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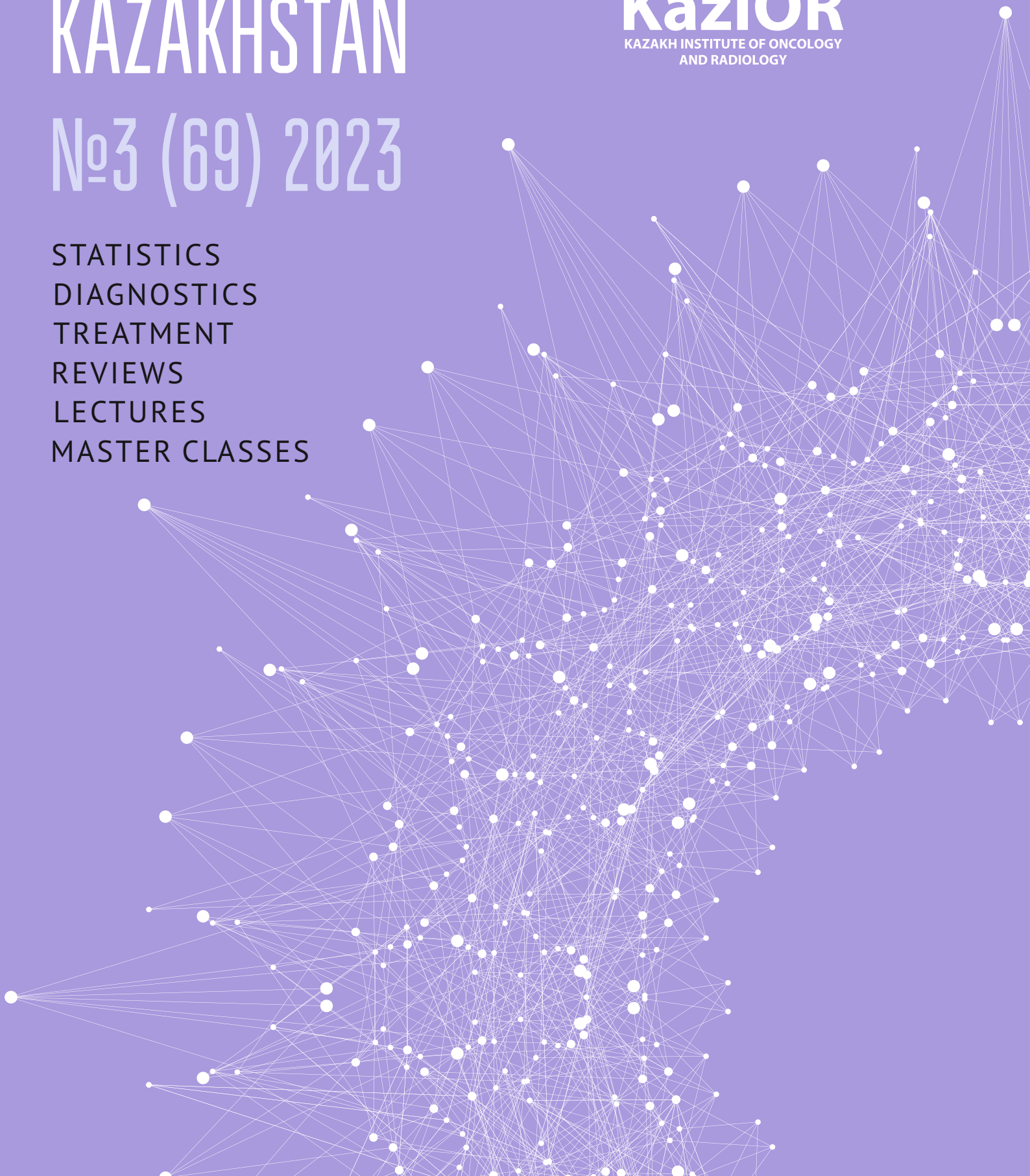

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Dear readers!

Welcome to the pages of the autumn issue of the "Oncology and Radiology of Kazakhstan" journal!

We are glad to meet our readers and authors again. Despite the vacation period, they actively write papers, go through strict checks and reviews, and burnish their manuscripts. Thanks to these joint efforts, we offer exciting practical results, clinical cases, and observations in this issue.

The authors explore the possibility of using the parenchymatous-stromal ratio as a metastasis indicator in colorectal cancer. Another article analyzes the awareness of the Karaganda region population on the incidence and prevention of colorectal cancer. Public awareness of cancer and its prevention is vital. Therefore, similar reviews in other regions of the country are required.

The topic of pediatric cancer is always acute and relevant. The article "Risk Factors and Early Signs of Critical Conditions in Children with Acute Lymphoblastic Leukemia admitted to the Intensive Care Unit" would interest pediatricians, oncologists, and ICU doctors.

Clinicians and resuscitators might be interested in the issues of nutritional support for cancer patients in the early postoperative period.

"The use of Argon Plasma Coagulation in Endoscopy" reflects new endoscopic diagnostics and treatment principles.

We appreciate the manuscripts of our colleagues from neighboring countries on topical aspects of cancer treatment and want to use this opportunity to thank them for their exciting materials and readiness to participate as reviewers.

We are sure the topics described by our respected authors will be of help to our readers.

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

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THE FIRST EXPERIENCE OF USING NON-INTUBATED VIDEO-ASSISTED THORACOSCOPIC RESECTIONS FOR LUNG CANCER IN THE REPUBLIC OF KAZAKHSTAN

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ABSTRACT

Relevance: *Several studies have shown that non-intubated surgical interventions, especially, have proven themselves well in patients with low reserve of the cardiovascular and respiratory systems, as well as in the diagnosis of interstitial lung diseases.*

The study aimed to *describe the experience of introducing into clinical practice surgical interventions without intubation on spontaneous breathing for malignant neoplasms of the lungs and mediastinal organs.*

Methods: *two clinical cases are described of the main points of the anesthesia and technical features of surgical intervention.*

Results: *A surgery in two patients with peripheral lung cancer was performed. In the first case, the operation included NI-VATS on the right and the resection of the upper (S2) and lower lobe (S6, S9); in the second case – NI-VATS on the right, lower lobectomy, and lymph node dissection. Based on the results of histological examination, both patients were diagnosed with NSCLC in the initial stages. Postoperative chemoradiotherapy is not indicated. The patients were registered at the dispensary in clinical group III.*

Conclusion: *As the literature data and our preliminary results of NI-VATS show, surgical interventions in the surgical treatment of lung cancer have places to be and should be widely introduced into clinical practice in oncothoracic departments of the Republic of Kazakhstan.*

Keywords: *lung cancer, non-intubated video-assisted thoracoscopic surgery (NI-VATS), video-assisted thoracoscopic surgery (VATS), video-assisted lung resection, non-intubated thoracoscopic lobectomy, non-intubated thoracic surgery.*

Introduction: The first experience of surgical interventions without tracheal intubation was presented in 1865 by Francis Richard Cruise, who used a cystoscope developed by Maximilian Nitze for thoracoscopy in a patient with pleural empyema [1, 2]. At the end of the XX century, thoracoscopic surgery entered clinical practice and became widespread due to the development of anesthesiology. Video-assisted thoracoscopic surgery (VATS) under general anesthesia (GA) with separate ventilation of the lungs have become a standard surgical intervention in oncothoracic surgery [3, 4]. It should be noted that tracheal intubation, especially with a double-lumen tube and positive-pressure pulmonary ventilation, leads to complications such as mechanical injuries of the respiratory tract and pulmonary barotrauma. These complications lead to severe long-term damage to the respiratory tract, lung parenchyma, and increased patient rehabilitation. Using a technique with spontaneous breathing reduces complications associated with tracheal intubation [5, 6]. Over the past 10 years, there has been a clear trend of increasing the number of clinics introducing the technique of non-intubated video-assisted thoracoscopic surgery (NI-VATS) for lobular, segmental, atypical lung resections and diagnostic surgical interventions [7, 8].

Literature analysis shows that in Europe, 62 of 105 thoracic surgeons (59%) among the members of the European Society of Thoracic Surgeons (ESTS) and 42% of thoracic surgeons of the German Society for Thoracic Surgery (*Deutsche Gesellschaft für Thorax* [DGT]) reported performing NI-VATS in patients with lung pathology. In particular, non-intubated surgical interventions have proven well in patients with low cardiovascular and respiratory systems reserve and in diagnosing interstitial lung diseases [9, 10]. NI-VATS are indicated for patients with COPD and low pulmonary reserve, where general anesthesia with intubation has high risks and is associated with complications [11].

NI-VATS can be performed for various chest pathologies, from the elimination of pneumothorax, empyema treatment, diagnosis of pleurisy, marginal, atypical resections to anatomical segmentectomies and lobar resections with lymph dissection in lung cancer [12, 13].

According to the literature data, the advantages of NI-VATS include less postoperative trauma, early activation of the patient, early recovery of oral nutrition [14], reduction

of postoperative pain, reduction of cardiovascular and respiratory events, reduction of the duration of hospital stay of patients without increasing the duration of surgery [15, 16] absence of a precursor to the development of ventilator-associated pneumonia, reduction of systemic postoperative inflammation, better restoration of cell-mediated and humoral immune functions [17].

The study aimed to describe the experience of introducing into clinical practice surgical interventions without intubation on spontaneous breathing for malignant neoplasms of the lungs and mediastinal organs.

Materials and Methods: This article describes clinical cases of the introduction of NI-VATS for malignant lung tumors. The main technical aspects of the procedure [7, 18] are adapted in the settings of the Almaty Regional Multidisciplinary Clinic.

Clinical cases are described below.

Clinical Case No. 1.

Patient information: Patient T., 67 years old. A periodic health examination at the local polyclinic revealed masses in the right lung. The patient was referred to ARMC for consultation. At the prehospital stage in a polyclinic setting, the patient was further examined and preliminarily diagnosed with peripheral cancer of the upper lobe of the right lung. He was hospitalized in the surgical department for surgical treatment. Specialized specialists consulted him, and no concomitant pathology was detected.

Clinical data: Upon admission, Karnofsky's performance status of the patient was 85%. No clinical signs in vital organs and systems were observed.

Diagnostics: The contrast-enhanced thoracic computed tomography revealed a cloud-shaped shadow with fuzzy lobular margins and a sign of reaction (retraction) of the interlobular pleura, of medium intensity, 1.0 x1.1 x 0.8 cm in size, in the second segment of the upper lobe of the right lung. The lower lobe in the sixth and ninth segments had subpleural spherical formations with clear margins of average intensity, with a diameter of 0.5 and 0.7 cm, respectively. The intrathoracic lymph nodes are intact (Figure 1, A-D).

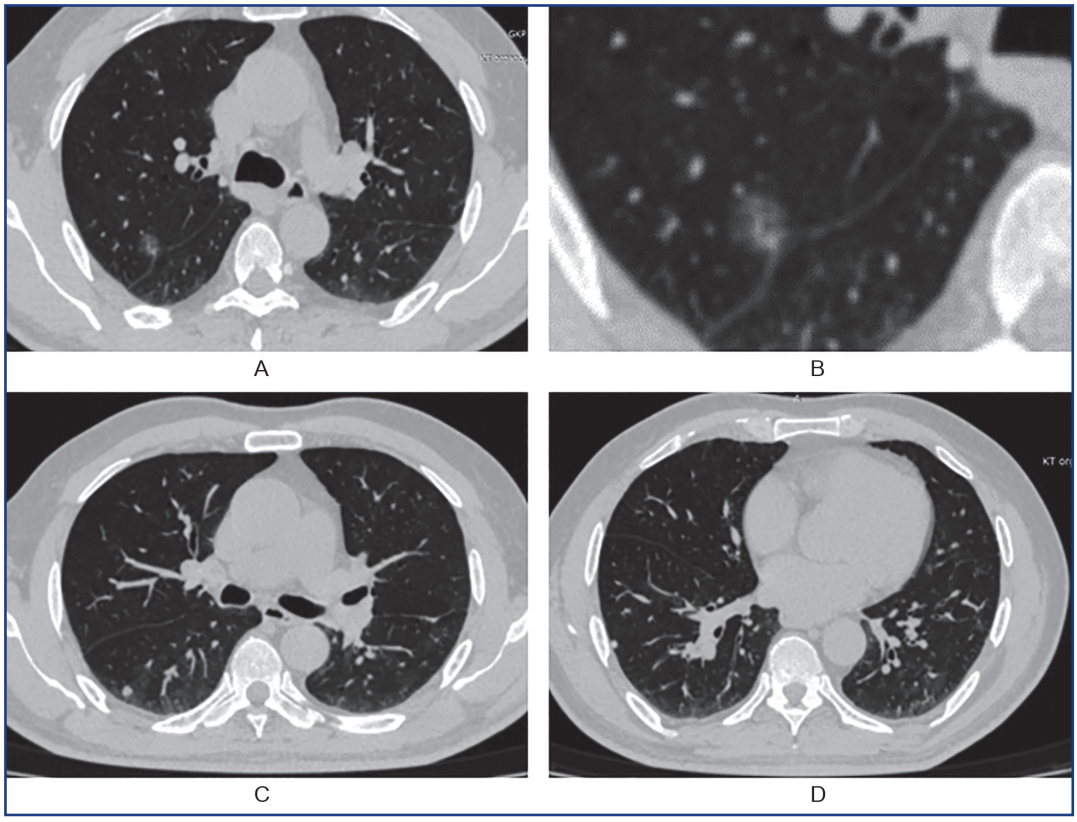

Figure 1 – Thoracic computed tomography of patient T., 67 years old: A, B – cloud-shaped shadow (S2) of the upper lobe of the right lung with visceral pleura reaction; C – cloud-shaped shadow (S2) of the upper lobe of the right lung with visceral pleura reaction (periapical X-ray); D – globular mass (S9) of the lower lobes of the right lung

Treatment: Surgical intervention was performed as planned. Anesthetic support was provided.

Initial hemodynamics: BP 135/82 mmHg; HR 82 per minute; RR 17 per minute; SO_2 93%

Preoperative preparation of the patient:

1) A central venous catheter was installed.

2) Antibiotic prophylaxis was given 30 minutes before the skin incision.

3) To prevent the cough reflex, lidocaine solution for inhalation was given.

4) Volemic preload: sterofundin solution.

5) In the patient's sitting position, catheterization of

the epidural space at the level of Th5-Th6 was performed. The clinical picture of the sympathetic block in the form of paresthesia at the level of Th2-Th8 with a moderate decrease in BP to 125/75 mmHg was achieved. There was no disorder or inhibition of vital organ function with sensory blockade (no pain and tactile sensitivity).

6) For sedation, Dexdor solution was intravenously administered using a dispenser. RASS score is 0 to -1.

7) Additionally, in order to enhance analgesia during skin incision, mobilization of the pulmonary ligament, and mediastinotomy, fentanyl solution was administered.

Continuous intraoperative monitoring of vital organ functions (ECG, pulse oximetry, BP) on spontaneous respiration with the supply of moistened oxygen through a nasal cannula.

Surgery: NI-VATS on the right; marginal resection of upper (S2) and lower (S6, S9) lobes with lymph dissection.

The patient's position is lying on the left side. Under local anesthesia with lidocaine solution, a 6-cm-long incision was made at the fifth intercostal space along the midaxillary line. The "surgysleeve" retractor was placed. An additional second port for the video camera was placed in two intercostal spaces below. During the revision of the pleural cavity, a tumor node in the second segment of the upper lobe was reported (Figure 2).

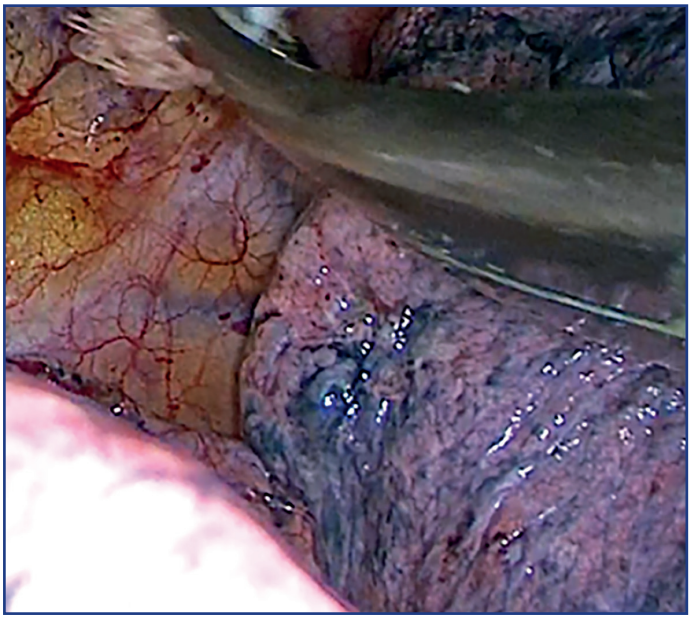

Figure 2 – Intraoperative view of the tumor of the upper (S2) lobe with a sign of visceral pleura retraction

Marginal resection of masses in S2, S6, and S9 was performed using crosslinking devices. Further inspection found no macroscopically altered lymph nodes. Lymphodissection of the bifurcation and paratracheal regions, lung root, and pulmonary ligament area was performed. Intraoperative blood loss was 30 mL. The surgery lasted for 2 hours 05 minutes.

The early postoperative period proceeded smoothly; the patient was activated 1 hour after transfer to the intensive care unit. Having stable hemodynamic and laboratory parameters, he was transferred to the specialized department 16 hours after the end of the surgery.

Results: Chest X-ray conclusion: shadow of the drainage tube in the pleural cavity; lung straightened; no hypoventilation zones and atelectasis. Sines are free.

The drainage tube was removed on the third day. On the fourth day, the patient was discharged with recommendations.

Histological conclusion: adenocarcinoma G-2 of micropapillary type with moderate lymphocytic infiltration. No tumor cells in the removed lymph nodes.

Final diagnosis: peripheral cancer of the right lung's upper (S2) lobe T1bN0M0 St-IA2.

Clinical case No. 2.

Patient information: Female patient Zh., 59 years old. Fluorography at the periodic health examination at the local polyclinic revealed a shadow in the lower lobe of the right lung. The patient was referred to ARMC for consultation. In a polyclinic setting, the patient was further examined and preliminarily diagnosed with peripheral cancer of the upper lobe of the right lung. Specialized specialists consulted her, and no concomitant pathology was detected. She was hospitalized in the surgical department for surgical treatment.

Clinical data: Upon admission, Karnofsky's performance status of the patient was 85%. No clinical signs in vital organs and systems were observed.

Diagnostics: The contrast-enhanced thoracic computed tomography revealed a medium-intensity shadow with fuzzy lobular margins in the tenth segment of the

lower lobe of the right lung, not associated with a visceral pleura, 1.5x2.5x1.2 cm in size, with a bronchovascular path to the root. The intrathoracic lymph nodes are intact (Figure 3).

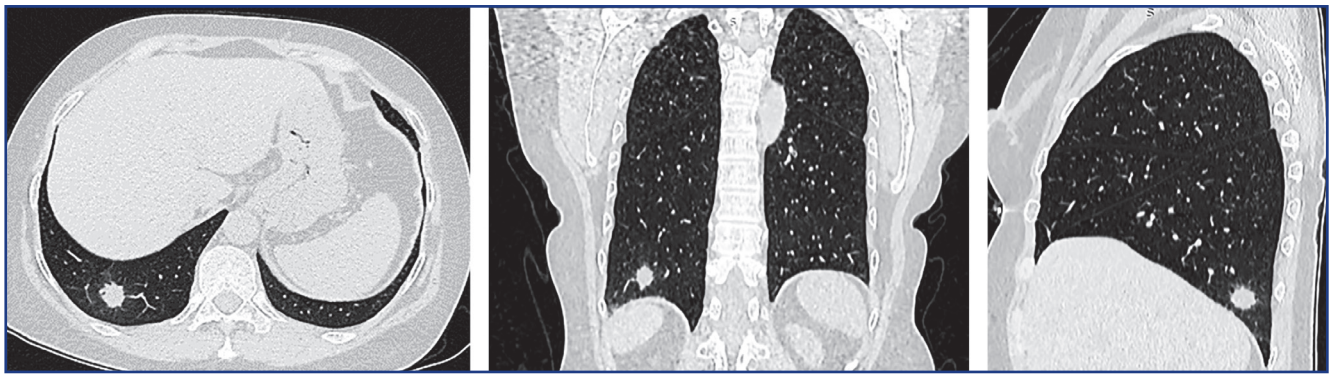

Figure 3 – Thoracic computed tomography of patient Zh., 59 years old: Peripheral cancer of the lower (S10) lobe of the right lung

Treatment: Surgical intervention was performed as planned. Anesthetic support was provided.

Initial hemodynamics: BP 130/75 mmHg; HR 75 per minute; RR 17 per minute; SO_2 94%

Preoperative preparation of the patient.

1) A central venous catheter was installed.

2) Antibiotic prophylaxis was given 30 minutes before the skin incision.

3) To prevent the cough reflex, lidocaine solution for inhalation was given.

4) Volemic preload: sterofundin solution.

5) In the patient's sitting position, catheterization of the epidural space at the level of Th6-Th7 was performed. The clinical picture of the sympathetic block in the form of paresthesia at the level of Th2-Th9 with a moderate decrease in BP to 110/65 mmHg was achieved. There was no disorder or inhibition of vital organ function with sensory blockade (no pain and tactile sensitivity).

6) A Dexdor solution was intravenously administered using a dispenser for sedation. RASS score is -1 – -2.

7) Additionally, in order to enhance analgesia during skin incision, mobilization of the pulmonary ligament, and mediastinotomy, a Fentanyl solution was administered.

Continuous monitoring of vital organ functions (ECG, pulse oximetry, BP) on spontaneous respiration with the supply of moistened oxygen through a nasal cannula.

Surgery: NI-VATS on the right; lower lobectomy; lymph dissection.

The patient's position is lying on the left side. Under local anesthesia with lidocaine solution, a 5 cm-long incision was made at the 5th intercostal space along the midaxillary line. The "surgysleeve" retractor was placed. Similarly, a second "surgysleeve" retractor was placed in the 7th intercostal space along the midaxillary line (Figure 4).

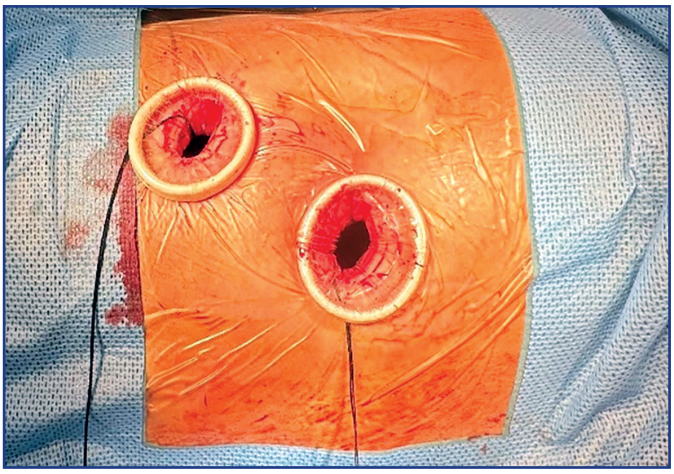

Figure 4 – General view of the port's location

Intraoperatively. Tumor in the lower (S10) lobe. A blockade of the diaphragmatic and vagus nerve was performed with a ropivacaine solution. The lower pulmonary ligament was mobilized. The interlobular furrow was divided. The basal artery was sequentially mobilized, and A6 was stitched with the device. The inferior pulmonary vein is isolated and stitched with the device. The lower lobe bronchus was mobilized, stitched with

a device, and crossed. The lobe was removed. Lymphodissection of the bifurcation and paratracheal regions, lung root, and pulmonary ligament area was performed. Drainage of the pleural cavity was carried out through the lower thoracoport; a drainage tube was placed from the diaphragm to the dome of the pleural cavity (Figure 5). Intraoperative blood loss was 70 mL. The surgery lasted for 2 hours 35 minutes.

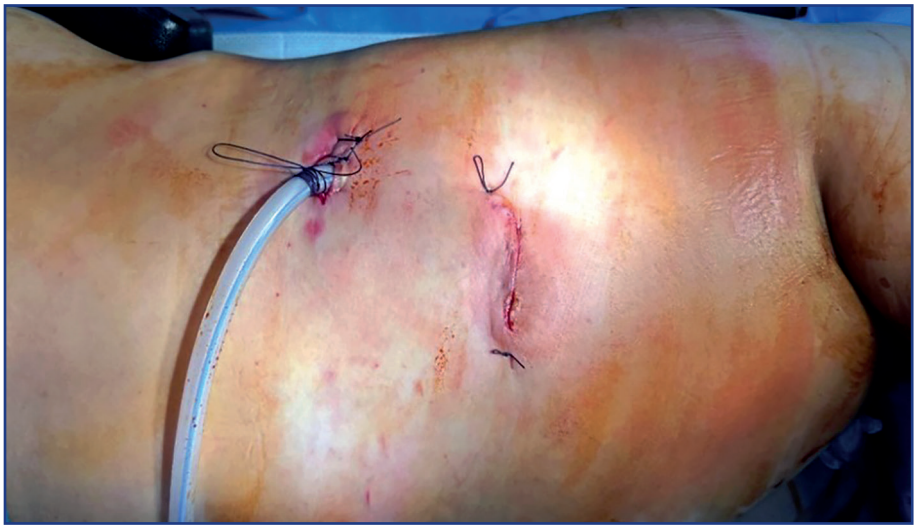

Figure 5 – Final view of the postoperative wound

The early postoperative period proceeded smoothly; the patient was activated 1.5 hours after transfer to the intensive care unit. Having stable hemodynamic and laboratory parameters, she was transferred to the specialized department 14 hours after the end of the surgery.

Results: Chest X-ray conclusion: shadow of the drainage tube in the pleural cavity; the remaining lobes occupy the entire pleural cavity; no regions of hypoventilation and atelectasis. Sines are free.

The drainage tube was removed on the 3rd day. On the 5th day, the patient was discharged with recommendations.

Histological conclusion: adenocarcinoma G-2. No tumor cells in the removed lymph nodes.

Final diagnosis: peripheral cancer of the lower (S10) lobe of the right lung T1cN0M0 St-IA3

Discussion: NI-VATS combines the advantages of non-intubated surgery with minimally invasive access. NI-VATS is performed in weakened patients when general anesthesia and orotracheal intubation are associated with a high risk of pulmonary complications [12, 13, 19]. This method of surgical intervention proved to be more effective than VATS under general anesthesia. It reduces hospitalization time and accelerates patient rehabilitation [20]. In addition, NI-VATS is associated with fewer pulmonary complications, the absence of respiratory distress syndrome, and a weakly expressed systemic inflammatory reaction [11].

The results of 28 NI-VATS lobectomies are shown by Furák J. et al. The surgery lasted for 91.04 ± 23.88 minutes; drainage was in the pleural cavity for 2.12 ± 1.16 days; there were no postoperative complications [21].

According to Starke H. et al., the duration of surgery for lobar resections was 124.05±74.49 min. The drainage tube was in place for 3.58 days; the median postoperative hospital stay was 6.40 ± 4.51 days [7].

According to Al Ghamdi Z. M. et al.(2018), postoperative hospital stay in the NI-VATS group was 6.9±3.8 days, and the drainage tube was in place for 5.6 days].

Conclusion: As the literature data and our preliminary results of NI-VATS show, surgical interventions in the surgical treatment of lung cancer have such advantages over open and VATS surgical interventions as minor postoperative trauma, rapid recovery of the patient, shorter stay of patients in the hospital, and, therefore, should be widely introduced into clinical practice in oncothoracic departments of the Republic of Kazakhstan.

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АҢДАТПА

ҚАЗАҚСТАН РЕСПУБЛИКАСЫНДА ӨКПЕ ОБЫРЫ КЕЗІНДЕ ИНТУБАЦИЯЛЫҚ БЕЙНЕ-АССИСТЕНТТЕЛГЕН ТОРАКОСКОПИЯЛЫҚ РЕЗЕКЦИЯЛАРСЫЗ ҚОЛДАНУДЫҢ АЛҒАШҚЫ ТӘЖІРИБЕСІ

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Өзектілігі: *Бірқатар зерттеулер көрсеткендей, интубациясыз хирургиялық араласулар, әсіресе жүрек-қан тамырлары мен тыныс алу жүйесінің резерві төмен науқастарда, сондай-ақ өкпенің интерстициальды ауруларын диагностикалауда жақсы нәтиже көрсетті.*

Зерттеудің мақсаты: *Өкпе мен медиастинальды органдардың қатерлі ісіктері кезінде өздігінен тыныс алуда интубациясыз хирургиялық араласуды клиникалық тәжірибеге енгізу.*

Әдістері: *анестезиологиялық көмек пен хирургиялық емнің техникалық ерекшеліктерінің негізгі сәттері көрсетілген екі клиникалық жағдай сипатталды.*

Нәтижелері: *өкпенің перифериялық қатерлі ісігі бар 2 науқасқа оперативті ем көрсетілді. Бірінші науқас: оң жақтық NI-VATS, жоғарғы (S2), төменгі (S6, S9) бөліктердің резекция, лимфодиссекция, екінші науқас: оң жақты NI-VATS, төменгі бөліктің лобэктомия, лимфодиссекция. Гистологиялық зерттеудің нәтижесі бойынша өкпенің қатерлі ісігі ерте сатыда анықталды. Операциядан соңғы химиясәулелі терапия көрсеткіш жоқ. Науқастар III клиникалық топ бойынша диспансерлік бақылауға алынды.*

Қорытынды: *Әдеби деректер мен алдын ала нәтижелеріне арналған деректер көрсеткендей, NI-VATS өкпенің қатерлі ісігін хирургиялық емдеуде хирургиялық араласулар орын алады және ҚР онкоторакальды бөлімшелерінде клиникалық практикаға кеңінен енгізілуі тиіс.*

Түйінді сөздер: *өкпенің қатерлі ісігі, NI-VATS, VATS, видео-ассистентті өкпе резекциясы, интубациясыз видеоторакоскопиялық лобэктомия, интубациясыз торакалды хирургия.*

АННОТАЦИЯ

ПЕРВЫЙ ОПЫТ ПРИМЕНЕНИЯ БЕЗИНТУБАЦИОННЫХ ВИДЕОАССИСТИРОВАННЫХ ТОРАКОСКОПИЧЕСКИХ РЕЗЕКЦИЙ ПРИ РАКЕ ЛЕГКОГО В РЕСПУБЛИКЕ КАЗАХСТАН

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Актуальность: *В ряде исследований было показано, что безинтубационные оперативные вмешательства, особенно хорошо себя зарекомендовали у больных с низким резервом сердечно-сосудистой и дыхательной систем, а также в диагностике интерстициальных заболеваний легких.*

Цель публикации *– описать опыт внедрения в клиническую практику оперативных вмешательств без интубации на спонтанном дыхании при злокачественных новообразованиях легких и органов средостения.*

Методы: *Описаны два клинических случая с освещением основных моментов анестезиологического пособия и технических особенностей проведения оперативного вмешательства.*

Результаты: *Двум больным с периферическим раком легких произведено оперативное лечение в объёме: в первом случае – NI-VATS справа, краевая резекция (S2) верхней, (S6, S9) нижней долей с лимфодиссекцией, во втором – NI-VATS справа, нижняя лобэктомия, лимфодиссекция. По результатам гистологического исследования у обоих больных диагностирован НМРЛ на начальных стадиях. Послеоперационная химиолучевая терапия не показана. Больные взяты на диспансерный учете по III клинической группе.*

Заключение: *Как показывают литературные данные и полученные нами предварительные результаты, оперативные вмешательства NI-VATS при хирургическом лечении рака легких имеют такие преимущества перед открытыми и VATS оперативными вмешательствами, как малая послеоперационная травма, быстрое восстановление больного, более короткое нахождение больных в стационаре, и поэтому должны широко внедряться в клиническую практику онкоторакальных отделений РК.*

Ключевые слова: *рак легких, видеоассистированная торакальная хирургия без интубации (NI-VATS), видеоассистированная торакальная хирургия (VATS), видеоассистированная резекция легких, безинтубационная видеоторакоскопическая лобэктомия, безинтубационная торакальная хирургия.*

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IMPACT OF CHLORIDE AND LEAD ION CONTENT IN OPEN WATER SOURCES IN KYZYLORDA REGION ON POPULATION'S CANCER INCIDENCE

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ABSTRACT

Relevance: *In 2004-2013, the cumulative cancer incidence was about 200 cases per 100 thousand in Kazakhstan, while in the disaster area of Aral Sea – about 225 cases per 100 thousand. For comparison, cancer incidence in the prosperous region of Karaganda was 140 cases per 100,000 people. As of 2021, the incidence of colorectal cancer in Kyzylorda was 17.73 compared to 5.81 per 100,000 people in 2015. Factors of the surrounding macro- and microenvironment are trigger factors for tumor initiation. Salt deposits of the dried Aral Sea in the form of solonchaks spread to the territory of the entire Kyzylorda region. Pesticides and process water have been discharged into rivers for many years, which has led to the accumulation of heavy metal salts in water and soil on the banks of the rivers and in the place of the dried-up Aral Sea, which in turn can affect the increase in cancer incidence.*

The aim was to *study the dependence of cancer incidence on water pollution by ions of chlorine and lead in open water bodies in the Kyzylorda region.*

Methods: *Analysis of cancer incidence in 2021 by localization: intestines, stomach, sarcomas, lungs, and melanomas in the Kyzylorda region. Determination of the content of chlorine ions by titration with silver nitrate, spectrophotometric determination of lead ions in the open water sources. Comparative correlation analysis of the concentration of chlorine ions and lead with cancer incidence in this region.*

Results: *The maximum permissible chlorine and lead ions concentrations in all studied open water sources of the Kyzylorda region exceeded the norm by 1.024-20.26 times and 1.4-14.1 times, respectively. The chlorides in the water increased intestine cancer incidence by 17% with an approximation certainty of 0.38. The lead in water increased the incidence of melanomas by 22%, with an approximation certainty of 0.79. The correlation coefficient was r=0.618; p=0.07 for exceeding chlorides' MPC and bowel cancer incidence.*

Conclusion: *Heavy metals like lead in water samples in regions with increased cancer incidence indicate a co-dependent relationship between these factors—pollutants such as chlorides and lead increase intestine cancer and melanoma incidence.*

Keywords: *Kyzylorda, melanoma, lung cancer, intestine cancer, chloride ions, lead ions.*

Introduction: New approaches in tumor diagnostics allowed studying the properties of tumor DNA and RNA, including coding and non-coding regions, size, structure, and other properties responsible for mutagenesis and malignancy in the body [1]. More accurate MN diagnostic methods can determine the influence of DNA-altering factors on the tumor initialization, prognosis, and response to treatment. K-ras and B-raf are classic tumor process markers in the mitogen-activated protein kinases' signaling cascade [2]. K-ras activates B-raf, which transmits a signal to MEK and ERK proteins. Then, the mitogen-activated protein kinase cascade triggers cell proliferation and differentiation; an excessive signal leads to malignization.

The surrounding macro- and microenvironment factors can initiate a tumor [3]. They affect the tumor volume and progression. Microenvironment factors include changes in the extracellular matrix's function and adipocytes, which support tumor progression close to tumor cells. Macroenvironment factors are systematic changes in the body that affect the growth of blood vessels and lymph nodes and changes in endocrine cascades, which can accelerate tumor growth and provoke resistance to therapy [4]. The pollutants, such as chloride and lead ions, originating from the environment, impact both the tumor and the systematic changes in the body, weakened by oncological processes. Mitogen-activated protein kinase cascade is also altered by pollutants since chemical elements such as chlorine and lead are specific ligands of enzyme proteins.

Studies of the environment and cancer development risk factors describe NaCl salt and heavy metals, including lead, as triggers for mutations and malignancy. They weaken the immune barrier, leading to cardiovascular, allergic, and oncological diseases [5-7]. Heavy metals can bind to receptors on the cell surface, activating altered cellular cascades, including proliferation and cell survival [8, 9].

Active agricultural activities such as cotton cultivation, a decrease in the water level in the Syrdarya and Amudarya rivers, and a gradual drying of the Aral Sea have increased the content of pollutants in the environment [10]. Salt deposits of the dried Aral Sea in the form of solonchaks spread all over the Kyzylorda region [11]. Many years of discharge of pesticides and process waters into rivers resulted in the accumulation of heavy metal salts in water and soil on the banks of the rivers and the place of the dried-up Aral Sea.

From 2004 to 2013, the cumulative cancer incidence in Kazakhstan was about 200 cases per 100,000 people, while in the disaster area of the Aral Sea, it reached 225 cases per 100,000 [12]. As a comparison, in the prosperous region of Karaganda, cancer incidence was 140 per 100,000. The colorectal cancer incidence in Kyzylorda was 17.73 in 2021 compared to 5.81 in 2015. This study was necessitated by an insufficient knowledge of chemical pollutants' effect on the Kyzylorda region population's health.

The aim was to study the dependence of cancer incidence on water pollution by ions of chlorine and lead in open water bodies in the Kyzylorda region.

The study tasks included an ecological analysis of chlorine and lead ions content in open water source samples in the Kyzylorda region and a comparative correlation analysis of chlorine and lead ions concentration with cancer incidence in this region.

Materials and methods: The water samples were taken from open sources (the Syrdarya River and its tributaries) in Zhanakorgan, Shieli, Kyzylorda, Terenozek, Baikonur, Kamysty Bas, and Aral localities to assess the ecological state of the Kyzylorda region (March 2021). The samples were examined for the content of chlorine and lead ions in the Republican Scientific Research Center "KAZEKOLOGIYA."

We determined water chlorides using the Mohr method and the International Organization for Standardization (ISO) standard. Chlorides were determined by titration with silver nitrate with potassium chromate indicator. We used 25 ml burettes, conical flasks, and graduated pipettes to conduct the reaction. If the initial pH of the water sample was higher than 5, nitric acid was used to titrate the probe to pH 4.4. If the sample pH was less than 5, calcium carbonate was used.

Lead was determined according to the ISO standard by flame absorption spectrometric method. The method involves aspirating the sample into the flame of an AAnalyst 400 atomic absorption spectrophotometer (Perkin Elmer, MA, USA). Hydrochloric and nitric acids were used to prepare the probe. Graduated pipettes, measuring flasks, and burettes were used to conduct the reaction. We used standard samples of lead ions dissolved in nitric acid to construct the calibration curve, which was measured and plotted as a standard. The reference peak for lead is 283.3 nm.

Based on the statistical department of the Regional Cancer Center of the city of Kyzylorda, incidence data were obtained in 2021 by localization: intestines, stomach, soft tissues, lungs, and melanomas.

The study was carried out as part of the dissertation work "Studying the influence of environmental factors on the occurrence of cancer in the Aral region" by F.K. Rakhimbekova, a candidate at Satpayev University.

We determined the indicators of maximum permissible concentrations (MPC) and compared them with the incidence in this region. Due to their relatively close location and similar environmental conditions, we united the Zhalagash, Terenozek, Kazaly, and Karmakshi districts. International sources recommend that the content of chlorides and lead should be low and not exceed 100 mg/l for chlorides and 0.005 mg/l for information in water [13-14]. Based on this comparison, we constructed graphs and analyzed the linear trend equations and the values of the accuracy of the R2 approximation. Further, the correlation coefficient between exceeding MPCs and cancer incidence was studied.

Results: All the studied water samples from open sources of the Kyzylorda region exceeded the MPCs (Table 1).

Table 1 – Chloride and lead ion content in open water sources in Kyzylorda region (March 2021)

Locality	Chloride and lead ion content in open water sources in Kyzylorda region (March 2021)					
	Chlorides (Cl^-), mg/l	Norm (Cl^-), mg/l	Multiplicity of MPC Cl^-	Pb^{2+}, mg/l	Norm Pb^{2+}, mg/l	Multiplicity of MPC Pb^{2+}
Zhanakorgan	175.2	100	1.752	0.022	0.005	4.4
Shieli	259.75	100	2.6	0.034	0.005	6.8
Kyzylorda	4355.5	100	43.555	0.0425	0.005	8.5
Terenozek	102.415	100	1.024	0.0206	0.005	4.12
Baikonur	256.6	100	2.566	0.007	0.005	1.4
Kamysty Bas	258.8	100	2.588	0.02	0.005	4
Aral	2025.97	100	20.26	0.0705	0.005	14.1

The highest cancer incidence (per 100,000 people) was observed in intestine cancer – 17.13 in Ky-zylorda vs. 8.6 in the Republic of Kazakhstan (RK); stomach cancer – 8,685 in Terenozek and

Zhalagash vs. 13.5 in the RK; breast cancer – 7.3 to 7.8 in Shieli, Zhanakorgan, and Kyzylorda vs. 26.3 in the RK; lung cancer – around 13 in Terenozek and Zhalagash vs. 18.9 in the RK.

