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STATISTICS
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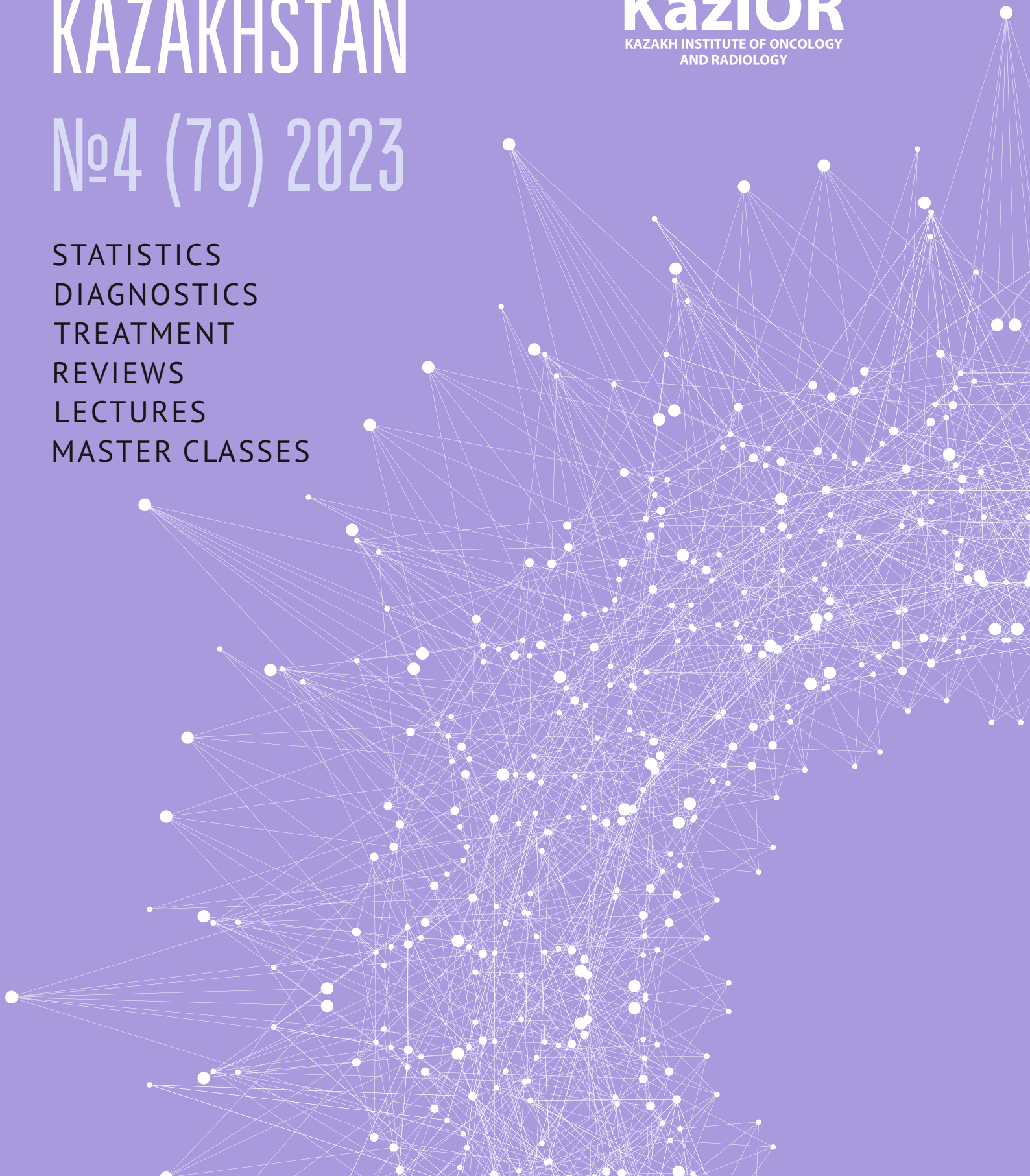

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Contents

Good day, dear readers!

Welcome to the pages of our New Year's issue!

Time flies at double speed on the eve of the New Year; a period of summing up, preparing for the holidays, and making wishes begins. Our editors worked hard to prepare this final issue. Articles were proofread, and controversial issues were argued with the reviewers. The Scientific Council discussed how to improve the journal and raise the activity of the authors and Editorial Board.

Based on the results of the seminar for journal editors conducted by the Ministry of Education and Science of the Republic of Kazakhstan, in the coming year, we will amend the Manual for Authors, change the composition of the Editorial Board, and expand the reviewers' list.

This issue offers a variety of topics and a wide geography of authors, from the organization of healthcare and analysis of epidemics and the logical situation in one of the country's regions to clinical cases of oncological pathologies of various localizations.

Readers are offered articles on applying the Japanese Gastric Cancer Association morphological classification to the Kazakhstani population, the influence of environmental factors on the risk of developing cancer, and reasons for admission to the intensive care unit of patients with acute lymphoblastic leukemia.

Other articles were devoted to gynecological, colorectal, and stomach cancer.

Though the journal's website was subjected to a hacker attack, we continue to accept and publish articles in a manual mode. The site will soon function as usual.

In the New Year, we wish all our readers and authors good health, creative success, new ideas, and inspiration for conducting research and preparing interesting publications!

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

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GASTRIC CANCER: EPIDEMIOLOGY AND PROSPECTS FOR THE DEVELOPMENT AND IMPLEMENTATION OF INNOVATIVE TECHNOLOGIES FOR EARLY DETECTION AND TREATMENT

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ABSTRACT

Relevance: *Gastric cancer is a heterogeneous group of malignant epithelial tumors arising from the cells of the gastric mucosa, one of the most common forms of malignant neoplasms in many coun-tries of the world. But, despite repeated attempts, there are no convincing approaches to early large-scale (screening) detection technology for this form of cancer. This causes a high rate of late detec-tion of advanced forms of gastric cancer in most countries of the world, a high one-year mortality rate of patients, and a low five-year survival rate. Currently, full screening for gastric cancer is car-ried out only in Japan, Korea, and China - countries with high incidence rates.*

The study aimed to *assess the epidemiologically disadvantaged regions of Kazakhstan for cancer to select optimal early detection techniques to improve the treatment results.*

Methods: *For the analysis, we used available epidemiological indicators on GC from the specialized literature, data obtained from annual reporting forms No. 7, approved by the Ministry of Health of the Republic of Kazakhstan, in the country code (ICD 10 - C16), publications with statistical and analytical materials on Kazakhstan. Morbidity and mortality rates were calculated based on data from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Re-public of Kazakhstan website on the aver-age annual population by region of Kazakhstan.*

Results: *A long-term decrease in the incidence and mortality from gastric cancer in Kazakhstan since 2021 has been replaced by a stable increase in the incidence of gastric cancer against the back-drop of a high frequency of advanced forms, relatively high mortality, and low five-year survival of patients. At the same time, there is experience in the world of certain approaches to screening the popula-tion for early detection of gastric cancer.*

Conclusion: *The high morbidity of gastric cancer in most regions of the country in recent years re-quires the search and devel-opment of optimal forms of screening for its early detection; this will re-duce mortality from gastric cancer and increase the five-year survival rate of patients.*

Keywords: *gastric cancer, morbidity, mortality, dynamics of indicators, regions of Kazakhstan, screening.*

Introduction: Gastric cancer (GC) is common in the world, with a morbidity of 31.9 (World standard per 100,000 population) according to WHO in 2005 in different countries worldwide. Men suffered from GC twice more often than women (21.5 vs. 10.4). The highest mortality was observed in Eastern Asia and Eastern Europe. Mean mortality from GC amounted to 15.6 per 100,000 males and 7.8 per 100,000 females. In far-abroad countries, the highest morbidity (per 100,000 World standard) was registered in Japan (47.6), Costa Rica (37.7), and China (26.8), with low rates in the U.S.A. (5.8), Egypt (3.4), and Indonesia (2.8) [1, 2].

The study aimed to assess the epidemiologically disadvantaged regions of Kazakhstan for cancer to select optimal early detection techniques to improve the treatment results.

Materials and Methods: For the analysis, we used available epidemiological indicators on GC from the specialized literature, data obtained from annual reporting forms No. 7, approved by the Ministry of Health of the Republic of Kazakhstan, in the country code (ICD 10 - C16), publications with statistical and analytical materials on Kazakhstan.

The authors conducted a retrospective analysis of literature data on GC epidemiology in separate countries and the world and the own materials summarized by experts of "Kazakh Institute of Oncology and Radiology" JSC (KazIOR, Almaty, Kazakhstan) on GC epidemics in the country and the types and results of GC early detection screenings in the world.

Morbidity and mortality rates were calculated based on data from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan website on the average annual population by region of Kazakhstan [3].

Results:

GC incidence in the world

In recent years, GC has ranked second among all can-

cers globally. However, the incidence rates in different countries vary. The incidence is still high in Japan, China, Chile, and Iceland. In the U.S.A., about 27,600 new GC cases and 11,010 deaths from GC are registered each year [4, 5].

Adenocarcinomas account for 95% of gastric malignancies; localized gastric lymphomas and leiomyosarcomas are less common. In the past decades, GC incidence has reduced in the U.S.; GC ranks 7th in cancer mortality. There, GC is more common among African Americans, Hispanics, and American Indians. More than 75% of patients are above 60 years [5].

Among ex-Soviet countries, in 2000, GC led the cancer incidence structure among men in Turkmenistan and Kyrgyzstan (18.3-21.7%) and consistently ranked 2nd in Russia (among both sexes), Kazakhstan, Armenia, and Azerbaijan (among men). Compared to 1990, GC's share in cancer incidence structure reduced in Russia, Kazakhstan, Armenia, and Tajikistan and increased in Kyrgyzstan and Turkmenistan. The number of new cases in Russia reduced by 10,000 (16%) since 1990 to reach 48,200 [6]. In 2008, the highest GC incidence per 100,000 population (World standard) was registered in Ukraine (34.9), Belarus (34.6), and Russia (27.2); the lowest – in Armenia (18.3), Kyrgyzstan (11.9), Georgia, and Azerbaijan (9.1) [7].

In 2020, GC ranked 6th in the world among all malignant tumors and was detected in 1.09 mln people; 769,000 people died from GC, making it 4th reason of death from malignancies. Age-standardized GC incidence in the world decreases annually by 4-5%. However, in some developed countries, the incidence of cancer of the gastric cardia is increasing [8].

In 2020, the highest GC incidence per 100,000 population was registered in Eastern Asia (22.4), Central and Eastern Europe (11.3), South America, Polynesia, and Western Asia (about 8.6); the lowest rate (3.3) was recorded in the south of Africa. According to the American Cancer Society, GC primarily affects older adults. About 6 of 10 people diagnosed with GC are above 65 years old. Men are at twice the higher lifelong risk of developing GC (about 1 in 96 vs. 1 in 152 women) [9, 10].

In 2018, in Russia, GC accounted for 7.4% of all malignancies in men and 4.6% in women. The average age at diagnosis increased from 66.4 years in 2008 to 67.5 years in 2018. Over the same period, the GC crude incidence per 100,000 population of both sexes decreased from 28.6 to 25.16, with an annual decrease of 1.36%; the standardized incidence went down from 17.37 to 13.55, with an annual decrease of 2.58%. GC ranked 2nd (9.5%) in men and 3rd (8.4%) in women in Russia's cancer mortality structure. The average age of those who died from GC has increased from 67.4 to 68.7 years since 2008. The mortality from GC per 100,000 population decreased significantly over the same period from 25.39 to 18.97 in crude rates and 15.02 to 9.94 in standardized rates [11].

In 2021, GC became 6th most prevalent malignancy and 2nd cause of death from cancer in Russia. According to the Russian National Cancer Register, 32,031 new cases of GC were registered in the country, and 26,311 patients died from that disease [12].

In recent years, the average five-year survival with GC amounted to 18% in Western Europe and 21% in the US. The highest five-year survival (53%) was registered in Japan, possibly due to a mass screening for GC in this country. Generally, five-year survival with GC varies within 10-20% globally [13].

GC incidence in Kazakhstan

In RK, till 1985, GC ranked first in total cancer incidence and, in subsequent years, moved to second place. KazIOR experts reported a persistent downward trend in GC incidence over several years: from 20.9 per 100,000 population in 2000 to 16.3 in 2012 and 10.9 in 2015 [14-16].

An epidemiology analysis of GC incidence in Kazakhstan in 2004-2014 conducted by KazIOR experts confirmed the downward trend in GC morbidity and mortality over time. Men suffered from GC 2.5 times more often than women. The incidence was high in the Pavlodar, Kyzylorda, Aktobe, and Akmola regions. In 2009-2014, the incidence rates increased in Astana and the Zhambyl, Akmola, and Aktobe regions and decreased in the North Kazakhstan and Mangistau regions [16]. The proportion of stage I-II cases increased by 1.8 times. The morbidity-to-mortality ratio decreased from 83.9% to 66.6% over the same period, evidencing an improvement in oncological care for the RK population and the efficacy of GC screening conducted in that period.

In 2015, the incidence per 100,000 population was high in Kostanay (23.9), Pavlodar (23.4), North Kazakhstan (North Kazakhstan) (23.0), East Kazakhstan (EKR) (22.9), Karaganda (21.9), and Akmola (21.2) regions; average – in West Kazakhstan (WKO) (17.4), Aktobe (16.8), Zhambyl (15.7), and Kyzylorda (15.1) regions; and low in in Atyrau (13.9), Almaty (13.14), Mangistau (11.5) and South Kazakhstan (SKO) (11.2) regions [17] (Figure 1).

According to operational data from KazIOR, in 2017-2019, the downward trend in GC incidence in Kazakhstan remained. GC then ranked 3rd in primary cancer incidence in both sexes (8.2% in 2019), 2nd in men (11.9%), and 5th in women (5.3%), and the incidence was gradually decreasing (per 100,000 both sexes) from 15.3 in 2017 to 14.9 in 2018, and 14.4 in 2019 in crude figures, and 14.4 to 13.6 and 12.9 in standardized figures, respectively. Sex-related incidence (per 100,000 of the relevant sex) in that period also steadily decreased from 22.8 to 20.5 in men and from 10.8 to 7.8 in women.

GC ranked 2nd in cancer incidence in both sexes in Kyzylorda and Turkestan regions and 5th in North Kazakhstan. In 2019, it was above the national average (14.4 per 100,000) in eight regions, including the Kostanay (21.0), Aktobe (20.8), Pavlodar (20.7), Karaganda (20.4), North Kazakhstan (20.4), Akmola (20.2), East Kazakhstan (20.0) and West Kazakhstan (17.9) regions. The incidence per 100,000 was low in the Turkestan (6.9), Almaty (10.5), Mangistau (11.0), and Kyzylorda (12.6) regions [18].

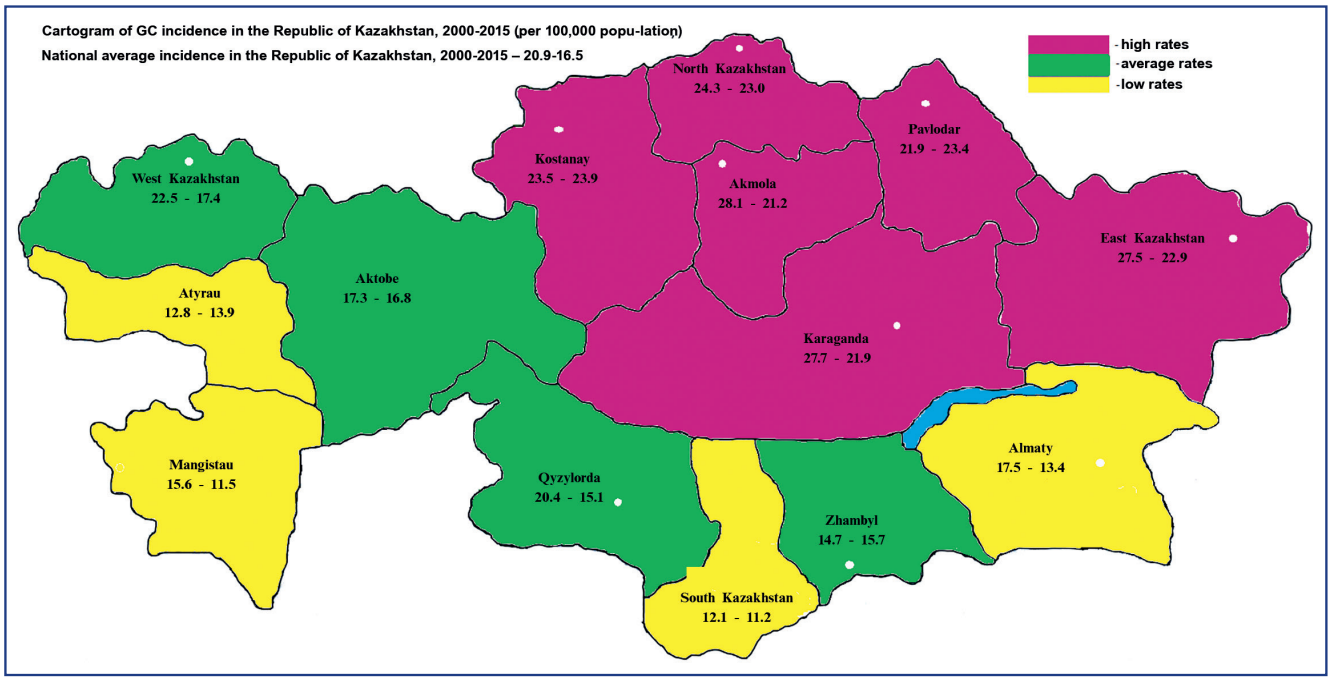

Figure 1 – GC incidence trends by region of Kazakhstan

Later, the GC incidence in Kazakhstan started growing; it increased from 13.2 to 13.5 in 2021 and 14.9 in 2022. The rates were above the national average per 100,000 in 2022 in the Kostanay (22.9), Karaganda (21.5), North Kazakhstan (21.1), East Kazakhstan (21.0), Pavlodar (20.4), Akmola (20.2), Abay (19.8), West Kazakhstan (19.3), and Aktobe (19.2) regions [19, 20].

Mortality from GC in the world

In the late 1980s, GC lost its leading place as the main cause of cancer mortality in the world to lung cancer, moving to second place. In Russia, it occurred in 1985. Despite an evident downward trend in GC mortality, GC still led the cancer mortality structure in the 1980s in Japan while occupying 14th place in the US [21].

Table 1 offers standardized GC mortality rates for men and women in 1994-1997, and GC ranks in cancer mortality structure by country according to WHO. The mortality rates differed 8.4 times in men and 7.7 times in women.

Table 1 – GC ranks and standardized mortality rates (per 100,000 population) by sex and country, 1994-1997 [21]

Men			Women		
Rank	Country	Index	Rank	Country	Index
1	Russia	36.9	1	Russia	15.3
2	Kazakhstan	33.1	2	Kazakhstan	13.9
3	Chile	33.2	3	Columbia	13.1
4	Japan	30.2	4	China	12.7
5	Kyrgyzstan	29.7	5	Japan	12.3
6	China	26.9	6	Estonia	12.0
7	Latvia	26.8	7	Latvia	11.8
8	Estonia	26.0	8	Канада	11.7
9	Lithuania	25.9	9	Туркмения	11.0
10	Azerbaijan	24.9	10	Kyrgyzstan	10.7
44	U.S.	4.4	44	U.S.	2.0

According to the ONCOLOGY.ru information portal, currently, the highest GC mortality (standardized per 100,000 population) is registered in Kyrgyzstan (men – 47.0, women – 19.0), Russia (men – 36.0, women – 15.0), and Japan (men – 31.0, women – 14.0). The mortality is also high in most East European countries but low in the US, Canada, New Zealand, and Western and Northern Europe [13].

Mortality from GC in Kazakhstan

According to KazIOR reports, the mortality from GC is steadily decreasing in Kazakhstan. Thus, it declined from 17.6 in 2000 to 10.9 in 2015 (per 100,000 population) (Figure 2).

In 2015, by region, the mortality per 100,000 population was high in the Pavlodar (17.6), East Kazakhstan (14.8), Zhambyl (14.6), North Kazakhstan (14.2), and Akmola (13.0) regions, average – in the Kostanay and Karaganda (11.9 each), West Kazakhstan region (11.4) and Atyrau (10.9) regions, and low – in the Kyzylorda, South Kazakhstan (9.1 each), Almaty (8.6), Aktobe (8.4), and Mangistau (6.5) regions [17].

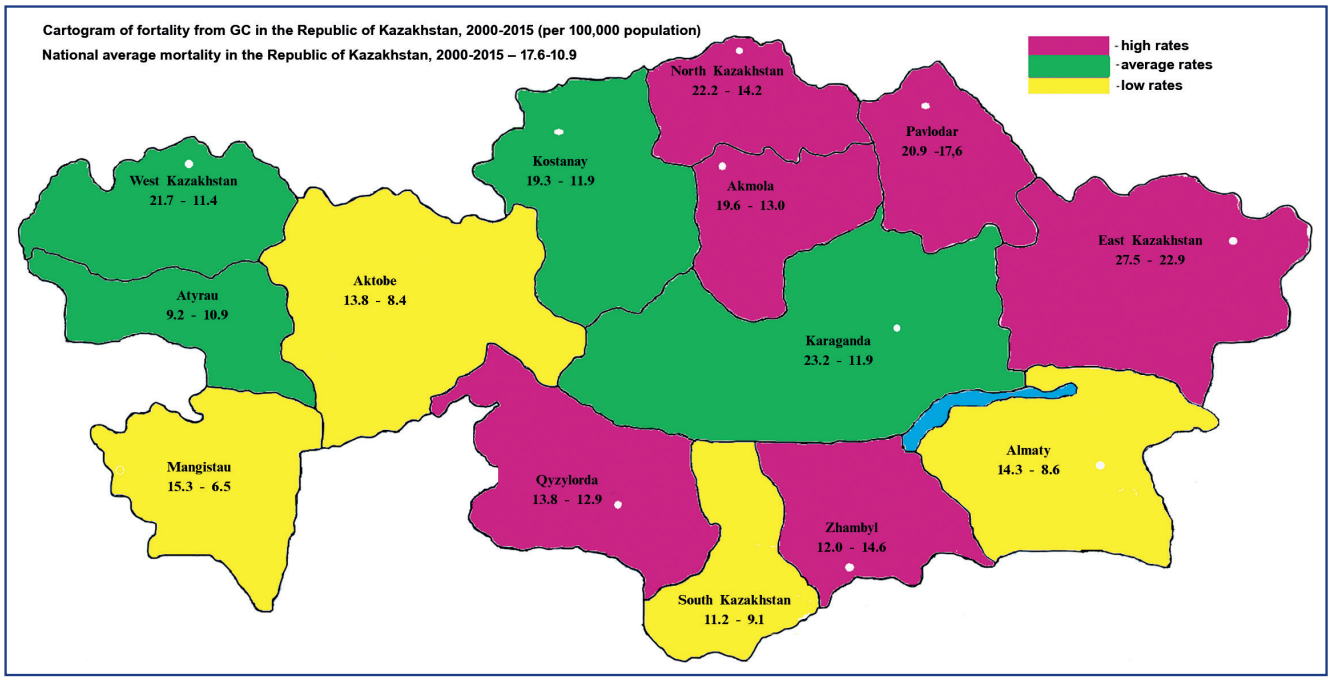

Figure 2 – GC mortality trends by region of Kazakhstan

In 2017-2019, this pathology ranked second in cancer mortality in RK, with a share of 11.5 to 12.1%. The crude mortality from GC decreased from 9.5 to 9.1 per 100,000 over those years, and the standardized mortality went from 8.9 to 8.2 [18, 22].

In 2019, the GC mortality per 100,000 population was above the national average in nine regions, including the Pavlodar (13.6) – the national maximum, East Kazakhstan (13.1), West Kazakhstan (12.0), Akmola (11.7), North Kazakhstan (10.8), and Karaganda (11.3) regions and Astana (10.9). The rates were low in the Almaty (6.2), Turkestan (6.5), Aktobe (7.6), Mangistau (7.7), and Kyzylorda (7.8) regions and the city of Shymkent (6.2). Morphological verification of the diagnoses achieved 95.8% in 2019. Early detection rate (GC stages I + II) amounted to 42.9%, with a late detection rate (stage IV) of 19.9% – one of the highest cancer neglect rates. Five-year survival improved over those three years from 42.1 to 44.5% [18].

The study by a group of Norwegian, Russian, and Kazakhstani experts covering 2004-2015 revealed statistically significant trends in decreasing morbidity and mortality from GC in the RK. Early detection rate (stages I-II) improved from 16,8 to 34.2%; however, five-year survival began to increase only in 2012 [23].

Discussion: Implementation of the State Health Care Development Program of the Republic of Kazakhstan "Salamatty Kazakhstan" for 2011-2015 and subsequent health care programs that provide for the priority development of oncology services and the expansion of screening programs for early detection of cancer became a key factor contributing to the reduction of morbidity, mortality, and improvement of early diagnosis of GC in the country over time.

As a result, the mortality from GC per 100,000 population has steadily decreased in Kazakhstan since 2000, including 8.6 in 2020 to 8.0 in 2022 [19, 20]. However, the mortality from GC in Kazakhstan still exceeds the rates in developed countries. To address this problem, KazIOR experts study the experience to select the optimal screening program for GC in the Republic of Kazakhstan, possibly starting with pilot regions with the highest incidence rates.

The A.A. Avanesyan et al. report utilizes various foreign sources to compare diagnostic criteria for GC adopted in Japan (East) and Western countries [24]. Thus, in Japan, non-invasive intraepithelial neoplastic lesions with a high degree of cellular and architectural atypia are called "non-invasive intra-mucosal cancer," while in Western countries, they are interpreted as "high-grade dysplasia" [25, 26]. These differences may lead to different approaches when counting this pathology, affecting the magnitude of epidemiological characteristics.

Countries in Western Europe and the U.S. have no national screening for GC. Screening of patients with dyspepsia, a GC development symptom, showed that this has no practical meaning [27, 28]. Studies in the U.S. showed the inappropriateness of routine screening of people at moderate risk of developing GC. According to the US National Cancer Institute, no evidence exists that screening for GC reduces mortality in the regions with a relatively low incidence of this disease [29, 30]. People with obvious risk factors for developing GC can benefit from screening [31]. Therefore, more studies are required to determine the screening population and methods [32, 33].

Several countries of Asia and Eastern Europe with a traditionally high GC incidence follow the screening procedure that includes double contrast fluorography, endoscopic examination with random or targeted biopsy, screening and treatment of Helicobakter pylori, se-

rological testing for antibodies to pepsinogens, gastrin and Helicobakter pylori, and breath tests for volatile organic compounds [34].

Other screening alternatives include measuring blood levels of gastrin-17 and pepsinogen I and assessing the ratio of pepsinogen I to pepsinogen II. A decrease in the level of these markers is a sign of atrophy of the gastric mucosa, which leads to the risk of developing GC.

Japan is studying the possibility of using a 13C breath test for H. Pylori (the «Screen & Treat H. Pylori» method) for GC screening. However, only 1% of H. pylori-infected develop GC, so more research into the effectiveness of this screening is needed.

Studies show that X-ray and endoscopic screenings can reliably reduce mortality from GC due to its early detection [35]. Still, there is no global consensus on the GC screening method that is most efficient for the general population [36].

Japan started screening for GC back in 1963. First, it covered people aged 40+ and included questioning and double-contrast radiography. Since 2016, it covers people aged 50+. The radiographic screening sensitivity was 80-90% [37, 38]. Therefore, early GC stages were detected in nearly 60% of cases, and five-year survival exceeded 65% [39]. However, according to recent research, endoscopic screening can reduce mortality from GC by 67% compared to radiographic screening [40]. The early detection rate was usually about 70% in the radiographic screening group and exceeded 80% in the endoscopic screening group. Endoscopy could diagnose earlier GC stages treated by endoscopic surgery dissection [40, 41]. Endoscopic screening also reduced mortality by 28-57% [42-44].

In 2016, the Japanese Government introduced endoscopic screening for GC as a National Program based on epidemiological case-control studies conducted in Japan and Korea. However, due to significant costs, radiographic examinations have been adopted for mass examinations using mobile buses [38], while endoscopic screening was carried out only in large cities [45].

Korea introduced GC screening in 2002 as part of the National Cancer Screening Program. The screening by esophagogastroduodenoscopy (main method) or double fluoroscopy is conducted every two years for people aged 40+ [46].

China started the National GC Screening Program in 2005 in rural areas and regions with a high prevalence of GC. Endoscopic examination with chromoscopy and target biopsy covers citizens aged 40 to 69 [44, 47]. The studies Результаты исследований provide good evidence that endoscopic screening detects not only potential invasive carcinoma but also early-stage cancer and precancerous lesions, which improves the effectiveness of subsequent treatment [48].

Several other countries implement regional screening for GC: Costa Rica has utilized the X-ray method since 1996; endoscopic examination offered in Kazakhstan every 2nd year since 2013 has covered 306,000 people. Some countries (like GB, the US, and Australia) are trying to develop AI- or neuron-network-based systems to relieve doctors from the enormous workload. Japan has been most successful in using AI in endoscopy. The accuracy of the new diagnostic system reaches 82.7%. The main technology breakthrough is the ability to perform optical biopsy in real time [24].

Conclusion: Therefore, today, further development and introduction of a single methodology for GC screening is vital for Kazakhstan and the rest of the world to significantly increase the GC early detection rate and reduce the related mortality [24].

Taking into account the still high incidence and mortality from GC in Kazakhstan, the steadily growing incidence in recent years, and a stable 3rd place in cancer incidence structure, while the neglect rate remains high (21.3%) and five-year survival does not improve (47.8%) [20], there is an evident need to implement a population screening program aimed at GC early detection and find new approaches to treating gastric cancer and pre-cancer considering modern approaches of genomics and proteomics.

