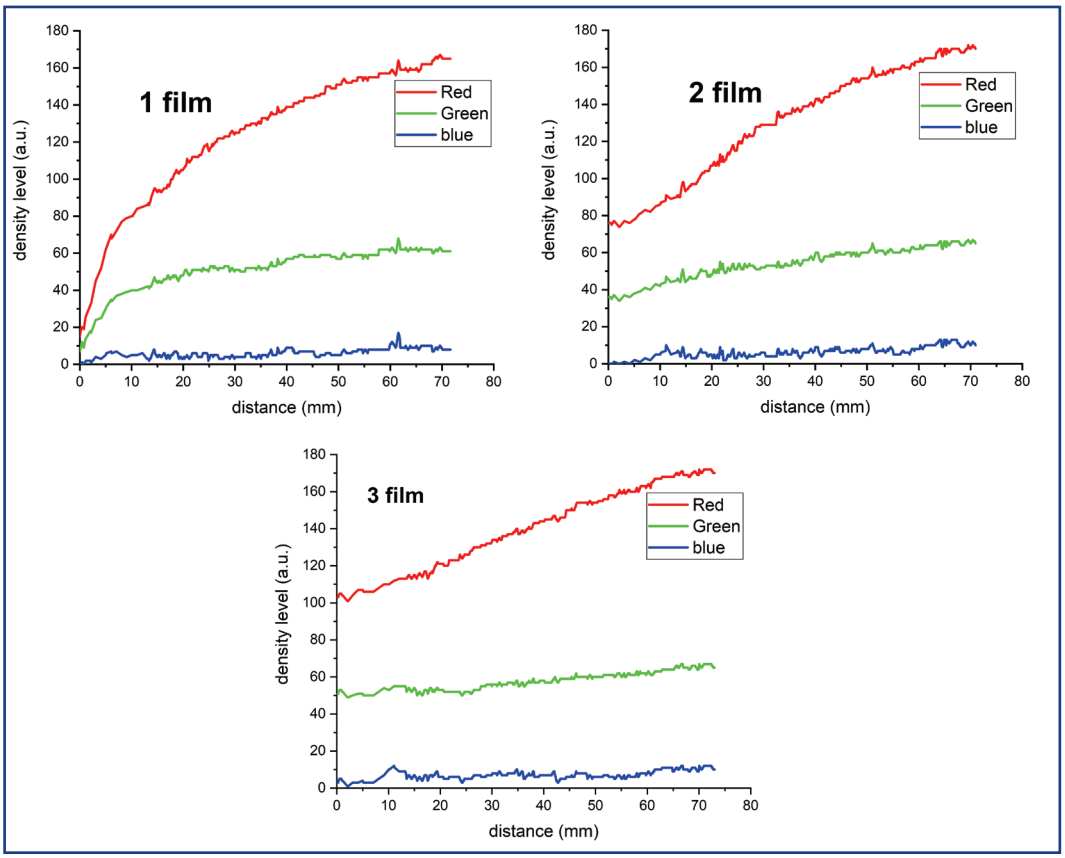

Figure 5 – Dependence of color level on the distance from the center of the applicator to the edge

Isodose distribution estimation. For dose distribution estimation, the data obtained using the planning system were compared with the experimental results of irradiation of the radiochromic film.

Table 1 – Comparison of experimental results with the values of the planning system

Film 1				Film 2				Film 3			
Dose, Gy	Dis-tance, mm	Horizontal distance, mm	Devi-ation, %	Dose, Gy	Dis-tance, mm	Horizontal distance, mm	Devi-ation, %	Dose, Gy	Dis-tance, mm	Horizontal distance, mm	Devia-tion, %
0.6	47.5	44.4	**6.5**	0.6	45.5	43.2	**5.1**	0.6	42.3	39.8	**5.9**
1	33.9	31.6	**6.8**	1	31.7	30	**5.4**	1	26.5	25.1	**5.3**
1.7	23.1	21.4	**7.4**	1.7	19.9	18.8	**5.5**	1.7	10.4	9.3	**10.6**
2	19.9	18.6	**6.5**	2	16.8	16.1	**4.2**				
2.5	17.2	15.8	**8.1**	2.5	12.5	11.9	**4.8**				
3	14.4	13.5	**6.3**	3	9.5	9.1	**4.2**				
4	11	10.5	**4.6**								

The percentage deviation (y) was calculated using formula (1), where x0 represents the actual measured value and x1 denotes the value from the planning system:

$$y = \frac{x_0 - x_1}{x_0} \cdot 100\% \quad (1)$$

Discussion: This study investigated a radiochromic film type RTQA2 for potential use in brachytherapy quality control. The radiation source was Ir-192 radionuclide used in the GammaMedPlus brachytherapy systems (Varian). A method for assessing dose distributions using the radiochromic film was developed. The films were placed relative to the applicator with a step of 1 cm, as shown in Figure 2. The first film was placed immediately adjacent to the applicator. A colorless solid phantom made of polymethyl methacrylate was placed between the radiochromic films. The main results showed that the red color channel gave the most accurate dose distribution data, exceeding the other channels in response by a factor of two. This indicates significant discrepancies between the colors, especially when compared with the blue channel, which gave the lowest response. The results of this study demonstrate that the RTQA2 radiochromic film, especially using the red color channel, can improve quality control in brachytherapy by increasing the accuracy of dosimetric measurements. However, this solution is not ideal because the film response varies between color channels, which can lead to potential errors. Despite this, the method is useful for assessing dose distributions, especially near the applicator.

Conclusion: The proposed method, combining flatbed scanning using an Epson Expression 10000XL, a solid-state phantom with a Gafchromic RTQA2 radiochromic film, and the free ImageJ program, provides a convenient and cost-effective approach to assessing the dose distribution around an applicator with a moving source and a given exposure time. In the study of isodose curves around the applicator, the following doses were selected: 0.6 Gy, 1 Gy, 1.7 Gy, 2 Gy, 2.5 Gy, 3 Gy, and 4 Gy. The deviation of the values obtained in the experiment with the values calculated by the planning system ranges from 4.2 to 10.6. However, if we compare the films, the value deviation for the first film closer to the applicator is 6.6%, for the second - 4.9%, and for the third - 7.3%. The deviation of the value on the second film, which is lower than that of the first and third, indicates a more stable and accurate dose distribution in its area. This fact may indicate that the dose homogeneity in the area of the second film better corresponds to the calculated values. The optimal position of the film relative to the source and smaller scattering and absorption effects can explain this.

Using the software, we created graphs displaying the relationship between distance and color levels in three channels. The results demonstrate changes in color levels in the isodose profiles from the center of the applicator to its edge. The constructed graphs allow us to estimate the distribution of the radiation dose emitted by the applicator by the isodose profiles depending on the distance. The change in color levels in the RGB channels directly reflects changes in the radiation density, which is important for accurate visualization and validation of dosimetric calculations. This approach is especially useful in brachytherapy planning, as it allows us to optimize the position of the sources and more accurately model the dose distribution in the tissues around the applicator, providing improved quality control. The radiochromic film technique agreed well with the planned dose distributions, especially when considering the chromaticity, confirming its potential applicability for quality control in brachytherapy.

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АҢДАТПА

БРАХИТЕРАПИЯНЫ ЖАҢА ӘДІСТЕРДІ ЕНГІЗУ МЕН ПАЙДАЛАНУДЫҢ ЖАҢА ТӘСІЛІ: САПАНЫ ҚАМТАМАСЫЗ ЕТУ ҮШІН КЕШЕНДІ ТАЛДАУ

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Өзектілігі: *Ғылыми жаңалық-Gafchromic RTQA2 радиохромды қабыршағын және қалыңдығы 1 см қатты күйдегі фантомды қолдана отырып, аппликатордың айналасындағы дозаның таралуын бағалау әдісін жасау. Радиохромды пленка мен қатты күйдегі фантомдарды қолдану дозалық профильдерді егжей-тегжейлі талдауға мүмкіндік береді, әсіресе жоғары дозалы брахитерапияда үш өлшемді жоспарлау жағдайында, бұл көздердің орналасуын оңтайландыруға және емдеу дәлдігін жақсартуға мүмкіндік береді.*

Зерттеудің мақсаты *– дозиметриялық өлшеулердің дәлдігін арттыру және брахитерапиядағы процедураларды жоспарлау сапасын жақсарту.*

Әдістері: *Зерттеуде Gafchromic RTQA2 радиохромды қабыршағы және полиметилметакрилаттан жасалған қатты күйдегі фантом (30×30×1 см^3, тығыздығы 1,05 г/см^3) қолданылды. Аппликатордың айналасындағы изодоздық қисықтарды талдау үшін мынадай дозалар таңдалды: 0,6 Гр, 1 Гр, 1,7 Гр, 2 Гр, 2,5 Гр, 3 Гр және 4 Гр.*

Нәтижелері: *Эксперимент нәтижелері бойынша радиохромды қабыршақ сәулелену сіңірілген дозаға тура пропорционалды түрде қараңғыланатындығы анықталды. Эксперимент нәтижелері өлшенген мәндерді, жоспарлау жүйесімен салыстырғанда 4,2-10,6% ауытқуын көрсетеді. Екінші қабыршақтағы ауытқудың төмен болуы, оның аймағында дәлірек және тұрақты дозаның таралуын көрсетеді, бұл оның көзге қатысты оңтайлы орналасуымен және шашырау мен сіңіру әсерінің төмендеуімен түсіндірілуі мүмкін.*

Қорытынды: *"Epson Expression 10000XL" планшеттік сканерлеуді, қатты күйдегі фантомды радиохромды қабыршағымен және "ImageJ" бағдарламасын біріктіретін ұсынылған әдіс аппликатордың айналасындағы дозаның таралуын ыңғайлы және тиімді бағалауды қамтамасыз етеді. Бағдарламалық жасақтаманың көмегімен біз үш арна арқылы қашықтық пен түс деңгейлері арасындағы байланысты көрсететін графиктер жасадық. Нәтижелер аппликатордың ортасынан оның шетіне дейін изодоза профильдеріндегі түс деңгейлерінің өзгеруін көрсетеді. Изодоздық профильдер бойынша сәулелену дозасының сызбалары қашықтыққа тәуелділікті көрсетеді. RGB арналарындағы түс деңгейлерінің өзгеруі сәулеленудің тығыздығын дәл көрсетеді, бұл дозиметриялық есептеулердің визуализациясы мен валидациясын жақсартуға көмектеседі. Бұл әдіс брахитерапия үшін маңызды, өйткені ол көздердің орналасуын оңтайландыруға және сапаны сенімді бақылауды қамтамасыз ете отырып, аппликатордың айналасындағы дозаны модельдеу дәлдігін арттыруға мүмкіндік береді.*

Түйінді сөздер: *Сапаны бақылау, радиохромды қабыршақ, дозаның таралуы, изодоза.*

АННОТАЦИЯ

НОВЫЙ ПОДХОД К ВНЕДРЕНИЮ И ЭКСПЛУАТАЦИИ В БРАХИТЕРАПИИ: КОМПЛЕКСНЫЙ АНАЛИЗ ДЛЯ ОБЕСПЕЧЕНИЯ КАЧЕСТВА

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Актуальность: *Научная новизна данного исследования заключается в разработке метода оценки дозовых распределений вокруг аппликатора с использованием радиохромной пленки Gafchromic RTQA2 и твердотельного фантома толщиной 1 см. Предлагаемая методика позволяет минимизировать отклонения между фактическим и планируемым дозовым распределением вокруг источника. Использование радиохромной плёнки и твердотельных фантомов обеспечивает возможность детального анализа дозовых профилей, что позволяет оптимизировать позиционирование источников и повысить точность лечения, особенно в условиях трёхмерного планирования в высокодозной брахитерапии.*

Цель исследования *– повысить точность дозиметрических измерений и улучшить качество планирования процедур в брахитерапии.*

Методы: *В исследовании использовались радиохромная плёнка Gafchromic RTQA2 и твердотельный фантом из полиметилметакрилата (30×30×1 см3, плотность 1,05 г/см³). Для анализа изодозных кривых вокруг аппликатора были выбраны дозы: 0,6 Гр, 1 Гр, 1,7 Гр, 2 Гр, 2,5 Гр, 3 Гр и 4 Гр.*

Результаты: *По результатам эксперимента было выявлено, что радиохромная пленка после облучения темнеет прямо пропорционально поглощенной дозе. Результаты эксперимента показывают отклонения измеренных данных от планировочной системы в пределах 4,2-10,6%. Более низкое отклонение на второй плёнке указывает на более точное и стабильное дозовое распределение в её области, что может объясняться оптимальным её расположением относительно источника и уменьшенным эффектом рассеяния и поглощения.*

Заключение: *Предложенный метод, сочетающий планшетное сканирование с применением Epson Expression 10000XL, твердотельного фантома с радиохромной плёнкой и программы ImageJ, обеспечивает удобную и недорогую оценку дозовых распределений вокруг аппликатора. С помощью программного обеспечения мы создали графики, отображающие связь между расстоянием и уровнями цвета по трем каналам. Результаты демонстрируют изменения уровней цвета в профилях изодозы от центра аппликатора к его краю. Построенные графики дозы излучения по профилям изодозы демонстрируют зависимость от расстояния. Изменения уровней цвета по каналам RGB точно отображают плотность излучения, что способствует улучшению визуализации и валидации дозиметрических расчетов. Этот метод важен для брахитерапии, так как позволяет оптимизировать положение источников и повысить точность моделирования дозы вокруг аппликатора, обеспечивая надежный контроль качества.*

Ключевые слова: *Контроль качества, радиохромная пленка, дозовое распределение, изодоза.*

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SIMULTANEOUS SURGICAL OPERATIONS FOR HEART DISEASES AND MALIGNANT TUMORS, PERFORMED FOR THE FIRST TIME IN KAZAKHSTAN: A SERIES OF CASES

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ABSTRACT

Relevance: *For patients with heart disease and concomitant neoplasms, simultaneous surgery may be the method of choice. However, there are currently no standard clinical guidelines for this intervention.*

The study aimed to *describe a series of clinical cases of simultaneous surgical intervention in simultaneously existing cardiac pathologies and malignant neoplasms, evaluate the feasibility of such an intervention method, and discuss its advantages and disadvantages as a treatment method.*

Methods: *A retrospective analysis included 13 patients (8 men and 5 women, age range – 49-74 years) with combined cardiac pathology and malignant neoplasm in other organs. The most common heart diseases were coronary artery disease and valvular defects, and the most common heart surgery was coronary artery bypass grafting. The analysis included clinical cases of neoplasms in the organs of the abdominal cavity and the chest.*

Results: *The average duration of simultaneous surgery was 322±76 minutes (mean ± standard deviation, range from 220 to 470 minutes), and the average intraoperative blood loss was 342±242 ml (range from 100 to 1000 ml). The mortality rate in the hospital was 0%, the average stay in the intensive care unit was 2.4 days (range from 1 to 5 days), and in the specialized department – 11.6 days (range from 5 to 21 days), respectively. All patients were discharged in satisfactory condition and underwent conservative treatment without additional surgical interventions. During the follow-up period after discharge, four patients died within 5 years. The 1-year, 3-year, and 5-year survival rates were 92.3%, 76.9%, and 69.2%, respectively.*

Conclusion: *Simultaneous operations may be the method of choice for patients with heart pathology and concomitant malignant neoplasms of the abdominal cavity and the chest. Such concomitant pathologies can be effectively treated simultaneously. This is the first such study conducted in the Central Asian region, particularly Kazakhstan.*

Keywords: *simultaneous operations, coronary artery bypass grafting, coronary artery disease, valvular heart disease, lung cancer, adenocarcinoma, renal cell carcinoma, pheochromocytoma.*

Introduction: It is always difficult to decide how to treat a patient with cardiac disorders and a comorbidity that requires surgical treatment. It is especially challenging when malignant neoplasms co-exist with severe ischemic heart disease. Today, the number of patients with heart disease and associated neoplasms is growing due to population aging and improved cancer diagnostics. There are no strict treatment recommendations for such patients since it depends on each case. Besides, a consistent intervention (first surgical treatment of one pathology, then patient recovery, then surgical treatment of the second pathology) can require much time. Therefore, patients admitted for cardiac pathologies and co-existing cancer diseases require special care and a thorough planning of surgical treatment.

The first paper on simultaneous heart surgery with lung resection was published in 1998 [1]. It described a series of cases of simultaneous surgery for ischemic heart disease and lung resection for lung carcinoma. These days' progress in surgery allows for quite volumetric simultaneous surgical interventions in such patients. A simultaneous operation provides several preferences for such patients, such as a single administration of anesthesia and a single post-surgery rehabilitation period.

Today, many publications focus on simultaneous surgeries on the heart and other organs. However, due to a diversity of pathologies, individual features of patients, and surgical techniques in different countries, nearly all information is presented as clinical case reports. Few papers describe a series of cases, mainly with cardiac pathologies and diseases of one anatomical group (thoracic or abdominal cavity). Besides, some regions like Central Asia have not reported successful simultaneous surgical treatment of combined pathologies.

This paper analyzes the treatment and post-operative period of 13 patients with heart pathologies and various

neoplasms in the abdominal cavity and chest organs who underwent simultaneous surgery in our Center.

The study aimed to describe a series of clinical cases of simultaneous surgical intervention in simultaneously existing cardiac pathologies and malignant neoplasms, evaluate the feasibility of such an intervention method, and discuss its advantages and disadvantages as a treatment method.

Materials and Methods: All surgical interventions were performed at the National Scientific Medical Center (Astana, Kazakhstan). The retrospective study was conducted with the relevant permission of the Local Ethics Committee. All the study participants were informed of the study's purpose and provided informed consent.

Patient selection. We analyzed patients who underwent simultaneous surgery in our Center in 2012-2022 to select those eligible for the study. The final sample included 13 patients (8 men and 5 women) with combined cardiac pathology and malignant operable neoplasm. Their medical records were studied to obtain the following information related to the patient and the simultaneous surgery: age and gender of the patient, type of heart disease, type of cancer, type of heart surgery, type of cancer surgery, sequence and duration of both surgeries, blood loss during the entire procedure, stay in the intensive care unit, stay in the emergency department. During the post-surgery long-term follow-up, the selected patients (or their relatives) were questioned by phone for the following data: actual general condition at the time of the interview, previous complaints and/or diagnosed complications in the period between the operation and the interview, or statements about the patient's death before the interview. The long-term follow-up included determining the survival after 1 month, 1, 3, and 5 years.

Methods of analysis. Raw data obtained from medical records was used to calculate mean/median values. Quantitative data in this paper is represented as a mean value ± standard deviation or as a median value with minimum and maximum values indicated. The Kaplan-Meier survival function calculated survival rates for 1-year, 3-year, and 5-year periods.

Results: The maximum age at the time of surgery was 74 years, the minimum was 49 years, and the average was 63.8±8.5 years. The sample included patients with certain pathologies of the cardiovascular system: coronary heart disease (CHD), valve defects, and congenital heart defects. Comorbidities that required surgical intervention included malignant neoplasms of the chest and abdomen. This paper provides a detailed structure of a series of clinical cases, including 1) cardiac and oncological diagnoses, 2) concomitant diseases, 3) histological diagnoses, 4) types and sequence of surgical interventions, 5) intervention details: total duration of simultaneous surgical intervention, blood loss, length of stay in the intensive care unit/surgical ward (Table 1).

Structure of comorbidities. The patients were diagnosed with the following comorbidities: arterial hypertension – 8 patients (62%), type 2 diabetes mellitus – 1 patient (8%), secondary infective endocarditis of aortic valve – 1 patient (8%), chronic obstructive pulmonary disease – 1 patient (8%); 4 patients (31%) had no concomitant diseases.

Patomorphology results. Pathological examination revealed malignant neoplasms of the following localizations and types: lungs (squamous cell cancer, adenocarcinoma), mediastinum (two teratocarcinomas), GIT (five adenocarcinomas), kidneys, and adrenal glands (three renal cell carcinomas, pheochromocytoma).

Surgical interventions. Most patients (8/13, 62%) underwent coronary artery bypass grafting (ACB) in combination with surgical treatment of the neoplasm. Other interventions included the Bentall de Bono procedure (two patients, 15%), heart valve replacement (three patients, 23%), and tricuspid valve repair with atrial septal reconstruction (one patient, 8%). Ten patients (77%) were first operated on the heart; the remaining three first underwent noncardiac surgery. For heart and lung surgeries, a median sternotomy was performed, and both surgeries were performed through a single approach. Nine patients required a cardiac pump, and eight patients – a blood transfusion. Table 1 provides a detailed structure of the surgical techniques used.

Outcomes and Complications. One patient developed a profuse intraoperative hemorrhagic bleeding through drainage from the anterior mediastinum and pericardium during stage two of surgery (about 700 ml, with total bleeding of 1000 ml) (see Table 1, patient No. 12). The examination of the pericardial cavity and anterior mediastinum after reexploration revealed diffuse bleeding from soft tissues and sternum, followed by hemostasis.

Postoperatively, one patient (No. 7) developed superficial wound infection, and another (No. 2) had paroxysmal atrial fibrillation.

The mean total duration of the simultaneous operation was 322±76 minutes (range 220-470 minutes). The mean operative blood loss was 342±242 ml (range 100-1000 ml). In-hospital mortality was 0%. The mean stay in the ICU was 2.4 days (range 1–5 days), and in the specialized hospital unit – 11.6 days (range 5–21 days). All patients underwent conservative treatment, and no additional surgical intervention was required. All patients were discharged in satisfactory condition, with recommendations for further treatment or monitoring.

One of 13 patients died after 1 month due to gastric bleeding (the diagnosed neoplasm was rectal adenocarcinoma), another patient died due to the progression of lung cancer 15 months after surgery, another patient died due to COPD complications 21 months after surgery, and another patient died due to the progression of mediastinal cancer 45 months after surgery. We revealed no specific relationships between comorbidities and/or complications and patient death. The survival rates were assessed using the Kaplan-Meier survival function and amounted to 92.3% for 1-year survival, 76.9% for 3-year survival, and 69.2% for 5-year survival.

Table 1 – Cardiological and oncological diagnoses, type, and details of surgical treatment of patients

#	Gender	Age	Cardiological diagnose	Oncological diagnose	Comorbidities	Stages of simultaneous surgery	Duration of use of cardiac pump (min)	Total blood loss (mL)	Total duration of surgery (min)	ICU/hospital stay (days)	Histological diagnosis
1*	M	57	IHD	Right upper lobe cancer	AH, type 2 DM.	(1) Right apical lobectomy (2) ACB 4	-	200	300	3 / 17	Adenocarcinoma
2*	M	74	IHD	Right lung cancer	AH	(1) ACB 1 (2) S3-segmentectomy of the right lung	-	300	260	1 / 7	G2 squamous cell carcinoma
3*	M	64	Stenosis of the bicuspid and aortic valves	Mediastinal tumor	-	(1) Resection of mediastinal tumor (2) Bentall-de Bono operation	145	300	270	1 / 11	Teratocarcinoma
4	F	58	Aortic valve regurgitation	Mediastinal tumor	-	(1) Thymectomy (2) Aortic valve replacement, ACB 1	81	300	270	1 / 16	Teratocarcinoma
5*	F	57	Aortic valve regurgitation	Rectal cancer	AH	(1) Aortic valve replacement (bio) (2) Laparoscopic abdominoperineal resection	51	200	305	5 / 11	G2 adenocarcinoma
6	M	49	Regurgitation of the bicuspid and aortic valves	Gastric cancer	Secondary infective endocarditis of the aortic valve	(1) Bentall-de Bono operation (bio) (2) Laparotomy, D2 gastrectomy	114	500	470	4 / 9	G3 adenocarcinoma
7	F	71	IHD	Rectosigmoid cancer	-	(1) ACB 3 (2) Laparoscopic front resection	48	240	310	2 / 10	G2 adenocarcinoma
8	M	73	IHD	Gastric cancer	AH, COPD	(1) ACB 2 (2) D2-gastrectomy	-	500	375	1 / 15	G2 adenocarcinoma
9	M	74	Aortic valve regurgitation	Sigmoid cancer	AH	(1) Aortic valve replacement (bio) (2) Sigmoidectomy	21	300	275	1 / 11	G2 adenocarcinoma
10	F	68	IHD	Right kidney cancer	AH	(1) ACB 1 (2) Right nephrectomy	-	100	220	3 / 10	Kidney carcinoma
11	M	70	IHD	Left kidney cancer	AH	(1) ACB 3 (2) Laparoscopic nephrectomy	57	250	330	4 / 8	Kidney carcinoma
12	M	61	IHD	Right kidney cancer	-	(1) ACB 4 (2) Right laparoscopic nephrectomy (3) Resternotomy, hemostasis	132	1000	470	3 / 5	Kidney carcinoma
13	F	53	Secondary atrial septal defect, tricuspid valve insufficiency	Right adrenal gland pheochromocytoma	AH	(1) Atrial septoplasty, tricuspid valve repair (2) Right adrenalectomy	38	110	335	2 / 21	Pheochromocytoma

Note : * – patients who died within 5 years of surgery. IHD – ischemic heart disease, AH – arterial hypertension, DM – diabetes mellitus, COPD – chronic obstructive pulmonary disease, ACB – aortocoronary bypass, ICU – intensive care unit, hospital stay – duration of stay in the specialized hospital unit.