Table 2 – Kyzylorda region population's cancer incidence, 2021

Sampling areas	Incidence (per 100,000 people)					
	Colorectal cancer	Stomach cancer	Sarcomas	Breast cancer	Lung cancer	Melanoma
Zhanakorgan	5.26	1.32	2.63	7.89	9.21	0
Shieli	5.1	6.36	3.82	7.64	11.46	2.56
Kyzylorda	17.13	3.26	4.1	7.35	14.7	2.45
Terenozek – Zhalagash	10.18	8.685	1.395	1.395	12.975	0
Baikonur	10.14	5.1	5.1	2.5	5.07	0
Karmakshy–Kazaly	8.66	3.25	1.3	7.15	8.435	1.52
Aral	4.11	1.3	2.5	1.3	5.48	0

The linear dependence of exceeding the MPCs of pollutants and the increase in cancer incidence showed a positive trend for chlorine ions, colorectal cancer, lead ions, and melanomas (Figures 1, 2). The chlorides in the water increased intestine cancer incidence by 17% with an approximation certainty of 0.38. The lead in water increased the incidence of melanomas by 22%, with an approximation certainty of 0.79.

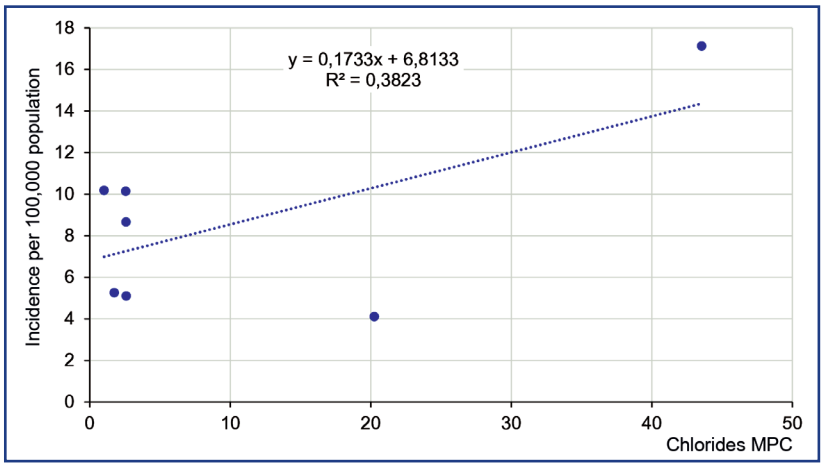

Figure 1 – Dependence of intestinal cancer incidence on exceeding the chlorides MPC in the Kyzylorda region water

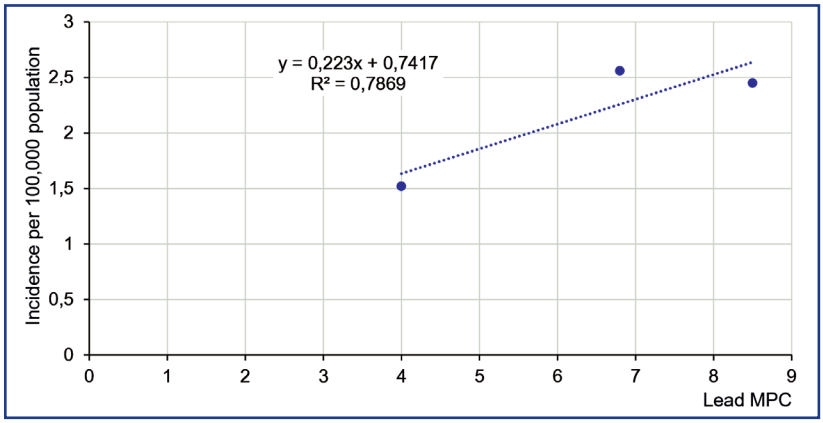

Figure 2 – Dependence of melanoma incidence on exceeding the lead MPC in the Kyzylorda region water

The correlation coefficient was r=0.618; p=0.07 for exceeding chlorides' MPC and bowel cancer incidence.

Discussion: Exceeding the chlorine and lead MPCs indicates significant environmental pollution in the Kyzylorda region (Table 1). As described by Morris et al., exceeding the pollutants' MPCs in water is a risk factor for developing many diseases, including cancer [15]. According to Li et al. [16], the pathogenic factor

of pollutants significantly reduces the polluted local population's quality of life and health [16].

Not all linear graphs of the correlation of exceeding MPCs and cancer incidence showed a significant increase in incidence, proving a multifactorial etiology of cancer [17]. Figures 1 and 2 show that pollutants increase intestine cancer and melanoma incidence by 17-22%. El-Tawil and Clapp et al. describe the pathogenic role of chlorides and lead in cancer development [18, 19].

When entering the body with water and food, chlorides mix with hydrogen protons, forming hydrochloric acid in the stomach (1). Its excess can enter the upper (esophagus) and lower (intestines) parts of the gastrointestinal tract [20].

$$Cl^- + H^+ = HCl \quad (1)$$

A reliable correlation between exceeding the MPCs of chlorides and intestinal cancer incidence increase indicates the role of increased Cl-content as a factor contributing to malignancy and subsequent cancer development [21].

Conclusion: Heavy metals like lead in water samples in increased cancer incidence regions indicate a co-dependent relationship between these factors: pollutants such as chlorides and lead increase intestine cancer and melanoma incidence.

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АҢДАТПА

ҚЫЗЫЛОРДА ОБЛЫСЫНДАҒЫ АШЫҚ СУ КӨЗДЕРІНДЕГІ ХЛОРИД ПЕН ҚОРҒАСЫН ИОНЫНЫҢ ХАЛЫҚТЫҢ ҚАТЕРЛІ ІСІК АУРУЫНА ӘСЕРІ

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Өзектілігі: *2004-2013 жылдар аралығында Қазақстанда онкологиялық аурулардың жиынтық көрсеткіші 100 мың адамға шаққанда 200 жағдайды құраса, Арал теңізінің апатты аймағында шамамен 100 мыңға шаққанда 225 жағдайды құрады. Салыстырмалы түрде айтсақ, өркендеген Қарағанды өңірінде қатерлі ісік ауруы 100 мың тұрғынға шаққанда 140 жағдайды құрады. 2021 жылы Қызылорда қаласында тоқ ішек қатерлі ісігімен сырқаттанушылық 2015 жылғы 100 000 тұрғынға шаққанда 5,81 көрсеткішпен салыстырғанда 17,73 құрады.*

Айналадағы макро- және микроорта факторлары ісік инициациясының триггер факторлары болып табылады. Кеуіп қалған Арал теңізінің сортаң түріндегі тұзды шөгінділері бүкіл Қызылорда облысының аумағына тарады. Көптеген жылдар бойы пестицидтер

мен технологиялық сулар өзендерге төгілуде, бұл өзендердің жағалауларында және кеуіп қалған Арал теңізінің орнында су мен топырақта ауыр металл тұздарының жиналуына әкеліп соқтырды, бұл өз кезегінде әсер етуі мүмкін. қатерлі ісік ауруының артуы.

Зерттеудің мақсаты *– Қызылорда облысындағы ашық су айдындарындағы хлор және қорғасын иондарымен судың ластануына қатерлі ісік ауруларының тәуелділігін зерттеу.*

Әдістері: *Қызылорда облысы бойынша 2021 жылы локализация бойынша онкологиялық ауруларды талдау: ішек, асқазан, саркомалар, өкпе және меланома. Күміс нитратымен титрлеу арқылы хлор иондарының құрамын анықтау, ашық су көздеріндегі қорғасын иондарын спектрофотометриялық анықтау. Хлор мен қорғасын иондарының концентрациясының осы аймақтағы ісік ауруымен салыстырмалы корреляциялық талдауы.*

Нәтижелері: *Қызылорда облысының барлық зерттелген ашық су көздерінде хлор мен қорғасын иондарының шекті рұқсат етілген концентрациясы нормадан 1,024-20,26 есеге жоғары болды; тиісінше 1,4-14,1 есе. Суда хлоридтердің болуы 0,38 жуық сенімділікпен ішек қатерлі ісігінің ауруын 17%-га арттырды. Суда қорғасынның болуы 0,79 жуық сенімділікпен меланома ауруын 22%-га арттырды. Корреляция коэффициенті r=0,618; p=0,07 хлоридтердің ШРК асып кетуі және ішек ісігінің жиілігі.*

Қорытынды: *Қатерлі ісік ауруы жоғары аймақтардағы су үлгілерінде қорғасын сияқты ауыр металдардың болуы осы факторлардың өзара тәуелді байланысын көрсетеді. Хлоридтер мен қорғасын сияқты ластаушы заттар ішек ісігі мен меланома ауруын арттырады.*

Түйінді сөздер: *Қызылорда, меланома, өкпе рагы, ішек ісігі, хлор иондары, қорғасын иондары.*

АННОТАЦИЯ

ВЛИЯНИЕ СОДЕРЖАНИЯ ИОНОВ ХЛОРА И СВИНЦА В ОТКРЫТЫХ ИСТОЧНИКАХ ВОДЫ В КЫЗЫЛОРДИНСКОЙ ОБЛАСТИ НА ОНКОЗАБОЛЕВАЕМОСТЬ НАСЕЛЕНИЯ

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Актуальность: *В 2004-2013 годах суммарная онкозаболеваемость составила около 200 случаев на 100 тысяч населения по Казахстану, в то время как в зоне бедствия Аральского моря – около 225 случаев на 100 тысяч населения. Для сравнения, онкозаболеваемость в благополучном регионе Караганды составила 140 случаев на 100 тысяч населения. На 2021 год, заболеваемость колоректальным раком в Кызылорде составила 17,73 по сравнению с 5,81 на 100 тысяч населения в 2015 году.*

Факторы окружающей макро- и микросреды являются триггерными факторами инициации опухоли. Отложения соли высохшего Аральского моря в виде солончаков распространились на территорию всей Кызылординской области. Пестициды, применяемые в сельском хозяйстве, и техническая вода сбрасывались на протяжении многих лет в реки, что привело к накоплению солей тяжелых металлов в воде и почве на берегах рек и на месте высохшего Аральского моря, что, в свою очередь, может влиять на повышение онкозаболеваемости.

Цель исследования *– изучить зависимость онкозаболеваемости от загрязнений воды ионами хлора и свинца открытых водоемов в Кызылординской области.*

Методы: *Проведен анализ онкозаболеваемости в 2021 году в Кызылординской области по локализациям: кишечник, желудок, саркомы, легкие и меланомы. Определено методом титрирования нитратом серебра содержание ионов хлора, спектрофотометрическое определение ионов свинца в воде открытых водоемов. Выполнен сравнительный корреляционный анализ концентрации ионов хлора и свинца с онкозаболеваемостью данного региона.*

Результаты: *Предельно допустимые концентрации (ПДК) ионов хлора и свинца во всех исследуемых открытых водоемах Кызылординской области превышали норму в 1,024-20,26 раз и 1,4-14,1 раз, соответственно. Присутствие хлоридов в воде повысило заболеваемость колоректальным раком на 17%, при достоверности аппроксимации 0,38. Наличие свинца в воде повысило заболеваемость меланомами на 22%, при достоверности аппроксимации 0,79. Коэффициент корреляции превышения ПДК хлоридов и увеличения заболеваемости колоректальным раком составил r=0,618; p=0,07.*

Заключение: *Наличие тяжелых металлов, в данном случае свинца, в пробах воды в регионах с повышенной онкозаболеваемостью указывает на созависимую связь этих факторов. Такие поллютанты, как хлориды и свинец, способствуют повышению заболеваемости раком кишечника и меланомой.*

Ключевые слова: *Кызылорда, меланома, рак легких, рак кишечника, ионы хлора, ионы свинца.*

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RARE CASES OF METHEMOGLOBINEMIA IN CANCER PATIENTS: CLINICAL CASES

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ABSTRACT

Relevance: *Methemoglobinemia is a serious disease characterized by impaired oxygen binding to iron in hemoglobin, followed by impaired oxygen delivery to body tissues. Various drugs, including antacids containing benzocaine, can cause acquired methemoglobinemia. The presented clinical cases describe methemoglobinemia that arose in connection with the use of the antacid Almagel A in a 32-year-old woman who underwent surgery on the laryngopharynx, suffering from T3NxM0 St III hypopharyngeal cancer and in a 45-year-old woman diagnosed with cancer of the left kidney St I. Condition after resection of the left kidneys.*

The study aimed to *describe clinical cases of acquired methemoglobinemia induced by Almagel A (antacid), widely used in post-antitumor therapy treatment of cancer patients with digestive system diseases.*

Methods: *We present clinical cases of methemoglobinemia in patients (32 and 45 years old) hospitalized at JSC "Kazakh Research Institute of Oncology and Radiology." Complaints, anamnesis of the disease, clinical picture, and clinical, laboratory, and instrumental test results were analyzed retrospectively.*

Results: *This article reports on the clinical picture of our patients, discusses the causes and mechanisms of possible poisoning, and reviews the latest recommendations for the treatment of methemoglobinemia. Treatment with intravenous methylene blue led to a rapid improvement in the patient's respiratory status.*

Conclusion: *Acquired methemoglobinemia is an acute condition that most often results from poisoning with certain drugs and compounds, which can be fatal. These clinical cases demonstrate the difficulties of diagnosing methemoglobinemia, highlight the value of taking anamnestic data, studying the acid-base state and blood gases, and the effectiveness of using methylene blue as an antidote drug in treatment.*

Keywords: *Methemoglobinemia, methylene blue, hypoxia, cyanosis, acrocyanosis.*

Introduction: Methemoglobinemia is a rare disease characterized by elevated levels of methemoglobin (MetHb), a hemoglobin (Hb) molecule containing an oxidized form of iron that cannot bind oxygen and leads to an insufficient supply of tissues by oxygen. Methemoglobinemia has two forms – genetic and acquired [1].

Genetic methemoglobinemia is a chronic disease that leads to numerous complications, and patients present cyanosis without other accompanying symptoms. On the other hand, an acquired methemoglobinemia is an acute condition most commonly due to poisoning after intake of certain drugs and compounds, which can lead to a fatal outcome [2].

The manifestation of symptoms depends on the percentage of MetHb in blood, and the clinical picture varies from fatigue, anxiety, dizziness, and cyanosis to qualitative disorders of consciousness, epileptic seizures, arrhythmia, and coma. Unexplained symptoms of refractory hypoxia, cyanosis-saturation, and chocolate-colored blood may raise suspicion of methemoglobinemia, but a definitive diagnosis is made by Co-oximetry and determination of MetHb levels in the blood. Treatment of methemoglobinemia is based on supportive care and withdrawal of the drug or substance that caused that condition. Although acquired methemoglobinemia is a rare disease, it can be a life-threatening condition, so emergency services should be provided with antidotes such as methylene blue and vitamin C [3].

The study aimed to describe clinical cases of acquired methemoglobinemia induced by Almagel A (antacid), widely used in post-antitumor therapy treatment of cancer patients with digestive system diseases.

Materials and Methods: The paper presents clinical cases of methemoglobinemia in patients (32 and 45 years old) who underwent inpatient treatment at "Kazakh Institute of Oncology and Radiology" JSC. Registered complaints, medical history, clinical picture, and clinical, laboratory, and instrumental test results were analyzed retrospectively. The PubMed Electronic Database (NCBI) was searched to identify the randomized controlled and prospective observational studies, systematic reviews and meta-analyses, and the scientific articles published in English in 2015-2023.

Description of the clinical case No. 1

Patient information: Female A., born in 1975, diagnosed with "Left kidney cancer, stage I," 6 days after planned left kidney resection.

Anamnesis: The patient mentioned she was taking Almagel A containing benzocaine at 1 dosing spoon TID, which could cause an increase in MetHb levels.

Clinical findings:

During the initial examination at the Urologic Oncology Department, the patient complained of acute malaise, dizziness, headache, and cyanosis of the nasolabial triangle, fingers, and toes, which appeared at night on the 6th day after surgery.

Diagnostics:

Normal consciousness, adequate, easy to contact. The patient maintained normal blood pressure (BP – 134/88 mm Hg) and heart rate (heart rate – 74/min); normothermia (T – 36.5°C), but tachypnea and hypoxia (SpO_2 – 78%) were observed. Over the lungs, the respiration is vesicular, with no pulmonary rales.

For severe conditions, the patient was transferred to the Anesthesiology, Resuscitation, and Intensive Care Department of "Kazakh Institute of Oncology and Radiology" JSC to determine the causes of respiratory failure and acute hypoxia, perform clinical, laboratory, and instrumental tests, and provide intensive care.

Chest CT scan: no pathology. Spirometry: VC – 82%, within the conditional norm. On the ECG: sinus rhythm, heart rate – 78 beats per minute. QRS axis – not deviated. Incomplete RBBB. Impaired repolarization processes along the anterior wall of the left ventricle. Echocardiogram: EF – 75%. The heart cavities were not dilated, with no areas of hypokinesis; the heart LV contractility and EF LV function were satisfactory.

Laboratory parameters: General and biochemical blood count and coagulogram were normal. The test for D-dimer, an active thrombosis marker, showed 217 ng/ml, a norm. Procalcitonin, the earliest and most reliable "blood inflammation" (sepsis) indicator, was normal at 0.1 ng/ml.

The arterial blood sample was dark brown. Analysis of arterial blood gases (acid-base balance) at normal room air showed pH – 7.44, normal partial pressure of oxygen (pO_2 – 212), normal oxygen saturation (SO_2 – 97.4%), MetHb fraction elevation to 24.4%, and oxyhemoglobin fraction A decline (FO_2Hb – 74.1%).

A clear correlation between the appearance of cyanosis of the nasolabial triangle, fingers, and toes with the intake of Almagel A, the signs of respiratory failure (RR – 20 per minute), acute hypoxia (SpO_2 level – 78%), and FMetHb high level (24.4%) revealed during physical examination made it possible to establish the diagnosis of Acute acquired methemoglobinemia of moderate severity.

Treatment:

The prescribed antidote therapy included the 1% methylene blue infusion at a dose of 1 mg/kg IV, oxygen therapy, and the monitoring of MetHb, SpO_2, and skin color.

Results: Against the infusion of methylene blue, the patient's lips, fingers, and toes turned pink, the headache stopped, and SpO_2 elevated to 96%. There was a gradual decrease of the MetHb fraction of FMetHb to 14.3%, then to normal FMetHb values of 3.0%. The oxyhemoglobin content (FO_2Hb) increased to 93.6%.

The patient with positive dynamics was transferred to a specialized department.

Description of the clinical case No. 2

Patient information: Patient B., born in 1991, was diagnosed with "Laryngeal cancer T3NxM0, stage III. Status after chemotherapy. Progression. Esophagopharyngotracheostoma" on Day 11 after the planned surgery in the scope of "Laryngopharyngoectomy with esophageal-pharynx-tracheostomy, with IJV ligation on the left side, and leftward hemithyroidectomy."

It was also known from the patient's history that the antacid drug Almagel A, containing benzocaine, had been taken uncontrollably for several days, which could have caused the MetHb elevation.

Clinical findings:

Upon examination in the department of head and neck tumors, the patient had the following symptoms: weakness, pronounced dyspnea, and cyanosis of the nasolabial triangle, lips, fingers, and toes.

The patient is hyposthenic, available for contact, hypotension (BP 90/60 mm Hg), tachycardia (heart rate – 102/min), tachypnea (RR – 22/min), and hypoxia (SpO_2 – 74%). Auscultatively: vesicular respiration over the lungs, no rales. The patient was transferred to the Anesthesiology, Resuscitation, and Intensive Care Department of "Kazakh Institute of Oncology and Radiology" JSC" to determine the causes of respiratory failure and acute hypoxia, perform clinical, laboratory, and instrumental tests, and provide intensive care.

Diagnostics:

The complete blood count and blood biochemistry, electrocardiogram, plain chest X-ray, ultrasound examinations of the heart and blood vessels, veins of the lower extremities, abdominal organs and kidneys, computed tomography of the chest cavity with contrast-enhanced, and doctor counseling excluded acute coronary syndrome, pulmonary embolism, respiratory obstruction, and acute surgical pathology.

The analysis of arterial blood gases (acid-base balance) at normal room air showed the following: pH – 7.47, normal partial pressure of oxygen (pO_2 – 85.5), normal oxygen saturation (SO_2 – 95.4%), elevation of the level of MetHb fraction (FMetHb – 49.3%), decline of oxyhemoglobin fraction (FO_2Hb – 47.8%), dark-brown color of the blood sample was noted.

Visible signs: cyanosis of the nasolabial triangle, lips, fingers, and toes revealed signs of respiratory failure (RR – 22 beats/min), acute hypoxia (SpO_2 – 74%), and high level of FMetHb (49.3%), as well as anamnestic data on the use of Almagel A, made it possible to establish the diagnosis: Acute acquired methemoglobinemia of moderate severity.

Treatment:

The patient was prescribed antidote therapy with 1% methylene blue at 1 mg/kg as an infusion, oxygen therapy, MetHb, SpO2, and skin color monitoring.

Results: Over time, against a positive effect of methylene blue infusion, the patient showed clinical improvement with the disappearance of cyanosis, the MetHb level returned to normal value (FMetHb – 1.8%), and the oxyhemoglobin fraction increased (FO_2Hb – 93.8%). The patient with positive dynamics was transferred to a specialized department.

Discussion: Methemoglobinemia is characterized by ferrous iron oxidation from divalent to trivalent form in a Hb molecule. Oxygen can bind with Hb only in the divalent (glandular) form, and as a result of binding, oxygen is temporarily oxidized to the trivalent form. The various substances listed below can lead to the state when Hb will remain permanently in the trivalent form and thus no longer be able to bind the oxygen. Consequently, the symptoms of methemoglobinemia directly result from inadequate oxygen transportation.

The specific mechanism is the Hb molecule allosteric change. Besides, due to further changes in the oxygen-hemoglobin dissociation curve (change in oxygen dissociation to the left), peripheral oxygen excretion, hypoxia, and functional anemia are reduced without a Hb level decline [1-4].

The Medline search revealed 71 cases of benzocaine-induced methemoglobinemia. The review of the listed links revealed 18 additional case reports. The earliest publication about benzocaine-induced methemoglobinemia was made by Ocklitz in 1949. He reported methemoglobinemia in two children treated with benzocaine powder sprayed into the mouth for symptomatic relief of stomatitis [5].

Benzocaine (ethylamine benzoate) is widely used as a local anesthetic and recognized as a cause of methemoglobinemia. Although this complication is uncommon, it can be potentially serious and even fatal. However, methemoglobinemia is not listed as a complication in the instructions for use or in the package inserts for some benzocaine-containing products. Benzocaine is also found in various over-the-counter medications (such as Almagel A), and methemoglobinemia can occur in case of their use. This can present a challenging diagnostic problem if the physician is not aware of the effect of benzocaine, resulting in a delay in establishing the correct diagnosis and initiating appropriate treatment [5].

Various common medications can lead to the development of methemoglobinemia (Table 1).

Table 1 – Drugs and substances that can lead to methemoglobinemia

Drug group	Represented by
Local anesthetics	Benzocaine (often used in endoscopic procedures) Prilocaine, tetracaine, lidocaine
Nitrates	Nitroglycerin Inhaled nitrogen oxide Nitroprusside, oral nitrates, amyl nitrate
Antibiotics	Dapsone Rifampicin, sulfonamides, antimalarials
Other drugs	Rasburicase (especially in G6PD deficiency) Oncology drugs: cyclophosphamide Metoclopramide Various preparations that use an oxidizing substance in their production
Environmental causes	Fertilizers, herbicides Plastics (various kinds) Paints & Rubber

The clinical picture of methemoglobinemia is diverse and depends on the percentage of methemoglobin, the patient's usual Hb level, and cardiovascular reserve. The normal percentage of MetHb is below 25%. Patients with levels between 3% to 15% are usually asymptomatic, and cyanosis is rare. Patients with a 20-30% MetHb fraction are always symptomatic, with mild symptoms such as fatigue, tachypnea, dyspnea, tach-

ycardia, anxiety, dizziness, qualitative disturbance of consciousness, nausea, and vomiting. When the MetHb level is above 40%, such serious and life-threatening symptoms as epileptic seizures, coma, arrhythmias, and elevated lactate levels, to the extent of death, are observed (Table 2) [1, 3].

Table 2 – Signs, symptoms, and causes of methemoglobinemia

MetHb level	Clinical indicators	Symptoms	Causes
<10%	Low pulse oximeter readings, skin discolora-tion (pale, gray, bluish)	Asymptomatic	Acquired
10%-30%	Cyanosis, dark-brown blood	Asymptomatic course / confused consciousness	Enzymopenic methemoglo-binemia, M-group variants of Hb acquired
30%-50%	Dyspnea, dizziness, faintness	Confused consciousness, chest pain, palpitations, headache, fatigability	Acquired, hereditary
50%-70%	Tachypnea, metabolic acidosis, arrhythmias, convulsions, delirium, coma	Confused consciousness, chest pain, palpitations, headache, fatigability	Acquired, hereditary
>70%	Severe hypoxemia, fatal outcome	-	Acquired, hereditary

The diagnosis of methemoglobinemia is confirmed by arterial or venous blood gas composition with Co-oximetry that determines the Hb for identification of concentration and percentage of methemoglobin; SpO_2 measurements cannot be used to directly determine the methemoglobinemia severity. However, the clinical suspicion itself can be made based on the following three objects [1, 2, 5]:

– Refractory hypoxia: methemoglobinemia can usually be suspected in a patient with an oxygen saturation of 82% to 86%, who is on high oxygen flow (FiO_2 100%), and there is no other explanation of hypoxia [5].

– "Cyanosis-saturated rupture": methemoglobinemia leads to central cyanosis (attention to the tongue's color). Oxygen saturation of 80-90% usually does not lead to cyanosis. Hence, methemoglobinemia is clinically suspected in patients with 80-90% saturation with central cyanosis [5].

– The brown color of blood: methemoglobinemia causes the blood color to change to chocolate. In addition, if the patient's blood is placed on white gauze, the blood will remain brown when it dries, unlike the deoxygenated blood, which will absorb the oxygen from the air and turn red again [5].

Treatment of methemoglobinemia involves the removal of the provoking agent and consideration of treatment with the antidote methylene blue (tetramethylthionine chloride). The high-velocity oxygen delivered through nasal cannulas or masks increases the oxygen delivery to tissues and enhances the natural degradation of MetHb [1, 3].

The methylene blue generally works quickly and efficiently due to its interaction with the aforementioned secondary MetHb recovery pathway, where NADPH-MetHb reductase reduces the methylene blue to leucomethylene blue using NADPH from G6PD-dependent hexose-monophosphate shunt. Subsequently, the leucomethylene blue acts as an electron donor, recovering the MetHb to Hb [1, 3, 5].

In cases of acquired methemoglobinemia, treatment with methylene blue should be given when MetHb levels are greater than 20-30% or lower if the patient has symptoms. Treatment decisions should be made based on clinical manifestations rather than delayed until confirmed laboratory findings. The dose of methylene blue is 1-2 mg/kg (0.1-0.2 ml/kg of 1% solution) intravenously for 5 minutes. The dose may be repeated after 30-60 minutes if significant symptoms or levels remain above the treatment threshold [1, 2, 5].

Practitioners should be aware of the side effects of methylene blue. Benign side effects include staining the urine to a green or blue, which patients should be alerted about. Caution should also be followed in treating newborns, as they are also very sensitive to oxidants. Besides, methylene blue is contraindicated for pregnant women [1].

When treatment with methylene blue is ineffective or not recommended, additional options may include ascorbic acid, substitution transfusion, and hyperbaric oxygen therapy [2, 4, 5]. High doses of ascorbic acid (vitamin C), up to 10 g/dose intravenously, may be considered for treating MetHb. However, it is generally ineffective and not considered the standard of treatment. High doses of ascorbic acid are associated with increased urinary excretion of oxalates. In the presence of renal insufficiency, high doses of ascorbic acid may predispose to renal failure due to hyperoxaluria [4].

Conclusion: Acquired methemoglobinemia is an acute condition that is most often the result of poisoning with some drugs and compounds and can lead to

a fatal outcome. The described cases could be unique since both patients presented tachycardia, tachypnea, and hypoxemia, with no other common manifestations. The only clinical symptom reported by both patients was general tiredness.

However, measurements of PaO_2, SpO_2, and MetHb concentrations indicated that both patients suffered from methemoglobinemia caused by benzocaine, a component of Almagel A.

Many patients and practitioners assume that over-the-counter medications (Almagel A) pose no risk. The presented clinical cases of acquired methemoglobinemia in cancer patients show that using the antacid drug Almagel A against the background of antitumor treatment for a long time without medical supervision leads to serious complications. These clinical cases demonstrate the complexity of diagnostics of methemoglobinemia and highlight the value of the anamnestic data collection, acid-base and blood gas studies, and the efficacy of methylene blue as an antidote for treating methemoglobinemia.

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АНДАТПА

ҚАТЕРЛІ ІСІКПЕН АУЫРАТЫН НАУҚАСТАРДАҒЫ МЕТЕМОГЛОБИНЕМИЯНЫҢ СИРЕК КЕЗДЕСЕТІН ЖАҒДАЙЛАРЫ: КЛИНИКАЛЫҚ ЖАҒДАЙЛАР

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Өзектілігі: *Метемоглобинемия – гемоглобиндегі оттегінің темірмен байланысуының бұзылуымен, одан кейін дене тіндеріне оттегінің жеткізілуінің бұзылуымен сипатталатын ауыр ауру. Әртүрлі препараттар, соның ішінде бензокаин бар антацидтер жүре пайда болған метгемоглобинемияны тудыруы мүмкін. Ұсынылған клиникалық жағдайлар жұтқыншақ ісігімен ауыратын, көмейге операция жасалған 32 жастағы әйелде және сол бүйректің қатерлі ісігімен диагнозы қойылған 45 жастағы әйелде сол бүйрек резекциясынан кейінгі Алмагель А антацидті препаратын қолданумен байланысты метгемоглобинемияны сипаттайды.*

Зерттеудің мақсаты *– Ісікке қарсы терапиядан кейін ас қорыту жүйесінің аурулары бар қатерлі ісікпен ауыратын науқастарды емдеуде кеңінен қолданылатын Алмагель А (антацид) индукцияланған метгемоглобинемияның клиникалық жағдайлын сипаттау.*

Әдістері: *Біз «Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ ауруханасына жатқызылған науқастарда (32 және 45 жаста) метгемоглобинемияның клиникалық жағдайларын ұсынамыз. Шағымдар, ауру анамнезі, клиникалық көрінісі, клиникалық, зертханалық және аспаптық зерттеу әдістерінің нәтижелері ретроспективті түрде талданды.*

Нәтижелері: *Бұл мақалада науқастарымыздың клиникалық көрінісі туралы баяндалады, ықтимал уланудың себептері мен механизмдері талқыланады және метгемоглобинемияны емдеуге арналған соңғы ұсыныстар қарастырылады. Көктамырішілік метилен көкпен емдеу науқастың тыныс алу жағдайының жылдам жақсаруына әкелді.*

Қорытынды: *Жүре пайда болған метгемоглобинемия – бұл көбінесе өлімге әкелуі мүмкін белгілі бір препараттармен және қосылыстармен уланудан туындайтын өткір жағдай. Бұл клиникалық жағдайлар метгемоглобинемияны диагностикалаудың қиындықтарын көрсетеді, анамнестикалық мәліметтерді алудың, қышқылдық-негіздік күйді және қан газдарын зерттеудің маңыздылығын, сонымен қатар емдеуде метилен көкін антидот ретінде қолданудың тиімділігін көрсетеді.*

Түйінді сөздер: *Метгемоглобинемия, метилен көк, гипоксия, цианоз, акроцианоз.*

АННОТАЦИЯ

РЕДКИЕ СЛУЧАИ МЕТГЕМОГЛОБИНЕМИИ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: КЛИНИЧЕСКИЕ СЛУЧАИ

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Актуальность: *Метгемоглобинемия представляет собой серьезное заболевание, характеризующееся нарушением связывания кислорода с железом в гемоглобине с последующим нарушением доставки кислорода к тканям организма. Различные препараты, включая антацидные средства, содержащие в составе бензокаин, могут вызывать приобретенную метгемоглобинемию. Представленные клинические случаи описывают метгемоглобинемию, которая возникла в связи с использованием антацидного средства Алмагель А у 32-летней женщины, перенесшей операцию на гортаноглотке, страдающей раком гортаноглотки T3NxM0 St III и у 45 летней женщины с диагнозом рак левой почки St I. Состояние после резекции левой почки.*

Цель публикации *– описать клинические случаи приобретенной метгемоглобинемии, индуцированной Алмагелем А – антацидным средством, которое широко используется в лечении онкологических больных с заболеваниями органов пищеварения после проведения противоопухолевой терапии.*

Методы: *Представлены клинические случаи метгемоглобинемии у пациентов (32 и 45 лет), находившихся на стационарном лечении в АО «Казахский научно-исследовательский институт онкологии и радиологии». Проанализированы ретроспективно жалобы, анамнез болезни, клиническая картина, результаты клинико-лабораторных и инструментальных методов исследований.*

Результаты: *В данной статье описана клиническая картина у пациентов с метгемоглобинемией, обсуждаются причины и механизмы возможного отравления, а также рассматриваются последние рекомендации по лечению метгемоглобинемии. Лечение внутривенным введением метиленового синего привело к быстрому улучшению респираторного статуса пациента.*

Заключение: *Приобретенная метгемоглобинемия, представляет собой острое состояние, которое чаще всего является результатом отравления некоторыми лекарствами и соединениями и может привести к летальному исходу. Представленные клинические случаи демонстрируют сложность диагностики метгемоглобинемии, подчеркивают ценность сбора анамнестических данных, исследования кислотно-основного состояния и газов крови, а также эффективность использования метиленового синего в качестве антидотного препарата при лечении метгемоглобинемии.*

Ключевые слова: *Метгемоглобинемия, метиленовый синий, гипоксия, цианоз, акроцианоз.*

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FEATURES OF ENDOSCOPIC DIAGNOSIS OF DIFFUSE GASTRIC CANCER

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ABSTRACT

Relevance: *Linitis plastica denotes a diffuse type of carcinoma, which accounts for 3-19% of gastric adenocarcinoma. It is characterized by rigidity of most or all of the stomach without a filling defect or extensive ulceration.*

The article describes *the experience of endoscopic diagnostics of patients diagnosed with Linitis Plastica during 2019-2022 and the 1st half of 2023 at the Center for Expert Endoscopy and Interventional Radiology of the National Research Oncology Center (NROC), Astana, Kazakhstan.*

The study aimed to *evaluate the features of the use of endoscopic diagnostic methods in diagnosing diffuse gastric cancer.*

Methods: *a retrospective analysis of diagnosed cases of diffuse gastric cancer in the center of expert endoscopy was carried out from 2019 to the 1st half of 2023.*

Results: *All patients were initially examined in polyclinics at their place of residence by computed tomography gastroscopy with biopsy and, upon receiving a negative morphological examination, were sent to us for expert examination and repeated biopsy. The cohort included seven patients (2 men and five women) with an average age of 54.6 years (33 to 71 years). Expert gastroscopy and a special technique for taking biopsy material from the gastric mucosa helped make the correct morphological diagnosis for all seven patients with suspected diffuse gastric cancer. Considering the local and generalized metastases and concomitant pathologies, only four patients underwent surgery, and three were administered only chemotherapy. Five patients have died, and two continue palliative chemotherapy.*

Conclusion: *Plastic gastritis is a form of adenocarcinoma that usually manifests itself at an advanced stage when drug therapy is usually unsuitable. The prognosis can be improved with complete resection. Surgical intervention should be performed only in cases where complete resection is expected. Expert gastroscopy and the use of a special technique for taking biopsy material (according to J. Rohl) from the gastric mucosa increases the morphological value of biopsies and gives a chance to confirm the diagnosis of diffuse gastric cancer and quickly begin surgical treatment or palliative chemotherapy.*

Keywords: *Linitis Plastica (LP), diffuse gastric cancer, gastrointestinal cancer, Bormann IV, endoscopy.*

Introduction: Linitis Plastica (LP) is a diffuse form of gastric cancer and accounts for about 10% of all cases of gastric adenocarcinoma; its exact distribution in the general population is unknown. LP affects women more often than men and is more common for Asians than Caucasians. The age group of patients is lower than in classic gastric adenocarcinoma, and the disease often begins below 40 years, sometimes among very young patients (20 to 25 years old). There are no distinctive or specific indicative symptoms; the symptoms are similar to other forms of gastric cancer and can include fullness after eating, nausea and vomiting, epigastric pain, weight loss, and progressive dysphagia [1]. LP is characterized by malignant glandular proliferation of cricoid cells in the fibrous stroma, ultimately leading to thickening and rigidity of the stomach wall. There are two types of LP: the 1st type of lesion begins from the proximal part of the stomach (body) in the folds thickening form; the 2nd type, the so-called "flat," begins from the antrum and is characterized by the folds flattening and stiffness (Figure 1).

These methods of radiation diagnostics give the right to suspect the presence of a diffuse process in the stomach wall but also require morphological verification. Thus, with this disease, the stomach fluoroscopy reveals a decrease in the stomach size, walls thickening, loss of motility, and pylorus ostium (Figure 2).

Computed tomography of the stomach shows diffuse walls thickening, decreased stomach lumen, and lymphadenopathy of paragastric lymph nodes (Figure 3).

The gastric endosonography reveals the thickening and blurring of the first three sonographic layers and a significant thickening of the 4th layer (Figure 4). The endosonographically guided needle biopsy (EUS with FNA) ensures a sensitivity below 30% since the cells are located in the fibrosis thickness both in a chain and alone.

Unlike other gastric cancers, LP often and quickly leads to lymphatic and peritoneal dissemination. Gastric LP can be primary or secondary due to infiltrating lobular breast carcinoma. LP is commonly sporadic, but family cases have also been reported [2].

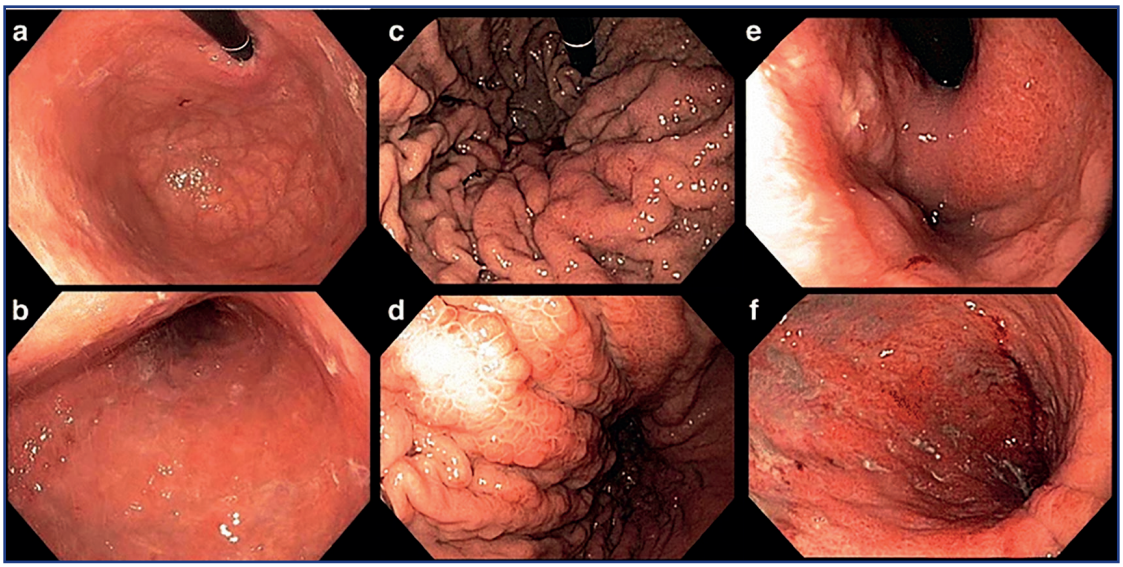

Figure 1 – Endoscopic types of diffuse gastric cancer: a-b – normal gastric mucosa, c-d – type 1 diffuse gastric cancer, e-f – type 2 (flat) diffuse gastric cancer [1]

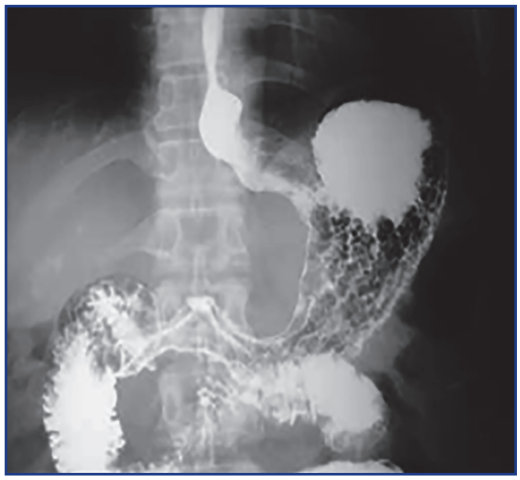

Figure 2 – X-ray picture of diffuse gastric cancer [1]

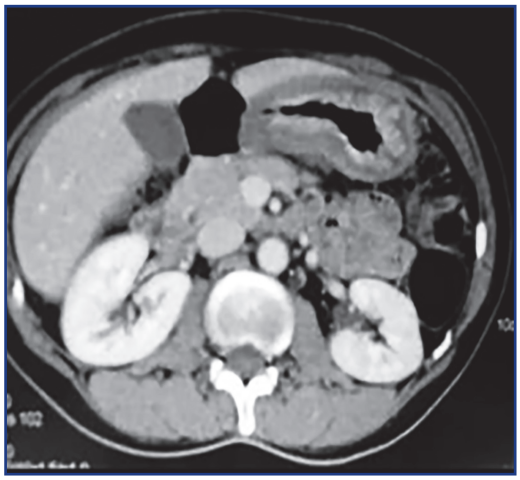

Figure 3 – Computed tomography of the stomach in diffuse gastric cancer [1]

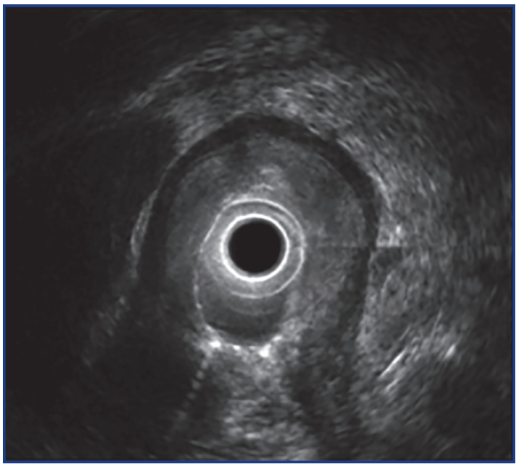

Figure 4 – Endosonographic picture in diffuse gastric cancer [1]

Materials and methods: This study is part of a single-center retrospective study evaluating the effectiveness of endoscopic technologies in diagnosing diffuse gastric cancer. The case histories of 7 patients with diffuse gastric cancer, diagnosed and treated in the clinic of the National Research Oncology Center

(NROC, Astana, Kazakhstan), have been retrospectively analyzed. Patients diagnosed with LP were identified from the cancer database, and their clinical and pathological data have been extracted from relevant case histories. All cases were discussed in a multidisciplinary group, and their clinical progress and outcome have been noticed.