With this in mind, a research team based at KazIOR, Atyrau Oncological Dispensary, Center of Nuclear Medicine in Semey, and East-Kazakhstan Regional Multi-Disciplinary "Oncology and Surgery Center" in Ust-Kamenogorsk started a project focused on improving the results of endoscopic diagnostics with the use of chromoscopy for GC and precancerous pathology. Since endoscopic methods of diagnosing diseases of the esophagus, stomach, and duodenum are considered most informative, in the framework of this project, they will be supported by chromoscopy (using methylene blue as a dye) with adapting the morphological classification of Japan Gastric Cancer Association (Japanese Classification of Gastric Carcinoma, 2nd English edition) for the use in Kazakhstani population. The study will involve men and women aged 40-75 years who have not been on dynamic record for GC after questioning and signing an informed consent.

In the future, after the project implementation, expanding the screening scope could be considered based on GC epidemiological peculiarities in problem regions of Kazakhstan.

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АНДАТПА

АСҚАЗАН ОБЫРЫ: ЭПИДЕМИОЛОГИЯ ЖӘНЕ ЕРТЕ АНЫҚТАУ МЕН ЕМДЕУДІҢ ИННОВАЦИЯЛЫҚ ТЕХНОЛОГИЯЛАРЫН ӘЗІРЛЕУ ЖӘНЕ ЕНГІЗУ ПЕРСПЕКТИВАЛАРЫ

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Өзектілігі: *Асқазан обыры – бұл асқазан шырышты қабығының жасушаларынан шығатын қатерлі эпителиалдық ісіктердің гетерогенді тобы, әлемнің көптеген елдерінде қатерлі ісіктердің ең кең таралған түрлерінің бірі. Бірақ, бірнеше рет жасалған әрекеттерге қарамастан, обырдың осы түрі бойынша ерте масштабты (скринингтік) анықтау технологиясына сенімді тәсілдер жоқ. Бұл әлемнің көптеген елдерінде асқазан обырының асқынған түрлерін кеш анықтаудың жоғары жиілігіне, науқастардың бір жылдық өлім-жітімінің жоғары болуына және олардың бес жылдық өмір сүруінің төмен болуына себепші болады. Қазіргі уақытта асқазан обыры бойынша толық скрининг аурудың жоғары деңгейі бар Жапонияда, Кореяда және Қытайда ғана жүргізіледі.*

Зерттеудің мақсаты *– науқастарды емдеу нәтижелерін жақсартуға мүмкіндік беретін ерте анықтаудың оңтайлы технологиясын таңдау үшін Қазақстанның асқазан обыры бойынша эпидемиологиялық қолайсыз өңірлерін бағалау.*

Әдістері: *Талдау үшін РЖ бойынша арнайы әдебиеттерден қол жетімді эпидемиологиялық көрсеткіштер, Қазақстан Республикасы Денсаулық сақтау министрлігі бекіткен ел бойынша жиынтықтағы (АХЖ 10 – С16) № 7 жыл сайынғы есептік нысандардан алынған деректер, Қазақстан бойынша статистикалық және талдамалық материалдармен жарияланымдар пайдаланылды. Сырқаттану мен өлім-жітім көрсеткіштерін есептеу үшін Қазақстан Республикасы Стратегиялық жоспарлау және реформалар жөніндегі агенттігінің Ұлттық статистика.*

Нәтижелері: *Қазақстанда 2021 жылдан бастап асқазан обырынан сырқаттанушылық пен өлім-жітімнің көпжылдық төмендеуі іске қосылған нысандардың жоғары жиілігі, науқастардың салыстырмалы жоғары өлімі мен бес жылдық өмір сүру деңгейінің төмендігі аясында РЖ сырқаттанушылықтың тұрақты өсуімен ауыстырылды. Бұл ретте әлемде халықтың асқазан обырын ерте анықтауға скрининг жүргізудің белгілі бір тәсілдерінің тәжірибесі бар.*

Қорытынды: *Елдің көптеген өңірлерінде асқазан обырымен сырқаттанудың жоғары деңгейі соңғы жылдары оны ерте анықтауға скрининг жүргізудің оңтайлы нысандарын іздестіруді және әзірлеуді талап етеді, бұл асқазан обырынан өлім-жітімді азайтуға және науқастардың бес жылдық өмір сүруін арттыруға мүмкіндік береді.*

Түйінді сөздер: *асқазан обыры, сырқаттану, өлім-жітім, көрсеткіштердің динамикасы, Қазақстанның өңірлері, скрининг.*

АННОТАЦИЯ

РАК ЖЕЛУДКА: ЭПИДЕМИОЛОГИЯ И ПЕРСПЕКТИВЫ РАЗРАБОТКИ И ВНЕДРЕНИЯ ИННОВАЦИОННЫХ ТЕХНОЛОГИЙ РАННЕГО ВЫЯВЛЕНИЯ И ЛЕЧЕНИЯ

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Актуальность: *Рак желудка (РЖ) – это гетерогенная группа злокачественных эпителиальных опухолей, исходящих из клеток слизистой оболочки желудка, и одна из самых распространенных форм злокачественных новообразований во многих странах мира. При этом, несмотря на неоднократные попытки, по данной форме рака до сих пор отсутствуют убедительные технологии раннего масштабного (скринингового) выявления, что обусловливает высокую частоту позднего обнаружения запущенных форм РЖ в большинстве стран мира, высокую одногодичную летальность и низкую пятилетнюю выживаемость больных. В настоящее время полноценный скрининг РЖ проводится только в Японии, Корее и Китае – странах с высоким уровнем заболеваемости.*

Цель исследования *– оценка эпидемиологически неблагополучных по РЖ регионов Казахстана для выбора оптимальной технологии раннего выявления, что позволит улучшить результаты лечения больных.*

Методы: *Для анализа использовались доступные эпидемиологические показатели по РЖ из специальной литературы, данные, получаемые из ежегодных отчётных форм №7, утверждённых Министерством здравоохранения Республики Казахстан (РК), в своде по стране (МКБ 10 – С16), публикации со статистическими и аналитическими материалами по Казахстану. Для расчёта показателей заболеваемости и смертности использовались данные с сайта Бюро национальной статистики Агентства по стратегическому планированию и реформам Республики Казахстан о среднегодовой численности населения по регионам Казахстана*

Результаты: *Многолетнее снижение заболеваемости и смертности от РЖ в Казахстане с 2021 года сменилось стабильным ростом заболеваемости на фоне высокой частоты запущенных форм, относительно высокой смертности и низкой пятилетней выживаемости больных. При этом, в мире существует определённый опыт проведения скрининга населения на раннее выявление РЖ.*

Заключение: *Высокий уровень заболеваемости РЖ в большинстве регионов страны в последние годы требует поиска и выработки оптимальных форм проведения скрининга на его раннее выявление. Это позволит снизить смертность от рака желудка и увеличить пятилетнюю выживаемость больных.*

Ключевые слова: *рак желудка (РЖ), заболеваемость, смертность, динамика показателей, регионы Казахстана, оптимальный скрининг.*

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THE RESULTS OF THE JAPANESE GASTRIC CANCER ASSOCIATION MORPHOLOGICAL CLASSIFICATION ADAPTATION FOR THE KAZAKH POPULATION

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ABSTRACT

Relevance: *Gastric cancer (GC) morbidity is growing in Kazakhstan every year. In 2022, 2 915 new GC cases were detected (15 per 100,000 population), making GC the third most common cancer. The early detection rate of GC does not exceed 10-20%, and advanced forms of GC are over 40%. Mortality increases in the first year after the diagnosis (up to 40%).*

The best way of solving early detection of gastric cancer is carrying out diagnostics at the stage of pre-tumor stomach diseases. Timely diagnosis and treatment of surgical and borderline diseases of the upper gastrointestinal tract (metaplastic and dysplastic changes in the mucous membrane of the esophagus, stomach, and duodenum and adenocarcinomas and early cancer arising against this background) are a complex medical and social problem.

Endoscopic methods for diagnosing esophagus, stomach, and duodenum diseases are the most highly informative nowadays. However, precancerous changes (atrophy, metaplasia, and dysplasia) in conventional endoscopic examination may not have specific features. It is necessary to improve the results of endoscopic diagnosis. The chromoscopy method may be one of the methods used to identify precancerous pathology and GC methods.

The study aimed to *increase the efficiency of early detection of gastric cancer by adapting the Japanese Gastric Cancer Association (JGCA) morphological classification for the Kazakh population.*

Methods: *We conducted endoscopic studies of 500 residents of the Republic of Kazakhstan using chromoscopy and morphological studies of the biopsy obtained during endoscopic examination. These patients had digestive system problems but previously did not have a GC diagnosis. We formed the risk groups according to JGCA (editions 13th and 14th).*

Results: *We identified 3(0.6%) morbidity of severe dysplasia according to the results of 500 patients' biopsy samples morphological study. This morphological structure is classified as a well-differentiated adenocarcinoma. We recommended a surgical treatment for identified patients.*

Conclusion: *The detected cases of obligate pre-cancer with an extremely high probability of malignancy prove the importance of using the JGCA classification for GC early diagnostics and allow us to recommend the use of chromoscopy in endoscopic examination of the stomach.*

Keywords: *gastric cancer (GC), chromoscopy, severe dysplasia, morphological classification of the Japanese Gastric Cancer Association (JGCA).*

Introduction: According to the national cancer registry, the number of newly diagnosed gastric cancer (GC) cases is growing annually in Kazakhstan, increasing by 1.9% in 2021 and 11.0% in 2022. However, it declined by 2.5% in 2018 and 8.1% in 2020. In 2022, 2,915 new cases of GC were revealed (15 per 100,000 population). GC ranked 3rd in the structure of oncopathology (8.3%) in both sexes, 2nd in men (12.5%), and 6th in women (5.12%) [1]. In 2020, GC ranked 2nd in the structure of deaths from cancer in Kazakhstan, with a one-year lethality of 44.1% in 2021 and 40.0% in 2022. The ratio between one-year mortality and advanced cases (stage IV) was 2.2 in 2021 and 1.9 in 2022 [1]. It is worth noting that the annual mortality rate reaches 40.0%, while the early detection rate for GC does not exceed 10-20%. Over 40% of cases are detected at stages III-IV of the disease [2].

Early diagnostics followed by the treatment of precancerous diseases of the gastrointestinal mucosa (atrophic, metaplastic, and dysplastic changes of the mucous membrane of the esophagus, stomach, and duodenum) is a daunting challenge for the oncology service [3-5].

These facts urge the search for methods of new early diagnostics at the stage of precancerous lesions and improved treatment efficacy for stomach diseases. A com-

plicated, controversial issue in early GC diagnostics is the discrepancy in assessing the condition of patients with newly established GC or precancerous diseases. First, it stems from different malignant neoplasm (MN) classifications adopted in various countries, which ultimately affect the adequacy of a patient's condition assessment to assign this patient to a particular risk group.

For example, the Japanese MN classifications adopted in 1998-2010 were not used in European and American clinics due to their more complex numbering of regional lymph nodes and significant differences from the UICC international classification [6-9].

The second, equally important point in the Japanese Classification of Gastric Carcinoma indicates the tumor's predominant location in the stomach (C – upper part, M – middle part, A – lower part). The degree of tumor invasion into the stomach wall is denoted by the index S, pointing out the invasion of serosa: S_0 – no invasion of serosa; S_1 – suspect for invasion of serosa; S_2 – the invasion of serosa; S_3 – tumor invasion into the neighboring organs [7, 8].

The third distinction between the Japanese and the generally accepted European classifications is the more detailed description of the lymph node condition. The Japanese classification considers the number and the group of lymph nodes (groups I-IV); each group is numbered depending on the lymph node size (1 to 16 cm). Usually, Japanese oncologists perform histological examination of up to 30 lymph nodes. In contrast to the commonly accepted European classification, the Japanese one uses "P" and "H" instead of the "M" symbol, where "H" characterizes the presence of metastases in the liver and their number (H_0 – no metastases in the liver, H_1 – the presence of metastases in one lobe of the liver, H_2 – the presence of several metastases in both lobes of the liver, H_3 – the presence of multiple metastases in the liver), and "P" is the degree of tumor dissemination over the peritoneum (P_0 – no peritoneal metastases, P_1 – the presence of dissemination in the peritoneum above the colon, P_2 – the presence of separate sites of dissemination on the peritoneum distant from the stomach; P_3 – the presence of multiple dissemination in the abdominal space). Considering all differences in the compared classifications, the GC stages are designated as follows: $S_0N_0P_0H_0$ – stage I, $S_1N_{0\text{-}1}P_0H_0$ – stage II, $S_2N_{0\text{-}}2P_0H_0$ – stage III, $S_3N_{3\text{-}4}P_{1\text{-}3}H_{1\text{-}3}$ – stage IV [7, 8].

Since the release of the 14th edition of the classification (2010) recommended by the Japanese Gastric Cancer Association (JGCA), the previous classification was remodified and brought closer to the commonly accepted international one. In the new classification, the lymph node dissection is taken into account only depending on the type of surgery (resection, gastrectomy), and the category N is taken into account by the number of nodes affected by the tumor [4-11].

Endoscopic methods of diagnosing gastrointestinal tract diseases are the most informative from the point of view of the amount of information [4]. However, conventional endoscopic examination, even when the high-tech equipment of the latest generation is used, makes it challenging to diagnose the degree of atrophic, metaplastic, and dysplastic changes in the mucous membrane that may be the cause of malignant neoplasm development [5]. This is especially essential in screening for MNs of the gastrointestinal tract [12-18].

Chromoscopy is a method to detect precancerous pathologies and GC. Even though chromoendoscopy has shown the potential to expand the use of endoscopic studies in diagnosing gastric diseases in some countries, Kazakhstan started to apply this method only in 2021. Therefore, there is a need to adapt the JGCA morphological classification for the population of Kazakhstan. This method focuses on the early detection of GC to perform organ-preserving surgery to rapidly recover these patients' working ability and improve their quality of life. Therefore, we applied several internationally recognized classifications to assess the findings of conducted morphological examinations.

The project aims to improve endoscopic diagnostics of GC using chromoscopy.

The study aimed to increase the efficiency of early detection of gastric cancer by adapting the Japanese Gastric Cancer Association (JGCA) morphological classification for the Kazakh population.

Materials and Methods: The JGCA morphological classification was adapted for the Kazakh population during the morphological study of biopsy material obtained from 500 endoscopic examinations (using chromoscopy by methylene blue staining) of Kazakhstani residents aged 40 and above. The inclusion criterion was the presence of "gastric problems" but without a previously diagnosed "gastric cancer." The study was carried out in four oncology centers: "The Kazakh Institute of Oncology and Radiology" JSC, Almaty (170 examinations), "Multidisciplinary Center of Oncology and Surgery" MSE on REM of the Healthcare Department of East Kazakhstan in Ust-Kamenogorsk (142 examinations), "Center for Nuclear Medicine and Oncology" MSE on REM of the Healthcare Department of Abay region in Semey (69 examinations), and "Atyrau Regional Oncology Dispensary" MSE on REM in Atyrau (119 examinations). The JGCA classification was used to interpret the findings of the morphological examination of biopsy material obtained during chromoscopy in addition to the generally accepted European classification since the Japanese classification considers factors that significantly impact the prognosis. According to the JGCA classification, patients with severe dysplasia were classified as at high risk of developing GC. After clarification of the diagnosis, they were classified as patients with high-grade GC adenocarcinoma.

Results: The analysis of the results of 500 patients examined in four regions of Kazakhstan showed that their average age was 67.74±2.61 years, suggesting that the patients were mainly older. The $\chi 2$ test showed a statistically significant correspondence between the sex and the GC detection: $\chi 2=45.97$; df=1; p=0.000. The GC was statistically less common in women than the expected MN=-4.2; p<0,001. Statistically, the odds for detection of GC in men were significantly higher than in women: OR=2.471, CI=1.883-3.242.

The findings of the endoscopic examination (by chromoscopy) of 500 patients from four regions of Kazakhstan showed the following results according to the generally accepted European classification: stomach without pathology – 0 cases, inflammatory diseases of the stomach – 439, stomach ulcer – 14 (3 patients had severe dysplasia), gastric submucosal tumor – 7, gastric polyp with a thin pedicle – 2, a gastric polyp on a wide pedicle – 5, malignant gastric tumor up to 3 cm in size – 13, and malignant gastric tumor over 3 cm – 20 patients. However, three of 14 patients in the "GS 4 stomach ulcer" group had severe dysplasia (obligate pre-cancer), so they were assigned to a separate risk group under the JGCA morphological classification (Table 1). Those patients were recommended surgical treatment.

The $\chi 2$ criterion showed a statistically significant correspondence between the locations of the surveyed by region and the study findings: $\chi 2=57.47$; df=10; p=0,000. For example, for the "city" location, when compared to expected, less frequently have been statistically detected, the results of "GS7. Gastric polyp with a wide pedicle" (MN=-2.2; $p<0.05$) and "GS11. Malignant gastric tumor with a focus over 3 cm, pathomorphologically verified" (MN=-3.1; $p<0.01$). For the "village" location, when compared to expected, more frequently have been statistically detected the results of "GS7. Gastric polyp with a wide pedicle" (MN=2.7; $p<0.05$) and "GS11. Malignant gastric tumor with a focus over 3 cm, pathomorphologically verified" (MN=3.8; $p<0.01$).

In light of the study findings, we adapted the JGCA morphological classification and developed an algorithm for GC detection at the earliest stage of the disease (Figure 1). According to this algorithm, the findings of a pathomorphological examination of biopsy material obtained during chromoendoscopy (after morphological verification of the pathological site) shall be reviewed to assign the patient to one of the three risk groups: pre-cancer, severe dysplasia (according to the morphological classification with consideration of the JCGA adaptation), or cancer. Further patient routing depends on their risk group.

Table 1 – Distribution of cases under the adapted morphological classification of the Japanese Gastric Cancer Association (using chromoscopy (n=500)

Distribution into groups based on study results	Total cases, abs. (%)	
	Under the European morphological classification	Under the European morpho-logical classification with the account of the adapted JGCA classification
GS 1 Stomach without pathology	-	-
GS 2 Hereditary stomach diseases, con-genital abnormalities	-	-
GS 3 Inflammatory diseases of the stom-ach	439 (87.8%)	439 (87.8%)
GS 4 Stomach ulcer	14 (2.8%)	11 (2.2%)
GS 5 Gastric submucosal tumor	7 (1.4%)	7 (1.4%)
GS 6 Gastric polyp with a thin pedicle	2 (0.4%)	2 (0.4%)
GS 7 Gastric polyp with a wide pedicle	5 (1.0%)	5 (1.0%)
GS 8 Malignant gastric tumor with a fo-cus up to 3 cm, without morphological verification (double gastroscopy)	-	-
GS 9 Malignant gastric tumor with a fo-cus of up to 3 cm, pathomorphologically verified	13 (2.6%)	13 (2.6%)
GS 10 Malignant gastric tumor with a focus size of larger than 3 cm, without morphological verification (double gas-troscopy)	-	-
GS 11 Malignant gastric tumor with a focus size of larger than 3 cm, pathomor-phological verified	20 (4.0%)	20 (4.0%)
Severe dysplasia (obligate pre-cancer)*	-	3 (0.6%)
Total number	500	500

*Note: *Severe dysplasia (obligate pre-cancer) under the morphological classification of the Japanese Gastric Cancer Association*

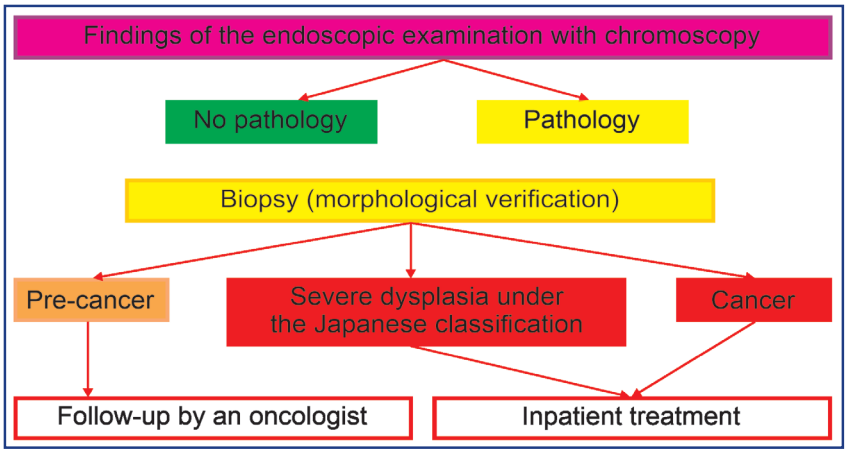

Figure 1 – Algorithm of endoscopic examination with chromoscopy with the account of the adapted morphological classification of the Japanese Gastric Cancer Association

Discussion: The proposed algorithm of endoscopic examination of the stomach with chromoscopy with the account of the adapted JGCA classification provides an attending physician with the results that help to choose an appropriate treatment method at an earlier stage of the disease. However, different approaches to GC classification in Japan and Western countries make it very difficult to compare the treatment outcomes of the two surgery schools.

A distinctive feature of GC diagnostics from the JGCA standpoint is a different approach to determining the morphological form: severe dysplasia is classified as a well-differentiated adenocarcinoma, and these patients undergo surgical treatment [11, 12]. This aspect has been tested in this study.

The Japanese classification considers the factors that significantly impact the disease prognosis. First, the chromoscopy method is based on the exceptional properties of methylene blue used for vital staining of the mucous membrane of the digestive tract epithelium. This allows visual detection of lesions during endoscopy and taking a biopsy from the most suspicious site. At that, the dye pigment binds to glycogen contained in the tissues. The afflicted mucous membrane is not stained, even at the earliest stage of the disease, because glycogen is found only in healthy cells. Unstained spots on the mucosa are well visible during endoscopy and require further examination. Thus, the probability of detecting cancer at stages 0 and I approaches 100%.

The difference from the generally accepted European classification is that the Japanese standards, represented by the JCGA morphological classification, are evident and detailed due to using a more accurate endoscopic examination method by applying chromoscopy. For example, in our study, the JGCA classification allowed identifying patients who would not be assigned to any groups under the generally accepted European classification widely used by clinicians in most countries. Morphological examination of biopsy materials obtained during 500 chromoscopy procedures to form a risk group based on the JCGA morphological classification revealed 3 (0.6%) cases with severe dysplasia. These three cases were determined to be obligate precancerous lesions with an extremely high likelihood of malignancy. The JCGA morphological classification (editions 13 and 14) determines this morphological structure as a well-differentiated adenocarcinoma. Therefore, all three patients diagnosed with severe dysplasia were assigned to a high-risk group and recommended surgical treatment.

Conclusion: The detected three cases of obligate pre-cancer with an extremely high probability of malignancy prove the importance of using the JGCA classification for GC early diagnostics and allow us to recommend the use of chromoscopy in endoscopic examination of the stomach. This approach is justified since severe dysplasia of the gastric mucosal epithelium can indicate the presence of undetected adenocarcinoma foci, which is essential for GC early detection at stages 0-I.

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АНДАТПА

ЖАПОН АСҚАЗАН ОБЫРЫ ҚОҒАМЫНЫҢ МОРФОЛОГИЯЛЫҚ ЖІКТЕМЕСІН ҚАЗАҚСТАН ХАЛЫҚЫНА БЕЙІМДЕУ НӘТИЖЕЛЕРІ

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Өзектілігі: *Қазақстанда жыл сайын асқазан обыры (АО) ауруларының саны артып келеді. Сонымен, 2022 жылы 2915 адам анықталды (100 000 тұрғынға 15 адам), онкопатология құрылымында 3 орынды алады, бұл ретте асқазан обырының ерте формаларын анықтау көрсеткіші 10-20%-дан аспайды, асқынған түрлері – 40%-дан жоғары; Диагноз қойылған сәттен бастап бірінші жылы өлім-жітім артады (40% дейін).*

Бастапқы кезеңде асқазанның обыры алды ауруларының сатысында диагностика жүргізу асқазан обырын ерте диагностикалау мәселесін шешудің жолы болып табылады. Жоғарғы асқазан-ішек жолдарының хирургиялық және шекаралық ауруларын (өңештің, асқазанның және он екі елі ішектің шырышты қабатындағы метапластикалық және диспластикалық өзгерістер мен аденокарциномалар және осы фоннан туындаған ерте обыры) дер кезінде диагностикалау және емдеу күрделі медициналық-әлеуметтік мәселе болып табылады.

Қазіргі уақытта өңештің, асқазанның және он екі елі ішектің ауруларын диагностикалаудың эндоскопиялық әдістері ең ақпараттылығы жоғары. Дегенмен, әдеттегі эндоскопиялық зерттеу кезінде обырға дейінгі өзгерістер (атрофия, метаплазия, дисплазия) ерекше белгілерге ие болмауы мүмкін. Осыған байланысты эндоскопиялық диагностика нәтижелерін жақсарту жолдарын іздестіру қажет. Қатерлі обырыға дейінгі патология мен асқазан қатерлі обырын анықтауға бағытталған әдістердің бірі хромоскопия әдісі.

Зерттеудің мақсаты *– Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктемесін Қазақстан халықына бейімдеу арқылы асқазан обырының ерте диагностикасының тиімділігін арттыру.*

Әдістері: *Хромоскопиялық әдіспен эндоскопиялық зерттеулер Қазақстан Республикасының 500 асқорыту жүйесі аурулары, бұрын анықталған асқазан обыры диагнозы жоқ және эндоскопиялық зерттеу кезінде алынған биопсияның морфологиялық зерттеулері, тәуекел тобын құра отырып жүргізілді. Жапон асқазан обыры қоғамына (JGCA) сәйкес (13-ші және 14-ші жарияланымдар).*

Нәтижелері: *500 науқастан алынған биопсия үлгілерін морфологиялық зерттеу нәтижелері бойынша ауыр дисплазиясы бар 3(0,6%) жағдай анықталды. Бұл морфологиялық құрылым жақсы дифференциацияланған аденокарцинома ретінде жіктеледі. Анықталған науқастарға хирургиялық емдеу ұсынылады.*

Қорытынды: *Осылайша, қатерлі обырына айналу ықтималдығы өте жоғары міндетті қатерлі обырына дейінгі жағдайлары асқазан обырын ерте диагностикалау үшін Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктемесін қолданудың маңыздылығын дәлелдейді және асқазанды эндоскопиялық зерттеуде хромоскопия әдісін қолдануды ұсынады.*

Түйінді сөздер: *асқазан обыры (АО), хромоскопия, ауыр дисплазия, Жапон асқазан обыры қоғамының (JGCA) морфологиялық жіктемесі.*

АННОТАЦИЯ

РЕЗУЛЬТАТЫ АДАПТАЦИИ МОРФОЛОГИЧЕСКОЙ КЛАССИФИКАЦИИ ЯПОНСКОГО ОБЩЕСТВА ПО ИЗУЧЕНИЮ РАКА ЖЕЛУДКА К КАЗАХСТАНСКОЙ ПОПУЛЯЦИИ

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Актуальность: *Ежегодно в Казахстане увеличивается число заболевших раком желудка (РЖ). Так, в 2022г. выявлено 2915 человек с РЖ (15 человек на 100000 населения), занимая в структуре онкопатологии 3 место, при этом частота обнаружения ранних форм РЖ не превышает 10-20%, запущенных форм – свыше 40%; увеличивается летальность на первом году с момента установления диагноза (до 40%).*

Проведение диагностики на стадии предопухолевых заболеваний желудка на начальной стадии – путь к решению проблемы ранней диагностики РЖ. Ранняя диагностика с последующей организацией лечения предопухолевых заболеваний слизистой желудоч-

но-кишечного тракта (атрофические, метапластические и диспластические изменения слизистой оболочки пищевода, желудка и двенадцатиперстной кишки) представляют сложнейшую проблему для онкологической службы. Для этой цели наиболее информативными в настоящее время считаются эндоскопические методы диагностики.

При этом эндоскопическое обнаружение предраковых изменений требует наличия высокотехнологического оборудования и использования методологических подходов, ориентированных на дифференциальную диагностику. Одним из методов, направленных на выявление предраковой патологии и РЖ, является метод хромоскопии.

***Цель исследования** – повышение эффективности ранней диагностики рака желудка путем адаптации морфологической классификации Японского общества по изучению рака желудка (JGCA) к казахстанской популяции.*

***Методы:** Проведены эндоскопические исследования с применением метода хромоскопии у 500 резидентов РК, имеющих заболевания органов пищеварения без ранее установленного диагноза «рак желудка» и морфологические исследования биоптата, полученного при эндоскопическом исследовании, с формированием групп риска согласно JGCA (13-е и 14-е издания).*

***Результаты:** Согласно результатам морфологического исследования полученных биоптатов 500 пациентов выявлено 3 (0,6%) случая с тяжёлой дисплазией. Данная морфологическая структура отнесена к высокодифференцированной аденокарциноме. Выявленным пациентам рекомендовано оперативное лечение.*

***Заключение:** Таким образом, выявленные случаи облигатного предрака с крайне высокой вероятностью перерождения в злокачественное новообразование доказывают важность применения JGCA для ранней диагностики РЖ и позволяют рекомендовать применение метода хромоскопии при эндоскопическом исследовании желудка.*

***Ключевые слова:** рак желудка (РЖ), хромоскопия, тяжелая дисплазия, морфологическая классификация Японского общества по изучению рака желудка (JGCA).*

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METHODS FOR IMPROVING THE DRG-05M DOSIMETER IN BRACHYTHERAPY

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ABSTRACT

Relevance: *The article discusses one of the ways to improve the DRG-05M dosimeter in brachytherapy by using new components and technologies in an improved scheme, which includes more accurate sensors, advanced signal processing techniques, efficient power cells, and other solutions. The application of such advanced components and technologies in the framework of DRG-05M dosimeter modernization is a new and original contribution to the field of dosimetry. The scientific novelty of the work is the improvement of the existing circuitry, namely, the improvement of the DRG-05M dosimeter's electrical circuitry based on the analysis of its shortcomings. It includes replacing components, optimizing circuit structure, eliminating noise and interference, and improving the stability and accuracy of measurements.*

The study aimed to *improve the DRG-05M dosimeter to provide more accurate and reliable radiation measurements in brachytherapy.*

Methods: *The paper analyses the existing components and their use in the electrical circuit to improve the measurement accuracy of the DRG-05M dosimeter, offers a new electrical circuit based on the collected data and requirements, considering the optimal location of components, their characteristics, performed calculations, and modeled circuit operation. We conducted this research within the PCF scientific program "Metrological support of dosimetric measurements in contact radiation therapy," IRN BR12967832.*

Results: *We have selected the components for improving the DRG-05M dosimeter: PMT, ADCs, indication unit, and power supply. The proposed changes to improve the DRG-05M dosimeter shall result in a very compact scintillation-type dosimeter. Its size and weight shall be reduced by at least 3 times; the accuracy and speed of measurement will increase, and the lifetime of the instrument shall improve.*

Conclusion: *Improvement of the dosimeter in brachytherapy is crucial to ensure the accuracy and reliability of measurement in treating cancer. Using components such as PMT, calibration source, battery charger, and microcontroller KR572PV5 can significantly improve the operation of the DRG-05M dosimeter and increase the accuracy of radiation dose measurement in brachytherapy.*

Keywords: *dosimeter, ADC, brachytherapy, radiation, electrical scheme.*

Introduction: The DRG-05M dosimeter is one of the most common dosimeters used in various fields related to radiation measurement. It is an indispensable tool in medical diagnostics and therapy involving ionizing radiation. It is used in brachytherapy and radiotherapy to measure the radiation that reaches the patient during a procedure. The DRG-05M dosimeter ensures accurate measurements and allows a controlled exposure, essential for patient safety and treatment efficacy. The DRG-05M dosimeter is also widely used in industrial and scientific research where radiation measurement is required. It is used in nuclear power engineering, scientific laboratories, and industries dealing with radioactive materials. It provides reliable dose measurements to ensure labor safety and control radiation risks. In emergencies related to radiation, the DRG-05M dosimeter is an integral tool for measuring exposure and assessing radiation risks. It allows for quick measuring of ambient radiation and taking appropriate measures to protect people and minimize radiation impact. The advantages of the DRG-05M dosimeter include reliability, wide measurement range, ease of use, and portability [1-4].