Discussion: To date, there is no consensus on the treatment strategy for patients with two simultaneous diagnoses, one of which is heart disease and the other is cancer. Since both diagnoses are extremely severe and fatal if not treated promptly, the best current treatment option must be found as quickly as possible to reduce mortality.

Till recently, cardiac surgery was rarely combined with noncardiac interventions (e.g., for cancer). Today, combined surgery mainly involves heart and chest surgery (e.g., lung removal or esophagectomy) but less commonly includes other operations such as abdominal. For example, many publications describe the series of clinical cases of simultaneous cardiac surgery + lung resection [2-5] or operations for esophageal cancer [6,7]. On the contrary, very few reports relate to non-chest pathologies, like heart surgery + gastric resection for cancer [8] or heart surgeries + various other cancer pathologies [9].

Our clinical research summarized the results of combined operations on and outside the heart (regardless of the organ). One important socioeconomic factor significantly affects the possibility of conducting targeted research in simultaneous surgery. In countries with high economic development, the oncosurgical department often possesses specialized units (for example, cardiac surgery or chest surgery) which allow simultaneous operations on the heart and certain organs. In developing countries, many of which are located in the Central Asian region, there is no such inter-structure cooperation, and the experience with using combined surgical treatment methods is limited. In such countries, cancer surgeons often have to conduct oncological interventions on different organs in close cooperation with cardiac surgeons in the presence of concomitant cardiac pathology. Clinical research on simultaneous cardio- and cancer surgery, with an assessment of the efficacy of such simultaneous approaches, is required to increase the quality of medical care in such countries. Our research is an example of such a strategy.

A simultaneous surgical approach is associated with some risks/complications, such as longer surgery, longer recovery, and more pain for the patient due to multiple surgical interventions (wounds). In addition, complications after the first operation can lead to complications during the second operation. For example, performing cancer surgery as a first stage increases the risk of cardiovascular complications. However, generalized data from several clinical studies have shown that a combined heart surgery and lung tumor resection lead to a relatively low mortality rate and provide an acceptable level of complications. For example, a recent meta-analysis covering 29 studies with 536 patients revealed a total intraoperational mortality of just 1% [3]. Despite a higher intraoperational mortality during simultaneous surgery than staged operations (0-20.8% vs. 0-10% according to ten studies), overall one-year survival reaches 79-100% [10]. Still, it should be noted that most published data describe clinical cases or series of cases. Therefore, a randomized controlled trial would provide more reliable information regarding postoperative outcomes.

Simultaneous and staged treatment have their pros and contras. In stages of treatment, when one operation is followed by rehabilitation and then another operation, the patient needs general anesthesia twice, and the overall duration of rehabilitation increases (this is a disadvantage of this approach). Besides, if surgery for cancer is performed as the second stage, the delay in oncological treatment increases the risk of metastasis [11]. On the other hand, performing cancer surgery as the first stage increases the risk of cardiovascular complications. A staged approach also delivers more pain for the patient (double anesthesia required) and increases the hospital stay and the relevant costs per patient. Alternatively, in simultaneous surgery, the patient suffers a more serious post-operative wound and remains under anesthesia longer. There is contradictory evidence of a risk of bleeding after heart surgery due to anticoagulants. Some authors report a higher risk [12]; others indicate it as a rare complication and state the same risk of bleeding in cancer operations with simultaneous cardiac surgery than without cardiac surgery [13]. Cardiac surgery is usually performed first in simultaneous operations. This improves blood flow to the heart and reduces the risk of heart complications in the second stage. In addition, cardiac surgery is an aseptic operation, whereas in most cases, the non-cardiac surgical stage is conditionally "septic." It means a reduced risk of contamination of a clean environment during cardiac surgery. Still, depending on the type of non-cardiac surgery, it can be performed first.

Simultaneous surgery on the heart and chest organs has obvious advantages: both stages can be performed through one incision with relatively easy access. Moreover, nowadays simultaneous surgery has nearly become a standard of surgical treatment of diseases of the heart and chest organs due to its efficiency and functional safety from the point of oncology [14]. For example, in our clinic, we perform such operations only simultaneously.

The use of cardiac pumps is critical in simultaneous surgery. One should consider the risk of long-term effects of extracorporeal circulation on the spread of the oncological process in the patient's body. Extracorporeal circulation reduces the immune system's strength, indirectly affecting the body's ability to eliminate cancer cells and increasing the risk of infection of the postoperative wound. Early studies recommended using off-pump techniques to reduce the risk of the risk of cancer cells spreading when using a heart-lung machine [15]. However, later studies showed no or little direct associative effect of cardiac pumps on the spread of cancer cells in the body [16, 17]. Still, it is recommended to use an off-pump coronary artery bypass technique to reduce possible complications [18]. In our study, 9/13 patients underwent surgery with extracorporeal circulation.

Planning a simultaneous surgery shall consider the above risks and benefits, taking into account each patient's individual condition. The applied techniques shall minimize the overall risk for the patient. Therefore, the order of cardiac and cancer interventions shall be determined based on the combination of risks – cancer metastasis, the patient getting secondary infections, consequences for the cardiovascular system, the development of immune reactions during surgery with extracorporeal circulation. Another important factor for successful outcomes and reduced risk of complications after simultaneous surgery is well-established intra-hospital coordination of the work of cardiac surgeons and specialized surgeons' teams. This requires the development of such multidisciplinary departments within national clinics.

Our results agree with similar clinical studies [4, 7, 9]. To obtain reliable statistical results in the future, we have to increase the current sample with patients with other forms of malignant and benign neoplasms to compare statistically the concomitant operations for heart disease in combination with certain types of cancer.

Limitations of the study. The main limitation of our study was a relatively small sample of patients with concomitant pathologies. However, the spectrum of cardiac and non-cardiac pathologies and concomitant diseases was quite wide, as was the volume of heart surgeries performed. Thus, within the sample of 13 patients, we conducted aortocoronary bypass grafting of various classes (1 to 4), aortic and tricuspid valve replacement, and Bentall-de Bono operations. Similarly, in these patients, we identified malignant neoplasms of the lungs, mediastinum, gastrointestinal tract, kidneys, and adrenal glands. Besides, we did not consider the stage of cancer, which could also impact the overall outcome of the simultaneous operation. Finally, we had limited opportunities to reveal the gender and age effects on the simultaneous surgery outcomes. All this together made it impossible to conduct a more detailed comparison of outcomes and complications for different combinations of factors (cardiac and non-cardiac pathologies, stage of cancer, age and gender of patients)within the framework of this study. Another limitation was the study's retrospective nature, which included only patients with simultaneous operations. This has limited the ability to obtain data on the success of a simultaneous approach for specific combinations of specific types of cardiac and non-cardiac diseases. On the other hand, this retrospective study is the initial stage of a detailed study of the effectiveness of simultaneous cardiac surgeries in patients diagnosed with cancer. Subsequently, it is possible to conduct a single- or multi-center prospective study in which patients with coexisting cardiac pathologies and oncological diseases will be divided into two cohorts: simultaneous operation and sequential operations. The third factor limiting this retrospective study was the lack of a single register for patients undergoing simultaneous surgical interventions in Central Asia. Therefore, we've included only patients who underwent simultaneous surgery in our clinic. Another limitation was related to our limited access to the information on the actual condition of patients after 5 years. Some were unavailable for remote interviews, and many refused a follow-up. Unfortunately, this is a result of the low motivation of the local population to participate in clinical research. However, despite the above limitations, the results of the described series of simultaneous surgical interventions confirm the good applicability of this approach as a method of choice, even in elderly patients.

Conclusion: Simultaneous operations may be the method of choice in patients with certain combinations of cardiac pathology and oncological diseases of the abdominal and chest organs. This retrospective study shows that patients with such pathologies can be effectively and safely treated simultaneously. However, they require a thorough selection considering their anamnesis to go through a simultaneous operation with minimal complications and consequences. Further clinical studies covering as many countries in the Central Asian region as possible could provide a better understanding of simultaneous surgery safety and economic efficacy in treating coexisting cardiac and non-cardiac pathologies.

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АҢДАТПА

ҚАЗАҚСТАНДА АЛҒАШ РЕТ ОРЫНДАЛҒАН ЖҮРЕК АУРУЛАРЫ ЖӘНЕ ҚАТЕРЛІ ІСІКТЕР КЕЗІНДЕГІ СИМУЛЬТАНДЫ ХИРУРГИЯЛЫҚ ОПЕРАЦИЯЛАР: ЖАҒДАЙЛАР СЕРИЯСЫ

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***Өзектілігі**: Жүрек аурымен қатар қосымша ісік ауруы бар науқастар үшін бір мезгілді хирургиялық араласу таңдаулы әдіс болуы мүмкін. Дегенмен қазіргі таңда осындай араласуда стандартты клиникалық нұсқаулар жоқ.*

***Зерттеудің мақсаты** – жүрек патологиясымен қатар жүретін қатерлі ісіктерді бір мезгілде хирургиялық араласудың бірқатар клиникалық жағдайларын сипаттау, бұл араласу әдісінің өзектілігін бағалау және емдеу әдісі ретінде оның артықшылығымен кемшіліктерін талқылау.*

***Әдістері:** Ретроспективті талдауға жүрек патологиясы және басқа ағзаларда қатерлі ісігі бар 13 науқас (8 ер және 5 әйел, жас аралығы – 49-74 жас) алынды. Ең жиі жүрек аурулары ол жүректің ишемиялық ауры және қақпақша ақауы, ал жүрекке жиі жасалатын ота – аортокоронарлы шунттау болды. Талдауға кеуде торының және іш қуысың түзілістері бар клиникалық жағдайлар алынды.*

***Нәтижелері:** Бір мезгілде жасалатын отаның орташа ұзақтылығы 322±76 минут (орташа ұ стандартты ауытқу, 220 дан 470 минутқа дейінгі диапазон), орташа қан жоғалту көлемі 342±242 мл (100 ден 1000 мл-ға дейінгі диапазон). Аураханада өлім-жітім 0% құрады, жан сақтау бөлімінде орташа 2,4 күн (1-ден 5 күнге дейінгі диапазон), ал бейіндік бөлімде 11,6 күнді (5-тен 21 күнге дейінгі диапазон) құрады. Барлық науқастар қанағаттанарлық жағдайда шығарылды, оларға қосымша хирургиялық араласусыз тек қана консервативті ем қолданыды. Шығарғаннан кейін бақылау кезеңінде 4 науқас 5 жылдың ішінде қайтыс болды. 1-жылдық, 2-жылдық, 3-жылдық өмір сүру уақыты сәйкесінше 92,3%, 76,9% және 69,2% құрады.*

***Қорытынды:** Жүрек аурымен қатар қосымша кеуде торының және іш қуысың қатерлі ісіктері бар науқастарға бір мезгілді хирургиялық ем таңдаулы әдіс болуы мүмкін. Мұндай қатарлас ауруларды бір уақытта тиімді емдеуге болады. Бұл Орталық Азия аймағында және атап айтқанда Қазақстандағы жүргізілген мұндай бірінші зерттеу.*

***Түйінді сөздер:** бір мезгілді ота, аортокоронарлы шунттау, жүректің ишемиялық ауруы, жүректің қақпақша аурулары, өкпенің қатерлі ісігі, аденокарцинома, бүйрек-жасушалы обыр, феохромоцитома.*

АННОТАЦИЯ

СИМУЛЬТАННЫЕ ХИРУРГИЧЕСКИЕ ОПЕРАЦИИ ПРИ ЗАБОЛЕВАНИЯХ СЕРДЦА И ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЯХ, ВПЕРВЫЕ ВЫПОЛНЕННЫЕ В КАЗАХСТАНЕ: СЕРИЯ СЛУЧАЕВ

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***Актуальность:** Для пациентов с заболеваниями сердца и сопутствующими новообразованиями симультанное хирургическое вмешательство может быть методом выбора. Однако стандартные клинические рекомендации по поводу этого вмешательства на данный момент отсутствуют.*

***Цель исследования** – описать серию клинических случаев симультанного хирургического вмешательства при одновременно существующих сердечных патологиях и злокачественных новообразованиях, оценить целесообразность такого метода вмешательства и обсудить его преимущества и недостатки как способа лечения.*

Методы исследования: *Ретроспективный анализ включал 13 пациентов (8 мужчин и 5 женщин, возрастной диапазон – 49-74 года) с сочетанной патологией сердца и злокачественным новообразованием в других органах. Наиболее частыми заболеваниями сердца были ишемическая болезнь сердца и пороки клапанов, а наиболее частой операцией на сердце было аортокоронарное шунтирование. В анализ были включены клинические случаи новообразований в органах брюшной полости и грудной клетки.*

Результаты: *Средняя продолжительность симультанной хирургической операции составила 322±76 минут (среднее стандартное отклонение, диапазон от 220 до 470 минут), средняя кровопотеря – 342±242 мл (диапазон от 100 до 1000 мл). Летальность в стационаре составила 0%, среднее время пребывания в отделении интенсивной терапии составило 2,4 дня (диапазон от 1 до 5 дней), а в профильном отделении – 11,6 дней (диапазон от 5 до 21 дней), соответственно. Все пациенты были выписаны в удовлетворительном состоянии, им проводилось консервативное лечение без дополнительных хирургических вмешательств. Во время периода наблюдения после выписки четверо пациентов умерли в течение 5 лет. Показатели 1-летней, 3-летней и 5-летней выживаемости составили 92,3%, 76,9% и 69,2%, соответственно.*

Заключение: *Симультанные операции могут быть методом выбора для пациентов с патологией сердца и сопутствующими злокачественными новообразованиями брюшной полости и грудной клетки. Такие сопутствующие патологии можно эффективно лечить одновременно. Это первое подобное исследование, проведенное в Центрально-Азиатском регионе и, в частности, в Казахстане.*

Ключевые слова: *симультанные операции, аортокоронарное шунтирование, ишемическая болезнь сердца, клапанные заболевания сердца, рак легкого, аденокарцинома, почечно-клеточный рак, феохромоцитома.*

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CHROMIUM-INDUCED CARCINOGENESIS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *According to the International Agency for Research on Cancer (IARC), hexavalent chromium Cr(VI) has been identified as a Group I occupational carcinogen. There is ample evidence that Cr(VI) is associated with lung, nasal, and sinus cancers. A study based on the Baltimore cohort, which consisted of 2357 participants, demonstrated a high positive correlation between cumulative Cr(VI) exposure and lung cancer mortality rates. In the western region of Kazakhstan in the Aktobe region, an anthropogenic stablegenic chromium biochemical province has been formed as a result of many years of activity of the enterprises of TNC Kazchrome JSC (Donskoy GOK, Ferrochrome JSC) and AZKhS JSC, which has an impact on the health of the population of this region. In a survey of workers at a ferroalloy plant in West Kazakhstan over 15 years, the mortality rate from cancer among plant workers was significantly higher than among the general public: the excess among people aged 50-59 years was 3.3 times for men and 7.9 times for women. There is a huge amount of material on the effects of hexavalent chromium on the body, which needs to be streamlined to reveal the role of chromium in carcinogenesis.*

The article aimed to *highlight the role of hexavalent chromium in carcinogenesis.*

Methods: *Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials were analyzed to select and analyze relevant information over the past 10 years using keywords: hexavalent chromium, carcinogenesis, heavy metals, oncogenesis. A total of 173 sources were found, and 50 were included in the analysis, considering the valency of the metal studied.*

Results: *Hexavalent chromium, while inside the human body, can react with cellular agents reducing to form Cr(V), Cr(IV), and, ultimately, Cr(III). The latter can lead to the formation of highly toxic Cr(III) DNA adducts in the cell nucleus. All of these intermediates can cause DNA damage or DNA-protein cross-links. Several mechanisms have been proposed to explain chromium-induced carcinogenicity. Cr-induced carcinogenesis is likely dependent on tissue, cell type, Cr(VI) concentration, exposure time and isoforms of certain heat shock proteins, chromosomal instability, nuclear protein 1 (Nupr) induction, DNA adduction, and free radical formation; reactivity of Cr(V) and Cr(IV) intermediates. Epigenetic gene expression changes are considered a key element of carcinogenesis.*

Conclusions: *Understanding the mechanisms of carcinogenesis is important for preventing and treating Cr(VI)-induced cancer. Strategic developments are needed to prevent oncogenesis in the chromium biogeochemical province.*

Keywords: *hexavalent chromium, carcinogenesis, heavy metals, oncogenesis.*

Introduction: According to the International Agency for Research on Cancer (IARC), hexavalent chromium is recognized as a Group I occupational carcinogen [1]. There is sufficient evidence in the scientific literature linking Cr $^{+6}$ with lung, nasal cavity, and paranasal sinus cancer [2]. A study on the Baltimore Cohort of 2,357 participants demonstrated a high positive correlation between cumulative exposure to Cr(VI) and lung cancer mortality [3]. In the EC assessment of socioeconomic impact on human health, hexavalent chromium and silicon dioxide were strongly associated with cancer death [4]. Exposure to Cr $^{+6}$ occurs in many industries, and workers are often exposed to it through inhalation and skin contact [5]. Hexavalent chromium is contained in car exhaust gases and tobacco products such as traditional electronic cigarettes and hookahs [6]. It is estimated that 66% of existing or former hazardous waste disposal sites included in the list of national priorities also contain Cr [7]. In the Aktobe region of the Republic of Kazakhstan, a stable anthropogenic chromium biochemical province has formed [8] as a result of long-term activities of the enterprises of JSC TNC Kazchrome and JSC AZHS, which affects the health of the population of this region and neighboring regions. A survey of workers of the ferroalloy plant showed that over 15 years, mortality from cancer among plant workers was higher than in the population: among people aged 50-59 years, among men - 3.3 times, among women - 7.9 times. The largest share of all cancer deaths was stomach cancer - 37% and lung cancer - 15.8% [9].

The article aims to highlight the role of hexavalent chromium in carcinogenesis.

Materials and methods: An analysis of MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials data was performed to select and analyze relevant information for the last 10 years using the keywords “hexavalent chromium,” “carcinogenesis,” “heavy metals,” and “oncogenesis.” Of 173 sources found, 50 were included in the analysis, considering the valence of the metal under study.

Results: Cr is a rare element; its most stable forms are trivalent Cr(III) and hexavalent chromium Cr(VI). Due to their stability in water and oxygen, they are considered biologically and ecologically significant. Cr(III) is an essential trace element in the human diet; it supports glucose metabolism and regulates blood glucose levels, which synergizes with insulin. Conversely, Cr(VI) is carcinogenic when inhaled and/or ingested in large quantities. Cytotoxicity of Cr refers to its ability to cause damage to living cells, especially at higher concentrations. In its hexavalent form, Cr exhibits strong cytotoxic effects due to its strong oxidizing properties. Cr(VI) can penetrate cell membranes and convert to Cr(III) inside the cell upon exposure. This conversion produces reactive intermediates and free radicals, leading to oxidative stress and subsequent cellular damage. Cr(VI) interferes with important cellular processes, disrupts DNA repair mechanisms, and causes genotoxicity, which ultimately contributes to cancer development. In addition, Cr(VI) can produce reactive oxygen species, causing lipid peroxidation and protein damage. Elevated levels of reactive oxygen species cause oxidative stress, leading to lipid peroxidation and cellular protein degradation. In addition, Cr(VI) can directly act on DNA, disrupting DNA mismatch repair and, as a result, causing genomic instability [10].

Chromium can exist in three different states: Cr(0), Cr(III), and Cr(VI); only Cr(VI) is a known carcinogen. Environmental and occupational exposure to Cr(VI) via water, air, or landfills has become a major public health concern and is associated with human lung cancer. Changes in signaling pathways and oxidative stress are considered causative factors in response to Cr(VI) exposure. Chromium alters the epigenome; histone modifications and the DNA methylation landscape alter the chromatin state. Recently, dysregulation of microRNAs has been shown to play an important role in Cr(VI)-induced cellular transformation, carcinogenesis, and angiogenesis. Interleukin-8 was induced by Cr(VI) treatment, a major inducer of angiogenesis upregulated by activating the IGF-IR/IRS1 axis and ERK/HIF-1α/NF-κB signaling pathway. This result suggests that miR-143/IL-6/HIF-1α signaling pathway plays a vital role in Cr(VI)-induced malignant cell transformation and carcinogenesis [11].

Ligand-bound Cr(III) enters cells via a phagocytic mechanism or non-specific diffusion. Subcellular Cr(VI) is stored as chromate oxyanion (CrO_4), and chromate anions utilize sulfate transporters on the cell surface to enter. Once Cr(VI) enters the cell, it becomes toxic because it is reduced to Cr(III) together with ascorbate and biological thiols such as glutathione (GSH) or because cysteine aminoalkanoic acid residues form reactive oxygen species. Cr(VI) remains a major health problem, contributing to a wide range of cancers: prostate, bone, leukemia, lymphoma, kidney, gastrointestinal, brain, and lung cancers [12].

Occupational exposure and environmental pollution are common routes of exposure to toxic metals. Accumulation of metals in the soil leads to their transfer to flora and fauna. The main source of human exposure to toxic elements is nutrition. There is an assumption about the bioaccumulation of toxic metals in the colon and their involvement in oncology development. A group of 104 patients with various diseases of the colon and rectum was examined, of which 76 were diagnosed with cancer. A significantly higher presence of Cr was observed in tumor biopsies. Molecular data on the effect of Cr on the colon were obtained in both in vivo and in vitro studies. Cr induces centrosome amplification in HCT116 colon cancer cells. It is known that the centrosome plays a role in oncogenesis and invasiveness of cancer cells. The authors found that Cr(VI) can induce centrosomes and promote cancer progression via the ROS-ATF6-PLK4 pathway [13].

Molecular studies have shown that Cr exposure results in decreased expression of p53 and RKIP, while an increase in galectin and c-myc is observed. It should be noted that Cr-induced disruption of p53 expression may significantly affect the development of colorectal cancer. Decreased p53 expression disrupts cell cycle control, leading to uncontrolled tumor proliferation and growth. Impaired p53 function disrupts DNA repair mechanisms, accumulating genetic aberrations and increasing tumor aggressiveness [14].