Results: All patients were initially examined at their local polyclinics and referred for CT and esophagogastroduodenoscopy with biopsy. Upon receiving a negative morphological examination, patients were sent to the NROC for expert examination and repeated biopsy. Their demographics, symptoms, endoscopy results, treatment details, and survival statistics are summarized in Table 1. The cohort included seven patients (2 males and five females) with an average age of 54.6 (33 to 71 years). The main manifested signs and symptoms were dysphagia and weight loss. The stomach was affected in 100% of cases. LP was detected in 100% of cases after a second biopsy by J. Rohl method, performed at the NROC. Primary and repeated biopsies were negative in all patients, and chronic hyperplastic gastritis was concluded.

In order to improve the accuracy of subsequent morphological examination, all patients referred to NROC with suspected diffuse gastric cancer during expert gastroscopy were biopsied using a special technique (according to J. Rohl, 2013). Namely, the biopsy material from the gastric mucosa has been taken polytopically from several points, step by step, using the Adson forceps. Besides, for reliability, the protruding part of the mucous membrane was resected using the diathermic loop and subsequent sampling of the biopsy specimen from the resected bed. One patient (case 1) was examined thrice since the first endoscopy revealed diffuse mucosa inflammation, and the biopsy showed only chronic inflammation without dysplasia signs. CT scan suspected LP but without a histological verification. A second endoscopy and biopsy were negative. Surgery was not offered to two patients with metastatic disease and one with extensive local organ involvement. Only four patients had local lymph node damage and no serious comorbidities, making performing a gastrectomy and subsequent chemotherapy possible. Five of 7 patients died within 2-7 months of follow-up period. At this point, the maximum survival rate recorded in that patient cohort was seven months.

Table 1 – Details of patients with diffuse gastric cancer

№	Age, gender	Symptoms	Endoscopic picture	No. of negative biopsies	Morphology	Treatment	Outcome at data collection time	Survival time
1	66 (female)	Dysphagia, weight loss	Type 2 (squamous)	3	Colloid cancer	Gastrectomy + 6 courses of neoadjuvant PCT	Death	6 months after gastrectomy
2	58 (female)	Dysphagia, loss of appetite, rapid food saturation	Type 1	1	Colloid cancer	4 courses of neoadjuvant PCT	Death	4 months after diagnosis
3	33 (female)	Dysphagia, vomiting of food, rapid food saturation	Type 1	2	Colloid Cancer Foci	3 courses of palliative PCT	Death	7 months after diagnosis
4	41 (female)	Dysphagia, weight loss, vomiting of food, loss of appetite, vomiting of food	Type 1	2	Diffuse undifferentiated adenocarcinoma with colloid cancer foci	Gastrectomy by Billroth-2	Death	2 months after gastrectomy
5	55 (male)	Dysphagia, loss of appetite, weight loss	Type 1	1	Non-differentiated cancer	2 courses of palliative PCT	Death	3 months after diagnosis
6	71 (female)	Dysphagia, loss of appetite, rapid food saturation	Type 1	2	Colloid cancer	Gastrectomy + 3 courses of adjuvant PCT	Alive	3 months after surgery
7	58 (male)	Dysphagia, loss of appetite, rapid food saturation	Type 1	1	Colloid cancer	Gastrectomy + 4 courses of adjuvant PCT	Alive	2 months after surgery

Note: PCT - polychemotherapy

Discussion: Gastric carcinoma is notorious for its inability to cause early symptoms, so patients do not seek care until the late stage of the disease. Due to the abundant lymph supply, the cancer quickly spreads beyond the reach of surgical resection. Consequently, the patients with symptoms tend to have a far-reaching malignant tumor. Diagnosing diffuse cancer is often challenging because there are endoscopically inactive and endoscopically active phases. In the endoscopically inactive phase, there are complaints on dysphagia, but there are no visually visible changes in the endoscopic picture, such as the folds thickening or flattening and the rigidity of the walls. In the endoscopically active phase, the folds thinning, walls rigidity, and absence or weakening of peristalsis are already observed, but multiple superficial biopsies are often negative, and by that

time, the peritoneal and lymphogenous dissemination is manifested [3]. Therefore, a deep sequential biopsy with morphological verification of colloid cells in the fibrous stroma of the stomach wall is required. X-ray of the stomach with contrast is one of the final stages of diagnosis and gives a distinctive picture of the lumen narrowing, reduction of stomach size, folds thickening, and lack of peristalsis. Endosonography reveals blurring and thickening of the first three layers and a significant thickening of the 4th layer of the stomach wall to 10-20 mm. Computed tomography and endosonography may be useful for diagnosing and assessing the local spread. The differential diagnosis should include malignant diseases (adenocarcinoma and lymphoma) and some benign diseases with thickening of the stomach wall (Menetrier's disease, lymphoid hyperplasia, and amyloidosis).

The surgical treatment is possible only in 20-25% of cases of that disease due to observed early peritoneal dissemination and distant metastases. The surgery in the volume of total gastrectomy is indicated only in case of localized lesions.

In most cases, LP chemotherapy is the only alternative to treatment, but its effectiveness in this form of cancer is very low. Even with complete surgical removal of the tumor, adjuvant chemotherapy does not have such a positive effect as observed in the case of classical gastric adenocarcinoma [4]. Consequently, the average survival rate is 6 months without gastrectomy and 14 months with gastrectomy. Due to early peritoneal dissemination, lymphatic invasion, and metastasis to neighboring organs, the prognosis for this disease is unfavorable. In Europe and Japan, the 5-year survival rate amounts to only 10-20% [5].

Recently, much attention has been paid to the use of preoperative hyperthermic intraperitoneal chemotherapy (Hyperthermic Intraperitoneal Chemotherapy, HIPEC) in gastric cancer, both for prevention and treatment of peritoneal diseases, and several randomized trials are currently underway [6]. Given the strong peritoneal tropism of cirrhosis and LP tumors, HIPEC may come to the forefront soon as routine management of this patient subgroup.

It is known that the neoadjuvant therapy has many theoretical advantages. Among them, a higher degree of treatment adherence compared to postoperative therapy and the possibility of reducing the tumor stage or size [7]. Since LP tumors are often advanced, neoadjuvant therapy may be of prime importance for improving local control and increasing the incidence of potentially curative gastrectomy.

Primary plastic gastric cancer is a diffuse carcinoma with a scirrhous stroma that invades the submucosa, occupying more than 1/3 of the stomach surface. Pre- or postoperative HIPEC may represent an alternative strategy, especially given this tumor's high peritoneal spread rates. Further progress is required in developing targeted therapies that will affect the cancer cells and their stroma.

Conclusion: Early diagnostics of diffuse gastric cancer is challenging. However, thickened folds, wall rigidity, and peristaltic movement deficiency shall alert the doctor. Multiple biopsies and loop resection of the affected area by the J. Rohl method increase the morphological value of the biopsy material, help verify the diffuse gastric cancer diagnosis, and quickly start surgical treatment or palliative chemotherapy.

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АНДАТПА

ДИФФУЗДЫ АСҚАЗАН ҚАТЕРЛІ ІСІГІНІҢ ЭНДОСКОПИЯЛЫҚ ДИАГНОСТИКАСЫНЫҢ ЕРЕКШЕЛІКТЕРІ

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Өзектілігі: *Linitis plastica асқазан аденокарциномасының 3-19% құрайтын карциноманың диффузды түрін білдіреді. Ол асқазанның көп бөлігінің немесе бүкіл бөлігінің қатты лығымен сипатталады, толтыру ақауы немесе кең жаралар жоқ. Мақалада ұлттық ғылыми онкологиялық орталығының (ҰҒОО) сараптамалық эндоскопия және интервенциялық радиология орталығында 2019-2022 жылдар және 2023 жылдың 1 жартысы ішінде пластикалық линит диагнозы қойылған пациенттерді эндоскопиялық диагностикалау тәжірибесі сипатталған, Астана, Қазақстан.*

Зерттеудің мақсаты: *– диффузды асқазан обырын диагностикалау кезінде эндоскопиялық диагностика әдістерін қолдану ерекшеліктерін бағалау.*

Әдістері: *2019 жылдан бастап 2023 жылдың 1-ші жартыжылдығына дейін сараптамалық эндоскопия орталығында асқазанның диффузды қатерлі ісігінің диагностикалық жағдайларына ретроспективті талдау жүргізілді.*

Нәтижелері: *Барлық пациенттер бастапқыда тұрғылықты жеріндегі емханаларда компьютерлік томография (КТ), биопсиялық гастроскопия арқылы тексерілді және морфологиялық зерттеудің теріс нәтижесін алғаннан кейін бізге сараптама мен қайталама биопсияға жіберілді. Когортқа орташа жасы 54,6 (33-тен 71 жасқа дейін) жеті пациент (2 ер адам және бес әйел) кірді. Асқазанның шырышты қабығынан биопсиялық материалды алудың білікті гастроскопиясы мен арнайы әдістемесі диффузды асқазан қатерлі ісігіне күдікті барлық жеті науқасқа дұрыс морфологиялық диагноз қоюға көмектесті. Жергілікті және жалпыланған метастаздар мен ілеспе патологияларды ескере отырып, тек төрт пациентке операция жасалды, ал үшеуіне тек химиотерапия тағайындалды. Бес науқас қайтыс болды, ал екеуі паллиативті химиотерапияны жалғастыруда.*

Қорытынды: *Қорытындылай келе, пластикалық гастрит аденокарциноманың бір түрі болып табылады, ол әдетте көп жағдайда дәрі-дәрмекпен емдеу мүмкін болмаған кезде кейінгі кезеңде көрінеді. Толық резекция кезінде болжамды жақсартуға болады. Хирургиялық араласу толық резекция қажет болған жағдайда ғана жасалуы керек. Сараптамалық гастроскопия және асқазанның шырышты қабығынан биопсиялық материалды алудың арнайы әдісін қолдану (J. Rohl бойынша) биоптаттардың морфологиялық құндылығын арттырады және диффузды асқазан обыры диагнозын растауға және хирургиялық емдеуді немесе паллиативті химиотерапияны тезірек бастауға мүмкіндік береді.*

Түйінді сөздер: *Пластикалық линит, асқазан қатерлі ісігінің диффузды түрі, асқазан-ішек қатерлі ісігі, Борман IV, эндоскопия.*

АННОТАЦИЯ

ОСОБЕННОСТИ ЭНДОСКОПИЧЕСКОЙ ДИАГНОСТИКИ ДИФФУЗНОГО РАКА ЖЕЛУДКА

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Актуальность: *Linitis plastica обозначает диффузный тип карциномы, на долю которого приходится 3-19% аденокарцином желудка. Он характеризуется ригидностью большей части или всего желудка при отсутствии дефекта наполнения или обширных изъязвлений.*

В статье описан опыт эндоскопической диагностики пациентов с пластическим линитом.

Цель исследования *– оценка особенностей применения методов эндоскопической диагностики в диагностике диффузного рака желудка.*

Методы: *Проведен ретроспективный анализ 7 случаев диффузного рака желудка, диагностированных в Центре экспертной эндоскопии и интервенционной радиологии Национального научного онкологического центра (ННОЦ, Астана, Казахстан) с 2019 по 2023 гг.*

Результаты: *Все пациенты были первично обследованы в поликлиниках по месту жительства, где были направлены на КТ и эзофагогастродуоденоскопию с биопсией. При получении отрицательного морфологического исследования пациенты были направлены в ННОЦ для экспертного осмотра и повторной биопсии. Когорта пациентов состояла из 2 мужчин и 5 женщин со средним возрастом 54,6 года (диапазон 33-71 год). Для морфологической верификации диффузного рака желудка всем пациентам в Центре экспертной эндоскопии ННОЦ проводилась гастроскопия с биопсией с использованием специальной методики забора биопсийного материала. С учетом наличия местного и генерализованного метастазирования и сопутствующей патологии, оперативное лечение проведено только 4 пациентам, 3 пациентам назначена только химиотерапия. Летальный исход зафиксирован у 5 пациентов, 2 пациента продолжали паллиативную химиотерапию на момент сбора данных.*

Заключение: *Пластический линит является одной из форм аденокарциномы, которая обычно проявляется на более поздней стадии, когда в большинстве случаев медикаментозное лечение невозможно. Прогноз может быть улучшен при полной резекции. Хирургическое вмешательство следует проводить только в тех случаях, когда предполагается полная резекция. Экспертная гастроскопия и применение специальной методики забора биопсийного материала (по J. Rohl) со слизистой желудка увеличивает морфологическую ценность биоптатов и дает шанс подтвердить диагноз диффузного рака желудка и быстрее начать хирургическое лечение или паллиативную химиотерапию.*

Ключевые слова: *Пластический линит (ПЛ), диффузный тип рака желудка, рак желудочно-кишечного тракта, Борман IV, эндоскопия.*

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THE USE OF ARGON PLASMA COAGULATION IN ENDOSCOPY

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ABSTRACT

Relevance: *Argon plasma coagulation (APC) is a minimally invasive, non-contact electrosurgery method. This procedure is performed in the following conditions: bleeding in hollow organs, including ulceration after radiation therapy, Barrett's esophagus, with the germination of a malignant tumor through a stent, benign neoplasms, precancerous conditions, and some malignant tumors at the earliest stages. In this article, the authors present the first successful experience of using APC in Kazakhstan during endoscopic interventions in patients with various pathologies.*

The study aimed to *evaluate the effectiveness of introducing APC as an endoscopic treatment in patients with precancerous pathology and complications of surgical treatment in oncological patients.*

Methods: *A retrospective analysis of the use and effectiveness of AIC involved 15 patients with various pathologies treated inpatiently at the National Research Oncology Center (NROC), Astana, Kazakhstan, in 2022.*

Results: *Barrett's esophageal APC was successfully performed in the NROC hospital in 6 patients; the biopsy showed no intestinal-type metaplasia of the esophageal epithelium. Two patients with post-radiation hemorrhagic proctitis underwent coagulation in Pulse 15Wt mode and argon flow of 0.4-1.0 L/min. A patient with GAVE syndrome with hemorrhages underwent two sessions of APC in 35Wt mode with a gas flow of 0.8 L/min. In 3 patients with fistulas of the suture of the main bronchus, coagulation was performed after pulmonectomy, and closure of the fistula was observed for one week. Two patients with esophagus-enteric anastomosis failure received two sessions of APC with 40-watt argon at a 5-day interval. After anterior rectal resection, the patient had a failure of the anastomosis with a multi-chamber cavity and purulent contents. Four courses of APC were administered with a 2-week interval. After APC, the mouth of the main chamber narrowed, and the discharge of pus stopped. The result was a blind pocket up to 2.0 cm, without additional chambers or inflammation signs.*

Conclusion: *The presented article describes the results of the introduction of APC as an endoscopic method of treating patients with various pathologies in an oncological clinic, and based on these results, APC can be recommended for widespread implementation throughout Kazakhstan.*

Keywords: *argonoplasmic coagulation (APC), Barrett's esophagus, endoscopy, neoplasms, anastomosis failure.*

Introduction: Argon plasma coagulation (APC) is a minimally invasive, non-contact electrosurgery method. During this procedure, the tissue is exposed to high-frequency electrical energy delivered by ionized argon gas. An argon plasma torch is created by an electric current that strongly heats the tissue. As a result, the liquid evaporates, the proteins coagulate, and the tissue completely burns out. This process is called coagulation.

APC is used in all areas of surgery, including cancer. This procedure is performed in the following patient conditions:

– Bleeding in hollow organs, including ulceration, esophagus varicose veins, and postradiation proctitis;

– Barrett's esophagus, a precancerous condition when uncharacteristic intestinal-type epithelium is found in the esophageal mucosa;

– Germination of tumor tissue into the lumen of the stent – APC is used for recanalization;

– Benign neoplasms and some malignant neoplasms in the early stages;

– A progressive malignant tumor that clogs the lumen of a hollow organ. APC is used as palliative treatment in this case;

– Gynecological pathologies: Erosion and dysplasia of the cervix, polyps, papillomatosis, hyperkeratosis, condylomas, leukoplakia.

For the patient, APC looks like a regular endoscopic examination. The operation usually takes less than an hour and can be performed without hospitalization. The coagulation device is a metal rod electrode placed inside a tube filled with argon. When alternating current is applied to the electrodes, argon transforms into a plasma state, producing flashes resembling sparks or miniature flashes. This "lightning" is used instead of a scalpel. The tool does not touch the tissue; the distance is 2-10mm [1].

This article presents the first and most successful experience of using APC in Kazakhstan during endoscopic interventions in patients with precancerous and oncological pathologies.

Materials and methods: This work is part of a retrospective study that assesses endoscopic technologies' efficiency in treating patients with pretumor pathology and complications of surgical treatment in cancer patients. The medical histories of patients treated in the multidisciplinary surgery department of the National Research Oncology Center (NROC, Astana, Kazakhstan) were retrospectively analyzed.

The study included patients with the following diagnoses:

1. Barrett's esophagus with signs of low-grade dysplasia;
2. Gastric arteriovenous malformation (GAVE syndrome) with recurrent gastric bleeding;

3. Esophageal anastomosis failure is not more than 0.5 cm and is not amenable to endoscopic clipping;

4. Bronchial stump suture failure up to 0.5 cm after pneumonectomy;

5. Rectal anastomosis failure in the presence of a functioning colostomy;

6. Chronic proctitis grade 2-3 according to the post-radiation proctitis severity scale (Rectal Toxicity Scale, 1995), proposed by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC);

7. Bleeding from the rectum, which is often an indication for blood transfusion;

8. Ineffective conservative therapy with 5-aminosalicylic acid (5-ASA) and rectal glucocorticosteroids for 30 days.

Exclusion criteria:

1. Barrett's esophagus with severe dysplasia;

2. Diffuse arteriovenous malformation of the stomach without bleeding events;

3. Esophageal anastomotic failure greater than 0.5 cm and amenable to endoscopic clipping;

4. Bronchial stump failure more than 0.5 cm requiring surgical treatment;

5. Chronic post-radiation proctitis without signs of rectal bleeding;

6. Severe general condition.

The following parameters of the early postoperative period (Days 0-7 after APC) were assessed: the clinical APC effect includes stopping bleeding from the rectum in chronic post-radiation proctitis, the absence of gastric bleeding events in patients with arteriovenous malformation of the stomach, and the cessation of airflow through the Bulau catheter in patients with bronchopleural fistulas, terms of inpatient treatment, patients' quality of life.

Changes in the patient's quality of life after APC were assessed according to certain parameters: discomfort, pain, and number of bowel movements per day.

No complications were recorded in all patients after APC use.

Findings were statistically processed with the Statistica 6.0 applied software package (StatSoft, Inc., USA) and the statistical criteria online calculator at medstatistic.ru.

The study conclusion report of the National Research Oncology Center local ethics commission was received on May 20, 2023, under number No. 12. Informed consent was obtained from all patients who underwent medical and surgical interventions in NROC and whose data was included in this review article.

Results:

Barrett's esophagus APC

APC is the most effective method of endoscopic treatment for Barrett's esophagus without severe dysplasia (pronounced changes in the mucous membrane cells) and malignant degeneration. Data shows that if the length of the affected organ area is not more than 3-4 cm, the APC effectiveness is 80-90% [2]. From May 2021, since the introduction of APC in the Scientific Research Center as an endoscopic ablation method for Barrett's esophagus, the multidisciplinary surgery department of the Scientific Research Center has successfully performed endoscopic treatment of Barrett's esophagus in 6 patients (Figure 1). Subsequent endoscopic monitoring with a collection of biopsy material did not find any signs of intestinal-type metaplasia of the esophageal epithelium in the morphological material.

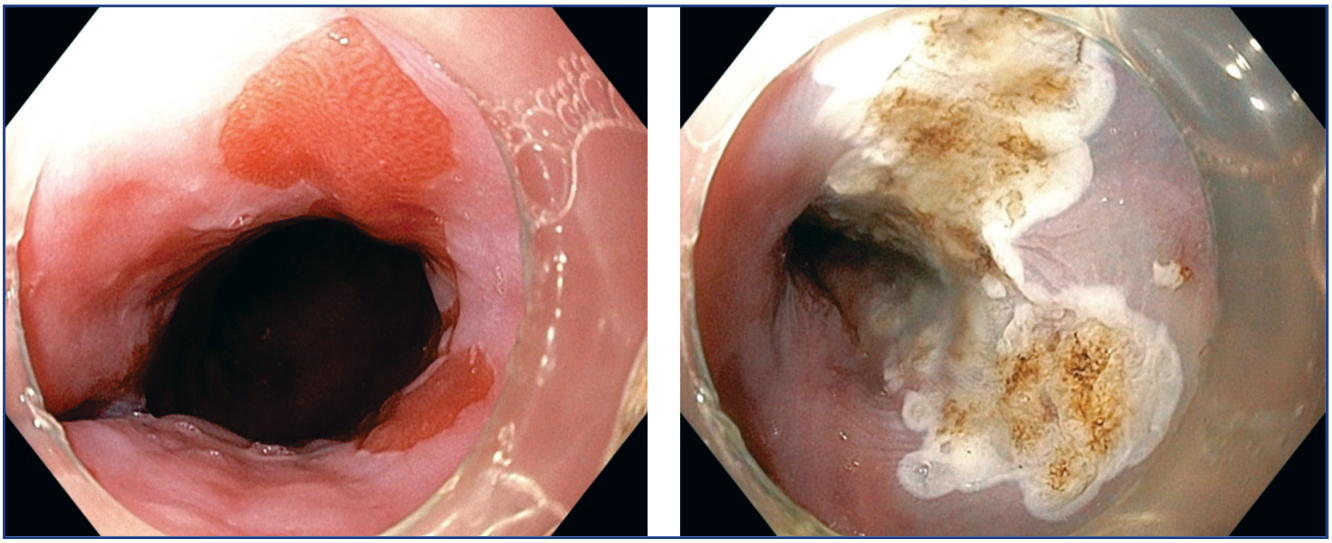

Figure 1 – APC application in Barrett's esophagus

Rectum APC in chronic post-radiation proctitis

APC is highly effective for chronic post-radiation proctitis, a pelvic organ radiation treatment complication. The disease causes the rectum bleeding and is recalcitrant. The frequency of this symptom in patients with pelvic cancer was 5-15% within six months after radiation treatment.

In the NROC multidisciplinary surgery department, endoscopic APC treatment was given to two patients with post-radiation proctitis complicated by bleeding (Figure 2). Rectal bleeding events stopped after the 1st session

of argon coagulation in a man after radiation therapy for bladder cancer and in a woman after radiation therapy for cervical cancer. In order to stop bleeding, all patients underwent APC of the rectal mucosa with areas of angioectasias with 15 Watts Pulse mode and an argon flow of 0.4-1.0 L/min.

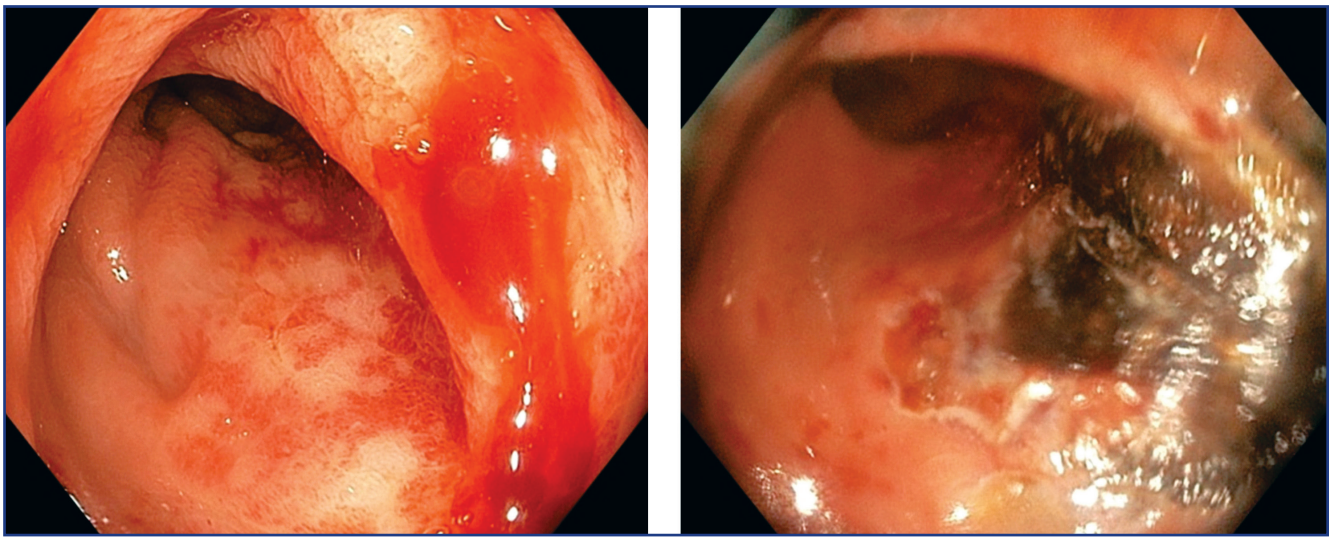

Figure 2 – Application of APC for post-radiation proctitis

APC in arteriovenous malformations of the gastrointestinal tract mucous membrane

Gastric antral vascular ectasia (GAVE) is a rare acquired vascular lesion of the gastric antrum. Iron deficiency anemia is the most common manifestation of GAVE. Endoscopic therapy is the mainstay of treatment. However, no consensus exists on the optimal treatment method [3].

Endoscopic treatment of a patient with GAVE syndrome suffered from gastric bleeding events with a decrease in hemoglobin to 49 g/L was performed successfully in our department. This patient underwent two APC sessions in 35 Wt coagulation mode with 0.8 L/min gas flow and had no bleeding episodes for two years after ablation (Figure 3).

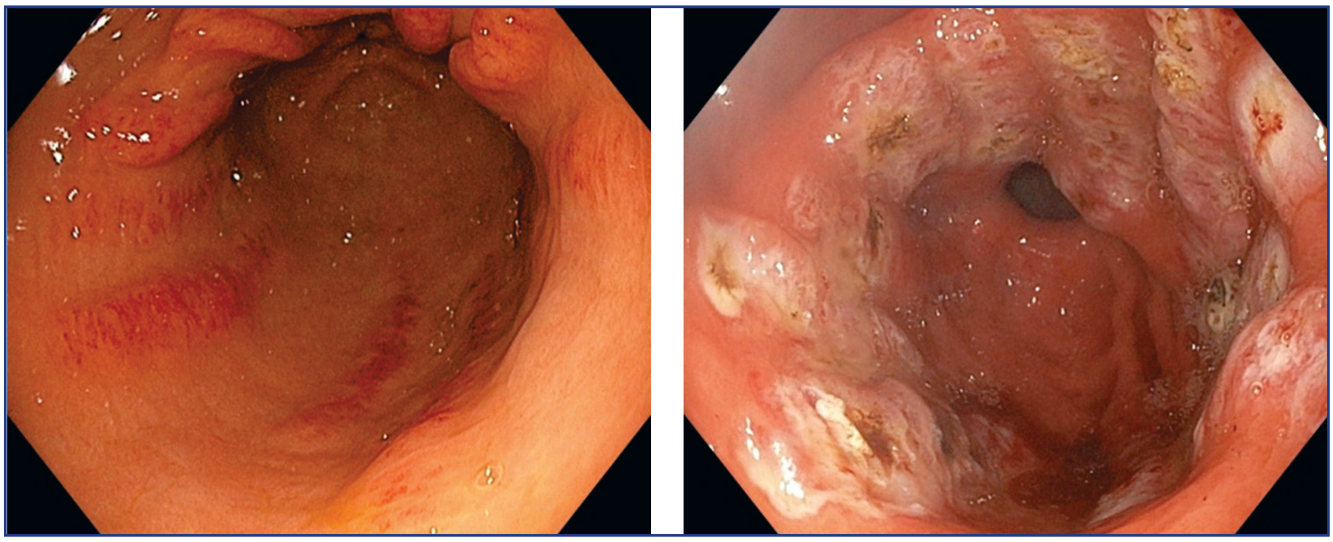

Figure 3 – APC application for GAVE syndrome

APC in bronchial stump suture failure

Tracheomediastinal fistula is a rare complication arising from lung cancer. These airway fistulas are often connected with the esophagus or pleural cavity. The bronchopleural fistula etiology is different. However, lung resection, various infections, chemotherapy, and radiation therapy, among others, are used to treat lung cancer; spontaneous persistent pneumothorax and tuberculosis are usually associated factors.

Most fistulas associated with lung cancer develop as a complication of lung resection [4].

Three patients with bronchopleural fistulas of the main bronchus stump suture after pneumonectomy were treated endoscopically in the NROC multidisciplinary surgery

department. The fistula opening was coagulated circumferentially using a 40-watt coagulator (Olympus, Japan), and the opening has closed within one week after the procedure (Figure 4).

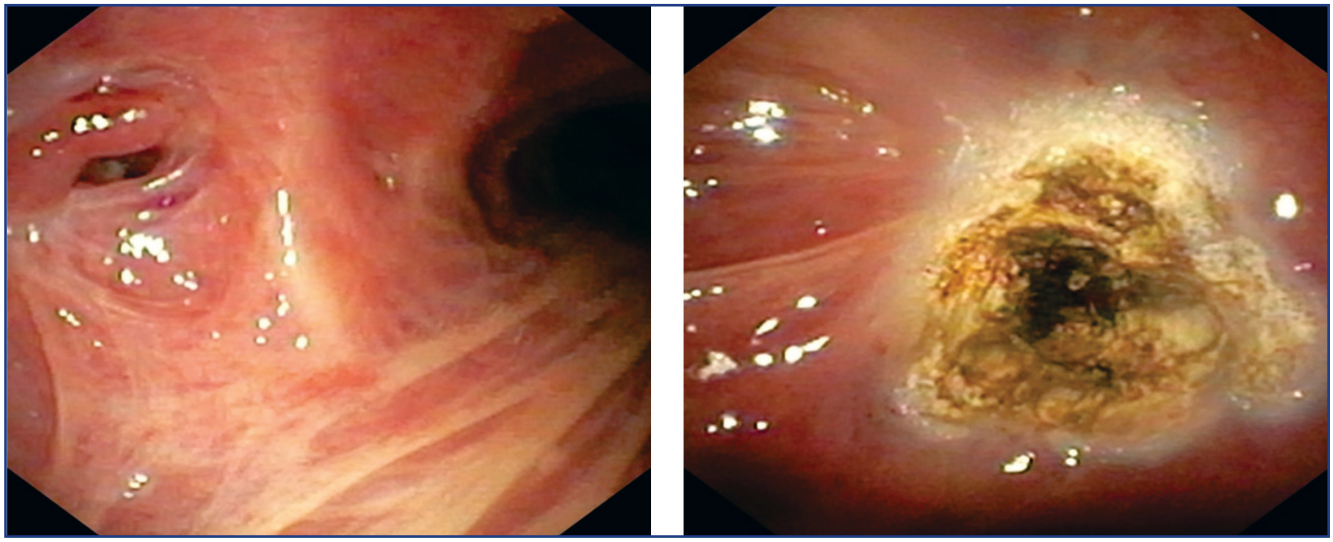

Figure 4 –APC for the main bronchus stump fistulas after pneumonectomy

APC in esophageal anastomosis failure

Suture failure occurs in 0.5-33% of esophagogastric anastomosis. The failure of esophagointestinal anastomosis develops in 5.9-12% of patients who underwent gastrectomy and is accompanied by high mortality, which approaches 100%. One of the most compelling prerequisites for developing esophageal anastomosis failure is a violation of the nutritional status of patients who need surgical operations in the upper gastrointestinal tract. We should not forget about the role of technical errors: misalignment of the mucous membranes, very frequent sutures, excessive tight knotting, needle piercing of the mucous membranes during the formation of the second row of sutures, the tension of the sutured organs, etc. [5].

Two patients with failed esophagojejunostomy after gastrectomy underwent endoscopic treatment using a 40-watt APC at the NROC clinic. Successful fistula closure took two sessions with an interval of 5 days (Figure 5).

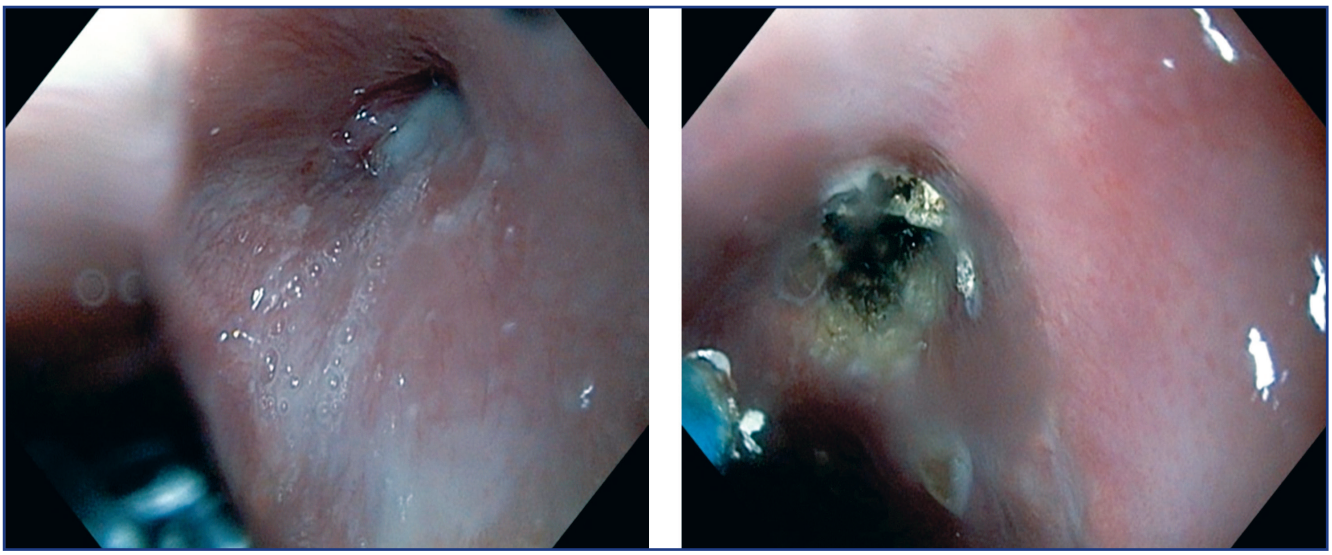

Figure 5 – Application of APC for esophageal anastomosis failure

APC for rectal anastomosis failure

Failure of the rectum anastomosis, one of the most severe complications, occurs in 1.5-1.0% of rectum resection, and the associated postoperative mortality reaches 6.0-9.3%. Both intraoperative and preoperative risk factors determine the development of complications. The height of the tumor location, radiation therapy exposure, male gender, and smoking are important predisposing factors for the development of rectal anastomotic failure.

APC was used in a patient after anterior resection of the rectum for rectal cancer at the NROC multidisciplinary surgery department. Anastomosis failure with a multi-chamber cavity with numerous mouths and purulent contents was found in the patient at the control colonoscopy 3rd month after the operation. 40-watt APC was performed in 4 courses with 2-week intervals. After endoscopic treatment, small mouths and cavities closed, the main chamber mouth significantly decreased, and the release of purulent contents stopped. A blind pocket up to 2.0 cm without additional chambers or inflammation signs remained after treatment (Figure 6).

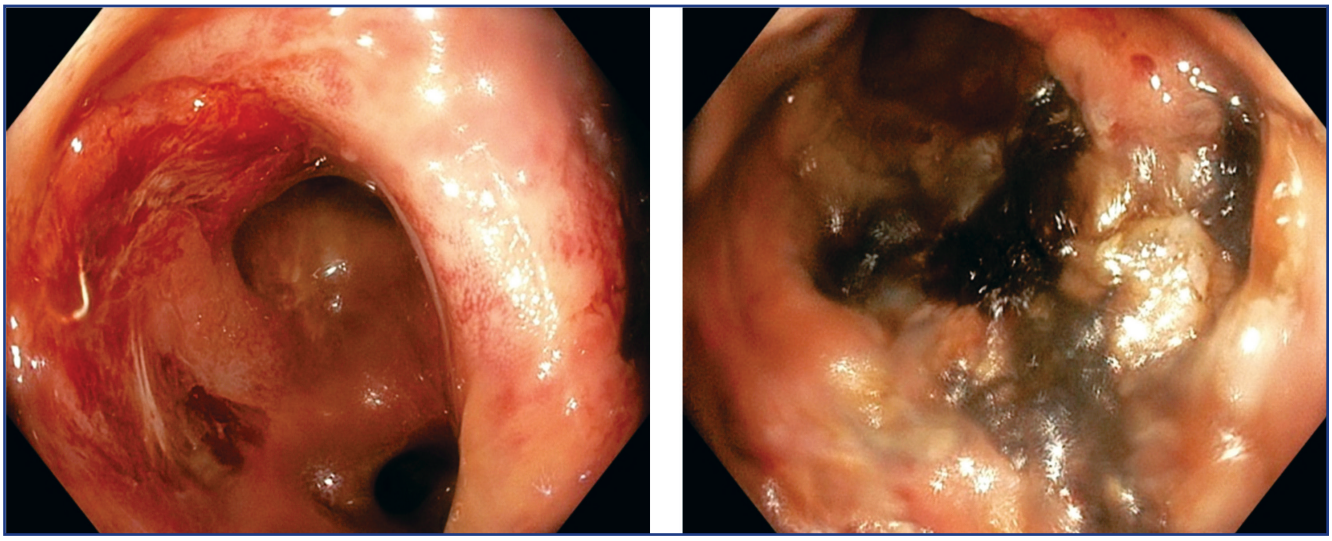

Figure 6 – APC application for rectal anastomosis failure

No complications were recorded in all patients after using APC in the early postoperative period. APC was performed on an outpatient basis in patients with post-radiation proctitis and rectal anastomosis failure. On average, patients with Barrett's esophagus and GAVE syndrome stayed in a hospital for 2.2 days. APC usage in patients with esophageal anastomosis failure, main bronchus stump failure, and rectal anastomosis failure averaged 8 to 14 days (Table 1).

Table 1 – Criteria for the effectiveness of the APC application

Nosology	Barrett's esophagus	Post-radiation proctitis	GAVE syndrome	Bronchial fistula	Esophageal anastomosis failure	Rectal anastomosis fail-ure
Clinical effect	+	+	+	+	+	+
Presence or ab-sence of complica-tions	-	-	-	-	-	-
Length of stay in hospital	2.2±0.69	out-patient treatment	2.0	8.0±0.82	14±2.0	out-patient treatment
Presence of relapse	-	-	-	-	-	-

Discussion: Endoscopic techniques described in the literature, such as electrocoagulation, ligation of vascular transformations, and radiofrequency ablation, have not been widely used due to the small amount of data on their effectiveness and safety.

APC is a non-contact electrocoagulation method that uses ionized gas to deliver high-frequency alternating current to the lesion. The risk of perforation, stenosis, or fistula is low due to the shallow coagulation depth of 0.5-3 mm. Unlike traditional bipolar devices, the APC can be applied in the axial and radial directions, which allows tangential coagulation of lesions around the flexures of the rectum without significant loss of efficiency. In addition, the APC generator is mobile and can be quickly used anywhere and anytime. Thus, APC is an established treatment for many pathologies, including vascular dysplastic lesions and bleeding from polypectomy areas. Additionally, APC therapy does not require sedation or anesthesia during the procedure and, therefore, can be performed in an outpatient setting.

The advantages of APC include ease of use, targeted coagulation of telangiectasia and fistulas, depth control and safety, and lower cost compared to radiofrequency ablation. The advantages of APC include the ability to rotate the probe in axial and radial directions that enable adequate coagulation

of the mucous membrane of the esophagus, stomach, bronchi, and rectum in curved areas.