This research is relevant today because the accuracy and reliability of portable dosimeters remain an issue in radiation therapy and can negatively impact human health and the environment. Technological progress and the new components make it possible to improve dosimeters, making them more accurate, reliable, and easy to use.

This research has a high degree of novelty and originality in the following aspects:

– Improvement of the existing circuitry, namely, the DRG-05M dosimeter electric diagram based on its shortcoming analyses. This includes replacing components, optimizing circuit structure, eliminating noise and interference, and improving measurement stability and accuracy. Improving an existing device is practical and can increase its performance and efficiency.

– The use of new components and technologies; utilization of new components and technologies in the improved electric diagram. This includes more accurate sensors, advanced signal processing techniques, efficient batteries, and other solutions. Utilizing such advanced components and technologies to improve the DRG-05M dosimeter will be a new and original contribution to dosimetry.

– Experimental proof of the results: comparing the improved electric diagram with the original version of the DRG-05M dosimeter. This includes comparisons of accuracy, stability, and other measurement parameters.

This research presents a new approach to improving the electric diagram of the DRG-05M dosimeter used to measure the exposure and is an original contribution to dosimetry in brachytherapy and radiation safety.

The study aimed to improve the DRG-05M dosimeter to provide more accurate and reliable radiation measurements in brachytherapy.

Materials and methods: We used the following research methods:

– Analysis of the existing electric diagram of the device: a detailed analysis of the existing electric diagram of the DRG-05M dosimeter, identifying its main components, operating principles, and shortcomings that require improvement.

– Determining specific targets and requirements for an improved electric diagram, considering the shortcomings.

– Study of the new components and technologies: exploring advanced components and technologies that can be used in the improved electric diagram. This includes searching for new sensors, amplifiers, filters, analog-to-digital converters, and other elements that can increase the dosimeter performance.

– Designing a new electric diagram of the device: developing a new electric diagram based on the collected data and requirements, taking into account the optimal arrangement of components, choosing their characteristics, carrying out calculations, and modeling the circuit operation.

– Analysis of the results obtained and conclusions about the improvements achieved.

Results: DRG-05M dosimeter is a scintillation radiometer that consists of a scintillator, a photomultiplier tube (PMT), an analog-to-digital converter (ADC), a display unit, and a power supply unit for the entire circuit. We used a pulse amplitude-to-number converter as an ADC.

Figure 1 shows the operating principle of the selected dosimeter, DRG-05M. Scintillators convert radiation energy into light signals. External radiation, such as X-rays and gamma rays, reaches the scintillator. The energy resulting from the radiation impact on the scintillator material is transmitted to the substance particles. This energy excites atoms or molecules of the scintillator, which emit light in response [5]. The duration and brightness of light radiation depend on the absorbed gamma and X-ray photons. The higher the photon energy, the greater the intensity of the glow. The generated light radiation is recorded using the PMT. A polystyrene optical fiber is placed in front of the PMT to direct the emitted light to the PMT, which converts the light into an electrical signal. Accordingly, the signal level depends in direct proportion to the glow level. Afterwards, the electrical signal comes to the ADC and is processed by the ADC, converting it into a digital signal (pulses), the number of pulses depending on the signal level. Next, the display unit reads these pulses and displays information as digits.

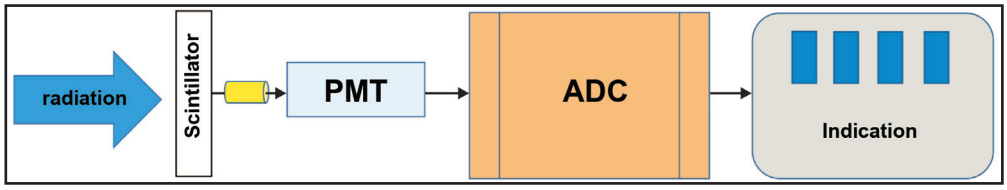


Figure 1 – Operating principle of the DRG-05M dosimeter

We selected the following components to improve the DRG-05M dosimeter: PMT, ADC, display unit, and power supply unit.

The PMT-31-1 sensor currently installed in the dosimeter consumes up to 1.5 kV, producing several volts as the signal measurement background and several millivolts of noise. Therefore, we selected a PMT H7826 series by HAMAMATSU (Japan). This PMT has better parameters than the current PMT-31-1 (higher sensitivity) and, most importantly, consumes 15 V voltage, much lower than the existing one.

We selected the KR572PV5 type microcontroller for ADC. This microcircuit can process and control signals in measuring devices. Due to its functionality, compactness, and low power consumption, it can be used in various measuring devices such as sensors, dosimeters, signal analyzers, and others where accurate signal processing and reliable measurement control are required.

Another reason to choose the KR572PV5 microcircuit was its built-in display unit. Figure 2 shows the KR572PV5 microcircuit block diagram and appearance. The block diagram incorporates an analog block, several decoders, and an impulse register. They can function as ADC, converting the digital signal into digital readings.

The power supply unit with a high-voltage module was replaced with a low-voltage power supply unit to increase sensitivity and increase the device's service life. The current PMT-31-1 required a voltage of about a thousand volts. With the new PMT, a voltage of 15 V will be sufficient. There are many options for power supply circuits on the Internet. We aimed to achieve 15 V instead of 1.5 kV voltage, sufficient for the selected components that consume a few microvolts of current.

Figure 3 shows a typical diagram of the converter connection with a liquid crystal indicator and the four elements that control the decimal points of the indicator. The device input voltage limits depend on the reference voltage U_{ref} and are determined by the ratio $U_{in.\,max}=\pm 1.999/U_{ref}$. The current indicator readings should

be expressed as a number equal to 1000 U_{in}/U_{ref}, but in practice, they are 0.1...0.2% lower. The measurement period at a clock frequency of 50 kHz is 320 ms. In other words, the device makes 3 measurements per second.

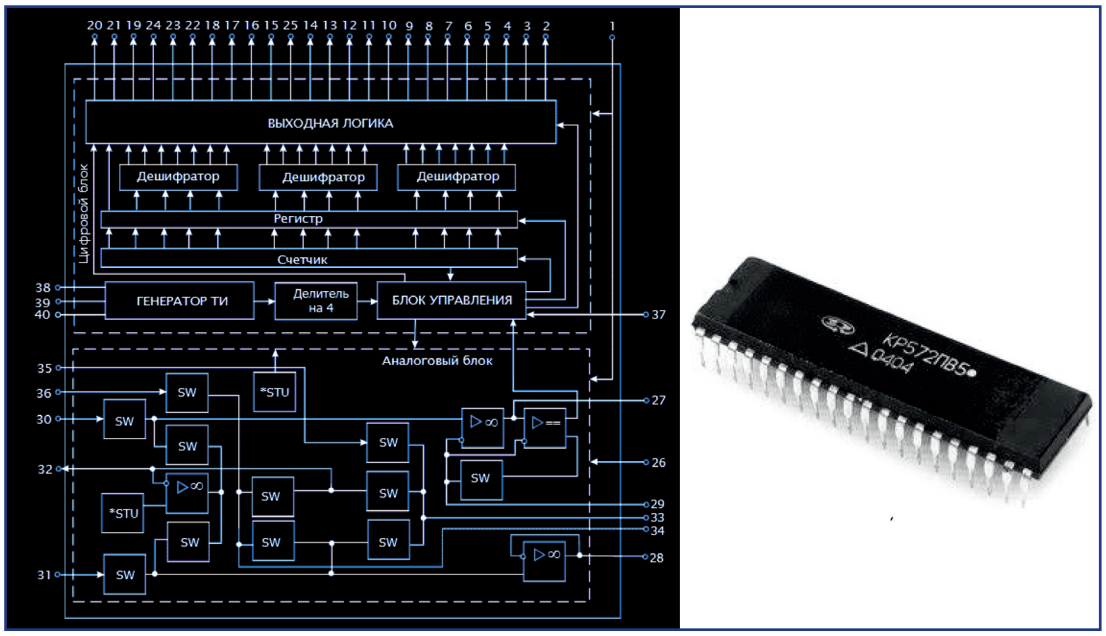
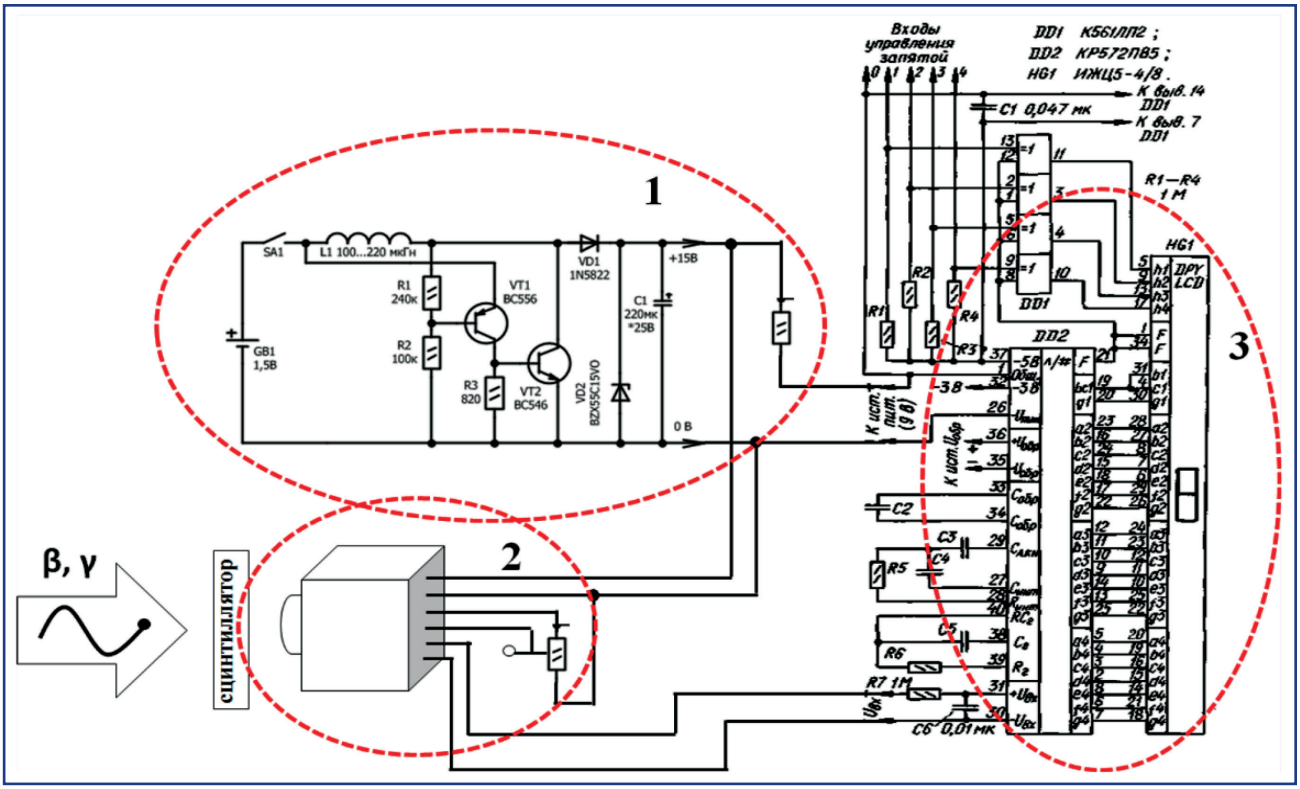


Figure 2 – The KR572PV5 microcircuit block diagram and appearance



1 – Power supply, 2 – PMT, 3 – ADC and indication
Figure 3 – Diagram of the improved DRG-05M dosimeter [6]

With all the suggested improvements to the DRG-05M dosimeter, we achieve a very compact scintillation-type dosimeter since the proposed components are twice smaller and perform better than the old ones. The size and weight of the device will be at least 3 times less while the accuracy, speed of measurements, and the device's service life shall increase.

Discussion: Improving the dosimeter used in brachytherapy is crucial to ensure the accuracy and reliability of measurements in treating oncological diseases. Components such as the new PMT, calibration source, battery charger, and KR572PV5 microcontroller can significantly improve the DRG-05M dosimeter operation and increase the accuracy of radiation dose measurement in brachytherapy.

We paid special attention to selecting and optimizing the circuit components. The proposed replacement of some circuit elements with more modern and accurate ones shall improve the overall performance of the dosimeter.

Conclusion: The research results presented in the paper demonstrate positive changes in the DRG-05M dosimeter operation after the following improvements:

1. The voltage consumed by the PMT dosimeter is 1.5 kV. We propose a 15 V PMT, which is two orders of magnitude lower than the current readings;

2. We suggest using a more modern ADC microcontroller than the one used in the existing dosimeter. The suggested microcontroller has higher characteristics that directly affects the measurement accuracy;

3. We suggest replacing the circuit power supply unit with a maximum 15 V supply. The power supply unit currently utilized in the dosimeter amplifies the voltage to 1.5 kV and produces noise of several volts.

The improved design with the original version of the dosimeter shows increased efficiency, reliability, and accuracy of dose measurements in brachytherapy.

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АНДАТПА

БРАХИТЕРАПИЯДА ДРГ-05М ДОЗИМЕТРІН ЖЕТІЛДІРУ ӘДІСТЕРІ

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Өзектілігі: *Мақалада жетілдірілген схемада жаңа компоненттер мен технологияларды қолдану арқылы брахитерапияда ДРГ-05М дозиметрін жетілдірудің бір әдісі қарастырылады. Ол дәлірек сенсорларды, сигналдарды өңдеудің озық әдістерін, тиімді қуат көздерін және басқа шешімдерді қамтиды. ДРГ-05М дозиметрін жаңарту аясында осындай озық компоненттер мен технологияларды қолдану дозиметрия саласына жаңа және ерекше үлес болып табылады. Жұмыстың ғылыми жаңалығы-қолданыстағы схеманы жетілдіру, атап айтқанда, оның кемшіліктерін талдау негізінде ДРГ-05М дозиметрінің электр схемасын жақсарту. Бұған компоненттерді ауыстыру, тізбек құрылымын оңтайландыру, Шу мен кедергілерді жою, өлшеудің тұрақтылығы мен дәлдігін жақсарту кіреді.*

Зерттеудің мақсаты *– брахитерапияда сәулеленуді дәлірек және сенімді өлшеуді қамтамасыз ету үшін ДРГ-05М дозиметрін жетілдіру.*

Әдістері: *Мақалада дозиметрдің ДРГ-05М өлшеу дәлдігін жақсарту үшін қолданыстағы компоненттерді талдау және оларды электр тізбегінде қолдану ұсынылған. Жаңа схеманы жобалау: жиналған мәліметтер мен талаптарға негізделген жаңа электр тізбегін жасаңыз. Компоненттердің оңтайлы орналасуын, олардың сипаттамаларын таңдауды, тізбектің жұмысын есептеуді және модельдеуді қарастырыңыз. Бұл ғылыми зерттеу ЖРН BR12967832 «Контактілі сәулелік терапияда дозиметриялық өлшемдерді метрологиялық қамтамасыз ету» БМҚ ғылыми бағдарламасын іске асыру шеңберінде жүргізілді.*

Нәтижелері: *Біз ДРГ-05М дозиметрін жақсарту үшін мынадай компоненттерді таңдадық: ФЭК, АЦТ, индикация блогы және сәйкесінше қуат көзі. ДРГ-05М дозиметрін жақсарту үшін ұсынылған барлық өзгерістерден кейін сцинтилляциялық типтегі шағын дозиметр алынады деп күтілуде. Мүмкін мөлшері мен салмағы кем дегенде 3 есе азаяды, сәйкесінше дәлдік пен жылдамдық өлшеу ұлғайту, сонымен қатар бұл құрылғының қызмет ету мерзіміне әсер етеді.*

Қорытынды: *Брахитерапияда дозиметрді жетілдіру онкологиялық ауруларды емдеуде өлшеудің дәлдігі мен сенімділігін қамтамасыз етуге бағытталған маңызды міндет болып табылады. Компоненттерді ФЭҚ, калибрлеу көзі, батареяларды зарядтағыш, КР572ПВ5 микроконтроллері ретінде пайдалану ДРГ-05М дозиметрінің жұмысын едәуір жақсартады және брахитерапиядағы сәулелену дозасын өлшеу дәлдігін арттырады.*

Түйінді сөздер: *дозиметр, АЦТ, брахитерапия, радиация, электр схемасы.*

АННОТАЦИЯ

СПОСОБЫ СОВЕРШЕНСТВОВАНИЯ ДРГ-05М ДОЗИМЕТРА В БРАХИТЕРАПИИ

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Актуальность: *В статье рассматривается один из способов совершенствования ДРГ-05М дозиметра в брахитерапии с помощью использования новых компонентов и технологий в усовершенствованной схеме, которая включает более точные датчики, передовые методы обработки сигналов, эффективные элементы питания и другие решения. Применение таких передовых компо-*

нентов и технологий в рамках модернизации дозиметра ДРГ-05М является новым и оригинальным вкладом в область дозиметрии. Научной новизной работы является усовершенствование существующей схемы, а именно, улучшения электрической схемы ДРГ-05М дозиметра на основе анализа его недостатков. Это включает замену компонентов, оптимизацию структуры схемы, устранение шумов и помех, а также улучшение стабильности и точности измерений.

***Цель исследования** – усовершенствование ДРГ-05М дозиметра для обеспечения более точных и надежных измерений радиации в брахитерапии.*

***Методы:** В статье представлен анализ существующих компонентов и использование их в электрической схеме для повышения точности измерения ДРГ-05М дозиметра. Предложена новая электрическая схема на основе собранных данных и требований, с учётом оптимального расположения компонентов, их характеристик, проведенных расчетов и смоделированной работы схемы. Данное научное исследование проведено в рамках реализации научной программы ПЦФ «Метрологическое обеспечение дозиметрических измерений в контактной лучевой терапии», ИРН BR12967832.*

***Результаты:** Научной группой были выбраны компоненты для усовершенствования ДРГ-05М дозиметра: фотоэлектронный умножитель (ФЭУ), аналогово-цифровой преобразователь (АЦП), блок индикации и блок питания. После всех предложенных изменений для усовершенствования ДРГ-05М дозиметра, ожидается получить очень компактный дозиметр сцинтилляционного типа. Габариты аппарата планируется уменьшить в 3 раза, точность и скорость измерения увеличить, а также это повлияет на срок службы эксплуатации прибора.*

***Заключение:** Совершенствование дозиметра в брахитерапии является важной задачей, направленной на обеспечение точности и надежности измерения в лечении онкологических заболеваний. Использование таких комплектующих как: ФЭУ, калибровочный источник, блок питания для зарядки батарей, микроконтроллер КР572ПВ5 могут существенно улучшить работу ДРГ-05М дозиметра и повысить точность измерения дозы в брахитерапии.*

***Ключевые слова:** дозиметр, аналогово-цифровой преобразователь (АЦП), брахитерапия, радиация, электрическая схема.*

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SIMULTANEOUS SURGICAL MANAGEMENT OF CONGENITAL BICUSPID AORTIC VALVE AND GASTRIC CANCER: A CASE REPORT

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ABSTRACT

Relevance: *Gastric cancer is the second leading cause of malignancies of the gastrointestinal tract and the fifth leading cause in overall cancer statistics. Diseases of the cardiovascular system are the leading cause of death worldwide. A high prevalence of both diseases increases the chances of their co-morbidity.*

The aim was to *present a case where a patient undergoes two simultaneous procedures for two diseases and discuss possible surgical tactics, advantages, and disadvantages.*

Methods: *In this case report, we performed simultaneous surgery on a 49-year-old man with a congenital bicuspid aortic valve and gastric cancer incidentally discovered during fibroesophagogastroscopy.*

Results: *In this case report, we present simultaneous surgical procedures performed on a 49-year-old male with a history of congenital bicuspid aortic valve and gastric cancer, found incidentally on upper gastrointestinal (GI) endoscopy. Since the patient was a good fit, he qualified for simultaneous surgery on the heart and abdomen.*

The surgery results were good, and the patient was discharged 8 days after surgery.

Conclusion: *Performing simultaneous surgery for both the abdomen and heart can be a safe procedure that allows people with malignant diseases to receive adjuvant therapy faster by minimizing the interval between surgeries.*

Keywords: *stomach, cancer, heart, aortic valve, Bentall, simultaneous surgery.*

Introduction: Aortic valvular abnormalities are very common in older populations; it is also the main cause of cardiovascular mortality and morbidity worldwide. Aortic stenosis is the most frequent valvular disease that requires surgical treatment in high-income countries [1]. The survival of symptomatic patients with aortic stenosis is diminished unless surgical intervention is done.

The true epidemiology of aortic valve diseases worldwide remains unknown due to a lack of diagnostic equipment, such as echocardiography, in low-income countries. In the early 1980s, the frequency of aortic aneurysms was described to be only 6 cases per 100,000 person-years. However, incidence rates have doubled due to advances in imaging techniques, the increased average age of the population, and a wider use of echocardiography for screening [2]. Most valvular abnormalities are found incidentally during echocardiography, and aortic aneurysms are not excluded. However, thoracic aortic aneurysm has a high risk of complications such as rupture and dissection, and there is a lack of data on the management of aortic aneurysms.

Bental procedure is the most prevailing method used worldwide for the surgical management of aortic root pathologies [3]. Since its introduction, it has undergone extensive modifications because of high rates of coronary button complications [4].

Gastric cancer, also known as stomach cancer, refers to the development of malignant tumors in the lining of the stomach. It is one of the most common types of cancer worldwide, although its incidence varies across different regions. Gastric cancer typically begins in the cells lining the innermost layer of the stomach and can gradually spread to other parts of the organ or metastasize to distant sites in the body. The symptoms of gastric cancer may vary depending on the stage of the disease, but they can include indigestion, abdominal pain or discomfort, persistent heartburn, unintentional weight loss, loss of appetite, nausea, vomiting, and blood in the stool. However, it should be noted that other conditions can also cause these symptoms, so a proper medical evaluation is necessary for an accurate diagnosis. Sometimes, stomach cancer can also be found accidentally during screening procedures such as upper gastrointestinal endoscopy. Other diagnostic techniques for gastric cancer often involve a combination of medical history review, physical examination, imaging tests (such as endoscopy, CT scans, or ultrasound), and biopsy of suspicious tissue. Treatment options for gastric cancer depend on the stage of the disease and may include surgery, chemotherapy, radiation therapy, targeted therapy, or immunotherapy.

Gastric cancer is considered a crucially important disease worldwide. Every year, 1 million new cases are diagnosed. The mortality from gastric cancer remains tremendous because it is often detected at later stages. Approximately 769,000 deaths from gastric cancer were reported globally in 2020, and the number of new cases was 1,089,103 [5].

Gastric cancer is a significant health concern in Kazakhstan, with relatively high incidence and mortality rates. According to the World Health Organization's Globocan 2020 database, in Kazakhstan, there were an estimated 3,357 new cases of gastric cancer diagnosed in Kazakhstan. The age-standardized incidence was 11.4 cases per 100,000 population, indicating a relatively high burden of the disease [6]. A high prevalence of both diseases increases the chances of their co-morbidity.

The aim was to present a case where a patient undergoes two simultaneous procedures for two diseases and discuss possible surgical tactics, advantages, and disadvantages.

Methods: In this case report, we performed simultaneous surgery on a 49-year-old man with a congenital bicuspid aortic valve and gastric cancer incidentally discovered during fibroesophagogastroscopy.

Case presentation

Clinical data: The article presents a clinical case of a 49-year-old male who had a history of chest pain, dyspnea on exertion, and weakness. Patients had those symptoms on and off for more than 2 years. The patient was diagnosed with a congenital bicuspid aortic valve, which resulted in severe aortic valve regurgitation (grade IV) and ascending aorta aneurysm. The patient was offered the Bentall-de Bono procedure, which involves the replacement of the aortic valve and ascending aorta.

Diagnostics: During the pre-operative diagnostic workup, the patient underwent an upper GI endoscopy, and a flat neoplasm was found in the body of the stomach. Biopsy was taken from the neoplasm, and the results came back as undifferentiated gastric cancer. Repeated upper GI endoscopy confirmed ulcerated gastric carcinoma. The patient further underwent computed tomography (CT) of the abdomen and chest, which showed no signs of distant metastasis of gastric cancer, as well as no enlarged lymph nodes in the abdomen and thoracic cavity. Colonoscopy also was insignificant for tumors and other colorectal pathologies. Abdominal magnetic resonance imaging (MRI) with contrast showed gastric wall thickening in the gastric body and no distant metastasis. An electrocardiogram (ECG) examination revealed a regular sinus rhythm with a heart rate of 62 beats per minute. Chest X-ray showed no abnormalities. Heart ultrasound examination showed aneurysm of the ascending aorta, bicuspid aortic valve, severe aortic valve regurgitation (grade IV), mild mitral regurgitation (grade I), dilation of the left ventricle, and left ventricular ejection fraction was estimated to be 48-50%. Upon hospitalization, the patient underwent diagnostic coronary angiography, which showed that the patient had no significant stenosis in the coronary arteries.

Management: The patient was consulted by a surgical oncologist and was offered radical surgery for gastric cancer since the patient's cancer was resectable, had no distant metastasis, and did not require neoadjuvant therapy. After pre-operative diagnostics, cardiac surgeons and anesthesiologists discussed the possibility of performing simultaneous surgery for this patient and its benefit-risk profile. Considering the discussion results and the patient's wish, it was decided to perform simultaneous surgery on the aortic valve and ascending aorta, followed by gastrectomy.

Results: The first part of the simultaneous surgery involved the Bentall-de Bono procedure, for which the thoracic cavity was opened by sternotomy. Then, after cannulation of the aorta, superior vena cava, inferior vena cava, and right superior pulmonary vein, the cardiopulmonary bypass (CPB) machine was connected. The aortic root, aortic valve, and ascending portion of the aorta were replaced with a valve containing conduit SJM Epic Valve #27 with initially formed vascular prosthesis Polythese #30. Esophageal echocardiography showed a normally functioning aortic valve. The total time of CPB was 114 minutes, after which the patient was returned to normal circulation without any complications. Protamine sulfate was used as a heparin antagonist. After the closure of the sternotomy, the second part of the simultaneous surgery took place, where a team of surgical oncologists performed midline laparotomy. Upon exploration of the abdominal cavity, no signs of distant metastasis or locally advanced tumor were seen. The cancer of the stomach was palpable along the lesser curvature in the body of the stomach with an approximate size of 15x20x20 mm with invasion of serosa. Total gastrectomy with D2 lymph node dissection was performed with end-to-side esophagojejunostomy (Figure 1). In addition, side-to-side jejune-jejunal anastomosis and feeding jejunostomy was done.