A meta-analysis of Cr(VI) exposure and gastrointestinal cancer showed an increased risk of gastric cancer in workers exposed to chromium and an increased mortality rate from gastric cancer in chromium-contaminated regions. Exposure to Cr^{+6} increased the risk of brain cancer and malignant lymphoma and mortality from lung, bladder, and pancreatic cancer among tanners.

A meta-analysis based on published epidemiological cohort studies showed that hexavalent chromium causes cancer of the respiratory system, oropharynx, prostate, and stomach and increases the risk of developing cancer of the larynx, bladder, kidney, testicles, thyroid, and bone [15].

Currently, chromium exposure is associated with a wide range of diseases, from cutaneous exposure that causes sensitization to haptens via the mechanism of inflammatory cell activation to carcinogenicity through various exposure modes and mechanisms, including genomic instability or epigenetic changes [16], as well as respiratory, hepatic, renal and reproductive problems and neurological disorders [17]. This brief review summarizes the most relevant results in Cr(VI) carcinogenesis, emphasizing molecular and epigenetic mechanisms.

Epithelial cells can transdifferentiate into motile mesenchymal cells through a dynamic process known as epithelial-mesenchymal transition (EMT). EMT is critical for embryonic development and wound healing but

also contributes to human diseases such as organ fibrosis and cancer progression. Hexavalent chromium has a dual effect on epithelial-mesenchymal transition, sometimes stimulating and sometimes inhibiting the EMT process. [18].

Initially, only inhalation exposure to Cr(VI) was of major concern, but it was subsequently noted that absorption from the gastrointestinal tract can also lead to carcinogenic activity. Although the effects of oral exposure are reduced by chemical reduction of Cr(VI) in the intestine, this phenomenon does not prevent chromium uptake into target tissues, allowing disease to develop [19]. Epidemiological studies conducted in populations consuming contaminated water and meta-analyses of epidemiological cohort studies have shown an increased risk of developing several types of cancer, including gastric, gastrointestinal, renal, genitourinary, bone, leukemia, lymphoma, brain, nose, and lung. Cr(VI) induces a wide range of DNA damage and promotes the induction of neoplasia in several organs other than the respiratory system due to its ability to biotransform in all types of cells [20].

The toxicity and carcinogenicity of Cr(VI) is due to its ability to readily enter cells through isoelectric and isostructural anion transport channels, which are used to transport HPO^{-2}_4 SO^{-2}_4 ions [21]. Although Cr(VI) compounds do not bind directly to DNA, intermediates and byproducts of Cr(VI) metabolism can cause a wide range of damages through DNA adducts and cross-links. Notably, the formation of reactive oxygen species (ROS) through detoxification is mainly responsible for Cr(VI)-induced cellular damages such as DNA damage, cytotoxicity, and tumor development [22]. Cr(III), (IV), (V), and (VI) species are known to produce intracellular ROS. During intracellular reduction of Cr(VI), hydroxyl radicals are generated through Fent-like reactions in the presence of hydrogen peroxide [23]. Endogenous superoxide anions and hydrogen peroxides produce hydroxyl radicals via Haber-Weiss-like reactions in the presence of Cr(VI) [24]. Reactive oxygen species scavengers ascorbic acid and glutathione can detect and reduce Cr^{+6} to Cr^{+3} but produce free radicals, hydroxyl radicals, and DNA-damaging intermediates such as Cr^{+5} and Cr^{+4} [25].

ROS, including hydroxyl radicals, singlet oxygen, peroxides, and superoxides, can be important second messengers and activators of various pathways, including apoptosis, cell signaling, and homeostasis [26]. Cr(VI) has been shown to induce the activation of NF-kB, AP-I, and Nrf 2, which are important in cancer development [27]. Hydroxyl radicals can react with guanine residues to form radical adducts such as 8-hydroxydeoxyguanosine (8-OH-dG), an important marker of oxidative damage in cancer [28]. ROS accumulation can lead to oxidative stress and promote chronic inflammation, metabolic reprogramming, genetic instability, and cancer development [29]. Adducts formed by conjugating Cr and ROS scavengers, including GSH-Cr-DNA, can generate bulky adducts and block proper DNA replication and repair [30]. Hexavalent chromium damages DNA by intracellular reduction as apurinic/apyrimidinic sites and by interacting with proteins, amino acids, or directly with DNA, causing DNA breaks [31]. Upon intracellular reduction, Cr(VI) can form bulky binary Cr(III) adducts (CrIII-DNA) as well as ternary adducts, i.e., Cr(III)-ligand-DNA, the latter being more mutagenic than the binary Cr(III)-DNA analogs and 90% of mutagenic damage occurs in ternary complexes [32]. The literature data on changes in chromatin structure in response to acute and chronic Cr(VI) exposure suggest that the mechanisms governing the transcriptional response induced by Cr(VI) often differ in a dose-dependent manner, and this may influence the molecular mechanisms leading to carcinogenesis, since structural changes in chromatin do not correlate with changes in the global transcriptional response, but do influence gene expression levels in target regions, which vary in a Cr(VI) concentration-dependent manner [33].

Several mechanisms have been proposed to explain chromium-induced carcinogenicity. Cr-induced carcinogenesis probably depends on tissue, cell type, Cr(VI) concentration, exposure time, and isoforms of some heat shock proteins, chromosomal instability, nuclear protein I (Nupr) induction, DNA adduction, and free radical formation; reactivity of Cr(V) and Cr(IV) intermediates [34]. Epigenetic alteration of gene expression is considered a key element in carcinogenesis.

More than the valence stability of chromium, Cr(VI) and Cr(III) are recognized as carcinogens in *vitro experiments* using Cr-induced DNA-protein complexes; *in vivo experiments* did not prove the Cr(III) carcinogenicity [35]. Although the mechanism of chromium carcinogenicity is not fully understood, it is generally accepted that it mainly occurs through DNA damage/genomic instability and ROS generation. Cr(VI) has been shown to alter the epigenetic profile of cells through DNA methylation, histone modification [36], and inhibition of the recruitment of DNA mismatch repair proteins, which facilitates the induction of g-H2AX foci leading to DNA breaks and initiation of p-53 mediated apoptosis [37]. Results such as these suggest a link between chromium-induced epigenetic changes and carcinogenesis [38]. Compared with DNA methylation and histone post-translational modifications, less is known about the effects of Cr(VI) on miRNAs. MiRNAs regulate broad transcriptional pathways; Cr(VI) disrupts specific transcriptional pathways by directly deregulating the miRNA expression profile [39].

Recently [40], it was reported that Cr(VI) induces persistent and heritable chromosome translocations, aneuploidy and polyploidy, centrosome amplification, and

DNA repair defects. The regulatory phenotype favored cancer cell growth due to the imbalance caused by heredity and the persistent nature of chromosomal translocations. In recent years, an increasing number of studies have shown that both short-term and long-term exposure to Cr(VI) causes global changes in epigenetic modifications and non-coding RNA (microRNA) expression in cells, the latter being important regulators of gene expression and have been recognized as important participants in tumor formation, development, and metastasis.

Metabolic reprogramming of key energy metabolism pathways is important for the survival and growth of cancer cells and tumors. All Cr(VI)-transformed cells had no changes in their mitochondrial respiratory functions compared to passenger control cells. However, although mitochondrial dysfunction does not occur during Cr(VI)-induced lung cell transformation, it does occur during tumor development [41].

The carcinogenic effects of Cr(VI) have been mainly studied in lung cancer since the lung is the main target of Cr(VI). Cr(VI) is well known for transforming normal human lung epithelial cells such as BEAS-2B and 16HBE cells; the transformed cells exhibit cancer and cancer stem cell (CSC)-like properties. Multiple mechanisms have been identified that contribute to Cr(VI)-induced lung carcinogenesis, including oxidative stress, DNA damage, abnormal signal transduction, and inflammatory responses. Although Cr(VI)-induced genotoxicity and mutagenicity are considered to be the main mechanisms of Cr(VI) carcinogenesis, an increasing number of studies indicate that altered epigenetic modifications and dysregulation of non-coding RNAs contribute to induced tumorigenesis in the subsequent years [42].

DNA methylation as a major type of epigenetic modification has been extensively studied in the context of Cr(VI) exposure. Fundamental changes in DNA methylation status have been found in blood and lung cancer tissues from Cr(VI)-exposed workers and in Cr(VI)-exposed and transformed lung epithelial cells. Since DNA damage is one of the major genotoxic effects of Cr(VI), some studies have investigated the role of DNA methylation in Cr(VI)-induced DNA damage and dysfunction of the DNA repair system. Cr(VI) exposure causes increased DNA damage and decreased p16INK4a expression in 16HBE cells [43]. Reduced p16INK4a expression and aberrantly increased p16INK4a promoter methylation were also found in workers with lung cancer and long-term (≥15 years) Cr(VI) exposure, suggesting that p16INK4a hypermethylation is involved in Cr(VI) carcinogenesis [44].

Cr(VI) induced gene-specific histone modifications that altered gene expression. Altered global and gene-specific histone modifications and resulting gene expression changes, such as inhibition of the MLH1 tumor suppressor, contribute to Cr(VI) carcinogenesis. Chronic low-dose hexavalent chromium exposure has been shown to transform cells with precancerous cell-like properties. Disruption of the histone DNA modification machinery contributes to the development of genotoxic effects, leading to the onset or progression of the cancer process [45]. Glycolytic shifts and the development of glycolysis play an important role in maintaining the malignant phenotypes of Cr(VI)-transformed cells since reversal of the glycolytic shift by glucose depletion significantly inhibited the growth, tumor-like properties, and tumorigenicity of transformed cells. Involvement of nuclear proto-oncogene-mediated histone hypoacetylation in Cr(VI)-induced lung carcinogenesis [46].

Dysregulation of microRNA expression plays an important role in Cr(VI)-induced cellular transformation, carcinogenesis, and angiogenesis. Cr(VI) exposure altered global microRNA expression in the human bronchial fibroblast cell line WTHBF-6. In silico pathway analysis revealed that these altered microRNAs were enriched in pathways involved in carcinogenesis [47].

Quercetin (antioxidant flavonoid) inhibited Cr(VI)-induced activation of miR-21/PDCD4 pathway in BEAS-2B cells by reducing ROS generation. Quercetin inhibited Cr(VI)-induced malignant transformation and suppressed xenograft tumor growth from Cr(VI)-transformed cells, indicating the preventive and therapeutic role of quercetin in Cr $^{+6-}$ induced lung cancer [36].

Cr(VI) exposure has been shown to induce DNA damage and subsequent activation of DNA repair genes. Exposure of human B lymphoblast HMy2. CIR cells to Cr(VI) induced global changes in miRNA expression. Mechanistic studies showed chronic Cr(VI) exposure increased c-Myc expression by downregulating miR-494. This suggests that inhibition of the miR-494/c-Myc pathway contributes to lung cancer initiation by chronic Cr(VI) exposure. [48].

However, most processes of carcinogenesis remain poorly understood, and an in-depth discussion of these studies is beyond the scope of this review.

Discussion: Chronic Cr(VI) exposure upregulates the expression of the proto-oncogene c-Myc, which significantly contributes to Cr(VI)-induced cell transformation, cancer stem cell (CSC) property, and tumorigenesis. c-Myc is a master regulator of abnormal metabolism in cancer cells, and accumulating evidence suggests that metabolic dysregulation plays an important role in both cancer development and progression. However, little is known about the role of metabolic dysregulation in Cr(VI) carcinogenesis. It was found that Cr(VI)-transformed cells exhibited a glycolytic shift that was dependent on c-Myc activation. The glycolytic shift in Cr(VI)-transformed cells increased acetyl-coenzyme A (acetyl-CoA) production and enhanced histone acetylation. This, in turn, increased the expression of acetyl-CoA, which pro-

duces the key enzyme ATP-citrate lyase, and c-Myc, forming a positive feedback loop between increased c-Myc expression, glycolytic shift, and increased histone acetylation [27].

Glucose depletion reverses the glycolytic shift in Cr(VI)-transformed cells and significantly reduces their growth, tumor-like properties, and tumorigenicity. These data indicate that the glycolytic shift plays an important role in maintaining the malignant phenotypes of Cr(VI)-transformed cells, suggesting that metabolic dysregulation plays a critical role in Cr(VI) carcinogenesis [49].

Although it is well known that Cr(VI) is one of the most common environmental carcinogens causing lung cancer and other cancers, the mechanism of Cr(VI) carcinogenesis is not clearly defined. Studies have shown that metabolic dysregulation plays a critical role in the development and progression of cancer. However, little is known about whether chronic Cr(VI) exposure causes metabolic dysregulation and whether metabolic reprogramming plays an important role in Cr(VI) carcinogenesis [38].

In addition, recent studies have shown that mRNA levels of several genes involved in the glycolytic pathway and lactate production increase in Cr(VI)-transformed cells. Cr(VI)-transformed cells exhibit abnormal metabolism as evidenced by increased glycolysis or glycolytic shift. Subsequent mechanistic studies have determined that the glycolytic shift in Cr(VI)-transformed cells depends on increased c-Myc expression [22, 50].

Importance of the glycolytic shift in Cr(VI) carcinogenesis. Increased glycolysis is thought to support some cancer features. The glycolytic shift is crucial for malignant phenotypes of Cr(VI)-transformed cells, suggesting an important role of the glycolytic shift in Cr(VI) carcinogenesis. However, further studies are needed to determine whether the glycolytic shift occurs early in the course of Cr(VI) exposure and whether it plays a causal role in Cr(VI)-induced malignant cell transformation, tumor-like properties, and tumorigenesis [19, 36].

Cr(VI) exposure also induces epigenetic dysregulation, which may be important in carcinogenesis. The existence of cross-regulation between metabolism and epigenetics suggests that, on the one hand, metabolic dysregulation may lead to epigenetic dysregulation. On the other hand, epigenetic dysregulation, such as increased histone acetylation, may increase the expression levels of key metabolic enzymes, causing metabolic reprogramming [41, 48].

Activation of c-Myc in Cr(VI)-transformed cells promotes a glycolytic shift that increases acetyl-CoA levels and subsequent activation of histone acetylation and non-histone protein acetylation. Upregulation of acetylation increases ACLY and c-Myc expression, forming a positive feedback loop to further promote the glycolytic shift in Cr(VI)-transformed cells. The glycolytic shift in cells explains the epigenetic dysregulation induced by Cr(VI) exposure but also offers additional evidence supporting its important role in carcinogenesis [16, 24].

Conclusion: Thus, it is likely that chronic Cr(VI) exposure induces c-Myc expression, which in turn enhances the expression of several important glycolytic regulatory enzymes, causing a metabolic shift towards glycolysis.

Cells transformed by chronic Cr(VI) exposure exhibit a glycolytic shift. Studies have shown that the glycolytic shift in Cr(VI)-transformed cells depends on the upregulation of the proto-oncogene c-Myc. It was further found that the glycolytic shift in Cr(VI)-transformed cells results in increased acetyl-CoA production and enhanced histone acetylation, which in turn enhances the expression of the key acetyl-CoA-producing enzyme ACLY and c-Myc expression. This results in a positive feedback loop between increased c-Myc expression, glycolytic shift, and histone acetylation. Moreover, glucose depletion reversed the glycolytic shift in Cr(VI)-transformed cells and significantly ameliorated their malignant phenotypes. These data together suggest that metabolic dysregulation plays an important role in Cr(VI) carcinogenesis.

Further animal and human studies are needed to evaluate their role as biomarkers for early diagnosis and to develop prevention methods and treatment options for human cancers induced by carcinogenic chromium in the future. Understanding the mechanisms of carcinogenesis is important for the prevention and treatment of Cr(VI)-induced cancer and the development of appropriate tumor strategies for both prevention and treatment of malignant tumors caused by exposure to various chromium compounds.

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АҢДАТПА

ХРОМ-ИНДУКЦИЯЛАНҒАН КАНЦЕРОГЕНЕЗ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Халықаралық қатерлі ісіктерді зерттеу агенттігінің (IARC) мәліметтері бойынша алты валентті хром Cr(VI) I топтағы кәсіптік канцероген ретінде анықталды. Cr(VI) өкпенің, мұрынның және синустың қатерлі ісігімен байланысты екендігі туралы көптеген дәлелдер бар. 2357 қатысушыдан тұратын Балтимор когортына негізделген зерттеу жинақталған Cr(VI) экспозициясы мен өкпе ісігінен болатын өлім-жітім көрсеткіштері арасындағы жоғары оң корреляцияны көрсетті. Қазақстанның батыс өңірінде Ақтөбе облысында «Қазхром» ТҰК» АҚ (Донской ГОК, «Феррохром» АҚ) және «Ақтөбе хром қосындылары зауыты» АҚ кәсіпорындарының көп жылдық қызметінің нәтижесінде тұрақты антропогендік хром биохимиялық провинциясы қалыптасты, бұл өз әсерін тигізуде. осы аймақ тұрғындарының денсаулығы туралы. Батыс өңіріндегі ферроқорытпа зауытының жұмысшылары арасында жүргізілген сауалнама 15 жыл ішінде зауыт жұмысшылары арасында онкологиялық аурулардан болатын өлім-жітім халықтың қалған бөлігімен салыстырғанда айтарлықтай жоғары екенін көрсетті: 50-59 жас аралығындағы адамдар арасында, ерлер арасында – 3,3 есе, әйелдер үшін – 7,9 есе. Алты валентті хромның ағзаға әсері туралы материалдардың үлкен көлемі бар, оны ретке келтіру және соңғысының канцерогенездегі рөлін ашу қажет.*

Зерттеудің мақсаты *– канцерогенездегі алты валентті хромның рөлін көрсету.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed, Cochrane бақыланатын сынақтардың орталық тізілімінен алынған деректер соңғы 10 жылдағы маңызды ақпаратты таңдау және талдау үшін: алты валентті хром, канцерогенез, ауыр металдар, онкогенез сияқты негізгі сөздерді пайдалана отырып талданды. Барлығы 173 дереккөз табылды, оның 50-і зерттелетін металдың валенттілігін ескере отырып талдауға енгізілді.*

Нәтижелері: *алты валентті хром адам ағзасында болған кезде жасушалық тотықсыздандырғыштармен әрекеттесіп, Cr(V), Cr(IV) және, сайып келгенде, Cr(III) түзеді. Соңғысы жасуша ядросында өте уытты Cr(III) ДНҚ қосындыларының түзілуіне әкелуі мүмкін. Осы аралық өнімдердің барлығы ДНҚ зақымдануын немесе ДНҚ-ақуыздың айқаспалы байланыстарын тудыруы мүмкін. Хромның канцерогенділігін түсіндірудің бірнеше механизмдері ұсынылды. Шын мәнінде, Cr-индукцияланған канцерогенез тінге, жасуша түріне, Cr(VI) концентрациясына, әсер ету уақытына және белгілі бір жылу соққысының белоктарының изоформаларына, хромосомалық тұрақсыздыққа, ядролық ақуыз I (Nupr) индукциясы, ДНҚ аддукциясы және бос радикалдардың түзілуіне байланысты болуы мүмкін; Cr(V) және Cr(IV) аралық өнімдерінің реактивтілігі. Ген экспрессиясының эпигенетикалық өзгерістері канцерогенездің негізгі элементі болып саналады.*

Қорытынды: *Канцерогенез механизмдерін түсіну Cr(VI)-индукцияланған қатерлі ісіктің алдын алу және емдеу үшін маңызды. Хром биогеохимиялық провинциясында онкогенездің алдын алу үшін стратегиялық әзірлемелер қажет.*

Түйінді сөздер: *алты валентті хром, канцерогенез, ауыр металдар, онкогенез.*

АННОТАЦИЯ

ХРОМ-ИНДУЦИРОВАННЫЙ КАНЦЕРОГЕНЕЗ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Согласно данным международного агентства по изучению рака (IARC), шестивалентный хром Cr(VI) признан профессиональным канцерогеном I группы. Доказано, что Cr(VI) связан с раком легких, полости носа и околоносовых пазух. Исследование на Балтиморской когорте (2357 человек) продемонстрировало положительную корреляцию между кумулятивным воздействием Cr(VI) и уровнем смертности от рака легких. В западном регионе Казахстана в Актюбинской области сформировалась устойчивая антропотехногенная хромовая биохимическая провинция, в результате многолетней деятельности предприятий АО ТНК «Казхром» и АО «Актюбинский завод хромовых соединений», которая оказывает влияние на здоровье населения данного региона. Обследование рабочих завода ферросплавов (возраст 50-59 лет) показало, что в течение 15 лет смертность среди них была существенно выше,*

чем у остального населения: у мужчин – в 3,3 раза, у женщин – 7,9 раза. Имеется огромный материал по воздействию на организм шестивалентного хрома, который нуждается в упорядочивании и раскрытии роли последнего в канцерогенезе.

***Цель статьи** – освещение роли шестивалентного хрома в канцерогенезе.*

***Методы:** Проведен анализ данных MEDLINE, Embase, Scopus, PubMed, Cochrane Central Register of Controlled Trials для отбора и анализа релевантной информации за последние 10 лет по ключевым словам: шестивалентный хром, канцерогенез, тяжелые металлы, онкогенез. Всего найдено 173 источника, включено в анализ 50.*

***Результаты:** В теле человека Cr(VI) может вступать в реакцию с клеточными восстановителями с образованием Cr(V), Cr(IV) и, в конечном счете, Cr(III). Последнее может привести к образованию высокотоксичных аддуктов Cr(III) ДНК в ядре клетки. Промежуточные соединения могут вызывать повреждения ДНК или перекрестных связей ДНК-белок. Предлагается несколько механизмов канцерогенности хрома. Cr-индуцированный канцерогенез, вероятно, зависит от ткани, типа клеток, концентрации Cr(VI), времени воздействия, хромосомной нестабильности, ядерного белка I индукции, аддукции ДНК и образования свободных радикалов; реакционной способности промежуточных соединений Cr(V) и Cr(IV). Эпигенетическое изменение экспрессии генов рассматривается как ключевой элемент канцерогенеза.*

***Заключение:** Понимание механизмов канцерогенеза важно для профилактики и лечения рака, индуцированного Cr(VI). Необходимы стратегические разработки по профилактике онкогенеза в хромовой биогеохимической провинции.*

***Ключевые слова:** шестивалентный хром, канцерогенез, тяжелые металлы, онкогенез.*

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THE QUALITY OF LIFE OF WOMEN WITH BREAST CANCER: A LITERATURE REVIEW

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АННОТАЦИЯ

Relevance: *Breast cancer (BC) is the most common type of cancer among women, with a steady increase in cases. In recent decades, more attention has been given to studying the quality of life of women with this diagnosis. Quality of life is assessed across four health aspects: physical, psychological, social, and sexual. Considering all these aspects is crucial when studying the quality of life of women with breast cancer. These assessments are important in modern medicine as they evaluate patient conditions before treatment and track changes during therapy.*

The study aimed to *examine scientific studies on the quality of physical life of women with breast cancer, considering psychological, social, and sexual health aspects to thoroughly understand the disease's impact on women's lives, which will help identify existing problems and needs.*

Methods: *An analytical review of sources from Scopus, PubMed, ScienceDirect, Web of Science, and eLibrary was conducted. Out of 185 analyzed sources, 46 were included in the review, comprising open full-text articles in English and Russian.*

Results: *Patients who had reconstructive surgery for BC reported a higher quality of life than those who had a radical mastectomy, with better physical and psychological health and less pain. However, all women experienced a general decrease in quality of life post-treatment, especially in emotional and sexual areas, due to psychological stress, body image changes, and altered sexual identity.*

Conclusions: *The study highlights the impact of different treatments on the quality of life of women with breast cancer, enabling measures to enhance their physical, psychological, social, and sexual health. This supports developing effective rehabilitation and support programs to improve their overall quality of life.*

Keywords: *woman, breast cancer (BC), quality of life, physical health, psychological health, social health, sexual health.*

Introduction: Breast cancer (BC) is the leading oncological disease in women, and according to statistics, its prevalence is increasing every year [1] (Figure 1). In developed countries, this type of cancer occurs in at least one in ten women [2]. It is a serious and multifaceted disease that has a physical, emotional, and practical impact. According to the GLOBOCAN 2020 estimate, 2.3 million new cases are registered each year, and the mortality rate from BC is 7%. This type of cancer accounts for a quarter of all cancer cases and one-sixth of all cancer deaths. It is the leading cause of cancer in countries with both highly developed and transitional economies [3].