Conclusion: The authors presented cases of successful and, most importantly, clinically effective use of APC as an endoscopic minimally invasive treatment for surgical treatment complications in patients with oncological and non-oncological pathologies in this clinical review. The endoscopic treatment method was often chosen due to the concomitant pathology, the patient's general condition that did not allow surgical treatment, and the possibility of conducting argon coagulation sessions on an outpatient basis without hospitalization. Based on the study results, we can recommend the widespread use of APC in all oncological and surgical hospitals for minimally invasive treatment of such complications.

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АНДАТПА

ЭНДОСКОПИЯДА АРГОНОПЛАЗМАЛЫҚ КОАГУЛЯЦИЯНЫ ҚОЛДАНУ

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Өзектілігі: *Аргоноплазмалық коагуляция (АПК) – электрохирургияның аз инвазивті байланыссыз әдісі. Бұл процедура келесі жағдайларда орындалады: қуыс мүшелердегі қан кетулер, соның ішінде сәулелік терапиядан кейінгі ойық жара, барреттің өңеші, стент арқылы қатерлі ісіктің өнуі, қатерсіз өсінділер, қатерлі ісікке дейінгі жағдайлар, кейбір қатерлі ісіктер. Бұл мақалада авторлар әртүрлі патологиясы бар пациенттерге эндоскопиялық араласу кезінде Қазақстанда АПК қолданудың алғашқы және табысты тәжірибесін ұсынады.*

Зерттеудің мақсаты *– қатерлі ісікке дейінгі патологиясы бар және онкологиялық науқастарда хирургиялық емдеудің асқынулары бар емделушілерде эндоскопиялық ем ретінде АПК енгізудің тиімділігін бағалау.*

Әдістері: *2022 жыл ішінде Ұлттық ғылыми онкологиялық орталықта (ҰҒОО, Астана, Қазақстан) стационарлық емдеуде болған әр түрлі патологиясы бар 15 пациентте АПК қолдану мен тиімділігіне ретроспективті талдау жүргізілді.*

Нәтижелері: *ҰҒОО стационарында 6 пациентке барреттің өңеш АПК сәтті жүргізілді, бақылау кезінде биопсиялық материалда ішек типі бойынша өңеш эпителийінің метаплазиясының белгілері анықталмады. Радиациядан кейінгі геморрагиялық проктитпен ауыратын екі пациентке Pulse 15wt режимінде коагуляция және аргон ағыны 0,4-1,0 л/мин. геморрагиясы бар GAVE синдромы бар пациентке 35wt режимінде 2 АПК сессиясы өткізілді, газ ағыны 0,8 л/ мин. негізгі бронх тігісі фистулалары бар 3 пациентте пульмонэктомиядан кейін коагуляция жүргізілді және фистуланың жабылуы байқалды 1 апта ішінде. Эзофагоэнтероанастомоздың дәрменсіздігі бар екі пациентке 5 күн аралықпен 40 ватт аргонды пайдалана отырып, 2 АПК сеансы өткізілді. Науқаста тік ішектің алдыңғы резекциясынан кейін көп камералы қуысы бар анастомоздың сәтсіздігі және іріңді құрамы болды. АПК-нің 4 курсы 2 апта аралықпен өткізілді, АПК-тен кейін негізгі камераның сағасы тарылды, іріңнің бөлінуі тоқтады, нәтижесінде қосымша камераларсыз және қабыну белгілерінсіз 2,0 см-ге дейін соқыр қалта қалды.*

Қорытынды: *Мақалада онкологиялық клиникада әртүрлі патологиялары бар пациенттерді емдеу әдісі ретінде АПК енгізу нәтижелері ұсынылған және осы нәтижелер негізінде АПК бүкіл Қазақстан бойынша кеңінен енгізу үшін ұсынылуы мүмкін.*

Түйінді сөздер: *аргоноплазмалық коагуляция (АПК), Барреттің өңеші, эндоскопия, неоплазмалар, анастомоздың сәтсіздігі.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ АРГОНОПЛАЗМЕННОЙ КОАГУЛЯЦИИ В ЭНДОСКОПИИ

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Актуальность: *Аргоноплазменная коагуляция (АПК) – малоинвазивный бесконтактный метод электрохирургии. Эту процедуру выполняют при следующих состояниях: кровотечения в полых органах, в том числе при изъязвлении после лучевой терапии, пищевод Барретта, при прорастании злокачественной опухоли через стент, доброкачественные новообразования, предраковые состояния, некоторые злокачественные опухоли на самых ранних стадиях. В этой статье авторы представляют первый и успешный опыт применения АПК в Казахстане при эндоскопических вмешательствах у пациентов с различной патологией.*

Цель исследования *– оценка эффективности внедрения АПК в качестве эндоскопического лечения у пациентов с предраковой патологией и осложнениями хирургического лечения у онкологических пациентов.*

Методы: *Проведен ретроспективный анализ применения и эффективности АПК у 15 пациентов с различной патологией, находившихся на стационарном лечении в Национальном научном онкологическом центре (ННОЦ, Астана, Казахстан) в течение 2022 года.*

Результаты: *В стационаре ННОЦ успешно проведена АПК пищевода Барретта 6 пациентам, при контроле в биопсийном материале не выявлены признаки метаплазии эпителия пищевода по кишечному типу. Двум пациентам с постлучевым геморрагическим проктитом выполнена коагуляция в режиме Pulse 15Wt и потоке аргона 0,4-1,0 л/мин. Пациенту с GAVE-синдромом с геморрагиями проведено 2 сеанса АПК в режиме 35Wt с потоком газа 0,8 л/ мин. У 3-х пациентов со свищами шва главного бронха после пульмонэктомии проведена коагуляция и закрытие свища наблюдалось в течение 1 недели. Двум пациентам с несостоятельностью эзофагоэнтероанастомоза проведено 2 сеанса АПК с использованием 40-ваттного аргона с интервалом по 5 дней. У пациента после передней резекции прямой кишки имелась несостоятельность анастомоза с многокамерной полостью и наличием гнойного содержимого. Проведено 4 курса АПК с интервалом в 2 недели, после АПК устье главной камеры сузилось, прекратилось выделение гноя, в итоге остался слепой карман до 2,0 см без дополнительных камер и признаков воспаления.*

Заключение: *В статье представлены результаты внедрения АПК как метода лечения пациентов с различными патологиями в онкологической клинике и на основании этих результатов АПК можно рекомендовать для широкого внедрения по всему Казахстану.*

Ключевые слова: *аргоноплазменная коагуляция (АПК),пищевод Барретта, эндоскопия, новообразования, несостоятельность анастомоза.*

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PARENCHYMATOUS-STROMAL RATIO IN COLORECTAL CANCER TUMORS AS AN INDICATOR OF METASTASIS

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ABSTRACT

Relevance: *Colorectal cancer (CRC) is one of the five most common cancers worldwide and is characterized by trends in incidence, disabi lity, and mortality. A significant recurrence rate and early metastasis characterize CRC. Many meta-analyses in the world literature are aimed at finding factors that determine the probable outcome of the disease.*

The study aimed to *evaluate the role of the parenchymal-stromal ratio in the progression of colorectal cancer.*

Methods: *When microcopying at 40x magnification, the parenchyma (Sp) and stroma (Sm) area were measured in superficial tumor growth and deep invasion. The parenchymal-stromal ratio (PSR) was calculated using the formula PSS=Sp/Sm, and the correlation with tumor metastasis was determined.*

Results: *With an increase in the depth of tumor invasion, the frequency of metastasis to the liver also increased. The metastasis rate for invasion into the muco-submucosal layer (T1) and the muscular layer (T2) was 4%, respectively. The rate increased to 80% with the involvement of the subserous membrane (T3). Metastases in regional lymph nodes worsened the outcome of the disease threefold. With locally widespread and locally regional in the zone of deep invasion, the parenchymal component predominates over the stroma. PSS is 2.5:1.0 and 1.6:1.0. With CRC disseminated growth in the zone of deep tumor invasion, PSS was 1.0:1.4 with a predominance of the stromal component up to 57%.*

Conclusion: *There is a decrease in PSS in superficial growth zones in disseminated forms of colorectal cancer compared with local and local-regional types of cancer. The predominance of the stromal component in the zone of deep invasion is directly proportional to the high adverse outcome.*

Keywords: *colorectal cancer (CRC), tumor microenvironment, parenchymal-stromal ratio (PSR).*

Introduction: Colorectal cancer (CRC) ranks 3rd among all malignancies globally. The CRC incidence is more than 1 million patients annually, and the mortality rate is about 700 thousand. According to data from several authors, the progression of CRC depends on the stromal microenvironment of the tumor: the extracellular matrix, blood vessels, inflammatory infiltrate cells, and fibroblasts. Dysregulation between the parenchyma and stroma leads to a change in normal stromal cells with the acquisition of abnormal phenotypes that promote neoplasm growth and progression.

There are relevant publications on determining the new morphological signs of the tumor progression risk, characterizing the internal properties of parenchymal cells, and interaction of the tumor microenvironment components. The AJCC study (1996-2015 years) of tumors in five locations (lung cancer, CRC, melanoma, breast, and prostate cancer) identified 176 prognostic tools (formulas, risk scores, calculators, nomograms, etc.) to establish additional independent prognostic markers that compensate the shortcomings of the system for determination of adverse outcomes risks [1].

In order to predict the survival of patients with CRC, 53 models have been identified [2]. These techniques combine clinical data and information from the pathology report of the tumor characteristics to assess the probability of a particular outcome occurring at a specific time [3, 4]. However, these models do not consider the tumor microenvironment's components. The analysis of the scientific publications showed the absence of universal systems for pathomorphological assessment of the probable outcomes of the disease. We could not find the model of pathomorphological characteristics of the primary tumor, which enabled us to predict the development of metastases in patients with localized CRC. The personification of the prognosis of adverse outcomes is required at disease stages I and II since the frequency of distant metastases after radical surgery can reach up to 10%. The permits above set the goal of the study.

The study aimed to evaluate the role of the parenchymal-stromal ratio in the progression of colorectal cancer**.**

Materials and methods: The clinical data of the medical records of 50 patients of the age range of 30-75 years old who were treated at the "Marat Ospanov West Kazakhstan Medical University" NCJSC from 2021 to 2022 have been studied—male and female patients composed 26 (52%) and 24 (48%), respectively. Of them, 21 patients had a tumor in the sigmoid colon, 11 (22%) – in the rectosigmoid region, 9 (18%) – in the colon, 6 (12%) – in the rectum, and 3 – in the cecum gut. Depending on the degree of tumor growth form, all patients have been divided into three groups: 1 – with locally advanced CRC, 2 – with local-regional CRC, and 3 – with disseminated growth of CRC. The patients were divided into groups: Group 1 included 17 people (9 men and eight women; 12 had CRC in the sigmoid colon, and 5 – in

the colon), Group 2 of 18 people (9 men and nine women; 3 had CRC in the cecum, 9 – in the sigmoid colon, 4 – in the colon, and 2 – in the rectosigmoid region), and Group 3 of 15 people (8 men and seven women; 6 had CRC in the rectum, and 9 – in the rectosigmoid region).

In order to check the normality of the distribution of the studied quantitative indicators in the groups, the KS test has been used. The statistical processing has been done using the Mann-Whitney U test of the Statistica 8.0 software package.

In fragments of the removed large intestine, a standard pathomorphological study assessed the degree of differentiation of the tumor, depth of invasion into the intestinal wall, and presence or absence of lymphogenous and hematogenous metastases. Using a Nikon Eclipse E200 microscope (Japan) with the application of Genesis software (Genesis Software, India) to assess the quantitative and qualitative microenvironment in 5 fields of view at 40-fold magnification, the area of superficial growth and deep tumor invasion was scanned, followed by measurement of the area of the parenchyma (Sp) and stroma (Sm). The parenchymal-stromal ratio (PSR) was calculated using the formula PSR=*Sp/Sm*.

Results: In analyzing clinical data, it was found that adenocarcinoma progression did not depend on gender, age, and the degree of tumor differentiation. However, the number of hematogenous metastases proportionally depended on the tumor's location, depth of invasion, and presence of lymphogenous metastases. When the tumor was localized in the sigmoid colon, hematogenous metastases reached 48%. The degree of depth of tumor invasion into the intestinal wall is directly proportional to the frequency of metastasis to the liver. The metastasis rate for invasion into the muco-submucosal layer (T1) and the muscular layer (T2) was 4%, respectively. The rate increased to 80% with the involvement of the subserous membrane (T3). Metastases in regional lymph nodes worsened the outcome of the disease threefold.

With locally advanced and locally regional in the zone of deep invasion, the parenchymal component predominates over the stroma. PSS is composed of 2.5:1.0 and 1.6:1.0.

With disseminated growth of CRC in the zone of deep tumor invasion, the PSR is 1.0:1.4 with a predominance of the stromal component up to 57% [5].

Discussion: For colorectal cancer, "degree of differentiation" is often used rather than the "degree of histological malignancy." There is no explicit link between the degree of differentiation and invasiveness or metastasis. The degree of differentiation does not mean the tumor aggressiveness in CRC. The ability to lead to an unfavorable outcome relatively quickly is based on the whole complex of properties of neoplastic cells and their microenvironment. Researchers describe the transition probability from one type to another depending on the tumor microenvironment [6-8]. The individual type of invasion is developed according to the epithelial-mesenchymal transition (EMT) mechanism. The morphological manifestation of the EMT phenomenon is considered to be so-called "budding," that is, the appearance of individual tumor cells in the invasive front of the tumor. "Budding" shows the degree of readiness for the separation of tumor cells at an early stage of the metastatic process and is one of the high-risk factors. "Budding" has a higher prognostic value compared to the degree of tumor differentiation [9-11].

Colorectal adenocarcinomas are characterized by a "kaleidoscope" of stromal-parenchymal elements. Many cell cooperation and collaboration variants, established during each tumor morphotype's development, determine the tumor's further behavior and the disease outcome. With maximum approaching of characteristics of the tumor parenchyma and stroma to the structure of normal mucous membrane of the colon and with retention of the "protective" function of the immune system, the CRC tumor is characterized by slow progression and a tendency to metastatic spread.

Conclusion: In summary, we have established the difference in PSR depending on the degree of tumor invasion. There is a decline of PSR in superficial growth zones in disseminated forms of CRC compared to local and local-regional distribution.

The predominance of the stromal component over the parenchyma in areas of deep invasion characterizes a high degree of metastasis.

The modern approach to cancer epidemiology and carcinogenesis qualifies malignant tumors as an invasive parasite. It occupies an appropriate place in the ecosystem of primary organs. Then, it spreads, forming regional and distant communities around metastases, forming a single system of interconnected ecosystems throughout the body. During metastatic spread, the tumor cells are exposed to certain risks [12, 13]. They acquire a metastatic phenotype, alter metabolism, lose their proliferative advantage, and transform from an epithelial to a mesenchymal cell. When the cell initiates an invasion, successfully evading the immune surveillance and infiltrating the blood vessels, it is exposed to a high risk of death during circulation in the bloodstream. The risks associated with metastatic spread explain the need for an external signal to start metastasis. Thus, the acquisition of metastatic capacity does not mean that the tumor cell necessarily has to leave the ecosystem of the maternal tumor. The metastatic migrants respond to the signal for the invasion to start. The existing angiogenic process does not provide rapid local cell proliferation, so the tumor outgrows the vascular network. Anabolically, the process entails local hypoxia and dystrophy, accumulation of metabolic decay products, and decreased pH, leading to an unproductive toxic swamp – tumor swamping [14, 15]. All of the above becomes a signal for the initiation of metastatic spread.

Considering that, according to several authors, the progression of colorectal cancer also depends on the stromal microenvironment of the tumor (extracellular matrix, blood vessels, inflammatory infiltrate cells, and fibroblasts), we will highlight that issue in the subsequent scientific publication.

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АНДАТПА

ҚОЛОРЕКТАЛЫҚ РАКТЫҢ ІСІКТЕРІНДЕГІ ПАРЕНХИМАТАЛЫҚ-СТРОМАЛДЫҚ ҚАТЫНАСЫ МЕТАСТАЗДАРДЫҢ КӨРСЕТКІШІ РЕТІНДЕ

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Өзектілігі: *Колоректальды қатерлі ісік әлемдегі ең көп таралған бес ісіктің бірі болып табылады және ауру, мүгедектік және өлім тенденцияларымен сипатталады. ККІ елеулі қайталану жылдамдығымен және ерте метастазбен сипатталады. Әлемдік әдебиеттердегі көптеген мета-талдаулар аурудың ықтимал нәтижесін анықтайтын факторларды табуға бағытталған.*

Зерттеудің мақсаты *– колоректальды қатерлі ісіктің өршуіндегі паренхимальды-стромальды қатынастың рөлін бағалау.*

Әдістері: *40 есе үлкейту кезінде микрокөшіру кезінде паренхиманың (Sp) және строманың (Sm) ауданы ісіктердің үстіңгі өсу және терең инвазия аймақтарында өлшенді. Паренхималық-стромальды қатынас PSS=Sp/Sm формуласы арқылы есептелді және ісік метастазымен корреляция анықталды.*

Нәтижелері: *Ісік инвазиясының тереңдігінің жоғарылауымен бауырға метастаздың жиілігінің жоғарылауы байқалады. Шырышты-су асты қабатына (T1) және бұлшықет қабатына (T2) инвазия үшін метастаздың жылдамдығы сәйкесінше 4% құрады. Субсерозды мембрананың (T3) қатысуы кезінде көрсеткіш 80%-ға дейін өсті. Аймақтық лимфа түйіндеріндегі метастаздар ауырудың нәтижесін 3 есе нашарлатты. Терең инвазия аймағында жергілікті кең таралған және жергілікті аймақтық болғандықтан, паренхималық компонент стромадан басым болады. PSS 2,5:1,0 және 1,6:1,0. Ісіктердің терең инвазиясы аймағындағы CRC диссеминирленген өсуімен PSS стромальды компоненттің 57%-ға дейін басым болуымен 1,0:1,4 құрайды.*

Қорытынды: *ісіктің жергілікті және жергілікті-аймақтық түрлерімен салыстырғанда колоректальды обырдың диссемирленген түрлерінде үстіңгі өсу аймақтарында PSS төмендеуі байқалады. Терең инвазия аймағында стромальды компоненттің басым болуы жоғары қолайсыз нәтижеге тікелей пропорционалды.*

Түйінді сөздер: *колоректальды қатерлі ісік, ісік микроортасы, паренхимальды-стромальды қатынас.*

АННОТАЦИЯ

ПАРЕНХИМАТОЗНО-СТРОМАЛЬНОЕ СООТНОШЕНИЕ В ОПУХОЛЯХ КОЛОРЕКТАЛЬНОГО РАКА КАК ИНДИКАТОР МЕТАСТАЗИРОВАНИЯ

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Актуальность: *Колоректальный рак (КРР) входит в пятерку самых распространённых раков во всем мире и характеризуется трендами заболеваемости, инвалидизации и смертности. КРР характеризуется значительной частотой рецидива и ранним мета-*

стазированием. Множество метаанализов в мировой литературе направлены на поиск факторов определения вероятного исхода заболевания.

***Цель исследования** – оценить роль паренхиматозно-стромального соотношения в прогрессировании колоректального рака.*

***Методы:** при микрокопировании в 40-кратном увеличении измеряли площадь паренхимы (Sp) и стромы (Sm) в зонах поверхностного роста опухоли и глубокой инвазии. Рассчитывали показатель паренхиматозно-стромального соотношения (ПСС) по формуле ПСС=Sp/Sm и определяли корреляционную взаимосвязь с метастазированием опухоли.*

***Результаты:** С увеличением глубины инвазии опухоли отмечается повышение частоты метастазирования в печень. Показатель метастазирования при инвазии в слизисто-подслизистый слой (Т1) и мышечную оболочку (Т2) составил 4% соответственно. Показатель возрастал до 80% при вовлечении субсерозной оболочки (Т3). Метастазы в регионарные лимфатические узлы ухудшали исход заболевания в 3 раза. При местно-распространённом и локально-регионарным в зоне глубокой инвазии преобладает паренхиматозный компонент над стромой. ПСС составляет 2,5:1,0 и 1,6:1,0. При диссеминированном росте КРР в зоне глубокой инвазии опухоли ПСС равен 1,0:1,4 с преобладанием стромального компонента до 57%.*

***Заключение:** отмечается снижение ПСС в поверхностных зонах роста при диссеминированных формах КРР по сравнению с местным и локально-регионарном типах рака. Преобладание стромального компонента в зоне глубокой инвазии прямо пропорционально с высоким неблагоприятным исходом.*

***Ключевые слова:** колоректальный рак, микроокружение опухоли, паренхиматозно-стромальное соотношение (ПСС).*

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RISK FACTORS AND EARLY SIGNS OF CRITICAL CONDITIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA ADMITTED TO THE INTENSIVE CARE UNIT

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ABSTRACT

Relevance: *Acute lymphoblastic leukemia (ALL) is the most common cancer among children, accounting for nearly a quarter of all childhood cancers.*

The study aimed to *determine the risk factors and signs of critical conditions in children with acute lymphoblastic leukemia admitted to an intensive care unit (ICU).*

Methods: *The approach used was a systematic review. Data was collected from sources published in 2019-2023. Four cohort studies, four retrospective analyses, two literature reviews, one case-control study, and one case study were included in this systematic review.*

Results: *The prognosis in pediatric ALL depends on the initial number of blast cells in the peripheral blood. Patients with B-cell precursor acute lymphoblastic leukemia (BCP ALL) and low blast cell numbers survived better than patients with T-cell acute lymphoblastic leukemia (T-ALL) and low cell count. IL1B and NLRP1 genetic polymorphisms enhanced ALL risk and reduced infectious comorbidity. However, these gene polymorphisms must be confirmed in juvenile leukemia. KRAS, FLT3, NRAS, PTPN11, KMT2D, PTEN, and NOTCH1 gene mutations affected pediatric ALL patient features and treatment results. These mutations demonstrate the relevance of genetic profiling in risk classification and tailored management. Gene variations and availability of effective medication contributed. Pediatric BCP-ALL patients with the PAX5P80R mutation had worse 5-year overall survival, higher white blood cell counts, male preponderance, and more genetic abnormalities. Pediatric BCP-ALL focused on genetic analysis and risk stratification. Children of African American and European American ancestry showed varied incidence, recurrence, and outcome rates for ALL. African American children exhibited lower incidence but greater recurrence rates and poorer prognosis than European American children.*

Conclusion: *Risk factors for these patients' admission to ICU include comorbidities, infectious diseases, hypoxia, and hemodynamic instability, as well as age and baseline white blood cell count at diagnosis.*

Keywords: *Clinical deterioration, signs of critical conditions, intensive care unit (ICU), acute lymphoblastic leukemia (ALL), children.*

Introduction: Acute lymphoblastic leukemia (ALL) is the most common cancer among children, accounting for nearly a quarter of all childhood cancers [1].

More than 6,600 new cases were diagnosed in the United States in 2022, and nearly 1,600 people died from ALL. Children make up about 60% of all cases, with the highest incidence rate occurring between the ages of two and five. A second peak in incidence comes beyond the age of fifty. Most childhood cancers and 75% of leukemia diagnoses in children below 15 years are ALLs. It ranks behind only accidents as the second-leading cause of death for children under 15 years. After reaching its mid-20s low, the risk progressively starts to grow again. This process continues until age 50. About 20% of adult acute leukemias are caused by ALL. For both sexes, the lifetime risk of ALL is around 0.1% (1 in 1000 Americans). Even though the overall survival rate for children with ALL has significantly increased over the last several decades, some kids still need to be brought to the critical care unit because of a decline in their clinical condition. This is the case even though the overall survival rate for children has significantly improved. Identifying signs or early warning indicators of severe conditions in children with ALL admitted to an intensive care unit (ICU) is vital for improving outcomes and reducing morbidity and mortality rates. It has been shown that the following criteria are both clinically and physiologically important predictors of prognosis in pediatric ALL: age, initial white blood cell count, leukemic blast genetics and immunophenotype, and treatment response.

It is significant to emphasize that over 80% of children with cancer live in LMICs, where treatment results are not optimum. This is mostly brought on by factors that lead to higher treatment-related mortality rates, such as delayed presentation, malnutrition, and a lack of supporting and critical care facilities. A high desertion rate further decreases the survival rates in LMICs. Anemia, thrombocytopenia, and neutropenia are common signs of bone marrow loss in children with ALL, along with visceromegaly and lymphadenopathy [2]. For severely sick patients, the ICU offers extensive monitoring and treatment. Children with ALL admitted to ICU often have a variety of clinical symptoms, such as organ failure, sepsis, respiratory distress, and fever. The underlying causes of clinical deterioration in these cases can vary widely, such as infectious complications, chemotherapy-related toxicities, or organ involvement by leukemia itself [2].

The diagnosis, therapy, and supplementary care of patients with malignancies of the blood have made significant strides over the last several decades, increasing survival rates. However, it is not yet known what the outcome will be for hematologic cancer patients who need admission to the critical care unit. According to recent statistics, these patients' in-hospital death rates vary from 46% to 90%. This is significantly higher than the mortality rates in general medical patients admitted to the ICU over the same period. Through a multivariable analysis, six factors are significant predictors of ICU admission. These factors relate to the patient's health, such as acute leukemia and curative intent chemotherapy, to the patient's laboratory results, such as a platelet count below 50 109/L, albumin levels below normal, and elevated LDH at the time of admission, and to the patient's doctor, such as discussions about advanced directives. These indicators are paramount and may aid healthcare personnel in starting timely and thorough dialogues with patients about treatment objectives, enabling proactive choices before the patient's health deteriorates. It is essential to remember that most patients diagnosed with hematologic cancers will need admission to ICU at some point during treatment. This highlights the significance of using the found predictors to enable efficient discussion with patients about their treatment choices [3].

Detecting early signs of impending clinical deterioration is crucial for timely intervention and improving outcomes in this vulnerable population. Identifying predictors or early harbingers of critical conditions in children with ALL admitted to the ICU is paramount. It allows healthcare providers to recognize subtle changes and initiate appropriate management strategies promptly. However, recognizing these predictors can be challenging, especially in the pediatric population, where symptoms can be nonspecific, rapidly evolving, and influenced by the child's age and developmental stage.

The study aimed to determine the signs in children hospitalized in the critical care unit with acute lymphoblastic leukemia.

Materials and Methods: For this systematic review of early signs of critical conditions in children with ALL admitted to ICU, the data was collected from sources published in 2019-2023. To conduct a PubMed search for early signs of critical conditions in children with ALL admitted to ICU, we use the keywords ("prognosis" AND "pediatric ALL"). Four years: There are 115 articles identified within a specific four-year timeframe. It implies that the search was conducted with a focus on a particular period or interval. Free full: Out of the total results, 66 articles are marked as "free full." This indicates that these articles can be accessed without payment or subscription restrictions. Selected: The dataset includes 17 articles marked as "selected." These articles were reviewed or curated to identify the most relevant and high-quality data. 12 of 295 articles were considered relevant (Fig. 1).

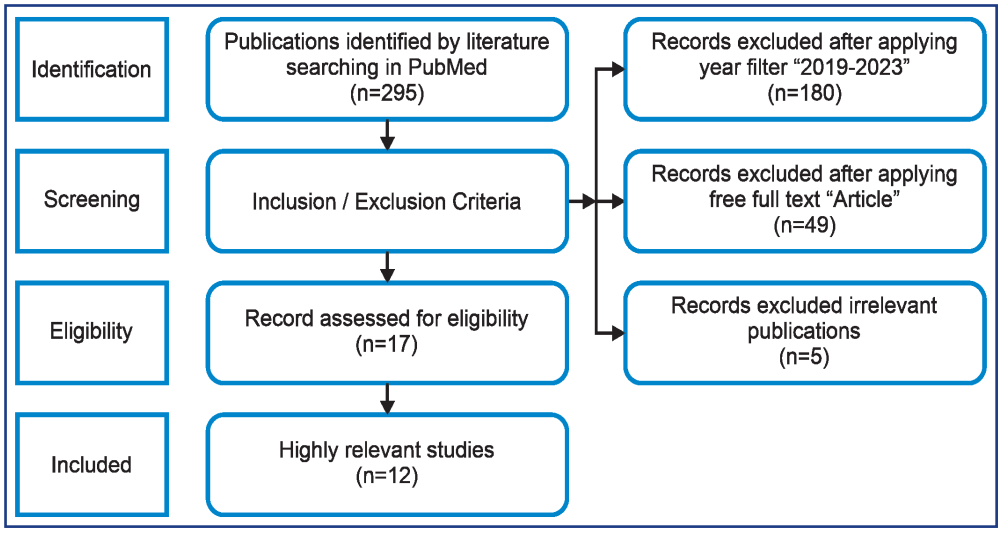

Figure 1 – A Four-Phase Literature Review Flow Diagram

The inclusion and exclusion criteria were:

1. Time Frame: The search was limited to a specific four-year period, possibly to focus on recent developments or to align with a particular study timeline.

2. Availability: "Free full" articles were preferred to open-access materials freely accessible without paywalls or subscription requirements to ensure broader access to the selected articles.

3. Manual Selection: 17 articles were manually selected for a more targeted review. Then, they were scrutinized to identify those of higher quality and relevance.

4. Relevance: Finally, 12 articles were considered relevant, meaning they were especially important or coincident with the research objectives.

Results: According to Table 1, a retrospective cohort study by Dai Q. et al. involved 367 patients with ALL aged 0 to 14 years [4]. F.S. Alves et al. conducted a case-control study involving 158 patients with ALL and 192 healthy individuals aged 2 to 15 years [5]. D. Shen et al. conducted a single-center cohort study with 219 patients diagnosed with pediatric ALL, ranging in age from 0.05 to 16.25 years, with a median age of 3.75 years [6]. W. Burke et al. performed a literature-based evaluation without specifying a sample size, focusing on individuals up to 15 years [7]. M. Jung et al. conducted a retrospective analysis involving 1237 patients with B-cell precursor ALL (BCP-ALL) over ten years [8]. J. Chu et al. conducted a retrospective analysis involving a large

sample of 5,161 children diagnosed with ALL, covering the age range of up to 18 years [9]. A.L. Brown et al. designed a prospective cohort study involving 208 pediatric patients with ALL, aged between 2 and 18 years [10]. F. Liu et al. conducted a retrospective analysis involving 178 patients with ALL, ranging in age from 1 to 13 years [11]. L. Küpfer et al. performed a retrospective analysis involving 110 unselected pediatric patients without specifying the age range [12]. J.T. Nearing et al. conducted a combined 16S rRNA gene and metagenomic shotgun sequencing study in an independent pediatric ALL cohort without providing a specific sample size [13]. A. Kashef et al. conducted a case study involving 241 observations of patients with ALL, ranging in age from 0 to 17 years [14]. Q. Zou et al. performed a literature review and analysis of existing studies, collecting 44 samples from individuals between 0.75 and 11.12 years of age [15].

Table 1 – Overview of study characteristics

Sr. No	Study	Study Design	Sample Size	Age Range
1	Dai Q. et al. [4]	Retrospective Cohort Study	367 patients with ALL	0 to 14 years
2	Alves F.S. et al. [5]	Case-Control Study	192 healthy and 158 ALL patients	2 to 15 years old
3	Shen D. et al. [6]	Single-Center Cohort Study	219 patients with pediatric ALL	0.05-16.25, median: 3.75 years
4	Burke W. et al. [7]	Literature-based evaluation	Not applicable	Up to 15
5	Jung M. et al. [8]	Retrospective analysis	1237 patients with BCP-ALL	Ten years
6	Chu J. et al. [9]	Retrospective analysis	5,161 children with ALL	Up to 18
7	Brown A.L. et al. [10]	Prospective cohort design	208 pediatric patients with ALL	2-18 years.
8	Liu F. et al. [11]	Retrospective analysis	178 patients	1-13 years
9	Küpfer L. et al. [12]	Retrospective analysis	110 unselected pediatric patients	Not specified.
10	Nearing J.T. et al. [13]	Cohort Study	An independent pediatric ALL cohort	Not specified
11	Kashef A. et al. [14]	Case study	241 observations	0 to 17 years
12	Zou Q. et al. [15]	Literature review	44 samples were collected	0.75-11.12 years of age

Early Signs of ALL

Table 2 of the systematic review examined a range of sign variables concerning pediatric ALL. Q. Dai et al. focused on the initial peripheral blood blast cell count at diagnosis [4]. F.S. Alves et al. investigated genetic polymorphisms, including IL1B and IL18, NLRP1, NLRP3, and P2RX7, genotyped using PCR-RFLP and qPCR [5]. D. Shen et al. utilized targeted sequencing through Next-generation sequencing (NGS) to identify gene mutations [6]. W. Burke et al. explored signs such as ALL incidence, relapse rates, prognostic indicators, environmental risk exposures, gene variants associated with treatment response, and access to treatment [7]. M. Jung et al. examined signs, including PAX5P80R status, white blood cell counts, sex, and copy number variations (CNVs) of IKZF1, PAX5, ETV6, RB1, BTG1, EBF1, CDKN2A, CDKN2B, and ERG [8]. J. Chu et al. assessed the response to dexamethasone, categorizing patients into dexamethasone good response (DGR) and dexamethasone poor response (DPR) groups based on peripheral lymphoblast count [9]. A.L. Brown et al. investigated patient-reported symptoms such as fatigue, pain, sleep disruptions, and nausea using surveys completed by patients or caregivers [10]. F. Liu et al. analyzed predictors, including the ETV6-RUNX1 fusion gene, CNS state at diagnosis, prednisolone response, risk level, gene positivity after induction chemotherapy, minimal residual disease (MRD) positivity, and gene positivity at the 12th week [11]. L. Küpfer et al. examined the impact of treatment with a reduced intensity ALL-Moscow Berlin (MB)-91 protocol [12]. J.T. Nearing et al. focused on the gut microbiome composition and its association with infectious complications during the initial six months of therapy [13]. A. Kashef et al. conducted an extensive analysis involving 31 attributes as potential signs in pediatric ALL [14]. Q. Zou et al. investigated genetic mutations (NOTCH1/FBXW7, PTEN, RAS, and KMT2D) and abnormal activation of the JAK-STAT signaling pathway as potential signs in ALL [15]. These studies contribute to understanding the diverse factors that may influence the development, prognosis, and treatment response of pediatric ALL.

Table 2 – Study Early Signs of ALL

Sr. No	Study	Sign Variables
1	Dai Q. et al. [4]	Initial peripheral blood blast cell count at diagnosis
2	Alves F.S. et al. [5]	IL1B and IL18 genetic polymorphisms (genotyped by PCR-RFLP), NLRP1, NLRP3, and P2RX7 genetic polymorphisms (genotyped using qPCR)
3	Shen D. et al. [6]	Gene mutations identified through targeted sequencing based on Next-generation sequencing (NGS)
4	Burke W. et al. [7]	ALL incidence, relapse rates, prognostic indicators, environmental risk exposures, gene variants associated with treatment response, access to treatment
5	Jung M. et al. [8]	PAX5P80R status, white blood cell counts, sex, copy number variations (CNVs) of IKZF1, PAX5, ETV6, RB1, BTG1, EBF1, CDKN2A, CDKN2B, and ERG
6	Chu J. et al. [9]	Response to dexamethasone (classified as dexamethasone good response [DGR] and dexamethasone poor response [DPR] groups based on peripheral lymphoblast count)
7	Brown A.L. et al. [10]	The signs variables were patient-reported symptoms, including fatigue, pain, sleep disruptions, and nausea. The patients or their primary caregivers completed symptom surveys at specific time points during the treatment
8	Liu F. et al. [11]	ETV6-RUNX1 fusion gene, Central nervous system (CNS) state at diagnosis, Prednisone response, Risk level, Gene positivity after induction chemotherapy, Minimal residual disease (MRD) positivity, Gene positivity at the 12th week

Table 2 (continued)

9	Küpfer L. et al. [12]	Treatment with a reduced intensity ALL-Moscow Berlin (MB)-91 protocol
10	Nearing J.T. et al. [13]	Gut microbiome composition, infectious complications during the first six months of therapy
11	Kashef A. et al. [14]	31 attributes
12	Zou Q. et al. [15]	Genetic mutations (NOTCH1/FBXW7, PTEN, RAS, and KMT2D), abnormal activation of signaling pathways (JAK-STAT pathway)

Table 3 summarizes important findings regarding pediatric ALL. Q. Dai et al. found that the initial peripheral blood blast cell count influenced the clinical prognosis of pediatric ALL. Specifically, patients with B-cell precursor acute lymphoblastic leukemia (BCP ALL) and low blast cell counts had better survival rates, while those with T-ALL and low counts had worse survival rates than intermediate and high counts [4]. F.S. Alves et al. focused on inflammasome gene polymorphisms and their association with ALL risk and infectious comorbidities. They discovered that certain genetic variants, such as IL1B and NLRP1, were linked to an increased risk of ALL and decreased susceptibility to infectious comorbidities. However, larger-scale investigations are required to validate the significance of these gene polymorphisms in juvenile leukemia [5]. D. Shen et al. identified 381 mutations in 66 different genes in pediatric ALL patients. They found that specific mutations, including KRAS, FLT3, NRAS, PTPN11, KMT2D, PTEN, and NOTCH1, were associated with particular patient characteristics and treatment outcomes. This highlights the importance of genetic mutations in risk stratification and personalized management of ALL [6]. W. Burke et al. investigated the disparities in ALL incidence, relapse rates, and prognostic markers between African American (AA) and European American (EA) children. They discovered that AA children had lower incidence but higher relapse rates and worse prognostic markers than EA children. Environmental risk factors had a limited impact, while gene variations and differential access to effective therapy contributed to these disparities. Precision medicine was suggested as a potential solution to address these gaps [7]. M. Jung et al. examined the presence of the PAX5P80R mutation in pediatric BCP-ALL patients and its impact on clinical outcomes. They found that patients with this mutation had worse 5-year overall survival, higher white blood cell counts, male predominance, and additional genetic abnormalities. This highlights the importance of genetic profiling and risk stratification in pediatric BCP-ALL [8]. J. Chu et al. focused on the response to dexamethasone as a prognostic factor in pediatric ALL. Based on the peripheral lymphoblast count, they divided the patients into groups for dexamethasone's excellent reaction and dexamethasone's poor response. DPR patients had higher relapse rates and lower 6-year event-free survival and overall survival rates, emphasizing the importance of early therapeutic response assessment and tailored management [9]. A.L. Brown et al. investigated the association between patient-reported symptoms and the incidence of relapse in pediatric ALL. They discovered that certain symptoms at various stages of treatment – such as weariness, discomfort, disturbed sleep, and nausea, were connected to an elevated chance of recurrence. Symptom clusters and higher symptom load were also associated with recurrence [10]. F. Liu et al. evaluated the prognostic factors and treatment outcomes in pediatric ALL. They reported favorable outcomes in ETV6-RUNX1-positive patients but highlighted the need to carefully consider CNS involvement and minimal residual disease levels for appropriate treatment decisions [11]. L. Küpfer et al. studied the outcomes of reduced-intensity ALL-MB-91 treatment in pediatric ALL patients. They found a 3-year event-free survival rate of 34.9% and suggested that tailored treatment intensity and improved platelet infusion might enhance outcomes [12]. J.T. Nearing et al. explored the relationship between gut microbiota composition and infectious complications in pediatric ALL patients during treatment. They discovered that specific gut microbiome characteristics were associated with increased vulnerability to viral problems, highlighting the potential role of the microbiome in patient outcomes [13]. A. Kashef et al. examined the necessity of cranial radiotherapy (CRT) in pediatric ALL patients and developed a classifier to predict the need for CRT based on disease recurrence. They found that CRT was cost-effective and beneficial for patients with a higher risk of recurrence [14]. Q. Zou et al. reviewed prognostic factors, genetic and molecular characteristics, and optimal treatment modalities in adult T-LBL. They emphasized the importance of genetic mutations, such as NOTCH1/FBXW7, PTEN, RAS, and KMT2D, and abnormal signaling pathways, particularly the JAK-STAT pathway. The study recommended specific treatment approaches while considering the benefits and risks of radiotherapy and highlighted the significance of prognostic models in guiding therapy selection [15].