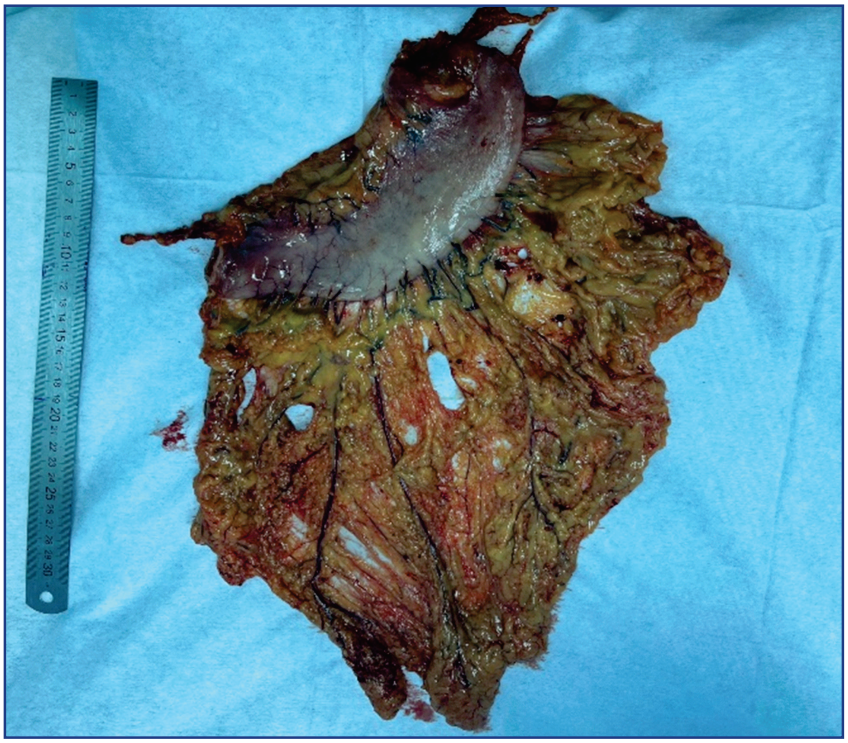

Figure 1 – Resected stomach specimen

Intraoperatively, a total of 4 doses of plasma were transfused due to a high risk of intraoperative bleeding. After placing drainage tubes, the laparotomy was closed, and the patient was admitted to an Intensive Care Unit (ICU), where the patient was extubated the night after the surgery. The patient was given 40 mg of enoxaparin sodium twice a day as anticoagulant therapy and acetylsalicylic acid 100 mg once a day as an antiplatelet drug. In the ICU, due to hypoproteinemia, the patient received 4 doses of 10% albumin 200 ml each. Enteral feeding with pure water through jejunostomy started on Day 1 post-op. After staying for 3 days in the ICU, he was transferred to the Cardiac Surgery Department. Physical rehabilitation sessions started immediately, and oral feeding was introduced on Day 7 after surgery. The post-surgical period went uncomplicated, and the patient was discharged 9 days after the surgery. Echocardiography on Day 5 post-op revealed no aortic valve prosthesis dysfunction; an ejection fraction was 51%. Barium swallow on Day 5 post-op revealed no leakage and a satisfactory passage. Postoperative histopathologic examination revealed poorly differentiated (G3) adenocarcinoma with infiltration of all gastric layers (T4a) without any metastasis to lymph nodes (0/11), Stage IIb (pT4aN0M0). The patient has been followed for 6 months without complications and further progression of gastric cancer. The patient refused the adjuvant chemotherapy he was recommended.

The time scale of the presented clinical scale is provided in Figure 2.

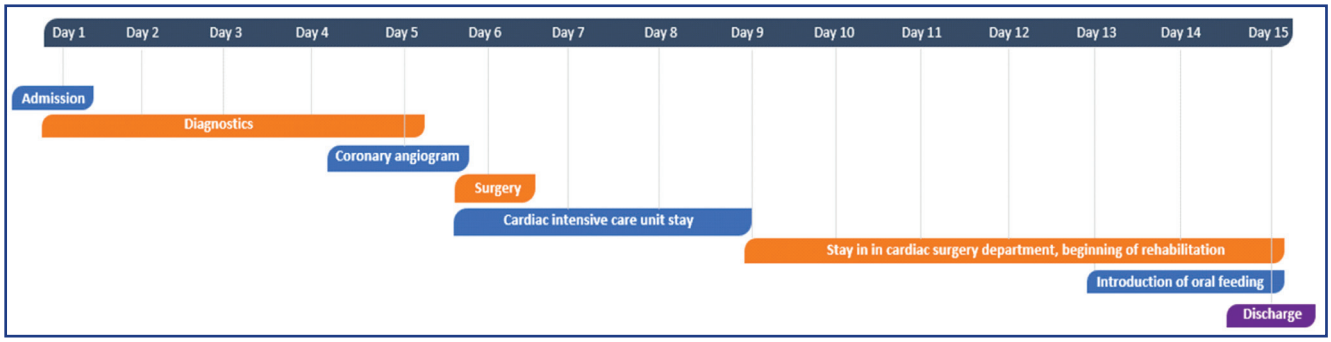

Figure 2 – Time scale showing major events during the patient's hospitalization

Discussion: This case presents the importance of thorough pre-operative patient preparation for surgery and ruling out the most common concomitant diseases. This case presents the importance of thorough pre-operative patient preparation for surgery and ruling out the most common concomitant diseases. Pre-operative blood tests, imaging studies, and endoscopic studies are made to rule out upper gastrointestinal tract pathologies. In this case, the neoplasm in the stomach was found to be ulcerated gastric carcinoma on histopathologic examination. Without performing the esophagogastroduodenoscopy, the cancer could have been missing. While preparing for cardiac surgery, the patient was consulted by a surgical oncologist. Additional imaging studies were done to stage gastric cancer and look for distant metastasis. After gastric cancer was considered resectable, the patient was offered surgical treatment.

Since the hospital is a tertiary referral hospital with different departments, including but not limited to cardiac, surgical departments, and intensive care units, the possibility of simultaneous surgery was discussed.

Firstly, it was necessary to make sure simultaneous surgery for the heart and stomach removal were safe and beneficial for the patient, and the pros outweighed the cons in this case. Due to the absence of internationally accepted guidelines for simultaneous surgeries of the heart and abdomen, every case should be discussed thoroughly by a multidisciplinary team of surgeons and healthcare professionals from different specialties, such as cardiovascular and gastrointestinal surgery. The ultimate goal of a multidisciplinary team is to provide an integrated and comprehensive treatment plan. This collaborative approach allows for comprehensive evaluation, planning, and execution of the procedures, potentially optimizing the overall surgical outcome.

For this patient, time was a clear advantage of simultaneous surgery. His gastric cancer was detected at an early stage before a spread to local and distant tissues. Symptomatic valvular heart disease worsened the patient's quality of life, and his overall health was deteriorating. So, heart surgery was no doubt a top priority for the patient's condition. However, any cancer where surgery is the first line of treatment requires immediate operation without delay to lower the chances of further cancer progression and increase overall survival and disease-free survival. Many cardiac surgeries require prolonged rehabilitation, and the patients might postpone a second surgery until they fully recover from the previous one. These and other factors might delay surgical treatment for malignant neoplasm. A simultaneous operation minimizes the interval between surgeries and potentially prevents cancer progression.

Combining surgeries into a single procedure can minimize the overall surgical trauma experienced by the patient. It means a single period of postoperative recovery, reduced overall hospitalization time, and potentially fewer instances of wound healing complications.

Knowing the possible disadvantages of performing simultaneous surgeries and discussing them with the patient is relevant. Combining two major surgeries increases the complexity and duration of the operation. In turn, this might increase the risk of complications such as bleeding, infection, and adverse events related to anesthesia. The higher the complexity, the

greater the potential for surgical and postoperative complications. Also, recovery from simultaneous surgeries can be more challenging than recovering from individual procedures performed separately. The combined physiological impact on the body, including the cardiovascular and digestive systems, may lead to a more extended and potentially more difficult recovery period.

In this case, we described a case of simultaneous Bentall-de Bono procedure and gastrectomy performed on a 49-year-old man. The outcome of this surgery was good. The advantages of simultaneous surgeries, as well as possible disadvantages, were also discussed.

Conclusion: Simultaneous surgeries in patients with concomitant heart and oncological disease can have some advantages over traditional staged surgeries. Firstly, by minimizing the time between surgeries, we make sure that patients receive oncological treatment as soon as possible, which would affect their overall survival. Another positive aspect of performing simultaneous surgeries can be reduced surgical trauma, decreased hospital stays, and potentially fewer instances of wound healing.

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АНДАТПА

ТУА БІТКЕН ҚОСЖАРНАҚТЫ ҚОЛҚА ҚАҚПАҚШАСЫ МЕН АСҚАЗАН ҚАТЕРЛІ ІСІГІН БІР МЕЗГІЛДЕ ХИРУРГИЯЛЫҚ ЕМДЕУ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Асқазан қатерлі ісігі-асқазан-ішек жолдарының қатерлі ісіктерінің екінші себебі және қатерлі ісіктің жалпы статистикасындағы бесінші себеп. Жүрек-қан тамырлары аурулары бүкіл әлемде өлім-жітімнің негізгі себебі болып табылады.*

Басылымның мақсаты: *Біз пациентке екі түрлі ауруға симультандық ота жасалатын клиникалық жағдайды ұсынғымыз келеді. Бұл мақалада мүмкін болатын хирургиялық тактика, симультандық операцияның артықшылықтары мен кемшіліктері талқыланады.*

Әдістері: *Бұл клиникалық жағдайда біз фиброэзофагогастроскопияда кездейсоқ табылған асқазан қатерлі ісігі және туа біткен қос жармалы қолқа қақпақшасы бар 49 жастағы ер адамға симультанды ота жасалды. Науқастың жағдайы симультандық операция жасауға мүмкіндік бергендіктен, оған бұл операция жасалды.*

Нәтижелері: *Операция ішілік және операциядан кейінгі кезең біркелкі өтті, науқас операциядан кейін 8 тәулікке қанағаттанарлық жағдайда шығарылды.*

Қорытынды: *Біздің клиникалық жағдайды пайдалана отырып, іш қуысының патологиясына және жүрек патологиясына бір мезгілдге хирургиялық ем жасау қатерлі аурулары бар адамдарға операциялар арасындағы аралықты азайта отырып, адъювантты терапияны жылдам алуға мүмкіндік беретін қауіпсіз процедура болуы мүмкін.*

Түйінді сөздер: *асқазан, қатерлі ісік, жүрек, қолқа қақпақшасы, Бенталл, бір мезгілде орындалатын операциялар.*

АННОТАЦИЯ

ОДНОМОМЕНТНОЕ ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ ВРОЖДЕННОГО ДВУСТВОРЧАТОГО АОРТАЛЬНОГО КЛАПАНА И РАКА ЖЕЛУДКА: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Рак желудка является второй по значимости причиной злокачественных новообразований желудочно-кишечного тракта и пятой по значимости причиной в общей статистике рака. Заболевания сердечно-сосудистой системы являются основной причиной смертности во всем мире. Поскольку распространенность обоих заболеваний высока, повышается вероятность того, что пациенты заболеют этими заболеваниями одновременно.*

Цель публикации: *представить клинический случай, когда пациенту проводится симультанная операция по поводу двух разных заболеваний. В данной статье обсуждается возможная хирургическая тактика, преимущества и недостатки симультанной операции.*

Методы: *В этом клиническом случае мы выполняем одномоментную операцию 49-летнему мужчине с врожденным двустворчатым аортальным клапаном и раком желудка, случайно обнаруженным при фиброэзофагогастроскопии.*

Результаты: *Интраоперационный период и послеоперационный период протекал гладко, пациент был выписан на 8 сутки после операции в удовлетворительном состоянии.*

Заключение: *На примере нашего клинического случая мы бы хотели показать, что проведение одномоментного хирургического лечения патологии брюшной полости и патологии сердца может быть безопасной процедурой, которая позволяет людям со злокачественными заболеваниями быстрее получать адъювантную терапию, сводя к минимуму интервалы между операциями.*

Ключевые слова: *желудок, рак, сердце, аортальный клапан, Бенталл, симультанные операции.*

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TARGETED IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA: A CLINICAL CASE

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver. HCC is one of the most important problems of the oncology service of Kazakhstan, as it has a progressive course, late detection, low survival, and unfavorable prognosis.*

The study aimed to *evaluate the use of targeted immunotherapy in treating hepatocellular carcinoma in a clinical example.*

Methods: *Clinical case of targeted immunotherapy in combination with Atezolizumab 1200 mg + Bevacizumab 800 mg, once every 3 weeks, in treating HCC in the Regional Oncology Center in Kyzylorda.*

Results: *The first symptoms of liver damage appeared in 2018, at which time HCC was discovered. Viral hepatitis B was diagnosed in 2016. MRI OBP from 15.08.20: a picture of the right lobe of the liver in S5 – 9×7×6 cm, in S3 – 3.7 cm, in S7 – 3.0 cm, in S8 – 2.5 cm. During the follow-up examination (July 2021), the enzyme immunoassay revealed a high angiotensin-converting enzyme (ACE) level of 450.56 IU/ml; the abdominal CT scan showed no deterioration. Later, despite the therapy, ACE increased rapidly: 2,595.3 IU/ml (August 2021) and 2,142.25 IU/ml (September 2021), and the therapy was changed to Regorafenib. ACE continued to rise to 4,405 IU/ml (November 2021) and 18,005 IU/ml (December 2021). A control abdominal CT scan showed a moderate reduction in the size of the tumor.*

Taking into account a steady ACE increase, in February 2022, the patient was recommended therapy with Atezolizumab and Bevacizumab. In January 2023, the patient has already received 13 courses, and ACE continued to decrease: 1,932 IU/ml (January 2023), 53.38 IU/ml (February 2023), 16.07 IU/ml (March 2023), and the abdominal CT scan showed positive dynamics.

Conclusion: *Targeted immunotherapy showed its effectiveness in the described case of inoperable HCC and allowed the patient to continue living, working, and leading an active lifestyle for more than 18 months.*

Keywords: *liver, hepatocellular carcinoma (HCC), targeted immunotherapy, clinical case.*

Introduction: According to the World Health Organization 2020, more than 905 thousand cases of liver cancer are diagnosed annually in the world. Liver cancer ranks 6th among all cancers, accounting for 4.7% of all cancer cases [1]. The National Cancer Registry reported 861 new cases of liver cancer in Kazakhstan in 2020 and 899 cases in 2021. They accounted for 3.5% of all MN cases in 2021 (14th place in both sexes) and 4.15% of all MN cases in men (10th place) [2, 3]. In 2022, 1003 cases of liver cancer were detected for the first time, which amounted to 4.5 cases per 100 thousand population, with an increase of 7.1% compared to 2021 [4].

Still, the high mortality rate from liver cancer is a problem both globally and in Kazakhstan. In 2020, 830,180 deaths from liver cancer were registered worldwide, which accounted for 8.3% of all deaths from malignant neoplasms (3rd place) [1]. In Kazakhstan, 580 deaths from liver cancer were registered in 2020 and 538 cases in 2021, which accounted for 3.9% of all deaths from malignant neoplasms in 2021 (10th place among both sexes) and 4.75% of deaths in men (7th place) [2, 3]. In 2022, 563 patients died due to liver cancer, which composed 2.9 cases per 100 thousand population, with an increase of 2.6% compared to 2021 [4].

The WHO's forecasts for liver cancer remain disappointing and indicate a rapid increase in the number of new cases – up to 1 million by 2025 worldwide [5].

Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver. HCC is one of the most important problems of the oncology service of Kazakhstan, as it has a progressive course, late detection, low survival, and unfavorable prognosis. In 2021, 44 new cases of HCC were detected in Kyzylorda region.

The study aimed to evaluate the use of targeted immunotherapy in treating hepatocellular carcinoma in a clinical example.

Materials and Methods: The paper presents a clinical case of targeted immunotherapy in combination with Atezolizumab 1200 mg + Bevacizumab 800 mg, once every 3 weeks, in treating HCC in the Regional Oncology Center in Kyzylorda.

Patient information: Patient: male, 63 years old, at the time of initiation of treatment, diagnosed with HCC of both lobes of the liver, cirrhosis of the liver in the viral hepatitis B outcome.

Anamnesis: The first symptoms of liver damage appeared in 2018, at which time HCC was discovered. Viral hepatitis B was diagnosed in 2016.

Diagnostics: MRI OBP from 15.08.20: a picture of the right lobe of the liver in S5 - 9×7×6 cm, in S3 – 3.7 cm, in S7 – 3.0 cm, in S8 – 2.5 cm; chronic cholecystitis with a kink in the cervical area.

Treatment: Since 2020, the dispensary registration and start of active treatment. In total, 7 courses of transarterial chemoembolization (TACE) were carried out at Syzganov National Scientific Center of Surgery (Almaty, Kazakhstan), with positive dynamics. On the abdominal CT scan in October 2020, the picture was consistent with HCC,

post-TACE status, cirrhosis of the liver, and adenopathy of porta hepatis. In 2021, the patient began to receive targeted therapy with Sorafenib.

During the follow-up examination (July 2021), the enzyme immunoassay revealed a high angiotensin-converting enzyme (ACE) level of 450.56 IU/ml; the abdominal CT scan showed no deterioration. Later, despite the therapy, ACE increased rapidly: 2,595.3 IU/ml (August 2021) and 2,142.25 IU/ml (September 2021), and the therapy was changed to Regorafenib. ACE continued to rise to 4,405 IU/ml (November 2021) and 18,005 IU/ml (December 2021). A control abdominal CT scan showed a moderate reduction in the size of the tumor.

Taking into account a steady ACE increase, in February 2022, the patient was recommended therapy with Atezolizumab and Bevacizumab.

Results: After 7 courses of Atezolizumab 1200 mg + Bevacizumab 800 mg, once every 3 weeks, there was noted ACE decline: 5,163 IU/mL (June 2022), 3,000 IU/mL (November 2022), as well as a positive trend on the abdominal CT in April 2022.

In January 2023, the patient has already received 13 courses, and ACE continued to decrease: 1,932 IU/ml (January 2023), 53.38 IU/ml (February 2023), 16.07 IU/ml (March 2023), and the abdominal CT scan showed positive dynamics.

Abdominal CT scan (10.01.23): liver cirrhosis; liver formations – the picture is more consistent with HCC, the state after TACE of formations in the projection S, III, V, VIII; without negative dynamics. At this time, the patient continues to receive therapy with Atezolizumab and Bevacizumab. All this time, the patient followed an active lifestyle, continued to work, and was involved in physical fitness. In April 2023, an abdominal CT scan during the follow-up examination showed no negative dynamics; ACE was 5.80 IU/ml. The last ACE result as of July 2023 was 0.72 IU/ml. The patient continues the therapy and tolerates it relatively well.

Table 1 presents the timeline of the described clinical case of HCC treatment.

Table 1 – Clinical Case Timeline of Immunotargeted Therapy in the hepatocellular carcinoma treatment

Date	Main events	Measures taken
2016	Viral hepatitis B	self-treatment
2018	HCC	self-treatment
15.08.20	MRI, regular medical check-ups, treatment	7 courses of TACE
2021	Initiation of targeted therapy	Sorafenib
July 2021	IFA on ACE 450,56 IU/ml	Sorafenib
September 2021	IFA on ACE 2142,25 IU/ml	Switching to Regorafenib
February 2021	IFA on ACE 18005 IU/ml	Inception of Atezolizumab and Bevacizumab
November 2022	IFA on ACE 3000 IU/ml	7 courses of Atezolizumab and Bevacizumab
February 2023	IFA on ACE 53,38 IU/ml	13 courses of Atezolizumab and Bevacizumab
April 2023	IFA on ACE 5,80 IU/ml	Continues therapy
July 2023	IFA on ACE 0,72 IU/ml	Continues therapy

Discussion: The Atezolizumab + Bevacizumab combination is recommended as a first-line standard of care in patients with advanced HCC [6] and was approved by the European Medicines Agency (EMA) at the end of 2020 [7]. Besides, according to the recommendations of the National Comprehensive Cancer Network (NCCN version 2.2023), the Atezolizumab + Bevacizumab combination is a preferred first-line therapy regimen for HCC [8, 9]. The ESMO guidelines 2021 recommend this combination in first-line HCC therapy with the highest score (5 points). Other therapy regimens are referred to as options [10].

Conclusion: Targeted immunotherapy showed its effectiveness in the described case of inoperable HCC and allowed the patient to continue living, working, and leading an active lifestyle for more than 18 months.

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АНДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫҚ КАРЦИНОМАҒА АРНАЛҒАН ИММУНДЫҚ МАҚСАТТЫ ЕМДЕУДЕ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Бауырдың ең көп таралған қатерлі ісігі – гепатоцеллюлярлық карцинома (ГСС). ГСК Қазақстандағы онкологиялық қызметтің маңызды мәселелерінің бірі болып табылады, өйткені оның прогрессивті ағымы, кеш анықталуы, өмір сүру деңгейі төмен және болжамы нашар.*

Зерттеудің мақсаты *– клиникалық мысалды пайдалана отырып, гепатоцеллюлярлық карциноманы иммундық мақсатты емдеуде қолдануды бағалау.*

Әдістері: *Қызылорда қаласының облыстық онкологиялық диспансерінде Атезолизумаб 1200 мг + Бевацизумаб 800 мг, 3 аптада 1 рет, ХКК емдеуде біріктірілген иммунотаргетациялық терапияның клиникалық жағдайы.*

Нәтижелері: *Бауырдың зақымдануының алғашқы белгілері 2018 жылы пайда болды, сол уақытта ГСС, 2016 жылдан бастап В вирусты гепатиті анықталды. МРТ АҚП 15.08.20: бауырдың оң жақ бөлігінің СҚК суреті S5 – 9×7×6 см, S3 – 3,7 см, S7 - 3,0 см, S8 - 2,5 см.Бақылау кезінде (шілде 2021 ж.)) КТ АҚҚ деректері бойынша теріс динамикасыз 450,56 ХБ/мл жоғары АСЕ ELISA индексі анықталды. Кейіннен, терапияға қарамастан, АСЕ деңгейі тез өсуде: 2 595,3 ХБ/мл (тамыз 2021 ж.), 2 142,25 ХБ/мл (2021 ж. қыркүйек). Науқастың терапиясы Регорафенибке өзгертілді. Әрі қарай, АСЕ-нің үздіксіз өсуі байқалады: 4 405 ХБ/мл (2021 ж. қараша), 18 005 ХБ/мл (2021 ж. желтоқсан). Бақылау компьютерлік томографиясы өлшемнің қалыпты төмендеуін көрсетеді. АСЕ тұрақты өсуін ескере отырып, 2022 жылдың ақпанында пациентке Атезолизумаб пен Бевацизумабпен емдеу ұсынылды. 2023 жылдың қаңтарында науқас 13 курс алды, АСЕ төмендеуі байқалады: 1932 ХБ/мл (2023 ж. қаңтар), 53,38 ХБ/мл (2023 ж. ақпан), 16,07 ХБ/мл (2023 ж. наурыз), жалғастырумен бірге. АҚҚ КТ оң динамика.*

Қорытынды: *иммундық мақсатты емдеуде операцияға жарамсыз НСС бар осы науқаста өзінің тиімділігін көрсетті және пациентке 18 айдан астам өмір сүруді, жұмысты және белсенділікті жалғастыруға мүмкіндік берді.*

Түйінді сөздер: *бауыр, гепатоцеллюлярлық карцинома, иммундық мақсатты емдеуде, клиникалық жағдай.*

АННОТАЦИЯ

ИММУНОТАРГЕТНАЯ ТЕРАПИЯ ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) является наиболее частой злокачественной опухолью печени и одной из важнейших проблем онкологической службы Казахстана, так как имеет прогрессирующее течение и позднюю выявляемость, больные имеют низкую выживаемость и неблагоприятный прогноз.*

Цель исследования *– оценить назначение иммунотаргетной терапии в лечении гепатоцеллюлярной карциномы на клиническом примере.*

Методы исследования: *В статье представлен клинический случай проведения иммунотаргетной терапии в комбинации Атезолизумаб 1200 мг + Бевацизумаб 800 мг, 1 раз в 3 недели, при лечении ГЦК в условиях областного онкологического центра г. Кызылорды.*

Результаты: *Первые симптомы поражения печени появились в 2018 г., тогда же и была диагностирована ГЦК, вирусный гепатит В с 2016 г. МРТ ОБП от 15.08.20 г.: картина ГЦК правой доли печени в S5 – 9×7×6 см, в S3 – 3,7 см, в S7 – 3,0 см, в S8 – 2,5 см. При контрольном обследовании (июль 2021 года) ИФА выявил высокий АПФ – 450,56 МЕ/мл, по данным КТ ОБП – без отрицательной динамики. В дальнейшем, несмотря на проводимую терапию, уровень АПФ стремительно рос: 2 595,30 МЕ/мл (август 2021 г.), 2 142,25 МЕ/мл (сентябрь 2021 года). Пациенту произведена смена терапии на препарат Регорафениб. Далее наблюдался продолжающийся рост АПФ: 4 405 МЕ/мл (ноябрь 2021 г.), 18 005 МЕ/мл (декабрь 2021 г.). На контрольном КТ ОБП – умеренное уменьшение размеров. Учитывая неуклонный рост АПФ, в феврале 2022 г. пациенту была рекомендована терапия препаратами Атезолизумаб и Бевацизумаб. В январе 2023 г. пациент уже получил 13 курсов, отмечается снижение АПФ: 1 932 МЕ/мл (январь 2023 г.), 53,38 МЕ/мл (февраль 2023 года), 16,07 МЕ/мл (март 2023 г.), наряду с продолжающейся положительной динамикой по КТ ОБП.*

Заключение: *Иммунотаргетная терапия показала свою эффективность у данного пациента с неоперабельной ГЦК и позволила пациенту продолжать жить, работать и вести активный образ жизни уже более 18 месяцев.*

Ключевые слова: *печень, гепатоцеллюлярная карцинома (ГЦК), иммунотаргетная терапия, клинический случай.*

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RECURRENCE OF OVARIAN CANCER: POSSIBLE CAUSES, EARLY DETECTION

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ABSTRACT

Relevance: *Early detection of ovarian cancer relapses and their treatment is among the most difficult in practical oncogynecology. Early diagnosis of ovarian cancer recurrence increases the effectiveness of treatment and gives a more favorable survival prognosis.*

The study aimed to *show the possible cause of ovarian cancer recurrence and methods for early detection of relapses.*

Materials and methods: *We systematically analyzed 31 cases of recurrent ovarian cancer treated at the Zhambyl Regional Center of Oncology and Surgery (Kazakhstan) in 2021-2022. We divided them by age, stage, period of relapse, type of histology, tumor grade, sites of recurrence, and symptoms of recurrence.*

Results: *Ovarian cancer is most often detected in the late stages since, in the early stages, the disease is asymptomatic. Patients with advanced stages showed more relapses and distant metastases. Most ovarian cancer and this disease's relapses are detected at 50-70 years old. The late stages give more distant and multiple relapses than the early stages and in terms of earlier. Moreover, according to histology results, mesenchymal tumors are more significant than epithelial and G3.*

Conclusion: *The recurrence of ovarian cancer is an aggressively occurring disease. Based on the analysis work carried out, more than 70% of patients with recurrent ovarian cancer were aged 50-70 years, and the recurrence rate was higher at later stages (St III) or with a low-grade form of the tumor. All patients received platinum-based combination therapy. Targeted therapy (Bevacizumab) was administered in generalization of the process. More than 20% of all patients are resistant to platinum, whose relapse occurred before six months; the rest are sensitive to platinum with a later relapse. Based on everything, there is an increase in distant and multiple relapses in the late stages of ovarian cancer. This indicates the need to introduce screening programs based on cancer markers (CA-125) and diagnostic instrumental examinations (MRI/CT) to detect ovarian cancer in the early stages. After the treatment, all patients with this disease should be under active supervision, especially patients with low-grade tumors and in late stages.*

Keywords: *ovarian cancer, recurrence of ovarian cancer, prevention.*

Introduction: Ovarian cancer is the most commonly diagnosed gynecologic malignancy and the leading cause of cancer-related deaths in women [1, 2]. Ovarian cancer ranks seventh among the eighteen most common oncopathologies in the world. At the same time, ovarian cancer occupies a leading position in the structure of mortality: the first place among deaths from oncogynecological diseases and the fifth place among the mortality of the female population due to oncopathology [3, 4]. One of the main causes of high mortality in ovarian cancer is the diagnosis of primary disease at advanced stages and a high risk of recurrence. According to some researchers, all patients with ovarian cancer die after relapses within three years [5]. Early detection of relapses makes it possible to perform secondary cytoreductive operations in combination with various chemotherapy regimens, which, according to some authors, increases the survival rate of patients up to 47%. [6]. Functional visceral fat activity assessed by 18F-FDG PET/CT is significantly associated with regional lymph node metastasis. Furthermore, it is a helpful factor in predicting such metastasis. Implementation of the study results into medical practice will help practitioners choose tactics and control for patients with recurrent ovarian cancer [7]. Early diagnosis of ovarian cancer recurrence increases the effectiveness of treatment and gives a more favorable survival prognosis.

To date, 354 people with ovarian cancer are registered in the Zhambyl region; 205 (57.9%) are on record for >5 years. Out of 58 women registered in 2022, 17 had stage I, 4 – stage II, 34 – stage III, and 3 – stage IV cancer.

The study aimed to show the possible cause of ovarian cancer recurrence and methods for early diagnosis.

Materials and methods: We systematically analyzed 31 patients with recurrent ovarian cancer treated at the Zhambyl Regional Center of Oncology and Surgery in 2021-2022. We divided them by age, stage, period of relapse, type of histology, tumor grade, sites of recurrence, and symptoms of recurrence.

Results: Out of 31 ovarian cancer recurrences, more than 70% occurred in women aged 50-70 years; 22.6% of patients were below 50, and only 3.2% were above 70 years. By stages, most were stage III-IV cases (58.1%), that is, more advanced; 19.4% were stage I, and 22.5% were stage II (Figure 1).

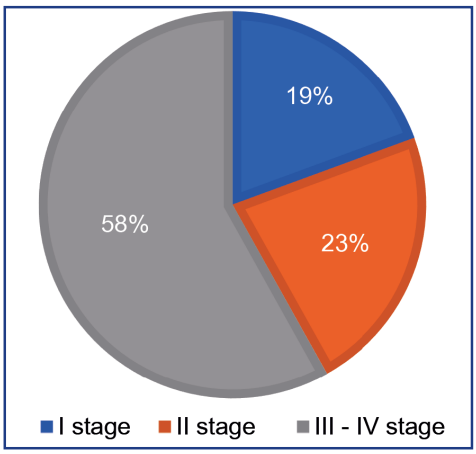

Figure 1 – Percentage of relapses by stage

Based on our data, late stages produce more and earlier relapses than stages I-II.

Figure 2 shows relapse periods by stage. Advanced stages produced earlier relapses than stages I-II. Early stages like stage I did not produce relapses until 6 months.

All patients were operated on and received adjuvant chemotherapy courses. 41.9% of patients (6.5% with stage II and 35.4% with stage III) received neoadjuvant chemotherapy courses.

22.5% of cases were symptomatic. In asymptomatic cases (77.5%), relapses were detected by instrumental laboratory tests.