According to GLOBOCAN 2022 data, the incidence of breast cancer in Kazakhstan is 12.6% of new cases and occupies a leading position (Figure 2). The mortality rate from breast cancer is 10.9%, and the 5-year prevalence rate per 100,000 population is 17.9 [4].

In medicine, one of the important areas is the study of a patient's quality of life, that is, an assessment of how satisfied a person is with his life from a physical, social, psychological, and spiritual point of view. In other words, this is an assessment of the general well-being of a person in various aspects of his life based on their perception [5]. The World Health Organization (WHO) defines quality of life as an individual relationship between the individual's position in society and his/her personal goals, opportunities, plans, and degree of distress [6]. Over the past decade, quality of life has become an important indicator of the treatment outcomes of cancer patients [7]. Breast cancer is a special disease because it can seriously impair the appearance of female patients, which directly or indirectly affects their quality of life, in addition to the fear of cancer, its recurrence, and possible death [8].

In oncology, the concept of quality of life is important due to the characteristics of the pathology itself and the radical nature of treatment methods (surgery, radiation, and chemotherapy) [6]. Treatment of breast cancer often begins with surgical intervention in the form of mastectomy (with or without reconstruction) or a conservative approach, including lumpectomy and oncoplastic procedures [9]. Various studies have assessed differences in quality of life depending on the method of breast cancer surgery [10].

The study used a diagnostic survey method with the use of standardized questionnaires to assess the quality of life in women treated for breast cancer, including the European Organization for Research and Treatment of Can-

cer (EORTC) questionnaires - Core-30 and Breast-23 module (QLQ-C30 and QLQ-BR23), the universal questionnaire "SF-36 Health status survey » (MOS SF-36), as well as a specialized questionnaire Breast -Q.

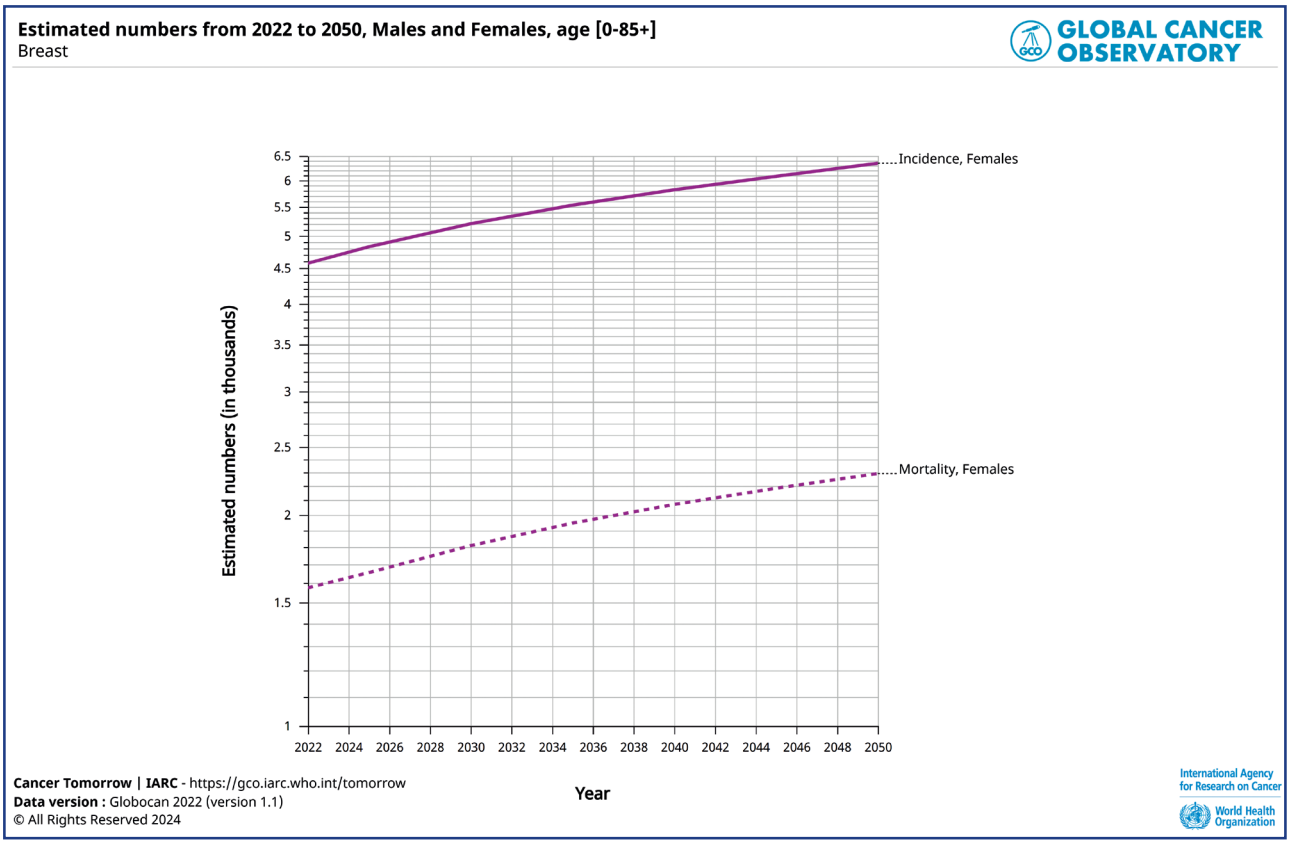

Figure 1 – Dynamic growth of breast cancer incidence and mortality in the world from 2022 to 2050, age (0-85+) [4]

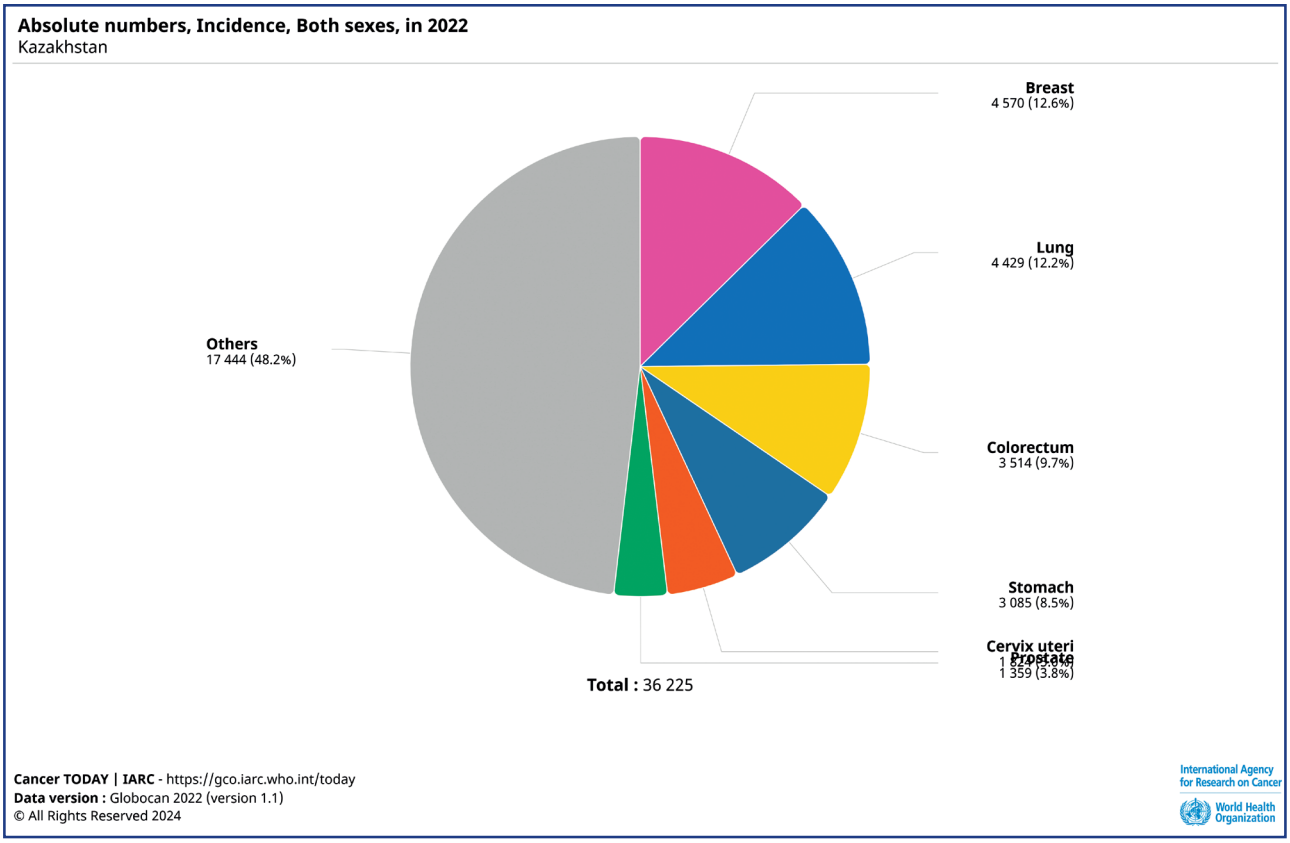

Figure 2 – Incidence of malignant neoplasms in Kazakhstan [4]

It is known that different surgical treatment options for breast cancer can have different effects on the quality of life of women who have undergone the operation [6]. Surgical intervention has not only physiological but also psychological and social consequences, as a woman can lose one of the main symbols of femininity – her breasts [11]. For many years, radical mastectomy was the only surgical method for treating breast cancer. However, this intervention is often accompanied by postmastectomy syndrome, which has an irreversible traumatic effect on the psychological state of a woman. Postoperative cosmetic defect forces a woman to change her lifestyle in order to hide the problem from others. This often leads to problems in her personal life, sexual dysfunction, emotional isolation, and the development of bad habits [12, 13]. This disease affects not only health but also affects the social and psychosexual aspects of patients' lives [14].

The study aimed to examine scientific studies on the quality of physical life of women with breast cancer, considering psychological, social, and sexual health aspects to thoroughly understand the disease's impact on women's lives, which will help identify existing problems and needs.

Materials and methods: A search of sources was conducted in open databases Scopus, PubMed, ScienceDirect, Web of Science, and eLibrary using the keywords: "woman," "breast cancer," "quality of life," "physical health," "psychological health," "social health," "sexual health." Full-text articles in English and Russian were included in the analysis. A total of 185 sources were selected, of which 46 were included in the analytical review.

Results:

Physical health. Particular attention was paid to the physical factor since patients often reported pain and decreased range of motion in the arm on the side where the surgery was performed [15]. All groups of patients with stage I-II breast cancer, locally advanced forms of breast cancer in stages III and IV, as well as progression of the tumor process, demonstrated a decrease in the level of physical functioning caused by the traumatic consequences of surgery, such as pain, limitation of physical activity and range of motion of the upper limb, and the development of lymphedema [16-18]. According to the physical condition scale, which assesses negative physical consequences, the highest level of physical functioning was recorded in women with stage I-II breast cancer (80.46 ± 2.64 points), while the lowest level was observed in patients with locally advanced forms of breast cancer (61.72 ± 1.99 points). Interestingly, the level of physical functioning in patients with progressive tumor process was relatively higher (65.34±2.38 points). It is worth noting that patients with advanced disease also had higher levels of fatigue, nausea, and vomiting, which are associated with intoxication and cancer cachexia. (56.4±2.38 and 17.83±2.38 points, respectively) [16, 1 7]. The development of lymphatic edema and upper limb dysfunction negatively impact the patient's daily activities. In particular, swelling of the hands makes it difficult for women to perform their usual household chores, as well as to select and wear clothes. In more severe cases, there may be a loss of the ability to self-care and the need for outside help even when performing basic tasks, such as zipping up a zipper [1, 19, 20].

Psychological health. The ability to perform role functions and psycho-emotional state is another important aspect that needs to be taken into account when measuring the quality of life of women with breast cancer [16]. The Psychosocial Status (PW) scale contains items covering body image feelings. At diagnosis, 45% of women had a severe level of state anxiety, while 15.2% had a severe level of personal anxiety. After treatment, only 18.9% had a severe level of state anxiety, indicating a statistically significant improvement ($p<0.001$). The same trend was observed for personal anxiety ($p = 0.009$) [21-23].

Cancer can be a hidden source of stress, affecting the psyche as an implicit factor that poses a threat to life and is reflected in emotional and cognitive aspects containing information about the disease. In women in remission, the level of role functioning associated with the emotional state is statistically higher compared to women with stage 4 breast cancer ($p = 0.001$) [24]. The majority of participants who underwent total mastectomy noted the presence of serious signs of depression ($p = 0.04$). More than 8% of participants also reported at least a moderate degree of anxiety. Among the participants who planned to undergo total mastectomy, pronounced symptoms of anxiety were often observed ($p = 0.04$). Fear of the spread of the cancer process, possible development of the tumor in other organs, as well as depression, sleep disorders, and limitations in everyday life, work, and professional opportunities significantly affect performance and psychological state. These factors often cause depression and other mental disorders in female patients [16]. Thus, anxiety and depression were observed in 20-30% of female patients [3]. Some studies have shown that increasing the level of education and knowledge of breast cancer patients who are in a serious condition before surgery can significantly reduce their anxiety levels before surgery [9].

A woman's psychological readiness for the outcome of the surgery is no less important than her preparation for the surgery itself. Postoperative shock is often observed after a mastectomy. Authors describe typical reactions of women after breast removal, such as sadness, apathy, fear, and despair [2, 25]. These manifestations can complicate the rehabilitation process and create additional stressful situations. Surgery itself does not guarantee a complete

recovery from cancer [2, 26]. The psychological reasons for this are associated with a sharp decrease in self-esteem, difficulties with social adaptation, changes in the perception of one's own body, and sometimes a temporary loss of one's own identity [2, 27]. Developed components of resilience in women with breast cancer have a positive effect on the assessment of their physical and mental state. The confidence of these women in their inherent value and the environment's safety can play a role in assessing their satisfaction with the quality of life. The indicator "risk acceptance" is also positively associated with parameters of quality of life such as role in society, emotional state (p = 0.020), life activity (p = 0.019), and mental health (p = 0.043). This means that women with breast cancer who have highly developed risk acceptance components feel more control over their mental state [28, 29]. The patient's mental state changes even more when complications arise that develop after radical treatment [1].

Psychoeducational support has a positive effect on breast cancer symptoms and the mental state of patients suffering from this disease [30]. Psychological support for patients with breast cancer should be available at all stages of treatment and rehabilitation and also continue after the completion of radical treatment. This is important for improving the quality of life of patients, which is becoming an increasingly important task, including aspects of cost-effectiveness [1, 31].

Sexual health. The need to study the quality of life of patients is because the breast is associated with sexuality and feminine nature in general, and as a result, this disease affects female identity and body image [32, 33]. Patients who have undergone radical surgical treatment may face the problem of low self-esteem, known as the "half-woman/body complex." They may feel insecure about their femininity and experience a low sense of self-worth in social terms. In addition, women who have undergone surgical treatment often experience depression [34, 35], and sexual dysfunctions often lead to dissatisfaction in intimate relationships [36]. The women included in the study were significantly concerned about their future (30.97±33.86, Me = 33.33). It should be emphasized that during the functional assessment, women rated sexual functioning as the lowest (17.49±23.56, Me = 0.00). The average scores of sexual satisfaction of sexually active patients were 46.41±33.86 points on the sexual state scale (SW), Me = 33.33). The average value of the body image assessment scale of patients was (61.57±32.95, Me = 66.67). Sexual functioning, sexual satisfaction, and body image were rated higher by women who had undergone breast conservation surgery and lower by respondents who had undergone mastectomy. In the group of women who had undergone mastectomy, a decrease in libido was more often noted, which led to a decrease in their quality of life [11, 34, 37]. Higher levels of anxiety were observed among married or partnered women. This may also be due to a feeling of insecurity about their partners' acceptance of the disease, with the additional fear that their partners may break up with them because of the disease or leave them for another woman. Women who were married or had a partner had a 2.28 times higher risk of severe anxiety compared to single women, and those who took anxiolytics had a 2.13 times higher risk of severe anxiety [21].

Also, iatrogenic menopause (low libido, vaginal lubrication, dyspareunia, and loss of sensation in previously sensitive breasts) can significantly impair sexuality. Overall mean scores for both sexual quality of life and dyadic adjustment were significantly lower among women who had undergone mastectomy than in the control group (p<0.001). When analyzing educational level, women with secondary education and above demonstrated higher sexual quality of life scores than women with primary education or less (mean scores: 56.5±28.02 and 36.54±28.10) (p = 0.002). Concerning the women's income, those whose income was equal to or greater than their expenses demonstrated significantly higher scores on the quality of sexual life (mean scores: 33.35±26.05 and 52.50±29.74) (p = 0.003) and dyadic adaptation (mean scores: 88.90±30.55 and 107.43±26.61) (p = 0.004) [2, 38].

Although treatment often has profound and distressing effects on self-esteem and sexual function, these issues are rarely addressed by physicians. Often, this silence is due to the lack of readily available resources and uncertainty about appropriate rehabilitation strategies. Cultural barriers may also be a factor [37, 39].

Social health. As for the social aspect, all the support from family members and loved ones of these women is a driving factor in improving the quality of life [15, 40]. The social functioning of women after surgery worsens due to cosmetic defects, swelling after mastectomy, limited mobility of the limbs, chronic pain, as well as itching and burning in locally advanced processes. The absence of a mammary gland also affects patients' behavior. A decrease in the level of social functioning can lead to family problems, isolation, and a reduction in the social circle. Women with locally advanced forms of breast cancer had a higher level of social functioning (73.12 ± 1.99 points), while in patients with a progressive tumor process, this indicator was the lowest (69.31 ± 2.38 points). In patients with stage I-II breast cancer, the level of social functioning was average (70.86 ± 2.64 points) [16, 1 7].

Education level also influences quality of life. It gives them access to information and more tools, resources, and strategies for coping with the disease [21].

Emotional support from families was a major factor in the quality of life of these women. The way families responded to the disease was very important. Women reported that they were looking for sympathy and pity; they wanted to be understood and treated as healthy people. The physical presence of the family was also very important: it helped the patients to perform daily activities and helped them cope with the cancer more easily. It was important to have their children nearby. Most patients reported that they received satisfactory support from their husbands, who accompanied them to appointments and helped them around the house [3, 18]. Women who had a conservative mastectomy had a better mean social relationship score (4.29) than women who had a radical mastectomy. Social relationships include social connections, social support, and sexual life [15]. However, sometimes, women might not receive very effective support [3]. Also, a person in a similar life situation can provide social support [41].

After treatment, a woman can consider social support as a coping resource that can improve their quality of life and ease the transition to life after treatment. Post hoc paired comparisons showed that women in the breast-conserving surgery group felt more social support than women in the mastectomy group ($p<0.001$). There were differences between surgical procedures in all subscale scores of the Multidimensional Scale of Perceived Social Support (MSPS) for the family/friends and significant others parameters in favor of breast-conserving surgery: MPS-family ($p=0.016$), MPS-friends ($p<0.001$), and MPS-significant other ($p=0.003$) [42]. Some women limit their contact with people, avoiding communication with friends and acquaintances. Their life is especially challenging in summer when it is difficult to hide the defect under clothing. This leads to social isolation. Many women are forced to give up activities they normally do, such as driving, playing sports, or gardening, which increases their social isolation and reduces or eliminates opportunities for communication and dialogue on various topics [1].

Breast cancer survivors are forced to make significant changes to their lifestyle and plans for the future, including the decision to return to work or regular activities. This can cause stress and long-term negative emotions [36]. Work can provide a distraction from the stress of surgery and help patients re-establish their social identity. Patients wanted to be identified by their careers rather than their illnesses. However, the financial impact of health care bills puts pressure on patients and their families. Some women have had time off or even lost their jobs, which adds to the burden [3, 39].

Social consequences of radical treatment of breast cancer include changes in the role of women in the family and possible disability [1].

Discussion: The obtained data show that reconstructive plastic surgery has a significant positive impact on the quality of life of women who survived breast cancer. This is confirmed by the increase in scores on all aspects of the questionnaires in women after reconstructive surgery compared to those who underwent radical mastectomy [1]. Women noted a worsening quality of life (the average score was 53.88 points out of 100), especially in the emotional (59.77) and sexual (17.49) spheres, and negatively assessed their bodies (61.57). Patients who underwent breast conservation surgery demonstrated better physical ($p = 0.001$) and sexual ($p = 0.007$) functioning and experienced less pain ($p = 0.003$) and shoulder discomfort ($p = 0.024$) compared to those who underwent radical mastectomy. Women who underwent breast reconstruction rated their quality of life higher ($p = 0.003$). Overall, patients who underwent breast conservation demonstrated higher quality of life in these domains compared to women who underwent mastectomy. Symptoms in patients after breast conservation were comparable to those who underwent mastectomy, except for pain, which was higher in the latter. Significant differences were noted in the subscales of the functional scales of the QLQ-BR23 questionnaire: body image ($p = 0.003$), sexual functioning ($p = 0.007$), and sexual satisfaction ($p = 0.005$), as well as in the subscale of shoulder-related symptoms ($p = 0.024$). Women who underwent mastectomy reported greater shoulder-related symptom severity compared to those who underwent breast-conserving surgery (mean 31.56 versus 26.56) [34].

Supportive educational activities should be provided at the family and community level through health systems to enhance psychological well-being, spiritual health, and access to social support resources so that women can cope with their disease, thereby improving their quality of life [43]. Involving their loved ones in preventive work is important to improve the patients' quality of life during and after treatment. Psychological work with patients and their relatives will help to better understand the nature of the disease, which will contribute to the dissemination of reliable information in society [44]. Therefore, healthcare providers are tasked with providing physical care, information, knowledge, and attention that support the individual woman's efforts to overcome difficulties [45].

In cancer research, quality of life assessment plays an important role in determining the success of treatment and in predicting the course of the disease. This assessment allows physicians to tailor symptomatic treatment to individual characteristics and provide valuable data on the prognosis of the disease [46].

Conclusion: This review confirms the importance of reconstructive surgery in improving the quality of life of women treated for breast cancer. The increase in scores on

all scales of the questionnaire after reconstructive surgery indicates a positive impact of these procedures on patients' physical, emotional, and social well-being. However, after radical mastectomy, there is a deterioration in the overall quality of life of women, especially in the areas of emotional and sexual well-being, as well as in self-esteem. It is worth noting that patients who underwent breast conservation surgery show better results in physical and sexual function and experience less pain and discomfort in the shoulder compared with women who underwent mastectomy. These results emphasize the importance of breast conservation and reconstructive methods during breast cancer treatment. In addition, the review shows that maintaining the previous lifestyle is an important aspect for patients after radical treatment of breast cancer. They face a variety of socio-psychological difficulties, such as fear of relapse, disruption of sexual relationships, and social isolation, which significantly affect their quality of life.

Comprehensive support, including medical treatment, psychological assistance, educational programs, and access to social resources, is required to improve the quality of life of women with breast cancer. Further research in this area will help to develop effective support and rehabilitation strategies for this group of patients.