Table 3 – Main results of the studies included in the analysis

Sr. No	Study	Outcome Measure	Results	Findings
1	Dai Q. et al. [4]	The clinical prognosis of pediatric ALL	BCP ALL was 91.6%, T-ALL 8.4%. BCP ALL and T-ALL patients' prognoses depended on their initial peripheral blood blast cell count	BCP ALL patients with low blast cell counts (<1×10^9/L) showed better survival rates than those with large counts (>30×10^9/L). T-ALL patients with low counts had worse survival rates than intermediate counts (1-29.9×10^9/L) and high counts

Table 3 (continued)

2	Alves F.S. et al. [5]	Inflammasome gene polymorphisms and ALL and infectious comorbidities	IL1B C/T rs19644 genotype increases ALL risk by 2.48-fold, whereas NLRP1 A/T rs12150220 genotype decreases infectious comorbidities by 0.37-fold. NLRP3 and P2RX7 polymorphisms did not affect risk	Larger-scale investigations are needed to validate the relevance of inflammasome gene polymorphisms in juvenile leukemia.
3	Shen D. et al. [6]	Patient characteristics, cytogenetics, genetic subtypes, risk stratification, and treatment results are correlated with gene mutation	381 gene mutations were identified in 66 different genes in 152/219 patients	KRAS, FLT3, NRAS, PTPN11, KMT2D, PTEN, and NOTCH1 mutations were related to particular patient features (P<0.050). PIK3R1 mutation was more common in babies (P=0.021). ETV6 and PHF6 mutations lowered steroid sensitivity (P=0.033 and 0.048, respectively)
4	Burke W. et al. [7]	ALL disparities between African American (AA) and European American (EA) children	AA children had a lower ALL incidence but greater recurrence rates and worse prognostic markers than EA children. Due to limited evidence, environmental risk factors for ALL had little effect, although treatment response gene variations increase AA children's recurrence rates. Risk-directed treatment, case management, and no out-of-pocket payments may reduce ALL recurrence rates	AA children had lower incidence, greater relapse rates, and worse prognoses than EA children. Due to insufficient data, environmental risk exposures on ALL are unknown, whereas gene variations and differential access to effective therapy contribute to the reported discrepancies. Precision medicine may address these gaps by personalizing treatment techniques for varied patient groups
5	Jung M. et al. [8]	5-year overall survival	PAX5P80R was detected in 2% of BCP-ALL patients, with greater white blood cell counts and male sex. Most PAX5P80R-positive individuals were ≥10 years old and had PAX5, IKZF1, CDKN2A, and CDKN2B deletions, leading to lower 5-year overall survival than in PAX5P80R-wildtype BCP-ALL	Pediatric BCP-ALL patients treated with the AIEOP-BFM ALL 2000 regimen who had PAX5P80R had worse clinical results, including poorer 5-year overall survival. PAX5P80R's association with other genetic abnormalities and intermediate-risk pediatric BCP-ALL risk classification requires more study
6	Chu J. et al. [9]	The prognosis (recurrence rate, 6-year event-free survival, and overall survival rates)	Compared to DGR, DPR had greater age, white blood cell counts, BCR/ABL1 and TCF3/PBX1 fusion genes frequency, and central nervous system recurrence (P<0.001). The DGR group had reduced recurrence rates (18.6% vs. 11%) and greater 6-year event-free survival (73% vs. 83%) and overall survival (86% vs. 92%). Only the intermediate-risk group differed (P<0.001)	Dexamethasone caused an early therapeutic response. Dexamethasone response and low residual disease were prognostic in the intermediate-risk group, possibly directing early management to minimize recurrence
7	Brown A.L. et al. [10]	The main outcome measure was the incidence of relapse in pediatric ALL patients	A total of 208 patients were followed up for a mean period of 2.6 years. A relapse occurred in 22 patients	The research found substantial connections between recurrence and certain symptoms at different treatment phases. Fatigue at the onset of delayed intensification (DI) and maintenance cycle 1 (MC1), pain at DI, nausea after induction, and sleep problems at the end of induction, DI, and MC1 all increased relapse risk. Symptom clusters with greater average DI symptom load were also related to recurrence
8	Liu F. et al. [11]	The induced remission rate, cumulative relapse incidence, 5-year and 10-year OS/EFS rates, and related prognostic variables affect medical research results	The median white blood cell count at diagnosis was 9.46×10^9/L, and the median age was 4 years. The initial induction treatment achieved a 97.8% remission rate, while 15.9% of patients relapsed, predominantly as isolated bone marrow relapse (83.3%) and late relapses (79.2%). The median relapse to first full remission was 35.5 months. ETV6-RUNX1-positive children had 5-year and predicted 10-year overall survival rates of 89.4% and 88.6% and event-free survival rates of 82.1% and 77.3%	ETV6-RUNX1-positive ALL has a good prognosis, although individuals with CNS2 at diagnosis or high MRD levels at 12 weeks should have stem cell transplantation

Table 3 (continued)

9	Küpfer L. et al. [12]	Event-free survival (EFS) and overall survival (OS)	No patients stopped therapy, and 57% were high-risk. 65.5% obtained full remission on day 36. The 3-year event-free survival (EFS) and overall survival (OS) rate was 34.9%, with infections (53.3%) and bleeding (20%) causing the most fatalities. Standard-risk (SR) individuals had 50.5% 3-year EFS	The lower intensity ALL-MB-91 treatment in a charity-funded public hospital in Cambodia had a 3-year event-free survival rate of 34.9% for pediatric ALL patients. Infections and bleeding killed most. The research also implies that leukemia treatment may be justified with selective lowering of treatment intensity and enhanced platelet infusion
10	Nearing J.T. et al. [13]	Gut microbiota composition and pediatric ALL infectious complications	Infectious problems within six months of medication were associated with unique gut microbiota alpha diversity, beta diversity, species abundance, and functional pathways. These results show that the gut microbiome's makeup and activity determine patients' vulnerability to viral problems during treatment	This research examines the gut microbiota and infectious problems in pediatric ALL patients following therapy. The findings emphasize taxonomic and functional microbiome differences. Machine learning models employing patient information and bacterial species had an 84.09% classification accuracy. Bacterial species were the most relevant characteristics. This connection and its implications for future research and therapeutic practice need more study
11	Kashef A. et al. [14]	The necessity of Cranial Radiotherapy (CRT) treatment in pediatric ALL patients	The stacked ensemble classifier used in the study demonstrated highly reasonable performance with an Area Under the Curve (AUC) of 87.52%	In pediatric ALL patients, disease recurrence is the main predictor of CRT therapy, which is cost-effective and beneficial
12	Zou Q. et al. [15]	Prognostic factors, genetic and molecular characteristics, optimal treatment modalities	Genetic mutations (NOTCH1/FBXW7, PTEN, RAS, KMT2D) and aberrant JAK-STAT signaling were studied in adult T-LBL. Leukemia treatment, CNS prophylaxis, and cranial radiation-free procedures were used. 5-miRNA, 11-gene, and 4-CpG classifiers predicted outcomes	The review study covered adult T-LBL's genetic and molecular features, recommended treatment options, and emphasized the significance of genetic mutations and abnormal signaling pathways. It also highlighted the importance of prognostic models and recommended specific therapies while considering the benefits and risks of radiotherapy

Discussion: This systematic review on Early Signs and risk factors of Critical Conditions in Children with ALL Admitted to ICU includes 4 cohort studies, 4 retrospective analyses, 2 literature reviews, 1 case-control study, and 1 case study.

Different research discovered that several clinical and laboratory prognostic markers utilized for B-precursor ALL were much less predictive in T-ALL; other criteria, such as the time to relapse and the relapse location, were significant prognostic factors for survival [16]. A separate study has also shown that ALL children below 15 years have a very good prognosis, with cure rates exceeding 85%. However, the prognosis for ALL grows less promising as people age. In the past, only 30% to 40% of individuals over 40 years were cured. Relapsed ALL continues to cause cancer-related deaths in people of all ages [17].

The systematic review of the original question focuses on various sign variables; the search results cover a broader range of topics related to ALL. Regular laboratory tests for pediatric ALL include lumbar puncture, bone marrow aspiration and biopsy, complete blood count, and peripheral blood smear [18]. Overall, the search results provide a more comprehensive understanding of the diagnosis, treatment, and prognosis of pediatric ALL, including the use of risk-adapted treatment protocols and the importance of genetic and molecular factors in determining prognosis. This systematic review focuses on signs of critical conditions in pediatric ALL, including initial peripheral blood blast cell count, genetic polymorphisms, gene mutations, prognostic indicators, treatment response, and access to treatment. Other literature from 2019 to 2023 provides additional insights into prognostic factors, treatment outcomes, genetic and molecular characteristics, and disparities in ALL. Pharmacological heterogeneity of ALL exists, and drug response varies across molecular subtypes [19]. Patient-reported symptoms such as fatigue, pain, sleep disruptions, and nausea are associated with the incidence of relapse in pediatric ALL. The gut microbiome composition is associated with infectious complications during ALL treatments. Genetic mutations and abnormal activation of signaling pathways play a role in ALL prognosis and treatment responses.

According to a study of pediatric patients, the typical risk factors for ICU admission are the following:

– Infectious and respiratory diseases, comorbidities, acute respiratory distress syndrome [20, 21];

– Hyperleukocytosis, neural leukosis, infections, hemorrhagic syndrome [22];

– Severe course of the underlying disease, hypoxia, inability to eat and drink [23];

– Age, neurologic impairment, chronic disease, and immunodeficiency [24].

These risk factors highlight the importance of monitoring and managing comorbidities, infectious diseas-

es, and respiratory and cardiovascular function in pediatric patients to prevent ICU admission.

The available information describes the primary reasons for patients with ALL admission to ICU. However, comparing these results with other research studies is crucial for a more comprehensive knowledge of the reasons for ICU admissions. The most frequent causes of ICU admission in the United States, according to research published in the BMC Emergency Medicine journal, were chest discomfort, heart failure, and pneumonia [25]. According to the Ottawa Hospital data, cancer patients sometimes require ICU admission for bleeding or infection, usually after chemotherapy or bone marrow transplantation. Overall, the reasons for ICU admission can vary depending on age, sex, type of hospital, and geographic location. However, respiratory issues, cardiac problems, renal issues, and sepsis are common reasons for ICU admission in various studies. Unified approaches to early precursors of critical conditions in children with ALL are required to prevent critical conditions and reduce adverse outcomes of the disease [26].

Conclusion: Based on the data presented, several conclusions can be drawn regarding prognostic factors, signs, and underlying reasons for admission to the ICU of pediatric patients with ALL and hematologic malignancies: age, initial white blood cell count at diagnosis, ALL subtypes, and initial response to treatment are important prognostic factors. However, genetic abnormalities and recurrence are also important for prognosis. Comorbid conditions, infectious diseases, hypoxia, organ dysfunction, etc. are common risk factors for ICU hospitalization. Larger studies show that sepsis, respiratory, cardiac, neurological, and renal diseases are frequent causes of ICU hospitalization. Hematologic malignancies require further examination of prognostic variables and prognosis of ICU admission. This will help to improve the understanding and management of these diseases. Pediatric patients with ALL, especially those at increased risk of ICU admission, require close monitoring and follow-up to address potential complications in due time and reduce the need for intensive care. Healthcare providers should allocate appropriate resources, including trained staff, equipment, and infrastructure, to effectively manage pediatric patients with ALL. This will optimize patient outcomes and reduce the burden on intensive care units.

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АНДАТПА

РЕАНИМАЦИЯ БӨЛІМІНЕ ТҮСКЕН ЖЕДЕЛ ЛИМФОБЛАСТИКАЛЫҚ ЛЕЙКЕМИЯМЕН АУЫРАТЫН БАЛАЛАРДАҒЫ АУЫР ЖАҒДАЙЛАРДЫҢ АЛҒАШҚЫ БЕЛГІЛЕРІ ЖӘНЕ ҚАУІП ФАКТОРЛАРЫ

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Өзектілігі: *Жедел лимфобластикалық лейкоз (ЖЛЛ) балалар арасындағы ең көп таралған қатерлі ісік болып табылады, ол барлық балалар ісіктерінің төрттен бір бөлігін құрайды.*

Зерттеудің мақсаты *– реанимация және қарқынды терапия бөліміне (РҚТБ) түскен жедел лимфобластикалық лейкозбен ауыратын балалардағы қауіп факторлары мен ауыр жағдайдың белгілерін анықтау.*

Әдістері: *Ретінде жүйелі шолу қолданылды. Деректер 2019-2023 жылдары жарияланған дереккөздерден жиналды. Жүйелі шолуға төрт когорттық зерттеу, төрт ретроспективті талдау, екі әдебиетке шолу, бір «жағдайды-бақылау»» зерттеуі және бір жағдайды зерттеу кірді.*

Нәтижелері: *Педиатриялық ЖЛЛ болжамына перифериялық қандағы бласт жасушаларының бастапқы саны әсер етеді. Бласт жасушаларының саны төмен деңгейдегі В-ЖЛЛ пациенттері, төмен деңгейлі Т-ЖЛЛ пациенттеріне қарағанда болжамы жақсы. IL1B және NLRP1 генетикалық полиморфизмдері жедел лимфобластикалық лейкоздың даму қауіпін арттырады және инфекциялық үйлесімділікті төмендетті. Алайда, бұл гендердің полиморфизмдері ювенильді лейкемияда расталуы керек. KRAS, FLT3, NRAS, PTPN11, KMT2D, PTEN және NOTCH1 гендерінің мутациялары педиатриялық ЖЛЛ бар науқастардың сипаттамалары мен нәтижелеріне әсер етті. Бұл мутациялар қауіп қатерді жіктеу және емдеуді даралау үшін генетикалық профильдеудің өзектілігін көрсетеді. Бұған гендік вариация және тиімді дәрі-дәрмектердің болуы ықпал етті. PAX5P80R мутациясы бар емделушілерде 5 жылдық жалпы өмір сүру ұзақтығы төмен, лейкоцит клеткаларының деңгейі жоғары, ерлерде басым және генетикалық ауытқулар көп болды. Педиатриялық В-ЖЛЛ генетикалық талдау мен қауіп қатерді стратификациялауға бағытталған. Афроамерикалық (АА) және еуроамерикалық (ЕА) тектес балаларда ЖЛЛ ауруының, қайталануының және нәтижелерінің әртүрлі көрсеткіштері байқалды. АА балаларының жиілігі төмен, бірақ қайталану жиілігі жоғары және болжам ЕА балаларына қарағанда нашар.*

Қорытынды: *Осы науқастардың реанимация бөліміне жатқызылу қауіп факторлары қатар жүретін аурулар, жұқпалы аурулар, гипоксия және гемодинамикалық тұрақсыздық, сондай-ақ диагноз кезінде жасы мен лейкоциттер санының бастапқы көрсеткіштері болып табылады.*

Түйінді сөздер: *Клиникалық нашарлау, критикалық жағдайлардың белгілері, қарқынды емдеу бөлімшесі (ҚЕБ), жедел лимфобластикалық лейкемия (ЖЛЛ), балалар.*

АННОТАЦИЯ

ФАКТОРЫ РИСКА И РАННИЕ ПРИЗНАКИ КРИТИЧЕСКИХ СОСТОЯНИЙ У ДЕТЕЙ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ, ПОСТУПИВШИХ В ОТДЕЛЕНИЕ ИНТЕНСИВНОЙ ТЕРАПИИ

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Актуальность: *Острый лимфобластный лейкоз (ОЛЛ) – наиболее распространенное онкологическое заболевание среди детей, составляющее почти четверть всех детских онкологических заболеваний.*

Цель исследования *– определить факторы риска и признаки критических состояний у детей с острым лимфобластным лейкозом, поступивших в отделение реанимации и интенсивной терапии (ОРИТ)*

Методы: *В качестве подхода использовался систематический обзор. Данные были собраны из источников, опубликованных в 2019-2023 гг. В систематический обзор были включены четыре когортных исследования, четыре ретроспективных анализа, два обзора литературы, одно исследование типа «случай-контроль» и одно исследование случая.*

Результаты: *Прогноз при педиатрическом ОЛЛ зависит от исходного количества бластных клеток в периферической крови. Больные с В-ОЛЛ и низким количеством бластных клеток выживали лучше, чем больные с Т-ОЛЛ с низким числом клеток. Генетические полиморфизмы IL1B и NLRP1 повышали риск развития ОЛЛ и снижали инфекционную коморбидность. Однако полиморфизмы этих генов должны быть подтверждены при ювенильном лейкозе. Мутации генов KRAS, FLT3, NRAS, PTPN11, KMT2D, PTEN и NOTCH1 повлияли на характеристики и результаты лечения пациентов с педиатрическим ОЛЛ. Эти мутации демонстрируют актуальность генетического профилирования для классификации риска и индивидуализации лечения. Этому способствовали генные вариации и доступность эффективных лекарственных препаратов. Пациенты с педиатрическим В-ОЛЛ с мутацией PAX5P80R имели худшую 5-летнюю общую выживаемость, более высокий уровень лейкоцитов, преобладали мужчины и имели больше генетических аномалий. При педиатрическом В-ОЛЛ основное внимание уделяется генетическому анализу и стратификации риска. У детей афроамериканского (АА) и евро-американского (ЕА) происхождения наблюдались различные показатели заболеваемости, рецидивов и исходов ОЛЛ. У детей АА заболеваемость ниже, но частота рецидивов выше, а прогноз хуже, чем у детей ЕА.*

Заключение: *Факторами риска госпитализации в отделение интенсивной терапии у таких пациентов являются сопутствующие заболевания, инфекционные болезни, гипоксия и гемодинамическая нестабильность, а также возраст и исходное количество лейкоцитов в крови при постановке диагноза.*

Ключевые слова: *клиническое ухудшение, признаки критических состояний, отделение интенсивной терапии (ОИТ), острый лимфобластный лейкоз (ОЛЛ), дети.*

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NUTRITIONAL SUPPORT FOR CANCER PATIENTS IN THE EARLY POSTOPERATIVE PERIOD

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ABSTRACT

Relevance: *In modern medicine, evaluating patients' nutritional status is a priority for many specialists. The incidence of malnutritional in cancer pathology increases annually by 65-85%. The nutritional status of patients is represented by a decrease in life expectancy, deterioration of immediate and long-term treatment results, a decrease in the tolerability of therapy, and a decrease in the quality of life. Early detection of nutritional insufficiency and evaluation of the patient's nutritional status makes it possible for early provision of nutritional therapy and has a positive effect before the operation, during and after the operating period, reduces postoperative complications, and reduces the duration of stay in the hospital. This article reflects on the features of evaluating the nutritional status and methods of correction of clinical nutrition.*

The study aimed to *analyze the effectiveness of cancer patients' nutrition in the early postoperative period and determine the optimal method of nutritional support.*

Methods: *We compared the clinical effectiveness of enteral and parenteral nutrition methods in the complex of postoperative therapeutic measures on the hepato-pancreatic-duodenal zone.*

Results: *On Days 10-12 after surgery, 12 out of 17 control group patients had normal nutritional status judging by their Subjective Global Assessment (SGA) and Nutritional Risk Index (NRI), and five had moderate malnutrition. After enteral nutrition was added (on Days 13-15), no malnutrition cases in this group were detected. The total blood protein in the subjects showed a significant difference between the average values of indicators in clinical groups for the entire study period ($p<0.05$). The average total blood protein by Day 8 after surgery was 62.5±10.0 g/L in the study group and 57.5±10.1 g/L in the control group. The change in the blood biochemical composition was due to the volume, duration, and nature of the surgical intervention.*

Conclusion: *When using nutritional therapy in cancer patients operated on for tumors of the hepato-pancreatic-duodenal zone in the early postoperative period, the enteral route of administration of nutrient mixtures is preferred, provided there is no pronounced intestinal paresis and purulent discharge from the stomach.*

Keywords: *malnutritional, nutritional support, cancer, cancer patients, enteral nutritional supplements, parenteral nutrition.*

Introduction: Treatment of hepato-pancreatic-duodenal zone tumors is a priority for modern clinical cancer. The growth of the hepato-pancreatic-duodenal zone tumors leads to cancer pathologies, and finding treatment methods is a priority task. Among the hepato-pancreatic-duodenal zone pathologies, those accompanied by a decrease in the permeability or closure of the central biliary tract, with the subsequent development of obstructive jaundice, can be recognized as the most severe. Malnutritional is one of the most important indicators of the onset of the tumor process. It is based on the following factors: loss of appetite, localization of the tumor, which makes it difficult to eat normally (depending on its localization in the oropharyngeal zone or gastrointestinal tract), tumor complications, antitumor therapy (dyspepsia, pain syndromes). The main changes in oncopathology are manifested by cancerous cachexia [1, 2].

More than 50% of patients in intensive care units have symptoms of malnutrition. Despite early preventive examinations and the proposed modern diagnostic measures, in most cases, patients continue to be hospitalized if various complications of tumors of the organs of the hepato-pancreatic-duodenal zone (obstructive jaundice, duodenal obstruction, liver and kidney failure, tumor invasion of hollow organs and bleeding of the gastrointestinal tract) develop. Eating disorders significantly affect the outcome and prognosis of the disease, dramatically increase the duration and cost of treatment, and contribute to an increase in the number of deaths and complications. Complications include a decrease in immunity, secondary infection of the body, slow wound healing, a decrease in the concentration of blood plasma proteins, changes in drug metabolism, and a decrease in the body's tolerability to surgical treatment [2, 3].

In evaluating these indicators, the priority task is to evaluate the state of nutrition and carry out nutritional therapy in the clinic at all stages of treatment in cancer patients.

The study aimed to analyze the effectiveness of cancer patients' nutrition in the early postoperative period and determine the optimal method of nutritional support.

Materials and methods: We reviewed the literature and an analysis of various medical studies on cancer patients' nutritional support methods in the early postoperative period.

The International Associations of Clinical Nutrition ASPEN (American Society for Parenteral and Enteral Nutrition)

and ESPEN (Europen Society for Parenteral and Enteral Nutrition) recommended screening methods to identify malnutrition, including patient questionnaires. These standard anthropometric and laboratory data allow for evaluating the nutritional status and the degree of impairment.

We evaluated the patient's clinical condition using the screening protocols Nutritional Risk Screening (NRS, 2002), Subjective Global Assessment (SGA), and Nutritional Risk Index (NRI) on Days 5, 10, and 15 before and after surgery.

We also evaluated some indicators of nutritional status in the cancer dispensary. These are body mass index (measured weight before surgery and after surgery on Days 5, 10, and 15), basal metabolic rate (Harris-Benedict Equation based on patient's anthropometric data, taking into account gender, age, weight, and total volume), laboratory indicators (hemoglobin in the blood, lymphocytes, total protein, serum albumin, serum transferrin, total and direct bilirubin, ALT and AST for evaluating nutritional status). Our study involved 17 people in the study group, 17 in the control group, and men and women aged 18 to 80. An appropriate volume of radical or palliative surgical interventions has been performed depending on the tumor size, cancer severity, and prevalence. We compared the clinical effectiveness of enteral and parenteral nutrition methods in the complex of postoperative therapeutic measures on the hepato-pancreatic-duodenal zone.

Results: We should evaluate the patient's nutritional status from cancer detection. There are screening methods to identify malnutrition, including a survey of patients, using standard anthropometric and laboratory data to evaluate the nutritional status and the degree of its violation.

The malnutritional indicator is evaluated in cancer patients using screening protocols: NRS 2002 (Nutritional Risk Screening), SGA (Subjective Global Assessment), and NRI (Nutritional Risk Index) [3, 4].

When evaluating NRS 2002 screening results, it is recommended to answer "yes" or "no" to four questions:

– Is the patient's body mass index below 20.5?

– Has the patient lost weight in the last three months?

– Has the patient's food intake decreased in the last week?

– Does the patient belong to the group of "serious illness"?

After receiving one positive response, a final screening is carried out to determine the degree of risk and further tactics. In case of negative answers to all four questions, re-screening is done at intervals of 1 per week to monitor the patient's condition. The SGA protocol can be an alternative to NRS 2002 [1, 2, 5]. SGA evaluates not only changes in anthropometric data but also the physiological parameters of the body. SGA includes the following evaluation criteria:

– Weight loss;

– Amount of food consumed;

– Gastrointestinal symptoms;

– Functional abilities;

– Effects depending on the underlying disease;

– Physical signs of malnutrition (loss of subcutaneous fat or muscle mass, edema, ascites).

According to the above criteria, patients were divided into three groups (A, B, C) – regular, moderate, and severe malnutrition.

An additional screening method for evaluating nutritional status is the NRI (Nutritional Risk Index). This protocol evaluates changes in body weight and serum albumin levels [5, 6].

The formula calculates the NRI: (1.519 × serum albumin, g/dL) + {41.7 × actual body weight (kg)/ideal body weight (kg)}.

After evaluating the test, the patient can be assigned to one of 3 groups:

1) no malnutritional (NRI>97.5),

2) moderate malnutrition (97.5 ≥ NRI ≥ 83.5),

3) severe malnutrition (NRI <83.5).

This type of screening is effective and used in cancer patients with gastrointestinal tumors [7-9].

We evaluated the nutritional status or violation risk during treatment using the screening protocol data to choose the method of treatment tactics.

The ASPEN recommends starting nutritional support as early as possible (within 24-48 hours) after stabilizing the patient's condition.

It is necessary to qualitatively determine the dosage of the drugs used and their composition to achieve the goal of therapeutic effect from nutrition.

Malnutrition correction is based on the patient's needs and requires consideration of the energy consumed and the quantitative combination of substrates. Considering energy consumption and preventing energy deficit, the required number of calories is set for each patient [10-12].

One of the methods for evaluating the energy needs of cancer patients is the calculation of constant indicators of body weight (energy – 35 kcal/kg, protein – 1.5 g/kg). Calculating the leading indicators is possible using modern computer programs to consider the peculiarities of the disease course and each patient treatment. These programs also allow calculating the individual patient's need for energy and essential nutrients.

Cancer patients need a systematic approach to nutrition. It is necessary to continue at all treatment stages, including in the future, in providing outpatient care. Patients with special metabolic needs and with primary metabolic disorders require special care before and after the surgery [13-15].

Scheme for determining the nutritional support:

1. Evaluation of nutritional status.

2. The patient's nutritional costs evaluation regarding essential nutrients (energy, protein).

3. Determination of correction methods of clinical nutrition (parenteral, enteral, or combined).

4. Monitoring the patient's condition.

The cancer patient's nutritional supply is based on therapeutic diet programming, considering energy and plasticity needs, which are a prerequisite for achieving the goal of cancer treatment and rehabilitation. Clinical nutrition in intensive care should begin from the first days [16, 17].

The study groups of nutritional support:

– Parenteral nutrition, partial or complete;

– Enteral nutrition;

– Combined nutrition (parenteral and enteral).

With parenteral nutrition, the mixture should be administered on the first day at a 50 mmL/h rate. Each subsequent day, the injection rate increases by 25 mmL/h. In this case, the mixture consumption should not exceed 125 mmL/h. The mixture introduction continues for 18-20 hours during the day [1, 2, 18].

The daily volume of 250-500-1000 ML is evenly distributed in 6-8 doses for 12-14 hours.

Basic requirements for food quality:

– sufficient caloric content (not less than 1 kcal / ML);

– lactose-free or low lactose;

– adapted, that is, it contains all the vitamins and minerals;

– low osmolarity – no more than 340 mmol/L;

– low viscosity for regular injection;

– high quality of ingredients texture (easily digested and absorbed);

– balanced, with an optimal ratio of ingredients;

– calorie content of the nutrient mixture and introduced nitrogen (under stress, the calorie/nitrogen ratio is considered optimal – about 120-180 non-protein kcal per 1 g of nitrogen);

– when the mixture is administered outside the gastroduodenal section of the digestive tract, it contains a small" slag" residue;

– does not cause dangerous stimulation of intestinal motility and evacuation activity of the large intestine [19].

Contraindications to enteral nutrition:

1. Ischemia and intestinal perforation;

2. Gastrointestinal bleeding;

3. Intestinal obstruction;

4. Severe nausea and vomiting that do not correspond to the standard regimens for taking antiemetics;

5. Abdominal compartment syndrome;

6. Persistent incurable diarrhea.

Parenteral nutrition is the introduction of nutrients into the body, bypassing the gastrointestinal tract (root bed). Parenteral nutrition can be complete or incomplete. In general, parenteral nutrition provides the entire daily caloric requirement of the body. Incomplete parenteral nutrition is necessary to partially compensate for the lack of nutrients that cannot be fully assimilated with enteral nutrition.

Semi-parenteral nutrition should be considered as an aid. Nevertheless, this type of nutritional supply is widely used in the pre-and postoperative period to meet the daily requirement for energy and plastic substrates to restore and maintain water-electrolyte and acid-base balance in cases where complete enteral nutrition is impossible.

The main components of parenteral nutrition:

1. Energy sources-glucose Solutions (10%, 20%, 30%) and oil emulsions.

2. Sources of plastic material for protein synthesis are solutions of crystalline amino acids.

3. Multivitamin complexes (water and fat-soluble vitamin preparations).

4. Microelement complexes for parenteral administration.

5. Mixed vessels "two in one" (amino acid solution+ glucose) and "three in one" (amino acid solution+glucose+fat emulsion) [1, 3, 20].

Parenteral feeding modes:

Round-the-clock input:

– Optimal for hospital patients;

– Best durability and use of substrates;

Infusion lasting 18-20 hours:

– Good endurance;

– It is recommended to introduce 5% glucose at intervals;

Cyclic mode-infusion for 8-12 hours:

– Convenient for Parenteral Nutrition at home;

– Good endurance after a period of adaptation.

Contraindications to parenteral nutrition:

– Shock (increase in the dose of vasopressors)

– Anuria or hyperhydration without dialysis;

– Fat embolism (for Fat Emulsions);

– Serum lactate>3 mmol/L, hypoxia pO_2<60 mmHg.St.;

– pCO_2>80 mmHg.St., acidosis-pH<7.2;

– Intolerance to individual food components or anaphylaxis.

Mixed food.

In the postoperative period, the patient can be administered simultaneously with a gradual increase in enteral and parenteral nutrition and a decrease in parenteral nutrition.

Patients nutritional status on Days 10-12 of the preoperative and postoperative period confirmed the nutritional status in two groups as usual and insufficient according to the NRI evaluation methods – 11/6 for the study group and 15/2 for the control group.

Thus, in 26 patients, the NRI index was considered harmful (normal nutritional status), and in 8 patients – actually positive (moderate malnutrition).

Before surgery, according to the SGA assessment, 11 patients in the study group ate usually, and six did not eat moderately. In the control group, SGA scores showed normal in 15 patients and average nutritional status in 2 patients.

Patients in the control group (n=17) on Days 10-12 were in a state of normal nutrition according to the SGA and NRI. 2 patients were in moderate malnutrition. After enteral nutrition was added (on Days 13-15), no malnutrition cases in this group were detected. According to the report, the aver-

age values of metabolic needs, namely energy and protein requirements, were 35.2±3.5 kcal/kg or 2200-2500 kcal/day and 1.5±0.09 kcal/kg/day in both groups or 80-100 kcal/day, respectively. The central metabolism showed that at the beginning of the control period – before the operation and later on postoperative Days 3, 8, and 15 there were no significant differences between the groups ($p<0.1$) [6, 7].

Thus, the magnitude of this difference was due to the preservation of parietal digestion in the gastrointestinal tract in the early postoperative period despite postoperative intestinal paresis. Patients' average weight of the leading and control groups was 79.2±4.11 and 80.8±6.1 kg, respectively, on Days 2-3 of the postoperative period, and there was a slight but significant difference between the groups in the comparative aspect up to Days 8-10.

The total blood protein in the subjects showed a significant difference between the average values of indicators in clinical groups for the entire study period ($p<0.05$). The average total blood protein by Day 8 after surgery was 62.5±10.0 g/L in the study group and 57.5±10.1 g/L in the control group.

The dynamics of the number of lymphocytes on Days 3-5 after the surgery revealed a significant, more than 2-fold decrease in the level in groups up to 10.5±4.8%, which was subsequently replaced by an increase and normalization of lymphocytes on Day 10 – up to 21.9±5.6% and the optimal level by the time of transfer of patients to a specialized department, on average 24.6 ±4.4%.

When evaluating the results of Days 5-7 of total bilirubin in both groups, the range of its values averaged 17.6±8.3 μmol/L. in patients with obstructive jaundice, bilirubin in the blood directly exceeded the norm on the first day of the preoperative and postoperative period more than 7-8 times. On Days 5-7, there was a tendency to reduce its level by 5-6 times, persisted until discharge from the hospital [10, 11].

The results of ALT and AST analysis of blood transaminases in groups reached a 10-fold increase on Day 1 after surgery, primarily ALT, as a more specific test for damage to the liver parenchyma, – 412.3±105.5 and to a lesser extent AST-102.3±17.9 EB/L, and then on Days 4-5 a decrease in ALT on average 153.8±55.6 EB/L.

Discussion: Analysis of the dynamics of clinical efficacy indicators of treatment in the study group, the duration of stay in the postoperative hospital was 13.0±5.0 days, significantly less than in the control group – 17.5±10.8 days ($p<0.09$). The results within the numerical values' limits adequately reflect more detailed information and are confirmed in a few literary sources [6, 10, 14, 16, 17].

According to the leading and control groups, the average time spent in the intensive care unit of patients has differed depending on the surgery volume. It amounted to 2.9±2.7 and 4.3±2.1 days ($p>0.06$).

Based on the results of this work, according to a consolidated analysis of clinical and laboratory data, the enteral method comes to the fore in the context of the comparative effectiveness of nutritional support, confirmed in several literary sources [2-7, 15, 18].

In the absence of pronounced intestinal paresis and persistent purulent discharge from the stomach in the early postoperative period, the effectiveness of enteral/tube nutrition prevails in this group of patients.

In general, the results obtained based on a specific contingent (cancer patients in the early postoperative period) adequately reflect the positive aspects of the use of the enteral/tube route of nutrition support compared to the parenteral method only in the absence of pronounced postoperative intestinal paresis and dynamic intestinal obstruction [1, 2, 9, 14, 16].

Each type of nutrition support has its characteristics of implementation. Of course, the natural way of eating is usually in the first place. It is preferable if the absorption of energy substrates and nutritional components is maintained in the gastrointestinal tract.

Conclusion: We conducted clinical trials to study the timing of the onset of nutritional support and methods for its implementation despite the proven relationship between the use of certain species (enteral, parenteral nutrition) worldwide for many years. In various pathological conditions, its duration remains the subject of clinical research.

However, not all of them found a significant effect of diet therapy on immediate and long-term outcomes, especially in patients with normal nutritional status or moderate malnutrition. The conducted studies are distinguished by the heterogeneity of the contingent of patients and the use of different options for nutritional support (parenteral nutrition, enteral nutrition) [1, 2, 20].

In patients with a general surgical profile, the positive effect of nutritional therapy is manifested mainly in severe nutritional insufficiency before the start of treatment or in the absence of complete enteral nutrition for a long time. The nature of the operation at that time and the effectiveness and expediency of nutritional support in patients with tumors of the oropharyngeal zone and esophageal cancer were beyond doubt and have been confirmed by numerous studies.

Conducting clinical nutrition before and after the surgery is crucial to treating cancer patients. Ineffectiveness and insufficient feeding of cancer patients can lead to a deterioration in the immediate and long-term treatment results, a decrease in the tolerability of therapy, and a deterioration in the quality of life.

Nutritional support is paramount for patients who cannot ensure a healthy diet for more than 14 days in the postoperative period. When planning nutritional therapy, preference should be given to its simplest and most physiological version – the oral intake of mixed and balanced nutritional mixtures. If oral administration is impossible, they resort to tubular enteral nutrition; only the last turn is parenteral.

Thus, nutritional support at various stages of cancer patients' complex treatment makes it possible to reduce the frequency of postoperative complications and the duration of hospital stay, prevent interruption of the course of treatment, and increase the tolerability of conservative anti-cancer therapy.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРДЫ ОПЕРАЦИЯДАН КЕЙІНГІ ЕРТЕ КЕЗЕҢДЕ ҚОРЕКТІК ҚОЛДАУ

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Өзектілігі: *Қазіргі заманғы медицинада науқастардың тамақтану жағдайын бағалау көптеген клиникалық медицина мамандарының назарында. Онкологиялық патологиялардың ішінде тағамдық жетіспеушілік жағдайларының саны 65-85% жетеді және өсу үрдісі бар.*

Науқастардың тамақтану жағдайының бұзылуы өмір сүру ұзақтығының қысқаруымен, емдеу нәтижелерінің дерегу және ұзақ мерзімді көрсеткіштерінің нашарлауымен, терапияның төзімділігінің және өмір сүру сапасының төмендеуімен бірге жүреді.

Онкологиялық науқастардың тамақтану жағдайын ерте бағалау және қоректік заттардың жетіспеушілігін анықтау тамақтану терапиясын уақтылы бастауға мүмкіндік береді, операцияға дейінгі және операциядан кейінгі кезеңдердің өтуіне оң әсер

етеді. Сайып келгенде, бұл операциядан кейінгі асқынулардың төмендеуіне әкеледі және науқастардың ауруханада болу ұзақтығын қысқартады. Мақалада онкологиялық науқастардың операциядан кейінгі ерте кезеңде тамақтану жағдайын бағалау ерекшеліктері мен клиникалық тамақтануды түзету әдістері көрсетілген.

***Зерттеудің мақсаты** – онкологиялық науқастарда операциядан кейінгі ерте кезеңде тағамдық тамақтанудың тиімділігін талдау және оны жүзеге асырудың оңтайлы әдісін анықтау.*

***Әдістері:** Гепатопанкреатодуоденальды аймақта операциядан кейінгі емдік шаралар кешенінде тамақтануды қолдау әдістерін – энтеральді және парентеральді тамақтануды қолданудың клиникалық тиімділігіне салыстырмалы бағалау жүргізілді.*

***Нәтижелері:** Операциядан кейінгі кезеңнің 10-12 күнінде бақылау тобындағы 17 пациенттің 12-сі Субъективті жаһандық бағалау (SGA) және тағамдық тәуекел индексі (NRI) бойынша қалыпты тамақтану күйінде, ал 5 адам күйде болды. орташа жеткіліксіз тамақтану. Парентеральді қоректену энтеральдіге ауысқаннан бері (13-15-ші күндері) – осы топта тамақтанбау белгілері бар науқастар анықталмады. Зерттелетіндердің жалпы қан ақуызын талдау зерттеудің бүкіл кезеңінде клиникалық топтардағы көрсеткіштердің орташа мәндері арасындағы айтарлықтай айырмашылықты көрсетті ($p<0,05$). Негізгі топта жалпы қан ақуызының орташа мөлшері 62,5±10,0 г/л, бақылау тобында операциядан кейінгі кезеңнің 8 күніне 57,5±10,1 г/л. Қанның биохимиялық құрамын талдау нәтижелерінің өзгеруі хирургиялық араласудың көлеміне, операцияның ұзақтығы мен сипатына байланысты.*

***Қорытынды:** Операциядан кейінгі ерте кезеңде гепато-панкреатодуоденальды аймақтың ісіктері бойынша операция жасалған онкологиялық науқастарда тағамдық тамақтануды қолданғанда, егер айқын ішек парезі және асқазаннан іріңді бөліністер болмаса, қоректік қоспаларды енгізудің энтеральді жолы қолайлы.*

***Түйінді сөздер:** тағамдық жетіспеушілік, тағамдық қолдау, қатерлі ісік, онкологиялық науқастар, энтеральді тамақтану, парентеральді тамақтану.*

АННОТАЦИЯ

НУТРИТИВНАЯ ПОДДЕРЖКА ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ В РАННЕМ ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ

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***Актуальность:** Оценка нутритивного статуса больных является первоочередной задачей для многих специалистов современной медицины. Заболеваемость онкологической патологией на фоне нутритивной недостаточности ежегодно возрастает на 65-85%. Нутритивный статус больных рекомендуется контролировать при уменьшении продолжительности жизни, ухудшении непосредственных и отдаленных результатов лечения, резистентности к лечению, снижении эффективности проводимой терапии и качества жизни. Раннее выявление нутритивной недостаточности и оценка нутритивного статуса больных позволяют своевременно назначить нутритивную терапию и оказывают положительный эффект до, во время и после операции, снижая частоту послеоперационных осложнений и сроки пребывания в стационаре. В данной статье показаны особенности оценки нутритивного статуса и методы коррекции лечебного питания.*

***Цель исследования** – анализ эффективности питания онкологических больных в раннем послеоперационном периоде и определение оптимального способа его проведения.*

***Методы:** Проведена сравнительная оценка клинической эффективности применения методов энтерального и парентерального питания в комплексе послеоперационных лечебных мероприятий на гепатопанкреатодуоденальной области.*

***Результаты:** На 10-12 сутки после операции, 12 из 17 пациентов контрольной группы находились в состоянии нормального пищевого статуса согласно Субъективной Глобальной Оценке (SGA) и Индексу нутритивного риска (NRI), а 5 пациентов были в состоянии умеренного недоедания. С момента подключения энтерального питания (13-15 сутки), пациентов с признаками недоедания в данной группе не выявлялось. При анализе общего белка крови у обследуемых выявлено достоверное различие между средними значениями показателей в клинических группах в течение всего периода исследования ($p<0,05$). В основной группе среднее содержание общего белка крови составило 62,5±10,0 г/л, в контрольной группе – 57,5±10,1г/л к 8 суткам послеоперационного периода. Изменение биохимического состава крови обусловлено объемом хирургического вмешательства, длительностью и характером операции.*

***Заключение:** При использовании нутритивного питания у пациентов онкологического профиля, прооперированных по поводу опухолей гепатопанкреатодуоденальной области, в раннем послеоперационном периоде предпочтителен энтеральный путь введения питательных смесей при условии отсутствия выраженного пареза кишечника и гнойных выделений из желудка.*

***Ключевые слова:** нутритивная недостаточность, нутритивная поддержка, рак, онкологические больные, энтеральное питание, парентеральное питание.*

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THE EFFECT OF THE EXTENT OF SURGERY AND LYMPH NODE DISSECTION ON THE DEVELOPMENT OF METACHRONOUS PERITONEAL DISSEMINATION IN GASTRIC CANCER

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ABSTRACT

Relevance: *Metachronous peritoneal dissemination (MPD) is among the top factors in the structure of gastric cancer (GC) progression, considerably worsening radical surgery outcomes. Since cancer cell dissemination in the peritoneal cavity is often triggered during surgery, assessing its role in MPD development is important.*

The study aimed to *assess the effect of the extent of radical surgery and lymph node dissection on the MPD development in radically operated gastric cancer patients.*

Methods: *The results of radical surgery performed on 1080 patients with gastric cancer (pT1-4N0-3M0) without spreading to the esophagus were assessed (647 males and 433 females) depending on the extent of surgical treatment (proximal/distal subtotal gastric resection (SGR), n=639/gastrectomy (GE), n=334; standard/combined surgery, n=973/107) and the extent of lymph node dissection (LD) – D1 (n=151) or D2 (n=929). Also assessed were survival rates (Kaplan-Meyer multiplier estimation method), cumulative incidence (CI) of competing events – MPD, metastases of other localizations, and mortality cases unrelated to gastric cancer (competing risks analysis).*

Results: *The analysis showed a statistically significant increase in the cumulative incidence (CI) of GC progression after combined operations (55.6±4.9%) as compared with the standard radical treatment (GE – 42.3±2.7%, SRG – 25.6±1.7%, respectively), including an increase in MPD CI in each of applied surgical procedures: after combined operations – 36.8±4.7%, after standard GE – 21.6±2.3% and after SRG – 11.1±1.2% (p_{Gray}<0.001). In the presence of lymphohematogenous metastases of other localizations, the relevant figures were 9.4±2.9% after combined operations, 9.3±1.6% after standard GE, and 5.0±0.9% after SRG (p_{Gray}=0.022). Lymph node metastases increased MPD CI after LD D1 from 8.3±2.8% (pN0) to 29.1±6.2% (pN1-3) (p_{Gray}<0.05), and after LD D2 – from 9.4±1.3% (pN0) to 27.3±2.1% (pN1-3) (p_{Gray}<0.05).*

Conclusions: *It is advisable to assess the extent of the planned surgical treatment and the condition of local lymph nodes when evaluating the probability of MPD development. The applied lymph dissection procedure did not affect the GC CI progression, including MPD development.*

Keywords: *gastric cancer, metachronous peritoneal dissemination (MPD), cumulative incidence (CI), surgical treatment.*

Introduction: According to A. Agnes et al., the combination of standard stages of rT (pT3-4) and pN (pN2-3) gastric cancer (GC) has a consequence of the risk of metachronous peritoneal dissemination (MPD) of the order of 30% [1]. In this case, exfoliation of tumor cells from the surface of the serous membrane and lymphogenic spread of tumor cells along the subperitoneal lymph plexus will be possible mechanisms [2, 3]. These factors contribute to the dissemination of tumor cells in the peritoneal cavity before the start of surgical treatment. Unfortunately, they are not limited to the list of all possible mechanisms of MPD, which has a high proportion in the structure of GC progression [1, 2, 4]. In particular, assessing the probability of progression of GC ignores the possibility of dissemination of tumor cells during the mobilization of the stomach and lymph dissection (LD) [1, 5]. This research is devoted to assessing the impact of the extent of surgery on its long-term results in the context of the possibility of further progression.