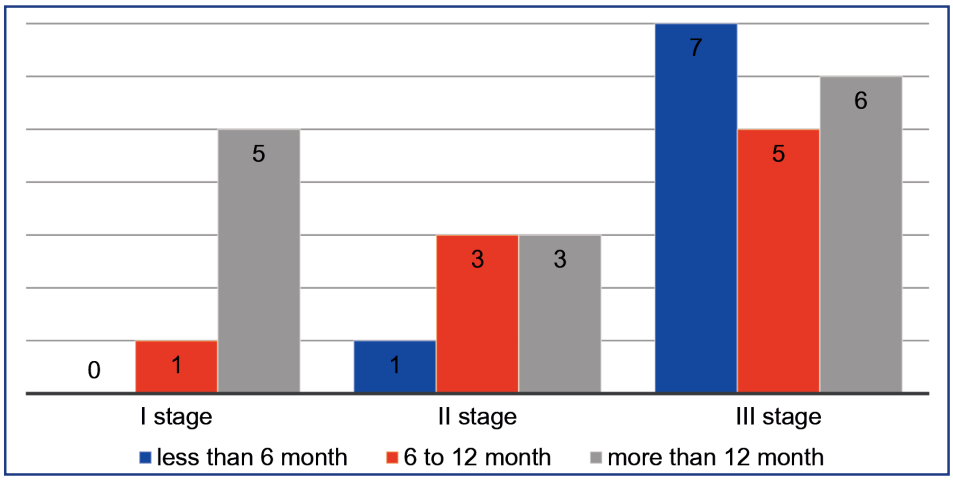

Figure 2 – Relapse periods by stage

51.6% of patients had single relapses; the rest had multiple relapses. Also, the recurrence of ovarian cancer could be local or remote. 74.2% of patients had distant relapses; the relapses were local in other cases.

If we divide by stages, local relapses (in the pelvis) were detected in patients with stage I-II of the disease, and distant relapses were registered with advanced stages.

According to the histological results, the tumors were 77.4% epithelial and 22.6% mesenchymal.

Regarding the tumor differentiation degree, low-grade tumors (G3) were more aggressive (42%) and caused relapses more often than G1 (12.9%) or G2 (29%) tumors. Moreover, in 16.1% of patients, the tumor differentiation degree was not determined because of the neoadjuvant therapy they had received.

Conclusion: The recurrence of ovarian cancer is an aggressively occurring disease. Based on the analysis work carried out, more than 70% of patients with recurrent ovarian cancer were aged 50-70 years, and the recurrence rate was higher at later stages (St III) or with a low-grade form of the tumor. All patients received platinum-based combination therapy. Targeted therapy (Bevacizumab) was administered in generalization of the process. More than 20% of all patients are resistant to platinum, whose relapse occurred before six months; the rest are sensitive to platinum with a later relapse. Low-grade ovarian cancer produces faster relapse, that is, before 6 months, and is more resistant to platinum drugs. Based on everything, there is an increase in distant and multiple relapses in the late stages of ovarian cancer. Therefore, such patients should be actively monitored by an oncogynecologist and regularly pass cancer markers (CA-125) tests and instrumental diagnostic examinations (MRI/CT) for early detection of ovarian cancer recurrence.

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АНДАТПА

АНАЛЫҚ БЕЗ ҚАТЕРЛІ ІСІГІНІҢ ҚАЙТАЛАНУЫ: МҮМКІН СЕБЕПТЕРІ ЕРТЕ АНЫҚТАУ

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Өзектілігі: *аналық без қатерлі ісігінің қайталануын ерте анықтау және емдеу практикалық онкогинекологиядағы ең күрделі болып табылады. Аналық без қатерлі ісігінің қайталануын ерте диагностикалау емдеудің тиімділігін арттырады және өмір сүрудің қолайлы болжамын береді.*

Зерттеудің мақсаты *– аналық без обырының қайталануының ықтимал себебін және ерте анықтау әдістері.*

Материалдар мен әдістері: *Біз Жамбыл облыстық онкология және хирургия орталығында 2021-2022 жылдары қайталанған аналық без обыры бар 31 науқасты жүйелі түрде талдадық. Біз оларды жасына, кезеңіне, қайталану кезеңіне, гистология түріне, ісік қатерлі ісігінің дәрежесіне, қайталану орындарына және қайталану белгілеріне қарай бөлдік.*

Нәтижелері: *аналық без қатерлі ісігі көбінесе кеш сатысында анықталады, өйткені ауру ерте сатысында асимптоматикалық болып табылады. Кеш сатыдағы науқастарда рецидивтер мен алыс метастаздар көп болды. Аналық без қатерлі ісігінің және аурудың қайталануының көпшілігі 50-70 жас аралығында анықталады. Кеш кезеңдер ерте кезеңдерге қарағанда және ертерек кезеңдерге қарағанда ұзақ және бірнеше қайталанулар береді. Сонымен қатар, гистология нәтижелеріне сәйкес, мезенхималық ісіктер эпителий мен G3-ке қарағанда маңыздырақ.*

Қорытынды: *аналық без қатерлі ісігінің қайталануы-бұл агрессивті ауру. Жүргізілген талдауға сәйкес, қайталанатын аналық без обыры бар науқастардың 70% - дан астамы 50-70 жаста болған және қайталану жиілігі кеш сатыларда (III кезең) немесе ісіктің төмен сараланған түрінде жоғары болған. Барлық пациенттер платина негізіндегі аралас терапия алды. Процесті жалпылау кезінде мақсатты терапия (бевацизумаб) тағайындалды. Барлық пациенттердің 20%-дан астамы алты айға дейін қайталанған платинаға төзімді; қалғандары кейінірек қайталанған платинаға сезімтал. Жоғарыда айтылғандардың барлығына сүйене отырып, аналық без қатерлі ісігінің кеш сатысында ұзақ мерзімді және бірнеше қайталанулардың жоғарылауы байқалады, бұл аналық без обырын ерте сатысында анықтау үшін ісік маркерлеріне негізделген скринингтік бағдарламаларды (CA-125) және аспаптық диагностикалық зерттеулерді (МРТ/КТ) енгізу қажеттілігін көрсетеді. Емдеуден кейін бұл аурумен ауыратын барлық науқастар белсенді бақылауда болуы керек, әсіресе төмен дәрежелі ісіктері бар және дамыған сатыдағы науқастар.*

Түйінді сөздер: *аналық без обыры, аналық без обырының қайталануы, алдын алу.*

АННОТАЦИЯ

РЕЦИДИВ РАКА ЯИЧНИКОВ: ВОЗМОЖНЫЕ ПРИЧИНЫ, РАННЕЕ ВЫЯВЛЕНИЕ

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Актуальность: *Раннее выявление рецидивов рака яичников и их лечение являются одними из наиболее сложных в практической онкогинекологии. Ранняя диагностика рецидива рака яичников повышает эффективность лечения и дает более благоприятный прогноз выживаемости.*

Целью исследования *– показать возможную причину рецидива рака яичников и методы раннего выявления рецидивов.*

Материалы и методы: *Мы провели систематический анализ данных 31 пациентки с рецидивирующим раком яичников, пролеченных в 2021-2022 годах в Жамбылском областном центре онкологии и хирургии (Казахстан). Мы разделили их по возрасту, стадии, периоду рецидива, местам рецидива и симптомам рецидива, типу гистологии, степени злокачественности опухоли,*

Результаты: *Рак яичников чаще всего выявляется на поздних стадиях, поскольку на ранних стадиях заболевание протекает бессимптомно. У пациентов с запущенными стадиями наблюдалось больше рецидивов и отдаленных метастазов. Большинство случаев рака яичников и рецидивов этого заболевания выявляются в возрасте 50-70 лет. Поздние стадии дают более отдаленные и множественные рецидивы, чем ранние стадии и с точки зрения более ранних сроков. Более того, согласно результатам гистологии, мезенхимальные опухоли являются более значимыми, чем эпителиальные и G3.*

Заключение: *Рецидив рака яичников является агрессивно протекающим заболеванием. Согласно проведенному анализу, более 70% пациенток с рецидивирующим раком яичников были в возрасте 50-70 лет, и частота рецидивов была выше на поздних стадиях (III стадия) или при низкодифференцированной форме опухоли. Все пациенты получали комбинированную терапию на основе платины. При генерализации процесса была назначена таргетная терапия (бевацизумаб). Более 20% всех пациентов устойчивы к платине, у которых рецидив произошел до шести месяцев; остальные чувствительны к платине с более поздним рецидивом. Исходя из всего вышесказанного, наблюдается увеличение отдаленных и множественных рецидивов на поздних стадиях рака яичников, что указывает на необходимость внедрения программ скрининга на основе онкомаркеров (CA-125) и инструментальных диагностических обследований (МРТ/КТ) для выявления рака яичников на ранних стадиях. После лечения все пациенты с этим заболеванием должны находиться под активным наблюдением, особенно пациенты с опухолями низкой степени злокачественности и на поздних стадиях.*

Ключевые слова: *рак яичников, рецидив рака яичников, профилактика.*

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ENDOSCOPIC TREATMENT FOR EARLY COLORECTAL CANCER

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ABSTRACT

Relevance: *In recent years, significant breakthroughs have occurred in the endoscopic treatment of cancerous and precancerous lesions of the gastrointestinal tract. Endoscopic mucosal resection (EMR) is a simple and effective method of treating most benign gastrointestinal tract lesions. However, with the introduction of endoscopic submucosal dissection (ESD) and full-thickness endoscopic resection (EFTR), the volume of lesions subject to endoscopic treatment has significantly expanded even in the colon. Currently, these methods are regularly used not only for the treatment of benign tumors but also for complex resection of early stages of colorectal cancer. For the first time in Kazakhstan, the presented article analyzed the cases of endoscopic removal of epithelial formations of the large intestine performed at an oncological clinic from 2020 to 2023.*

The aim was to *evaluate endoscopic treatment of early colorectal cancer.*

Methods: *The article presents a retrospective analysis of 68 cases of endoscopic removal of epithelial formations of the colon performed from 2020 to 2023 at the Center of Expert Endoscopy and Interventional Radiology of the National Scientific Cancer Center (Astana, Kazakhstan).*

Results: *In 2020-2023, 68 endoscopic extractions of colon tumors were performed, including 25 outpatient and 43 inpatient manipulations. Out of 43 inpatient cases, endoscopic dissection in the submucosal layer was performed in 9 cases, and endoscopic mucosal resection of tumors of the large intestine was performed in 34 cases. Morphologically, we found hyperplastic polyps in 11 cases, lipomas in 2 cases, tubulovillous adenomas with mild dysplasia – 43 cases, tubulovillous adenomas with severe dysplasia – 11 cases, carcinoma in situ – 3 cases, and adenocarcinoma with invasion – 3 cases.*

Conclusion: *When detecting benign neoplasms with dysplasia and early colorectal cancer, minimally invasive technologies (EMR, ESD, EFTR) should be the first preferred treatment method and only if they cannot be performed and there is a high risk of invasion into the underlying layers, and therefore, if endoscopic treatment is not radical, clinicians should choose surgical radical treatment. Patients should be informed about the availability of the latest methods of local treatment in the Republic through funding via the Compulsory Medical Insurance Fund (CMIF).*

Keywords: *early colorectal cancer, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), full-thickness endoscopic resection (EFTR), Lateral spreading tumor (LST).*

Introduction: In recent decades, endoluminal operative endoscopy has developed rapidly abroad and in Kazakhstan. The leading endoscopic centers are being set up in Astana and Almaty. In this vein, the latest methods of endoscopic treatment of precancerous and cancerous lesions of the gastrointestinal tract (GI) at early stages, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and full-thickness endoscopic resection (EFTR), have become widely available for treatment of benign neoplasms and early forms of gastrointestinal cancer of citizens of the Republic of Kazakhstan.

Compared to endoscopic treatment and surgical treatment, the advantages of the first are apparent, for example, the lower cost and shorter hospital stay. Besides, endoscopic resection almost always allows radical resection en bloc, which is very important and should be considered an indicator of quality [1].

EMR is a method of endoscopic mucosal resection using a diathermic loop. The lesion is trapped in the loop and excised under the mucosal surface during the loop closure. The main advantage of this technique is, first of all, its minimally invasive nature: general anesthesia is not required, postoperative morbidity is low (bleeding occurs in about 5% of cases with lesions above 20 mm), and the operative time is relatively short (the literature reports an average operation time of about 15 minutes). The main shortcoming is the low en bloc resection rate for large lesions. The en bloc resection rate is about 84% for lesions below 20 mm and 50% – for lesions above 20 mm. Therefore, this method is contraindicated in intestinal lesions above 20 mm in diameter (Figure 1).

In ESD, a modified needle knife dissects the lesions through the submucosa. This endoscopic method appeared 15 years ago to perform epy complex resection of laterally spreading tumors (LST) of the gastrointestinal tract. The technique consists of marking the edge of the lesion about 5 mm proximal with an electric knife, followed by submucosal injection. An electric knife makes an incision around the circumference to create a flap that gradually lifts to dissect the submucosal space (Figure 2).

Compared to other endoscopic techniques, the ESD requires the longest time for surgery (70 to 130 minutes) and sedatives. With lesions above 20 mm, the reported complication rate is about 10% (complications mainly include bleeding and perforation). The en bloc resection rate ranges from 86% to 90%, and the R0 resection rate is 72% to 80% [2].

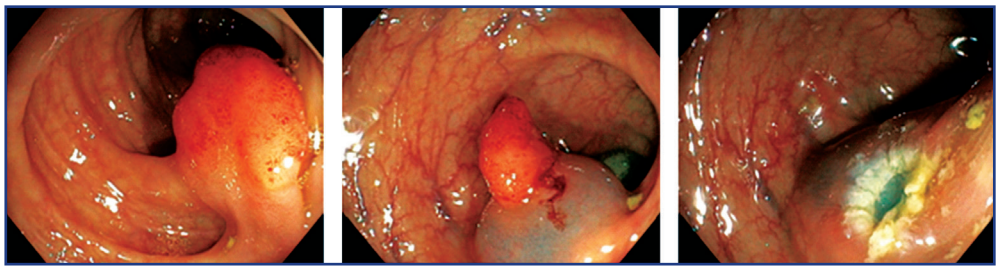

Figure 1 – EMR stages of endoscopic mucosal resection

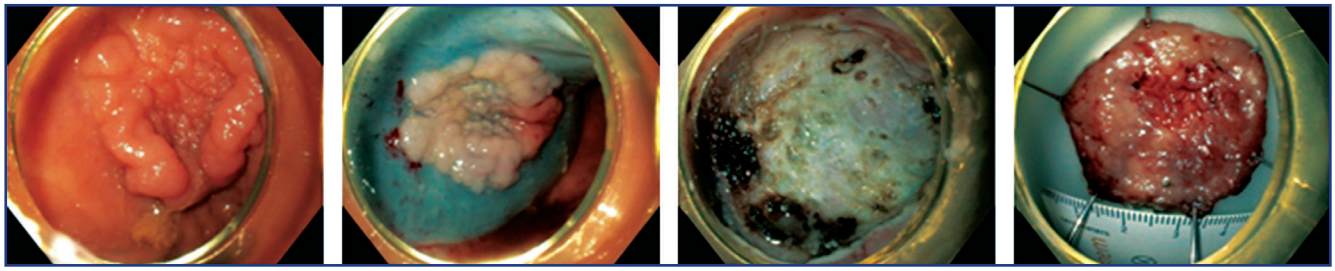

Figure 2 – Stages of endoscopic dissection in the submucosal layer

With the introduction of the EFTR method, there was a significant breakthrough in the endoscopic treatment of gastrointestinal neoplasms. In the review article of Schmidt et al., the classic indications for EFTR have been described and included the "repeated resection" of T1 carcinomas, curative treatment of early colorectal lesions, and resection of polyps of complex anatomical location. When early colorectal cancer is misdiagnosed as a benign adenoma and then classically removed using partial EMR, the R-status or depth of submucosal invasion might be impossible to determine. In this case, EFTR becomes a valuable tool for obtaining a full-size sample of the resection site, expanding the diagnostic arsenal [1]. Full-thickness endoscopic resection starts with marking the formation with an electric knife 0.5-0.8 cm away from the formation boundaries. Then, the formation is extracted from the surrounding mucosa with a vacuum suction unit into the endoscope cap with a clamp. After that, the endoscopist uses a screw on the endoscope handle to pull off the clamp. The clamp cuts off the formation with the base and the underlying stroma and clips the removal site tightly. Then, a mechanical suture is performed at the full-thickness resection site. The preliminary marking of the mucosa around the formation allows the endoscopist and morphologist to assess the removal's radicality and the resection margins' cleanliness (Figure 3).

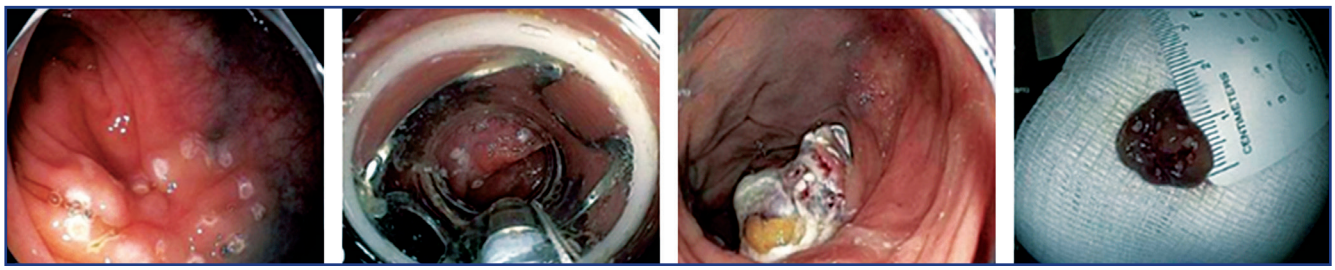

Figure 3 – Stages of endoscopic full-thickness resection (EFTR)

In the case of correctly diagnosed early colorectal cancer, EFTR leads to complete (R0) resection of the neoplasm, including the underlying muscle tissue, and allows for an accurate histological assessment of the depth of submucosal invasion [3]. For the first time in Kazakhstan, the presented article analyzed the cases of endoscopic removal of epithelial formations of the large intestine performed at an oncological clinic from 2020 to 2023.

Materials and Methods: The article presents a retrospective analysis of 68 cases of endoscopic removal of epithelial formations of the colon performed from 2020 to 2023 at the Center of Expert Endoscopy and Interventional Radiology of the National Scientific Cancer Center (Astana, Kazakhstan).

Results: In 2020-2023, 68 outpatient and inpatient endoscopic extractions of large intestine neoplasms were performed in the endoscopy department.

The patients were divided into two groups by gender: 36 males and 32 females. The patients were divided into five groups by age according to the WHO characteristics. Among males, most patients were 60 to 74 years (29.4%), fewer were 45-59 years (17.6%), and the smallest number were aged 18 to 44 (2.9%) or 75 to 90 (2.9%). Among females, most patients (39.8%) were aged 45 to 74, and fewer were 18 to 44 years old (5.9%) or 75 to 90 years old (1.5%) (Table 1).

Table 1 – Sex and age characteristics of patients

Sex	Age				
	18-44 years	45-59 years	60-74 years	75-90 years	90+
Male, abs. (%)	2 (2.9%)	12 (17.6%)	20 (29.4%)	2 (2.9%)	-
Female, abs. (%)	4 (5.9%)	8 (11.8%)	19 (28%)	1 (1.5%)	-

Endoscopic mucosal resection of neoplasms was the method of choice for lesions up to 20 mm in size, in the presence of a broad basis or a pedicle, and with no visual signs of malignancy. In all outpatients and inpatients, endoscopic mucosal resection was performed using hydro-lifting with sterile gelofusine stained with sterile indigo carmine since preliminary hydro-lifting allows the radical removal of the tumor. In the presence of neoplasms in the proximal colon (cecum, ascending, transverse colon), neoplasms were removed under general sedation to reduce the discomfort for the patient. In the localization of neoplasms in the distal parts of the large intestine (descending, sigmoid, rectum), EMR was performed without sedation. The removed neoplasms ranged from 1.0 to 5.0 cm in size and had a long or short pedicle. Morphological examination of the removed substrate was performed in all cases of EMR neoplasms of the large intestine. The following lesions were morphologically confirmed: hyperplastic polyps – 6, lipomas – 2, tubulovillous adenoma with mild dysplasia – 42, tubulovillous adenoma with severe dysplasia – 6, carcinoma *in situ* – 1 and adenocarcinoma with invasion to a muscular plate of the mucous membrane – 1, which has been assessed as the radical resection R0.

Endoscopic dissection in the submucosal layer was performed for radical endoscopic removal of masses exceeding 20 mm, as well as in severe dysplasia and suspected malignancy (according to the classification of the superficial and vascular pattern JNET2B and JNET3). Dissection was performed only in hospital settings and under general sedation, with a mandatory insufflation of the intestinal lumen with carbon dioxide. In ESD and EMR, pre-lifting was performed with sterile gelofusine stained with sterile indigo carmine. The dissection was made with a Fınemedıx Q-type dissection knife in the Spray 35Wt and Force 40Wt coagulation modes. All neoplasms were removed en bloc. The tumor boundaries after resection were marked for subsequent morphological verification of the resection margins' cleanliness in case of tumor invasion. In nine cases of endoscopic dissection in the submucosal layer, the following lesions were revealed: tubulovillous adenoma with severe dysplasia – 5, carcinoma *in situ* – 2, and adenocarcinoma with muscle invasion that required further surgical resection of the bowel to ensure radical treatment – 2 (Table 2).

Table 2 – Morphological types of removed neoplasms

Treatment type	Morphology					
	Hyperplastic polyp	Lipoma	Tubulovillous adenoma with mild dysplasia	Tubulovillous adenoma with severe dysplasia	Carcinoma *in situ*	Adenocarcinoma with invasion
EMR	6	2	42	6	1	1
ESD	-	-	-	5	2	2
EFTR	-	-	-	-	1	-

EFTR is an expensive procedure in terms of the cost of medical accessories. Therefore, this procedure was performed in the department once on a patient primarily diagnosed with rectal carcinoid. The removed mass was 1.2 cm in size, corresponding to the full-thickness resection device cap size.

Discussion: In a bowel lesion, the tumor characteristics (spread, biopsy histology, fossae pattern, and the NICE, JNET, or Kudo classification) should be assessed.

If non-invasive surgery is planned, the local staging with echo-endoscopy provides the highest accuracy, and if non-invasiveness is confirmed, the local excision is indicated. Due to the relatively low relation between the preoperative and postoperative stages, the en bloc and R0 removals are essential to reduce further operations for oncological reasons. Endoscopic en bloc mucosal resection may be performed for tumors below 2 cm in diameter with no signs of malignancy. Otherwise, ESD is recommended, which can be an acceptable alternative in specialized centers with extensive experience in endoscopic manipulations [4].

A final histological assessment allows the discovery of tumors that require further surgical intervention based on their local stage and characteristics. In early colorectal cancer with the invasion into the submucosal layer up to 1 mm of (up to T1sm1), the local excision may be adequate from the oncological point of view. Other risk factors for developing lymph node metastases, such as tumor differentiation, tumor budding, and lymphovascular invasion, should be considered when determining patients who require radical surgery [5].

Conclusion: In benign neoplasms with dysplasia and early colorectal cancer, minimally invasive technologies (EMR, ESD, EFTR) should be the first method of choice. Only if these manipulations are not impossible and there is a high risk of invasion into the underlying layers, and therefore endoscopic treatment is not radical, clinicians should choose surgical radical treatment. However, minimally invasive endoscopic inter-

ventions require using additional equipment (carbon dioxide insufflator, water jet pump) and a wide range of disposable supplies (dissection knives, injectors, clippers, etc.). Besides, the doctor-endoscopist must be skilled in dissections, so it is relevant to establish several expert endoscopic centers in the country. Finally, since colorectal cancer screening programs have increased the number of early detected colorectal cancer cases, oncologists, surgeons, gastroenterologists, and, most importantly, patients should be informed about the availability in the country of the latest methods of local treatment financed from the Compulsory Medical Insurance Fund (CMIF).

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АНДАТПА

ЕРТЕ КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІККЕ АРНАЛҒАН ЭНДОСКОПИЯЛЫҚ ЕМДЕУ

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Өзектілігі: *соңғы жылдары асқазан-ішек жолдарының қатерлі ісігі мен қатерлі ісікке дейінгі зақымдануларын эндоскопиялық емдеуде айтарлықтай жетістіктер болды. Эндоскопиялық шырышты резекция (EMR) - асқазан-ішек жолдарының қатерсіз зақымдануларының көпшілігін емдеудің қарапайым және тиімді әдісі. Алайда эндоскопиялық субмукозальды диссекцияны (ESD) және бүкіл қалыңдықтағы эндоскопиялық резекцияны (EFTR) енгізумен эндоскопиялық емдеуге жататын зақымданулардың көлемі тіпті тоқ ішекте де айтарлықтай кеңейді. Қазіргі уақытта бұл әдістер қатерсіз өсінділерді емдеу үшін ғана емес, сонымен қатар колоректальды қатерлі ісіктің ерте кезеңдерін кешенді резекциялау үшін де үнемі қолданылады. Ұсынылған мақалада Қазақстанда алғаш рет онкологиялық клиника жағдайында 2020 жылдан 2023 жылға дейін жүргізілген тоқ ішектің эпителий түзілімдерін эндоскопиялық жоюдың емделген жағдайларына ретроспективті талдау жүргізілді.*

Зерттеудің мақсаты *– ерте колоректальды қатерлі ісікті эндоскопиялық емдеу әдістерін қолдану ерекшеліктерін бағалау.*

Әдістері: *Ұлттық ғылыми онкологиялық орталықтың (Астана, Қазақстан) сараптамалық эндоскопия және интервенциялық радиология орталығында 2020 жылдан 2023 жылға дейінгі кезеңде жүргізілген тоқ ішектің эпителий түзілімдерін эндоскопиялық жоюдың 68 жағдайына ретроспективті талдау жүргізілді.*

Нәтижелері: *2020-2023 ж.ж. кезеңінде тоқ ішектің неоплазмаларын 68 эндоскопиялық алып тастау жүргізілді, оның ішінде 25 пациентке және стационарлық жағдайда 43 пациентке амбулаториялық негізде. 43 стационарлық жағдайдың 9-9 субмукозды қабатта эндоскопиялық диссекция және 34 жағдайда тоқ ішек ісіктерінің эндоскопиялық мукозрезекциясы жүргізілді. Морфологиялық құрылымы бойынша барлық саннан гиперпластикалық полиптер 11 жағдайда, 2 жағдайда липома, 43 жағдайда жеңіл дисплазия дәрежесі бар тубуло-Вилла аденомалары, 11 жағдайда ауыр дисплазия дәрежесі бар тубуло-Вилла аденомалары, 3 жағдайда carcinoma in situ және 3 жағдайда инвазиясы бар аденокарцинома болды.*

Қорытынды: *Дисплазиямен және ерте колоректальды қатерлі ісікпен қатерсіз өсінділерді анықтаған кезде, емдеудің бірінші таңдаулы әдісі аз инвазивті технологиялар (EMR, ESD, EFTR) болуы керек және оларды орындау мүмкін болмаған кезде және олардың астындағы қабаттарға ену қаупі жоғары болған кезде ғана, сондықтан эндоскопиялық емдеудің радикалдылығы болмаған кезде дәрігерлер хирургиялық радикалды емдеуді таңдауы керек. Пациенттер міндетті медициналық сақтандыру қорының (ММСҚ) қаржыландыру желісі бойынша республикада жергілікті емдеудің жаңа әдістемелерінің қолжетімділігі туралы хабардар болуға тиіс.*

Түйінді сөздер: *ерте колоректальды қатерлі ісік, эндоскопиялық шырышты резекция (EMR), эндоскопиялық субмукозальды диссекция (ESD), эндоскопиялық толық қабырғалы резекция (EFTR), бүйірлік сойылатын масса (LST).*

АННОТАЦИЯ

ЭНДОСКОПИЧЕСКИЕ МЕТОДЫ ЛЕЧЕНИЯ РАННЕГО КОЛОРЕКТАЛЬНОГО РАКА

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Актуальность: *В последние годы достигнуты значительные успехи в эндоскопическом лечении раковых и предраковых поражений желудочно-кишечного тракта. Эндоскопическая резекция слизистой оболочки (EMR)является простым и эффективным методом лечения большинства доброкачественных поражений желудочно-кишечного тракта. Однако внедрение эндоскопической подслизистой диссекции (ESD) и эндоскопической полностенной резекции (EFTR) значительно расширило спектр поражений, которые можно лечить эндоскопически в толстой кишке. В настоящее время эти методы регулярно используются не только для лечения доброкачественных образований, но и для комплексной резекции ранних стадий колоректального рака. В представленной статье впервые в Казахстане проведен ретроспективный анализ случаев эндоскопического удаления эпителиальных образований толстого кишечника, пролеченных в условиях онкологической клиники с 2020 г. по 2023 г.*

Цель исследования *– оценка особенностей применения методов эндоскопического лечения раннего колоректального рака.*

Методы: *Представлен ретроспективный анализ 68 случаев эндоскопического удаления эпителиальных образований толстого кишечника, проведенных в Центре экспертной эндоскопии и интервенционной радиологии Национального научного онкологического центра (Астана, Казахстан) с 2020 по 2023 годы.*

Результаты: *В 2020-2023 гг. было проведено 68 эндоскопических удалений новообразований толстого кишечника, из них амбулаторно– 25 пациентами 43 пациентам – в стационарных условиях по пакету ГОМП/ОСМС. Из 43 стационарных случаев в 9 случаях проведена эндоскопическая диссекция в подслизистом слое и в 34 случаях – эндоскопическая мукозрезекция новообразований толстого кишечника. По морфологическому строению, из всего количества гиперпластические полипы были отмечены в 11 случаях, липома– 2, тубуло-ворсинчатые аденомы с легкой степенью дисплазии – 43, тубуло-ворсинчатые аденомы с тяжелой степенью дисплазии – 11, carcinoma in situ – 3 случаях и аденокарцинома с инвазией – в 3 случаях.*

Заключение: *При выявлении доброкачественных новообразований с дисплазией и раннего колоректального рака первым предпочтительным методом лечения должны быть малоинвазивные технологии (EMR, ESD, EFTR) и только при невозможности их выполнения и высоком риске наличия уже инвазии в подлежащие слои, а следовательно при нерадикальности эндоскопического лечения клиницисты должны выбирать хирургическое радикальное лечение. Пациенты должны быть информированы о доступности новейших методик местного лечения в Республике по линии финансирования Фонда обязательного медицинского страхования (ФОМС).*

Ключевые слова: *ранний колоректальный рак, эндоскопическая резекция слизистой оболочки (EMR), эндоскопическая подслизистая диссекция (ESD), эндоскопическая полностенная резекция (EFTR), комплексная резекция латерально стелющихся образований (LST).*

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CARCINOGENICITY OF IONIZING RADIATION: A LITERATURE REVIEW

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ABSTRACT

Relevance: *According to WHO, malignant neoplasms rank second in population mortality structure due to a constantly increasing influence of technogenic factors that have a direct carcinogenic effect on the body and suppress defense mechanisms. Ionizing radiation plays a special role in the development of cancer. It is used in industry, agriculture, medicine, and scientific research as a diagnostic tool in modern healthcare and radiation therapy for cancer treatment. The consequences of radiation influence are not only the result of a direct effect on the body but also a delayed one through generations of parents and grandparents. According to the radiobiological hypothesis, any level of radiation, no matter how small, poses a risk of long-term consequences, including cancer, in exposed people and their descendants of the first two generations. That is, cancerous tumors are likely consequences of the influence of radiation. Despite various theories of the biological effect of low doses of ionizing radiation, most authors attach primary importance to DNA damage in the manifestation of genetic effects (the concept of non-threshold mutational action).*

The study aimed to *highlight the role of ionizing radiation in tumorigenesis.*

Methods: *Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials was analyzed to select and analyze relevant information over the past 10 years using such keywords as "gamma irradiation," "spontaneous oncogenesis," and "prevention of oncogenesis."*

Results: *Radiation exposure may increase the risk of cancer development due to epigenetic changes leading to increased genomic instability (GI) and/or specific suppression of tumor suppressor genes. Changes in the TP53 gene network expression occur; the most significant genes as predictors of carcinogenesis are ST13, IER3, BRCAI, LRDD, and MRAS. Epigenetic changes also influence individual susceptibility to radiation-induced cancer. In addition to the mutagenic effects of ROS and AFN, there is also evidence that oxidative stress plays a fundamental role in epigenetic modifications.*

Conclusion: *As a result of radiation exposure, damage occurs that causes genetic and epigenetic changes, leading to changes in the level of protein expression due to changes in the methylation of cytosine residues in DNA, modification of histones, and regulation of microRNA expression.*

Keywords: *gamma irradiation, spontaneous oncogenesis, prevention of oncogenesis.*

Introduction: Oncological diseases remain one of the most important problems of modern health care and medicine. According to the Minister of Health of the Republic of Kazakhstan, at the end of 2022, "in Kazakhstan, oncological diseases ranked 7th among all diseases, while circulatory system diseases ranked 2nd in mortality. As of today, over 205,000 patients with cancer are under dynamic follow-up in Kazakhstan. Besides, more than 37 thousand new cases are detected annually. Of these cases, 56% are people of employable age." The generally recognized reason for such morbidity and mortality from malignant neoplasms (MN) is a constantly growing influence of technogenic factors. They have a direct carcinogenic effect on the human body and suppress its protective mechanisms, primarily immune reactivity. Ionizing radiation occupies a special place among factors contributing to MN development. The scientific and technological achievements increase the number and power of radiation sources, including nuclear power stations and various less-capacity sources widely used in industry, medicine, and science.