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІ БАР ӘЙЕЛДЕРДІҢ ӨМІР САПАСЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі. *Қазір сүт безінің қатерлі ісігі (СБҚІ) әйелдер арасында ең көп таралған қатерлі ісік болып табылады және статистика аурушаңдықтың тұрақты өсуін көрсетеді. Соңғы онжылдықтарда осы диагноз анықталған әйелдердің өмір сүру сапасын зерттеуге көбірек көңіл бөлінді. Өмір сапасы денсаулықтың төрт негізгі аспектісі бойынша бағаланады: физикалық, психологиялық, әлеуметтік және сексуалды. Сүт безі қатерлі ісігі бар әйелдердің өмір сүру сапасын зерттеу кезінде осы аспектілердің барлығын ескеру өте маңызды. Қазіргі заманғы медицинада өмір сапасын бағалау әдістері кеңінен қолданылады, өйткені олар пациенттерді емдеуге дейінгі өмір сүру сапасын бағалауға және терапия процесінде оның өзгеруін бақылауға мүмкіндік береді.*

Зерттеудің мақсаты *– денсаулықтың физикалық, психологиялық, әлеуметтік және сексуалды аспектілерін ескере отырып, сүт безі қатерлі ісігі бар әйелдердің өмір сүру сапасын бағалауға арналған ғылыми зерттеулерді зерттеу. Осы зерттеу аурудың әйелдер денсаулығының аспектілеріне әсерін терең түсіну қажеттілігімен негізделген, ал бұл қазіргі проблемалар мен қажеттіліктерді анықтауға мүмкіндік береді.*

Әдістері. *Түйінді сөздер бойынша Scopus, PubMed, ScienceDirect, Web of Science, eLibrary ғылыми дерекқорларынан дереккөздерге аналитикалық шолу жүргізілді. Барлығы 185 дереккөз талданды, оның 46-сі шолуға енгізілген. Әдебиет шолуына енгізілген жарияланымдар ағылшын және орыс тілдеріндегі ашық толық мәтінді мақалалар болды.*

Нәтижелері. *Алынған нәтижелер СБҚІ кейін реконструктивті-пластикалық операциядан өткен пациенттердің радикалды мастэктомиядан өткендермен салыстырғанда өмір сүру сапасы жоғары екенін көрсетті. Бұл физикалық және психологиялық функцияның жақсаруымен, сондай-ақ ауырсынудың төмендеуімен расталады. Алайда барлық әйелдер СБҚІ-н емдегеннен кейін өмір сапасының жалпы төмендеуін сезінеді, әсіресе эмоционалды және сексуалды салаларда, бұл диагноз бен емдеуден туындаған күйзеліске, сондай-ақ дене бейнесінің өзгеруіне және сексуалды өзін-өзі анықтауға байланысты.*

Қорытынды. *Зерттеу нәтижелері әртүрлі емдеу әдістерінің СБҚІ бар әйелдердің өмір сапасына әсерін көрсетеді, бұл олардың физикалық, психологиялық, әлеуметтік және сексуалды денсаулығын жақсарту үшін негізделген шаралар қабылдауға мүмкіндік береді. Бұл СБҚІ бар әйелдердің жалпы өмір сүру сапасын арттыру үшін тиімді оңалту және қолдау бағдарламаларын әзірлеуге ықпал етеді.*

Түйінді сөздер: *әйел, сүт безі қатерлі ісігі, өмір сапасы, физикалық денсаулық, психологиялық денсаулық, әлеуметтік денсаулық, сексуалды денсаулық.*

АННОТАЦИЯ

КАЧЕСТВО ЖИЗНИ ЖЕНЩИН С РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Сейчас рак молочной железы (РМЖ) – самый распространенный вид рака среди женщин, и статистика показывает устойчивый рост числа случаев. В последние десятилетия уделяется повышенное внимание изучению качества жизни женщин с этим диагнозом. Качество жизни оценивается по четырем аспектам здоровья: физическому, психологическому, социальному и сексуальному. При изучении качества жизни женщин с РМЖ особенно важно учитывать все эти аспекты. Методы оценки качества жизни важны в современной медицине, так как позволяют оценить состояние пациенток до лечения и отслеживать его изменения в процессе терапии.*

Цель исследования *– изучить научные исследования по оценке качества жизни женщин с РМЖ, учитывая физические, психологические, социальные и сексуальные аспекты здоровья, для более глубокого понимания воздействия болезни на жизнь женщин и выявления существующих проблем и потребностей.*

Методы: *Был проведен поиск источников в базах данных Scopus, PubMed, ScienceDirect, Web of Science, eLibrary по ключевым словам исследования. В анализ были включены открытые полнотекстовые статьи на английском и русском языках. Всего было отобрано 185 источников, из которых 46 включены в обзор.*

Результаты: *Полученные результаты показали, что пациентки, перенесшие реконструктивно-пластическую операцию при РМЖ, имеют более высокое качество жизни по сравнению с теми, кто перенес радикальную мастэктомию. Это выражается в улучшении физического и психологического здоровья, а также в снижении болевых ощущений. Однако у всех женщин после лечения*

РМЖ наблюдается общее снижение качества жизни, особенно в эмоциональной и сексуальной сферах, что связано с психологическим стрессом, вызванным диагнозом и лечением, а также изменениями в образе тела и сексуальной самоидентификации.

Заключение: *Результаты исследования позволяют получить четкую картину влияния различных методов лечения на качество жизни женщин с РМЖ, что определяет возможность проведения обоснованных организационно-методических мероприятий по улучшению физического, психологического, социального и сексуального здоровья пациенток. Это способствует разработке эффективных программ реабилитации и поддержки для повышения общего качества жизни женщин с РМЖ.*

Ключевые слова: *женщина, рак молочной железы (РМЖ), качество жизни, физическое здоровье, психологическое здоровье, оциальное здоровье, сексуальное здоровье.*

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RECONSTRUCTIVE SURGERIES AS AN OPTION FOR SURGICAL REHABILITATION IN BREAST CANCER TREATMENT: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Today, breast cancer (BC) occupies a leading position in the structure of cancer inci-dence among the female population. According to WHO, in 2022, over 2,296,840 million cases of primary detection worldwide were registered. Therefore, 11.7% of the total number of primary detected cancers and more than 685,000 women died from this disease (6.9% of the total mortality). The surgical method remains the leading one and is being improved yearly due to the increasing early detection in relatively young and nondisabled patients. Reconstructive surgery is gaining more and more popularity as a component of a rehabilitation program.*

The study aimed to *evaluate the effectiveness of reconstructive surgeries (RS) on the mammary gland during surgical rehabilitation.*

Methods: *Starting in 2014, we searched the databases Scopus, PubMed, and e-Library for scientific publications published over the past 10 years. The search results revealed more than 2,700 articles, of which 36 sources were selected according to the inclusion and exclusion criteria.*

Results: *The effectiveness of RS in the surgical rehabilitation of patients with breast cancer has been established, depending on the localization and pathomorphological characteristics of the tumor. Patients' satisfaction with the aesthetic result, a crucial aspect of their emotional and psychological wellbeing, was assessed using the Breast-Q questionnaire. According to the results of randomized, single-center, and multicenter studies and meta-analyses, there is a steady increase in simultaneous and delayed RS in treating BC.*

Conclusion: *RS is an advanced method of surgical rehabilitation. Its main objective is to ensure a high level of psychosexual well-being and satisfaction with the quality of life in patients while maintaining oncological safety. However, pursuing oncological safety requires constant improvement and a deeper study of each technique. Analyzing RS's early and longterm results will allow you to choose the optimal method for each patient based on the need for aesthetically safe and reliable surgical rehabilitation. This underscores the importance of ongoing research in this field.*

Keywords: *breast cancer (BC), reconstructive surgeries (RS), surgical rehabilitation.*

Introduction: Breast cancer (BC) is the most common cancer among women in the Republic of Kazakhstan, accounting for 23% of the total cancer incidence, and is also the leading cause of mortality among cancer patients (12.3% of cancer deaths). Modern high-tech screening programs increase the detection of cancer at early stages, and the use of effective treatment regimens increases the survival rate of patients. Despite the widespread use of radical mastectomy as the primary method of surgical treatment, new methods of oncoplastic therapy are gaining popularity [1], as mastectomy hurts women's body acceptance, psychosexual well-being, and quality of life [2]. The concept of "quality of life" in cancer patients has changed the technique of surgical treatment in breast cancer [3].

The main goal of oncological surgery is cancer resection, that is, the removal of the tumor along with the breast tissue with clean margins. However, there is a growing realization that the aesthetic results of these procedures are significant [4].

Skin-sparing mastectomy (SSM), first proposed by B. Torth in 1991, allows for the maximum preservation of the skin and muscles while removing the nipple-areolar complex (NAC) and performing immediate reconstruction afterward. Such a procedure meets the requirements for radical treatment and patients' cosmetic expectations. Over the next 30 years, it was proved that SSM does not increase the risk of regional metastases [5].

In 1979, T. Robbins first used an ellipsoidal lower transverse rectus abdominis musculocutaneous (TRAM) flap of the anterior abdominal wall for breast reconstruction [6].

The two main principles that should guide surgeons when performing breast-conserving surgery (BCS) are achieving negative resection margins and obtaining as satisfactory cosmetic results as possible [7].

The advantages of immediate reconstruction include superior aesthetic results, improved psychosocial well-being after mastectomy, at least in the short term, shorter operative time, fewer surgical interventions, lower costs, and accelerated social reintegration compared to delayed reconstruction. Immediate reconstruction requires higher quality skin flaps than mastectomy, followed by prolonged rebuilding, and may also increase the risk of complications. The main advantage of delayed reconstruction is that like-

ly complications do not affect the efficacy of adjuvant treatment. In addition, with planned adjuvant radiotherapy after surgical treatment, the patient has more time to make an informed decision about the type and features of reconstruction, which positively affects the balance of preoperative expectations and satisfaction with the final result.

The study aimed to evaluate the effectiveness of reconstructive and reparative surgery (RRS) on the breast in the surgical rehabilitation of patients with breast cancer.

Materials and methods: This review included domestic and foreign publications from the last 10 years (2014-2023) found in PubMed, Google Scholar, and Scopus databases. The search was based on the following key phrases: "breast cancer," "reconstructive and reparative surgery," and "surgical rehabilitation." *Inclusion criteria:* articles describing the results of randomized single-center and multicentre trials, meta-analyses, and systematic reviews with access to the full text. *Exclusion criteria:* case reports, literature reviews, conference abstracts, and articles without access to the full text. More than 2,700 articles were retrieved from the search results, of which 40 were selected according to the criteria. The concordance of the authors' opinions is 95%.

Results:

1. Reconstruction techniques using own tissue

In a multicentre randomized controlled trial, J.A. Ter Stege et al. used a questionnaire to find that more than 60% of breast cancer patients considering immediate breast reconstruction after mastectomy experienced clinically significant decisional conflict (CSDC) related to personal preference for breast shape and anxiety. Patients who doubted the choice of RRS, did not favor RRS, were opposed to RRS, or refused RRS were likelier to experience CSDC than patients who initially opted for RRS. Moreover, patients with higher levels of anxiety were more likely to experience CSDC.

This is the first study to assess the conflict in the decision to undergo immediate RRS in a large sample of female breast cancer patients. The level of decision conflict in this sample was comparable to the level of decision conflict in the sample of breast cancer patients considering delayed RRS in the two previous studies, relatively high compared to the level of decision conflict in the sample of breast cancer patients considering immediate RRS (mean = 33 (24)), and higher than the level of decision conflict in the sample of breast cancer patients considering various health-related factors. The group with the highest standardized (pre-decision) level of decision conflict were patients who made decisions on their own [2].

The four most commonly used techniques for autologous breast reconstruction include latissimus dorsi (LD) flaps, transverse rectus myocutaneous (TRAM) flaps-either free (fTRAM) or muscle-sparing free flaps (pTRAM)-and the deep inferior epigastric artery perforator (DIEP) flap [8].

1.1. Reconstruction with TRAM

Hartrampf first described using a transverse rectus abdominis myocutaneous flap (TRAM) in 1982. This technique involves elevating the abdominal myocutaneous flap with perforator vessels coming off the upper epigastric vessels [9].

The technique using the TRAM flap has undergone numerous modifications, resulting in different variations such as the muscle-sparing TRAM flap (MS-TRAM), DIEP, and superficial inferior epigastric artery (SIEA) flaps to reduce the morbidity of the abdominal donor site by reducing the amount of muscle [10].

The perfect flap for breast reconstruction can simultaneously provide improved vascularisation and reduce donor site morbidity. However, surgeon preference is another critical factor in achieving permanent and sustainable results. If the surgeon is not familiar with microsurgery, the use of pTRAM is a better option than fTRAM or DIEP for autologous breast reconstruction. Flap selection can be based on patient characteristics if the surgeon is familiar with TRAM, DIEP, and pTRAM techniques. Our results suggest that fTRAM may be appropriate for patients with large breast volume and low risk of herniation. Partial flap necrosis and fat necrosis prevent breast tissue volume preservation [11].

Flap type was found to be the only independent factor affecting patient satisfaction with surgical outcomes, considering limiting factors such as age at the time of surgery, country of surgery, timing of reconstruction, and adjuvant therapy [12].

Our results show that the most technically challenging option is not always superior to the traditional option. Compared with fTRAM and DIEP flaps, pTRAM flaps are losing popularity because they reduce vascularisation and increase the risk of abdominal complications. However, pTRAM flaps are a significant option because they have several advantages over fTRAM and DIEP flaps, including no need for microsurgery, shorter operative time, shorter hospital stay, and lower treatment costs. Thus, surgeons need not insist on using fTRAM or DIEP flaps and exclude pTRAM because a single flap cannot guarantee superior results concerning flap vascularisation and donor site vascularisation [11].

1.2. Reconstruction with DIEP

The DIEP flap was first described for breast reconstruction in 1989 by Koshima and Soeda and popularised by Allen and Treece [13]. This perforator flap has a theoretical advantage in reducing donor site morbidity compared to pTRAM and fTRAM flaps by eliminating muscle harvesting. This flap has become better known in recent years due to the increasing number of surgeons trained in this technique. The DIEP flap is more likely to preserve the intercostal nerves because the vascular pedicle is usually completely skeletonized when such a flap is taken. In particular, the risk of nerve injury is reduced when the medial row of the perforator is chosen. This flap shows a significant dif-

ference in postoperative hernia formation compared to pTRAM flaps [14].

DIEP flaps can be recommended for patients at increased risk of herniation, for example, obese and elderly patients. The pTRAM can be used by patients with smaller breast volumes and a lower risk of hernia [11].

According to the results of a prospective randomized five-year study, K. Seidenstuecker et al. noted that the main limiting factors for all types of RRS, affecting the results of healing after reconstruction are smoking, postoperative radiation therapy, body mass index >30, presence of DM, and flap circulatory disorders. It is worth noting that smoking significantly slows down the healing of the donor site on the abdomen (p=0.025) compared to non-smoking patients (p=0.019). With the implant-based technique, the development of capsular contracture was found in 50.7% of patients who received radiation treatment after expander-to-implant replacement versus 10.3% in non-irradiated patients [15]

1.3. Reconstruction with a skin and muscle flap based on the broadest muscle of the back (SMFBMB)

The thoracodorsal flap is a SMFBMB on the thoracodorsal vessels [16].

The SMFBMB has been a reliable option for breast reconstruction since it was first described in 1906. 1995, Angrigiani et al. first described a flap with a thoracodorsal artery perforator. Schwabegger et al. reported in 2003 the advantages of the "muscle-sparing" approach of removing a larger skin flap held by a relatively small segment of inferior muscle. J. Cook presented his study using muscle-sparing LD flaps for breast reconstruction. Over 8 years, 26 immediate and 100 delayed reconstructions using the LD flap were performed on 83 patients. Comparison of preoperative and postoperative photo analyses and registration of complications and additional procedures showed that the muscle-sparing latissimus dorsi (MSLD) flap is a universal option for breast reconstruction in various clinical conditions, with few complications and satisfactory aesthetic results [17].

The absence of capsular contracture and flap necrosis and faster cessation of postoperative lymphorrhea characterize the SMFBMB technique. Its disadvantages are the technical complexity and duration of the surgery, an additional scar in the back region, and lifelong restriction of several physical exercises (pulling up on the bar and climbing rope) [18].

Previous studies of BCS with SMFBMB have shown that marginal rates of positive resection margins after primary surgery ranged from 0% to 13%, comparable to our study's results (4%). The rates of positive resection margins after primary surgery in the BCS with SMFBMB group were significantly lower than in the BCS alone group (4% vs. 11%; P = 0.006). A meta-analysis comparing oncoplastic BCS and BCS alone showed that the marginal rate of positive resection margins in the group receiving oncoplastic surgery was significantly lower than in the group receiving BCS alone (12% vs. 21%; P<0.0001), which was similar to the results of our study. In our patients, tumors were more significant in the BCS with SMFBMB group than in the BCS alone group. However, the favorable outcome rates after primary surgery were lower in the BCS with SMFBMB group than in the BCS-only group. This may be because SMFBMB reconstruction allows for a wider resection without compromising cosmetic appearance, which is one of the most attractive features of BCS with SMFBMB [19].

More recently, the use of TDAP (thoracodorsal artery perforator) from the broadest muscle of the back for partial or total replacement of a breast tissue defect has been described. The TDAP flap uses residual lateral lipodystrophic tissue, often present after mastectomy, as autologous tissue for breast reconstruction. This results in volume enhancement in breast reconstruction and the removal of dystrophic fat under the axilla [20]. The technique is based on using a percutaneous myocutaneous perforator or thoracic artery perforator. A flap of significant size can be obtained with a single perforator, which avoids partial or complete flap loss in the postoperative period, as well as primary closure of the donor site. According to the results of a study of patients selected by computer randomization into LD and TDAP groups, E.M. Abdelrahman et al. state that the TDAP flap demonstrates efficacy on par with the LD flap in terms of feasibility, postoperative complications, cosmetic outcome, and finally early functional outcome, which is significantly better than that of the LD flap [21].

Figures 1 and 2 show a visual analysis of the algorithm for techniques using LD and TDAP flaps [21].

2. Reconstruction techniques using endoprosthesis

2.1. Implant-assisted endoprosthetic's

One-stage breast reconstruction with placement of silicone implants under the remaining skin pouch after mastectomy was first described in 1971 by surgeons R.K. Snyderman and R.H. Guthrie [22]. T. Cronin and F. Gerow introduced the silicone breast implant in 1963, and C. Radovan introduced a tissue expander for breast reconstruction in 1982. In 1984, H. Becker described a dual-chamber tissue expander with a silicone gel outer lumen with an inflatable physiological lumen, allowing one-stage breast reconstruction [3].

The use of silicone prostheses dramatically simplifies the technical aspect of RRS on the breast due to the absence of an additional donor site. Such surgeries are less traumatic, so they are most often used in oncomammological practice [23].

One of the main goals of implant-based breast reconstruction is to improve the quality of life of female patients. Well-developed test tools, such as the Breast-Q developed by A. Pusic et al. at Memorial Sloan-Kettering Cancer University of British Columbia in 2009, have allowed direct comparison of different types of breast reconstruction [24].

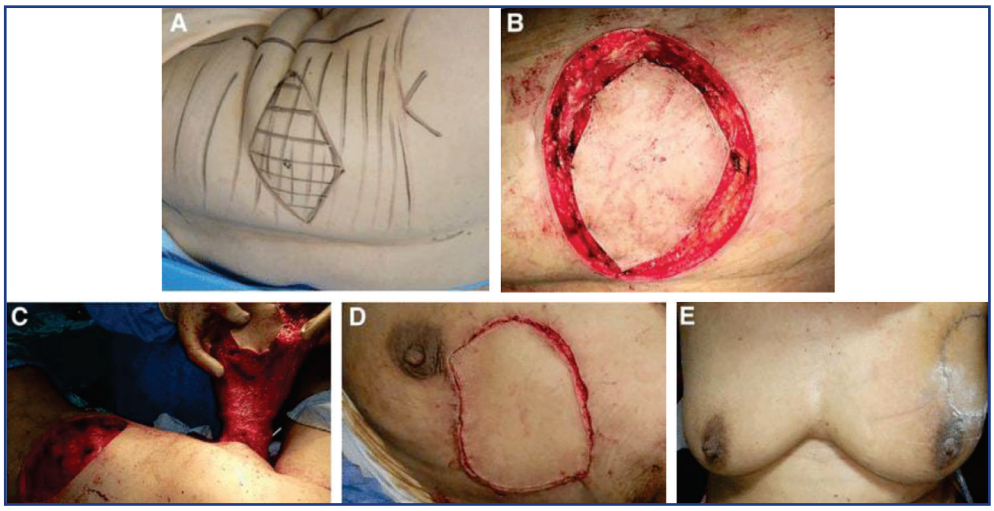

Figure 1 – Reconstruction process using LD flap: A – flap marking, B – resection and dissection, C – complete mobilization and tunnel formation, D – flap insertion, E – final result [21]

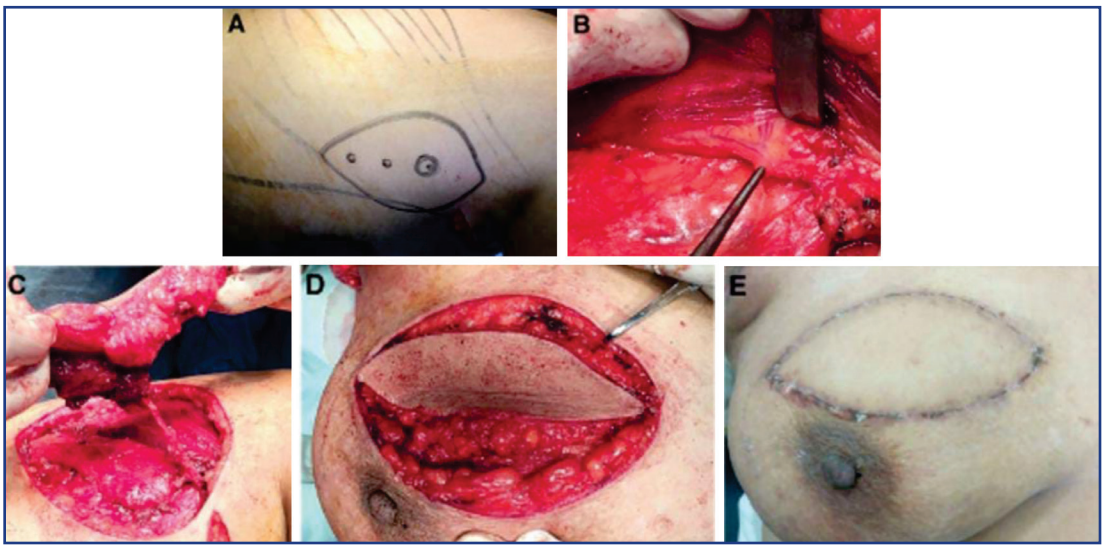

Figure 2 – Reconstruction process using TDAP flap: A – flap marking, B – identification of the thoracodorsal artery, C – complete mobilization on the vascular pedicle, D – flap insertion, E – final result [21]

The report of the first documented implant-assisted breast reconstruction was published by B. Freeman in 1962. As plastic surgeons were frustrated by the high complication rate, attempts were made to improve the technique. A shift from the subcutaneous to the submuscular plane was made, causing complete muscle coverage to become the main focus. Today, reconstructive surgeons have a full range of tools to return to subcutaneous breast reconstruction, including next-generation tissue expanders, breast implants, cell-free dermal matrices, intraoperative perfusion analysis, and fat grafting. The primary outcome was successful breast reconstruction with implants in the subcutaneous plane. Secondary outcomes included hematoma, infection, severe edema, suture deviation, skin necrosis, implant extrusion, device removal, and flap salvage. Demonstrated patient data, including age, BMI, and comorbidities (diabetes mellitus, arterial hypertension), were recorded [25].