The study aimed to evaluate the effect of the extent of radical surgery and lymph dissection on MPD development in radically operated gastric cancer patients.

Materials and Methods: The material for the research was the data of 1080 patients who have undergone radical surgery for GC (rT1-4N0-3M0) without spreading to the esophagus (647 men and 433 women). In these patients, neoadjuvant and adjuvant treatment was not carried out according to the standards in force in the Republic of Belarus in 2012-2018 [6]. The choice of this cohort was due to the need to determine the features of the structure of GC progression in patients who have undergone radical surgery under the condition of different extent of surgeries and LD but in the absence

of the influence of antitumor drug treatment aimed at preventing the development of various variants of GC progression.

The research assessed the effect on the development of MPD of the extent of radical surgery (proximal/distal subtotal gastric resection (SGR), n=639/gastrectomy (GE), n=334; standard/combined surgery, n=973/107) and the extent of LD – D1 or D2. LD in D2 was performed in 929 patients and included monoblock removal of fiber together with lymph nodes of stages I-II of metastasis according to the recommendations of the Japanese Association for the Study of GC [7]: Stage I (N1) – perigastric lymph collectors (No. 1-6); Stage II (N2) – lymph nodes located along the branches of the celiac axis (left gastric (No. 7), common hepatic (No. 8) and splenic (No. 11) arteries), the celiac axis (No. 9), in the splenic hilum (No. 10), as well as lymph nodes of the hepatoduodenal ligament (No. 12). LD in D1 was performed in 151 patients and included removal of lymph nodes of the first stage of metastasis, as well as lymph nodes of the left gastric artery (No. 7).

The assessment of long-term treatment outcomes included the calculation of the following survival rates:

Overall survival (OS) – the events included deaths from cancer-related causes, antitumor treatment, or a concomitant pathology.

Adjusted survival rate (AS) – the events included deaths caused by underlying diseases.

Progression-free survival (PFS) – the events included GC progression and deaths from GC-associated causes.

Dissemination-free survival (DFS) – the events included tumor dissemination along the peritoneum and deaths from GC-associated causes.

Survival was assessed with a standard error (SE) using the Kaplan-Meyer multiplier method (comparative survival analysis by log-rank test). SE was calculated using the Greenwood formula. The monitoring was considered complete when a relevant event was reported; in other cases, the monitoring was «censored.»

The study assessed the cumulative incidence (CI) of competing events: CI of MPD and CI of distant lymphohematogenous metastases (DLHM) (in cases when MPD and DLHM were the only variants of distant metastases at the time of confirmation of GC progression); CI of a combination of MPD and DLHM; CI of deaths from causes not related to GC progression; CI of deaths from complications of treatment. The competing nature of the above events suggests the inevitability of the occurrence of one of them as the first during the period after the completion of radical treatment.

The assessment of CI of various events mentioned above used the analysis of competing risks [8]. The incidence for different groups was compared using the Gray test (p_{Gray}) [9]. When identifying the general heterogeneity by the log-rank test, posterior (post-hoc) pairwise analysis of groups with Holm's correction for multiple comparisons was carried out.

Statistical data analysis was performed using the GC statistical package. 3.1.1 (GPL license) using *survival* [10] and *cmprsk* [11] packages.

Results: The median follow-up in the sample under consideration was 97 months.

An increase in the extent of surgery from standard radical GRF to standard radical GE and, for a more common tumor process, to combined operations was accompanied by decreased survival rates (Table 1).

Table 1 – Five-year survival in groups with different types of surgery

Test criterion	Survival rates			
	OS (%±SE)	AS (%±SE)	PFS (%±SE)	DFS (%±SE)
Type of surgery				
Gastrectomy, n=334	47.4±2.7#	58,5±2.9#	53.9±2.9#	55.8±2.9#
Combined operations*, n=107	31.3±4.5†	40.0±5.2†	36.9±5.1†	39.5±5.2†
Subtotal gastric resection**, n=639	64.5±1.9	76.2±1.8	72.5±1.8	74.3±1.8
$p_{log\text{-}rank}$	<0.001	<0.001	<0.001	<0.001
Extent of lymph dissection				
D1, n=151	51.0±4.1	68.9±4.1	65.7±4,2	67.5±4.2
D2, n=929	56.8±1.6	67.2±1.6	63.2±1,7	65.0±1.6
$p_{log\text{-}rank}$	0.04	0.826	0.551	0.519

Notes:
When the DFS indicators are calculated, the development of MPD, both isolated and in combination with DLHM, was taken into account as an event;
* – combined gastrectomy/subtotal gastric resection;
** – proximal/distal subtotal gastric resection;
# – statistically significant differences in post-hoc pair-wise comparisons between the group of patients who have undergone gastrectomy and the rest with Holm's correction;
† – statistically significant differences in post-hoc pair-wise comparisons between the group of patients who have undergone combined operations and the rest with Holm's correction

The expected worse treatment results with low survival rates and high CI of GC progression were reported in the group of patients who have undergone combined operations and were due to both a more common pT4b tumor process and a higher CI of treatment complications in these patients compared to the

cohort in which standard operations have been performed (Table 1, 2):

1) a more common tumor process that usually requires GE (in comparison with SGR), as well as combined operations, which resulted in a more frequent progression of the tumor process, where CI was 42.3±2.7% and 55.6±4.9%, respectively, exceeding that for SGR (25.6±1.7 (p_{Gray}<0.001);

2) a higher incidence of complications and the associated CI of deaths from complications of treatment after performing GE and combined surgery, i.e., 3.6±1.0% and 4.7±2.1%, respectively, compared to GRF 11.0±1.2% (p_{Gray}=0.006).

Previously, a similar dependence of survival on the extent of surgery performed was described by J. Deng et al. (2015) [12] and FF. Chen et al. (2016) [13].

A detailed analysis of the progression structure established that an increase in MPD CI was the main reason that harmed the long-term results of treatment after performing combined operations (Table 2).

Table 2 – Five-year cumulative incidence of variants of gastric cancer progression and cases of mortality not related to the progression of the tumor process in groups with different types of surgery

Type of surgery	Five-year cumulative incidence (%±SE)			
	MPD	DLHM	MPD +DLHM	Deaths from non-oncological pathologies and treatment complications
Gastrectomy, n=334	21.6±2.3#	11.4±1.7	9.3±1.6#,‡	13.5±1.9
Combined operations*, n=107	36.8±4.7†	9.4±2.8	9.4±2.9	15.0±3.5
Subtotal gastric resection**, n=639	11.1±1.2	9.1±1.1	5.0±0.9	12.4±1.3
p_{Gray}	<0.001	0.657	0.022	0.757

Notes:
* – combined gastrectomy/subtotal gastric resection;
** – proximal/distal subtotal gastric resection;
# – statistically significant differences in post-hoc pair-wise comparisons between the group of patients who have undergone gastrectomy and the rest;
† – statistically significant differences in post-hoc pair-wise comparisons between the group of patients who have undergone combined operations and the rest of the groups:
‡ – statistically significant differences in post-hoc pair-wise comparisons between the patients who have undergone gastrectomy and those who have undergone subtotal gastric resection.

The latter can be explained by the more intensive dissemination of tumor cells in the peritoneal cavity in the case of combined operations compared to standard ones, which is due not only to the more intensive dissemination of cells from the tumor surface but also to the dissemination of cells from metastatically altered regional lymph nodes. Thus, the extent of surgery performed allows us to consider a possible variant of GC progression, particularly MPD, and can be used to assess the likelihood of progression.

Comparison of groups with different LD extent did not reveal statistically significant differences in survival functions and progression CI (Table 1, 3), which corresponds to the literature data stating that there is no clear relationship between the increase in LD extent and the frequency of GC progression, in particular, MPD [14].

Table 3 – Five-year cumulative incidence of adverse events in groups with different extent of lymph dissection

Extent of lymph dissection	Five-year cumulative incidence (%±SE)		
	gastric cancer progression	deaths from treatment complications	deaths from non-oncological pathologies
D1, n=151	29.8±3.7	4.6±1.7	16.6±3.0
D2, n=929	34.3±1.6	1.9±0.5	9.6±1.0
Gray test	0.229	0.331	0.002

Attention is drawn to the statistically significant increase in CI of deaths from non-oncological pathology in the group of patients with D1 LD, which is explained by the implementation of this reduced extent of LD in patients with concomitant pathology, which is often competitive in comparison with the underlying disease.

However, the assessment of CI of the considered variants of progression in the pN+ and pN0 groups revealed an increase in CI of MPD in patients with lesions of regional lymph collectors, regardless of the variant of MPD (Table 4), which confirms the results of several studies demonstrating the possibility of increasing the frequency of MPD if LD is performed in patients with pN+ and the absence of adjuvant intraperitoneal chemotherapy [4, 15].

Thus, the development of MPD does not depend on the variant of LD (D1 or D2) but on the presence of a metastatic lesion of regional lymph collectors when LD (as a mandatory component of radical treatment) causes intraoperative dissemination of tumor cells.

Table 4 – Five-year cumulative incidence of variants of gastric cancer progression and cases of mortality not related to gastric cancer in groups with different extent of lymph dissection

Extent of lymph dissection; state of regional lymph nodes pN	Five-year cumulative incidence (%±SE)			
	MPD	DLHM	MPD+DLHM	deaths from non-oncological pathology and treatment complications
D1–pN0, n=96	8.3±2.8*†	8.3±2.8	0	19.8±4.1***
D2–pN0, n=488	9.4±1.3‡	3.9±0.9‡	3.1±0.8‡	11.7±1.5
D1–pN1-3, n=55	29.1±6.2**	20.0±5.5	1.8±1.8	23.6±5.8§
D2–pN1-3, n=441	27.3±2.1	15.5±1.7	11.1±1.5	11.6±1.5
p_{Gray}	<0.001	<0.001	<0.001	0.002

Notes:
* – for pairwise comparisons, groups D1– pN0 and D2–pN0 do not differ;
** – for pairwise comparisons, groups D1–pN1-3 and D2–pN1-3 do not differ;
† – Statistically significant differences in post-hoc pair-wise comparisons between group D1–pN0 and groups D1–pN1-3, D2–rN1-3;
‡ – Statistically significant differences in post-hoc pair-wise comparisons between group D2–pN0 and groups D1–pN1-3, D2–rN1-3;
*** – statistically significant differences in post-hoc pair-wise comparisons between group D1–N0 and group D2–rN1-3;
§ – statistically significant differences in post-hoc pair-wise comparisons between group D1–pN1-3 and group D2–N1-3.

In connection with the above, assessing the probability of MPD should consider both the extent of surgery and the presence of metastatic lesions of regional lymph nodes (pN+). The latter may be associated with such characteristics of the tumor process as an infiltrative form of primary tumor growth, a non-adhesive variant of adenocarcinoma, subtotal gastric lesion, etc. In other words, developing prognostic models requires comprehensive consideration of several potential predictors of poor prognosis.

Discussion: The analysis of survival rates, which is traditional for oncological studies, indicates that it needs to be more informative to clarify the influence of certain factors, particularly the extent of surgery and LD, on the structure of GC progression, including its variants. It is due to the lack of the possibility of distinguishing cases of mortality unrelated to the underlying disease (in this case, to GC), e.g., when calculating the indicators of OS. The second reason for the lack of information content is the need for more possibility of distinguishing specific progression variants, which implies taking into account the occurrence of various localizations of metachronous distant metastases, particularly MPD.

The analysis of competing risks carried out in this study made it possible to determine the CI of various GC progression variants for a more accurate picture of the factors (in this case, the extent of surgery and LD) responsible for the development of a particular variant of progression, and separating them from lethality not related to GC progression. It has been established that the development of MPD, where CI prevails in the progression structure, is the main variant of progression that determines the poor prognosis after performing radical surgeries, both in the standard and combined variants. According to the literature, the assessment of the effect of the extent of surgery on the frequency of MPD after treatment of GC needs to be clarified. In particular, according to Kang L.-Y. et al. (2013) [16], there were no differences in the number of disseminated peritoneal lesions in the long term after standard radical and combined surgeries. On the contrary, the results of our research demonstrated a high frequency of MPD, which occupies a leading position in the structure of cases of GC progression after combined operations. It was also reported that the number of MPD cases in the follow-up dynamics is determined not by the LD variant but by the presence of a metastatic lesion of regional lymph collectors. The latter requires adjuvant intraperitoneal chemotherapy to eliminate tumor cells disseminated in the peritoneal cavity.

Thus, the analysis of CI of GC progression variants shows a relative radicality of surgical treatment when the tumor process extends beyond the stomach. This is due to a high probability of metachronous distant metastases, MPD being their most common variant. All of the above justifies the need to develop and administer adjuvant treatment (e.g., intraperitoneal chemotherapy) to prevent carcinomatosis long after radical surgery. At the same time, it is more rational to supplement the standard extent of therapeutic measures with intraperitoneal chemotherapy under an individual approach with an assessment of the likelihood of MPD development based on the predictors of possible GC progression, which may include both the extent of surgery and clinical and morphological features of the tumor process (pN+ and associated morphological characteristics of the primary tumor).

Conclusions:

1. The conventional approach with the assessment of survival rates does not allow for determining the impact of the extent of surgery on the nature of the progression of the tumor process, which determines the feasibility of using the approach based on the assessment of the cumulative incidence of competing events which, for locally advanced GC, maybe metachronous peritoneal dissemination and its combination with distant lymphohematogenous metastases, deaths from complications of treatment and deaths from concomitant pathology.

2. An advanced tumor process requiring combined operations causes a statistically significant increase in the 5-year cumulative incidence of progression (55.6±4.9%) as compared with standard radical treatment (42.3±2.7% after GE, 25.6±1.7% after GRP), including an increase in 5-year CI of metachronous peritoneal dissemination in an isolated variant (36.8±4.7% after combined operations and 21.6±2.3% and 11.1±1.2% after standard GE and GRF, respectively (p_{Gray}<0.001) and combination with distant lymphohematogenous metastases of other localization (9.4±2.9% after combined operations or 9,3±1,6% and 5,0±0,9% after standard GE and SGR, respectively (p_{Gray}=0.022).

3. The variant of the performed lymph dissection does not affect the cumulative incidence of gastric cancer progression, which is 29.8±3.7% after D1 LD, 34.3±1.6% after D2 LD (p=0.229), including the cumulative incidence of metachronous peritoneal dissemination, which is 15.9±3.0% and 17.0±1.2% after D1 and D2 dissections, respectively (p=0.530).

4. Metastatic lesion of regional lymph collectors caused more frequent tumor progression during D1 and D2 dissection. In contrast, the 5-year CI of progression for D1 and D2 LD was 52.7±6.9% and 53.9±2.4%, respectively, for patients with rN1-3, exceeding similar indicators for patients with pN0 – 16.7±3.8% and 16.6±1.7% (pGray<0.001), including MPD CI after D1 LD – 8.3±2.8% at pN0 to 29.1±6.2% at rN1-3 (pGray<0.05); after D2 LD 9.4±1.3% at pN0 to 27.3±2.1% at pH1-3 (pGray<0.05).

5. It seems relevant to develop risk assessment models for an individual approach to the scope of antitumor treatment to prevent MPD. Considering the extent of surgery and the condition of regional lymph collectors is reasonable when assessing the MPD probability.

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АҢДАТПА

ОПЕРАЦИЯ МЕН ЛИМФОДИССЕКЦИЯ КӨЛЕМІНІҢ АСҚАЗАН ҚАТЕРЛІ ІСІГІНДЕГІ МЕТАХРОНДЫ ПЕРИТОНЕАЛЬДІ ДИССЕМИНАЦИЯНЫҢ ДАМУЫНА ӘСЕРІ

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Өзектілігі: *Метахронды перитонеальді диссеминация асқазан қатерлі ісігінің прогрессиясының құрылымындағы жетекші факторлардың бірі, бұл оны түбегейлі емдеу нәтижелерін айтарлықтай нашарлатады. Перитонеум қуысындағы ісік жасушаларының таралу процестері көбінесе хирургиялық емдеу процесінде басталады, олардың метахронды перитонеальді диссеминация дамуына әсерін бағалау маңызды.*

Зерттеудің мақсаты *– түбегейлі операция мен лимфодиссекция көлемінің асқазан қатерлі ісігімен ауыратын науқастарда метахронды перитонеальді диссеминацияның дамуына әсерін бағалау.*

Әдістері: *Орындалған операция көлеміне байланысты өңешке ауыспай (ерлер 647, әйелдер 433) асқазан обырына (pT1-4N0-3M0) түбегейлі операция жасалған 1080 пациенттің (асқазанның проксимальды/дистальды субтотальды резекциясы, n=639 / гастрэктомия, n=334) түбегейлі хирургиялық емдеу нәтижелеріне талдау жүргізілді; стандартты/аралас операция, n=973/107) және орындалатын лимфодиссекция көлемі – D1 (n=151) немесе D2 (n=929). Сондай-ақ, өмір сүру деңгейі (Каплан-Мейердің көбейту әдісі), шоғырланымдық инциденттінің – метахронды перитонеальді диссеминация, басқа локализацияның метастаздары, асқазан қатерлі ісігімен байланысты емес өлім жағдайлары (бәсекелес тәуекелдерді талдау) бағаланды.*

Нәтижелері: *Стандартты түбегейлі емдеумен салыстырғанда (гастрэктомиядан кейін 42,3±2,7%, асқазанның субтотальды резекциясынан кейін 25,6±1,7%) шоғырланымдық прогрессия инцидентінің статистикалық маңызды өсуі (55,6±4,9%) анықталды, оның ішінде оқшауланған нұсқадағы метахронды перитонеальді диссеминацияның шоғырланымдық инцидентінің жоғарылауы (аралас операциялардан кейін 36,8ұ4,7%, стандартты гастрэктомиядан және асқазанның субтотальды резекциясынан кейін сәйкесінше 21,6±2,3% және 11,1±1,2% (pGray<0,001)) және біріктірілген кезде метахронды перитонеальді диссеминация, басқа локализацияның алыс лимфогематогендік метастаздарымен (аралас операциялардан кейін 9,4±2,9%, стандарты гастрэктомия және асқазанның субтотальды резекциясы кейін сәйкесінше 9,3±1,6% және 5,0±0,9%, (pGray=0,022)) құрайды. Лимфа түйіндерінде метастатикалық зақымдануының болуы D1 лимфодиссекциясынан кейінгі метахронды перитонеальді диссеминацияның шоғырланымдық инцидентінің 8,3±2,8%-нен (pN0) 29,1±6,2%-ге дейін (pN1-3) (pGray<0.05) және D2 лимфодиссекциясынан кейін 9,4±1,3%-дан (pN0) жоғарылауына әкелді. 27,3±2,1%-ге дейін (pN1-3) (pGray<0.05).*

Қорытынды: *Даму ықтималдығын бағалау кезінде метахронды перитонеальді диссеминация операция көлемін және аймақтық лимфа түйіндерінің жағдайын бағалау ұсынылады. Қолданылған лимфодиссекция процедурасы метахронды перитонеальді диссеминацияның дамуын қоса алғанда, асқазан қатерлі ісігінің дамуының жиынтық жиілігіне әсер етпеді.*

Түйінді сөздер: *асқазан қатерлі ісігі, метахронды перитонеальді диссеминация, шоғырланымдық инцидент, хирургиялық емдеу.*

АННОТАЦИЯ

ВЛИЯНИЕ ОБЪЕМА ОПЕРАЦИИ И ЛИМФОДИССЕКЦИИ НА РАЗВИТИЕ МЕТАХРОННОЙ ПЕРИТОНЕАЛЬНОЙ ДИССЕМИНАЦИИ ПРИ РАКЕ ЖЕЛУДКА

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Актуальность: *Метахронная перитонеальная диссеминация (МПД) составляет высокий удельный вес в структуре прогрессирования рака желудка (РЖ), существенно ухудшая результаты его радикального лечения. Процессы диссеминации опухолевых клеток в полости брюшины зачастую запускаются в процессе выполнения хирургического лечения, что определяет целесообразность оценки их влияния на развитие МПД.*

Цель исследования *– оценить влияние объема радикальной операции и лимфодиссекции на развитие МПД у пациентов, радикально оперированных по поводу РЖ.*

Методы: *Проведен анализ результатов радикального хирургического лечения 1080 пациентов, радикально оперированных по поводу РЖ (pT1-4N0-3M0) без перехода на пищевод (мужчин 647, женщин 433) в зависимости от объема выполненной операции (проксимальная/дистальная субтотальная резекция желудка (СРЖ), n=639/гастрэктомия (ГЭ), n=334; стандартная/комбинированная операция, n=973/107) и объема выполняемой лимфодиссекции (ЛД) – D1 (n=151) или D2 (n=929). Оценены показатели выживаемости (метод множительных оценок Каплана-Мейера), кумулятивной инцидентности конкурирующих событий – МПД, метастазов другой локализации, случаев летальности, не связанной с РЖ (анализ конкурирующих рисков).*

Результаты: *Установлено статистически значимое увеличение кумулятивной инцидентности прогрессирования (55,6±4,9%) в сравнении со стандартным радикальным лечением (после гастрэктомий 42,3±2,7%, после СРЖ 25,6±1,7%), в том числе увеличение КИ МПД в изолированном варианте после комбинированных операций – 36,8±4,7% и после стандартных ГЭ и СРЖ – 21,6±2,3% и 11,1±1,2%, соответственно; p_{Gray}<0,001) и при сочетании МПД с отдаленными лимфогематогенными метастазами другой локализации (после комбинированных операций – 9,4±2,9% и после стандартных ГЭ и СРЖ – 9,3±1,6% и 5,0±0,9%, соответственно; p_{Gray}=0,022). Наличие метастатического поражения регионарных лимфоколлекторов обусловливает увеличение КИ МПД после ЛД D1 – с 8,3±2,8% (pN0) до 29,1±6,2% (pN1-3) (p_{Gray}<0,05); после ЛД D2 – с 9,4±1,3% (pN0) до 27,3±2,1% (pN1-3) (p_{Gray}<0,05).*

Заключение: *При оценке вероятности развития МПД целесообразной представляется оценка объема операции и состояния регионарных лимфоколлекторов. Вариант выполненной ЛД не влияет на кумулятивную инцидентность прогрессирования РЖ, включая развитие МПД.*

Ключевые слова: *рак желудка, метахронная перитонеальная диссеминация, кумулятивная инцидентность, хирургическое лечение.*

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PRELIMINARY RESULTS OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) FOR OVARIAN CANCER WITH PERITONEAL METASTASES IN TAJIKISTAN

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ABSTRACT

Relevance: *Ovarian cancer is the most aggressive form among all nosologies of the female reproductive system. More than 75% of women are diagnosed at advanced stages, and about 60% have metastases to other organs at diagnosis. Systemic chemotherapy has a limited effect on the peritoneum and a high incidence of side effects. There is a need for more effective approaches to prolong survival and preserve quality of life by reducing disease symptoms and treatment side effects, especially in countries with limited health resources.*

The study aimed to *evaluate the preliminary results of using pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with ovarian cancer with peritoneal metastases.*

Methods: *18 women with disease stage T3a-cN0M0 treated at the Republican Cancer Research Center for 2022-2023 were studied. The first group included six patients who underwent cytoreduction + PIPAC at the 1st stage, and the second group (12 women) underwent exploratory laparotomy + biopsy + PIPAC at the 1st stage. Patients in both groups received two courses of chemotherapy followed by a repeat of PIPAC. Taxanes + platinum-containing drugs were used in the PIPAC process – cisplatin or carboplatin with doxorubicin. Each patient received 2 PIPAC sessions and 4 to 6 chemotherapy courses with cytoreductive surgery. All patients underwent laparoscopic control with a reassessment of the Peritoneal Carcinomatosis Index (PCI) by Sugarbaker (2010) and repeated biopsy of the peritoneum.*

Results: *The use of cytoreductive surgery + PIPAC at the first stage made it possible to level the symptoms of peritoneal carcinomatosis, to achieve a complete radiological response in 12 (67%) cases, a complete morphological response in the form of complete regression in 44%, a moderate response in 39% of cases*

Conclusion: *Using PIPAC with a cytoreductive component at the first stage of combined treatment of ovarian cancer with peritoneal metastases improves immediate results and the patient's quality of life and reduces the hospital stay. The research is ongoing.*

Keywords: *PIPAC, ovarian cancer, peritoneal carcinomatosis.*

Introduction: There is no need to remind that ovarian cancer (OC) is the most aggressive form among all nosologies of the female reproductive system. More than 75% of women are diagnosed at advanced stages, and about 60% have metastases to other organs at diagnosis [1, 2].

Usually, OC remains local; it metastasizes directly to neighboring organs or by transperitoneal dissemination of detached cancer cells to all intraperitoneal structures.

Secondary peritoneal cancer occurs due to metastasis and is the most common cancer of the abdomen. OC, gastric, and colorectal cancer metastases are associated with high recurrence and mortality rates [3].

The best approach to treating peritoneal cancer from ovarian cancer metastases is multimodal, including surgical, chemotherapy components, and targeted therapy.

The effect of systemic chemotherapy (SCT) on the peritoneum remains limited due to poor vascularization and low penetration. The side effects after SCT of peritoneal metastases are relatively frequent. The quality of life of these patients is constantly deteriorating due to the disease itself and the drug therapy.

Therefore, there is a need for more effective approaches to prolong survival and preserve quality of life by reducing disease symptoms and treatment side effects, especially in countries with limited health resources.

One such approach is the pressurized intraperitoneal aerosol chemotherapy (PIPAC), proposed by German colleagues in 2011. Using the physical properties

of gas and pressure by creating an artificial pressure gradient contributes to increased absorption of cytostatics by tissues and their homogeneous distribution in the abdominal cavity.

Based on relevant experience and support of Russian colleagues in their use of PIPAC in recent years for gastric cancer, we also decided to introduce and test this technique in our institution for patients with OC [4, 5].

The PIPAC technique is implementable in practice and well tolerated, also stabilizes and improves the quality of life of patients even with terminal stages, and can cause severe therapeutic pathomorphosis with the use of significantly lower doses of cytotoxic drugs (up to 10% of the commonly used dose), which reduces toxicity, allows the patient to be discharged the next day after manipulation, and thereby reduce the economic costs. Besides, there is an opportunity for recurrent PIPAC implementation in contrast to cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy [6-11].

The study aimed to evaluate the preliminary results of using pressurized intraperitoneal aerosol chemotherapy (PIPAC) in ovarian cancer patients with peritoneal metastases (OCPM).

Materials and Methods: The study involved 18 women with OCPM at T3a-cN0M0 stage by FIGO classification examined and treated at the Republican Cancer Research Center from October 2022 to March 2023.

In the study, the patients' age averaged 55 years. The main complaints included pain, palpable abdomen swelling, enlargement, and dysuric disorders (Table 1).

Table 1 – Characteristics of patients with OCPM (n=18)

Parameters	Abs.	%
Median age	55.5±10.5	
ИМТ, кг/м^2 (M±m)	27.7±6.5	
Complaints:		
- Increasing the abdomen volume	11	61.1
- Pain in the lower abdomen and lumbar region	18	100
- Palpable tumor	6	33.3
- Pain in the epigastric region	14	77.8
- Dysuric disorders	6	33.3
- Constipation	10	55.6
- Discharge from the genital tract	2	11.1
- Weight loss	6	44.4

During an ultrasound examination, 83% of patients had less than 5 L of free fluid in the abdominal cavity; in 61%, the ovarian tumor volume did not exceed 5 cm^3; in 89%, the tumor was hyperechoic or had a mixed structure (Table 2).

In 78% of cases, the tumor histology represented a serous adenocarcinoma with moderate differentiation (Figure 1).

The tumor differentiation was G2 in 11 (61.1%) cases and G3 in 7 (38.9%) cases.

Table 2 – Results of ultrasound examination of the abdominal cavity and pelvic organs of patients with OCPM (n = 18)

Signs	Abs.	%
Ascites (amount of fluid, L):		
- up to 5 l	15	83.3
- up to 10 l	2	11.1
- more than 10 l	1	5.6
Tumor volume:		
- up to 5 cm	11	61.1
- up to 10 cm	3	16.7
- more than 10 cm	4	22.2
Tumor structure:		
- Tissue	9	50.0
- Liquid	2	11.1
- Mixed	7	38.9

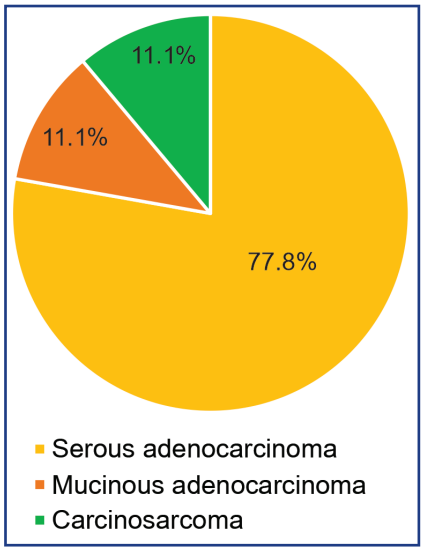

Figure 1 – Histological options of ovarian tumors in patients with OCPM (n=18)

Half of the patients had the T3aN0M0 stage, 33% had the T3cN0M0 stage, and the remaining proportion (16.7%) accounted for the T3bN0M0 stage by FIGO classification of the tumor extent.

Based on the study design, the patients were divided into two groups. The first group included six patients who received the CS + PIPAC at the 1st stage, and the second group received the exploratory laparotomy, biopsy + PIAC at the 1st stage. Subsequently, patients in both groups received two courses of SCT followed by a repetition of PIPAC. SCT scheme included taxanes + platinum-containing drugs, and PIPAC utilized cisplatin or carboplatin with doxorubicin. Overall, each patient received two sessions of PIPAC and from 4 to 6 courses of SCT with CS. All patients underwent a comprehensive laboratory (including tumor markers), cytological, histological, and instrumental examination, as well as laparoscopic control with a reassessment of the peritoneal carcinomatosis index (PCI) by Sugarbaker method (2010) [12] (Figures 2, 3).

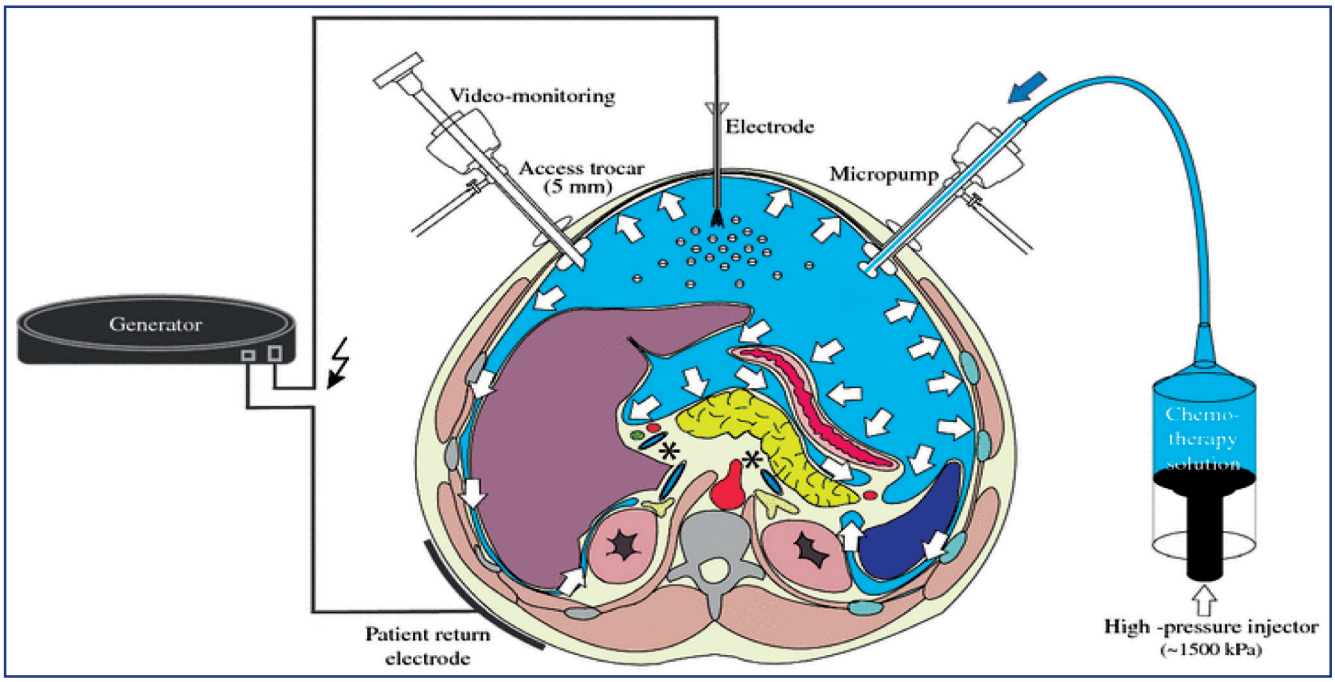

Figure 2 – Schematic illustration of the PIPAC methodology performance [12]

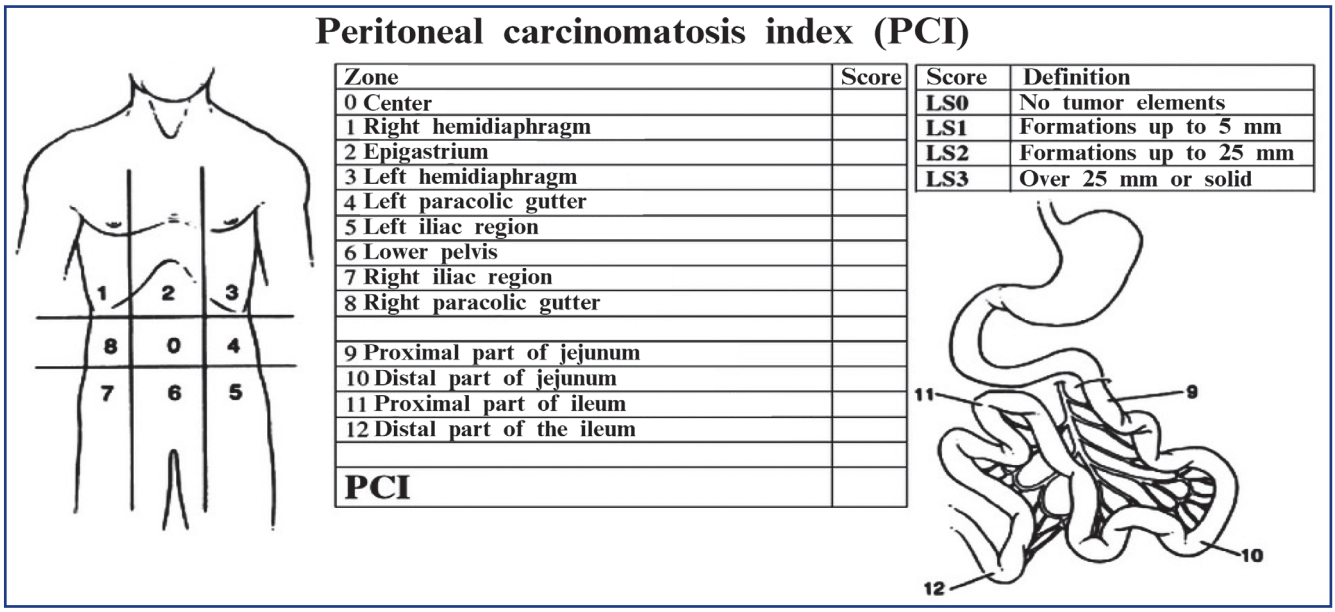

Figure 3 – PC index rating scale according to Sugarbaker P.H. (2010) [12]

Results: Within the study, during six months of 2022-2023, at stage 1, we performed CS with a simultaneous PIPAC in 9 (50%) cases. Due to the technical difficulties and the process prevalence, the remaining patients underwent only diagnostic laparotomy + biopsy + PIPAC at stage 1 (Table 3).

Table 3 – Results of surgical treatment of patients with OCPM

Surgical interventions	Abs.	%
Cytoreduction:		
- Optimal	9	50
- Suboptimal	5	27.8
- Nonoptimal	4	22.2

Subjective assessment of patients after combined treatment showed a leveling of symptoms associated with peritoneal carcinoma (Figure 4).

During an assessment of the effectiveness of treatment after 2 PIPAC sessions according to the RECIST system, a complete radiological response was achieved in 12 (67%) cases, and progression was noted in only one case.

Assessment of the morphological response showed that complete regression with an absence of cancer cells took place in 44%, a moderate response was obtained in 39% of cases, and a minor response in 17% of cases. No cases of lack of morphological response to therapy have been registered (Table 5).

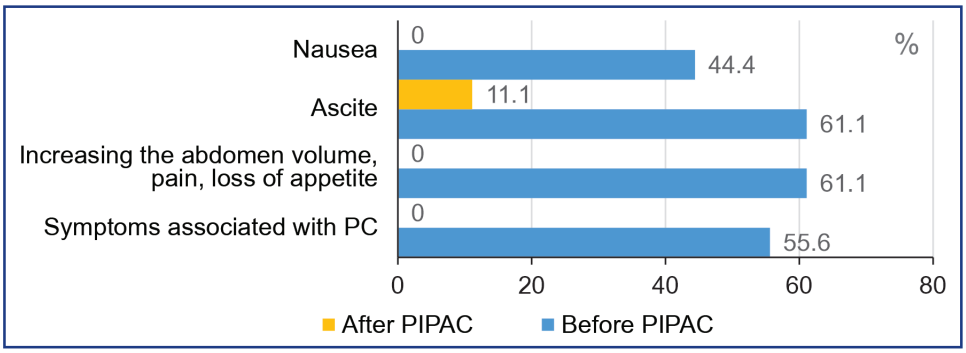

Figure 4 – Dynamics of the severity of symptoms of peritoneal carcinomatosis before and after PIPAC

Laboratory parameters also showed a marked decline of the tumor markers Ca-125 and HE4 (Table 4).