The first test nuclear explosion at the Semipalatinsk Test Site occurred on August 29, 1949. The power capacity of the first bomb was 22 kilotons. In total, from 1949 to 1989, at least 468 nuclear tests, both surface and underground, have been carried out at this test in Kazakhstan. During the period of unprecedented nuclear weapons tests, the radioecological situation in the region changed dramatically, affecting the morbidity indicators, the course of certain nosological forms, and a higher contribution to radiation-induced pathologies. Recent research revealed a higher frequency of MNs, hereditary pathologies, and general somatic diseases among the population exposed to radiation. The age at exposure, the time from the exposure, and the radiation dose were found to influence cancer morbidity and mortality. In a directly irradiated population, the cancer pathologies are dominated by MNs of the digestive and respiratory organs. In contrast, cancers of the breast, female genital organs, lymphoid and hematopoietic tissues, eye, brain, and other parts of the central nervous system, as well as bones and articular cartilag-

es, prevail in the descendants of the second and third generations [1-4].

The study aimed to highlight the role of ionizing radiation in tumorigenesis.

Materials and methods: Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials was analyzed to select and analyze relevant information over the past 10 years using such keywords as "gamma irradiation," "spontaneous oncogenesis," and "prevention of oncogenesis."

Results:

Carcinogenicity. Radiation-induced cancer

Vast accumulated experimental material and clinical observations show that MNs can develop in almost any body tissue under the influence of ionizing radiation. However, the most common are MNs of the skin and bones, endocrine-dependent tumors (ovarian, breast, thyroid, and prostate cancers), and leukemias [5].

The absorbed dose and several other factors, like inherited body type, sex, age, and others, determine the probability of developing radiation-induced solid tumors and leukemias. The immunological and hormonal status, vascular trophism, cell kinetics, and other features can decisively affect tumor incidence [6-10]. Cancer was once considered a "genetic accident" that results from accumulating random (stochastic) DNA mutations. The stochastic effects, currently more associated with ionizing radiation effects, appear as mutations and then develop into latent genome damage and clinical manifestations such as oncological and genetic pathologies. Currently, there is a broad consensus that cancer is a result of both genetic and epigenetic changes. Several studies indicate that cancer is a failure of genome regulation due to the malfunction of mechanisms that regulate the antimutation activity and prevent epigenetic modification [11, 12]. Sharp changes in DNA methylation are common in cancer and are considered early events in many cancer cases. They appear even more frequent than genetic mutations [13-15]. Loss of methylation throughout the genome, especially in repetitive elements [16], contributes to gastrointestinal neoplasms and is a main sign of cancer [17, 18]. Over 300 genes and gene products are epigenetically altered in various types of human cancer [19]. A meta-analysis of altered genes in colorectal cancer confirms their involvement in oncogenesis [20].

The role of tumor suppressor gene hypermethylation in radiation-induced cancer was demonstrated. Suppression of the suppressor genes has been demonstrated in the studies in mouse models of radiation-induced lymphoma, lung tumors in rats, and lung adenocarcinoma in workers at the "Mayak" plutonium plant in Russia [21, 22]. The aberrant hypermethylation was observed in many patients with renal cell carcinoma living in areas radioactively contaminated after the Chornobyl Atomic Power Station accident [23]; the DNA hypermethylation of tumor suppressor genes was found in workers exposed to radon in uranium mines [24].

The above results indicate that radiation exposure, although generally considered pathogenic due to DNA damage such as deletions and point mutations [25], may also increase cancer risk due to epigenetic changes that increase genomic instability (GI) and/or the specific suppression of tumor suppressor genes.

It is now recognized that epigenetic and genetic changes are involved in cancer initiation and progression [26, 27]. Epigenetic changes also affect individual susceptibility to radiation-induced cancer. Differences in sensitivity to radiation between individuals or groups of individuals may be associated with gender, age at exposure, health status, genetic and epigenetic changes, lifestyle, and age lived [28].

Several studies have shown that epigenetic regulation underlies the radiation-induced instability of the transgenerational genome [29-33], i.e., radiation-induced damage can induce GI. Small doses of ionizing radiation induce cellular replication of primary and delayed dysgenic effects, resulting in a poly-genomic imbalance in the body and dysfunction of cells, tissues, and organs. This affects the differentiation processes by reducing the biological stability of the organism and increasing the risk of stochastic diseases, including MNs [34, 35]. At the cytogenetic level, the transmissible chromosomal instability is transmitted through the parents' irradiated germ cells to their offspring's somatic cells [36].

The most relevant radiation-induced changes include 1) radiation-induced epigenetic effects, i.e., changes in the gene expression, e.g., by altering the structure of DNA and chromatin without altering the DNA sequence; 2) nonlinear responses, such as non-target effects (NTES), i.e., effects observed in cells not directly exposed to radiation (side effects, BE) or occurring in the offspring of irradiated cells or observer cells (GI), as well as (radio)-adaptive response. All these NTES can be described as the expression of inter- or intracellular signaling and are considered particularly relevant for cellular response to low-dose radiation [8].

Molecular mechanism of radiation oncogenesis

Ionizing radiation can cause various DNA changes, including base damage, sugar-phosphate backbone damage, single-strand breaks, double-strand breaks (DSBs), and the DNA-DNA cross-links and DNA-protein cross-links. The clustered DNA lesions, such as complex DSBs and non-DSB clustered lesions, are the most biologically significant radiation-induced DNA damage [37-40]. Unrepaired or incorrectly repaired DNA damages cause changes in DNA sequence, the genetic mutations,

which are the main cause of harmful biological effects, and lead, even at low doses, to an elevated incidence of MNs and hereditary diseases inherent in the population [41]. The most common consequence of wrong reparations is the loss of heterozygosity. In addition to the gene with broken DNA, heterozygosity extends to proximal and distal genes. Wrong reparation leads to deletions and reciprocal translocations. They inactivate suppressor genes and proto-oncogenes, which leads to the induction of MNs (leukemias, lymphomas, and others). Expression of the TP53 gene network changes. The ST13, IER3, BRCAI, LRDD, and MRAS genes are the most significant predictors of carcinogenesis [8]. Structural and functional disorders of the genome of immunocompetent cells include an increased number of proliferating cells with CD71 marker and $CD95^+$ and $CD16^+$ cells, which are markers of readiness for apoptosis [42].

Main mechanisms of radiation-induced genetic and epigenetic changes

It is well known that ionizing radiation can cause DNA damage through direct accumulation of energy in DNA and indirect action of active chemical particles formed near DNA [38]. Radiation with high linear energy transfer (LET) mainly causes direct DNA damage, while radiation with low LET mainly leads to indirect DNA damage by free radicals in water. These radicals are formed by water radiolysis. Under aerobic conditions, these free radicals convert into reactive oxygen species (ROS); organic radicals appear, which produce peroxyl radicals and hydroperoxides [43]. Reactive nitrogen species (ANS), generated by radiation, produce nitric oxide, which reacts with superoxide radicals to form peroxynitrite [44]. The radiation quality modulates the output and spatial distribution of ROS and ANS. They can cause several changes, including DNA breaks, base damage, and destruction of sugars, which, if not addressed, can lead to genetic mutations in surviving cells. ROS can be generated directly by radiation and indirectly through mitochondrial damage. This activates the signal pathway that supports the elevation of ROS due to increased oxidase expression and creates a cycle of high oxidative stress, i.e., an excess of ROS/ANS, not compensated through mechanisms of antioxidant cell protection [45].

In addition to ROS and ANS mutagenic effects, there is evidence of a fundamental role oxidative stress plays in epigenetic modifications [46, 47]. Oxidative stress can modify the epigenome through various mechanisms, the most important of which include DNA base oxidation and changes in mitochondria, the primary target being the CpG sites, especially in CpG islets [48-50].

Discussion: Children exposed to radiation or radiation-chemical effects or born from irradiated or chemically exposed parents are at risk of developing stochastic pathologies, including genetic diseases, undifferentiated mental retardation, malignant neoplasms, leukemias, etc. According to international organizations [10], these effects can theoretically be caused by exposure of any magnitude. Stochastic effects, which are now largely attributed to the impact of ionizing radiation or other chemical, physical, and biological agents, reappear in various mutations. They increase the likelihood of spontaneous mutations registered under natural conditions and expressed as hidden genomic damage, ultimately resulting in oncological or genetic pathology.

Ionizing radiation causes direct damage to cell DNA and indirect cell damage by ROS impact. The resulting mutations of all types – chromosomal and genomic, single- and two-strand breaks (or other changes), – and cell repair disorders can lead to cell apoptosis, chromosomal instability, mutation, and/or oncogenesis.

The study of direct radiation effects in modern radiobiology and radiation medicine pays much attention to the dynamics of free radical oxidation of lipids, which are important energy substrates, and their role in developing "genome instability." The descendants of exposed persons present a pathological imbalance of "peroxidation/antioxidative defense" at the cellular (chromosomal aberrations, mutations, iatrogenic cell death, etc.) and cytogenetic levels. Chromosomal instability is transmitted through parental germ cells and manifests in somatic cells of the descendants. Low-intensity ionizing radiation does not kill the body cells but modifies cell-tissue processes. It activates free radical mechanisms, increases DNA breaks' frequency, accelerates aging, and intensifies apoptosis and compensatory cell proliferation.

The body responds by activating the reparative and compensatory-restorative processes. The genomic DNA repair system is an anti-mutagenic defense mechanism that restores the broken and/or lost DNA strands. The level of such protection is determined by genetic characteristics (how effectively the genotype of an individual or species forms the antitumor immune system, the genome repair system) and the intensity of oxidative stress – the lipid peroxidation and antioxidative defense ratio and interrelation.

These environmental risk factors affect the genetic apparatus responsible for precisely reproducing features and traits in generations and regulating all body processes. These factors underlie the current increase in the frequency of mutations, congenital deformities, and MNs. The most important environmental risk factors include air and drinking water pollution. Among the consequences are carcinogenesis, mutagenesis, embryo- and gonadotropic effects of physical and chemical agents, and relevant effects with long-term implications.

Since radiation acting independently or in combination with other exo- and endogenous factors increas-

es the risk of free radical and genomic damage, the descendants of exposed parents are at high risk of genetic consequences. Radiation-induced changes in the body have a phase character: at different times after the irradiation of parents, they are manifested by activation or inhibition of adaptive and, most importantly, reparative processes. Therefore, the study of the genesis and development of spontaneous MNs in descendants of irradiated parents is one of the priorities of radiation medicine. Prevention of such induced pathologies is a primary task of radiobiology, radiation medicine, oncology, and pediatrics.

Conclusion: Consequently, radiation-induced oxidative stress plays an important role in the epigenetic landscape of the entire genome [51]. This landscape is formed by cross-coupling effects of DNA methylation and histone and non-coding RNA (particularly microRNAs) modification [52, 53]. Genetic and epigenetic mechanisms may have a common origin in radiation-induced ROS/AFN and be the basis of the observed nonlinear phenomena. The carcinogenic effect of ionizing radiation is implemented through DNA damage, either direct or mediated by generated free radicals (ROS/AFN).

These damages might cause genetic and epigenetic changes that affect protein expression levels due to alterations in cytosine residues' methylation in DNA, histone modification, and microRNA expression regulation [54]. Finally, the results of this literature review (knowledge of mechanisms of carcinogenesis) allow the use of primary prevention strategies in the field of carcinogenesis from the points of genetic and/or epigenetic paradigms to contribute to the identification of innovative "informational" therapeutic strategies [55].

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АНДАТПА

ИОНДАУШЫ СӘУЛЕЛЕНУДІҢ КАНЦЕРОГЕНДІЛІГІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *ДДҰ деректері бойынша халық өлімінің құрылымында қатерлі ісіктердің (МНТ) үлесі екінші орында. Оның себебі – организмге тікелей канцерогенді әсер ететін және қорғаныс механизмдерін басатын техногендік факторлардың әсерінің үнемі артуы. Қатерлі ісіктің дамуында иондаушы сәулелер ерекше рөл атқарады. Ол өнеркәсіпте, ауыл шаруашылығында, медицинада және ғылыми зерттеулерде, заманауи денсаулық сақтауда диагностикалық құрал ретінде, сондай-ақ қатерлі ісіктерді емдеуге арналған сәулелік терапияда қолданылады. Радиациялық әсердің салдары денеге тікелей әсер етудің нәтижесі ғана емес, сонымен бірге ата-аналар мен ата-әжелер ұрпақтары арқылы кейінге қалдырылады. Радиобиологиялық гипотезаға сәйкес, сәулеленудің кез келген деңгейі, қаншалықты аз болса да, ұзақ мерзімді салдарлардың, соның ішінде қатерлі ісіктің, зардап шеккен адамдарда және олардың алғашқы екі ұрпақтарының ұрпақтарында қауіп төндіреді. Яғни, радиация әсерінің салдары қатерлі ісік болуы мүмкін. Иондаушы сәулеленудің төмен дозаларының биологиялық әсерінің әртүрлі теорияларының болуына қарамастан, авторлардың көпшілігі генетикалық әсерлердің көрінісінде ДНҚ-ның зақымдалуына бірінші кезектегі мән береді (табалдырықсыз мутациялық әрекет тұжырымдамасы).*

Зерттеудің мақсаты *– ісік пайда болудағы иондаушы сәулеленудің рөлін көрсету.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed, Cochrane бақыланатын сынақтардың орталық тізілімінің деректеріне талдау «гамма-сәулелену», «стихиялы онкогенез», «онкогенездің алдын алу» кілт сөздерін пайдалана отырып, соңғы 10 жылдағы сәйкес ақпаратты таңдау және талдау үшін жүргізілді.*

Нәтижелер: *радиациялық әсер эпигенетикалық өзгерістерге байланысты қатерлі ісіктің даму қаупін арттыруы мүмкін, бұл геномдық тұрақсыздықтың (GI) жоғарылауына және/немесе ісік супрессоры гендерінің спецификалық басылуына әкеледі. TP53 гендік желісінің экспрессиясында өзгерістер орын алады; канцерогенездің болжаушылары ретінде ең маңызды гендер ST13, IER3, BRCA1, LRDD, MRAS болып табылады. Эпигенетикалық өзгерістер жеке адамның радиациядан туындаған ісікке бейімділігіне де әсер етеді. ROS және AFN мутагендік әсерлерінен басқа, тотығу стрессінің эпигенетикалық модификацияларда іргелі рөл атқаратыны туралы дәлелдер де бар.*

Қорытынды: *Сәулелену әсерінің нәтижесінде генетикалық және эпигенетикалық өзгерістерді тудыратын зақымданулар пайда болады, бұл ДНҚ-дағы цитозин қалдықтарының метилденуінің өзгеруіне, гистондардың модификациясына және микроРНҚ экспрессиясының реттелуіне байланысты белок экспрессиясының деңгейінің өзгеруіне әкеледі.*

Түйінді сөздер: *гамма-сәулелену, спонтанды онкогенез, онкогенездің алдын алу.*

АННОТАЦИЯ

КАНЦЕРОГЕННОСТЬ ИОНИЗИРУЮЩЕГО ИЗЛУЧЕНИЯ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *По данным ВОЗ, злокачественные новообразования (ЗНО) находится на втором месте в структуре причин смертности населения. Поводом для этого служит постоянный рост влияния техногенных факторов, оказывающих прямое канцерогенное воздействие на организм и подавляющих защитные механизмы. Особая роль в развитии ЗНО отводится ионизирующему излучению. Оно используется в промышленности, сельском хозяйстве, медицине и научных исследованиях, как диагностическое средство в современном здравоохранении, а также в лучевой терапии – для лечения ЗНО. Радиационное облучение оказывает не только прямое действие на организм, но и отсроченное, через поколения родителей и прародителей. Согласно радиобиологической гипотезе, любой сколь угодно малый уровень облучения представляет риск возникновения отдаленных последствий, в том числе*

ЗНО, у облучённых людей и их потомков первых двух поколений. То есть ЗНО являются вероятными последствиями влияния радиации. Несмотря на существование различных теорий биологического действия малых доз ионизирующего излучения, большинство авторов придают повреждению ДНК первостепенное значение в возникновении генетических эффектов (концепция беспорогового мутационного действия).

***Цель исследования** – освещение роли ионизирующей радиации в онкогенезе.*

***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: «гамма-облучение», «спонтанный онкогенез», «профилактика онкогенеза».*

***Результаты:** Радиационное воздействие может повышать риск развития рака из-за эпигенетических изменений, приводящих к увеличению геномной нестабильности и/или специфическому подавлению генов-супрессоров опухоли. Происходят изменения экспрессии генной сети TP53; наиболее значимыми в качестве предикторов канцерогенеза являются гены ST13, IER3, BRCA1, LRDD, MRAS. Эпигенетические изменения также влияют на индивидуальную восприимчивость к радиационно-индуцированному раку. Помимо мутагенного действия активных форм кислорода и азота, есть также доказательства того, что окислительный стресс играет фундаментальную роль в эпигенетических модификациях.*

***Заключение:** В результате воздействия радиации происходят повреждения, вызывающие генетические и эпигенетические изменения, приводящие к изменению уровня экспрессии белков вследствие изменения метилирования остатков цитозина в ДНК, модификации гистонов и регуляции экспрессии микро-РНК.*

***Ключевые слова:** гамма-облучение, спонтанный онкогенез, профилактика онкогенеза.*

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MAJOR REASONS FOR HOSPITALIZATION TO ICU OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Acute lymphoblastic leukemia (ALL) is a common malignancy in children. Approximately 85% of ALLs have B-cell origin, and 15% are T-cell ALLs. Many patients diagnosed with hematologic cancer will require hospitalization in the intensive care unit (ICU) at some point in their treatment.*

The study aimed to *study the available literature on clinical deterioration in patients with ALL admitted to the ICU, the clinical significance and prognostic value of causes of clinical deterioration, and adverse outcomes in patients with ALL staying in the ICU.*

Methods: *A descriptive cross-sectional study approach was used. We reviewed published sources from 2016 to 2023 to collect data on major reasons for ALL patients' hospitalization to ICU.*

Results: *First, the patient's age at the time of initial diagnosis of ALL is crucial. Cure rates for B-cell ALL are higher between 1 and 9 years of age than in other age groups. Second, the initial white blood cell count during diagnosis is a prognostic indicator. Third, the specific subtype of ALL also affects prognosis. The risk factors emphasize the importance of comorbidities and infectious diseases, as well as monitoring and managing pulmonary and cardiovascular function in patients to avoid hospitalization in the ICU. The main causes of hospitalization in the ICU are complications related to chemotherapy, infection, and unplanned hospitalizations. Compared to normal-risk patients, high-risk patients had a higher rate of OIT hospitalization in the ICU. It is important to control chemotherapy and infections to reduce the number of admissions to the ICU in this group.*

Conclusion: *Chemotherapy, concomitant and infectious diseases, hypoxia, and hemodynamic instability are reasons for hospitalization of these patients to ICU. The condition of various organs and systems shall be monitored.*

Keywords: *children, clinical deterioration, intensive care unit, acute lymphoblastic leukemia (ALL), critical conditions.*

Introduction: Acute lymphoblastic leukemia (ALL) is one of the common malignant neoplasms (MNs) in childhood; it accounts for up to 80% of all leucosis. About 85% of ALL cases have B cell origin, and 15% have T cell origin [1]. ALL leads to anemia, leukocytosis, hyperleukocytosis, thrombocytopenia, leukopenia, neutropenia, or pancytopenia, and all these changes require extreme alertness in combination with clinical symptoms of ALL. The survival of children diagnosed with ALL has significantly improved over recent years. However, there are still patients who require admission to an intensive care unit (ICU) due to the worsening of their clinical condition. Timely detection of early warning signs of critical conditions in children with ALL before admission to ICU has vital importance [2]. Other criteria are clinically and physically important indicators of prognosis in ALL. They include age, number of leukocytes detected for the first time, genetic and immunophenotypic characteristics of the leukemic blast, and individual response to treatment [3]. Patients with ALL are admitted to ICU with various clinical symptoms, such as hyperthermia, hemorrhagic syndrome, sepsis, and respiratory and other organ failures. These clinical deteriorations are associated with infectious complications, toxicity of chemotherapy, or damage to the organ due to leukemia [4]. It is important to keep in mind that at a certain point of treatment, many patients diagnosed with "hematological cancer" might require hospitalization to ICU; this highlights the importance of using indicators for effective treatment selection [5]. Assessment of the number of residual leukemic blast cells in the bone marrow (minimal residual disease, MRD) at various stages of treatment of oncohematological patients is one of the main prognosis and risk stratification factors for ALL from B-lineage precursors [6]. The T-cell ontogenesis peculiarities allow unifying immunological approaches to assessing MRD at all stages of T-ALL therapy [7]. Neutrophilic granulocytes (NG) are an important component of the immune response. They have a wide range of mechanisms that promote the attraction of adaptive immune effectors to the site of inflammation, induction of their maturation, differentiation, proliferation, and activation. Impaired NG function can lead to inadequate activation of adaptive immune response effectors and the development of pathological conditions that threaten the life and health of patients [8]. It is worth noting that many patients suffer from immediate and long-term undesirable effects of antitumor treatment [9].

The study aimed to study the available literature on clinical deterioration in patients with ALL admitted to the ICU, the clinical significance and prognostic value of causes of clinical deterioration, and adverse outcomes in patients with ALL staying in the ICU.

Materials and Methods: A descriptive cross-sectional study approach was used. The authors searched PubMed, CyberLeninka, and Wiley for articles published in 2016-2023 to collect data on "early warning signs and causes of clinical deterioration in patients with ALL admitted to ICU." The search was made using keywords such as "clinical deterioration," "intensive care unit," "acute lymphoblastic leukemia," and "critical conditions." Secondary data was collected from four studies. We collected both quantitative and qualitative data. The findings were presented in a Table and a graph. Quantitative data was presented as frequency rates or percentages; qualitative data – was in the nominal form.

Results:

Prognostic factors for ALL. Table 1 presents several prognostic factors that determine outcomes in children with ALL. Age at diagnosis is the first significant factor. E.g., children with B-cell ALL aged 1 to 9 years demonstrate better outcomes than other age groups. Initial white blood cell (WBC) count at diagnosis is the second prognostic indicator: WBC count >50,000 cells/mm^3 indicates a higher risk to the patient. The ALL subtype also influences the prognosis since early B-cell ALL has a better prognosis than a mature B-cell leucosis (Burkitt's disease). Besides, there are gender differences: girls have better chances for recovery than boys. Finally, the response to initial treatment is decisive since an early remission characterized by a significant decrease in cancer cell count within 1-2 weeks of chemotherapy expects a better overall prognosis.

Table 1 – Prognostic factors for ALL [10]

Prognostic factors	Outcomes
Age at diagnosis	Children with B-cell ALL aged 1 to 9 years demonstrate better out-comes.
WBC count	A higher risk is associated with a WBC count >50,000 cells/mm^3 at diagnosis.
ALL subtype	Early B-cell ALL has a better prognosis than a mature B-cell leucosis (Burkitt's disease).
Gender	Girls might have a slightly better prognosis than boys.
Initial treatment	Early remission (a significant decrease in cancer cell count within 1-2 weeks of chemotherapy) expects a better prognosis.

Cohorts, admitted to ICU for ALL, in the study by Ranta S. et al. Fig. 1 provides research data on admission to ICU split by gender and cell type. In each category, they calculated those admitted to ICU and those who did not require ICU hospitalization. No differences by gender or mean age at admission to ICU were registered among 637 patients in the Ranta et al. study. By type of precursors, 24.7% of patients with B-cell ALL and 56.6% of patients with T-cell ALL required admission to ICU. This data provides insight into the distribution of ICU admissions by gender, cell types, and mean age.

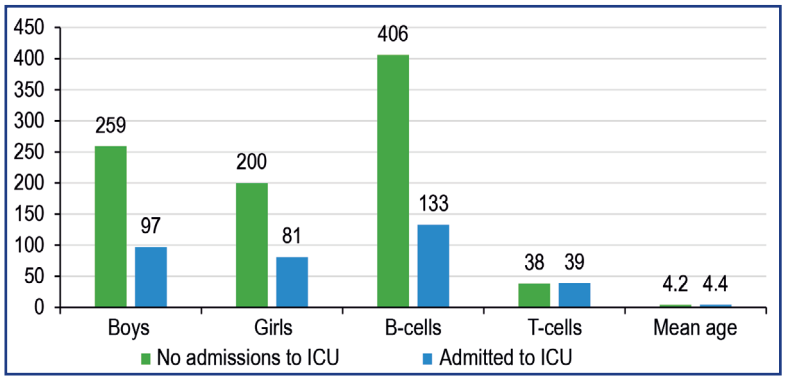

Figure 1 – Cohorts admitted to ICU [11]

Three major reasons for admission to ICU in the retrospective cohort study by Leahy A.B. et al. The research data in Table 2 indicates three major reasons for admission to ICU of children with ALL. Accordingly, 25.6% were admitted for factors related to chemotherapy. At that, high-risk patients had one median of admissions (0 to 23 range), with no patients with a standard risk of admission (0 to 21 range). Infection-related factors caused other 49.1% of cases, including three admissions on average among high-risk patients (0 to 26 range) and two admissions on average among standard-risk patients (0 to 20 range). Unscheduled admissions accounted for 24.3%, including one admission on average among high-risk and standard-risk patients each (0 to 22 range). This evidences that factors related to chemotherapy and infections significantly contribute to ICU admission of children with ALL and highlights the importance of managing these aspects of care to reduce the risk of ICU admissions in this population.

Table 2 – Major reasons for admission to ICU [12]

Variable	All admis-sions	High-risk patients (median value)	Standard-risk patients (median value)
Chemotherapy-related factors	26.5%	1 (0-23 range)	0 (0-21 range)
Infection-related fac-tors	49.1%	3 (0-26 range)	2 (0-20 range)
Unscheduled referral	24.3%	1 (0-22 range)	1 (0-22 range)

Discussion: Different studies show that some clinical and laboratory prognostic markers have lower prognostic value in B-ALL than T-ALL. At the same time, other criteria, like time to relapse or location of relapse, are important factors for survival with B-ALL [13]. Similar studies in low- and middle-income countries found the age, gender, and initial WBC count to be prognostic markers for ALL in children [14]. In a separate study, children below 15 years had a very good prognosis with ALL (the survival rate exceeded 85%), which got worse with age. An ALL relapse is still the main reason for cancer death in all ages [15]. The literature reviews showed that age at diagnosis, initial WBC count, ALL type and subtype, and initial response to treatment are important prognostic factors. Still, other factors like genetic abnormalities and relapse also play a role in determining prognosis. According to Dendir et al., comorbidities are typical risk factors for patients with ALL admitted to ICU since they contribute to higher ICU mortality [16]. In Ungar et al.'s study, infectious diseases were another reason for ICU admission [17]. Those risk factors emphasize the importance of monitoring and treating concomitant and infectious diseases and respiratory and cardiovascular disorders in patients to minimize ICU admissions. The above data describes major reasons for children with ALL admission to ICU. According to a study in Canada, cancer patients can require admission to ICU for bleeding or infection, usually during or after chemotherapy or bone marrow transplantation [18]. Other reasons for ICU admissions are intracranial hemorrhage or brain infarction. Finally, septicemia or severe sepsis, a serious bloodstream infection, also often requires ICU care, even when mechanical ventilation is not needed [19].