G. Tanos et al. state that skin-sparing mastectomy followed by immediate reconstruction provides the best aesthetic results. Two-stage reconstruction using expanders and implants is recommended for women with an inappropriate amount of skin for immediate closure after implant placement or after extensive skin resection. The second stage of breast reconstruction is usually performed six months after the completion of the tissue expansion procedure. During this surgery, the expander is removed and replaced with a permanent anatomical implant, and a partial or complete capsulectomy is also performed to ensure that the permanent prosthesis fits perfectly in the pocket without any possibility of rotation or displacement. Usually, access to the implant pocket is in the submammary fold, so this method allows the surgeon to recreate the fold [26].

Implant-assisted reconstruction usually requires several procedures with refinements and modifications to complete and maintain aesthetics over time. The high rate of revision surgery becomes particularly prominent in the elective treatment of breast cancer, where unilateral

breast reconstruction often requires opposing procedures for symmetry [27].

According to a single-center randomized study conducted from 2012 to 2015, early mobilization of patients after surgery and physical exercises from the first day of the postoperative period helped prevent contracture in all patients. No breast cancer patient, regardless of the type of adjuvant therapy, had to have the implant removed after the second stage of breast reconstruction (replacement of the expander with a permanent implant) [28].

Breast reconstruction using a tissue expander can be considered as one of the acceptable options for patients who are scheduled to undergo radiotherapy [29].

Silicone gel implants are safe and acceptable components of the reconstructive range. Is this correct? Advances in gel structuring have reduced bleeding due to silicone, and cohesive gel implants are expected to have fewer problems associated with capsular rupture [30].

Additionally, it was reported that patient satisfaction rates with reconstruction in the context of radiotherapy for breast-conserving therapy (BCT) were significantly higher than with implant-based reconstruction. However, with careful patient selection, other authors have reported a relatively lower failure rate with such reconstruction [31].

The analysis of the results of the 2012-2015 single-center randomized study showed that reconstructive-plastic surgery with subcutaneous mastectomy and retained NAC as a surgical stage does not significantly affect the long-term surgical results in combined and complex treatment of breast cancer patients. Both overall and recurrence-free survival rates depended only on the prognostic factors generally recognized for this disease [32].

In general, all the described breast reconstruction techniques had comparable results and a relatively high level of aesthetic satisfaction of the patients [18].

3. Reconstruction of the nipple-areolar complex

Removal or preservation of the NAC is a current issue in oncology [33]. Oncoplastic techniques can achieve good cosmetic results even with a large volume of breast tissue resection. The problem arises in NAC reconstruction, as it is pretty challenging to achieve a natural-looking NAC. Consequently, the preservation of the NAC will achieve a better aesthetic result. While the oncological safety of NAC preservation has long been debated, there is now sufficient evidence supporting its preservation in cases of pathological non-involvement [34]. NAC preservation leads to optimal psychological satisfaction and provides a sense of less mutilating treatment [35].

NAC reconstruction should be deferred until chemotherapy and radiotherapy are completed. Some surgeons do not advise NAC reconstruction in the irradiated breast and recommend NAC tattooing to improve the cosmetic effect. Performing NAC reconstruction too early may lead to improper positioning of the NAC, spoiling the excellent result [36].

Discussion: Rehabilitation of patients with breast cancer has recently gained momentum as a comprehensive long-term intervention for a woman's comfortable return to physical and psychological fitness and adaptation to new living conditions after diagnosis and treatment. Since 1970, surgeons around the world have been working on the task of maintaining clean resection margins while maintaining aesthetic symmetry. Considering that in the Republic of Kazakhstan, the financing of oncological care is performed at the expense of Compulsory Social Health Insurance (CSHI), financial justification also plays a significant role. Since reconstructive surgeries are performed one-stage or delayed, and in the case of planned radiotherapy, one should prefer delayed reconstruction. The authors note the effect of radiotherapy on the rate of healing and preservation of the shape of the operated breast. The decision on the choice of level I and II reconstructive and reparative techniques is based on the breast's tumor location, stage, shape, and ptosis. The limiting factors may be muscle volume, subcutaneous fat, and skin of the resected and contralateral mammary glands.

In both reconstruction techniques, reduction symmetrization of the contralateral breast is performed according to the decision of the multidisciplinary team and the patient, considering the patient's characteristics, such as age, comorbidities, and other risks.

RRS using its tissue produces more positive patient feedback due to symmetry during age-related ptosis and weight changes in the late postoperative period. Bilateral reconstruction allows for almost perfect breast proportionality. The disadvantages of the method include the formation of a defect on the donor site, longer rehabilitation time, and volumes of blood loss. Complications such as ischemia, flap, and fat necrosis affect the optimal result.

Reconstruction with implants immediately after tumor node removal with skin preservation and NAC gives an immediate aesthetic result. However, in cases of extensive skin resection, a two-stage approach is the optimal solution: a temporary expander is placed in the pocket for 6 months and then replaced with a permanent anatomical implant. The disadvantages of this method are the development of capsular contracture, implant migration, and the potential for infection.

Conclusions:

1. Reconstruction should preferably be performed using a TRAM flap to preserve the functionality of the abdominal muscles in patients with a smaller breast volume and a low risk of hernia development.

2. Reconstruction with a DIEP flap is recommended in patients with a high risk of hernia development, such as obese and elderly patients.

3. TDL is a solution when there is a possible risk of postoperative lymphorrhea or radiation therapy, as there is a low risk of necrosis due to the preservation of an adequate blood supply.

4. Implant-based reconstruction is gaining incredible popularity because it is more straightforward than autologous tissue techniques. However, adjuvant radiotherapy increases the risk of implant loss and requires careful timing coordination.

Conclusion: RRSs are an advanced method of surgical rehabilitation. The main objective of this method is to provide a high level of psychosexual well-being and quality of life satisfaction in female patients while maintaining oncological safety. Despite this, oncological safety requires continuous improvement and more in-depth study of each technique. Early and long-term RRS results analysis will enable the selection of optimal methods for each patient, considering the aesthetically satisfactory and reliable surgical rehabilitation.

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АҢДАТПА

РЕКОНСТРУКТИВТІ ҚАЛПЫНА КЕЛТІРУШІ ОТАЛАР СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ЕМІНДЕ ХИРУРГИЯЛЫҚ ОҢАЛТУДЫҢ НҰСҚАСЫ РЕТІНДЕ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі. *Бүгінгі таңда сүт безі қатерлі ісігі (СБҚІ) әйелдер арасында онкологиялық аурулардың құрылымында жетекші орын алады. ДДҰ мәліметтері бойынша, 2022 жылы бүкіл әлем бойынша 2,296,840 миллионнан астам бастапқы анықтау жағдайлары тіркелді, сәйкесінше бастапқы анықталған қатерлі ісіктің жалпы санының 11,7%-ы және аурудан 685 000-нан астам әйел қайтыс болды (жалпы өлімнің 6,9%). Хирургиялық әдіс жетекші болып қала береді және салыстырмалы түрде жас және жұмыс істейтін науқастарда ерте анықталудың артуына байланысты жылдан жылға жақсарады. Реконструктивті хирургия оңалту бағдарламасының құрамдас бөлігі ретінде танымал бола бастады.*

Зерттеудің мақсаты *– СБҚІ науқастардың хирургиялық оңалтуы кезінде реконструктивті-қалпына келтіру операцияларының (РҚКО) тиімділігін бағалау.*

Әдістері: *ғылыми жарияланымдарды іздеу 2014 жылдан бастап соңғы 10 жылда жарияланған Scopus, PubMed, e-Library дерекқорларында жүргізілді. Іздеу нәтижелері бойынша 2700-ден астам мақала табылды, оның ішінде қосу және алып тастау критерийлері бойынша 36 дереккөз таңдалды.*

Нәтижелері: *ісіктің орналасуына және патоморфологиялық сипаттамаларына байланысты СБҚІ бар науқастарды хирургиялық оңалту кезінде РҚКО қолдану тиімділігі анықталды. Пациенттердің эстетикалық нәтижеге қанағаттануы Breast-Q сауалнамасының көмегімен бағаланды.рандомизацияланған, бір орталықты және көп орталықты зерттеулердің, мета-талдаулардың нәтижелері бойынша СБҚІ емдеуде бір мезгілде де, кейінге қалдырылған РҚКО-ны қолдану үрдісінің тұрақты өсуі байқалды.*

Қорытынды: *РҚКО хирургиялық оңалтудың ең жақсы әдісі болып табылады. Бұл әдістің негізгі міндеті-онкологиялық қауіпсіздікті сақтай отырып, пациенттерде психосексуалдық әл-ауқаттың жоғары деңгейін және өмір сапасына қанағаттануды қамтамасыз ету. Осыған қарамастан, онкологиялық қауіпсіздік үнемі жетілдіруді және әдістердің әрқайсысын тереңірек зерттеуді қажет етеді. РҚКО-ның ерте және алыс нәтижелерін талдау эстетикалық тұрғыдан қауіпсіз және сенімді хирургиялық оңалту қажеттіліктеріне негізделген әрбір пациент үшін оңтайлы әдісті таңдауға мүмкіндік береді.*

Түйінді сөздер: *сүт безі қатерлі ісігі (СБҚІ), реконструктивті-қалпына келтіру операциялары (РҚКО), хирургиялық оңалту.*

АННОТАЦИЯ

РЕКОНСТРУКТИВНО-ВОССТАНОВИТЕЛЬНЫЕ ОПЕРАЦИИ КАК ВАРИАНТ ХИРУРГИЧЕСКОЙ РЕАБИЛИТАЦИИ ПРИ ЛЕЧЕНИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *На сегодняшний день рак молочной железы (РМЖ) занимает лидирующую позицию в структуре онкологической заболеваемости среди женского населения. По данным ВОЗ в 2022 году было зарегистрировано свыше 2,296,840 первичных случаев РМЖ в мире, что составило 11,7% от общего количества первичных случаев рака, и более 685 000 женщин умерли от этой болезни (6,9% от общей смертности). Хирургический метод лечения остается ведущим, и совершенствуется из года в год ввиду нарастающей ранней выявляемости у сравнительно молодых и работоспособных пациенток. Реконструктивная хирургия набирает все большую популярность как компонент реабилитационной программы при РМЖ.*

Цель исследования *– оценка целесообразности применения современных методик реконструктивно-восстановительных операций (РВО) на молочной железе при хирургической реабилитации больных с РМЖ.*

Методы: *В базах данных Scopus, PubMed, e-Library проведен поиск научных работ, опубликованных за последние 10 лет (2014-2024 гг.). По результатам поиска было найдено более 2700 статей, из них по критериям включения и исключения было отобрано 36 источников.*

Результаты: *По результатам анализа установлено, что онкологическая эффективность применения РВО при хирургической реабилитации больных с РМЖ в зависимости от локализации и патоморфологических характеристик опухоли не хуже, чем при применении радикальной мастэктомии. Удовлетворенность пациенток эстетическим результатом с помощью опросника Breast-Q выше при применении реконструктивных методик по сравнению с радикальной мастэктомией. По результатам рандомизированных, одноцентровых и многоцентровых исследований и мета-анализов был выявлен стабильный рост проведения как одномоментных, так и отсроченных РВО при лечении РМЖ.*

Заключение: *РВО являются передовым методом хирургической реабилитации. Основной задачей данного метода является обеспечение высокого уровня психосексуального благополучия и удовлетворенности качеством жизни у пациенток с сохранением онкологической безопасности. Несмотря на это, онкологическая безопасность требует постоянного совершенствования и более глубокого изучения каждой из методик. Анализ ранних и отдаленных результатов РВО позволит выбирать оптимальный метод для каждой пациентки, исходя из потребностей в эстетически благополучной и надежной хирургической реабилитации.*

Ключевые слова: *рак молочной железы (РМЖ), реконструктивно-восстановительные операции (РВО), хирургическая реабилитация.*

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THE IMPORTANCE OF THE RESECTION EDGE IN THE TREATMENT OF BREAST CANCER: A LITERARY REVIEW

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ABSTRACT

Relevance: *Optimal surgical approaches in the treatment of breast cancer are essential for modern oncology, aiming to reduce the risk of recurrence and improve survival. This literature review analyzes the importance of edge resection in surgical breast cancer treat-ment. It includes an extensive analysis of scientific publications, systematizing knowledge about the clinical significance of the resection margin, its impact on recurrence risk and survival, and its role in organ-preserving operations.*

The study aimed to *evaluate the significance of the resection margin in the surgical treatment of breast cancer.*

Methods: *The research methodology included a systematic search in electronic databases, including PubMed, Web of Science, Scopus, and Cochrane Library, as well as in national scientific repositories and databases of the Republic of Kazakhstan. This approach made it possible to cover significant domestic research in the review. The search was performed using keywords and phrases including "breast cancer," "edge of resection," "organ-preserving surgery," "breast cancer," "resection margin," "margin width," "breast cancer recurrence," "breast-preserving surgery" and "mastectomy."*

Results: *The resection edge definition is key for the successful surgical treatment of breast cancer. Studies show that the molecular subtype of the tumor does not determine the status of surgical margins in patients undergoing breast preservation therapy. An adequate width of the resection margin, determined by considering clinical recommendations and patient characteristics, increases the likelihood of removing all tumor cells, reducing the risk of recurrence and increasing the chances of long-term remission.*

Conclusion: *The importance of the resection margin in the treatment of breast cancer remains the subject of active research and discussion. Although there is much data, there are still contradictions regarding the optimal width of the resection margin and its effect on recurrence and survival. Most studies confirm the importance of adequate resection margin width to reduce the risk of local recurrence, especially during organ-preserving operations. Modern innovative methods such as intraoperative imaging and advances in molecular biology and genetics of breast cancer help to improve the definition of the resection edge.*

Keywords: *oncology, surgery, organ-preserving surgery, relapse, mastectomy.*

Introduction: Breast cancer is one of the most pressing and prevalent oncological diseases affecting women globally. Notwithstanding considerable progress in diagnostics and therapy, breast cancer continues to exhibit a high incidence of recurrence and metastasis, rendering the search for optimal treatment strategies highly pertinent.

Breast cancer is the predominant cause of mortality among women and ranks as the fifth largest cause of cancer-related deaths globally. In 2020, there were 2.3 million new instances of cancer, including 11.7% of all new cancer cases, and 684,996 fatalities attributed to the disease. Asia has the predominant proportion, with 1,026,684 (45.4%) of new cases and 345,559 (50.4%) of deaths globally [1].

The analysis of morbidity and mortality associated with malignant neoplasms underpins regional and national cancer control initiatives and is crucial for the validation of disease prevention strategies, early diagnostic approaches, and the development of screening programs. The morbidity and mortality rates of breast cancer vary across high-risk and low-risk countries, with some discrepancies attributable to the efficacy of reporting and screening practices. Epidemiological studies of breast cancer enable the identification of goals and objectives for disease prevention programs, including the planning of screening and diagnostic measures for early disease detection, as well as the development of efficiency indicators and assessment of program implementation outcomes [2].

A critical component of effective breast cancer treatment is surgery aimed to excise the tumor to the greatest extent possible while conserving good tissue [3]. In surgical treatment, the resection margin, i.e., the distance from the tumor's edge to the surrounding healthy tissue, is critically significant. Determining the ideal width of the resection margin continues to be a topic of extensive research and debate within the medical community. An excessively narrow margin may result in the persistence of tumor cells within the body, consequently leading to disease recurrence. In contrast, an overly broad margin can adversely impact patients' quality of life by increasing the procedure's invasiveness and compromising additional healthy tissues. In 2018, A. Nurmanova et al. observed that recurrences of breast cancer correlate with a substantial reduction in patient survival [4].

The challenge of establishing optimal resection margin criteria is further complicated by advancements in breast cancer treatment, such as organ-preserving surgery and the implementation of cutting-edge radiation and chemotherapy methods. The correlation between resection margin width and recurrence risk, the necessity for a tailored treatment strategy, and the pursuit of an optimal equilibrium between tumor excision efficacy and patient quality of life are pivotal elements of contemporary research in this domain. In 2022, L. Zh. Sultonova et al. provided a comprehensive account of breast cancer recurrences in the initial stages of the disease. The study findings demonstrate that even with initial-stage breast cancer detection, the likelihood of disease recurrence is a minimum of 5%. It underlines the necessity of meticulous surveillance and subsequent therapy, even with early cancer detection, to reduce the likelihood of recurrence [5].

This literature analysis aims to analyze the current scientific findings about the importance of the resection margin in breast cancer treatment. Special emphasis is placed on the study of clinical trials, the assessment of guidelines from prominent oncology organizations, and the analysis of statistical data about the impact of resection margin width on prognosis and treatment results. This work will consolidate existing scientific knowledge in this field, pinpoint deficiencies in current research, and delineate future scientific endeavors to enhance breast cancer treatment's efficacy while optimally preserving patients' quality of life.

The study aimed to evaluate the significance of the resection margin in the surgical treatment of breast cancer.

Materials and methods: During the preparation of this literature review, a thorough method intended to discover and assess scientific literature was employed to identify and systematize data about the impact of resection margin width on breast cancer treatment results. A careful selection of keywords and their combinations was conducted, encompassing such terms as "breast cancer," "resection margin," "organ-preserving surgery," "resection margin," "margin width," "breast cancer recurrence," "breast-conserving surgery," "mastectomy," "local disease control," "oncological outcomes," "quality of life," along with more specific terminology pertinent to treatment outcomes and surgical methodologies. This procedure utilized Boolean operators to formulate intricate queries that enhance and streamline database searches.

The chosen databases for the search emphasized esteemed medical and biological resources, including PubMed, Web of Science, Scopus, and Cochrane Library. These databases were selected due to their extensive coverage, relevancy of content, and the availability of tools for comprehensive searches. Upon formulating the search queries, the search procedure was customized to the particularities of each database, employing their own filtering and searching capabilities, utilizing keywords in titles, abstracts, and full-text articles. Alongside international databases, supplementary searches were conducted in national scientific repositories and databases, enabling the incorporation of significant domestic research into the review, thus enhancing a comprehensive and nuanced understanding of the topic. This methodology ensured a thorough examination of the subject, considering both global and national experiences in breast cancer treatment.

A manual search was conducted in the reference lists of selected papers to find additional pertinent research that may have been overlooked in the computerized search procedure. The cross-referencing process facilitated the identification of substantial work that may have been overlooked due to the constraints of search engines. After identifying potentially appropriate papers by their titles and abstracts, the full texts underwent a comprehensive examination for ultimate selection based on established criteria. The criteria encompassed the accessibility of original data, a detailed account of the study methodology, and an emphasis on examining resection margins in breast cancer. The investigation concentrated on methods for assessment of the resection margin, the influence of margin size on treatment results, and pertinent clinical guidelines.

Each chosen article underwent a comprehensive assessment to evaluate the study methodology, the trustworthiness of the data, and the relevance of the conclusions for breast cancer therapy practice to guarantee the high quality of the analysis. Special focus was devoted to studies addressing various facets of resection margins, encompassing their dimensions, assessment methods, and influence on recurrence risk and overall patient survival. The literature selection and analysis methodology included verifying each article by two independent specialists to reduce the likelihood of overlooking critical information and subjective data interpretation. A third expert was called to achieve consensus in a disagreement among experts. The acquired data were combined to establish a comprehensive overview of the current scientific knowledge regarding resection margins in breast cancer, pinpoint deficiencies in existing research, and delineate directions for future scientific inquiry.

Results:

Concept of the resection margin in breast cancer surgery. The assessment of the resection margin is crucial in the surgical management of breast cancer and significantly influences treatment outcomes. The resection margin is defined as the distance between the periphery of the excised tumor and the closest boundary of the post-surgery residual healthy tissue. This parameter functions as a metric for the thoroughness of tumor tissue excision and is a critical indicator of treatment quality since it directly correlates with the risk of local recurrences (LR) of the disease. I. Horattas et al. (2022) showed that the molecular subtype of breast cancer does not forecast the status of surgical margins in patients receiving breast-preserving therapy. The research indicated that the selection of surgical approach

should not be contingent upon the genetic subtype of the tumor [6].

Research conducted by E.A. Bonci et al. in 2021 assessed the impact of surgical resection margin width (SRMW) on the probability of local recurrence following lumpectomy in patients with triple-negative breast cancer, a notably aggressive subtype. The study involved 92 individuals who received lumpectomy between 2005 and 2014, including a median tumor size of 2.5 cm and no distant metastases at diagnosis. The majority of patients underwent neoadjuvant and/or adjuvant chemotherapy in addition to adjuvant radiotherapy targeting the entire breast. Following a median follow-up duration of 110.7 months, there were five local recurrences and eight regional/distant recurrences, resulting in an overall incidence of 5.4% of LR. The likelihood of local and long-term recurrence was comparable across groups with varying SRMWs. The findings validate the safety of the "no ink on the tumor" methodology for individuals with triple-negative breast cancer [7].

An adequate resection margin width, defined by clinical guidelines and the particulars of each case, substantially increases the likelihood of complete tumor cell removal. The objective of surgical intervention is accomplished - it reduces the danger of residual tumor foci, enhancing the likelihood of long-term remission. A comprehensive review and meta-analysis of 68 studies involving 112,140 patients who underwent conservative breast surgery for early invasive breast cancer identified a correlation between resection margin involvement and an increased risk of long-term recurrence. Positive margins were observed in 9.4% of patients, leading to delayed recurrences in 25.4% of instances, whereas in patients with negative margins, the rate was 7.4%. Narrow margins (under 2 mm without tumor cells) correlated with distant recurrences in 8.4% of instances. The compromised margins elevated the probability of long-term recurrences by 2.1 times and local regional recurrences (LRRs) by 1.98 times compared to negative margins, whereas nearby margins increased this risk by 1.38 times and 2.09 times, respectively [8].

The study by A. Bodilsen et al., which involved 11,900 patients receiving breast-conserving invasive cancer treatment, showed a cumulative tumor recurrence rate of 2.4% in the same breast at 5 years and 5.9% at 9 years. Positive surgical margins elevated the recurrence risk by 2.51 times (95% CI 1.02-6.23). The negative margin width did not influence the recurrence risk (HR for margins >0 to <2 mm versus ≥2 to <5 mm versus ≥5 mm – 1.54 (95% CI 0.81–2.93) versus 0.95 (95% CI 0.56–1.62) versus 1). A positive surgical margin markedly elevates the likelihood of tumor recurrence in the same breast, whereas the extent of negative margins does not influence recurrence risk, hence contributing to the increasing prevalence of organ-preserving surgery in recent years [9].

No universal standard exists for identifying the best resection margin width, as each clinical case is distinct and necessitates a tailored strategy. A positive or narrow resection margin, defined as the presence of tumor cells near the resection border or in its immediate proximity, is considered an adverse factor [10, 11]. This circumstance correlates with an elevated risk of recurrence because of the increased probability of residual tumor cells in the remaining breast tissue. In the study, M. Pilewskie and M. Morrow 2019 examined the ideal negative resection margin widths for the surgical management of invasive cancer and ductal carcinoma in situ (DCIS) to reduce the chance of LRR. The study shows that a 2 mm margin reduces the chance of LRR in women with DCIS having lumpectomy and radiation therapy due to variations in growth patterns and systemic therapy application [12].

The significance of meticulous assessment of the width of the resection margin is underscored by its influence on the ensuing treatment strategy. In certain instances, if a limited resection margin is identified, further surgery may be necessary to enlarge the resection or to employ adjuvant therapy, such as radiation, to reduce the likelihood of recurrence. Such judgments are predicated on a complex review of the clinical presentation, disease stage, histological tumor type, and additional criteria, underlining the multifaceted approach to breast cancer treatment.

The significance of establishing the resection margin in the surgical management of breast cancer is underestimated. Clinicians must be exceptionally vigilant and exact during surgery, considering that the resection margin width correlates with other treatment factors and influences overall patient outcomes.