Table 4 – Laboratory parameters of the tumor markers Ca125 and HE4 before and after two PIPAC sessions

Parameters	Before PIPAC	After PIPAC
Ca125, Me(1q-3q)	595.58 (55-2000)	15.4 (12.9-59)
HE4, Me(1q-3q)	222.5 (46-372)	77.7 (44.9-153)

Table 5 – X-ray and morphological responses after two PIPAC sessions

Response according to the RECIST scale	Abs.	%
X-ray response:		
Complete response	12	66.7
Partial response	3	16.7
Stabilization	2	11.1
Progression	1	5.6
Morphological response:		
PRGS 1 (complete regression with absence of tumor cells)	8	44.4
PRGS 2 (moderate histological response with signs of regression, residual tumor cells predominate)	7	38.9
PRGS 3 (insignificant histological response with a predominance of residual tumor cells over regressive features)	3	16.7

Discussion: Our preliminary data showed PIPAC to be safe and effective in treating peritoneal cancer from OC metastases. This inspires to continue the study in our country.

Several studies also demonstrated a higher quality of life in patients treated by the new method than those who underwent a traditional multi-course SCT.

Conclusion: The newly developed approaches in diagnosing and combined treatment of OCPM using PIPAC with CS at the first stage will allow determining the effectiveness of radiation methods depending on the tumor prevalence degree, as well as improve the immediate and long-term treatment outcome in this category of patients and their quality of life and reducing the hospital stay. The research is ongoing.

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АҢДАТПА

ТӘЖІКСТАНДА АНАЛЫҚ БЕЗ ҚАТЕРЛІ ІСІГІ КЕЗІНДЕ ІШПЕРДЕГЕ ТАРАҒАН МЕТАСТАЗДАРҒА ҚҰРСАҚІШІЛІК ҚЫСЫМ АРҚЫЛЫ АЭРОЗОЛЬДІ ХИМИОТЕРАПИЯНЫ (PIPAC) ҚОЛДАНУДЫҢ АЛДЫН АЛА НӘТИЖЕЛЕРІ

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Өзектілігі: *Аналық без қатерлі ісігі – әйелдердің ұрпақты болу жүйесі мүшелерінің барлық нозологияларының ішіндегі ең агрессивті түрі. Бұл сырқат әйелдердің 75%-дан астамында кеш сатысында анықталады және диагноз қойылған кезде шамамен 60% басқа органдарға метастаз беріп үлгереді. Жүйелік химиотерапия құрсаққа шектеулі әсер етеді және жаңама әсерлердің жоғары жиілігіне иелік етеді. Аурудың белгілері мен терапияның жаңама әсерлерін азайту арқылы өмір сүруді ұзарту және өмір сүру сапасын сақтау үшін, әсіресе денсаулық сақтау ресурстары шектеулі елдерге тиімді тәсілдер қолдану қажет.*

Зерттеудің мақсаты *аналық без қатерлі ісігі кезінде ішпердеге тараған метастаздарға құрсақішілік қысым арқылы аэрозольді химиотерапияны (PIPAC) қолданудың алдын ала нәтижелерін бағалау.*

Әдістері: *2022-2023 жылдары T3a-cN0M0 (FIGO) ауру сатысы бар республикалық онкологиялық ғылыми орталықта тексеріліп, емделіп жатқан перитонеальді метастаздары бар аналық без обырымен ауыратын18 әйел зерттелді. Пациенттер 2 топқа бөлінді: бірінші топтағы 6 пациентке 1-ші кезеңде + PIPAC циторедукциясын орындалды, ал екінші топ (12 әйел) – 1-ші кезеңде эксплоративті лапаротомия + биопсия + PIPAC орындалды. Екі топтың пациенттері де жүйелік химиотерапияның 2 курсын алды, содан кейін PIPAC-ты қайталады. Жүйелік химиотерапия ретінде таксандар + платинасы бар препараттар схемасы қолданылса, PIPAC процесінде цисплатин немесе карбоплатин доксорубицинмен қолданылды. Жалпы алғанда, әрбір пациент 2 PIPAC сеансын және циторедуктивті операциямен 4-тен 6-ға дейін жүйелік химиотерапия курсын алды. Барлық науқастарға Sugarbaker P.H. (2010) әдісі бойынша перитонеальді канцероматоз индексін (PCI) қайта бағалаумен және перитонеальді биопсия алу арқылы кешенді зертханалық, цитологиялық, гистологиялық және аспаптық әдістер тексеру, сондай-ақ лапароскопиялық бақылау жүргізілді.*

Нәтижелері: *Бірінші кезеңде ЦО+PIPAC қолдану перитонеальді канцероматоздың белгілерін нивелирлеуге, 12 (67%) жағдайда толық рентгенологиялық жауапқа, 44% толық регрессия түрінде толық морфологиялық жауапқа, 39% жағдайда орташа жауапқа қол жеткізуге мүмкіндік берді.*

Қорытынды: *Бірінші кезеңде циторедуктивті компоненті бар PIPAC-ты жедел нәтижелерді жақсарту, олардың өмір сүру сапасын жақсарту, стационарда болу уақытын қысқарту түрінде біріктірілген емдеуде қолдану тиімділігі көрсетілген. Зерттеу жалғасуда.*

Түйінді сөздер: *интраперитонеальді қысымды аэрозольді химиотерапия (PIPAC), аналық без обыры, перитонеальді канцероматоз.*

АННОТАЦИЯ

ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ ВНУТРИБРЮШИННОЙ АЭРОЗОЛЬНОЙ ХИМИОТЕРАПИИ ПОД ДАВЛЕНИЕМ (PIPAC) ПРИ РАКЕ ЯИЧНИКОВ С ПЕРИТОНЕАЛЬНЫМИ МЕТАСТАЗАМИ В ТАДЖИКИСТАНЕ

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Актуальность: *Рак яичников (РЯ) является самой агрессивной формой среди всех нозологий органов женской репродуктивной системы. Более чем 75% женщин выявляются на поздних стадиях, и около 60% на момент постановки диагноза имеют*

метастазы в другие органы. Системная химиотерапия (СХТ) имеет ограниченное влияние на брюшину и высокую частоту побочных эффектов. Существует потребность в более эффективных подходах для продления выживаемости и сохранения качества жизни за счет уменьшения симптомов заболевания и побочных эффектов терапии, особенно для стран с ограниченными ресурсами здравоохранения.

***Цель исследования** – оценить предварительные результаты применения внутрибрюшинной аэрозольной химиотерапии под давлением (PIPAC) у больных раком яичников с перитонеальными метастазами (РЯПМ).*

***Методы:** Исследованы 18 женщин с РЯПМ, находившихся на обследовании и лечении в Республиканском онкологическом научном центре в 2022-2023гг. со стадией заболевания T3a-cN0M0 (FIGO). Пациентки были распределены на 2 группы: первая группа – 6 пациенток, которым на первом этапе удалось выполнить циторедукцию + PIPAC, и вторая группа – 12 пациенток, которым на 1м этапе была проведена эксплоративная лапаротомия + биопсия + PIPAC. Пациентки обеих групп получали по 2 курса СХТ с последующим повторением PIPAC. В качестве СХТ применялась схема таксаны+платиносодержащие препараты, в процессе PIPAC – цисплатин или карбоплатин с доксорубицином. В целом каждая пациентка получила по 2 сеанса PIPAC и от 4 до 6 курсов СХТ с циторедуктивной операцией (ЦО). Всем больным проведено комплексное лабораторное, цитологическое, гистологическое и инструментальные методы обследование, а также лапароскопический контроль с переоценкой индекса перитонеального канцероматоза (PCI) по методу Sugarbaker P.H. (2010) и повторной биопсией брюшины.*

***Результаты:** Применение ЦО+PIPAC на первом этапе позволило нивелировать симптомы перитонеального канцероматоза (ПК), добиться полного рентгенологического ответа в 12(67%) случаях, полного морфологического ответа в виде полной регрессии в 44%, умеренного ответа в 39% случаев.*

***Заключение:** Показана эффективность применения PIPAC с циторедуктивным компонентом на первом этапе в комбинированном лечении РЯПМ, в виде улучшения непосредственных результатов, повышения качества их жизни, сокращения времени пребывания в стационаре. Исследование продолжается.*

***Ключевые слова:** внутрибрюшинная аэрозольная химиотерапия под давлением (PIPAC), рак яичников (РЯ), перитонеальный канцероматоз.*

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***The author's input:** contribution to the study concept, study design, execution of the study, interpretation of the study, preparation of the manuscript – Hojieva M.M.*

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APPLICATION OF ^{68}GA-FAPI PET/CT IN CLINICAL PRACTICE – PERSPECTIVES FOR MALIGNANT TUMOR IMAGING: A LITERATURE REVIEW

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ABSTRACT

Relevance: *The incidence of malignant neoplasms in various localizations is growing worldwide and in Kazakhstan. The mortality rate from oncological diseases is also alarmingly high. To facilitate early diagnosis and optimal therapy, scientists are exploring molecular diagnostics, including PET/CT, using various markers, like ^{18}F-fluorodeoxyglucose, widely used in oncology but lacking specificity for certain types of tumors. The finding of Fibroblast Activation Protein (FAP) has sparked interest in FAP-targeted radiolabeled inhibitors (FAPI), which could serve as a universal marker for diagnosing different types of cancer. Various FAP markers for PET/CT are being studied, with special attention given to 68Ga-FAPI.*

The study aimed to *analyze the potential value of FAPI PET/CT for detecting malignant tumors.*

Materials: *A literature review was conducted using the MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials databases for the past decade using the following keywords: "malignant lesions," "PET/CT," and "FAPI." This review analyzes 48 literature sources with A1-level evidence dedicated to the ^{68}Ga-FAPI PET/CT diagnostic accuracy in detecting and staging malignant tumors and assessing treatment efficacy.*

Results: *According to the analyzed sources, the ^{68}Ga-FAPI PET/CT sensitivity and specificity in diagnosing cancer are 95% to 100% and 62% to 100%, respectively. However, clear indications for use in clinical practice require further study of ^{68}Ga-FAPI PET/CT diagnostic capabilities on larger cohorts and more homogeneous datasets.*

Conclusion: *The available literature data on FAPI PET/CT diagnostic capacity shows this marker's potential in diagnosing oncological disorders. Information provided by ^{68}Ga-FAPI PET/CT supplements the existing methods and generally impacts the treatment strategy for each unique case.*

Keywords: *malignant lesions, PET/CT, FAPI.*

Introduction: To date, cancer of various localizations ranks high in the global morbidity structure. The number of cancer cases has been growing worldwide and in Kazakhstan in recent years. In 2020, GLOBOCAN reported 19,292,789 new cases and 9,958,133 deaths from cancer worldwide [1].

According to Kaidarova et al., in Kazakhstan, cancer ranked 7th in total morbidity in 2020 but with a very high mortality rate. Over 13 thousand deaths from cancer per year post it second in mortality structure after circulatory system diseases. More than 37,000 new cancer cases are registered annually in Kazakhstan, and the number of patients under dynamic follow-up exceeds 205,000 [2].

Early diagnostics improvement and timely initiation of optimal therapy are of particular importance to reduce cancer mortality. For that reason, scientists worldwide conduct relevant clinical studies to reinforce the mission for health, increase life expectancy, and reduce the burden of disease and disability.

Global medicine has focused on morphological characteristics when diagnosing tumors for a long time. Today, special attention is paid to molecular diagnostics, which seeks to identify physiological activity in tissues and allows for the assessment of tumor biological properties [3]. Molecular diagnostics enables visualizing the body's processes at the cell level. Positron emission tomography/computed tomography (PET/CT) is a hybrid method that provides additional information about the tumor's functionality and structure [4].

^{18}F-fluorodeoxyglucose (^{18}F-FDG), originally developed in the late 1970s to study brain metabolism, today is the most widely used PET marker with numerous applications in oncology and other fields [4, 5]. Despite its undeniable clinical value, the capture of ^{18}F-FDG is a sign of glucose transport and metabolism and is not specific to tumors. Further studies led to the development of more specific markers, such as radiolabeled agents targeting the somatostatin receptors and ligands of prostate-specific membrane antigen, which have been successfully implemented in modern methods of diagnosis and treatment of neuroendocrine tumors and prostate cancer [6]. The search for cellular

targets has led to the discovery of the fibroblast activation protein (FAP). This transmembrane glycoprotein has been expressed on activated fibroblasts, including cancer-associated fibroblasts (CAFs) [7]. Preliminary data have sparked interest in FAP as a promising marker for diagnosing various types of cancer in nuclear medicine [8]. Several radiolabeled fibroblast activation protein inhibitors (FAPIs) are currently being investigated as markers for PET/CT.

The study aimed to analyze the potential value of FAPI PET/CT for detecting malignant tumors.

Material and methods: A literature review was conducted using the MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials databases for the past decade using the following keywords: "malignant lesions," "PET/CT," and "FAPI."

A total of 253 articles on the search topic were found, of which 48 literature sources with an A1 level of evidence were included in this literature review.

Results: FAP is a transmembrane protein actively synthesized in the tumor stroma and inflamed tissues during the wound healing. FAP is actively synthesized on the surface of cancer-associated fibroblasts, which play an important role in tumor cell growth, aggressiveness, and migration. The elevation of the CAFs and FAPs expression was most commonly recorded in developing epithelial cancers [9]. In addition, FAP is synthesized on the tumor tissue stromal cells surface. In this microenvironment, tumor cells grow, proliferate, and spread, and drug resistance develops [9, 10].

The molecules that can be selectively connected with specific markers are required to create imaging techniques. Of all FAP markers developed up-to-date, ^{68}Ga-FAPI has the most promising characteristics that largely meet the specified requirements, supported by a growing number of clinical evidence.

It should be noted that FAP expression is practically absent in healthy tissues, except for stromal cells in the tissues of the uterus and placenta, alpha cells of the pancreas, as well as some dermal fibroblasts [10]. Due to the low FAP expression in normal tissues, it acts as a promising marker for diagnosing and treating cancer using radiopharmaceuticals [9, 10].

In 2018, Loktev et al. conducted a study of the FAPI PET/CT concept, in which, for the first time, they demonstrated a high level of marker capture in tumors in three patients with breast cancer (BC), lung cancer and pancreatic cancer [11]. Subsequently, Kratocwill et al., from the same group of researchers, presented the results of ^{68}Ga-FAPI-04 PET/CT in 80 patients with 28 different types of tumors. The accumulation values varied significantly depending on the tumor type and the patient's individual characteristics. The highest accumulation of ^{68}Ga-FAPI (SUVmax >12) was found in patients with sarcoma, esophageal cancer, breast cancer, cholangiocarcinoma, and lung cancer. In contrast, pheochromocytoma, renal cell carcinoma, differentiated thyroid cancer (TC), and gastric cancer (GC) had the lowest accumulation (SUVmax <6). Despite the intratumoral and interindividual variability, low background activity provided excellent contrast in the images, even with low tumor activity [12].

In the published literature sources, there are data on the sensitivity of PET/CT using ^{68}GaFAPI in diagnosing cancer of various localizations, which vary from 95% to 100%, and specificity indices range from 62% to 100% [12-39]. However, the study sample was small – from 12 to 80 patients.

The positive results from previous studies on various cancers have led to follow-up studies using ^{68}Ga-FAPI PET/CT in certain types of cancer, including head and neck cancer. In a cohort of 45 patients with nasopharyngeal cancer, ^{68}Ga-FAPI-04 PET/CT showed its efficacy, surpassing ^{18}F-FDG PET/CT in detecting primary tumors, metastatically affected lymph nodes, and distant metastases, resulting in treatment change in 18% of patients [13]. Another study included 14 patients with head and neck cancer, including a comparison of ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT to distinguish between healthy and tumor tissues [40]. As a result, it was demonstrated that ^{68}Ga-FAPI-04 PET/CT increased the staging accuracy in a cohort of 12 patients with adenocystic cancer [41]. Besides, the possibility of using ^{68}Ga-FAPI-04 PET/CT was studied in 10 patients with oral squamous cell carcinoma, while the authors did not come up with conclusions [14].

The Serfing et al. study demonstrated the excellent efficacy of 68Ga-FAPI and 18F-FDG PET/CT for detecting primary pharyngeal lymphoid ring tumors [15]. However, ^{18}F-FDG was more effective in staging lymph nodes than ^{68}Ga-FAPI.

It was established that ^{18}F-FDG PET/CT had limited importance in diagnosing malignant brain tumors and was most useful for differential diagnosis of tumor recurrence and radiation necrosis. On the other hand, studies with FAPI PET/CT show high image contrast due to the absence of background activity, and this advantage over ^{18}F-FDG PET/CT has been highlighted in various publications, especially in the context of brain metastases. Concerning primary brain tumors, two studies focused on using FAPI PET/CT for glioblastoma. In the research of Windisch with co-authors, a group of 14 patients with glioblastoma was studied within the frames of the radiation therapy planning [16]. The diagnostic study of Rohrich M. et al., conducted on 18 patients with glioma, highlighted the prospects of applying FAPI PET/CT as a new tool for identifying differences between poorly differentiated and highly differentiated tumors [17].

CAFs in tumor tissues are positively associated with loss of differentiation and aggressive course of thyroid cancer [18]. Fu and co-authors were the first to describe the case of differentiated thyroid cancer with elevated thyroglobulin levels and negative iodine scintigraphy results, in which ^{68}Ga-FAPI-04 PET/CT revealed an intensive accumulation in the foci of local recurrence and

distant metastases [19]. In a follow-up study, the same group reported the additional metastatic foci that were detected by ^{68}Ga-FAPI-04 PET/CT but not by ^{18}F-FAPI PET/CT in a patient with differentiated thyroid cancer, which was explained by a better ratio between the focus and background on ^{68}Ga-FAPI PET/CT [20].

Breast cancer and other gynecological malignancies are characterized by a high degree of genetic and molecular diversity. The receptor expression plays an important role in the biological behavior of various breast cancer subtypes, directly affecting the diagnostic and treatment strategies [21].

In a study of patients with various gynecological tumors by Dendl et al., 14 women with breast cancer had a strong and moderate accumulation of the marker in the stroma of the mammary gland formations [22].

In a pilot study by Komek et al., where ^{68}Ga-FAPI PET/CT and ^{18}F-FAPI PET/CT were prospectively compared in 20 women with breast cancer, ^{68}Ga-FAPI showed a higher sensitivity (100% vs. 78.2%), compared to ^{18}F-FDG PET/CT, while maintaining a comparable specificity (96.5% vs. 100%) in detecting primary breast tumors. ^{68}Ga-FAPI showed a significantly higher accumulation in primary tumors of the breast, lymph nodes, and pulmonary and bone metastases compared to ^{18}F-FDG ($p<0.05$) [23].

In a retrospective study, Elboga et al. found that ^{68}Ga-FAPI PET/CT had a higher ability to detect foci and exhibited higher marker activity than ^{18}F-FDG PET/CT in 48 patients with invasive breast cancer [24].

The accumulation properties of ^{18}F-FDG in primary liver tumors, especially for hepatocellular carcinoma (HCC), are complex due to factors such as low metabolism and physiological activity of the liver [25]. A study involving 17 patients showed that ^{68}Ga-FAPI-04 accumulated more in liver malignancies than benign tumors [26].

Another study evaluated patients with HCC (n=14) and cholangiocarcinoma CGC (n=3) and found the predominance of ^{68}Ga-FAPI-04 PET/CT over ^{18}F-FDG PET/CT in the detection of primary liver tumors. The efficacy of ^{68}Ga-FAPI-04 PET/CT was confirmed in 20 patients with HCC and 12 patients with CGC; the results were equivalent to contrast-enhanced CT and MRI. There were also two cases of benign liver tumors in which ^{68}Ga-FAPI was negative, emphasizing its potential to distinguish between benign and malignant liver tumors [27].

Röhrich et al. compared the diagnostic efficacy of ^{68}Ga-FAPI PET/CT and contrast-enhanced CT in patients with primary and recurrent pancreatic tumors. Application of ^{68}Ga-FAPI PET/CT led to stage reversal in 10 out of 19 patients [28].

Of particular interest is the study of the effectiveness of ^{68}GaFAPI PET/CT in the visualization of esophageal and breast cancer. According to the results of several studies, it was noted that GC was characterized by a high accumulation of ^{68}Ga-FAPI [29, 30]. Quin et al., in a study involving 20 patients with GC, also demonstrated high efficacy of PET/CT using ^{68}Ga-FAPI for imaging both primary and metastatic lesions [31]. Similar results were obtained by Pang et al. on a sample of 20 patients with GC. The study also included two patients with duodenal cancer and 13 with colon carcinoma. ^{68}Ga-FAPI PET/CT revealed all foci and was characterized by high image contrast due to high SUVmax values in pathological foci and low SUVmax values of background accumulation, contributing to more precise tumor differentiation [32]. Lin et al. reported an additional benefit of ^{68}Ga-FAPI-04 PET/CT as the control of therapy efficacy in patients with GC [33].

S. Koerber et al. studied the efficacy of ^{68}Ga-FAPI PET/CT in patients with colon, sigmoid colon, rectal, and anal cancer. They confirmed this marker's high efficacy in detecting primary and metastatic foci, which affects the determination of the process stage and treatment tactics [34].

Several studies evaluated the ^{68}Ga-FAPI PET/CT sensitivity and specificity in patients with abdominal carcinomatosis. One study enrolled 46 patients, the other – 35. Both groups of researchers obtained a high sensitivity and specificity of the method in detecting peritoneal metastases regardless of the type of carcinomatosis [35, 36].

Visual diagnostics of colorectal cancer by applying nuclear medicine technologies is difficult due to the peculiarities of the histological structure of cancer of these localizations and frequent physiological conditions leading to increased radiopharmaceutical capture and follow-up increase of the number of false-positive results. It has been revealed that the degree of FAP expression was directly proportional to the high aggressiveness and poor prognosis for colorectal cancer [37].

Numerous studies confirm that ^{68}Ga-FAPI PET/CT improves the detection of malignant lesions in the abdominal cavity, which are often difficult to detect using standard imaging methods [38, 39].

Almost simultaneously, studies have been conducted in several countries to assess the accumulation of ^{68}Ga-FAPI in patients with ovarian, cervical, endometrial, and fallopian tube cancer.

Depending on the age and hormonal status of the woman, there is a physiologically increased accumulation of FAPI in the endometrium [22]. However, in the presence of the tumor, the high image contrast is maintained due to the high accumulation of the marker in the tumor tissue [22]. Dendl et al. investigated the degree of marker accumulation in tumor foci in a diverse group of 31 patients with various gynecological tumors [22]. The ratio of standardized assimilation of tumor foci to background assimilation for distant metastases remained significantly high, contributing to the detection of metastatic foci. Some studies have demonstrated that FAP was highly expressed in the majority (>90%) of ovarian malignancies but had little expression in normal ovarian tissues, as well as in benign and borderline ovarian tumors [42, 43].

Based on the results of their work, K.Kessel and co-authors proved that ^{68}Ga-FAPI PET/CT was not inferior in effectiveness to other markers and could be used as an additional method for imaging of prostate cancer in assessing the prevalence of the process and searching for distant metastases [44].

^{68}Ga-FAPI PET/CT is a technique with high potential for visualization of various subtypes of sarcomas. For example, Koerber et al. conducted ^{68}Ga-FAPI PET/CT in 15 patients and noted the qualitative signal-background ratio in primary tumors and metastases. A special feature was the preservation of high image contrast when visualizing poorly differentiated sarcomas. The researchers also found that the degree of accumulation of the marker was directly proportional to the degree of malignancy and severity of the clinical course of the disease [45].

L. Kessler et al. analyzed the relationship between marker accumulation and the degree of FAP expression in 47 patients with bone and soft tissue sarcomas. ^{68}Ga-FAPI PET/CT demonstrated a high sensitivity due to the detection of additional foci in 8 patients, which accounted for 13% of the total number of participants [46].

There is no consensus on the effectiveness of ^{68}Ga-FAPI-04 PET/CT in diagnosing lymphomas. X.Jin et al. found a high accumulation of ^{68}Ga-FAPI in Hodgkin's lymphoma (n=11) and moderate accumulation in non-Hodgkin's lymphoma (n=62) [47].

Discussion: ^{68}Ga-FAPI PET/CT opens a new chapter in nuclear medicine, having a high potential for identifying, staging, and evaluating the effectiveness of treatment of malignant tumors. However, its clinical role and application in practice are not fully determined.

Based on the results of that review, it can be concluded that most of the studies focused on oncological disorders that have difficulties in diagnostics by use of other markers. Besides, most studies have limitations in the methodology due to a small sample of patients, heterogeneity of the sample, and imperfect study design, which does not permit the final conclusions.

FAP expression by inflamed tissues and further increased accumulation of the marker in chronic diseases allow the use of ^{68}Ga-FAPI PET/CT in the diagnostics of non-oncological diseases. Most studies in this area are devoted to cardiovascular and rheumatological diseases [48].

In any case, the diagnostic capacities of ^{68}Ga-FAPI PET/CT still require further research to form clear indications in practical use.

Conclusion: The increase in cancer morbidity and mortality worldwide encourages the creation and development of new diagnostic approaches that include nuclear medicine and molecular diagnostic capabilities.

The review of available literature data on FAPI PET/CT diagnostic capacity demonstrates this marker's potential in diagnosing oncological disorders. Information provided by ^{68}Ga-FAPI PET/CT supplements the existing nuclear medicine methods and generally impacts the treatment strategy for each unique case.

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АНДАТПА

КЛИНИКАЛЫҚ ТӘЖІРИБЕДЕ ^{68}GA-FAPI ПЭТ/КТ-НЫ ҚОЛДАНУ – ҚАТЕРЛІ ІСІКТЕРДІ ВИЗУАЛИЗАЦИЯЛАУ ПЕРСПЕКТИВАЛАРЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Әртүрлі локализациялардағы қатерлі ісіктермен сырқаттанушылық бүкіл әлемде де, Қазақстанда да өсуде. Онкологиялық аурулардан болатын өлім – жітім де жоғары. Ерте диагностика және оңтайлы терапия үшін ғалымдар молекулалық диагностиканы, соның ішінде әртүрлі маркерлерді қолданатын ПЭТ/КТ әдісін зерттейді. ^{18}F-фтородезоксиглюкоза онкологияда кеңінен қолданылады, бірақ кейбір ісіктердің түрлерін нақты ажырата алмайды. Белсендіретін фибробластикалық ақуыздың (FAP) анықталуы әртүрлі қатерлі ісіктерді диагностикалаудың әмбебап маркері бола алатын FAP-бағытталған радио таңбаланған ингибиторларға (FAPI) қызығушылық тудырды. Қазіргі уақытта ПЭТ/КТ үшін әртүрлі FAP маркерлері зерттелуде, олардың арасында ^{68}Ga-FAPI ерекше орын алады.*

Зерттеудің мақсаты *– қатерлі ісіктерді анықтаудағы FAPI ПЭТ/КТ-ның мүмкіндіктерін талдау.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed Cochrane Central Register of Controlled Trials дерекқоры бойынша келесі түйінді сөздермен: "қатерлі ісіктер", "ПЭТ/КТ" және "FAPI" шолу жүргізілді. Бұл шолуда әртүрлі локализациялардағы ісіктерді анықтау, сатылау, емдеу тиімділігін қарастыруда ^{68}Ga-FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктерін бағалауға арналған А1 дәлелдеу деңгейі бар 48 дерекқоздің нәтижелері сипатталған.*

Нәтижелері: *68Ga-FAPI PET/CT маркерінің сезімталдығы мен өзгешелігі туралы мәліметтерді жинайтын жұмыстарды талдау келесі көрсеткіштерді айқындайды: сәйкесінше 95%-дан 100%-ға дейін және 62%-дан 100%-ға дейін. Алайда, тәжірибеде қолдануға нақты көрсеткіштерді қалыптастыру үшін ^{68}Ga-FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктері әлі де қатысушылардың саны мен біртектілігін арттыра отырып қосымша зерттеулерді қажет етеді.*

Қорытынды: *FAPI ПЭТ/КТ-ның диагностикалық мүмкіндіктері туралы деректерге шолу маркердің қатерлі ісік диагностикасында қолданылу әлеуетін көрсетеді. 68Ga-FAPI ПЭТ/КТ-ның көмегімен алынатын ақпарат ядролық медицинаның өзге маркерлары арқылы алынған мағлұматты толықтырады және науқастардың әрбір нақты жағдайдағы емдеу тактикасына әсер етеді.*

Түйінді сөздер: *қатерлі ісіктер, ПЭТ/КТ, FAPI.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ 68GA-FAPI ПЭТ/КТ В КЛИНИЧЕСКОЙ ПРАКТИКЕ – ПЕРСПЕКТИВЫ ДЛЯ ВИЗУАЛИЗАЦИИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Заболеваемость злокачественными опухолями различных локализаций имеет тенденцию к росту, как во всем мире, так и в Казахстане. Смертность от онкологических заболеваний также имеет высокие показатели. Для ранней диагностики и оптимальной терапии ученые исследуют молекулярную диагностику, включая метод ПЭТ/КТ с использованием различных маркеров. ^{18}F-фтордезоксиглюкоза широко применяется в онкологии, но не является специфичным для некоторых опухолей. Открытие*

активирующего фибробластического белка (FAP) привело к интересу к FAP-ориентированным радиомеченым ингибиторам (FAPI), которые могут стать универсальным маркером для диагностики различных видов рака. На данный момент исследуются различные FAP маркеры для ПЭТ/КТ, среди которых особое место занимает ^{68}Ga-FAPI.

***Цель исследования** – проанализировать возможности FAPI ПЭТ/КТ в диагностике злокачественных опухолей.*

***Методы:** проведен литературный обзор по базе данных MEDLINE, Embase, Scopus, PubMed, Cochrane Central Register of Controlled Trials за последние 10 лет по следующим ключевым словам: «злокачественные новообразования", "ПЭТ/КТ" и "FAPI". В данном обзоре описаны результаты анализа 48 литературных источников с уровнем доказательности А1, посвященных оценке диагностических возможностей ^{68}Ga-FAPI ПЭТ/КТ в выявлении, стадировании, оценке эффективности лечения опухолей различных локализаций.*

***Результаты:** Чувствительность и специфичность ^{68}Ga-FAPI ПЭТ/КТ в диагностике рака различных локализаций составляют от 95% до 100% и от 62% до 100%, соответственно. Однако для формирования четких показаний к применению в практической деятельности, диагностические возможности ^{68}Ga-FAPI ПЭТ/КТ все еще требуют дальнейших исследований с большим количеством участников и более однородной выборкой.*

***Заключение:** Имеющиеся литературные данные о диагностических возможностях FAPI ПЭТ/КТ демонстрируют потенциал маркера для применения в диагностике онкологических заболеваний. Информация, полученная с помощью ^{68}Ga-FAPI ПЭТ/КТ, дополняет уже используемые методы ядерной медицины и в совокупности влияет на тактику лечения пациентов в каждом конкретном случае.*

***Ключевые слова:** злокачественные новообразования, fibroblast activation protein inhibitor (FAPI), ПЭТ/КТ.*

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GENOME-WIDE ASSOCIATION STUDY IN BREAST CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Breast cancer (BC) is one of the major health problems in the Republic of Kazakhstan. Genome-wide association studies (GWAS) are used to identify genetic factors contributing to breast cancer development in Kazakhstan and worldwide. The GWAS method consistently helps to find associations between certain single nucleotide polymorphisms (SNPs) in the genome and the development of pathological conditions, including breast cancer, by identifying more than 170 genomic sites. In addition to searching for loci associated with BC, these studies have expanded our understanding of BC heritability using SNPs located in regulatory areas and identifying DNA variants associated with drug metabolism for treatment personalization purposes.*

The study aimed to *highlight the key concepts of modern methods in genetics based on GWAS.*

Materials and methods: *A literature search in PubMed, Scopus, GWAS Catalog, Cochrane Database of Systematic Reviews, etc., was performed to select and analyze relevant information.*

Results: *The article describes significant GWAS studies in the field of breast cancer, describes certain genes associated with the development of the disease, identifies shortcomings, and identifies further strategies for the development of GWAS in the Republic of Kazakhstan.*

Conclusion: *The results of this study have improved our understanding of the biological mechanisms that contribute to breast cancer risk and may ultimately lead to the development of new targeted therapies for the disease.*

Keywords: *Breast cancer, Genome-Wide Association Studies (GWAS), Single Nucleotide Polymorphism (SNP), polygenic risk score (PRS).*

Introduction: Breast cancer (BC) is one of the most common malignancies. In 2020, 2.3 million women have been diagnosed worldwide [1]. Since 2011, breast cancer has taken the 1st rank in the structure of malignant neoplasm incidence in the Republic of Kazakhstan (RK). According to the statistics of indicators of the oncology service of the Republic of Kazakhstan for 2021, the structure of patients with breast cancer composed 15.4% for both sexes. Among women, this figure made up 27.1%. In the structure of causes of death of the population, breast cancer occupies the 3rd position, accounting for 8.7% [2]. Despite higher detection at stages I-II, high 5-year survival rates comparable to OECD countries (over 85.0%) are not achievable by introducing breast cancer screening. In the Republic of Kazakhstan, 5-year survival does not exceed 68.4% [3]. An individual's genetic pattern is a major component in determining the risk for disease development. In order to better understand the genetic factors that contribute to developing breast cancer, genome-wide association studies (GWAS) are being conducted to identify genetic variants associated with this disease. GWAS research has been conducted since the early 2000s. GWAS uses microarrays, or sequencing technologies, to screen for hundreds of thousands or even millions of Single Nucleotide Polymorphisms (SNPs) and other variants in the human genome to look for disease-related gene locus. GWAS is usually based on the prevalent disease-pervasive variation hypothesis using a case-control approach (Figure 1) [4].

Figure 1 shows the correlation between the allele frequency and disease severity. Accordingly, diseases with the Mendelian type of inheritance (left circle from the top) strongly impact the patient, but the frequency of such mutations is very rare. On the other hand, there are very rare and ineffective variants (left circle from the bottom). These traits hinder the establishment of a reliable correlation between the phenotype and genotype. GWAS focused on identifying genetic variants, which could be divided into common variants with a high effect (upper right circle) and common variants with a clear low effect on human health (bottom right circle) [5]. In order to determine the correlation of SNP with the disease, the allelic frequency of the studied SNP markers has to differ significantly between the observation group and the control group [4]. In order to visualize the GWAS results depending on the location of chromosomes, Manhattan graphs are used (Figure 2) [6].

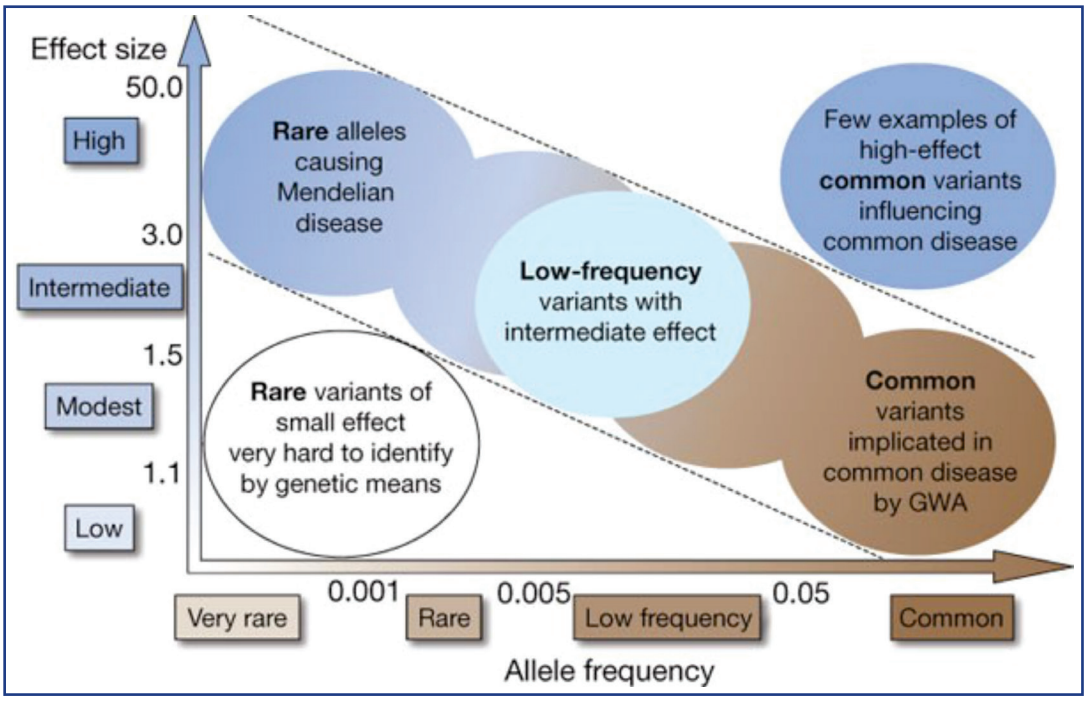

Figure 1 – Features of genetic variants and correlation with disease severity [5]

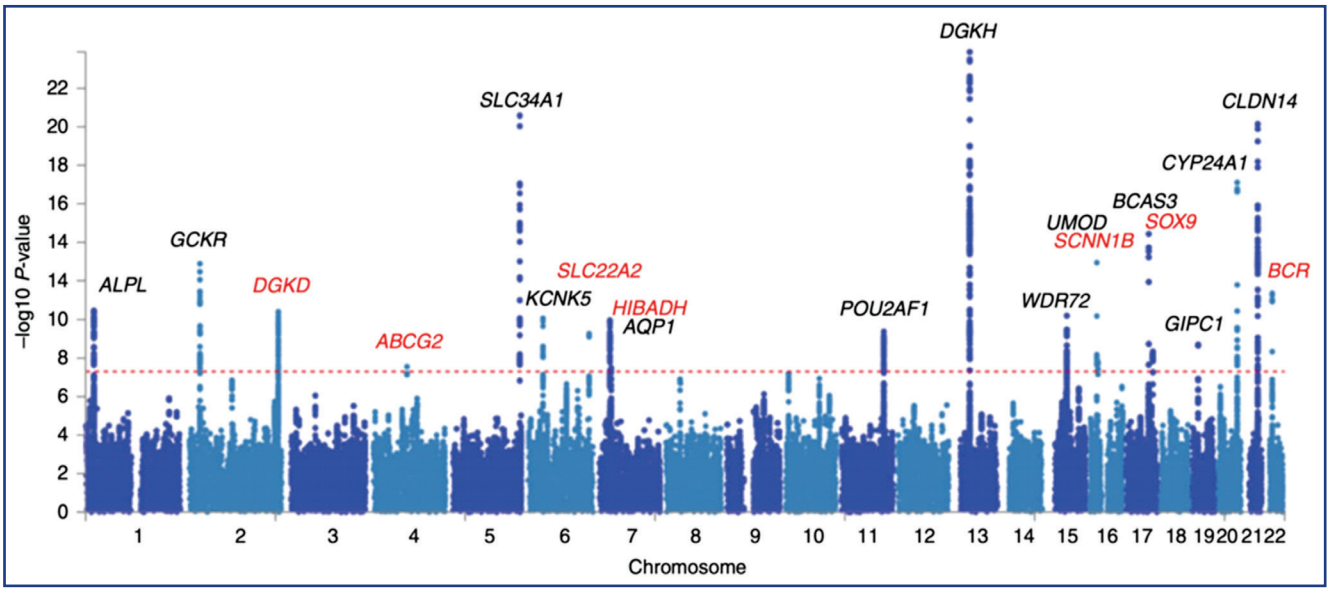

Figure 2 – A Manhattan diagram presenting several closely related loci. Each dot is an SNP; the X-axis shows the genomic location, and the Y-axis – the level of association [7]

The impetus for the start of GWAS was the development of high-precision genotyping technologies and the completion the Human Genome Project in 2003, which provided a reference genome sequence that allowed researchers to identify genetic variations associated with complex diseases and traits [8].

The first successful GWAS study was published in 2005 that identified genetic variants associated with age-related macular degeneration [9].

Since then, GWAS studies have been conducted for various diseases and conditions, including heart disease, diabetes, Alzheimer's disease, and many types of cancer. The technology used for GWAS has also evolved over time: new techniques allow for analyzing large data sets and identifying more complex genetic associations [10].

The world's first GWAS study in breast cancer was published in 2007 and revealed the new predilection loci. The study examined the data of 4398 patients with breast cancer and 4316 subjects of the control group. 227,876 SNPs were analyzed, accounting for about 77% of known total SNPs among Europeans at $r^2>0.5$. As a result, five new independent loci associated with breast cancer ($P<10^{-7}$ using the Cochran-Armitage stratified test) were discovered. The FGFR2, TNRC9/TOX3, MP3K1, and LSP1 genes around the four

loci have been identified as risk genes for breast cancer. The most strongly associated SNP was in intron 2 of the FGFR2 gene, a receptor tyrosine kinase amplified and overexpressed in 5-10% of breast tumors [11]. Locus 16q contains the candidate genes TNRC9/TOX3 and LOC643714. TNRC9/TOX3 plays an important role in various cellular processes, including gene regulation and transcriptional control [12]. MAP3K1, located at locus 5q, is a gene involved in signal transduction and has not previously been reported to be involved in cancer development. LSP1 is located at locus 11p, a cytoskeletal protein that binds F-actin expressed in hematopoietic and endothelial cells. Other evidence of the association points to SNPs around the H19 gene, a maternally imprinted gene that encodes untranslated mRNA closely involved in IGF2 regulation. The fifth locus is a 110 kb interval not containing the known genes and located in the 8q24 genomic region. Despite the absence of genes in the 110 kb segment, the 8q24 region contains loci associated with prostate and colorectal cancer [11].