In general, reasons for ICU admission vary depending on factors such as patient age and gender and hospital type and location. Still, Kalicińska et al. mentioned breathing, heart, kidney problems, and sepsis as common reasons for ICU admission and long stay [20]. Vijenthira et al. reported that reasons for ICU admission of patients with hematological malignancies included infections and febrile neutropenia, pain, elevated creatinine and lactate dehydrogenase, and decreased albumin [21]. In a nationwide cohort study in Denmark by Maeng et al., ICU admission of patients with ALL was associated with high mortality [22]. In the study by McLaughlin et al., respiratory rate and increase in FiO_2 compared to the baseline level 24 hours before ICU admission were statistically significant, suggesting that changes in these vital signs are most predictive for ALL treatment outcomes [23]. The above studies indicate that chemotherapy- and infection-related factors were major reasons for ICU admission. The findings show that managing chemotherapy-related factors and infections is important to reduce the ICU admission risk for patients with ALL.

Table 3 provides cumulative findings of the studies included in the analysis.

Table 3 – Reasons for ICU admission according to different studies

Variable	Leahy et al., 2018	Dendir et al., 2023	Society of Critical Care Medicine, 2023	Kalicińska et al., 2020	Vijenthira et al., 2020
Respiratory sys-tem		+	+	+	
Cardiac system		+		+	
Kidney system				+	+
Sepsis (infectious diseases)	+		+	+	+
Comorbidities		+			
Pain syndrome					+
Chemotherapy-related	+		+		
Bleeding			+		

Conclusion: In general, the search findings show the need for additional research on the reasons for ICU admission of children with hematological malignancies. The provided data summarizes the reasons for ICU admission: they are related to chemotherapy and infections, concomitant diseases, and respiratory, cardiac, and renal dysfunction. This data is important for patient management and treatment. Monitoring and treatment of concomitant and infectious diseases and dysfunctions of organs of various systems is vital to reduce or prevent the hospitalization to ICU of patients with ALL.

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АНДАТПА

ЖЕДЕЛ ЛИМФОБЛАСТИКАЛЫҚ ЛЕЙКЕМИЯМЕН АУЫРАТЫН БАЛАЛАРДЫ ҚАРҚЫНДЫ ЕМДЕУ БӨЛІМІНЕ ЖАТҚЫЗУДЫҢ НЕГІЗГІ СЕБЕПТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Балалардағы қатерлі ісіктердің кең таралған түрлерінің бірі жедел лимфобластикалық лейкемия (ЖЛЛ). Шамамен 85 пайызы В-жасушалы және 15 пайызы Т-жасушалы ЖЛЛ барлық жағдайларынан. Гематологиялық қатерлі ісік диагнозы қойылған көптеген науқастар емдеудің белгілі бір кезеңінде қарқынды емдеу бөлімшесіне (ҚЕБ) жатқызуды қажет етеді.*

Зерттеудің мақсаты *– ҚЕБ-қа жатқызылған ЖЛЛ науқастарның клиникалық нашарлауы туралы өзекті әдеби деректерді зерттеу болып табылады. Олардың клиникалық маңыздылығы және ҚЕБ-ғы ЖЛЛ науқастардың клиникалық нашарлау себептері мен жағымсыз нәтижелердің болжамдық мәні.*

Әдістері: *Көлденең зерттеуге сипаттамалық тәсіл қолданылды. Біз 2016-2023 жылдар аралығында жарияланған дереккөздерді талдап, ЖЛЛ науқастарды ҚЕБ-қе жатқызудың негізгі себептері туралы деректерді жинадық.*

Нәтижелер: *Біріншіден, ЖЛЛ диагнозын алғаш рет қойғанда науқастың жасы өте маңызды. В-жасушалық ЖЛЛ емдеу басқа жас топтарына қарағанда 1 жастан 9 жасқа дейінгі аралықта жоғары нәтижелі. Екіншіден, диагноз қойылған кездегі лейкоциттердің бастапқы саны болжамды көрсеткіш болып табылады. Үшіншіден, ЖЛЛ-дің белгілі бір түрі емдеу болжамына әсер етеді. Тәуекел факторлар қосымша және жұқпалы аурулар, өкпе мен жүрек-қантамыр жүйесінің функцияларын бақылаудың және басқарудың маңыздылығын атап көрсетеді. ҚЕБ жатқызудың келесі негізгі себептері химиотерапиямен, инфекциямен және жоспардан тыс ауруханаға жатқызумен байланысты асқынулар болып табылады. Қалыпты қауіпті науқастармен салыстырғанда, жоғары қауіпті науқастарда ҚЕБ жатқызу жиілігі жоғары болды. Осы топ арасында ҚЕБ жатқызуды азайту үшін химиотерапия мен инфекцияларды бақылау маңызды болып табылады.*

Қорытынды: *химиотерапия, қосымша және жұқпалы аурулар, гипоксия және гемодинамиканың тұрақсыздығы – бұл науқастарды ҚЕБ жатқызудың қосымша себептері. Әр түрлі органдар мен жүйелерді бақылау өте маңызды.*

Түйінді сөздер: *балалар, клиникалық нашарлау, қарқынды емдеу бөлімі, жедел лимфобластикалық лейкемия, жағдайдың нашарлауы.*

АННОТАЦИЯ

ОСНОВНЫЕ ПРИЧИНЫ ГОСПИТАЛИЗАЦИИ В ОТДЕЛЕНИЕ ИНТЕНСИВНОЙ ТЕРАПИИ ДЕТЕЙ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Одним из распространенных видов злокачественных новообразований у детей является острый лимфобластный лейкоз (ОЛЛ). Примерно 85 процентов имеют В-клеточное происхождение и 15 процентов Т-клеточное ОЛЛ от всех случаев заболевании. Многим пациентам с диагнозом «гематологический рак» на определённом этапе лечения требуется госпитализация в отделения интенсивной терапии (ОИТ).*

Цель исследования *– изучение литературных данных о клинических ухудшениях пациентов с ОЛЛ, госпитализированных в ОИТ, определение клинической значимости и прогностической ценности причин клинического ухудшения и неблагоприятных исходов у пациентов с ОЛЛ, госпитализированных в ОИТ.*

Методы: *Использовался подход «описательное поперечное исследование». Авторы изучили источники, опубликованные с 2016 по 2023 годы, по основным причинам госпитализации в ОИТ пациентов с ОЛЛ.*

Результаты: *Во-первых, решающее значение имеет возраст пациента во время постановки первичного диагноза ОЛЛ. Излечения В-клеточного ОЛЛ выше в возрасте от 1 до 9 лет, чем в других возрастных группах. Во-вторых, начальное количество лейкоцитов на момент постановки диагноза служит прогностическим показателем. В-третьих, конкретный подтип ОЛЛ также влияет на прогноз. Факторы риска подчеркивают важность сопутствующих и инфекционных заболеваний, мониторинга и ведения функций легких и сердечно-сосудистой системы у пациентов во избежание госпитализации в ОИТ. Основными причинами госпитализации в ОИТ являются осложнения, связанные с химиотерапией, с инфекцией и внеплановые госпитализации. По сравнению с пациентами с нормальным риском, у пациентов с высоким риском частота госпитализации в ОИТ была выше. Чтобы уменьшить количество госпитализаций в ОИТ среди этой группы, важно контролировать химиотерапию и инфекции.*

Заключение: *Химиотерапия, сопутствующие и инфекционные заболевания, гипоксия и гемодинамическая нестабильность являются причинами госпитализации этих пациентов в ОИТ. Очень важен мониторинг различных органов и систем.*

Ключевые слова: *дети, клиническое ухудшение, отделение интенсивной терапии, острый лимфобластный лейкоз (ОЛЛ), критические состояния.*

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MODIFIABLE RISK FACTORS FOR COLORECTAL CANCER DEVELOPMENT: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Colorectal cancer (CRC) is one of the most commonly diagnosed types of cancer worldwide. CRC incidence has increased in Kazakhstan, as in many other countries in the past decade. Therefore, it is important to identify risk factors contributing to this pathological process to develop primary prevention programs at regional and national levels.*

The study aimed to *investigate modifiable risk factors for the development of colorectal cancer.*

Methods: *A systematic search was conducted in electronic databases, including PubMed, Cochrane Library, eLibrary, CyberLeninka, and Google Scholar. The study included reports of randomized and cohort studies conducted on large populations, meta-analyses, systematic reviews, and original full-text articles in English and Russian, available in open access and containing statistically validated conclusions. Exclusion criteria encompassed brief reports, newspaper articles, and personal communications. The search depth covered ten years (2012-2022).*

Results: *Published data reflect the significant influence on the development of colorectal cancer (CRC) of modifiable risk factors such as dietary habits, smoking, alcohol consumption, obesity, and physical inactivity.*

Conclusion: *CRC is a polyetiological disease that arises under the influence of both internal and external factors. However, only 25-30% of CRC cases are associated with non-modifiable risk factors, such as genetic factors, personal history of polyps, and inflammatory bowel diseases. 70-75% of CRC cases occur sporadically and are linked to modifiable risk factors, including smoking, alcohol consumption, unhealthy diet, sedentary lifestyle, lack of physical activity, and obesity.*

Keywords: *colorectal cancer (CRC), epidemiology, risk factor, Republic of Kazakhstan.*

Introduction: Colorectal cancer (CRC) is a collective concept that includes malignant neoplasms of various parts of the colon and rectum.

According to global cancer statistics for 2022, CRC is the third most common cancer among the adult population of the planet. Notably, the share of CRC is 8% among all malignant neoplasms in both women and men. That is, the global nature of the problem of the prevalence of CRC can be clearly seen from the global and regional statistics [1-3].

According to JSC KazNIIOiR, in 2022 in the Republic of Kazakhstan, CRC was in third place in the structure of malignant neoplasms (9.3%, 3654 cases) and the structure of mortality (10.7%, 1,242 cases) [4].

CRC is a polyetiological disease caused by the interaction of genetic (endogenous) and modifiable exogenous factors. However, cumulative epidemiological data based on meta-analyses of 5000 cases and 5000 controls showed an association between the development of CRC and hereditary factors of gene mutations [5-8]. People with hereditary disorders such as familial adenomatous polyposis (FAP), hereditary non-polyposis CRC (Lynch syndrome), and MUTYH gene-associated polyposis make up only 5% of patients with CRC.

CRC predominantly affects older people, with most cases occurring in people aged 50 years and older. However, about 11% of CRC cases are registered in people under the age of 50 years [9]. Modifiable factors, such as physical activity, dietary patterns, and bad habits, play an important role in CRC development in youngsters.

Therefore, studies of modifiable risk factors for the development of CRC are of great scientific and practical significance. The role of primary prevention, based on understanding the etiology of the pathological process, in the fight against CRC necessitates improving approaches to forming risk groups when conducting screening programs, considering the factors to which patients are exposed.

The study aimed to investigate modifiable risk factors for the development of colorectal cancer.

Materials and methods: A systematic search was conducted in electronic databases PubMed, Cochrane Library, eLIBRARY, CyberLeninka, and Google Scholar. The study included reports of randomized and cohort studies conducted on large populations, meta-analyses, systematic reviews, original full-text articles in English and Russian, open access, and containing statistically confirmed conclusions. Exclusion criteria: brief reports, newspaper articles, paywalled articles, abstracts, and personal communications. The search depth was 10 years (2013-2023). The selection algorithm produced 5085 articles. The final analysis included 35 sources that were tested for relevance.

Results: CRC is a common complex disease caused by a combination of endogenous (genetic) and exogenous factors, such as diet and bad habits.

FAP is a fairly rare inherited disease that accounts

for less than 1% of CRC cases. FAP is inherited in an autosomal dominant manner and occurs in approximately 1/8300 newborns with equal frequency in both sexes [10].

It is extremely rare (up to 1% of all cases in the world) that mutations in the MUTYH gene cause colon cancer. MUTYH-associated polyposis is the only polyposis syndrome with an autosomal recessive mode of inheritance, often phenotypically similar to an attenuated form of familial adenomatosis of the colon. Mutations in both alleles of the gene are required to develop the disease, but an increased risk of developing CRC has been noted in carriers of monoallelic mutations. The diagnosis of MUTYH-associated polyposis should be suspected in cases of CRC in a patient over 45 years of age in the presence of polyps in the colon [11, 12].

In turn, age is one of the important factors with which the development of this disease is most clearly associated. The likelihood of developing CRC increases as the body ages. More than 90% of patients with CRC are over 50 years old; the average age of patients with CRC is about 60 years. Thus, after 50 years, the risk of developing CRC doubles in each subsequent decade of life [13].

The incidence of CRC has steadily decreased among patients aged 50 years and older, but the opposite trend has been observed among younger people. Thus, in the United States, the incidence of local, regional, and distant colon and rectal cancer at the age of 20-34 years, as well as rectal cancer at the age of 35-49 years, has increased. Based on current trends, by 2030, the incidence of colon and rectal cancer will increase by 90.0% and 124.2% in patients of 20-34 years old and by 27.7% and 46.0% in patients of 35-49 years, respectively [14]. Notably, CRC incidence has increased exclusively in young people in eight high-income countries spanning three continents (Australia, Finland, New Zealand, Norway, Sweden, etc.), potentially signaling changes at an early age. Influencing colon carcinogenesis [15].

Thus, an increasing trend in diagnosing a young onset of CRC before 50 years is observed worldwide. Consequently, modifiable factors, such as lifestyle and dietary habits, play a large role in developing this pathology.

A clear link has been identified between the consumption of ultra-processed foods and the development of CRC. Scientists from Tufts Research University (Massachusetts, USA) conducted a study in which more than 200 thousand people over 25 participated. The participants were given a list of 130 products and had to mark the foods they often consume. The relationship between the presence of CRC in the participants and their diet was analyzed based on the data obtained. People who liked to snack on sausage, bacon, ham, and sausages were at risk. From this, it can be concluded that high consumption of fully processed foods, regardless of gender, is associated with an increased risk of developing CRC [16-18].

The main concerns regarding the risk of developing CRC are food additives that improve palatability, nutritional value, and shelf life, including food colors, sweeteners (saccharin, cyclamate, aspartame), antioxidants, and nitrites. The role of low-calorie and low-nutrient sweeteners in carcinogenesis has been widely debated over the past few decades. Thus, aspartame studies have shown that it increases chromosomal aberrations and DNA fragmentation in the liver and bone marrow of maternal albino rats and their offspring [19]. Therefore, the genotoxicity and carcinogenicity of food additives such as saccharin and aspartame are likely, and caution should be exercised regarding their consumption. Currently, there is no reliable data on the effect of nutritional supplements on the development of CRC alone. There is only a prospective epidemiological study that provides convincing evidence of their general carcinogenic potential [20].

Regarding preventing CRC based on dietary changes, in 2011, scientists from the UK and the Netherlands conducted a meta-analysis of prospective observational studies examining the association of high dietary fiber intake, in particular grains and whole grains, with a reduced risk of developing CRC. Whole grains are important sources of dietary fiber and may reduce the risk of developing CRC by increasing stool bulk, diluting fecal carcinogens, and reducing contact between carcinogens and the colon mucosa by reducing transit time. Fiber, fermented by the intestinal microbiota, leads to the formation of short-chain fatty acids, which resist the malignant transformation of intestinal cells. Other components of whole grains, such as antioxidants, vitamins, trace elements, phytates, phenolic acids, lignans, and phytoestrogens, also positively affect bowel function. At the same time, whole grains are high in folic acid and magnesium, the consumption of which reduces the risk of CRC [21].

Researchers from the World Cancer Research Fund and the American Institute for Cancer Research have found that drinking more than 30 grams of ethyl alcohol in alcoholic beverages per day is a strong cause of CRC in men and a likely cause in women. According to a meta-analysis that included results from 16 cohort studies of more than 6,300 patients with CRC, increased alcohol consumption was associated with an increased risk of CRC, with the risk increasing by 15% for every 100 g of pure alcohol per week. High alcohol consumption (>24.6 g/day) has been associated with an increased risk of CRC [22, 23].

Cigarette smoking increases the risk of CRC in a dose- and duration-dependent manner and smoking cessation reduces the risk of CRC. The risk of CRC increases linearly with the intensity and duration of smoking. However, it is worth noting that former smokers who have quit smoking for more than 25 years have a significantly reduced risk of developing CRC compared to current smokers [23-25].

Obesity is associated with significant metabolic and endocrine abnormalities, including changes in sex hormone metabolism, insulin, insulin-like growth factor signaling, adipokines, or inflammatory pathways. Cellular and molecular mechanisms that change during car-

cinogenesis may be associated with obesity, but the mechanism by which obesity influences the development of CRC is not fully established. It is believed to be due to hyperinsulinemia [26-29].

In observational studies, glycemic features such as hyperinsulinemia (i.e., high fasting insulin levels) support a causal influence on the increased risk of CRC. Therefore, pharmacological interventions or lifestyle changes that reduce circulating insulin levels may be useful in preventing colorectal tumorigenesis [30-33].

Independent of exercise and obesity, long periods of sedentary television viewing, a surrogate for an inactive lifestyle, were associated with an increased risk of early-life CRC, particularly in the rectum. These results further prove the importance of maintaining an active lifestyle [34, 35].

Discussion: According to the analysis of foreign and domestic literature, the cause of the development of CRC is the simultaneous influence of endogenous and exogenous factors, which consistently contribute to the tumor phenotype. The analysis showed convincing evidence of the influence of modifiable factors caused by the spread of the "Western" lifestyle. We assume that giving up bad habits and sufficient physical activity reduces the risk of developing this pathology, but this requires larger studies.

Conclusion: CRC is widespread globally and annually claims the lives of approximately 500 thousand people. Public health is faced with the problem of diagnosing this disease since, in most cases, the disease in the early stages is asymptomatic, and the cause of CRC is a whole complex of reasons. It should be noted that only 25-30% of CRC cases are associated with non-modifiable risk factors such as genetic factors, personal history of polyps, and inflammatory bowel disease. 70-75% of CRC cases occur sporadically and are associated with modifiable risk factors such as smoking, alcohol consumption, unhealthy diet, sedentary lifestyle, physical inactivity, and obesity. Therefore, improving the primary prevention program at the state level is necessary, focusing on younger people exposed to modifiable risk factors for developing CRC.

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АНДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІК ДАМУЫНЫҢ МОДИФИЦИРУЛАЙТЫН ҚАУІП ФАКТОРЛАРЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Колоректальды қатерлі ісік (КҚІ) – қатерлі ісік профиліндегі ең көп таралған орындардың бірі. Қазақстанда, әлемнің көптеген елдеріндегідей, соңғы онжылдықта КҚІ-пен халықтың ауырушаңдығының артуы байқалады. Демек, аймақтық және мемлекеттік деңгейлердің бастапқы алдын алу бағдарламаларын әзірлеу үшін, осы патологиялық процеске әкелетін қауіп факторларын білу маңызды.*

Зерттеудің мақсаты *– колоректальды қатерлі ісік ауруының модифицирулайтын қауіп факторларын зерттеу.*

Әдістері: *PubMed, Cochrane library, elibrary, Cyberleninka, Google Scholar электрондық дерекқорларында жүйелі іздеу жүргізілді. Зерттеуге үлкен популяцияларда жүргізілген рандомизацияланған және когорттық зерттеулер туралы есептер, мета-талдаулар және жүйелі шолулар, ашық қолжетімді және статистикалық расталған қорытындылары бар ағылшын және орыс тілдеріндегі түпнұсқа толық мәтінді мақалалар кірді. Ерекшелік критерийлері: қысқаша есептер, газет мақалалары және жеке хабарламалар. Іздеу тереңдігі 10 жыл болды (2012-2022).*

Нәтижелері: *жарияланған деректер диета, темекі шегу, алкогольді тұтыну, семіздік және физикалық белсенділік сияқты колоректальды қатерлі ісіктің дамуына өзгертілетін қауіп факторларының елеулі әсерін көрсетеді.*

Қорытынды: *КҚІ-бұл ішкі және сыртқы факторлардың әсерінен пайда болатын полиэтиологиялық ауру. Алайда, КРР жағдайларының тек 25-30% - ы генетикалық факторлар, полиптердің жеке тарихы және ішектің қабыну аурулары сияқты өзгермейтін қауіп факторларына байланысты. КРР жағдайларының 70-75%-ы анда-санда пайда болады және темекі шегу, алкогольді тұтыну, дұрыс емес тамақтану, отырықшы өмір салты, физикалық белсенділіктің болмауы, май басу сияқты өзгертілетін қауіп факторларына байланысты болады.*

Түйінді сөздер: *колоректальды қатерлі ісік (КҚІ), эпидемиология, қауіп факторы, Қазақстан Республикасы.*

АННОТАЦИЯ

МОДИФИЦИРУЕМЫЕ ФАКТОРЫ РИСКА РАЗВИТИЯ КОЛОРЕКТАЛЬНОГО РАКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Колоректальный рак (КРР) – это одна из самых часто встречающихся локализаций онкологического профиля. В Казахстане, как и в большинстве стран мира, в последнее десятилетие отмечается увеличение заболеваемости населения КРР. Следовательно, важно знать факторы риска, приводящие к данному патологическому процессу, для разработки программ первичной профилактики как регионального, так и государственного уровней.*

Цель исследования *– изучение модифицируемых факторов риска развития колоректального рака.*

Методы: *Проведен систематический поиск в электронных базах данных PubMed, Cochrane library, eLIBRARY, CyberLeninka, Google Scholar. В исследование включались отчеты о рандомизированных и когортных исследованиях, проведенных на больших популяциях, мета-анализы и систематические обзоры, оригинальные полнотекстовые статьи на английском и русском языках, находящиеся в открытом доступе и содержащие статистически подтвержденные выводы. Критерии исключения: краткие отчеты, газетные статьи и личные сообщения. Глубина поиска составила 10 лет (2013-2023).*

Результаты: *Опубликованные данные отражают значительное влияние на развитие КРР модифицируемых факторов риска, таких как особенности рациона питания, курение, употребления алкоголя, ожирения и гиподинамия.*

Заключение: *КРР является полиэтиологическим заболеванием, которое возникает под влиянием как внутренних, так и внешних факторов. Однако всего лишь 25-30% случаев КРР связаны с немодифицируемыми факторами риска, такими как генетические факторы, личный анамнез полипов и воспалительные заболевания кишечника. 70-75% случаев КРР возникают спорадически и связаны с модифицируемыми факторами риска, такими как курение, употребление алкоголя, нездоровое питание, малоподвижный образ жизни, отсутствие физической активности, ожирение.*

Ключевые слова: *колоректальный рак (КРР), эпидемиология, фактор риска, Республика Казахстан.*

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PHOTODYNAMIC THERAPY FOR CERVICAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Cervical cancer is a significant public health problem worldwide, with human papillomavirus infection playing a vital role as a risk factor. Photodynamic therapy is a minimally invasive treatment for HPV-related cervical lesions that uses photosensitizers and light to destroy abnormal cells selectively.*

The study aimed to *review the different types of molecules used in PDT to reduce the morbidity and mortality associated with cervical cancer.*

Methods: *We conducted a comprehensive search for all relevant articles investigating the ef-ficacy and safety of PDT in the treatment of HPV-associated cervical cancer. We determined PICO scores for the review and performed a literature search of the PubMed database. An examination of the PubMed online database using keyword combinations identified 71 studies conducted between 2013 and 2023 that investigated using PDT to treat RSM cells.*

This article reviews ongoing clinical trials examining the efficacy of PDT in treating low-grade squamous cell intraepithelial neoplasia and high-grade squamous cell intraepithelial lesions, as well as preclinical approaches using different molecules for PDT in cervical cancer.

Results: *Potential molecules for PDT are described, their advantages and disadvantages evalu-ated, and solutions to improve their compatibility with antitumor treatment are proposed. Our review shows that PDT is a promising therapeutic approach for diagnosing and treating HPV-related cervi-cal lesions. At the same time, we observe that using different classes of dyes enhances the anticancer effects of PDT.*

Conclusion: *Fullerene and ALA-PDT are potential leaders for more intensive use in PDT, which will further help reduce the global incidence and mortality from cervical cancer. However, further studies are needed to evaluate its long-term efficacy and safety.*

Keywords: *cervical cancer; human papillomavirus (HPV); Photodynamic therapy (PDT); Squamous intraepithelial neoplasia.*

Introduction: Cervical cancer (CC) is one of the leading causes of cancer mortality among women worldwide [1]. The presence of human papillomavirus (HPV) is a significant factor contributing to the development of cervical cancer [2]. Traditional methods of diagnosis and treatment often face difficulties in detecting and treating precancerous lesions that precede the onset of cancer. The cell lining of the cervix can cause a variety of precancerous lesions, including cervical dysplasia – cervical intraepithelial neoplasias (CIN1, CIN2, CIN3), high-grade squamous intraepithelial lesions (HSIL), and low-grade squamous intraepithelial lesions (LSILs).

LSIL specifies the mildest form of these lesions, while CIN2 is in the intermediate category, and CIN3 represents the most severe condition. HSIL includes CIN2 and CIN3 and is considered a high-risk cervical cancer precursor. If left untreated, HSIL has a higher chance of progression to cancer compared to CIN1 or LSIL. In order to overcome this obstacle, scientists have developed an innovative technology that aims to improve the diagnosis and treatment of primary and precancerous cervical lesions associated with HPV [3]. This technology is a photodynamic therapy (PDT), which is a minimally invasive therapeutic method that uses photosensitizers (PS) and light for targeted action and elimination of abnormal cells [3].

The new approach includes a combination of a fluorescent dye and a specialized imaging system, which facilitates visualizing cervical lesions in real time [4, 5]. During that procedure, the cervix is covered with PS, and the target area is exposed to a specific wavelength of light [6]. This process triggers PS to generate the reactive oxygen species that selectively destroy abnormal cells [7]. By precisely targeting the affected cells, this method reduces the risk of damage to healthy tissues, thereby increasing the effectiveness of treatment [8]. In addition, the applied imaging system provides an accurate and effective identification of cervical lesions associated with HPV [9]. Early detection of these lesions with this technology could lead to more effective treatment and improved patient outcomes [4, 10].

The PDT introduction highlights significant progress in the diagnostics and treatment of HPV-related cervical lesions. Choosing a suitable dye is an important aspect when working with PDT. Over the years, various

molecules have been used in this technique. However, it is crucial to identify and evaluate these molecules to develop the new PS with higher antitumor activity and more excellent usability [11].

The study aimed to review the different types of molecules used in PDT to reduce the morbidity and mortality associated with cervical cancer.

Materials and Methods: A comprehensive search was conducted for all relevant articles investigating the efficacy and safety of PDT in the treatment of HPV-associated cervical cancer. Numerous studies examining the application of PDT in this area were reviewed, focusing on photochemotherapy, nanoparticles, and PS agents.

PICO scores were determined for the review, and a literature search of the PubMed database was performed, where P (population) = women with HPV-associated cervical cancer; I (intervention, exposure in our case) = PDT; C (comparison group) = Placebo or other treatment method groups, and O (outcome) = PDT clinical efficacy and safety.

The PubMed online database has been examined to find relevant articles related to the research topic. The search process lasted from April to July 2023. The VOS viewer tool (Centre for Science and Technology Research, Leiden University, Netherlands) was also used to identify the research topic's concept, keywords, and authors. Combinations of the following terms were used in the search: CIN1, CIN2, CIN3, HSIL, LSIL, CERVICAL CANCER, HPV, and PDT.

Results: A study of the online database PubMed identified 71 studies conducted from 2013 to 2023 that investigated the use of PDT to treat cervical cancer. Of these, 13 clinical trials were identified as studying the HPV-associated early stages of cervical cancer (Table 1).

Table 1 – Studies on PDT in cervical cancer according to PubMed, 2013-2023

#	Author, Year, Study Design	Intervention	Efficiency
1	Choi et al., 2013 Retrospective study [20]	Photogem IV and red laser light with a wavelength of 630 nm (CERALAS, Germany), 150 J/cm^2. Group 1: PDT only Group 2: PDT + LEEP/Cone Group 3: PDT within 3 months of LEEP/cone. Group 4: PDT 12 months after LEEP/Cone due to CIN recurrence.	Complete response for high-frequency HPV DNA: • 3-month follow-up: 89.8% (44/49); • 12-month follow-up period: 87,0% (40/46); Complete response to PDT at 12 months follow-up: 98.1% (52/53) Group 1: CIN2: 100% (2/2), CIN3: 100% (6/6), CIS: 80% (4/5). CRR=100% (13/13)
2	Hillemanns et al., 2014 Clinical study [21]	The experimental group (EG) – HAL vaginal suppositories 100 mg; red coherent light with a wavelength of 633 nm (Biolitec, Germany), 50 J/cm^2 Control group (CG) – only Placebo vaginal suppositories + PDT, only follow-up	Complete response for CIN1 after 6 months: • EG: 57.1% (20/35) • CG: 25.0% (4/16) [Placebo + PDT: 40.0% (4/10) and follow-up group: 0% (0/6)], p=0.040 Complete response for HPV • EG: 73,3% (11/15) • CG: 50% (5 of 10) [Placebo + PDT: 28.6% (2 of 7) and follow-up group: 100% (3 of 3)], p=0.397
3	Hillemanns et al., 2014 Clinical study [22]	Topical HAL hydrochloride treatment 0,2%, 1%, 5% EG1: HAL 5% EG2: HAL 1% EG3: HAL 0.2% CG: Placebo	There was no statistically significant result in CIN1 and CIN1/2 and in HAL1% and HAL0.2% com-pared to the Placebo group Complete response in CIN2: After 3 months: EG – 95% (18/19), Placebo – 57% (12/21), p=0,009. After 6 months: EG – 95% (18/19), Placebo – 62% (13/21), p=0.021 Complete response for high HPV risk: After 3 months: EG – 83% (5/6), Placebo – 0% (0/6) After 6 months: EG – 83% (5/6), Placebo – 33% (2/6) Dose-dependent response for CIN2+HPV eradica-tion: After 6 months: HAL5% – 84% (16/19), HAL1% – 48%. (14/29), HAL0.2% – 42% (8/19), Placebo – 38% (8/21)
4	Fu et al., 2016 Prospective study [23]	EG – Local PDT with 5-ALA (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd.) with 635 nm diode laser (LD600-C; Wuhan Yage Photo-Electronic Co. Ltd, Wuhan, China), light irradiation 100 J/cm^2; CG – untreated	• 3-month follow-up period for VR-HPV remission: Complete response: 64.10% in EC vs. 24.32% in CG (x^2=12.152, p<0.01) • 9-month follow-up for VR-HPV remission: Com-plete response = 76.92% at TG vs. 32.40% at CG (x^2=15.202, p<0.01) • Follow-up at 9 months for CIN1 conversion: 83.33% in EG vs. 0% in CG (x^2=7.639, p<0.001).