Clinical importance of the resection margin width. The resection margin width is crucial in several parameters that influence the efficacy of surgical treatment for breast cancer. The optimal width of resection margins correlates directly with a diminished risk of LR, hence enhancing overall patient survival. The significance of obtaining an appropriate width of the resection margin is particularly apparent in organ-preserving surgeries, such as lumpectomy and quadrantectomy, which seek to optimize the preservation of the mammary gland while ensuring effective oncological control.

The sufficiency of the resection margin width is assessed by the complete excision of all visible tumor cells, accompanied by an adequate margin of healthy tissue, hence preventing the retention of residual tumor cells within the patient's body. This method reduces the probability of disease recurrence at the main tumor location and enhances the chances of sustained remission. Oncologists and surgeons agree that an appropriate resection margin is essential for a favorable treatment outcome, particularly in organ-preserving operations. The excessive excision of healthy tissue to attain "wide" resection margins can adversely impact patients' quality of life, resulting in alterations to breast morphology, functionality, and overall body image perception.

The study conducted by D. Livingston-Rosanoff et al. (2021) demonstrates that in cases of DCIS with narrow resection margins (less than 2 mm), the recurrence likelihood was 19%. However, following routine resection to margins above 2 mm, this probability diminished to 11%. The data underscore the clinical importance of adequate resection margin width in DCIS surgery [13].

As per M. Mrdutt et al. (2021), among patients who received breast-conserving surgery following neoadjuvant chemotherapy, the 4-year chance of LR was 2%. Furthermore, no statistically significant difference in recurrence likelihood was observed between groups with resection margins exceeding 2 mm and those with margins less than 2 mm. This outcome suggests the possibility of customizing the method to establish margin widths based on certain clinical circumstances [14].

J. Bundred et al. demonstrated in a 2022 systematic review that patients with positive resection margins had a 33.1% chance of distant recurrence, whereas those with negative margins exhibited a markedly reduced risk of 7.3%. These findings validate the significance of attaining negative resection margins to mitigate the incidence of both local and distant recurrences [15].

Research conducted by B. Koca et al. (2022) demonstrated that intraoperative assessment of surgical margins decreased the necessity for revision procedures from 18.5% to 0%. This outcome underlines the significance of intraoperative margin assessment in enhancing surgical results and preventing the necessity for further surgical procedures [16].

These trials together underscore the clinical importance of establishing the ideal resection margin width in breast cancer management. They show the necessity for a personalized approach in establishing margin widths, grounded in a thorough analysis of clinical data and prognostic factors, considering tumor type, response to preoperative treatment, and other significant clinical characteristics. Consequently, a crucial element in surgical practice is the balance between obtaining a sufficient resection margin width and conserving maximal healthy tissue [17]. It necessitates that surgeons possess advanced ability and experience, along with meticulous planning of the surgical procedure, considering the unique characteristics of the tumor and the breast anatomy of each patient. The significance of this balance is underscored in contemporary treatment protocols, which advocate for a personalized strategy for each instance of breast cancer. Enhancing the width of the resection margin not only augments oncological results but also preserves patients' quality of life, rendering it a crucial component of a comprehensive breast cancer therapy strategy.

Clinical guidelines regarding the resection margin width. Numerous professional groups engaged in breast cancer treatment have issued guidelines regarding the ideal width of the resection margin. The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) are the preeminent organizations that have established these guidelines.

The ASCO regulations stipulate that the resection margin must be negative, indicating the absence of invasive tumor or non-invasive malignancy in situ. ASCO does not establish a specific minimum distance for the resection margin. The NCCN recommendations stipulate that the resection margin must be a minimum of 2 mm for invasive cancer and at least 5 mm for non-invasive in situ cancer. ESMO advises a resection margin of no less than 1 mm for invasive cancer and a minimum of 2 mm for non-invasive cancer in situ. In the study conducted in 2021, A. Tremelling et al. studied the effects of the 2016 consensus guidelines that established a 2 mm free margin as the standard for negative margins in patients undergoing lumpectomy for DCIS. The objective of the advice was to standardize the procedures for recurrent operations. A retrospective analysis of patient records was conducted to assess margin status and revision rates two years before and after the guideline's publication to assess its effect on revision rates within the hospital. Notwithstanding a minor reduction in the overall revision rate, the percentage of patients with narrow margins who received revision surgery rose following the issuance of the guideline. This study indicates that the issuance of the guidelines had minimal influence on the practices of their establishment since many surgeons' practices were already aligned with the guidelines' recommendations before 2016 [18].

Nonetheless, there are problems with the interpretation of the guidelines. The analysis of clinical guidelines from multiple organizations about breast cancer treatment disclosed methodological quality and relevance variations. The ASCO and CCO PEBC recommendations received superior ratings relative to the NCCN and St. Gallen guidelines. All guidelines had limited applicability, and recommendations regarding critical issues, such as using SLNB following neoadjuvant chemotherapy, were inconsistent [19]. Despite the 2 mm threshold being a universal recommendation across all guidelines, notable discrepancies were observed in the adjuvant chemotherapy and radiotherapy criteria.

Impact of resection margin width on recurrence and survival rates. Multiple studies have shown that a broader resection margin correlates with a reduced risk of breast cancer. This finding is only recorded in the initial phases. A study conducted by C. Shah in 2020 reported a median follow-up duration of 7.25 years, revealing that absolute LR scores diminished with time across all groups with the resection margin width from 1 mm to 5 mm, with the greatest disparity across the negative margin groups being under 1% in the last follow-up period. The comparative parameters of LR across various margin groups have exhibited consistency over time [20].

N.J. Bundred et al. assessed the correlation between resection margin width following conservative breast sur-

gery and the incidence of recurrences and survival rates in invasive breast cancer in the 2022 meta-analysis. The study, encompassing 68 investigations involving 112,140 patients, revealed that a tumor at the margin correlated with an increased probability of distant recurrence (25.4%) in contrast to negative margins (7.4%). Margins adjacent to the tumor correlated with a greater incidence of distant (8.4%) and local recurrences [21].

The study conducted by D. Livingston-Rosanoff et al. (2021) assessed the ideal width of resection margins in patients with DCIS having lumpectomy. The research examined data from 559 patients who underwent the procedure between 1997 and 2006, with follow-up extending to 2016. In this study, narrow resection margins (< 2 mm) correlated with an increased incidence of LRR, irrespective of radiation therapy. The total incidence of LRR was 12%, with relapses occurring more frequently in those who did not undergo radiotherapy (19% compared to 11% among those who did). The findings confirm that multiple resections before achieving margins exceeding 2 mm may diminish the recurrence risk in patients with DCIS [22]. The results underscore the significance of adequate resection margin width to reduce recurrence risk and enhance survival in breast cancer patients.

Intraoperative ultrasound evaluation of margins can effectively reduce positive superficial margins in the nipple and skin-preserving mastectomy for breast cancer patients, enhancing surgical precision and minimizing disease recurrence risk [23].

In the study by S.J. Schnitt et al. (2020), a resection margin less than 2 mm wide correlated with inferior disease-free survival but did not affect overall survival. This could be because LRs are often successfully re-treated without significantly impacting overall survival rates [24].

The precise correlation between margin width and recurrence risk is still under discussion. Certain studies indicate a linear correlation; however, others propose that further increases in margin do not contribute to a decreased risk of recurrence once a specific threshold width is attained. Intraoperative approaches for assessing resection margins can substantially diminish the chance of recurrence.

Discussion: The effect of resection margin width on overall and recurrence-free survival in breast cancer patients is a contentious topic. Certain studies indicate a positive correlation between broader resection margins and enhanced survival; others have identified no relationship.

The excision of a cavity or specimen during lumpectomy for breast cancer is a crucial component of surgical intervention designed to provide clear resection margins and reduce the likelihood of disease recurrence [25]. The impact of resection margin width on survival may differ based on the biological characteristics of the tumor, adjuvant therapy protocols, and other prognostic variables.

The study conducted by L.M. DeStefano et al. (2021) assessed patients with invasive stage I-III breast cancer who had undergone partial mastectomy and re-surgery between July 2010 and June 2015 to discover clinical markers that indicated the presence of residual disease in the lumpectomy bed. Among the 184 patients, 47% exhibited persistent illness following re-surgery. The tumor and node stage, surgical type, disease type at the margins, and quantity of positive margins were substantially correlated with residual disease. Multivariate logistic regression study indicated that only DCIS at the margin, the surgical type (partial mastectomy with cavity margins), and the number of positive margins (3 or more) predict residual disease necessitating reoperation. These data can assist surgeons in determining the necessity of a subsequent procedure [26].

Organ-preserving procedures and the resection margin. In organ-preserving procedures like lumpectomy or quadrantectomy, obtaining a sufficient resection margin is essential to reduce the risk of LR and preserve cosmetic appearance. These operations prioritize breast preservation, making it essential to get a negative resection margin of enough width for effective cancer control.

Another study by J. Lin et al. (2020) examined the application of conservative surgery following neoadjuvant chemotherapy within a single medical organization, emphasizing the correlation between the microscopic condition of resection margins and the likelihood of LRR. Analysis of data from 161 patients who underwent partial mastectomy indicated that 28 patients had resection margins of less than 1 mm, 21 patients had margins of 1 to 2 mm, and 112 patients had margins above 2 mm. LRRs occurred in 16 patients (9.9%) and distant metastases – in 27 (16.8%). The Kaplan-Meier statistical analysis revealed no significant disparity in recurrence rates between the groups with margins exceeding or less than 2 mm. Furthermore, categorizing patients into groups with margins above and less than 1 mm found no significant difference in recurrence-free survival. The findings highlight that the lack of tumor presence at the resection margins may suffice to avert recurrence in patients with stages I-III of invasive breast cancer undergoing neoadjuvant chemotherapy and conservative surgery, provided there are no multiple microscopic tumor foci [27].

K. Wimmer et al. (2020) analyzed the data from 406 patients with invasive breast cancer who received neoadjuvant chemotherapy and conservative breast therapy in Austrian medical centers between 1994 and 2014. Local Recurrence-Free Survival (LRFS), disease-free survival (DFS), and overall survival (OS) were compared among groups with resection margins of < 1 mm, > 1 mm, and those with pathological complete response (pCR). At a median follow-up duration of 84.3 months, no significant differences were observed in LRFS, DFS, and OS among narrow, wide, and undefined margins following pCR [28].

In the research, H. Kim et al. (2024) examined the efficiency of personalized radiation doses for resection margins under 2 mm and the optimal margin width for high-risk DCIS. A retrospective review of 137 patients

who underwent neoadjuvant radiotherapy following breast-conserving surgery for DCIS from 2013 to 2019 revealed that the median radiation doses for the groups with positive, approximate (< 2 mm), and negative (≥ 2 mm) margins were 66.25 Gy, 61.81 Gy, and 59.75 Gy, respectively. The LR rates for these groups were 15.0%, 6.7%, and 4.6%. The positive margin group exhibited markedly inferior 5-year LRFS compared to the approximate and negative margin groups (84.82%, 93.27%, and 93.20%, respectively; p=0.008). It was also shown that the disparity in 5-year LRFS between patients with well-differentiated tumors and those with poorly differentiated tumors diminished when margin width increased. Modifying the radiation dose according to margin width shows that positive margins diminish local control efficacy relative to negative margins, although the differences among approximate margins lack statistical significance. The ideal resolution for high-risk DCIS was to obtain distinctly negative margins (≥ 2 mm) [29].

The probability of LRR is contingent upon lymph node involvement and tumor aggressiveness. Axillary metastases and resection margins are significant indicators of LLR in breast cancer patients. The study conducted by O.O. Ayandipo et al. (2022) investigates the predictive significance of positive lymph nodes, lymph node index, and resection margins on the survival of women undergoing breast cancer treatment at the Department of Oncosurgery, University College Hospital, Ibadan, from December 2009 to December 2014. An examination of the Ibadan Population Cancer Registry for 2012 found that the incidence of breast cancer was 52.0 cases per 100,000 individuals. The patient cohort exhibited a predominance of advanced cancer, a high malignancy grade of tumors, and a negative response to hormone receptors, indicating a prevalence of an aggressive disease phenotype. Ultimately, it was determined that the existence of positive resection margins in patients treated at a tertiary care facility in Ibadan, Nigeria, correlated with an increased risk of LLR in breast cancer. 72.4% of research participants had negative resection margins following modified radical mastectomy, underlining the need to obtain negative margins during surgery to reduce the risk of LLR [30].

Lumpectomy is an established therapeutic approach for the initial phases of invasive breast cancer. The status of the surgical margin substantially influences the probability of LR. Achieving a negative lumpectomy margin is difficult because of the many risks and predictors of a positive margin that the radiologist must be familiar with. The contributions of the pathologist and surgeon in minimizing the incidence of failure during breast preservation procedures are crucial. Despite the widespread use of imaging, the limitations of standard intraoperative radiographs must be considered. A negative resection margin during lumpectomy diminishes the probability of LR, enhances cosmetic outcomes, and increases long-term survival rates [31].

Assessment of the efficacy of organ-preserving procedures based on the resection margin width. Multiple studies indicate that adherence to the recommended width of the resection margin allows organ-preserving surgery to achieve survival rates comparable to those of radical mastectomy while also maintaining the mammary gland and enhancing esthetic results [32].

A comprehensive analysis of the national database conducted by W.J. Hotsinpiller et al. (2021) shows that merely 5% of individuals receiving breast-conserving surgery are in danger of having a positive operative margin. Patients with invasive lobular histology exhibit nearly double the likelihood of positive resection compared to those diagnosed with invasive ductal carcinoma. Elevated HER2 levels augment the likelihood of a positive surgical margin, although the degree and status of estrogen and progesterone are not substantially associated with this parameter. These findings offer essential insights for counseling patients regarding the dangers and the necessity for revision surgery in individuals opting for conservative breast treatment in contemporary clinical practice [33].

International guidelines for invasive breast cancer or DCIS recommend adherence to appropriate resection margins. An examination of 13 guidelines and 31 research conducted from 2011 to 2016 uncovered variations in defining positive resection margins in clinical practice, from the localized presence of cancer cells to a 3-5 mm distance from the resection margin. Research involving 59,979 patients established that the overall frequency of positive resection margins for invasive breast cancer varied between 9% and 36%, while for DCIS, it ranged from 4% to 23%. For invasive breast cancer, the prevailing standards posit that the absence of a tumor at the margins of excised tissue is adequate. However, the guidelines for DCIS are less rigorous. Due to the variation in tumor boundary definitions among countries, quality control data represented as rates of positive resection margins or recurrences must be interpreted with caution. Moreover, the general definition of a positive resection margin has become more permissive in both invasive carcinoma and DCIS, underlining the necessity for additional research and refinement of the criteria for assessment [34].

Conventional breast-conserving surgery (CBCS) combined with postoperative radiation therapy continues to be the primary approach for locoregional treatment in early-stage breast cancer, yielding survival rates comparable to those of mastectomy. The efficacy of CBCS relies on the thorough excision of the tumor, ensuring sufficient surgical margins, preserving the breast's natural contour, and enhancing patient satisfaction. Nevertheless, in certain instances, CBCS fails to yield satisfying cosmetic outcomes, prompting the advancement of novel breast surgical methods, such as oncoplastic breast surgery (OBS).

Achievement of an acceptable resection margin may be more difficult in organ-preserving surgeries than in mastectomy, highlighting the necessity for meticulous planning and execution by skilled surgeons.

Contemporary methodologies for assessment of the resection margin. In recent years, innovative techniques have been developed to improve the accuracy of resection edge detection during surgery. One of these methods is biophotonic technology. Biophotonic technologies, including photoacoustic imaging and Raman spectroscopy, are emerging as viable intraoperative instruments for evaluating surgical margins in lumpectomy at microscopic and macroscopic levels [36].

Preoperative modalities such as MRI and CT are also effective. Selective use of preoperative MRI improves margin status after lumpectomy in patients with invasive breast cancer. Microcalcifications, architectural deformities, elevated mammographic density (>75%), lobular histology, and substantial tumor size were correlated with positive resection margins (>4 mm), indicating the necessity for preoperative MRI. Assessment of these characteristics before surgery might enhance planning and diminish the likelihood of positive margins following lumpectomy. It was determined in a multivariate regression analysis involving 2,483 patients with invasive breast cancer that preoperative MRI correlated with a decreased likelihood of positive resection margins following lumpectomy. Factors independently correlated with favorable resection margins included lobular histological type, substantial tumor size, elevated breast density on mammography, microcalcification, and architectural deformities. Consequently, preoperative MRI may effectively mitigate the likelihood of positive resection margins in lumpectomy, whereas specific mammography and tumor attributes can be utilized to evaluate the risk [37].

Contemporary methods, including scanning microscopy with deep ultraviolet fluorescence contrast, enable rapid and precise viewing of tissue surfaces, differentiating between malignant and normal/benign regions. The implementation of automated deep learning methods utilizing features derived from convolutional neural networks markedly enhances the efficiency of intraoperative evaluation of breast cancer margins, achieving high accuracy (95%) and sensitivity (100%) on samples acquired through scanning microscopy with deep ultraviolet fluorescence contrast [38].

Quantitative micro-elastography (QME) is an imaging technology that reveals tissue stiffness at the microscopic level and has shown a high diagnostic accuracy of 96% in identifying cancer in excised surgical tissues [39].

Micro-CT demonstrated a comparable incidence of positive margins to conventional specimen palpation and radiography; however, challenges differentiating radiodense fibroglandular tissue from malignancy resulted in an elevated rate of false-positive margin assessments [40, 41]. High-frequency ultrasonic waves (22-41 MHz) were used for the analysis with the help of both the pulse-echo approach and the "catch" and "through-pass" methods, which have also exhibited high efficacy in identifying malignant cells [42].

A promising approach involves the use of fluorescence methods. This approach facilitates intraoperative assessment of resection margins, yielding more precise information regarding the presence of tumor cells at the peripheries of the excised tissue. This study assessed the feasibility and accuracy of near-infrared fluorescence imaging technology for margin evaluation in conservative breast cancer surgery. A study was conducted with the participation of 43 patients who underwent surgical procedures. The near-infrared fluorescence image exhibits high sensitivity and specificity for the assessment of margins in conservative breast cancer surgery, affirming its potential as an intraoperative diagnostic and therapeutic tool, ensuring precise determination of surgical margins, and serving as a crucial guide for the conservative treatment of breast cancer [43].

Gamma-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) is recognized as a compound that can elicit fluorescence in breast cancers. A dependable and reproducible methodology has been established using this chemical to quantify fluorescence levels for enhanced tumor identification [44].

Future research prospects. Notwithstanding extensive studies on the resection margin in breast cancer, many gaps remain and require addressing in future studies. A notable gap exists in comprehending the significance of the resection margin concerning various molecular subtypes of breast cancer.

Moreover, additional research is required to explore the relationship between resection margin width and other prognostic and therapeutic variables, including tumor biological features, adjuvant therapy protocols, and radiotherapy utilization (Table 1).

Continuing research to ascertain the ideal resection margin width for several clinical settings, including organ-preserving procedures, revision surgeries following a positive margin, and various disease stages, is also crucial.

Recommendations for subsequent investigations of the resection margin. Future research ought to concentrate on creating more precise and reproducible methods for assessing the resection margin, including intraoperative imaging and confocal microscopy, which have been previously detailed. Implementing these novel strategies can enhance the precision of resection margin evaluation and increase the accuracy of the surgical procedure.

Moreover, additional research integrating resection margin width data with the tumor's molecular and genetic attributes is essential. Such investigations can facilitate the development of more individualized strategies for ascertaining the ideal resection margin width for particular individuals, contingent upon the biological features of their tumors.

A significant direction for future investigation is examining the impact of resection margin width in conjunction with other variables, including adjuvant therapy protocols and the application of radiation therapy. These integrated methodologies can assist in the determination of the most effective treatment solutions for various clinical situations.

Table 1 – Summary of resection margin data in breast cancer treatment

Division	Principal conclusions
The notion of the resection margin	- The resection margin indicates the thoroughness of tumor excision and the likelihood of local recurrences.
	- A positive or narrow margin elevates the chance of recurrence.
Clinical significance of margin width	- Adequate margin width diminishes the likelihood of recurrence and enhances survival rates.
	- A compromise must be achieved between margin width and the preservation of breast tissue.
Clinical protocols	- Various standards exist for the minimum margin width, ranging from 1mm to 5mm.
	- The recommendations exhibit methodological discrepancies and contradictions.
Impact of margin width on recurrence and survival rates	- A broader margin correlates with a diminished likelihood of local recurrence.
	- The effect on overall and recurrence-free survival is more disputable.
Organ-preserving surgical procedures	- Attaining a sufficient margin is essential for disease management
	- Contemporary imaging methodologies enhance the precision of margin estimation

Furthermore, extensive prospective studies with prolonged follow-up durations are necessary to evaluate the impact of resection margin width on the long-term survival of breast cancer patients more precisely. Studies should be meticulously developed to control for potential confounding variables and employ consistent data measurement and analysis methodologies.

Studies shall continue to optimize organ-preserving surgeries to achieve an optimum resection margin width. Such studies can include developing novel surgical techniques, implementing innovative imaging methods, and improving surgical planning using computer simulation.

Future studies should aim to elucidate the significance of the resection margin concerning diverse biological, clinical, and therapeutic aspects while also formulating individualized strategies to ascertain the ideal resection margin width for each breast cancer patient.

Conclusion: The resection margin significance in breast cancer treatment remains a topic of ongoing debate and investigation. Notwithstanding the substantial amount of data accumulated, there is controversy and disagreement regarding the resection margin optimal width, its impact on recurrence and survival, and the role of other factors such as tumor biologic characteristics and adjuvant therapy regimens.

Nevertheless, most research affirms that achieving an adequate resection margin width is essential to minimize the risk of LLR, particularly in organ-preserving surgery. The precise threshold level associated with an acceptably low recurrence risk is still a subject of discussion.

Modern innovative methods, like intraoperative imaging and confocal microscopy, provide enhanced opportunities for precise resection margin assessment during surgery. Furthermore, advances in molecular breast cancer biology and genetics contribute to a better understanding of the role of resection margin and its connection with tumor biological characteristics.

Further advances in this area require extensive prospective research with a long follow-up period, standardized data measurement and analysis methods, and a thorough control of potential bias factors. This research shall examine the relationship of the resection margin width with other prognostic and therapeutic parameters, including tumor biology, adjuvant therapy protocols, and radiation therapy utilization.

It is also important to continue developing tailored approaches to determining the resection margin width ideal for each patient based on molecular and genetic features of their tumors. This could enhance the efficacy of surgical interventions and improve outcomes for patients with breast cancer.

In general, despite the existing challenges and controversies, continued study on resection margins is essential to improve surgical approaches and achieve better breast cancer treatment results.