In 2009, to obtain a more comprehensive understanding of the genetic factors that control developing breast cancer, the "Collaborative Oncological Gene-Environment Study" (COGS) project was created through the cooperation of four consortia. The project comprised a meta-analysis of nine GWAS involving 10,052 breast cancer cases and 12,575 control cases. 29,807 SNPs were selected for further genotyping, and the results from 41 Breast Cancer Association Consortium (BCAC) studies using 45,290 cases and 41,880 controls in a population of European ancestry have been added. As a result of joint efforts, SNP was identified in 41 new loci of predisposition to breast cancer with genomic significance ($P < 5\times10^{-8}$) [13].

Notwithstanding the GWAS's successes in identifying multiple genetic variants, there is a gap between the ability to detect these associations and meaningfully interpret their biological significance [14]. Currently, the challenges for GWAS include identifying loci associations to address the challenges posed to researchers [15, 16]. The new trend in identifying susceptibility loci has advanced to accurately describe the functional effects and target genes. Although identifying common risk variants is an emerging field, it will enable the routine screening method for earlier diagnostics and guide strategies for breast cancer treatment. The link of SNPs with a particular disease is called the polygenic risk score (PRS). A major challenge in developing and using such scores is to ensure they are equally suitable for patients of all ethnic groups. If not properly studied, the use of RPS in these populations will be limited, exacerbating more existing ethnic disparities in health care systems [17].

In studies by Wang S. et al., most of the gene variants associated with breast cancer were found in representatives of the Caucasian population. However, many of these genetic risks are not transferable to other populations, with some variants causing risk in one population and being protective in another. This study showed that of the approximately 100 variants identified that increased the risk of breast cancer in Europeans and Asians, 30-40% were protective among the population of African origin [18]. These findings suggest that GWAS studies should be population-specific, especially in non-European origin, considering all hereditary factors, as risk stratification is not automatically transferred from one population to another.

Since using PRSs to predict breast cancer risk is relatively new, the best approach for communicating personalized risk assessment to the patient and the wish of patients to know this information compared to standard screening are yet to be determined. PROCAS (Predicting Risk of Breast Cancer at Screening), WISDOM (Women Informed to Screen Depending on Measures of Risk), and MyPeBS (My Personalized Breast Screening) are all large-scale studies that are investigating the feasibility of PRS in breast cancer and how clinical implementation can be facilitated [19].

Materials and Methods: The literature data were searched in PubMed and Scopus databases, GWAS Catalog, Cochrane Database of Systematic Reviews, and other sources. The search depth was 20 years, with a focus on modern publications.

Inclusion criteria:

– Studies published within the last 10 years (2013 to 2023).

–Studies have used GWAS to analyze genetic factors associated with breast cancer development.

–Studies that provide sufficiently reliable data for analysis.

Exclusion Criteria:

–Studies that do not focus on genetic factors associated with breast cancer.

–Studies that do not provide enough reliable data for analysis.

The search was performed using the following keywords: "breast cancer," "Genome-Wide Association Studies (GWAS)," "Single Nucleotide Polymorphism (SNP)," "polygenic risk score (PRS)," etc.

Results: Based on the exclusion and inclusion criteria used, keywords in the PubMed, Scopus, GWAS Catalog Cochrane Database of Systematic Reviews, etc., we selected 11 significant publications [20-30]. The results of 8 studies that reflect specific data from the study are presented in Table 1.

Table 1 – List of significant GWAS publications with identified SNPs associated with breast cancer development

Study title	Year of publi-cation	Number of new SNP found	Examples of detected SNPs	SNP location	Authors
Michailidou K. et al.	Large-scale genotyping identifies 41 new loci associated with breast cancer risk [13]	2013	41	rs4808801	ELL
				rs3760982	LYPD5, KCNN4
				rs132390	EMID1
				rs6001930	MRTFA
				rs13387042	RN7SKP43, LINC01921
Michailidou K. et al.	Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer [20]	2015	15	rs6507583	SETBP1
				rs6507583	
				rs12405132	RNF115
Palomba G. et al.	Genome-wide association study of susceptibility loci for breast cancer in Sardinian population [21]	2015	2	rs2912780	FGFR2
				rs2193094	TOX3
Han M.R. et al.	Genome-wide association study in East Asians identifies two novel breast cancer susceptibility loci [22]	2016	2	rs12118297	LINC02801, LMO4
				rs16992204	LINC01426, LINC00160
Couch F.J. et al.	Identification of four novel suscep-tibility loci for estrogen receptor negative breast cancer [23]	2016	4	rs67073037	WDR43
				rs6562760	RNY1P8, MARK2P12
				rs188686860	CLK1/PPIL3
				rs115635831	PPIL3
Michailidou K.	Association analysis identifies 65 new breast cancer risk loci [25]	2017	65	rs60954078	ESR1, CCDC170
				rs141061110	FOXN3, FOXN3-AS1
				rs2965183	GATAD2A
Milne R.L. et al.	Identification of ten variants asso-ciated with risk of estrogen-recep-tor-negative breast cancer [26]	2017	10	rs200648189	NCOA1
				rs6569648	L3MBTL3
				rs66823261	RPL23AP53
				rs17350191	ANXA13
Zhang H. et al.	Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses [29]	2020	32	rs5776993	GSTM2
				rs13277568	TRPS1
				rs4742903	SMC2

Discussion: By 2015, more than 90 established predilection loci to breast cancer were identified by GWAS studies. Data revealing new predilection loci are published annually, so by 2020, their number exceeded 200 loci (Table 1).

The team of researchers conducted a meta-analysis limited to women of European origin. They worked with 11 GWASs, including 15,748 breast cancer cases and 18,084 control cases, and additionally used data from 41 studies, including 46,785 cases and 42,892 control cases, genotyped to assess more than 11 million SNPs. As a result, 15 new loci associated with breast cancer ($P<5x10^{-8}$) were identified (Table 1) [20]. Following the assumption that the analysis of a genetically homogeneous population may represent an additional approach to identify alleles with low penetrance, the GWAS study was conducted, which compared the data of 1431 patients from Sardinia with BRCA1/2-negative breast cancer and 2171 healthy patients. Overall, 2,067,645 SNPs have been analyzed. The study concluded the role of TNRC9/TOX3 and FGRF2 as predisposition genes in patients with BRCA1/2 type breast cancer from the Sardinian population (Table 1) [21].

It is consistent with the widespread belief that breast cancer patients from different regions may have different genetic backgrounds, which affects the risk of the disease due to the expression of predisposition genes with low penetrance.

In 2016, three GWAS studies describing the new genetic predilection loci were published. One study included 14,224 cases of breast cancer and 14,829 healthy women from East Asia, where two SNPs at two loci were found to be associated with the risk of developing breast cancer at the genome-wide significance level (one at 1p22.3 and the other at 21q22.12) (Table 1) [22].

The meta-analysis of 11 GWAS studies engaging 4,939 cases of hormone-negative breast cancer and 14,352 controls, combined with 7,333 hormone-negative cases and 42,468 controls and 15,252 carriers of the BRCA1 mutation, genotyped from the Collaborative Oncological Gene-environment Study (iCOGS), identified four previously unidentified loci: 13q22 (KLF5), 2p23.2 (WDR43), and 2q33 (PPIL3) – with a significant genomic association (Table 1) [23].

GWAS may also be useful in detecting SNPs associated with response to anthracycline-containing neoadjuvant chemotherapy in breast cancer patients. Two SNPs were identified that were significantly associated with pathologic complete response after the neoadjuvant chemotherapy. An analysis of the genomic struc-

ture of 401 patients treated with anthracyclines revealed that only one SNP located in the WT1 gene was associated with a pathological complete response, suggesting that the WT1 gene may be a potential target of anthracycline-based neoadjuvant therapy in breast cancer [24].

Sixty-five new predilection loci were identified in the study of Michailidou et al. (2017) and another 10 in the study of Milne et al. (2017), bringing the total number of known genetic variants to more than 170 (Table 1) [25, 26].

Ferreira et al. (2019) identified 26 genes that had never been discovered and could be targeted for all variants of breast cancer risk genes. As a result of the study, it was found that seven regions were associated with all breast cancer phenotypes, and four regions were associated with hormone-negative breast cancer [27]. In addition, Morton et al. (2017) confirmed that the TAGLN gene (rs74949440) on chromosome 11q23 and the RPS6KC1 gene (rs17020562) on chromosome 1q32.3 were significantly associated with the risk of developing breast cancer in women who underwent the chest radiation therapy in childhood for any malignant pathology [28]. The study of H. Zhang et al. examined the genes of more than 133,000 women with breast cancer, 113,000 controls, and more than 18,000 women with the BRCA1 gene mutation. As a result, 32 new SNPs were identified that increase the risk of developing breast cancer, and 5 of these loci demonstrated a reverse causality with hormone-positive and hormone-negative breast cancer. The authors assume that these results permit a better understanding of the genetic predisposition to breast cancer subtypes and will be the basis for developing polygenic risk scores for specific subtypes (Table 1) [29].

Pilot projects conducted in the Republic of Kazakhstan to study polymorphisms associated with breast cancer development have involved small cohorts [30]. A GWAS study performed in 2021-2023 within the framework of the scientific and technical program "National Program for Introduction of Personalized and Preventive Medicine in the Republic of Kazakhstan," initiated by the Ministry of Health and the Ministry of Education and Science of the Republic of Kazakhstan, included over 1300 women of the Kazakh population diagnosed with breast cancer. The project is at the stage of data analysis and identification of polymorphisms specific to women of the Kazakh population.

Conclusion: GWAS studies are important for understanding breast cancer's genetic grounds. In those studies, many genetic variants have been found that were associated with an elevated risk of developing breast cancer. GWAS allows us to better understand the biological underlying mechanisms for breast cancer and provides new opportunities for individualized approaches to diagnostics, prevention, and treatment of that disease. An advanced understanding of the genetic basis of breast cancer through the data obtained by GWAS opens new prospects in breast cancer control.

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АНДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ГЕНОМДЫҚ АССОЦИАТИВТІ ЗЕРТТЕУІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сүт безі обыры (СБО) Қазақстан Республикасындағы денсаулық сақтаудың негізгі проблемаларының бірі болып табылады. Қазақстанда және бүкіл әлемде сүт безі қатерлі ісігінің дамуына ықпал ететін генетикалық факторларды анықтау үшін геномдық ассоциативті зерттеулер жүргізілуде (ағылш. genome-wide association studies, GWAS). GWAS әдісі белгілі бір бір нуклеотидті полиморфизмдер арасындағы байланысты табуға көмектеседі (ағылш. Single Nucleotide Polymorphism, SNP) геномда және патологиялық жағдайлардың дамуында, соның ішінде СБО, 170-тен астам геномдық учаскелерді анықтау. СБО-мен байланысты локустарды іздеуден басқа, бұл зерттеулер реттеуші аймақтарда орналасқан SNP арқылы СБО тұқым қуалаушылық туралы түсінігімізді, сондай-ақ емдеуді жекелендіру мақсатында дәрілік заттардың метаболизмімен байланысты ДНҚ нұсқаларын анықтауды кеңейтті.*

Зерттеудің мақсаты *– GWAS негізіндегі генетика саласындағы заманауи әдістердің негізгі тұжырымдамаларын қамту.*

Әдістері: *Тиісті ақпаратты іріктеу және талдау үшін PubMed, Scopus, WOS Catalog Cochrane database of Systematic Reviews және т.б. базаларында әдебиет деректерін іздеу жүргізілді.*

Нәтижелері: *Мақалада СБО саласындағы маңызды GWAS зерттеулері сипатталған, аурудың дамуымен байланысты белгілі бір гендер сипатталған, кемшіліктер анықталған, сондай-ақ Қазақстан Республикасында GWAS одан әрі даму стратегиялары анықталған.*

Қорытынды: *GWAS нәтижелері сүт безі қатерлі ісігінің даму қаупіне ықпал ететін биологиялық механизмдер туралы түсінігімізді жақсартуға көмектесті және сайып келгенде, ауруды емдеудің жаңа мақсатты әдістерінің дамуына әкелуі мүмкін.*

Түйінді сөздер: *Сүт безі обыры, толық геномдық қауымдастырылған зерттеулер (Genome-Wide Association Studies), бір нуклеотидті полиморфизм (Single Nucleotide polymorphism), полигендік тәуекел индексі (polygenic risk score).*

АННОТАЦИЯ

ПОЛНОГЕНОМНОЕ АССОЦИАТИВНОЕ ИССЛЕДОВАНИЕ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак молочной железы (РМЖ) является одной из основных проблем здравоохранения в Республике Казахстан. Для выявления генетических факторов, способствующих развитию РМЖ в Казахстане и во всем мире, проводятся полногеномные ассоциативные исследования (англ. genome-wide association studies, GWAS). Метод GWAS последовательно помогает находить связь между определенными однонуклеотидными полиморфизмами (англ. Single Nucleotide Polymorphism, SNP) в геноме и развитием патологических состояний, в том числе РМЖ, выявив более 170 геномных участков. Помимо поиска локусов, ассоциированных с РМЖ, эти исследования также расширили наше понимание наследственности РМЖ с помощью SNP, расположенных в регуляторных зонах, а также идентификации вариантов ДНК, ассоциированных с метаболизмом лекарственных средств в целях персонификации лечения.*

Цель исследования *– освещение ключевых концепций современных методов в области генетики на основе GWAS.*

Методы: *Проведен поиск данных литературы в базах PubMed, Scopus, GWAS Catalog Cochrane Database of Systematic Reviews и др. для отбора и анализа релевантной информации.*

Результаты: *В статье описаны значимые GWAS исследования в области РМЖ, описаны определенные гены, ассоциированные с развитием заболевания, выявлены недостатки, а также были идентифицированы дальнейшие стратегии развития GWAS в Республике Казахстан.*

Заключение: *Результаты GWAS помогли улучшить наше понимание биологических механизмов, способствующих риску развития РМЖ, и в конечном итоге могут привести к разработке новых целевых методов лечения этого заболевания.*

Ключевые слова: *рак молочной железы (РМЖ), полногеномные ассоциированные исследования (GWAS), однонуклеотидный полиморфизм (SNP), полигенный индекс риска (PRS).*

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THE DEGREE OF AWARENESS OF THE POPULATION OF THE KARAGANDA REGION ON THE INCIDENCE AND PREVENTION OF COLORECTAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Colorectal cancer (CRC) is the leading cancer in yearly morbidity and mortality. WHO forecasts that 2030 CRC incidence will exceed 2.2 million cases yearly, and mortality will increase to 1.1 million yearly. More than 3,000 new cases of colorectal cancer are detected annually in Kazakhstan. In disease control, it is necessary to develop preventive measures as much as possible. Preventive measures play a crucial role in reducing mortality from this disease. One of the most critical issues is the lack of public awareness about the disease.*

The study analyzes *the global experience in preventing colorectal cancer to develop measures to raise public awareness.*

Methods: *A continuous search was performed in the PubMed, CrossRe, Scopus, and Cochrane databases for 2013-2023 for the keywords "colorectal cancer," "risk factors," "public awareness," "medical literacy," "morbidity," and "prevention." In total, more than 75 scientific articles and 500 abstracts were reviewed.*

Results: *The problem is aggravated by the fact that among patients with an oncological diagnosis, patients with colorectal cancer, or patients with a confirmed diagnosis of the disease, there is insufficient information about this disease, and they neglect preventive measures. Firstly, we insist that the population is not fully aware of the responsibility for their health (this is influenced by a false sense of shame and insufficient awareness of the disease), and secondly, primary prevention is essential. Accordingly, it is necessary to increase the effectiveness of screening programs, improve awareness, and organize full-fledged assistance from the state in disease control.*

Conclusion: *Colorectal cancer is an urgent disease that occupies an essential place in Kazakhstan's list of oncological diseases. Due to the increased awareness of the population about this disease and the correct solution to prevention issues, it will be possible to reduce the incidence among patients. In this regard, it is necessary to widely disseminate information about the disease among the population and increase patients' responsibility for their health.*

Keywords: *colorectal cancer, risk factors, public awareness, medical literacy, morbidity, prevention.*

Introduction: Colorectal cancer (CRC) is the leading cancer in the most common non-contagious diseases of the last 20 years. Colorectal cancer control is becoming increasingly important and challenging to solve. In particular, among socially significant diseases, cancer incidence ranks second after cardiovascular diseases. Colorectal cancer ranks second in men and third in women in prevalence worldwide. According to statistics, cancer is more common in men than women. The disease got younger in recent years. A decade or more ago, cancer was frequent in people over 65, and now it is common below 50. However, the bold reforms of the state in health control are decisive and vital for disease prevention. In particular, thanks to the regular organization of screening measures and the public awareness that these measures will be effective, it will be possible to prevent the disease early.

The study analyzes the global experience in preventing colorectal cancer to develop measures to raise public awareness.

Materials and methods: A search was performed using PubMed, CrossRef, Scopus, and Cochrane databases for 2013-2023, publications of the world scientific literature on the risk factors of CRC and their prevention and on the issue of determining the degree of public awareness were studied. A continuous search was used for the keywords "colorectal cancer," "risk factors," "public awareness," "medical literacy," "morbidity," and "prevention." More than 75 scientific articles and more than 500 theses were reviewed.

Results: Colorectal cancer (CRC) consistently ranks third in the structure of cancer cases. There is a tendency to increase the morbidity of CRC in people under 50. The WHO considers colorectal cancer the third most common after lung and breast cancer (1.9 million cases in 2020). It accounts for 10.2% of all tumor types worldwide and is the second leading cause of cancer mortality (935 thousand cases in 2020). WHO forecasts that 2030 CRC incidence will exceed 2.2 million cases yearly, and mortality will increase to 1.1 million yearly [1]. More than 3,000 new cases of colorectal cancer are detected annually in Kazakhstan. Colorectal cancer (CRC) screening has been carried out in Kazakhstan since 2011. Every year, as part of CRC screening, about 850-980 thousand

men and women are examined at 50-70 years old. However, over the past 4-5 years, there has been a decrease in CRC detection from 6 to 3 cases per 10,000 screened patients, an increase in colonoscopy rejection with positive tests, and, as a result, an increase in missed CRC detection cases.

The low awareness of the male population should be noted in matters of awareness of the symptomatic and prevention of colorectal cancer [2]. The International Agency for Research on Cancer considers that the highest incidence of CRC is observed in Australia, New Zealand, North America, Europe, and Japan. The lowest is in Asia and Africa (India, Oman, Pakistan, Algeria, etc.), which may be due to changes in lifestyle and diet patterns of the population. It is due to the need for timely diagnostics, the low economic potential of these countries, and the poor quality of the information provided. In regions where the highest level of CRC morbidity is determined, morbidity trends are multidirectional, so CRC morbidity is stabilized in Europe and declined in North America [3-5]. A statistical analysis of epidemiological data from 2015-2020 showed that CRC morbidity and mortality are heterogeneous and vary in countries with high and low human development indices (HDI). According to these data, the division of countries into three groups was carried out: in the first group, there is a tendency to increase morbidity and mortality simultaneously; in the second group, there is an increase in morbidity but a decrease in mortality; in the third group – a decrease in morbidity and mortality [6].

Lifestyle-related risk factors make a dominant contribution to the increase in CRC frequency. However, genetic predisposition plays a minor role (about 30% of CRC cases are classified as genetically deterministic) [7]. Several epidemiological control studies data confirmed it. It has been shown that CRC is more common in countries with a "Western lifestyle" (low dietary fiber content, mainly refined foods, high percentage of red meat consumption). In addition, some countries with a low CRC at first (Vietnam, India) can note their growth after economic growth and adaptation to the "Western way of life" [8].

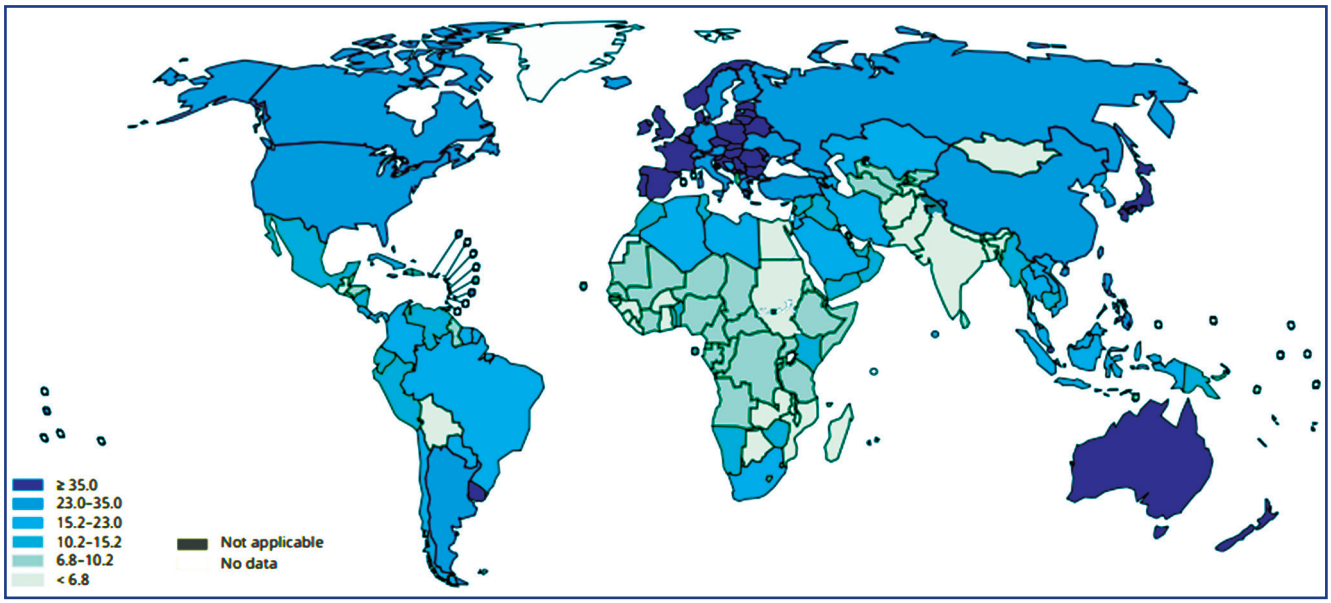

Figure 1 – Cartogram of standardized indicators of global colorectal cancer (GLOBOCAN 2020 data, both sexes, all ages) [9]

CRC primary prevention aims to prevent the disease by eliminating modifiable risk factors. These include consuming foods rich in dietary fiber and ballast, a sedentary lifestyle, excessive consumption of refined fats and red meat, smoking, alcohol abuse, and obesity [10]. A diet rich in dietary fiber (rich in vegetables and fruits) is the most studied protective factor about the development of CRC, characterized by a decrease in the incidence of about 40%. However, the role of this factor in CRC prevention of different localization is different: it is effective in preventing proximal CRC. It practically does not change the anus cancer morbidity.

On the other hand, eating large amounts of red meat and refined fats increases the risk of developing CRC [11]. Smoking increases the risk of CRC twice and gives a poor standard of living [12]. Data on the impact of alcohol consumption on the morbidity and mortality of CRC vary among the authors. It has been shown that an increase in the incidence of CRC (distal and proximal localization) is associated only with excessive (more than 23 g per day) consumption of alcohol, moderate and moderate use of which is not associated with an increase in the incidence [13]. The probability of the occurrence of CRC in drinks consumed daily was studied. Drinking chlorinated water for 30 years increases the risk of colon cancer by 1.4 times [14]. Inflammation also plays a vital role in the pathogenesis of CRC: activation of inflammatory signaling pathways

is fundamental, the most important of which is the signaling pathway regulated by the transcription factor NF-kB; methylation of several sensitive genes in which cytokines (especially tumor necrosis factor) play an important role [15]. However, bad diet, obesity, smoking, alcohol intake, toxins exposure, and infectious diseases activate signaling inflammatory pathways. The authors of reports published in recent decades indicate that inflammation plays an essential role in all stages of malignant cell transformation [16].

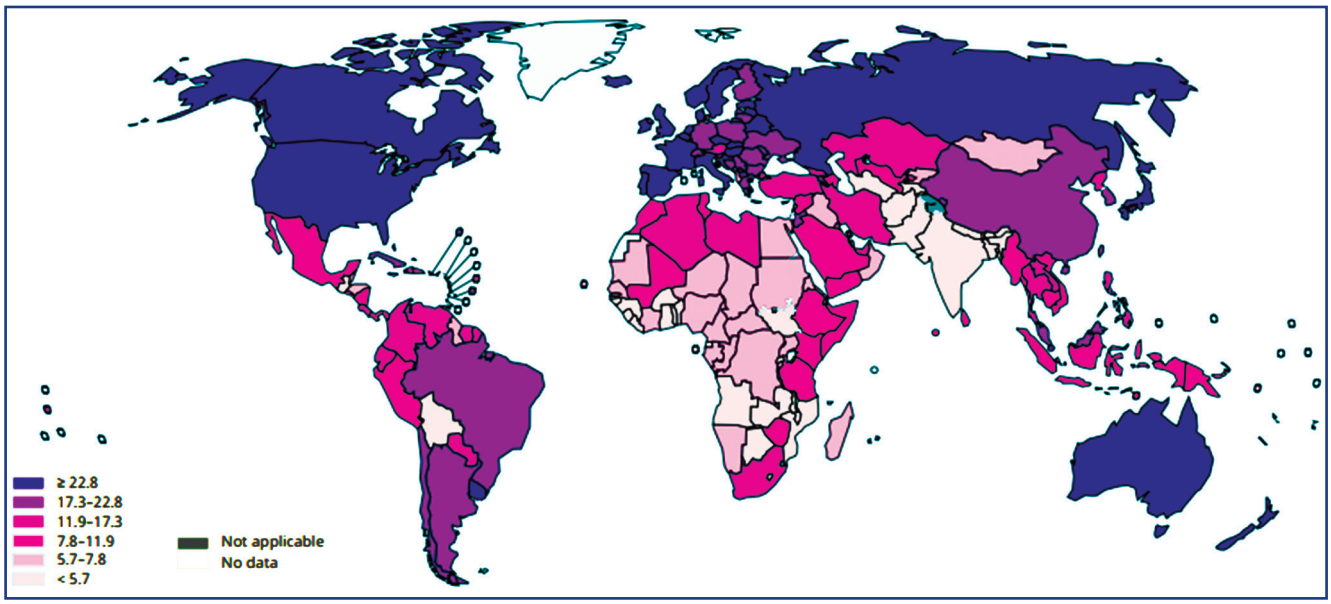

Figure 2 – Cartogram of standardized global colorectal cancer mortality (GLOBOCAN 2020 data, both sexes, all ages) [9]

Many authors consider that the level of physical activity is of great importance in preventing CRC. For the first time in an experiment in mice in 1952, a decrease in the risk of HPV of various localizations, including CRC, was observed with increased physical activity [17-18]. A meta-analysis of 52 studies showed that physical activity reduced the risk of CRC by 20-30%. At the same time, the authors indicate that even a small load (walking 3-4 hours a week) contributes to a decrease in risk by more than 15% [19]. The main mechanisms of a mobile lifestyle's preventive effect are stimulating the motility of the gastrointestinal tract and preventing obesity [20]. Various meta-analyses and systematic reviews discuss screening programs' role in preventing CRC incidence and mortality. In part of the studies, CRC screening has been shown to reduce both the incidence and mortality from cancer. However, the authors of many works note that screening programs can reduce mortality but not the incidence of CRC [21].

There are invasive screening methods (colonoscopy, sigmoidoscopy) and non-invasive (stool and blood tests, radiation examination methods). Fecal occult blood tests are often used: (gFOBT and FIT. Gfobt) or guaiac occult blood test (guaiac fecal occult blood test) is based on the determination of heme peroxidase activity in feces. This method is one of the most studied, used since the 1970s for screening in many European countries (Croatia, Portugal, Finland, etc.). The advantages of the test include low cost and ease of execution. To increase the effectiveness of Gfobt, its highly sensitive modifications — Hemoccult Sensa and Hemoccult ICT- have been developed, making it possible to detect low hemoglobin concentrations. According to different CRC results, the sensitivity of different Gfobt tests varies from 31-63%, and the specificity is 92-96%. Colonoscopy is the "gold standard" for CRC screening with high sensitivity and specificity [22-24]. Precancerous significant intestine diseases include one or more adenomas (polyps) of the large intestine, nonspecific ulcerative colitis, and Crohn's disease. Detecting polyps is vital in cancer prevention, as colon cancer often develops from polyps. The risk of a colon polyp becoming cancerous is high: in a polyp less than 1 cm in size – 1.1%, 1-2 cm – 7.7%, more than 2 cm – 42%, in the middle – 8.7% [25]. Risk factors include whether the patient's age is over 50 years, if he has previously suffered from female genital and breast cancer, or if he has colon cancer. Timely detection of colorectal cancer involves early diagnosis, that is, in the absence of all clinical manifestations of the disease and preclinical stages. Screening or early detection of colorectal cancer is done through the finger, endoscopic, and hemocult tests. About 70% of all rectal carcinomas are detected by a finger examination of the rectum.

Therefore, digital rectum examination is mandatory in preventive examinations by a gynecologist, urologist, and doctors of other specialties. When using modern flexible sigmoidoscopes with a length of 60 cm, it is possible to detect 55% adenoma and carcinoma of the de novo developing Sigmoid and rec-

tum. The sensitivity of this method is 85%. The American Association of Doctors recommends performing a sigmoidoscopy every 3-5 years from age 50 in people who do not complain of intestinal dysfunction. However, the possibility of using these methods for extensive screening seems doubtful due to their complexity and high cost. Therefore, most oncologists recommend limiting themselves primarily to these examination methods among people with increased risk factors for colorectal cancer [26-27]. The primary and early symptom of colorectal cancer is the appearance of blood in the stool. That is why the fecal occult blood test is a "classic" test used to diagnose colon and rectal cancer early. To date, it is considered a laboratory study recommended for annual examination for the timely diagnosis of colorectal cancer in all people over 50 [28]. Patients face multifaceted problems resulting from the disease due to a lack of awareness of CRC risk factors and symptoms [29]. Research has shown that raising awareness of CRC in the general population and participating in cancer screening early treatment may increase opportunities for disease control, decrease prevalence, and increase survival [30].

Discussion: It was mentioned above that the main event in colorectal cancer control is a preliminary examination. In this regard, the implementation of screening programs in the country's healthcare system is supported as much as possible. As a result, we can detect malignant diseases promptly, reducing the mortality rate from diseases. Scientific articles in the literature review show that colorectal cancer is increasing over the years, is getting younger, and is more prevalent in men than women. Adopting a healthy lifestyle, as well as a healthy diet, reduces the risk of CRC. Territorial levels of incidence of malignant neoplasms, including CRC, showed that there are regions that are leading in terms of annual incidence indicators (Pavlodar, Kostanay, North Kazakhstan, East Kazakhstan, Karaganda regions), which determines the need for active primary and secondary prevention of CRI in these regions, as well as the work of other specialists. At the same time, the South Kazakhstan region, Kyzylorda, and Mangistau regions gave meager rates of CRC incidence not only by the country's standards but also on a global scale. However, these indicators may be lower due to other factors.

There are changes in indicators due to false feelings of shame, lack of timely examination due to incorrect information, etc. As noted, screening measures are essential to prevent CRC mortality and morbidity. The following simple rules can be included in the screening measures. On the day of the procedure, the number of patients who refused a colonoscopy and those who gave consent but changed their minds during the procedure should be recorded. According to the calculations, on the day of the procedure, the number of cases of cancellation of the consent to the study should be less than 5%, and during the study — less than 1% of cases of cancellation of the consent. The screening program must also guarantee compliance with the consent procedure; it should include a detailed explanation of the essence of the upcoming study and the need to prepare for it, as well as a discussion of all the risks and benefits associated with conducting the study. Patients should also be aware that a severe illness can be missed and that early and late complications are very likely. After the examination, patients should be allowed to consult directly 24 hours a day in case of complications after the procedure. In the study, people can deny their consent. In addition, patients should be informed that there are cases in which the study cannot be stopped immediately (for example, during a polypectomy cycle). Cases of cancellation of the agreement must be recorded and taken into account in the screening program. It is necessary to carefully periodically monitor the following indicators: the level of participation in the screening program, the organization of re-screening, and subsequent examination of patients with positive screening results.

In the context of an increase in the incidence of colorectal cancer CRC and its tendency to "rejuvenate," it is essential to improve the quality of endoscopic studies that reduce the incidence of CRC. Currently, the main obstacles in Kazakhstan are such problems as low awareness of the population about CRC, a low percentage of prescribing hidden blood tests by outpatient doctors, insufficient high-quality colonoscopies, and the lack of unified national recommendations for managing patients with suspected CRC. Early colon and rectal cancer diagnosis today is crucial in minimizing cancer mortality risk. It should be borne in mind that this is available to all people who come to undergo an examination. In addition, colorectal cancer is more accessible to treat than many other cancers. The probability of successful cancer treatment at an early stage is more than 80%. Priority should be given to developing and disseminating structured educational programs among representatives of the public, supply and medical institutions, politicians, and political leaders.

Conclusion: In conclusion, we can point out the following recommendations for preventing cancer:

– Effective educational programs are applied appropriately for each participant, and the development and dissemination of cheap, easy-to-use, non-troublesome clinical methods.

– It is essential to develop colorectal cancer screening as part of general preventive medicine, promoting screening on a national and regional scale.

– It is necessary to determine the target group of the population – for example, asymptomatic men and women of a certain age with risk factors (e.g., family). In addition, the decision to conduct screening for colorectal cancer should be based on the assessment of the prevalence of this pathology among the population being screened, as well as the screening strategy (the tests being carried out, the frequency of their conduct, the age of the subjects), the recommendations of the rel-

evant medical guidelines, the availability of resources, the degree of risk and the cultural level of the population. In this regard, supporting reputable specialists, active segments of the population, and the media is especially important.

Take up the assessment of the feasibility of the proposed program– the availability and allocation of resources (financial, personnel, diagnostic equipment). It is essential to assess the population's particular cultural and linguistic characteristics. It is necessary to identify the places of screening and ensure interconnection (training and training) with doctors who carry out the examination (general practitioners, etc.) and with the groups of the studied population.

Developing and disseminating patient-oriented screening guidelines, diagnostic methods, treatment, and monitoring is essential. It is necessary to involve patients in the screening program and improve the methods of their further monitoring. Future research should include all recommended screening methods to understand patient preferences in colorectal cancer screening. The recommended methods for screening for colorectal cancer vary depending on their effectiveness, safety, cost, and usability.

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АҢДАТПА

ҚАРАҒАНДЫ ОБЛЫСЫ ХАЛҚЫНЫҢ КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІКПЕН СЫРҚАТТАНУ ЖӘНЕ ОНЫҢ АЛДЫН АЛУ МӘСЕЛЕЛЕРІ БОЙЫНША ХАБАРДАР БОЛУ ДӘРЕЖЕСІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Онкологиялық аурулардың тізімінде колоректальды қатерлі ісік (КҚІ) жыл сайын аурушаңдылық және өлімжітім көрсеткіштері бойынша жетекші орынды алып келеді. Дүниежүзілік денсаулық сақтау ұйымының (ДДҰ) алдын ала болжамдары бойынша, 2030 жылға қарай колоректальды қатерлі ісік (КҚІ) аурушаңдығы жылына 2,2 млн-нан асады, ал өлімжітім жылына 1,1 млн-ға дейін артады. Қазақстанда жыл сайын колоректальды қатерлі ісіктің 3000-нан астам жаңа жағдайы анықталады. Аурумен күресте профилактикалық іс-шараларды барынша дамыту керек. Алдын алу шараларын қолдану аталған дерттен болатын өлім-жітімді азайтуда шешуші рөлге ие. Оның ішіндегі маңызды мәселелердің бірі – халықтың ауру туралы жеткіліксіз ақпараттануы.*

Зерттеудің мақсаты *– колоректальды қатерлі ісіктен болатын сырқаттанушылықтың алдын алу бойынша әлемдік тәжірибені пайдалана отырып, халықты ақпараттандыруды арттыру үшін қолданылатын іс-шараларды ұсыну.*

Әдістері: *2013-2023 жылдардағы PubMed, CrossRef, Scopus және Cochrane дерекқорларынан «колоректальды қатерлі ісік», «қауіп факторлары», «халықтың хабардарлығы», «медициналық сауаттылық», «сырқаттанушылық», «алдын алу» кілт сөздері бойынша үздіксіз іздеу пайдаланылды. Нәтижесінде 75-тен астам ғылыми мақалалар мен 500-ден астам тезистер қаралды.*

Нәтижелері: *Онкологиялық диагнозы бар науқастардың, колоректальді қатерлі ісікпен ауыратын немесе ауру диагнозы расталған науқастар арасында аталған дерт туралы жеткілікті түрде ақпарат алынбағаны және алдын алу шараларына немқұрайлы қарайтындықтары – мәселенені ушықтырған. Себебі, біріншіден, халықтың өз денсаулығы алдында жауапкершілікті толық сезінбеуі (оған әр түрлі себептердің әсер етуі: жалған ұят сезімі, толыққанды ақпараттанбау), екіншіден, профилактикада біріншілік алдын алудың маңызды екендігін алға тартамыз. Сәйкесінше скринингтік бағдарламалардың нәтижелілігін арттыру, ақпараттануды жетілдіру және дертпен күресте мемлекет тарапынан толыққанды көмекті ұйымдастыру керек.*

Қорытынды: *Колоректальді қатерлі ісік – Қазақстандағы онкологиялық аурулардың тізімінде маңызды орынды алатын, өзекті дерт болып табылады. Халық арасында аталған ауру туралы хабардар болуды арттыру және алдын алу мәселелерін дұрыс шешу арқылы, науқастар арасындағы аурушаңдылықты азайтуға мүмкіндік туады. Осы орайда ауру туралы ақпаратты халық арасында кеңінен тарату сонымен қатар, науқастардың өз денсаулығы алдында жауапкершілігін арттыру қажет.*

Түйінді сөздер: *Колоректальды қатерлі ісік, қауіп факторлары, халықтың хабардар болуы, медициналық сауаттылық, аурушаңдылық, алдын-алу.*

АННОТАЦИЯ

СТЕПЕНЬ ИНФОРМИРОВАННОСТИ НАСЕЛЕНИЯ КАРАГАНДИНСКОЙ ОБЛАСТИ ПО ВОПРОСАМ ЗАБОЛЕВАЕМОСТИ И ПРОФИЛАКТИКИ КОЛОРЕКТАЛЬНОГО РАКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *В списке онкологических заболеваний колоректальный рак (КРР) ежегодно занимает лидирующие позиции по показателям заболеваемости и смертности. По предварительным прогнозам ВОЗ, к 2030 году заболеваемость КР превысит 2,2*

млн в год, а смертность увеличится до 1,1 млн в год. Ежегодно в Казахстане выявляется более 3000 новых случаев КРР. В борьбе с болезнью необходимо максимально развивать профилактические мероприятия. Применение профилактических мер играет решающую роль в снижении смертности от данного заболевания. Одна из самых важных проблем – недостаточная информированность населения о болезни.

***Цель исследования** – предложить меры по повышению осведомлённости населения на основе изучения мирового опыта профилактики заболеваемости колоректальным раком.*

***Методы:** В базах данных PubMed, CrossRe, Scopus и Cochrane за 2013-2023 гг. был проведен непрерывный поиск по ключевым словам «колоректальный рак», «факторы риска», «осведомленность населения», «медицинская грамотность», «заболеваемость», «профилактика». Всего было изучено более 75 научных статей и 500 тезисов.*

***Результаты:** Проблема усугубляется тем, что среди больных с онкологическим диагнозом, больных КРР или пациентов с подтвержденным диагнозом КРР недостаточно информации о данном заболевании, и они пренебрегают профилактическими мерами. Во-первых, мы настаиваем на том, что население не полностью осознает ответственность перед своим здоровьем (на это влияют различные причины: ложное чувство стыда, недостаточное осведомленность о болезни и так далее), а во-вторых, первичная профилактика важна. Соответственно, необходимо повысить результативность скрининговых программ, улучшить информированность и организовать полноценную помощь со стороны государства в борьбе с болезнью.*

***Заключение:** КРР является актуальным заболеванием, занимающим важное место в списке онкологических заболеваний Казахстана. Благодаря повышению осведомленности населения о данном заболевании и правильному решению вопросов профилактики, появится возможность снизить заболеваемость среди больных. В этой связи необходимо широкое распространение информации о заболевании среди населения, а также повышение ответственности пациентов перед собственным здоровьем.*

***Ключевые слова:** Колоректальный рак (КРР), факторы риска, осведомленность населения, медицинская грамотность, заболеваемость, профилактика.*

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THE PURPOSE is to assist the development of the oncological service of Kazakhstan, including actions to support:

- efficient prevention
- early diagnostics
- quality treatment
- accessible palliative care

Public Fund «TOGETHER AGAINST CANCER»
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IBAN (RUB): KZ636017131000057923
Almaty Regional Branch of
Halyk Bank of Kazakhstan
BIC: HSBKKZKX
Beneficiary code – 18

Payment purpose code
for sponsorship transfers – 119

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