5	Liu et al., 2016 Clinical study [24]	EG – local PDT with 5-ALA; He-Ne red light laser 632.8 nm, 100 J/cm^2; CG – High-frequency electro-ion treatment	• 6-month follow-up period for VR-HPV Response: 81.81% in EG and 52.73% in CG (x^2=4.9381, p<0.05); • 9-month follow-up period for VR-HPV Response: 10.91% in EG and 7.27% in CG (x^2=2.1164, p<0.05); • Overall response for VR-HPV DNA: 92.73% in EG and 60.0% in CG (x^2=4.2615, p<0.05)
6	Park et al., 2016 Retrospective study [25]	EG: Photogem and diode laser with a wavelength of 632 nm and photoprint and diode laser with a wavelength of 630 nm 240 J/cm^2	• Complete response for CIN = 95% • Disease progression: 4.5% • Recurrence: 4.5% (18 months)
7	Inada et al., 2019 Clinical study [26]	EG: MAL cream and about 150 LEDs of the system, emitting at a wavelength of 630 nm, light output of 80-180 J/cm^2; CG: illumination of the cervix only (n=8) or application of MAL cream only (n=6)	Complete response for CIN1: 75% (42/56) at 1 (12.5%) and 2 (62.5%) years of follow-up; CIN1 persisted in 5.4%, CIN2 progression in 8.9%, and CIN1 recurrence in 8.9% for 2 years after PDT. In patients with CIN2/3, Complete response = 90% after 1 (30%) and 2 (60%) years of follow-up. CG: abstinence – 28.57% and persistence of lesion – 14.3%; The overall response rate was 57.14% at 1 and 2 years of follow-up.
8	Murakami et al., 2020 Clinical study [16]	Intravenous sodium talapoporphine (NPe6) at a dose of 40 mg/m^2 with a PDT of 100 J/cm^2	Через три и шесть месяцев: After 3 and 6 months: PDT was used in 9 patients (2 with CIN2 and 7 with CIN3). Treatment was confirmed in eight cases: 89%
9	Mizuno et al., 2020 Clinical study [27]	5-ALC, 633nm wavelength light, 1000-150 J/cm^2	Positive results: 96.1% Complete response for CIN: 70.6% Complete response for HPV: 79.4% Recurrence: 3.7% (1/51)
10	Li et al., 2020 Prospective study [28]	EG: 5-ALC and LED-IB type, wavelength 633 nm and 80 J/cm^2	Complete response for VR-HPV: 3 months: 75.32% (58/77), 6 months: 80.52% (62/77), 12 months: 81.82% (63/77) Complete response at CIN1 at 6-month follow-up: 88.31%, at 12-month follow-up: 94.81%
11	Zhang et al., 2022 Retrospective study [29]	5-ALC heat-sensitive gel and light irradiation at 635 nm and 100 J/cm^2	6 months after ALA-PDT Residual lesion incidence – 9.1% (3/33), p=0.004 Complete HPV Response rate – 66.7%, p=0.01 Recurrence rate was 3.3% at 2-year follow-up, p=0.021
12	Chen et al., 2022 Retrospective study [30]	5-ALC and LD600-C with 635 nm red light wavelength at 80 MW/cm^2	After 6 months of follow-up: EG: Complete response for HPV: 79.0%, LSIL 80.6%, KG: HPV CR – 62.3%, LSIL: 64.2% (p<0.05)
13	Yao et al., 2022 Retrospective study [17]	Chlorine E6 with STBF-PDT	The Complete response rate was 72.22% (13/18), and the rates of HPV remission and complete removal were 88.89% (16/18) and 83.33% (15/18), respectively, at 1-month follow-up. Complete response: 88.89%, and the HPV remission rate reached 94.44% after 6 months.

Numerous clinical trials, pilot studies, retrospective analyses, and prospective studies have investigated the use of PDT for the treatment of CIN, LSIL, and HSIL and have demonstrated *promising results using a variety of PS molecules:*

1. 5-aminolevulinic acid (ALA): ALA is the PS used in PDT for cervical cancer. Clinical trials have shown a positive result on the safety and efficacy of ALA-PDT in patients with CIN [12].

2. Aluminium phthalocyanine chloride: Second-generation PS, used in PDT to treat various types of cancer, including cervical cancer, and has higher photodynamic activity in the red spectrum and the ability to treat the deeper placed tumors [13].

3. Photofrin: PS was approved for use in PDT for many types of cancer, including cervical cancer [14]. An analog of FS Photogem (made in RF).

4. Hexaminolevulinate: allows effective detection of tumor zones due to the contrast of the protoporphyrin IX red fluorescence with excitatory short-wave light and direct use of its photodynamic activity to destroy superficial or cavitary tumors [15].

5. Sodium talaporphin: Sodium Talaporphin is a PS approved for the photodynamic therapy of various types of cancer, including cervical cancer [16].

6. Chlorin e6: its high absorption rate in the near-infra-red range supports deeper tissue penetration than other PS. Chlorin e6 has also shown a higher selectivity for cancer cells than healthy cells, making it a promising candidate for PDT [17].

7. Porphyrin derivatives: Porphyrin derivatives such as protoporphyrin IX and hematoporphyrin derivatives are naturally occurring PS used in PDT for cervical cancer. These compounds occur naturally in the body and

exhibit a higher accumulation rate in cancer cells than in healthy cells. When exposed to light of a specific wavelength, these PS generate the reactive oxygen species capable of destroying the cancer cells [18].

8. Tehafirins: These are synthetic molecules that are being studied for their potential use in PDT in various types of cancer, including cervical cancer, and have effectively induced cancer cell apoptosis [19].

In addition, below are presented relevant *preclinical studies of the potential use of other types of molecules in PDT in cervical cancer:*

1. Curcumin is a naturally occurring low-toxicity polyphenolic compound with anti-inflammatory and antioxidant properties that have demonstrated anticancer effects [31-32].

2. Hypericin is a compound present in St. John's wort. It has photosensitizing properties and is used in PDT for cervical cancer [33]. When light activates, hypericin generates the reactive oxygen species that can damage the cancer cells. In vitro and animal studies have shown the efficacy of hypericin in killing cancer cells [34]. However, further studies are needed to evaluate its efficacy in humans.

3. Indocyanine green (ICG) is a water-soluble dye of the near infra-red range. Preclinical studies have shown the potential use of ICG for PDT in cervical cancer [35-36]. FDA approved it for clinical use.

4. Methylene blue is a blue dye that has been used in medicine for several years. It has demonstrated the efficacy of PDT for cervical cancer [37]. Available data indicate that PDT mediated by methylene blue successfully induces cervical cancer cell death by generating reactive oxygen species (in vitro in animals) [33, 37]. Further research is needed to evaluate its effectiveness in humans.

5. Bengal rose is a red dye with photosensitizing properties, which has been used in medicine for many years and in PDT for cervical cancer. When light is activated, the Bengal rose produces the reactive oxygen species that can damage the cancer cells. In vitro and animal studies have shown the efficacy of the Bengal rose in killing cancer cells [34]; however, further study is needed to determine its efficacy in humans.

6. Zinc phthalocyanine exhibits high absorption in the red-light spectrum, making it practical for PDT. When exposed to light of a certain wavelength, PS generates the reactive oxygen species that can destroy the cancer cells [19, 38].

7. Chlorophyll derivatives, other than chlorine e6, have shown that chlorophyll-based PDT can induce the apoptosis of cancer cells [39-40].

8. Methyl violet (methyl violet) is a cationic dye exhibiting photodynamic activity. Preclinical studies have assessed its use in cancer treatment [41].

9. Bacteriochlorins have been studied for their potential use in PDT in various types of cancer [42]. However, there are currently no studies showing the efficacy of bacteriochlorin-based PDT for the treatment of cervical cancer.

10. Fullerenes are the carbon molecules. Preclinical studies have shown that fullerene-based PDT can effectively induce cancer cell death [43-44].

11. Xanthene molecules, such as eosin and erythrosine, are a class of fluorescent molecules used as PS in PDT of various types of cancer [45].

Discussion: Studies have shown that the overexpressed receptors on the surface of cancer cells can serve as potential PS binding sites. Consequently, PSs that exhibit a stronger tendency to attach to these overexpressed receptors facilitate their delivery to cancer cells [46]. Thus, PS that exhibit a higher affinity for these receptors can be considered promising candidates for PDT. In addition, using in-silico analysis, the scientists found that fullerene showed the highest affinity to overexpressed receptors in cervical cancer cells.

Therefore, fullerene has significant potential as a PS for PDT in the treatment of cervical cancer. However, further studies "in vitro" and "in vivo" are needed to confirm this finding. Due to its unique molecular properties, Chlorin e6 has high absorption rates in the red spectral range and targeted storage or accumulation in the corresponding tumor tissue [47]. On the other hand, Porphyrin derivatives occur naturally in the body and exhibit a higher accumulation rate in cancer cells than in healthy cells, destroying them [48].

The literature review in our study includes RCTs and prospective and retrospective studies of the efficacy of PDT in cervical cancer treatment. The studies mainly used 7 types of PS, such as topical 5-ALC thermogel (46.1%), vaginal HAL suppositories (7.7%), HAL hydrochloride (7.7%), MAL cream (15.4%) and intravenous photohem (15.4%), chlorin e6 (7.7%) and sodium thalaporphine (7.7%). According to the results, 5-ALA is the most widely implemented PS, which used wavelengths of 633 or 635 nm at 80, 100, or 150 J/cm^2 and produced HPV elimination results of 66.7% to 92.73% in the experimental groups compared to 32.40% to 62.3% in the control groups. HAL is an advanced ALA ester and a more potent lipid-soluble derivative. In early studies, the use of topical PS showed a Complete response rate (CR) of 33% to 71%, which was significantly lower [51]. Although topical PS, such as 5-ALA, is more convenient and cheaper than intravenous PS, the therapeutic effect is not always univocal. According to the results of other authors, attempts have been made to conduct PDT using the topical hexyl ether 5-ALK, advanced by 5-ALC PS, with still low results of the Complete response rate of 63% [10, 51]. Intravenously administered sodium salt of hematoporphyrin derivative (photogem) showed a more than 95% positive result.

PDT is currently used to treat patients who want to preserve their fertility and those who would prefer to

avoid the surgery intervention. Previous studies have used photofrin and 5-ALA in the treatment/prevention of cervical cancer. Although systemic photofrin was effective, it (photofrin) caused the skin photosensitivity. To the contrary, 5-ALC has been used topically to treat cervical lesions that could lead to cancer, as well as to eradicate the human papillomavirus (HPV) infection [49].

Phthalocyanines are standard PS used in PDT due to their high tumor uptake efficiency, high production of reactive oxygen species, and strong absorption in the 650 to 850 nm wavelength range. The second generation of zinc (II) phthalocyanine has Q-distract absorption at longer wavelengths (670-770 nm), which allows the light to penetrate the tissues as much as possible [50].

Scientists are also trying to increase the effectiveness of antitumor therapy for cervical cancer by combining PDT with chemotherapy [51]. Moreover, researchers have studied strategies to increase the delivery and efficacy of PS in PDT, and one such strategy is the use of nanoparticles [46]. The nanoparticles make it possible to combine multiple therapeutic agents and other functions within a single system, which facilitates solving various aspects associated with cancer treatment.

For example, the liposomal technology combining chlorin e6 as a PS, ICG as a PTT agent, and hypoxia-activated by the prodrug tirapazamine as a cytotoxic agent resulted in 97% of cell death after PDT at 808/660 nm.

Below are presented the *challenges and solutions associated with using PDT molecules in cervical cancer.*

The limited solubility of the molecules in water presents a significant problem when using them for cancer treatment, as it can reduce their efficacy and increase toxicity. However, nanotechnology offers a potential solution by increasing molecules' solubility, stability, and targeted delivery to cancer cells [34]. Nanoparticle-based delivery systems have been developed for various PS, including porphyrins, chlorophylls, and phycobilins.

These nanoparticles can be designed for the targeted exposure of cancer cells, improve the solubility and stability of PS, and improve its distribution and pharmacokinetics. Moreover, some nanoparticles have intrinsic antitumor properties and may enhance the therapeutic effects of PDT. In general, the combination of PS and nanotechnology opens up excellent prospects for developing effective and targeted PDT for treating cervical cancer and other types of cancer.

In addition to the limited solubility, several other challenges are associated with using molecules for PDT in cervical cancer.

These challenges include:

– Tumor targeting: Achieving specific dye targeting to tumor cells while minimizing uptake by healthy tissues is a challenge that needs to be addressed to avoid potential toxicity.

– Depth of penetration: The depth to which the activating light can penetrate is limited, making it difficult to treat the tumors deep inside the body.

– Photobleaching: Molecules can undergo photobleaching, losing their ability to generate reactive oxygen species when exposed to light. It may limit their effectiveness in PDT.

– Stability: Some molecules may exhibit instability in the biological environment, which affects their efficacy and safety.

– Approval from regulatory authorities: Obtaining regulatory approval for clinical use can be time-consuming and costly, hindering the availability of molecules for PDT in cervical cancer.

– The following possible solutions can be considered to address these issues:

– Solubility: Encapsulating the dye in lipid or polymer nanocarriers can improve solubility and stability.

– Tissue penetration: Exploring alternative delivery methods, such as intra-tumoral injection or topical application, may enhance tissue penetration.

– Specificity: Increasing specificity through ligand conjugation or using activated molecules selectively activated in cancer cells.

– Photobleaching: Optimizing the dye concentration and light dose and using photostable molecules can reduce the photobleaching.

– Toxicity: Reduced toxicity by using lower doses of dye and light and optimizing the drug delivery methods to minimize the side effects.

– Regulatory Approval: Compliance with Regulatory Guidelines for Drug Development and Clinical Trials.

– Tumor targeting: Targeted delivery systems such as nanoparticles, stem cell-derived exosomes, or liposomes can improve tumor targeting. These systems can be conjugated to specific ligands or antibodies that recognize and bind the tumor cells, increasing the accumulation of PS in the tumor and minimizing its uptake by healthy tissues. Another approach involves using light sources with specific wavelengths that selectively activate PS in tumors, minimizing activation in surrounding healthy tissues [52].

Conclusion: Photochemotherapy, nanoparticles, and photosensitizing agents are widely used in PDT for cervical cancer. It is noteworthy that fullerene is promising as a dye for PDT due to its high binding affinity for overexpressed receptors in cervical cancer cells. However, further studies are needed to confirm the potential of fullerene and develop effective treatments for cervical cancer with PDT. The use of PDT, which combines a fluorescent dye with a specialized imaging system, represents a significant advance in the diagnostics and treatment of HPV-related cervical lesions.

This minimally invasive approach offers targeted therapy to abnormal cells, minimizing harm to healthy tissues. In addition, relevant studies have shown that

ALA-PDT is a safe and effective alternative for treating HPV-related CIN and HSIL.

Continued research and development in this area is likely to drive further progress in the diagnostics and treatment of HPV-related cervical lesions, leading to improved patient outcomes and a reduced global cervical cancer burden.

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АНДАТПА

ЖАТЫР МОЙНЫ ОБЫРЫНЫҢ ФОТОДИНАМИКАЛЫҚ ТЕРАПИЯСЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Жатыр мойны обыры бүкіл әлем бойынша денсаулық сақтаудың негізгі проблемасы болып табылады, мұнда адам папилломавирусының инфекциясы қауіп факторы ретінде маңызды рөл атқарады. Фотодинамикалық терапия - бұл қалыпты емес жасушаларды іріктеп жою үшін фотосенсибилизаторлар мен жарықты пайдаланатын АПВ-мен байланысты жатыр мойны зақымдануының минималды инвазивті емі.*

Зерттеудің мақсаты *– жатыр мойны обырына байланысты сырқаттанушылық пен өлімді азайту үшін ФДТ-да қолданылатын молекулалардың әртүрлі түрлеріне жан-жақты шолу жасау.*

Әдістері: *АПВ инфекциясымен байланысты жатыр мойны обырын емдеудегі ФДТ тиімділігі мен қауіпсіздігін зерттеуге арналған барлық тиісті мақалаларға жан-жақты іздеу жүргізілді. Шолу үшін PICO көрсеткіштері анықталып, PubMed дерекқорында әдебиеттерге іздеу жүргізілді. PubMed онлайн дерекқорында кілтті сөздер тіркестерін пайдалана отырып 2013 және 2023 жылдар аралығында жатыр мойны обыры жасушаларын емдеу үшін ФДТ қолданылуына зерттеу жүргізілген 71 жұмыс анықтады.*

Бұл мақалада төмен дәрежелі скамозды интраэпителиальды неоплазияны және жоғары дәрежелі скамозды интраэпителиальды зақымдануларды емдеудегі ФДТ тиімділігін зерттейтін ағымдағы клиникалық зерттеулер, сондай-ақ жатыр мойны обырында ФДТ арналған әртүрлі молекулаларды қолданатын клиникаға дейінгі тәсілдер қарастырылады.

Нәтижелері: *ФДТ үшін потенциалды молекулалар сипатталып, олардың артықшылықтары мен кемшіліктері бағаланып, обырға қарсы терапиямен үйлесімділігін арттыру үшін шешімдер ұсынылды. Біздің шолуымыз көрсеткендей, ФДТ АПВ-мен байла-*

ныcты жатыр мойынының зақымдануын диагностикалау және емдеу үшін перспективті терапиялық әдіс болып табылады. Сонымен қатар, біз боғғыштардың әртүрлі кластарын қолдану ФДТ-ның обырға қарсы әсерін күшейтетінін байқадық.

Қорытынды: *Фуллерен және АЛК-ФДТ – жатыр мойны обырынан болатын жаһандық сырқаттанушылық пен өлімді азайтуға көмектесетін ФДТ-да интенсивті қолдану үшін әлеуетті көшбасшылар. Дегенмен, оның ұзақ мерзімді тиімділігі мен қауіпсіздігін бағалау үшін қосымша зерттеулер қажет.*

Түйінді сөздер: *жатыр мойны обыры; адам папилломавирусы (АПВ); фотодинамикалық терапия (ФДТ); скамозды жасушаішілік эпителий неоплазиясы.*

АННОТАЦИЯ

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ РАКА ШЕЙКИ МАТКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак шейки матки (РШМ) представляет собой серьезную проблему для здравоохранения во всем мире, и инфицирование вирусом папилломы человека (ВПЧ) играет жизненно важную роль в качестве фактора риска РШМ. Фотодинамическая терапия (ФДТ) представляет собой минимально инвазивное лечение поражений шейки матки, связанных с ВПЧ, при котором используются фотосенсибилизаторы и свет для избирательного разрушения аномальных клеток.*

Цель исследования *– изучение различных типов молекул, используемых в фотодинамической терапии рака шейки матки.*

Методы: *Был проведен всесторонний поиск статей, посвященных изучению эффективности и безопасности ФДТ при лечении РШМ, связанного с ВПЧ-инфекцией. Для обзора были определены показатели PICO и проведен поиск литературы в базе данных PubMed с использованием комбинаций ключевых слов. Было выявлено 71 исследование, проведенное в период с 2013 по 2023 год, в котором изучалось использование ФДТ для лечения РШМ.*

В статье рассмотрены текущие клинические испытания, изучающие эффективность ФДТ при лечении плоскоклеточных интраэпителиальных неоплазий низкой и высокой степени, а также доклинические подходы с использованием различных молекул для ФДТ при РШМ.

Результаты: *Описаны потенциальные молекулы для ФДТ, оценены их преимущества и недостатки и предложены решения для повышения их совместимости с противоопухолевым лечением. Наш обзор показывает, что ФДТ является перспективным терапевтическим подходом для диагностики и лечения поражений шейки матки, связанных с ВПЧ. Вместе с тем, согласно результатам обзора литературы, использование различных классов красителей усиливает противораковые эффекты ФДТ.*

Заключение: *Фуллерен и АЛК-ФДТ являются потенциальными лидерами для более интенсивного использования в ФДТ РШМ. Однако необходимо проведение дальнейших исследований для оценки долгосрочной эффективности и безопасности данного метода.*

Ключевые слова: *рак шейки матки (РШМ), вирус папилломы человека (ВПЧ), фотодинамическая терапия (ФДТ), плоскоклеточная интраэпителиальная неоплазия.*

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AZAT SHIBANOVA – LIFE DEDICATED TO MEDICINE. DEVOTED TO THE 90th ANNIVERSARY

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ABSTRACT

Azat Shibanova is a veteran of the Kazakhstan Oncology Service, founder of the Clinical Cytology in the Republic of Kazakhstan, Doctor of Medical Sciences, Professor, Honorary President and founder of the Clinical Cytologists Association of the Republic of Kazakhstan, Honorary Member of the International Academy of Cytology. Professor Azat Shibanova, during her career, has trained a series of cytologists and cytotechnicians working successfully throughout Kazakhstan.

Figure 1 – Professor A.I. Shibanova

It is challenging to write about Professor Azat Shibanova in the past tense. Especially now, while perceiving that you will never again be able to listen to her lecture, discuss a new article or book, or talk about the next congress of the International Academy of Cytology. Prof. A.I. Shibanova marked an entire domestic oncology and medical science development era. Her devotion to science will always serve as an example for her students and followers.

On August 5, 2023, Azat Shibanova, a veteran of the oncology service of the Republic of Kazakhstan, the founder of the Clinical Cytology, Doctor of Medical Sciences, Professor, Honorary President of the Clinical Cytologists Association of the Republic of Kazakhstan, Honorary Member of the International Academy of Cytology, would have turned 90 years (Figure 1).

Azat Shibanova was born into the family of a famous orientalist, diplomat, journalist, teacher, and political and public figure, Ilyas Akhmetov, who significantly contributed to the Kazakh language and culture development and preservation. She continued the family tradition by devoting her life to science.

In 1957, Azat Shibanova graduated with honors from the Alma-Ata State Medical Institute and entered graduate school at the Departments of Normal and Pathological Anatomy.

In 1960, Azat Shibanova was invited, among other promising young scientists, to work at the Kazakh Institute of Oncology and Radiology. She began her career as a junior researcher at the Tumor Cytology Laboratory.

In 1967, Azat Ilyasovna successfully defended her Master's thesis on the topic, "On the issue of ductus arteriosus mor-

phogenesis." In 1969, she headed the Tumor Cytology Laboratory, where she worked for over half a century.

In 1978, Azat Shibanova was appointed a Chief Cytologist of the Ministry of Health of the Republic of Kazakhstan. She created the national cytological service system of the RK and initiated the establishment of centralized cytological laboratories at every regional oncology clinic. The laboratories still function successfully today (Figure 2).

Figure 2 – Master class on cytological diagnostics, Almaty, 2018

In 1982, Azat Shibanova became a Doctor of Medical Sciences having defended her doctoral thesis at Blokhin Russian Oncological Research Center of RAMS on the topic, "Cytological method in diagnosing and assessing the efficacy of treatment for esophageal precancer and cancer." In 1990, the Higher Attestation Commission under the Council of Ministers of the USSR awarded her the academic title of Professor in Oncology.

All scientific studies supervised by A.I. Shibanova were devoted to urging issues of cytomorphological diagnostics of tumors and pre-tumor diseases of the esophagus and uterine body, automation of cytological studies, using the cytological method to screen for dysplastic conditions and early forms of cervical cancer during mass preventive examinations of the population. The results of those studies were incorporated in the International Cytological Classifications of CMEA member countries for esophageal and endometrium diseases. The RK Government adopted the National Screening Program for Cervical Cancer Early Detection (2008).

Prof. Azat Shibanova substantiated and prepared an Order of the Ministry of Health of the Republic of Kazakhstan No. 509 of 1993 in Clinical Cytology, which incorporated all standards and staffing requirements currently used and observed in the industry.

Prof. Azat Shibanova focused on preserving the national medicine scientific traditions and training and retraining experts in oncomorphology. She organized licensed courses in clinical cytology at the institute's laboratory, where over 150 highly qualified clinical cytology specialists were trained. Azat Shibanova was the scientific supervisor of two doctoral and 16 candidate theses.

She authored over 200 scientific papers and more than 30 guidelines, including a methodological guide for cervical cancer screening. Co-authored 5 patents on methods of collecting material for cytological diagnostics of the esophagus and ENT organ diseases and assessing the cervical cancer treatment efficacy, and an atlas, "Cytological diagnosis of diseases of the esophagus, stomach, and intestines," published in Moscow in 2012.

Prof. A.I. Shibanova reported on the results of cervical cancer screening at the International Congresses of Cytologists in Paris (France) in 2013 and Yokohama (Japan) in 2016, and the European Congresses of Cytologists in Geneva (Switzerland) in 2014 and Milan (Italy) in 2015.

A.I. Shibanova helped to organize international conferences and master classes with the participation of scientists from the Netherlands, Germany, Japan, South Korea, and the USA (Figure 3).

The scientific and social activities of A.I. Shibanova were as multifaceted. She was on the editorial boards of several specialized Kazakhstani and foreign journals, was a corresponding member of the International Academy of Cytology, and repre-sented Kazakhstan as a national and regional editor of the "Acta Cytologica" interna-tional journal.

This year, the Professional Association of Clinical Cytologists of the RK, founded by Azat Shibanova, has celebrated its 30th anniversary. Since its establishment on April 30, 1993, the Association's activities were supported by the enthusiasm of its participants. The Association is an affiliate member of the International Academy of Cytology. This allows its participants to publish in "Acta Cytologica," "Analytical and Quantitative Cytology and Histology," and "News of Clinical Cytology of Russia" journals.

Figure 3 – At the VII International Congress of the Kazakhstani Association of Medi-cal Laboratory Diagnostics, 2019

Till December 2020, Prof. A.I. Shibanova continued active practice, screening the female population for early detection of cervical pathologies, monitoring the quality of cytological diagnostics, participating in differential diagnostics of complex cases, sharing her many years of experience and training oncologists in advanced courses, delivering reports and lectures at numerous scientific forums, congresses, and seminars (Figures 4-5).

Figure 4 – At the VI Congress of Oncologists and Radiologists of Kazakhstan, 2017

Everyone was amazed by her breadth of vision, adherence to principles, original approach to the problems she studied, and ability to formulate her thoughts clearly and imaginatively and convey the most important information to the listener. Her scientific reports served as an excellent school for the young staff of the institute, regardless of their field of activity.

For her merits, A.I. Shibanova was awarded the Order of the Badge of Honor of the USSR (1981), the Al-Farabi Medal of the 1st degree (1983), the medals of the Presidium of the Supreme Soviet of the USSR "Veteran of Labor" (1988) and "For Valiant Labor" (1970), "Expert in Clinical Cytology" certificate from the American Biographical Institute (2006), "2000 Intellectuals of the 21st Century" medal from the International Biographical Center (Cambridge, UK, 2007), "Sanofi" award (2012), "Densaulyk saktau isinin uzdigi" [Excellence in Health care] (2000, 2010, 2015) badge, "Enbek ardageri" [Veteran of Labour] (2016) medal, and medal of the Republic of Kazakhstan "Kurmet" (2019).

Azat Shibanova made a tremendous contribution to the development of medicine. She left a mark in the hearts of her students, colleagues, friends, and those who collaborated with her in the country and abroad. She supported those stranded, helped those in whom she saw great potential for scientific and professional growth and helped realize it, determining their further successful activities

and life path, gave others helpful advice, smiled in the morning at the start of the working day or asked about recent results, praised the others for their first scientific articles or reports, congratulated on successfully passing the candidate exams. Others were just fascinated by her brilliant performances at seminars.

Figure 5 – Speech at the cytology section, 2017

Her students continue Azat Shibanova's life work. Over time, we see what determined the depth and uniqueness of Prof. Azat Shibanova's personality. Every single story and detail associated with her will remain in the overall picture of the kind and bright memories of Azat Shibanova. Blessed memory, **Teacher!**

АНДАТПА

АЗАТ ІЛЯСҚЫЗЫ ШИБАНОВА – МЕДИЦИНАҒА АРНАЛҒАН ӨМІР. ТУҒАНЫНЫҢ 90 ЖЫЛДЫҒЫНА

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Азат Ілиясқызы Шибанова – Қазақстан онкологиялық қызметінің ардагері, Қазақстан Республикасындағы «Клиникалық цитология» пәнінің негізін қалаушы, медицина ғылымдарының докторы, профессор, Қазақстан Республикасы Клиникалық цитологтар қауымдастығының құрметті президенті, «ҚР клиникалық цитологтар қауымдастығының құрметті мүшесі. Халықаралық цитология академиясы. Қазақстан Республикасы Клиникалық цитологтар қауымдастығының негізін қалаушы ол өзінің еңбек жолында қазіргі уақытта бүкіл Қазақстан бойынша жұмыс істейтін цитологтар мен цитотехниктердің тұтас галактикасын дайындады.

АННОТАЦИЯ

АЗАТ ИЛЬЯСОВНА ШИБАНОВА – ЖИЗНЬ, ПОСВЯЩЕННАЯ МЕДИЦИНЕ. К 90-летию СО ДНЯ РОЖДЕНИЯ

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