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АҢДАТПА

СҮТ БЕЗІ ОБЫРЫН ЕМДЕУДЕГІ РЕЗЕКЦИЯ ЖИЕГІНІҢ МАҢЫЗЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сүт безі қатерлі ісігін емдеудегі оңтайлы хирургиялық тәсілдер қайталану қаупін азайтуға және өмір сүруді жақсартуға бағытталған қазіргі онкология үшін өте маңызды. Осы әдебиеттерге шолу сүт безі обырын хирургиялық емдеуде резекция жиегінің маңыздылығын талдайды. Ол резекция аймағының клиникалық маңыздылығы, оның қайталану қаупі мен өмір сүру деңгейіне әсері және ағзаны сақтау операцияларындағы рөлі туралы білімді жүйелейтін ғылыми жарияланымдарды кең талдауды қамтиды.*

Зерттеудің мақсаты *– сүт безі қатерлі ісігін хирургиялық емдеуде резекция жиегінің мәнін бағалау.*

Әдістері: *Зерттеу әдістемесі PubMed, Web of Science, Scopus және Cochrane Library сияқты электрондық деректер базаларында, сондай-ақ Қазақстан Республикасының Ұлттық ғылыми репозиторийлері мен деректер базаларында жүйелі іздеуді қамтыды. Бұл тәсіл шолуда маңызды отандық зерттеулерді қамтуға мүмкіндік берді. Іздеу "сүт безі қатерлі ісігі", "резекция шеті", "ағзаны сақтау операциясы", "Брест қатерлі ісігі", "қалпына келтіру маржасы", "маржаның ені", "Брест қатерлі ісігін қалпына келтіру", "Брест-консервация хирургиясы" және "мастектомия"сияқты түйінді сөздер мен сөз тіркестерін қолдану арқылы жүзеге асырылды.*

Нәтижелері: *резекция жиегін анықтау сүт безі қатерлі ісігін сәтті хирургиялық емдеуде шешуші рөл атқарады. Зерттеулер көрсеткендей, ісіктің молекулалық кіші түрі сүт безін сақтайтын терапиядан өтіп жатқан науқастарда хирургиялық жиектердің күйін анықтамайды. Науқастың клиникалық ұсыныстары мен ерекшеліктерін ескере отырып анықталған резекция жиегінің барабар ені барлық ісік жасушаларын алып тастау ықтималдығын арттырады, бұл қайталану қаупін азайтады және ұзақ мерзімді ремиссия мүмкіндігін арттырады.*

Қорытынды: *Сүт безі қатерлі ісігін емдеудегі резекция жиегінің маңызы белсенді зерттеулер мен пікірталастардың тақырыбы болып қала береді. Деректер көп болғанымен, резекция жиегінің оңтайлы еніне және оның рецидивтер мен өмір сүруге әсеріне қатысты қайшылықтар әлі де бар. Зерттеулердің көпшілігі жергілікті қайталану қаупін азайту үшін резекция жиегінің жеткіліктілігінің маңыздылығын растайды, әсіресе орган сақтайтын операцияларда. Интраоперациялық бейнелеу сияқты заманауи инновациялық әдістер және сүт безі қатерлі ісігінің молекулалық биологиясы мен генетикасындағы жетістіктер резекция жиегін анықтауды жақсартуға көмектеседі.*

Түйінді сөздер: *онкология, хирургия, ағзаны сақтайтын хирургия, рецидив, мастэктомия.*

АННОТАЦИЯ

ЗНАЧЕНИЕ КРАЯ РЕЗЕКЦИИ ПРИ ЛЕЧЕНИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Оптимальные хирургические подходы в лечении рака молочной железы (РМЖ) имеют важное значение для современной онкологии, стремясь уменьшить риск рецидивов и улучшить выживаемость. Настоящий обзор литературы анализирует значимость края резекции в хирургическом лечении РМЖ. Он включает обширный анализ научных публикаций,*

систематизируя знания о клинической значимости края резекции, его влиянии на риск рецидивов и выживаемость, а также роль в органосохраняющих операциях.

***Цель исследования** – оценить значение края резекции при хирургическом лечении рака молочной железы.*

***Методы:** Методика исследования включала систематический поиск в базах данных PubMed, Web of Science, Scopus и Cochrane Library по ключевым словам «рак молочной железы», «край резекции», «органосохраняющая операция», «breast cancer», «resection margin», «margin width», «breast cancer recurrence», «breast-conserving surgery» и «mastectomy».*

***Результаты:** Определение края резекции играет ключевую роль в успешном хирургическом лечении РМЖ. Исследования показывают, что молекулярный подтип опухоли не определяет статус хирургических краев у пациентов, проходящих терапию с сохранением молочной железы. Адекватная ширина края резекции, определенная с учетом клинических рекомендаций и особенностей пациента, повышает вероятность удаления всех опухолевых клеток, что снижает риск рецидива и увеличивает шансы на долгосрочную ремиссию*

***Заключение:** Значение края резекции играет ключевую роль в хирургическом лечении РМЖ и существенно влияет на исход лечения. При хирургическом вмешательстве важно добиться отрицательных краев резекции, что означает отсутствие опухолевых клеток на границе удаленной ткани. Это является важным фактором для снижения риска рецидива заболевания и улучшения выживаемости пациентов. Результаты проведенных исследований демонстрируют, что положительные края резекции ассоциируются с повышенным риском местного рецидива, что требует дополнительных терапевтических вмешательств, таких как повторная операция или лучевая терапия. Таким образом, край резекции является фактором, определяющим успех хирургического лечения РМЖ. Достижение отрицательных краев резекции должно быть основной целью хирургов, что требует применения современных технологий и мультидисциплинарного подхода. Улучшение методов оценки и контроль краев резекции будут способствовать повышению эффективности лечения и улучшению прогноза для пациентов.*

***Ключевые слова:** онкология, хирургия, органосохраняющая операция, рецидив, мастэктомия.*

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INVESTIGATION OF ESOPHAGEAL CANCER SUBTYPES, EPIDEMIOLOGICAL TRENDS, AND ASSOCIATED RISK FAC-TORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Esophageal cancers represent a significant public health and health problem in many parts of the world. Esophageal cancer development is a multifactorial process associated with various risk factors. Many studies have been identified that have examined various etiologic factors, including genetics, diet, infections, oral health, and underlying diseases.*

This brief review aims to provide a comprehensive survey of cancer epidemiology and a thorough assessment of established and suspected risk factors associated with esophageal cancer by distinct histologic subtypes.

The purpose was to study *the relationship between risk factors and genetic susceptibility in the development of esophageal cancer, with particular emphasis on two distinct histopathological subtypes.*

Methods: *The literature review included a search for scientific publications in the following databases: PubMed, Medline, and Cochrane Lab, using the scientific search engine Google Scholar. The search depth was 10 years.*

The literature review included epidemiology studies and assessing the strength of the relationship between risk factors for esophageal cancer. The review included all studies only among adults, publications in English, as well as publications with clearly formulated conclusions;

The exclusion criteria were case series, case reports, editorials, and conference abstracts. Out of 462 sources found, 45 were included in the analysis.

Results: *Studies show that several factors increase susceptibility to esophageal cancer, including tobacco use, excessive alcohol consumption, opioid abuse, hot food and beverage consumption, gastroesophageal reflux disease, obesity, gastric atrophy, poor oral hygiene, changes in esophageal microbiota, suboptimal diets, viral and bacterial infections, and others. In addition, mutational profiles of esophageal cancer cells have revealed frequent mutations in specific genes, including TP53, NFE2L2, MLL2, ZNF750, and NOTCH.*

Conclusion: *The pathogenesis of squamous cell carcinoma cancer exhibits multifactorial properties, with multiple recognized risk factors contributing to its occurrence. In contrast, the etiology of adenocarcinoma esophageal cancer remains relatively unknown, requiring ongoing research efforts to elucidate its fundamental causal mechanisms.*

Keywords: *squamous cell carcinoma, esophageal adenocarcinoma, epidemiology, risk factors, genetics of esophageal cancer.*

Introduction: In 2020, Esophageal cancer ranked 7th in the structure of oncological morbidity (604,000 new cases) and 6th in mortality (544,000 deaths) [1]. Comparing GLOBOCAN 2020 and GLOBOCAN 2022 data, we found an increase in esophageal cancer incidence and mortality (data for 2022 are presented below).

This disease has two main histological types: squamous cell carcinoma and adenocarcinoma. In Western countries, adenocarcinoma predominates [2], while squamous cell carcinoma predominates in Asia, Eastern Europe, and Africa, accounting for 90% of esophageal carcinoma cases [3].

Esophageal cancer is a significant public health and public health problem in many parts of the world. Esophageal cancer development is a multifactorial process associated with various risk factors. Numerous studies have been identified that have examined various etiologic factors, including genetics, diet, infections, oral health, and underlying medical conditions.

This article briefly reviews the epidemiology of esophageal cancer and provides an overview of confirmed and potential risk factors for esophageal cancer by distinct histopathological subtypes.

The purpose was to study the relationship risk factors and genetic susceptibility in the development of esophageal cancer, with particular emphasis on two distinct histopathological subtypes.

Materials and Methods: A search for scientific publications was conducted in the following databases: PubMed, Medline, and Cochrane Lab, using the scientific search engine Google Scholar. The review included studies devoted to the epidemiology and study of the relationship between risk factors for esophageal cancer. The analysis included publications in English with clearly formulated conclusions, except for case reports and case series, editorials, and conference abstracts. The search depth was 10 years. Out of 462 sources found, 45 scientific publications were included in the analysis.

Results: According to Globocan statistics for 2022, esophageal cancer ranks 11th in the world in terms of prevalence, with an estimated 511,054 cases per year,

and also ranks seventh in the world in terms of mortality, with a total of 445,391 deaths registered per year [4]. In 2022, at the country level, the highest age-standardized incidence rates of esophageal cancer were reported in Bangladesh (16.0 per 100,000 people per year) and Uganda (13.2 per 100,000 people per year). The lowest age-standardized rate in the world was in the Republic of Congo (0.43 per 100,000 people per year). By continent, the highest age-standardized incidence rates of esophageal cancer worldwide were reported in Asia (164.4), Africa (132.3), North America (364.7), and Europe (280) [10].

In the Republic of Kazakhstan, in 2022, 36,225 cases of esophageal cancer were verified, including 16,947 in men and 19,278 in women; 20,686 patients died from this disease, including 11,365 men and 9,321 women [5]. There are significant differences in the incidence of esophageal cancer between different population groups [6-9].

Esophageal squamous cell carcinoma and esophageal adenocarcinoma are the two main histological types of esophageal cancer with distinct epidemiological and clinical features. Worldwide, squamous cell carcinoma is the most common subtype of esophageal cancer, accounting for 80% of cases [11]. In contrast, esophageal adenocarcinoma (20%) is the most common subtype in the white population of developed countries and typically occurs in the distal esophagus [11].

Risk factors differ between esophageal squamous cell carcinoma and esophageal adenocarcinoma. Squamous cell carcinoma is a multifactorial disease with a long list of putative risk factors, whereas adenocarcinoma has far fewer established risk factors [12].

A brief description of these risk factors is presented below in Table 1.

Despite the proactive study of the role of genetic factors in the development and prognosis of esophageal cancer, our knowledge in this area remains insufficient. Unlike some other gastrointestinal malignancies, such as colorectal cancer, there is no clear path of tumor ontogenesis for esophageal cancer.

The Cancer Genome Atlas network published the results of a comprehensive genomic analysis of esophageal carcinoma. The analysis of DNA methylation, mRNA expression, and transcriptional profiles unambiguously revealed significant differences between squamous cell carcinoma and esophageal adenocarcinoma, confirming that they belong to two different tumor types. At the gene expression level, adenocarcinoma showed increased E-cadherin signaling and activation of the ARF6 and FOXA pathways through modulation of E-cadherin. Squamous cell carcinoma is characterized by increased activity of the Wnt, syndecan, and p63 pathways, which play a key role in cell differentiation processes. Mutation profiling analysis confirmed frequent mutations of TP53, NFE2L2, MLL2, ZNF750, NOTCH1, and TGFBR2 in esophageal squamous cell carcinoma, while recurrent mutations of TP53, CDKN2A, ARID1A, SMAD4, and ERBB2 were confirmed in esophageal adenocarcinoma [4 3].

Table 2 presents a variety of genetic abnormalities associated with the development of esophageal cancer.

Table 1 – Risk factors for the development of esophageal cancer depending on histological types (adapted from [12])

Factor	Squamous cell carcinoma	Risk Impact Coefficient	Adenocarcinoma	Risk Impact Coefficient	Links
Smoking	Strong relationship	Magnification 3-9 times	Moderate dependence	Increase by 2-3 times	13-14
Alcohol	Strong relationship	5x magnification	There is no connection.	-	15-17
Opium	Moderate connection	Increase by 1.6-2 times	No data	-	18-19
Consumption of beverages at temperatures ≥ 65 °C is classified as "possibly carcinogenic to humans."	Moderate connection	Increase by 2-3 times	There is no connection.	-	20-22
Gastroesophageal reflux disease	Strong relationship	Magnification 5-9 times	There is no connection.	-	23-24
Body mass index	Weak to moderate connection	30% reduction	Light to moderate correlation	Increase by 1.5-2 times	25
Gastric atrophy	Moderately strong connection	Increase by 2 times	There is no connection.		26-27
Deterioration of oral hygiene	• Not brushing one's teeth regularly is associated with a moderately increased risk. • Tooth loss shows a mild to moderate association. • Periodontitis is also associated with an increased risk, but to a lesser extent (40%).	Increase by 2 times Increase by 30-100% 40% increase	Statistically significant correlation between tooth loss and periodontal disease on one hand and an increased risk of developing esophageal adenocarcinoma on the other.	Tooth loss is associated with 1.3-2 times increased risk, and periodontitis – 1.4 times.	28-30
Microbiological properties	The structure of unique bacte-rial populations in the oral cav-ity and esophagus and the de-crease in species richness of microflora in these areas may be associated.	Possible impact	Changes in the composition of gram-negative microflora in the esophagus may contribute to the development of Barrett's esopha-gus, a precursor to adenocarcino-ma.	Possible increase in risk	31-32

Окончание Таблицы 1

Diet	• High-quality diet. • Adherence to vegetarian diets, such as the Mediterranean diet.	Reducing risk Reducing risk	Following dietary guidelines, physical activity, and monitoring BMI can help minimize your risk of develop-ing esophageal cancer.	Reducing risk	33-34
Introducing certain foods	• Excessive consumption of canned vegetables is associated with a moderate increase in risk. • Higher red and processed meat consumption was associated with a weak but statistically significant cor-relation. • Increased consumption of fruits and vegetables greatly reduces the risk. • Higher carbohydrate intake significantly reduces the risk. • Consumption of poultry and fish produces inconsistent results. • Consumption of dietary fats and dairy products.	Increase by 2 times Increase by 30-70% Reduction by 45% Reduction by 40% Connection not established Connection not established	• Increased consumption of fruits and vegetables • Increased consumption of red and processed meat • Increased carbohydrate consumption • Increased consumption of poultry and fish • Increased consumption of dairy products	Reduction by 25% Increase by 30-70% Reduction by 40% Connection not established Unknown	35-40
Viral infection	• There is no reliable association between most subtypes of human papillomavirus (HPV) and the occur-rence of esophageal cancer. Some rare HPV subtypes may be associated with an increased risk. • Data on the association of other viruses with the development of esophageal cancer are contradictory and re-quire further study.	-	No correlation.	-	41
Bacterial infection	*Helicobacter pylori bacteria*	50% reduction	No correlation.	-	42

Table 2 – Overview of genetic abnormalities associated with esophageal cancer [44]

Genetic abnormality	Squamous cell carcinoma	Adenocarci-noma
Cell cycle	90%	86%
RTK anomaly	59%	76%
Cell differentiation	57%	42%
Chromatin remodeling	36%	22%

Studies of molecular abnormalities in esophageal cancer have revealed similarities with tumors in adjacent anatomical regions. Thus, esophageal adenocarcinoma exhibits similar molecular characteristics to gastric adenocarcinoma, and esophageal squamous cell carcinoma exhibits significant similarities to head and neck squamous cell carcinoma [4 4].

Discussion: This review analyzes the current understanding of the epidemiology, predisposing, and possible risk factors for the development of esophageal cancer, distributed by the main histological subtypes of the disease. The identified risk factors were categorized into genetic predispositions, dietary and eating habits, concomitant diseases, infections, microbiome composition, metabolic disorders, and other factors. It is important to note that the available literature does not contain data on the relationship between these risk factors and the prognosis of the disease. Additional studies are needed to confirm the identified results and clarify their impact on tumor biology.

Recent advances in the molecular analysis of esophageal cancer have convincingly demonstrated that adenocarcinoma and squamous cell carcinoma are genetically and biologically distinct oncological diseases. The identified specific genetic abnormalities indicate differences in the physiological mechanisms of development of these tumors, which requires the development of individual therapeutic approaches.

It is important to note that the molecular profile of esophageal adenocarcinoma shows similarities with the chromosomal instability characteristic of gastric cancer. However, esophageal squamous cell carcinoma shows genetic similarities with other categories of malignancies.

The studies demonstrate the need for personalized treatment of each histological subtype of esophageal cancer and their separate consideration in clinical trials. This is especially important when studying the effectiveness of neoadjuvant, adjuvant, and systemic chemotherapy.

Conclusion: The pathogenesis of squamous cell carcinoma is multifactorial, with well-established risk factors contributing to its development. In contrast, the etiology of esophageal adenocarcinoma remains poorly understood and requires continued research to identify the underlying causal mechanisms.

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АҢДАТПА

ӨҢЕШ ҚАТЕРЛІ ІСІГІНІҢ ГИСТОЛОГИЯЛЫҚ ТИПТЕРІН ЭПИДЕМИОЛОГИЯЛЫҚ ТЕНДЕНЦИЯЛАРЫН ЖӘНЕ ОНЫМЕН БАЙЛАНЫСТЫ ҚАУІП ФАКТОРЛАРЫН ЗЕРТТЕУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі. *Өңеш қатерлі ісігі – әлемнің көптеген бөліктерінде денсаулық сақтаудың күрделі мәселесі болып табылады. Өңеш қатерлі ісігінің дамуы әртүрлі қауіп факторларымен байланысты көп факторлы процесс болып табылады. Әртүрлі этиологиялық факторларды, соның ішінде генетикалық, диеталық, инфекциялық, ауыз қуысының денсаулығын және онымен байланысты ауруларды талқылайтын көптеген зерттеулер жүргізілді.*

Бұл қысқаша шолу қатерлі ісік эпидемиологиясына жан-жақты шолу жасайды және өңеш қатерлі ісігінің анықталған және күдікті қауіп факторларын нақты гистологиялық типтер бойынша бағалайды.

Зерттеудің мақсаты *– бұл зерттеудің мақсаты өңеш қатерлі ісігінің дамуындағы қауіп факторлары мен генетикалық бейімділік арасындағы қарым-қатынасқа баса назар аудара отырып, екі түрлі гистологиялық субтиптерге ерекше назар аудара отырып, кешенді эпидемиологиялық зерттеу жүргізу болып табылады.*

Әдістері: *Әдебиеттерді шолу келесі мәліметтер базасындағы ғылыми жарияланымдарды іздеуді қамтыды: PubMed, Medline, Cochrane Lab, Google Scholar ғылыми іздеу жүйесін қолдану арқылы. Іздеу тереңдігі – 10 жыл.*

Әдебиеттерге шолу мыналарды қамтиды: эпидемиология, өңеш қатерлі ісігінің қауіп факторларының байланысының күшін сипаттайтын және бағалайтын зерттеулер. Шолу тек ересектерге арналған барлық зерттеулерді, ағылшын тілдеріндегі жарияланымдарды, сондай-ақ нақты тұжырымдары бар басылымдарды қамтиды;

Шығарылу критерийлеріне жағдайлар сериясы, жағдай туралы есептер, редакциялық мақалалар және конференция тезистері кірді. Барлығы 462 дереккөз табылып, талдауға 45 ғылыми жарияланым енгізілді.

Нәтижелері: *Зерттеулер өңештің қатерлі ісігіне сезімталдықты бірнеше факторлардың жоғарылататынын көрсетеді, соның ішінде темекі тұтыну, алкогольді шамадан тыс тұтыну, опиоидтерді теріс пайдалану, ыстық тамақ пен сусындарды тұтыну, гастроэзофагеальды рефлюкс ауруы, семіздік, асқазанның атрофиясы, ауыз қуысының гигиенасы нашар болуы, өңеш микробиотасының өзгеруі, субоптималды емес диеталар, вирустық және бактериялық инфекциялар және т.б. Сонымен қатар, өңештің қатерлі ісік жасушаларының мутациялық профильдері TP53, NFE2L2, MLL2, ZNF750, NOTCH қоса алғанда, арнайы гендерде жиі мутацияларды анықтады.*

Қорытынды: *Жалпақ жасушалық карцинома қатерлі ісігінің патогенезі оның пайда болуына ықпал ететін көптеген мойындалған қауіп факторларымен бірге көп факторлы қасиеттерді көрсетеді. Керісінше, өңеш қатерлі ісігінің аденокарциномасының этиологиясы салыстырмалы түрде белгісіз болып қала береді, бұл оның негізгі қоздырғыш механизмдерін анықтау үшін үздіксіз зерттеулерді қажет етеді.*

Түйінді сөздер: *жалпақ жасушалы карцинома, өңеш аденокарциномасы, эпидемиология, қауіп факторлары, өңеш обырының генетикасы.*

АННОТАЦИЯ

ИССЛЕДОВАНИЕ ПОДТИПОВ РАКА ПИЩЕВОДА, ЭПИДЕМИОЛОГИЧЕСКИХ ТЕНДЕНЦИЙ И СВЯЗАННЫХ ФАКТОРОВ РИСКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак пищевода представляют собой значительную проблему в области здравоохранения во многих странах мира. Развитие рака пищевода – это многофакторный процесс, связанный с различными факторами риска. Было выявлено множество исследований, в которых изучались различные этиологические факторы, включая генетические, диетические, инфекции, здоровье полости рта, фоновые заболевания.*

Данный литературный обзор описывает эпидемиологию рака пищевода и оценки установленных и возможных факторов риска по раздельным гистологическим подтипам, такими как плоскоклеточный рак и аденокарцинома.

Цель исследования *– проведение всестороннего эпидемиологического обследования, сосредоточенного на взаимосвязи между факторами риска и генетической чувствительности при развитии рака пищевода, с особым акцентом на отдельные гистопатологические подтипы.*

Методы: *Проведен поиск научных публикаций в следующих базах данных: PubMed, Medline, Cochrane Lab при помощи научной поисковой системы Google Scholar. В обзор были включены исследования, посвящённые эпидемиологии и изучения связи между факторами риска рака пищевода. В анализ вошли публикации на английском языке с четко сформулированными выводами, за исключением отчётов о случаях и сериях случаев, редакционных статей и тезисов конференций. Глубина поиска – 10 лет. Всего было найдено 462 источника, включено в анализ 45 научных публикаций.*

Результаты: *Исследования показывают, что некоторые факторы повышают чувствительность к раку пищевода, в том числе курение, алкоголь, потребление наркотических веществ, потребление горячих пищевых продуктов и напитков, гастроэзофагеальная рефлюксная болезнь, ожирение, атрофия желудка, плохая оральная гигиена, изменения в микробиоте пищевода, субоптимальные диеты, вирусные и бактериальные инфекции и другие. Кроме того, мутационные профили раковых клеток пищевода обнаружили частые мутации, такие как TP53, NFE2L2, MLL2, ZNF750, NOTCH.*

Заключение: *Патогенез рака плоскоклеточной карциномы проявляет многофакторные свойства, с множеством признанных факторов риска, способствующих его возникновению. Напротив, этиология аденокарциномы рака пищевода остается относительно изученной, требуя постоянных исследовательских усилий по выявлению ее фундаментальных причинных механизмов.*

Ключевые слова: *эпидемиология, факторы риска, генетика рака пищевода, плоскоклеточная карцинома, аденокарцинома пищевода.*

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THE PURPOSE is to assist the development of the oncological service of Kazakhstan, including actions to support:

- efficient prevention
- early diagnostics
- quality treatment
- accessible palliative care

Public Fund «TOGETHER AGAINST CANCER»
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Bank details:
IBAN (KZT): KZ526017131000056375
IBAN (USD): KZ406017131000054457
IBAN (EUR): KZ456017131000053785
IBAN (RUB): KZ636017131000057923
Almaty Regional Branch of
Halyk Bank of Kazakhstan
BIC: HSBKKZKX
Beneficiary code – 18
Payment purpose code
for sponsorship transfers – 119

ВМЕСТЕ ПРОТИВ РАКА
общественный фонд

ҚА ТЕРЛІ ІСІКПЕН КҮРЕСЕЙІК
TOGETHER AGAINST CANCER
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